Use of advanced echocardiography imaging techniques in the critically ill

by

Sam Orde

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy (Faculty of Medicine and Health)
This is to certify that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

I certify that if candidature is successful the thesis will be lodged with the Director of University Libraries and made available for immediate use.

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<th>Name</th>
<th>Sam Orde</th>
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The research work presented in this thesis was supervised by Professor Antony Mclean and Professor Stephen Huang. The thesis is sufficiently well presented to be examined and does not exceed the prescribed word limit.

**Primary supervisor**
Professor Antony Mclean  
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Signed Date  
14/6/2019

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Signed Date  
14/6/2019
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The thesis is dedicated to Caz, my wife, for her support and friendship. Nothing feels impossible with you.

The publications within this thesis have had the help of several different departments and organisations:

(a) Department of Intensive Care Medicine, Nepean Hospital, Sydney, Australia
(b) Cardiovascular Ultrasound Unit, Nepean Hospital, Sydney, Australia
(c) Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota, USA
(d) Department of Cardiology, Nepean Hospital, Sydney, Australia

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### Abstract

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**Explanation of technique**

**Literature review**

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**Sepsis: Public In, Massal M, Gillespie S, Spoon J, Kane G, Oh J (2014)**

**Outcomes prediction in sepsis: Speckle tracking echocardiography based assessment of myocardial function.**

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SECTION A

CHAPTER 2: EXPLANATION OF TECHNIQUE AND LITERATURE REVIEW


SO designed the manuscript, performed the literature review and prepared the manuscript under the supervision of SH and AM, both of whom edited and approved the final manuscript. The manuscript was revised after Anaesth Intensive Care reviewer’s feedback.


HS and SO were invited to write this manuscript for Current Opinion in Critical Care. HS designed the manuscript and HS & SO performed the literature review and prepared the manuscript. Both authors edited and approved the final manuscript.
CHAPTER 3: SEPTIC CARDIOMYOPATHY


SO designed the study, performed data analysis and prepared the manuscript. JNP, MM, SG, JNS, GCK and JKO contributed to data acquisition. SO, JNP, GCK and JKO had access to the data, and contributed to study conception and design, statistical analysis and preparation of the manuscript. MM and SG contributed to study conception and design, and preparation of the manuscript. JNS contributed to data analysis, interpretation and drafting of the manuscript. All authors read and approved the final manuscript. The manuscript was revised after Critical Care reviewer’s feedback.
CHAPTER 4: ACUTE RIGHT VENTRICLE FAILURE


Invitation was made from the editorial board of Intensive Care Medicine for experts from around the world to contribute to a paper on acute RV failure. SO, SM, MP and HB were asked to write the section on diagnostic work-up, recent advances, best standard of care, key points, controversies and areas of future advance. SO prepared the manuscript for these sections for review by the group and then all the authors. SO prepared table 2 & 3 and figures 3 & 4. All authors helped prepare and review the final manuscript. The manuscript was revised after Intensive Care Medicine reviewer’s feedback.


Invitation was made by the editorial group of the ‘Oxford textbook of advanced echocardiography’ for experts from around the world to contribute to this book. SO was requested to produce 2 chapters. SO was the sole author for both chapters and designed and prepared the manuscript. The chapter was revised after review by the editorial group. The chapter is included as a word document below as the pdf was not made available. It has not been altered since accepted for publication.
CHAPTER 5: EFFECT OF CARDIAC SURGERY ON THE RIGHT VENTRICLE

(2019) Minimally invasive vs standard mitral valve repair effect on right ventricular systolic function assessed by echocardiography (under review with the Australasian journal of cardiothoracic surgery ‘Heart, Lung and Circulation’)

*joint first authors

SO and S-YC designed the study and performed data analysis. SO performed the prospective study (see Appendix A after manuscript references) used to guide sample size for the retrospective study. CSY performed the data analysis for the retrospective study. SO analysed and interpreted the data and prepared the initial manuscript. JP, RS, JO, GC all made contributions to the conception and design of the study. RS, JS, RD made substantial contributions to the acquisition and interpretation of data. JP, JO, SP, HM, GC made substantial contributions to analysis and interpretation of data. All authors helped draft and revise the manuscript for intellectual content and approved the final version. All authors agree to be accountable for all aspects of the work.

The included manuscript is currently under review by ‘Heart, Lung and Circulation’ reviewers and has not been altered since original submission.
CHAPTER 6: EFFECT OF PEEP ON THE RIGHT VENTRICLE IN AN ANIMAL MODEL


SO designed the study, analysed the data and prepared the manuscript. SO, AB, PS, GK and JO contributed to study conception and design, preparation and revision of the manuscript and take responsibility for the integrity and accuracy of the data and analysis. SO, SG, AB and PS contributed to data acquisition. SO, AB, SG, GK and JO contributed to analysis and interpretation of the data and revision of the manuscript. All authors read and approved the final manuscript. The manuscript was revised after ‘BMC Anaesthesiology’ reviewer’s feedback.

CHAPTER 7: EFFECT OF PEEP ON RIGHT VENTRICLE FUNCTION IN PATIENTS WITH ARDS


Work from Chapter 6 of this thesis helped design the study (references 17 and 18). MP, JM, LK and MS designed the study, participated to the data acquisition, wrote the draft of the article; MN, SH, SO and AM analyzed the data, interpreted the findings, modified and corrected the first draft. The manuscript was revised after ‘Critical Care Medicine’ reviewer’s feedback.
**CHAPTER 8: SUBJECTIVE ANALYSIS OF THE RIGHT VENTRICLE IN THE CRITICALLY ILL**


SO conceived and designed the study, acquired the data and performed the majority of the echocardiograms, performed analysis of the data and preparation of the manuscript. MS assisted with the data analysis and interpretation and drafting of the manuscript. AM and SY assisted with the study design, data acquisition and drafting of the manuscript. SH assisted with study design, statistical analysis and drafting of the manuscript. All authors drafted and reviewed the manuscript. All authors read and approved the final manuscript. The manuscript was revised after ‘Critical Care’ reviewer’s feedback.
CHAPTER 9: FEASIBILITY OF TRANSTHORACIC 3D ECHOCARDIOGRAPHY IN THE CRITICALLY ILL


SO conceived and designed the study, acquired the data and performed the majority of the echocardiograms (including all the 3D imaging), analysis of the data and preparation of the manuscript. MS assisted with the data analysis and interpretation and drafting of the manuscript. AM and NS assisted with the study design, data acquisition and drafting of the manuscript. SH assisted with study design, statistical analysis and drafting of the manuscript. All authors drafted and reviewed the manuscript. All authors read and approved the final manuscript. The manuscript was revised after ‘Critical Care’ reviewer’s feedback.
**SECTION C**

**CHAPTER 10: EXPLANATION OF TECHNIQUE AND LITERATURE REVIEW**


SO designed the manuscript, performed the literature review and prepared the manuscript under the supervision of AM, who edited and approved the final draft.


Invitation was made by the editorial group of the ‘Oxford textbook of advanced echocardiography’ for experts from around the world to contribute to this book. This is the second chapter SO was requested to write. SO was the sole author and designed and prepared the manuscript. The chapter was revised after review by the editorial group. The chapter is included as a word document below as the pdf was not made available. It has not been altered since acceptance for publication.
CHAPTER 11: MYOCARDIAL CONTRAST PERFUSION ECHOCARDIOGRAPHY IN THE CRITICALLY ILL


SO conceived and designed the study, acquired data including performing the echocardiograms, analysis of the data and preparation of the manuscript. MS and FP assisted with data analysis, interpretation and drafting of the manuscript. AM assisted with study design, data analysis and drafting of the manuscript. SH assisted with study design, data analysis, statistical analysis and drafting of the manuscript. All authors drafted and reviewed the manuscript and approved the final draft. The manuscript it currently under the second round of review by ‘Critical Care’ reviewers and is included below and has not been altered since original submission.
## Presentations during PhD candidature

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Oral presentation: Role of advanced echocardiography imaging in the Intensive Care Unit of the future | Intensive Care Society (ICS) annual meeting  
London, UK |
| 2014 | *Poster presentation:* Effect of cardiac surgery on right ventricle function – a speckle tracking study  
*Poster presentation:* Effect of PEEP on pig right ventricle function assessed by Speckle Tracking Echocardiography  
Plenary speaker: Role of advanced echocardiography imaging in the Intensive Care Unit | Society of Critical Care Medicine (SCCM) annual congress  
San Francisco, California, USA  
34th International Symposium on Intensive Care and Emergency Medicine  
Brussels, Belgium  
Critical care echocardiography course  
Leura, Sydney, Australia |
| 2018 | *Poster presentation:* Biventricular 3D volumetric analysis with transthoracic echo in the critically ill | 38th International Symposium on Intensive Care and Emergency Medicine  
Brussels, Belgium |
| 2019 | *Poster presentation:* Feasibility of myocardial perfusion assessment with contrast echocardiography: can it improve recognition of type I myocardial ischaemia.  
*Poster presentation:* Subjective right ventricle assessment by echo qualified intensive care specialists: assessing agreement with objective measures | 39th International Symposium on Intensive Care and Emergency Medicine  
Brussels, Belgium |

* Awards received for these presentations
## Awards related to PhD thesis

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Abstract

Background: Critical care echocardiography has become a standard of care in the ICU. Recently, new technologies have been developed, including:

   a) Speckle tracking echocardiography (STE)
   b) 3D transthoracic echocardiography (3D TTE)
   c) Myocardial contrast perfusion echocardiography (MCPE)

These relatively novel ultrasound modalities have been shown in the cardiology literature to have potential clinical utility to elucidate myocardial dysfunction not seen with conventional imaging. We sought to determine the feasibility of advanced ultrasound imaging techniques in critically ill patients and investigate their potential clinical benefit in common situations seen in the ICU:

   • Septic shock
   • Right ventricle (RV) failure
   • Patients receiving mechanical ventilation
   • Acute coronary artery occlusion vs stress induced cardiomyopathies

Hypothesis: Advanced echocardiography techniques would be feasible in the majority of critically ill patients and would have prognostic significance, clinical utility and be able to diagnose cardiac abnormalities, potentially in a more sensitive manner than conventional techniques.

Aims: Assess the feasibility, and potential clinical role, of each imaging modality (STE, 3D TTE, MCPE) in common clinical situations seen in the critical care environment.
Abstract

With each imaging method it is easy to get erroneous results if one does not have the necessary experience. Before embarking on these studies there was a suitable training period, under the supervision of cardiology experts in each modality, at Mayo Clinic in Rochester, Minnesota, USA.

a) Speckle tracking echocardiography (STE)

Methods: Assessment of STE was initially assessed in patients with septic shock: one of the most common situations where cardiac dysfunction occurs in the ICU. Findings from this study (along with invited review articles) focused the remaining part of the STE section of the thesis on RV analysis. In particularly, we examined common clinical situations where RV dysfunction is known to commonly occur in the ICU: post cardiac surgery and in patients receiving mechanical ventilation. In addition, we compared conventional techniques of RV assessment (especially subjective assessment) with STE analysis.

Results: STE was found to diagnose cardiac dysfunction that conventional imaging could not elucidate in patients with septic shock, after cardiac surgery and in those undergoing mechanical ventilation (including an initial animal project). For example, in the septic shock cohort 32% had RV dysfunction based on conventional assessment compared to 72% assessed with STE. 33% of patients had LV dysfunction based on ejection fraction compared to 69% assessed with global longitudinal strain.

STE analysis in the critically ill was found to be feasible in the majority of ICU patients: global longitudinal strain could be performed in 60/74 (80%) of those in the septic shock study; RV free wall strain could be performed in 158/188 (85%) of those in the cardiac surgery study, 20/24 (83%) in those with ARDS and 80/101 patients (79%) in those in the subjective RV assessment study.
Abstract

RV dysfunction assessed by STE was found to hold prognostic significance in those with septic shock, particularly those with severe RV dysfunction: RV free wall longitudinal strain (RVfwS) was moderately associated with six-month mortality (OR 1.1, 95% confidence interval, CI, 1.02-1.26, p = 0.02, area under the curve, AUC, 0.68). No other conventional echocardiography or STE method was associated with survival. RVfwS also elucidated more dysfunction than conventional parameters including RV subjective analysis in the critically ill and RV dysfunction induced by mechanical ventilation both in animal studies as well as in patients with ARDS.

**Conclusions:** STE appears feasible to perform in the majority of critically ill patients who may be considered difficult to image: those with septic shock, receiving mechanical ventilation or post cardiac surgery. STE may unmask biventricular systolic dysfunction not seen with conventional echocardiography. In particular, RV dysfunction unmasked by STE, especially when severe, is associated with high mortality in patients with sepsis.

**b) 3D transthoracic echocardiography (3D TTE)**

**Methods:** Using dedicated 3D TTE imaging probes, LV and RV volumetric assessment was assessed in critically ill patients receiving mechanical ventilation with a ventilation:perfusion mismatch (P:F ratio <300) within 24hours of admission. The feasibility of 3D TTE was assessed in this population as they encompass typical ICU patients who are considered challenging to image. 3D LV and RV volumetric assessment was compared to stroke volume assessment with Doppler as a reference standard, as it is suggested to be accurate in the critically ill.
Abstract

**Results:** 92 patients were included (83 in sinus, 9 in atrial fibrillation). 3D volumetric assessment of the LV and RV was feasible in 72% and 55% of patients respectively, however underestimated stroke volume compared to Doppler assessment by 2.6ml (+/-10.4) and 4.1 (+/-15.4) respectively. Limits of agreement for 3D LV and RV volumetric analysis techniques were large.

**Conclusions:** 3D LV and RV volumetric analysis appear feasible in the majority of mechanically ventilated ICU patients. Compared to Doppler method, 3D LV and RV underestimate stroke volume. The large limits of agreement between the methods also cast doubt about their comparability. Given the scenarios in which stroke volume analysis is required (e.g. assessment of cardiac performance, volume responsiveness), our study cautioned against the use of 3D stroke volume assessment clinically.

**c) Myocardial contrast perfusion echocardiography (MCPE)**

Diagnosis of acute myocardial infarction (MI) caused by coronary artery occlusion in ICU can be difficult and inappropriate intervention is potentially harmful. MCPE examines ultrasound contrast intensity replenishment curves in individual myocardial segments as an index of myocardial blood flow. MCPE could possibly serve as a triage tool to invasive angiography by estimating blood flow in the myocardium. We sought to assess the feasibility in the critically ill and if MCPE could add incremental value to clinical acumen in predicting acute coronary artery occlusion.

**Methods:** Adult ICU patients with Troponin I >50ng/L and cardiology referral being made for consideration of inpatient angiography for acute coronary artery occlusion underwent MCPE examination. Medical history, ECG, troponin and 2D echo images were used to estimate likelihood of MI (clinical acumen) by 7 cardiologists and 6 intensivists blinded from the MCPE results. Clinical acumen, quantitative MCPE and subjective (visual) MCPE
Abstract

assessment were assessed in their ability to predict acute MI from coronary artery occlusion.

**Results:** 40 patients were included with 6 (15%) having acute coronary artery occlusion. MCPE was feasible in 68.8% [IQR 50-81] of segments (median 11 out of a 16 segment LV model). No adverse events occurred. A significant difference was found in overall MCPE blood flow estimation between those diagnosed with acute coronary artery occlusion and those without (3.3 vs 2.4dB/s, p=0.050). A MCPE value of 2.8dB/s had 67% sensitivity and 88% specificity in detecting acute coronary artery occlusion. Clinical acumen showed no significant association in prediction of acute coronary artery occlusion (OR 0.6, p=0.09), however if quantitative or visual MCPE analysis was included significant association occurred (OR 17.1, p=0.01; OR 23.0, p=0.01 respectively).

**Conclusions:** MCPE is feasible in the critically ill and shows better association with predicting acute coronary artery occlusion vs clinical acumen alone. MCPE adds incremental value to initial assessment of presence of acute coronary artery occlusion which may help guide those who require angiography.

**Overall conclusions:** Advanced echo imaging techniques of STE, 3D TTE and MCPE appear feasible to perform in the majority of ICU patients with common clinical conditions such as septic shock, receiving mechanical ventilation, post cardiac surgery or being assessed for myocardial ischaemia. STE may help elucidate LV and RV dysfunction that is not recognised by conventional imaging. 3D TTE for LV and RV volumetric analysis, unfortunately, appears to lack sufficient agreement with current reference methods to be used in the clinical environment at this time. MCPE may help guide interventions in those with acute coronary artery occlusion vs reversible cardiomyopathies (eg: Takostubo’s syndrome). Larger multicentre, multi-operator, blinded analysis studies are required to investigate each of
Abstract

ten ultrasound modalities further. However, initial results from this thesis suggest that particularly STE and MCPE analysis in the critically ill may hold potential clinical benefit.
INTRODUCTION
Critical care echocardiography is developing rapidly with a number of international organisations now mandating new intensive care specialists have competency in focused cardiac ultrasound [1]. The use of clinician performed ultrasound is common among Intensive Care Units worldwide, as is research investigating its utility[2]. What began as ICU clinicians performing simple focused echo studies investigating aetiology of shock has developed into robust haemodynamic assessment, interrogation of heart-lung interactions, valvular assessment and beyond, in severely unwell patients. In addition, increased research in this area has led to current international evidence-based guidelines able to be published[3].

More recently, advanced echocardiography imaging techniques have begun to appear in the clinical and research field of cardiology, including: speckle tracking echocardiography (STE) [4], 3D transthoracic echocardiography (3D TTE) for biventricular volumetric analysis [5, 6] and myocardial contrast perfusion echocardiography (MCPE) [7]. These techniques have been found to have several advantages over conventional imaging but performing the studies often requires a high degree of training[8], and both imaging and analysis can be challenging[9]. In the critical care environment these advanced techniques have not been studied adequately and are not mentioned in recent evidence-based guidelines compared to the cardiology literature where advanced techniques have a prominent place [10].

We sought to examine initially the feasibility, but more importantly the potential clinical role, of each of these advanced techniques in common clinical scenarios seen in the intensive care environment. We aimed to investigate if some of the advantages described in the cardiology literature (eg: detection of subtle cardiac dysfunction, 3D assessment, non-invasive estimates of myocardial blood flow) could be translated to the critical care field.
Introduction

Each section of the thesis refers to a separate technique.

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<td>3D transthoracic echocardiography</td>
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<tr>
<td>C</td>
<td>Myocardial contrast perfusion echocardiography</td>
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In each section, a detailed description of the method as well as a literature review of the studies to date in the critical care field will be discussed. In this introduction chapter an overview of each technique and their potential clinical benefit in the ICU population will be described.

**Speckle tracking echocardiography (STE)**

Characterization of tissue movement in echocardiography starts with visual assessment of the regular grey-scale 2D imaging measurements and Doppler assessment. However, some of the intricate nature of the myocardial motion may be missed by conventional analysis. STE is one of the latest advanced echo imaging techniques available: a non-Doppler, angle-independent, semi-automatic method of examining movement in echo images.

A standing echo image is made up from ‘speckles’ which have the potential to be ‘tracked’, frame-by-frame, by the STE software. This provides the ability to determine how the speckles move in relation to each other and provide an estimate of myocardial movement and ‘deformation’. The primary parameter of deformation described is ‘strain’ and has been shown to be a sensitive marker of cardiac dysfunction [11] and has been validated against suitable reference standards [12].

Strain analysis can be performed on both the left ventricle (LV) and right ventricle (RV) and has the potential to describe myocardial dysfunction hidden from conventional assessment[13]. It is not without its limitations (see Table 1) but a wealth of information can be obtained: subtle systolic and diastolic dysfunction, dyssynchrony, regional wall motion abnormalities, twist and torsion etc...
Introduction

<table>
<thead>
<tr>
<th><strong>Advantages</strong></th>
<th><strong>Limitations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Biventricular assessment</td>
<td>A relatively high degree of echo experience is required to perform imaging</td>
</tr>
<tr>
<td>Angle independent</td>
<td>Analysis is time consuming</td>
</tr>
<tr>
<td>Describes cardiac function not recognised</td>
<td>Learning the technique takes time</td>
</tr>
<tr>
<td>by conventional echo measurements</td>
<td>Low frame rates need to be avoided</td>
</tr>
<tr>
<td>Can describe additional cardiac motion</td>
<td>Imaging can be challenging</td>
</tr>
<tr>
<td>such as torsion</td>
<td>Much information gleaned from analysis is far from validated, particularly in the</td>
</tr>
<tr>
<td>Accurate vs MRI in cardiology studies</td>
<td>critically ill</td>
</tr>
<tr>
<td>Can differentiate active motion from tethering.</td>
<td></td>
</tr>
</tbody>
</table>

*Table 1*: Advantages and limitations of speckle tracking echocardiography

The vast majority of research to date on the use of this technology is in the cardiology setting, indeed it is currently used clinically in many larger centres particularly for assessment of pulmonary hypertension [14] and chemotherapy induced cardiotoxicity[15]. From a critical care perspective there are only a handful of studies, but there are several areas where there is potential clinical benefit which are begun to be investigated in this thesis. Areas considered are all very common clinical situations seen in the ICU: septic cardiomyopathy, critically ill patients on mechanical ventilation or with acute myocardial ischaemia being considered.

One of the major advantages of STE is the ability to elucidate subtle LV dysfunction which may be missed by conventional echo parameters. For example, the STE parameter assessing LV systolic function (known as global longitudinal strain [GLS]) has been frequently shown, both in cardiology and critical care literature, to describe abnormalities missed by measures such as ejection fraction[16]. Septic cardiomyopathy is one of the more common acute cardiac abnormalities seen in the ICU[17]. The prognostic implications of cardiac dysfunction are controversial[18], however assessment previously had been limited to assessment tools such as ejection fraction or fractional area change. We sought to perform
Introduction

one of the first studies to assess the incidence of cardiac dysfunction using STE technology in patients with septic shock, as well as assessing the prognostic implications of STE dysfunction.

It is increasingly recognised that cardiac dysfunction should not simply be focused on the LV. RV dysfunction has been shown to be a highly prognostic factor in heart failure[19], ischaemic heart disease[20], pulmonary hypertension[21], pulmonary embolism[22] among other aetiologies. Again, STE technology can determine dysfunction not recognised by conventional imaging methods and this is validated vs reference standards such as MRI[23]. Further, we sought to perform some of the first studies in the critically ill to determine feasibility and clinical relevance of STE analysis of the RV, by a parameter known as RV free wall strain, investigating the effect of mechanical ventilation (including PEEP) on the RV and in clinical situations such as ARDS. In addition, we compared RVfwS against conventional parameters, especially subjective assessment of RV function (a commonly performed method of RV assessment in the critical care environment).

Subjective analysis plays a particularly important role detecting regional wall motion abnormalities. STE can detect subtle cardiac dysfunction and use of the parametric display of longitudinal strain (also known as ‘bull’s eye plots’) has been shown to provide valuable information for detection of cardiomyopathies [24]. Regional wall motion abnormalities are extremely common in the ICU population along with Troponin elevation, but not all of these patients have acute coronary artery blockage [25]. We sought to determine in STE could add diagnostic information in this group of ICU patients (see Chapter 11).

In summary, STE can provide a huge amount of information and elucidate cardiac dysfunction potentially hidden from conventional echo parameters. We sought to perform some of the first studies in the critically ill. We sought to determine feasibility, but more importantly the potential clinical role in common ICU pathological states (including sepsis, mechanical ventilation, myocardial ischaemia) to either diagnose cardiac dysfunction, provide prognostic information or guide therapy.
3D transthoracic echocardiography (3D TTE)

Since early this century, 3D TTE has been a feature of most major ultrasound systems being used for volumetric assessment as well as valvular analysis[26]. LV volumetric analysis with 3D TTE is touted as more accurate than 2D echocardiography volumetric estimation, using MRI as the gold standard[27]. Structures can be seen in the context of the whole myocardial volume rather than single plane. Ejection fraction, for example, can be hindered by foreshortening, malrotation or assumptions about ventricular shape, which may lead to inaccuracies. In addition, it is much more automated and may therefore provide rapid image analysis without additional human error or bias and has been shown to be repeatable in the cardiology setting[27].

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single beat 3D volumetric analysis possible</td>
<td>Temporal resolution low</td>
</tr>
<tr>
<td>Avoids assumptions about LV shape</td>
<td>Imaging often challenging</td>
</tr>
<tr>
<td>More accurate than 2D ejection fraction vs</td>
<td>Use not validated in critically ill</td>
</tr>
<tr>
<td>MRI as reference standard</td>
<td>Expensive technology, advanced echo</td>
</tr>
<tr>
<td>Automated / semi-automated</td>
<td>machines required</td>
</tr>
<tr>
<td>Rapid analysis with wealth of information</td>
<td>Specific training required</td>
</tr>
<tr>
<td>possible to obtain</td>
<td></td>
</tr>
<tr>
<td>Repeatable in cardiology studies</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Advantages and limitations of 3D transthoracic echocardiography

Cardiac volume assessment in the critically ill is important in many circumstances such as heart failure, fluid administration and assessing effect of treatment (eg: response to catecholamine infusion). Critically ill patients can be notoriously difficult to image, however, and the role of 3D TTE for volumetric analysis has not be assessed. We sought to investigate if ejection fraction and stroke volume obtained from pulsed-wave Doppler, Simpson’s biplane and 3D TTE, were comparable in an ICU population who were mechanically ventilated.
**Myocardial contrast perfusion echocardiography (MCPE)**

In the 1990s initial studies investigated the hypothesis that myocardial blood flow could be assessed at the bedside with echocardiography contrast by destroying the contrast microbubbles with a ‘flash’ of high diagnostic intensity ultrasound and then assessing the rate of replenishment of the microbubbles into the myocardium[28] [29] [30]. The replenishment is assessed by the change in intensity or brightness in individual myocardial segments. The microbubbles behave like red blood cells, hence the theory that any change in signal intensity represents a change in myocardial blood flow (see *Table 3*).

<table>
<thead>
<tr>
<th><strong>Advantages</strong></th>
<th><strong>Limitations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-invasive estimation of myocardial blood flow at the bedside</td>
<td>Challenging imaging</td>
</tr>
<tr>
<td>Subjective and quantitative assessment</td>
<td>Not validated in the critically ill</td>
</tr>
<tr>
<td>Echo contrast safe in the critically ill</td>
<td>Accuracy uncertain</td>
</tr>
<tr>
<td></td>
<td>Requires injection of a drug</td>
</tr>
</tbody>
</table>

*Table 3*: Advantages and limitations of myocardial contrast perfusion echocardiography

The diagnosis of acute coronary syndromes in the ICU can be challenging. Troponin elevation, ECG and regional wall motion abnormalities are frequently seen in conditions other than coronary artery occlusion [31], for example Takotsubo’s and septic cardiomyopathy amongst other causes [32]. Further, investigating for possible acute coronary artery occlusion with angiography can be dangerous due to the risks of patient transport, contrast induced nephropathy, radiation, access issues, anticoagulation, delay in diagnosis and cost etc... Potentially MCPE could aid clinical acumen and help identify patients with acute coronary artery occlusion vs those without at the bedside in the ICU.
**Introduction**

WE do not see MCPE as a replacement for angiography, but potentially as a triage tool or simply to add confidence to the physicians clinical acumen [33].

**Conclusions**

Advanced echocardiography techniques such as STE, 3D TTE and MCPE have the potential to elucidate myocardial dysfunction that can be missed by conventional imaging. We sought to perform a number of studies in the critically ill to determine if these techniques were feasible and if they had potential clinical benefit in common clinical scenarios where myocardial dysfunction occurs and accurate cardiac analysis with echocardiography is essential.
Introduction

References


Introduction


SECTION A:

SPECKLE TRACKING ECHOCARDIOGRAPHY
Section A: Speckle tracking echocardiography

Section overview

This section is comprised of 7 chapters (chapters 2-8) including 9 manuscripts: 7 manuscripts published in leading peer-reviewed critical care journals, 1 manuscript remains under review and 1 textbook chapter (accepted for publication).

Chapter 2: Explanation of technique and literature review


These two review articles explain in detail the technique of speckle tracking echocardiography (STE) and include the literature review in the critical care setting. Further, an outline is provided of possible areas where STE may be clinically useful in the critically ill.

In particular, two areas are mentioned which form the focus of the remaining chapters:

1. Septic shock
2. Acute right ventricle (RV) failure

Chapter 3: Septic cardiomyopathy


This initial study of the thesis investigated the feasibility and association of biventricular STE assessment with outcomes in patients with severe sepsis. In particular, RV dysfunction assessed by STE was found to hold prognostic significance (especially when severe). This
Section A: Speckle tracking echocardiography

holds practical relevance as RV analysis by STE is simpler to perform than LV analysis. This study helped focus the remaining studies in this thesis section on STE analysis of the RV.

Chapter 4: Acute right ventricle failure and speckle tracking imaging


Both of these publications were invited ‘expert’ review articles: the first in one of the leading critical care journals (Intensive Care Medicine) and the second a chapter in the ‘Oxford Textbook of Advanced Echocardiography’. The ‘state of the art’ review article on acute RV failure includes the potential role of advanced imaging modalities (including speckle tracking echocardiography and 3D imaging). The textbook chapter explains the technique of STE analysis of the RV in particular and clinical relevance. An outline is provided of possible areas where acute RV failure is particularly seen in the ICU:

1. Post cardiac surgery
2. Mechanical ventilation (particularly effect of PEEP)
3. Acute respiratory distress syndrome (ARDS) and the application of PEEP
4. Comparison with conventional parameters (particularly subjective RV analysis)

Chapter 5: Effect of cardiac surgery on the right ventricle


RV dysfunction is commonly seen after cardiac surgery in the ICU and can persist for years. The exact aetiology, associated factors and significance are not well understood. Recent studies have suggested there may be a difference in the effect of cardiac surgery on the RV
Section A: Speckle tracking echocardiography

comparing ‘open’ sternotomy approach vs minimally invasive surgery, however this has only been evaluation in a relatively small number of patients and the longer-term outcomes have not been well described.

We sought to use STE as a sensitive, non-invasive manner to analyse RV function in the post-operative period after cardiac surgery in a prospective pilot study. This data was used to guide one of the largest retrospective studies comparing RV systolic function, assessed by STE, before and after minimally invasive vs open sternotomy mitral valve repair surgery.

Chapter 6: Effect of PEEP on the right ventricle in an animal model


Mechanical ventilation is commonly performed for respiratory failure in the critically ill. Positive end expiratory pressure (PEEP) is a universally used parameter for trying to encourage open lung ventilation: ‘splinting’ open airways to optimise gas exchange. The disadvantage of PEEP is that excessive pressure may increase RV afterload by compressing the pulmonary vasculature leading to RV dysfunction and potential cardiovascular compromise. Echo is extremely useful for assessing RV size and function in these patients, however the most sensitive parameter for assessing RV dysfunction is not known.

We performed an animal study to determine if STE analysis of RV function could determine deterioration in RV function induced by escalating levels of PEEP and to compare this to a commonly used method of RV analysis: fractional area change.
**Section A: Speckle tracking echocardiography**

**Chapter 7: Effect of PEEP on right ventricle function in patients with ARDS**


Results from our animal study in Chapter 6 helped show STE assessment of the RV was sensitive and feasible in determining RV dysfunction induced by higher levels of PEEP. These results help guide this subsequent study in critically ill patients with moderate to severe ARDS, who are significant at risk of RV failure and cardiovascular compromise from their respiratory failure and mechanical ventilation. STE analysis of RV function was used to help analyse the effect of an open lung strategy with a recruitment manoeuvre (escalating PEEP levels) to determine the optimal PEEP.

**Chapter 8: Subjective analysis of the right ventricle in the critically ill**


In the above studies the feasibility and clinical relevance of STE analysis of the RV in the critically ill was shown. We sought to compare this method of assessment with one of the most frequently used echo methods for analysis of the RV: subjective assessment. To our knowledge, this is the largest and most robust analysis of subjective RV assessment vs objective measures performed.
Section A: Speckle tracking echocardiography

Chapter 2: Explanation of technique and literature review


Speckle tracking echocardiography in the critically ill: enticing research with minimal clinical practicality or the answer to non-invasive cardiac assessment?

S. Orde*, S. J. Huang†, A. S. Mclean‡

Summary
Echocardiography is developing rapidly. Speckle tracking echocardiography is the latest semi-automatic tool that has potential to quantitatively describe cardiac dysfunction that may be unrecognised by conventional echocardiography. It is a non-Doppler, angle-independent, feasible and reproducible method to evaluate myocardial function in both non–critically ill and critically ill populations. Increasingly it has become a standard measure of both left and right ventricle function in specific patient groups, e.g. chemotherapy-induced cardiomyopathy or pulmonary hypertension. To date there are few studies in the critically ill, predominantly in sepsis, yet all describe dysfunction beyond standard measures. Other areas of interest include heart–lung interactions, right ventricle function and twist and torsion of the heart. A word of caution is required, however, in that speckle tracking echocardiography is far from perfect and is more challenging, particularly in the critically ill, than implied by many published studies. It takes time to learn and perform and most values are not validated, particularly in the critically ill. We should be cautious in accepting that the latest software used in cardiology cohorts will automatically be the answer in the critically ill. Even with these limitations the technology is enticing and results fascinating. We are uncovering previously undescribed dysfunction and although it currently is essentially a research-based activity, there is great promise as a clinical tool as echocardiography analysis becomes more automated, and potentially speckle tracking echocardiography could help describe cardiac function in critical illness more accurately than is possible with current techniques.

Key Words: speckle tracking echocardiography, critically ill, intensive care unit, cardiac dysfunction

Introduction
Cardiac dysfunction, either temporary or chronic, is common in the intensive care unit (ICU) and the field of critical care echocardiography (echo), although in its relative infancy, is growing rapidly. Echo is well suited to the critical care environment with its safety profile, portability and rapid feedback of results. The question arises: ‘Is there dysfunction present that traditional echocardiography methods are failing to elucidate?’. One promising advance is speckle tracking echocardiography (STE) where the principal parameter described is ‘strain’, a measure of deformation of a structure, i.e. how a structure changes its relative length, height or width.
is human nature to be enticed by new devices and as a specialty group we are no different. However, not all new technology realises its original promise and STE should be seen in this light. Although data obtained from STE is tantalising, it is not always straightforward to perform STE analysis and specific imaging is required to get accurate results. It takes a degree of training to avoid erroneous readings; indeed in performing research-related STE analysis, calculations are repeated up to three times to ensure that readings are precise. There are studies showing that with suitable training the technique is feasible and reproducible. The technique has also been validated against sonomicrometry and tagged magnetic resonance imaging (MRI) as gold standards, and can be done on both the left and right ventricle. It should be noted that studies to date are almost entirely in the cardiology setting.

There are only a handful of studies using STE in the critically ill and all describe possible benefits from its use. It is likely to remain a research tool only at this stage but as technology improves and the critical care community progresses in its understanding of advanced echocardiography there may be a future role for this equipment.

This article reviews the theory of STE, values derived, basic image acquisition, analysis techniques, limitations and what role (if any) STE may play in the future evaluation of cardiac function in the critically ill.

### Table 1

**Advantages and disadvantages of speckle tracking echocardiography**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle-independent</td>
<td>Time required to perform analysis</td>
</tr>
<tr>
<td>Can describe cardiac dysfunction that cannot be recognised by standard echo measures</td>
<td>Time required to learn technique</td>
</tr>
<tr>
<td>Accurate vs gold standard (e.g. MRI)</td>
<td>Specific imaging required to get accurate results</td>
</tr>
<tr>
<td>Can differentiate tethering from ‘active’ movement</td>
<td>Low frame rates need to be avoided</td>
</tr>
<tr>
<td>Can describe additional cardiac motion such as torsion, dyssynchrony, diastolic function</td>
<td>Limited studies in the critically ill</td>
</tr>
<tr>
<td></td>
<td>Entire myocardium needs to be viewed throughout cardiac cycle</td>
</tr>
<tr>
<td></td>
<td>Wealth of information available that has not been validated, including right ventricle and atrial analysis</td>
</tr>
<tr>
<td></td>
<td>Clinical relevance of all parameters has not been fully investigated</td>
</tr>
</tbody>
</table>

MRI, magnetic resonance imaging.

**Speckle tracking echocardiography technology**

STE analyses cardiac function based on tracking, frame by frame, the movement of groups of greyscale ‘speckles’ (known as ‘kernels’) that make up the image of the myocardium. The speckled appearance is a naturally occurring ultrasound artifact: they do not represent actual structures present in the myocardium. The speckles are caused by interferences of scattered ultrasound wave

![Figure 1: Process of speckle tracking echocardiography. The software tracks groups of pixels (known as kernels) throughout the cardiac cycle and determines the degree of relative deformation (known as strain) as a marker of contractility. For example: if kernels are 10 mm apart at end-diastole and at end-systole are 7 mm apart, strain is -30%.](image-url)

\[
\text{Strain} = \frac{L - L_0}{L_0} = \text{eg: } \frac{7 - 10}{10} = -30\% 
\]
reflections, from small reflectors that are spaced closer together than can be separated on the ultrasound image. The pixelated appearance of the myocardium is relatively stable and the groups of speckles that make up kernels are like a fingerprint specific for that area of myocardium.

STE is a semi-automated post-processing method (i.e. analysis occurs after the images have been stored), which evaluates the degree of deformation of the kernels relative to each other, known as ‘strain’. This value is used as an estimation of contractile function: the concept being that the closer the speckles move towards each other, the better the contractile function. Strain is also a negative value as it describes relative deformation (i.e. movement of one kernel versus another), therefore the more negative a number, the greater the degree of deformation, the greater the systolic function (see Figure 1).

Similar to estimating ventricular function with methods such as ejection fraction, STE relies on good image quality, and background image ‘noise’ can disrupt the tracking process. Whereas ejection fraction by Simpson’s biplane method only requires definition of the endocardial border, with STE the entire myocardium should be viewed throughout the cardiac cycle. Individual ventricle segments can be ignored if they are unable to be visualised, but this may impede the accuracy of final results. In our opinion, specific imaging to optimise for higher frame rates is required to get accurate STE results (see ‘How to perform Speckle Tracking Echocardiography’ for details).

## Definitions of values and terminology

STE analysis delivers a wealth of information both from strain curves (measuring the percentage deformation of the myocardium between two kernels) and strain rate curves (see Table 2). Strain rate (SR) is the rate of change in strain (dS/dt) and is expressed as 1/s. SR is used as a surrogate of systolic function and has been described to be less dependent on preload than strain, hence a better reflection of contractility.

One-dimensional movement is commonly assessed, and the most reported and validated parameter described is longitudinal strain (in the base to apex direction) measured from apical windows. The average of the longitudinal strain in the apical four-chamber, two-chamber and three-chamber views can be averaged to give global longitudinal strain (GLS) (see Figure 2). This value is thought to be particularly relevant in detecting subendocardial myocardial dysfunction, the subendocardium the most sensitive to ischaemia. Parasternal

### Table 2

**Speckle tracking echocardiography terminology**

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strain (S)</td>
<td>Relative deformation between groups of kernels, i.e. measure of speckles (or kernels) coming together</td>
</tr>
<tr>
<td>Strain rate (SR)</td>
<td>Speed (or rate) of deformation</td>
</tr>
<tr>
<td>Strain rate early relaxation (SRe)</td>
<td>Speed (or rate) of speckles separating after contraction</td>
</tr>
<tr>
<td>Time to peak strain</td>
<td>The difference in timing of individual segments reaching peak strain</td>
</tr>
<tr>
<td>End-systolic strain</td>
<td>Strain value at end-systole: deemed effective systolic function</td>
</tr>
<tr>
<td>Post-systolic peak strain</td>
<td>Strain value after closure of the atrioventricular valve: deemed ineffective systolic function</td>
</tr>
<tr>
<td>Longitudinal strain</td>
<td>Assessment of myocardial deformation in the base–apex direction</td>
</tr>
<tr>
<td>Global longitudinal strain</td>
<td>Average of apical 4-chamber, 2-chamber and 3-chamber longitudinal strain analysis</td>
</tr>
<tr>
<td>Bullseye plot</td>
<td>Pictorial representation of global longitudinal strain</td>
</tr>
<tr>
<td>Circumferential strain</td>
<td>Assessment of myocardial deformation in the short-axis view in a circular direction</td>
</tr>
<tr>
<td>Radial strain</td>
<td>Assessment of myocardial deformation in the short axis in an inward manner (deformation towards the centre)</td>
</tr>
<tr>
<td>Twist</td>
<td>Angle difference at systole between apical rotation (anticlockwise direction viewed from apex) and basal rotation (clockwise direction)</td>
</tr>
<tr>
<td>Torsion</td>
<td>Normalised twist: twist angle divided by distance change between base and apex</td>
</tr>
<tr>
<td>Untwist</td>
<td>Angle difference during diastole between apical and basal rotation</td>
</tr>
</tbody>
</table>

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Figure 2: Global longitudinal strain: the most commonly reported parameter assessed by speckle tracking echocardiography. Longitudinal strain is the relative deformation in the base–apex direction (see white arrow) assessed on the apical views. Global longitudinal strain is the average of the (a) Apical 4- (b) Apical 2- and (c) Apical 3-chamber views and can be displayed as (d) a bullseye plot, where red indicates normal contractility.

Figure 3: (a) Circumferential strain: deformation along the circular perimeter. Kernels move closer together hence negative value representing relative deformation. (b) Radial strain: deformation in the radial direction (towards left ventricular cavity); kernels move away from each other hence positive value.
short-axis views can be used to describe movement in the circumferential and radial directions (see Figure 3).

Various strain values relating to the curves have been described, including end-systolic strain, peak strain, and post–peak systolic strain, each attempting to describe systolic function (see Figure 4). This confusing nomenclature led the echocardiography industry and leading task forces from Europe and the US to recommend end-systolic strain be the default parameter to describe systolic function in a consistent manner. Although STE was originally used to describe left ventricular function, it is also used to assess right ventricle (RV) and left atrial deformation.

### How to perform speckle tracking echocardiography

#### Image acquisition

A certain degree of training is required to perform image acquisition and analysis of STE. The learning process is not excessively challenging but a sound knowledge of conventional echocardiography is important, e.g. Level II competency as per the American Society of Echocardiography as well as Australasian training standards. Specific imaging optimising for frame rate and myocardium definition is important to obtain suitable images for STE analysis. The entire myocardium, including medial and lateral mitral annulus, should be seen throughout the cardiac cycle and apical foreshortening needs to be avoided. A frame rate ideally between 50–110 frames per second should be obtained using a single focal point and minimising width and depth.

#### Speckle tracking analysis

Specific software is required for the semi-automated, off-line analysis, usually on dedicated workstations. There are vendor-specific as well as vendor-independent analysis packages available. The image is paused at end-diastole and the endocardium is traced to define the ‘regions of interest’, starting at one end of the mitral annulus and finishing at the other, typically with 7–15 points placed. The software automatically separates the myocardium into six segments and tracks the movement throughout the cardiac cycle. Adequate assessment of the tracking is essential to ensure accuracy of results. Segments where tracking is not adequate can be either ignored or re-traced.

### Potential applications of speckle tracking echocardiography in the critically ill

STE has the potential to describe systolic and diastolic myocardial mechanics additional to those obtained by conventional echocardiography techniques. It has been shown to be of use in myocardial evaluation in a broad range of patient groups, however, in research in the critically ill the application is still in its infancy.

In the clinical setting STE is used predominantly to detect subclinical disease using LV GLS for early detection of systolic dysfunction not recognised by LV ejection fraction (LVEF). Examples include chemotherapy-induced cardiomyopathy, heart failure with preserved ejection fraction and hypertrophic cardiomyopathy. RV free wall strain is becoming a well-recognised parameter in cohorts such as pulmonary hypertension where it has been shown to be a sensitive prognostic marker as well as predictor of treatment response. Many excellent review articles on the utility of STE in the cardiology setting are available, however summaries of the role in the critically ill are scant.
Sepsis-induced cardiac dysfunction has attracted the most attention in the use of STE in the critically ill, predominantly with longitudinal strain. To date there are 12 published studies: ten human (see Table 3) and two animal studies.3,17-27 These studies vary in their approach to LV longitudinal strain analysis: some using just the four-chamber view,24 others both four- and two-chamber views and others all three apical views to get the entire LV GLS.3,27 One of the challenging issues using STE analysis is the lack of an agreed common method of obtaining values (see Limitations).

### Table 3

**Summary of studies using speckle tracking echocardiography analysis in severe sepsis and septic shock**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients included</th>
<th>Feasibility of STE Imaging for STE</th>
<th>LV GLS vs LVEF</th>
<th>Association with mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ng et al, 201627</td>
<td>33 septic shock 29 sepsis only 60/62 (97%)</td>
<td>Echo on day 1 and on day 3 (or recovery) All apical views</td>
<td>Significant difference in GLS between septic shock group and sepsis patients No difference in EF seen between the groups</td>
<td>No association of GLS with mortality</td>
</tr>
<tr>
<td>Palmieri et al, 201518</td>
<td>115 115/149 (77%)</td>
<td>Echo on day 1 Apical 4- and 2-chamber views</td>
<td>Higher variability in longitudinal strain with EF &gt;30%, lower variability with EF &gt;30%</td>
<td>Worse longitudinal strain associated with mortality, LVEF was not</td>
</tr>
<tr>
<td>Chang et al, 201521</td>
<td>111 111/120 (93%)</td>
<td>Echo on day 1 All apical views</td>
<td>Patients with EF &gt;50% had significantly reduced LV GLS which was prognostic</td>
<td>Worse LV GLS associated with mortality especially if LVEF &gt;50% LVEF was not associated with mortality</td>
</tr>
<tr>
<td>Shahul et al, 201521</td>
<td>45 45/51 (88%)</td>
<td>Echo on day 1 and 2 Apical 4-chamber</td>
<td>Longitudinal strain worsened over 24 hours in septic shock but LVEF did not change significantly</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Dalla et al, 201521</td>
<td>38 Not reported</td>
<td>All apical views</td>
<td>50% of those with preserved LVEF had impaired LV GLS (defined as &gt;-15%)</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Lanspa et al, 201524</td>
<td>68 68/89 (76%)</td>
<td>Echo within 6 hours of meeting inclusion criteria 4-chamber view</td>
<td>50% of those with preserved LVEF had impaired longitudinal strain and 6.5% had severely abnormal strain</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>De Geer et al, 201525</td>
<td>44 44/50 (88%)</td>
<td>Echo on day 1 and 3 or 4 All apical views</td>
<td>Marked overlap between groups: 22/44 abnormal LVEF, 18/44 abnormal LV GLS, 4 (18%) abnormal LV GLS with normal LVEF</td>
<td>No association of either LV GLS or LVEF with mortality All measures except LV GLS improved over time</td>
</tr>
<tr>
<td>Landesberg et al, 201426</td>
<td>106 106/120 (88%)</td>
<td>225 echos on 106 patients First echo on day 1 Apical 4- and 2-chamber views</td>
<td>Not reported</td>
<td>No association of either LV GLS or LVEF with mortality</td>
</tr>
<tr>
<td>Orde et al, 20144</td>
<td>60 60/74 (80%)</td>
<td>Echo on day 1 All apical views</td>
<td>33% patients had LVEF &lt;55%, 7% &lt;30% 69% LV GLS abnormal, 21% severely abnormal</td>
<td>No association of LV GLS or LVEF with mortality</td>
</tr>
<tr>
<td>Basu et al, 201227</td>
<td>15 15/23 (63%)</td>
<td>Retrospective review from 2002/3 Echo on day 1 Apical 4-chamber view</td>
<td>LVEF same for septic patients vs controls Longitudinal strain less in septic patients vs controls</td>
<td>Not evaluated</td>
</tr>
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</table>

STE, speckle tracking echocardiography; echo, echocardiography; LV, left ventricle; EF, ejection fraction; GLS, global longitudinal strain.

(a) Septic cardiomyopathy

Sepsis-induced cardiac dysfunction has attracted the most attention in the use of STE in the critically ill, predominantly with longitudinal strain. To date there are 12 published studies: ten human (see Table 3) and two animal studies.3,17-27 These studies vary in their approach to LV longitudinal strain analysis: some using just the four-chamber view, others both four- and two-chamber views and others all three apical views to get the entire LV GLS.3,27 One of the challenging issues using STE analysis is the lack of an agreed common method of obtaining values (see Limitations). All the above studies suggest that myocardial dysfunction is frequently seen in sepsis and also that LV GLS is reduced in a large number of cases where LVEF is normal.22 Hestenes et al26 showed that LV GLS was reduced prior to LVEF and a reduction in cardiac output and similar findings were seen in a study using a rabbit model of severe sepsis by Li et al.25 Lanspa et al used STE to image 68 patients with severe sepsis or septic shock; of the patients with normal LVEF, 50% had abnormal strain and 6.5% had severely abnormal strain.24 Orde et al, in a 60 patient cohort, found double the number of patients had poor LV function based on GLS versus LVEF and triple the number had severe abnormalities.43
Obtaining adequate images when performing transthoracic echocardiography in critically ill patients often becomes a major challenge. It is encouraging to note that the feasibility of performing STE analysis in patients with severe sepsis and septic shock is reported between ~63%–98%.

The prognostic significance of LV dysfunction in septic cardiomyopathy is controversial with a recent meta-analysis suggesting that LVEF is not associated with mortality. The underlying mechanisms of septic cardiomyopathy have yet to be established but a favoured hypothesis is microvascular insufficiency resulting in ischaemia of the highly vulnerable subendocardial muscle layer. LV GLS may be particularly sensitive in detecting subendocardial myocardial dysfunction, although results to date are inconclusive. Conflicting results from studies exist with three showing no association but two more recent studies suggesting the contrary. Further research is required to tease out a possible relationship between LV GLS and prognosis in septic cardiomyopathy.

(b) Regional wall motion abnormality

GLS gives an overall description of cardiac function. Strain values of individual segments can also be described or displayed as ‘bullseye’ plots by certain vendors. These regional patterns can potentially differentiate causes of LV hypertrophy; e.g. cardiac amyloid, hypertrophic cardiomyopathy, and hypertensive heart disease have been shown to be easily recognisable, accurate and reproducible.

Although to our knowledge, no research is published on the application of simple pattern recognition using strain polar maps in the critically ill, it has the potential to assist with Takotsubo’s cardiomyopathy, amyloid, and coronary ischaemia, for example (see Figure 5). Although the classical patterns assist in identifying the pathology in patients with a single underlying process, in our experience the additional benefit of this technology in improving diagnostic accuracy in the clinical setting of the ICU is still uncertain. Regional wall motion abnormalities, conduction abnormalities, electrocardiographic changes and troponin elevation are common in the critically ill and therefore polar maps may add more more confidence in regional wall motion analysis.

(c) RV free wall strain

It is in assessing RV function that STE has possibly the greatest clinical potential in the critically ill patient. RV assessment with STE is known as RV free wall strain. RV dysfunction is a common and under-recognised phenomenon. It is caused by a multitude of pathologies (e.g. sepsis, acute lung injury, pulmonary embolism) and interventions (e.g. mechanical ventilation) and is associated with significant morbidity and mortality. Unfortunately, traditional measures fail to identify early RV dysfunction due to the RV’s complex anatomical and physiological function. STE can distinguish dysfunction unrecognised by conventional echo both in septic cohorts showing a high proportion of RV dysfunction, and with mechanical ventilation–induced RV failure. Through this, further insight into heart–lung interactions with mechanical ventilation may be shown. STE offers a unique insight into the way the RV responds to positive end-expiratory pressure: with RV dilation, decreased systolic function and dyssynchrony. Potentially through the use of STE, RV dysfunction can be recognised earlier and treatment tailored towards a ‘RV protective approach’. STE has provided insight into the RV response to acute pressure overload from pulmonary embolism, where the apical and mid RV free wall segments appear to deteriorate first, rather than be spared as suggested by McConnell, and where dyssynchrony and RV dilatation may play significant roles.

In terms of determining clinical outcome and directing therapy, RV free wall strain assessment has been shown to have prognostic importance and provide a better estimation of RV systolic performance than conventional measures in patients with severe heart failure being considered for device implantation or transplantation.
(d) **Twist and torsion**

Leonard Da Vinci first noted that the ventricles twisted during systole about the LV long axis. In the 17th century, physiologists and anatomists such as William Harvey, Lower and Borelli described the spiral ventricle myofibres and ventricular torsion in more detail and compared it to “wringing a cloth”. Physiologists now recognise that the twisting of the LV during systole and untwisting prior to diastole is essential for normal cardiac function. Viewed from the apex, the base of the LV typically rotates clockwise and the apex counterclockwise. Twist is the total angle difference between the base and apex and torsion describes the twist normalised to the length. By twisting and untwisting the heart uses less force to counter the pressures of the vascular system and hence works more effectively.

There is limited available information on the role of LV torsion and recoil in critically ill patients and to our knowledge there is only one published study on the LV twist in septic shock. The main findings were that peak torsion and apical rotation were reduced in the septic shock group versus normals (without a major impairment in LVEF seen) and that fluid loading increased peak torsion. It seems logical that this fundamental cardiac movement has important implications for systolic and diastolic function.

**Limitations of speckle tracking echocardiography**

Despite STE being available for more than a decade, the uptake of STE in the clinical setting has been relatively slow. The complexity, variability and sensitivity is not readily and easily undertaken, particularly when applied to the critically ill population. As analysis is dependent on the quality of the images, significant user variability is a problem. Such limitations also apply to echocardiography as a whole but small changes in placement of regions of interest in tracking analysis can result in significant differences in overall values, hence the importance of repeated measures to ensure congruence. The interested clinician should be aware that when exploring the use of STE, the analysis and training is time-consuming.

Similar to other echocardiography parameters, myocardial deformation may be influenced by preload and heart rate. In the critically ill both of these parameters can change rapidly, which may influence the clinical utility of STE. While some studies indicate STE may be the best method to accurately assess contractility, other studies have produced conflicting evidence.

One major hurdle in the widespread use of STE is vendor-dependent values, particularly for segmental analysis. Each vendor uses different algorithms for strain analysis. This has led to lack of consistency in robust cut-off measures for normal versus abnormal and severity scales. Task forces have been set up between various societies and industry to help address this and the current recommendations are to report global results from multiple views (e.g. use an average of four-, three- and two-chamber apical LV views for LV GLS and not a single apical four-chamber view) rather than segmental analysis, and ensure the use of compatible software for repeated analysis or if comparing patient groups.

**Future applications**

(a) **3D strain**

3D echo is emerging as a useful addition to 2D imaging of both the left and right ventricle and STE analysis can provide rapid, sensitive comprehensive assessment of ventricular dynamics. Data obtained from STE analysis of 2D images is available in a fraction of the time compared to that obtained from 3D data. The image quality necessary and low frame rates limit the utility of 3D to relatively few patients compared to 2D imaging, particularly with STE.

(b) **Diastolic function assessment**

Similar to strain rate assessing the rate at which peak strain is reached as a surrogate for systolic function, STE can analyse the rate at which the myocardium returns to its original position as a substitute for diastolic function. Known as strain rate early relaxation (SRe) it is similar to e' with TDI (see Figure 4). Validation of this value as a relevant parameter clinically is lacking but there is evidence to show that SRe can identify ischaemic areas versus viable myocardium in coronary artery disease. Increasing evidence in severely septic patients suggests that LV size and diastolic function play an important role in prognostication. Future studies employing SRe to elucidate diastolic function in septic patients are anticipated.

(c) **Atrial strain**

2D and 3D STE analysis has been performed on the atria, although no specific validation has been performed. Left atrial strain is feasible with both transthoracic and transoesophageal echo and has been shown to be associated with myocardial fibrosis and development of atrial fibrillation. To date there are no published studies on the critically ill population.

**Conclusions**

Although the level of experience required to use this modality accurately may limit the utility and research of STE in the critically ill, it has the potential to help recognise subtle cardiac dysfunction and improve our understanding of complex heart–lung interactions and critical illness. The use of STE is likely to remain a research tool in the immediate future in the ICU setting but with improved software and ultrasound technology, it offers considerable potential and promise in moving from the research to the clinical domain.
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From speckle tracking echocardiography to torsion: research tool today, clinical practice tomorrow

Stephen J. Huang and Sam Orde

Purpose of review
Speckle tracking is the latest available technology in echocardiography. However, the technology is still mainly used as a research tool. The potential applications of speckle tracking are many, including cardiac synchronization, regional wall motion analysis, and in the areas of cardiac mechanic studies. This review presents the background theory of speckle tracking echocardiography (STE) and how this technology can be extended to velocity vector analysis, strain, and torsion measurements. The interpretations of these measurements are covered. We also present some potential applications in the critical care setting.

Recent findings
Speckle tracking is almost always available in high-end ultrasound machines. The technology has been applied to velocity vector analysis, strain and strain rate measurements, and twist and torsion analysis. Torsion analysis and velocity vector analyses are impossible without using speckle tracking. Speckle tracking-derived strain is superior to tissue Doppler strain because it is angle-independent. A number of studies demonstrated that STE is useful in left and right heart assessments and can be used in assessing preload and afterload.

Summary
Speckle tracking can be used to measure instantaneous myocardial contractility, strain, and left ventricular torsion. It is still a research tool at present, but shows the promise of being a clinical tool in the future.

Keywords
echocardiography, speckle tracking, strain, torsion, twist

INTRODUCTION

Two-dimensional (2D) speckle tracking echocardiography (STE) is the latest technology available in the market. This technology tracks the motion of the ultrasonic speckles in the myocardium allowing frame-by-frame analysis of myocardial motion. It sheds light to the understanding of cardiac physiology and mechanics. STE is translated into various forms of analyses, including velocity vector analysis, strain and strain rate measurements, and twist and torsion analysis. In contrast to 2D and Doppler analysis, STE is free from subjective interpretations of myocardial motion and is independent of the insonation angle. The clinical applications of STE have been investigated widely in cardiology [1**], but relatively little work has been done in the critically ill population and the role of STE in the ‘real-life’ working of an intensive care unit seems a long way away. Hopefully, through the understanding of the technology and principles, potential applications in critical care can be explored. This review presents the background theory of STE and how this technology can be extended to velocity vector analysis, strain, and torsion measurements. The interpretations of these measurements are covered. The potential applications in critical care are also presented.

SPECKLE AND SPECKLE TRACKING ECHOCARDIOGRAPHY

Ultrasound suffers from inherent artifact known as ‘speckle’ (Fig. 1). Speckle artifacts give rise to granular tissue appearance, which is otherwise homogeneous to bare eyes. These speckles do not represent any physical structures, but are the...
complex constructive and destructive interferences of ultrasound echoes resulting from reflections (and scatterings) of reflectors spaced closer than the resolution limit of the ultrasound system (Fig. 2). Interestingly, the relative positions of speckles in the myocardium are quite stable, and if followed (‘tracked’) frame-by-frame during the cardiac cycle, important information such as myocardial deformation can be extracted. For example, speckle tracking can be used to quantify left ventricular myocardial strain and strain rate [2,3].

It is inevitable that some speckles may be ‘lost’ during the tracking process, for example as a result of motion of the heart due to twisting or respiration. To improve the tracking process, a cluster of speckles, known as a kernel, is used in modern machines for tracking. The speckle pattern of the kernel is unique for each region of the myocardium and is relatively stable throughout the cardiac cycle. These kernels act as a ‘fingerprint’ for that region. The most common algorithm used for tracking is known as the sum-absolute-difference (SAD): the minimum sum of the absolute distances traveled by each pixel in the kernel [4]. In the SAD algorithm, the machine defines a small region of kernel, and tracks the movement of the kernel in the next frame (Fig. 3) [5]. The kernel with the closest speckle pattern (resemblance) in the next frame is identified by searching predefined regions in the vicinity of the original kernel’s location. The identification is done by comparing the SAD obtained from these regions. As each kernel contains numerous speckles, interframe disappearance of a few speckles within the kernel does not significantly compromise the accuracy of tracking. However, poor image quality and high background noise do affect the tracking process.

VELOCITY VECTOR IMAGING

The interframe displacements of the kernels can be depicted as arrows and superimposed on the 2D image. These arrows represent the distance and direction ‘traveled’ by the kernels. As the time gaps between successive frames are the same, these arrows (or vectors) reflect the interframe (or instantaneous) velocities of the corresponding kernels, hence the name velocity vectors (Fig. 4) [6]. To improve the accuracies in both tracking and timing, speckle tracking of the myocardium is combined with the tracking information obtained from the endocardial border and the annulus motions. Because force is proportional to the change in velocity (acceleration), the change in the vector magnitudes or directions therefore corresponds to the change in the instantaneous myocardial contractile force (or contractility) during systole. By observing and comparing the moving velocity vectors from different regions of the myocardium, one can appreciate the relative regional wall contractility during systole. However, the interpretation of myocardial velocity vectors can be perverted by paradoxical wall motions or abnormal heart motions, for example, paradoxical interventricular septal motion due to right-sided pressure or volume overload and left bundle branch block. These paradoxical motions can displace the

FIGURE 1. Ultrasound speckles. The appearance of left ventricular myocardial speckles in echocardiography. Inset shows the enlarged speckle pattern observed in the ventricular septum. Note the randomness of the speckle distribution and shapes.
myocardial walls, creating vectors and falsifying motion artifacts as true ventricular contraction or relaxation.

At present, because of the difficulties in quantification and interpretation, velocity vector measurements are mainly confined to research studies. The most common uses of velocity vector are detection of regional wall motion abnormality and cardiac synchronization studies [7,8]. Velocity vector data are also translated into strain or strain rate [9], and extended to the study of left ventricular twist and torsion (see below).

**STRAIN AND STRAIN RATE**

Systole and diastole result in shortening and elongation of the myocardium, respectively. This cyclical change in shape (deformation) allows the use of strain to quantify cardiac function.

Lagrangian strain, or simply strain, is defined as the change in myocardial fiber length (Fig. 5), and can be measured in three different dimensions in the left ventricle (LV): longitudinal, radial, and circumferential (Fig. 6).

Traditionally, myocardial strain is obtained by tissue Doppler imaging (TDI). TDI strain is derived from strain rate, the rate of deformation, which is the velocity gradient between two points on the myocardium (strain rate = ΔV/d, where ΔV is the difference in velocities between two points which are separated by distance d). TDI strain is obtained by temporal integration of the strain rate. TDI strain accuracy is subject to random noise, and suffers from Doppler angle error and undersampling. STE offers a direct measurement of myocardial deformation. By following the displacement of two selected kernels, STE yields the strain directly by subtracting the initial separation of the kernels from
the final separation, which is independent of insonation angle. Instantaneous strain rate can be obtained by dividing the interframe strain by the frame rate. Strain is normally expressed as percent change. A positive value denotes lengthening or thickening, whereas a negative value represents shortening or thinning. Strain rate is expressed as per second, which is the fractional change in length or thickness per second.

Initial evidence suggested that global longitudinal strain might correlate with LV systolic function in patients with post myocardial infarction (MI), and could unmask LV dysfunction not picked up

**FIGURE 4.** Velocity vector imaging. Apical four-chamber view showing the left ventricular velocity vectors (arrows) during peak systole. The vectors are constructed by following the kernels frame by frame and hence represent the regional instantaneous contractile force (contractility) of the left ventricle during systole. The same can be done for the right ventricular wall. Note that at peak systole, the vectors, hence contractile forces, of the basal myocardium are directed inward and toward the apex of the left ventricle.

**FIGURE 5.** Definition of strain in speckle tracking echocardiography. The figure illustrates the apical two-chamber view of the left ventricle. Myocardial strain is defined as the change in displacement between two kernels normalized to their original distance apart. Strain is a measure of deformation.

<table>
<thead>
<tr>
<th>Diastole</th>
<th>Systole</th>
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<tr>
<td></td>
<td></td>
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<tr>
<td>$D_1$</td>
<td>$D_2$</td>
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<tr>
<td>Strain</td>
<td>$\frac{D_2 - D_1}{D_1}$</td>
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**FIGURE 6.** Three types of strain measurements. Left ventricular strains can be measured longitudinally (longitudinal strain or $S_L$), radially (radial strain or $S_R$), or circumferentially (circumferential strain or $S_C$).
by conventional echocardiography [2]. A recent study in 89 patients with acute MI showed that global longitudinal strain is the single most powerful marker of LV hemodynamic deterioration in the acute phase of MI [10]. In a study involving children with severe sepsis, it was found that the myocardial function as measured by strain rate was significantly reduced, whereas the ejection fraction and fractional shortening were essentially the same as matched controls [11]. Stress-induced cardiomyopathy is common in the critical care setting, and strain analysis can potentially differentiate such cardiomyopathy from left anterior descending coronary artery occlusion [12].

Strain measurements have also been used to assess right ventricular function in patients with pulmonary hypertension. When compared with normal controls, the right ventricular free wall longitudinal strain was significantly lower than normal controls, and correlated with right ventricular ejection fraction [13]. In acute pressure overload, like pulmonary thromboembolism, the right ventricular longitudinal peak systolic strain is reduced and delayed [14].

TORSION

2D strain echocardiography assumes myocardial deformation is either lengthening or shortening in a linear fashion (Fig. 5). However, myocardial motion also presents rotational deformation, or shear strain. Shear is the amount of lateral displacement per perpendicular distance (Fig. 7a). When the LV contracts or relaxes, the rotational motion of the myocardium also causes lateral displacement perpendicular to the heart axis. This lateral rotational displacement of the myocardium is composed of longitudinal shear strain ($\phi_L$), in which the base of the heart is displaced laterally with reference to the apex when viewed from the side; and circumferential shear strain ($\phi_C$), in which the myocardium displays clockwise or counterclockwise rotation in the cross-sectional view (Fig. 7b). These two shear strains together form the longitudinal–circumferential shear strain of the LV.

The LV myocardium consists of three layers of myofibers, each with different arrangement and orientation: the epicardial layer runs obliquely from base to apex and counterclockwise when viewed from the apex (left-hand helix); the endocardial layer is also arranged obliquely but is clockwise (right-hand helix); and the midwall fibers run circumferentially (Fig. 8). As the epicardial and endocardial myofibers are opposite in directions, they exert opposite forces during contraction: epicardial contraction results in counterclockwise rotation in the apex (as viewed from apex) and

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**FIGURE 7.** Simple shear strain and left ventricular myocardial shear strains. (a) Simple shear strain is the amount of lateral displacement ($\delta$) per perpendicular distance. It can be imagined that the block consists of many layers and each layer ‘slides’ in the same direction over the underlying layer. When $\delta$ is small compared with $L$, shear strain can be represented by the angle $\phi$. (b) During contraction (and relaxation) of the left ventricle, the ventricle experiences both circumferential ($\phi_C$) and longitudinal ($\phi_L$) shear strains. $L$, length of the left ventricle; $r$, radius of the left ventricle.
clockwise rotation in the base; and endocardial contraction causes a clockwise rotation in the apex and counterclockwise rotation in the base. However, as the epicardium is further away from the heart axis than the endocardium, the torque generated will be greater. As a consequence, myocardial twist, defined as the relative rotation between the apex and base, of the LV is primarily determined by the epicardial layer. An understanding of this is important to explain some of the paradoxes seen. For instance, limitation of blood supply to the endocardial fibers, such as in hypertrophy or ischemic heart disease, will diminish the contractile force of the endocardium. As the overall torsion of the LV is determined by the relative torques of the endocardial and epicardial fibers, the diminishing endocardial torque will paradoxically increase the twist of the LV.

By twisting, the LV uses less force (better mechanical advantage) to work against the high systolic pressure than by contracting longitudinally alone during systole. The word ‘torsion’ is used to describe the twisting motion of the LV in recent years, and is related to LV function and performance. Despite the understanding, the definition of LV torsion is confusing. There are at least three different definitions of LV torsion. One defines torsion as the twist – the angle difference between the base and apex (torsion = Φb – Φa) (Fig. 9) [15]. The second definition takes the length of the LV into account and defines torsion as the twist normalized to its length [torsion = (Φb – Φa)/L] [16]. The third definition of torsion incorporates the mean radius of the LV [(Rb + Ra)/2] into the second definition [torsion = (Φb – Φa)(Rb + Ra)/2L] [17]. The last definition reflects the longitudinal–circumferential shear strain, which is the most appropriate for measuring LV torsion. Definition based on the longitudinal–circumferential shear strain is also available, but it yields similar result as the third definition [18].

Although torsion mechanics are important for proper myocardial function, clinical applications of LV twist and torsion are still limited. Several studies on STE provided some interesting results. First, LV rotation and twist were not sex-related but were affected by age. Paradoxically, aging seemed to associate with higher rotation and twist [19∗]. It was reasoned that the augmented twist observed in the older age group was because of the depressed endocardial layer resulting from hypertension and ischemia, leaving the epicardial torque unopposed (see above; Fig. 8) [19∗]. Second, LV dysfunction is associated with a reduction in twist and torsion. LV twist has been shown to correlate with left ventricular ejection fraction but was confounded by LV dyssynchrony in heart failure.

**FIGURE 8.** Myocardial arrangement of the ventricle and the resulting torques. Left, the left ventricle composed of three layers of myocardia with fibers arranging in different directions: the endocardial layer, the mid-layer, and the epicardial layer. Contraction of the epicardial layer results in counterclockwise rotation in the apex and clockwise rotation in the base (viewed from the apex). Right, cross-section of the left ventricle (viewed from above) showing the opposing direction of endocardial and epicardial torques during contraction. Torque is defined as the product of force and the perpendicular distance from the center (F × R). The epicardium results in a larger torque because of the further distance from the center of the left ventricle. F_epi and F_endo denote the epicardial and endocardial force, respectively; R_i and R_o denote the inner and outer radius of the left ventricle. (R_o – R_i) is the left ventricular wall thickness.
patients [20]. Park et al. [21] showed that although the torsions were reduced to the same extent in acute myocardial infarct, apical rotation was reduced in anterior infarct, whereas the basal rotation was reduced in inferior infarct. Takotsubo cardiomyopathy also resulted in severe impairment in apical rotation [22]. Third, LV twist and torsion are associated with loading condition. An inverse relationship existed between LV filling pressure and torsion in the normal population or subjects with preserved ejection fraction [23,24]. However, such relationship was absent in dilated cardiomyopathy [25]. As dyssynchrony is commonly observed in dilated cardiomyopathy, and torsion also depends on timing, it is perhaps not surprising to find a lack of normal torsion pattern in such patients.

**TECHNICAL LIMITATIONS OF SPECKLE TRACKING ECHOCARDIOGRAPHY**

Several major limiting factors affect the quality and accuracy of speckle tracking. First, slow frame rate may result in decorrelation in which the kernel is displaced too far (beyond the default search regions) in the next frame. Hence, a higher frame rate should be used, particularly in tachycardia. Second, random background noise is inconsistent from kernel to kernel and interferes with interframe kernel displacement identification. An effective filter is therefore necessary to filter the random noise. Unfortunately, different vendors may use different filter algorithms resulting in inter-vendor differences in measurements. Further, out of plane motion, such as because of transducer and/or respiratory motions should be eliminated.

Standardization poses a major challenge to STE and is not without controversy. Inter-vendor variability of strain analysis results renders comparison across different platforms difficult. This is mainly because of different software packages and acquisition methods [26,27,28]. Serial evaluations should therefore be done with the same machine or machines from the same vendor. That said, global longitudinal strain appears to be a robust measurement with good comparability between different machines. The definition of torsion also needs to be standardized.

**CONCLUSION**

Compared with other well established echocardiographic assessments, STE is still in the developmental stage. Most research in this area is still exploratory in nature and of small size. Although strain and strain rate measurements are useful, torsion yields the most information on how the LV works. However, a standardized definition of torsion is wanting. The clinical applications of

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**FIGURE 9.** The left ventricular twist and torsion. Left, because of the larger torque, the rotations of the base ($\phi_b$) and apex ($\phi_a$) of the left ventricle are primarily determined by the epicardium. ‘Twist’ is defined as the sum of the rotations of the base and the apex ($\text{twist} = |\phi_b| + |\phi_a|$). Right, although there are different definitions of ‘torsion,’ the proper definition takes both the length ($L$) and the mean radius of the left ventricle $[(R_a + R_b)/2]$ into account $\text{torsion} = (|\phi_b| + |\phi_a|)(R_b + R_a)/2L$ (see text).
STE are limited. The most relevant applications in the critical care setting are the assessments of right ventricle and LV functions and prediction of loading conditions. Unfortunately, the lack of definitive research precludes its use as a clinical tool today.

Acknowledgements
None.

Conflicts of interest
The authors have no conflicts of interest to declare.

REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:
* of outstanding interest
** of special interest
Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 273–274).

A decent size study examined the effect of age and sex on left ventricular torsion. Results may have implications in interpretations.
This article describes the different impact of anterior and inferior AMI on basal and apical rotation of the LV.
This article demonstrated softwares from different vendors result in different global longitudinal strain in a neutral imaging platform. Users should be aware of the impact of vendor difference in software algorithms on their results.
Section A: Speckle tracking echocardiography

Chapter 3: Septic cardiomyopathy

Outcome prediction in sepsis: Speckle tracking echocardiography based assessment of myocardial function

Sam R Orde1,2, Juan N Pulido3, Mitsuru Masaki4, Shane Gillespie3, Jocelyn N Spoon1, Garvan C Kane1 and Jae K Oh1*

Abstract

Introduction: Speckle tracking echocardiography (STE) is a relatively novel and sensitive method for assessing ventricular function and may unmask myocardial dysfunction not appreciated with conventional echocardiography. The association of ventricular dysfunction and prognosis in sepsis is unclear. We sought to evaluate frequency and prognostic value of biventricular function, assessed by STE in patients with severe sepsis or septic shock.

Methods: Over an eighteen-month period, sixty patients were prospectively imaged by transthoracic echocardiography within 24 hours of meeting severe sepsis criteria. Myocardial function assessment included conventional measures and STE. Association with mortality was assessed over 12 months.

Results: Mortality was 33% at 30 days (n = 20) and 48% at 6 months (n = 29). 32% of patients had right ventricle (RV) dysfunction based on conventional assessment compared to 72% assessed with STE. 33% of patients had left ventricle (LV) dysfunction based on ejection fraction compared to 69% assessed with STE. RV free wall longitudinal strain was moderately associated with six-month mortality (OR 1.1, 95% confidence interval, CI, 1.02-1.26, p = 0.02, area under the curve, AUC, 0.68). No other conventional echocardiography or STE method was associated with survival. After adjustment (for example, for mechanical ventilation) severe RV free wall longitudinal strain impairment remained associated with six-month mortality.

Conclusion: STE may unmask systolic dysfunction not seen with conventional echocardiography. RV dysfunction unmasked by STE, especially when severe, was associated with high mortality in patients with severe sepsis or septic shock. LV dysfunction was not associated with survival outcomes.

Introduction

Characterized by hemodynamic distress, severe sepsis is frequently associated with cardiopulmonary dysfunction driven by a cascade of cellular and molecular processes [1]. Myocardial dysfunction occurs frequently, early and involves both ventricles [2,3]. Whether myocardial dysfunction is related to outcome is unclear and may in part be related to the definition and modality of assessment. Echocardiography plays a crucial role in the noninvasive assessment of cardiac function in the ICU [4], but the optimal measure of ventricular dysfunction, particularly for the right ventricle (RV), has not been well established.

Interpretation of changes in volumetric measures such as fractional area change (FAC) or ejection fraction can be affected by swings in volume status and loading conditions, frequent features in sepsis, and may not reflect well underlying contractility. Furthermore, such measures may lack sensitivity.

Two-dimensional speckle tracking echocardiography (STE) has emerged as an angle-independent technique for quantifying systolic function by assessing myocardial deformation [5,6]: strain and strain/time (strain rate). STE has been shown to be a feasible and sensitive quantitative technology for assessing ventricular contractile function in a variety of different cardiovascular diseases such as chemotherapy-induced cardiotoxicity [7], amyloidosis [8,9], preeclampsia [10] and in a pediatric cohort with severe sepsis [11]. The main focus of STE has been
left ventricle (LV) global longitudinal strain (GLS), reflecting the function of the subendocardial myocardial fibers, which are oriented longitudinally. These fibers are especially sensitive to ischemia and increased wall stress [12]. STE has potentially even greater applicability to the quantitative assessment of RV function. Distinct from the LV, the RV has a preponderance of longitudinal fibers and therefore a greater proportion of contractility of the RV occurs from base to apex [13]. Longitudinal STE is hence well poised to act as a robust measure of RV contractility: RV free wall strain and RV free wall strain rate.

The objectives of this study were to assess: the prevalence of RV and LV dysfunction in severe sepsis and septic shock assessed with STE; factors related to RV and LV longitudinal strain dysfunction; and whether myocardial dysfunction assessed by STE is associated with mortality at 30 days and 6 months.

**Methods**

We prospectively studied 60 adult patients (>18 years) with severe sepsis or septic shock admitted over an 18-month period at St. Mary’s Hospital, Rochester, MN, USA. The study was approved by the Mayo Institutional Review Board and written consent was obtained from all patients or authorized representatives (next of kin) before enrollment. Individuals were included by American College of Chest Physicians criteria for severe sepsis or septic shock [14]. Sepsis was defined by two or more criteria: temperature >38°C or <36°C, heart rate >90 beats/minute, respiratory rate >20 breaths/minute or arterial partial pressure of carbon dioxide <32 Torr (<4.3 kPa), white cell count >12,000 cells/mm³, <4,000 cells/mm³, or >10% immature (band) forms. Severe sepsis was defined as sepsis associated with organ dysfunction (Sequential Organ Failure Assessment (SOFA) score ≥2), hypoperfusion (lactate ≥2.3 mmol/dl, our institutional high normal value) or hypotension (systolic blood pressure <90 mmHg or decreased 40 mmHg below baseline). Severe sepsis with hypotension resistant to intravenous fluids was considered septic shock. Exclusion criteria were supraventricular tachyarrhythmias, pregnancy, congenital heart disease, cardiomyopathy, moderate or severe valvular disease and valvular prosthesis and insufficient image quality for STE.

**Echocardiography**

Transthoracic echocardiography was performed within 24 hours of meeting sepsis criteria with a Vivid 7 echocardiography machine (GE Medical Systems, Milwaukee, WI, USA) by research sonographers or research fellows fully trained in echocardiography and strain imaging. A comprehensive echocardiogram was performed according to American Society of Echocardiography guidelines [15]. Physiologic parameters were recorded at the time of echocardiography. LV systolic dysfunction was classified by ejection fraction: present (<55%) or absent (>55%), and mild (45 to 54%), moderate (30 to 44%) or severe (<30%). The RV was assessed at end expiration in a multimodal fashion as per American Society of Echocardiography guidelines (tricuspid annular plane systolic excursion, lateral tricuspid annular velocity, RV wall motion, FAC) [16] and was classified as normal, mild, moderate or severe dysfunction. Parameters for abnormal RV systolic function were defined as tricuspid annular plane systolic excursion <16 mm, FAC <35%, Tricuspid valve systolic motion velocity <10 cm/second or reduced RV wall motion. For severe dysfunction, RV wall motion was severely reduced and/or FAC was <17% [16]. RV size was measured – basal, mid and longitudinal dimensions (abnormal above 42 mm, 35 mm and 86 mm respectively) – and compared with the LV size. Images were analyzed by physicians fully trained in echocardiography (MM, JKO, JNP).

**Speckle tracking echocardiography analysis**

Three-beat two-dimensional digital clips were transferred to a Syngo Velocity Vector Imaging workstation (Siemens Medical Solutions USA Inc., Pleasanton, CA, USA) for STE analysis by SRO, who had performed more than 100 hours of analysis in STE prior to commencing the study. The endocardium was traced manually from the medial annulus with 7 to 15 points. LV values were averages of the 16 LV segments. If STE could not be calculated on one apical view, the LV was considered to have insufficient image quality. RV values were an average of the three free wall segments. Once accuracy of tracking was ensured, displacement, velocity, strain and strain rate curves were assessed for motion, smoothness, time to peak, delay and correlation (Figure 1a, b). The same cardiac cycle was chosen for STE values. All images were analyzed three times to ensure accuracy of results. Strain and strain rate are negative values; the more negative the value, the greater the degree of deformation and the better the function. Strain values were separated into normal (more negative than –21% for RV and more negative than –17% for LV), mild/moderately impaired (–21 to –13% for RV and –17 to –10% for LV) and severely abnormal (less negative than –13% for RV and less negative than –10% for LV). A consensus on normal values for strain of the RV and LV has yet to be defined primarily due to vendor differences in analysis methods [17]. The cutoff values chosen in this study are based on normal subjects at our institution [18] and on meta-analysis of normal subjects [19], and are similar to recent studies investigating LV ischemia [20] and pulmonary hypertension [21] as well as analysis of our sample group: receiver operating curve, interquartile range and logistic regression analysis.
**Statistical analysis**

Statistical analysis was performed with JMP version 9.0.1 (SAS Institute Inc., Cary, NC, USA). Continuous variables are expressed as mean ± standard deviation or median with interquartile range and were analyzed between groups using analysis of variance. Categorical variables are expressed as the number and percentage with comparisons by Pearson’s chi-square analysis or Fisher’s exact test. All probability values are two-sided and of $P \leq 0.05$ was considered significant. Univariate and multivariate logistic regression analyses were used to assess the association between risk factors and mortality. Discriminatory performance is assessed by odds ratios.
ratio, 95% confidence interval and area under the receiver operating characteristic curve. Multivariate models were developed with stepwise inclusion and exclusion at a significance level of 0.1 and by consideration of variables that were clinically relevant.

Results
Of 106 patients who were enrolled at our institution during the 18-month study period with severe sepsis or septic shock, 60 patients were included in our observational study. Of those excluded, 21 patients (20%) had supraventricular arrhythmia and 14 patients (13%) had insufficient image quality for STE analysis (10 of the 14 were mechanically ventilated). The mean age was 62 years (±15) with 50% female, 67% alive at 30 days (n = 40) and 52% alive at 6 months (n = 31) (Table 1). The SOFA score, arterial partial pressure of oxygen/fraction of inspired oxygen ratio, partial pressure of carbon dioxide and lactate levels were significantly worse in nonsurvivors at 30 days. Thirty-nine patients (65%) were mechanically ventilated at the time of imaging; at 30 days a greater portion of these patients were alive (21 of 39 patients), but only 15 of the 39 were alive at 6 months. No difference was seen in comorbidities between the patient groups.

Echocardiographic analysis
There was no difference seen between survivors and nonsurvivors in any standard echocardiography measure of ventricle size or function at 30 days or 6 months, or in their peak systolic pulmonary artery pressures (Tables 2 and 3 and Figure 2). There was a significant difference in RV free wall strain between survivors and nonsurvivors at 6 months (−19% ± 5 vs. −16% ± 6, P = 0.02). There was no difference in survivors’ LV GLS or GLS rate compared with nonsurvivors.

The incidence of myocardial dysfunction was different based on the method of assessment (Table 4). Based on conventional assessment, 19 patients (32%) had RV dysfunction, 20 patients (33%) had LV dysfunction and 10 patients (17%) had both LV and RV dysfunction. Based on strain analysis, 43 patients (72%) had RV dysfunction, 36 patients (69%) had LV dysfunction and 30 patients

Table 1 Baseline physiological and clinical data with comparison for survival at 30 days and 6 months

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>Survivor</th>
<th>Nonsurvivor</th>
<th>30-day mortality</th>
<th>Survivor</th>
<th>Nonsurvivor</th>
<th>6-month mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>60</td>
<td>40 (67%)</td>
<td>20 (33%)</td>
<td>31 (52%)</td>
<td>29 (48%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>62 ± 15</td>
<td>60 ± 16</td>
<td>65 ± 13</td>
<td>60 ± 17</td>
<td>65 ± 13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>50</td>
<td>30</td>
<td>20</td>
<td>21.7</td>
<td>28.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOFA score</td>
<td>11 ± 4</td>
<td>10 ± 4*</td>
<td>13 ± 3*</td>
<td>10 ± 4*</td>
<td>12 ± 4*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>62 ± 13</td>
<td>63 ± 15</td>
<td>60 ± 8</td>
<td>63 ± 13</td>
<td>61 ± 61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>10.1 ± 1.6</td>
<td>10.2 ± 1.6</td>
<td>9.8 ± 1.6</td>
<td>10.4 ± 1.6</td>
<td>9.7 ± 1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NE dose (μg/kg/minute)</td>
<td>0.2 (0.06 to 0.34)</td>
<td>0.15 (0.04 to 0.74)</td>
<td>0.225 (0.08 to 0.32)</td>
<td>0.18 (0.07 to 0.5)</td>
<td>0.2 (0.1 to 0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasopressin (u/minute)</td>
<td>0.04 (0.03 to 0.04)</td>
<td>0.04 (0.03 to 0.04)</td>
<td>0.04 (0.03 to 0.04)</td>
<td>0.04 (0.03 to 0.04)</td>
<td>0.04 (0.03 to 0.04)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ScvO₂ (%)</td>
<td>72 ± 11</td>
<td>70 ± 13</td>
<td>75 ± 8</td>
<td>72 ± 11</td>
<td>72 ± 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO₂/FiO₂ (mmHg)</td>
<td>195 (128 to 290)</td>
<td>247 (153 to 310)*</td>
<td>163.5 (113 to 199)*</td>
<td>248.5 (76 to 300)</td>
<td>175 (124 to 260)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pCO₂ (mmHg)</td>
<td>40 ± 12</td>
<td>38 ± 9*</td>
<td>45 ± 14*</td>
<td>38 ± 11</td>
<td>43 ± 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.29 ± 0.1</td>
<td>7.3 ± 0.1</td>
<td>7.27 ± 0.1</td>
<td>7.3 ± 0.1</td>
<td>7.29 ± 0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate (mmol/l)</td>
<td>3 ± 2.8</td>
<td>2.4 ± 0.4*</td>
<td>4.2 ± 0.6*</td>
<td>1.45 (1 to 3.78)</td>
<td>2.4 (1.4 to 4.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.9 ± 1</td>
<td>2.1 ± 1.2</td>
<td>1.6 ± 0.7</td>
<td>1.84 ± 0.9</td>
<td>2 ± 1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Troponin T (ng/ml)</td>
<td>0.03 (0.01 to 0.16)</td>
<td>0.03 (0.01 to 0.2)</td>
<td>0.03 (0.01 to 0.12)</td>
<td>0.025 (0.01 to 0.2)</td>
<td>0.03 (0.01 to 0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory issues</td>
<td>18 (30%)</td>
<td>12</td>
<td>6</td>
<td>7</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>8 (13%)</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>7 (12%)</td>
<td>5</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>25 (42%)</td>
<td>17</td>
<td>8</td>
<td>12</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>39 (65%)</td>
<td>21*</td>
<td>18*</td>
<td>15*</td>
<td>24*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data presented as n (%), mean ± standard deviation or median (interquartile range). *P <0.05 by analysis of variance. MAP, mean arterial pressure; NE, noradrenaline; pCO₂, partial pressure of carbon dioxide; PaO₂/FiO₂, arterial partial pressure of oxygen/fraction of inspired oxygen ratio; ScvO₂, central venous oxygen saturation; SOFA, Sequential Organ Failure Assessment.
had both LV and RV strain dysfunction. When subgroups were created based on severity of dysfunction, strain function analysis also revealed a greater portion of patients with severe RV or LV dysfunction.

Analysis of variance of the association between 6-month mortality and the RV strain dysfunction subgroups was significant (\(P<0.001\)). Separate analysis within these groups exposed those patients with severe RV strain dysfunction as having the statistically significant association (Table 5). Multivariate analysis (Table 6) showed that severe RV free wall strain dysfunction remained an independent predictor of outcome at 6 months, accounting for mechanical ventilation (\(P=0.03\)). This subgroup was also associated with a greater severity of disease (SOFA score), lower arterial partial pressure of oxygen/fraction of inspired oxygen ratios, mechanical ventilation, worse LV GLS, reduced RV FAC, higher echo-based right atrial pressures, lower tricuspid velocity, and higher echo-based peak systolic pulmonary artery pressure (Figure 3). Furthermore, there was a tendency towards higher levels of lactate. There was no association with RV dimensions. By comparison, RV systolic functional assessment by FAC was only associated with reduced LV GLS, and increased echo-based right atrial and RV systolic pressures. Kaplan–Meier curves show severe RV free wall longitudinal strain dysfunction was associated with 1-year mortality (\(P<0.001\)) due to all patients in this subgroup dying before 6 months (Figure 4). Those with mild/moderate RV strain dysfunction and normal RV strain function had similar 1-year survival estimates (57.1% and 54.9% respectively).

Pulmonary hypertension was not an exclusion criterion, but no patient had a formal diagnosis at time of enrollment. Fifteen patients had echocardiograms performed in the preceding 6 months to admission and four of these patients had peak systolic pulmonary artery pressure estimation >36 mmHg, considered raised pulmonary pressure by the American Society of Echocardiography [16]. Although no significant RV dysfunction was reported, there may have been unrecognized prior RV strain dysfunction.

Table 2 Echocardiography data at baseline and compared for survival at 30 days and 6 months

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>30-day mortality</th>
<th>6-month mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Survivors</td>
<td>Nonsurvivors</td>
</tr>
<tr>
<td>Structure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV basal length (mm)</td>
<td>39 ± 7</td>
<td>40 ± 8</td>
<td>38 ± 5</td>
</tr>
<tr>
<td>RV mid length (mm)</td>
<td>33 ± 7</td>
<td>33 ± 7</td>
<td>33 ± 5</td>
</tr>
<tr>
<td>RV longitudinal length (mm)</td>
<td>75 ± 9</td>
<td>75 ± 10</td>
<td>74 ± 8</td>
</tr>
<tr>
<td>LV diastolic diameter (mm)</td>
<td>47 ± 5</td>
<td>47 ± 6</td>
<td>48 ± 4</td>
</tr>
<tr>
<td>LV systolic diameter (mm)</td>
<td>32 ± 7</td>
<td>33 ± 7</td>
<td>30 ± 5</td>
</tr>
<tr>
<td>Ventricular function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV FAC (%)</td>
<td>40 ± 10</td>
<td>40 ± 10</td>
<td>39 ± 10</td>
</tr>
<tr>
<td>Lateral tricuspid annular TDI velocity (cm/second)</td>
<td>15 ± 5</td>
<td>14 ± 5</td>
<td>17 ± 5</td>
</tr>
<tr>
<td>Cardiac index (l/minute/m²)</td>
<td>3.5 ± 1.5</td>
<td>3.5 ± 1.7</td>
<td>3.5 ± 1.2</td>
</tr>
<tr>
<td>SVI (cm³/m²)</td>
<td>37 ± 15</td>
<td>37 ± 16</td>
<td>38 ± 13</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>57 ± 16</td>
<td>56 ± 17</td>
<td>60 ± 13</td>
</tr>
<tr>
<td>Other parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echo assessed SPAP (mmHg)</td>
<td>42 ± 15</td>
<td>41 ± 14</td>
<td>44 ± 17</td>
</tr>
</tbody>
</table>

Data presented as mean ± standard deviation. FAC, fractional area change; LV, left ventricle; RV, right ventricle; TDI, tissue Doppler imaging; SVI, stroke volume index; SPAP, peak systolic pulmonary artery pressure.

Table 3 Baseline ventricular longitudinal strain with comparison for survival at 30 days and 6 months

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>30-day mortality</th>
<th>6-month mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Survivors</td>
<td>Nonsurvivors</td>
</tr>
<tr>
<td>RV free wall strain (%)</td>
<td>−17.7 ± 5.5</td>
<td>−18.1 ± 5.4</td>
<td>−16.9 ± 5.6</td>
</tr>
<tr>
<td>RV free wall strain rate (1/second)</td>
<td>−1.14 ± 0.4</td>
<td>−1.14 ± 0.33</td>
<td>−1.14 ± 0.4</td>
</tr>
<tr>
<td>LV GLS (%)</td>
<td>−14.1 ± 4.2</td>
<td>−13.92 ± 4.2</td>
<td>−14.6 ± 4.3</td>
</tr>
<tr>
<td>LV GLS rate (1/second)</td>
<td>−0.89 ± 0.3</td>
<td>−0.86 ± 0.2</td>
<td>−0.96 ± 0.3</td>
</tr>
</tbody>
</table>

Data presented as mean ± standard deviation. *\(P<0.05\) by analysis of variance. GLS, global longitudinal strain; LV, left ventricle; RV, right ventricle.
Excluding these patients from the analysis did not alter the relationship between 6-month mortality and RV free wall strain dysfunction.

Measurement variability

Blinded interrater variability for STE analysis was assessed by JNS on a random 10% subgroup. Bland–Altman analysis demonstrated good intraobserver and interobserver agreement. The interobserver and intraobserver mean difference (±standard deviation) were respectively: RV free wall longitudinal strain, $-2$ (±1.2) and $-1.4$ (±0.9); RV free wall longitudinal strain rate, $-0.3$ (±0.1) and $-0.1$ (±0.05); LV GLS, $-0.9$ (±0.9%) and $-0.8$ (±0.5); and LV GLS rate, $-0.1$ (±0.05) and $-0.1$ (±0.05).

![Figure 2](http://ccforum.com/content/18/4/R149)

**Figure 2** Left and right ventricle segmental longitudinal strain values. (A) Graphical representation of left ventricle segmental longitudinal strain with three concentric circles representing apex (inner circle), mid and base (outer circle). (B) Graphical representation of right ventricle segmental free wall longitudinal strain. Data presented as mean ± standard deviation.

Excluding these patients from the analysis did not alter the relationship between 6-month mortality and RV free wall strain dysfunction.

**Table 4 Univariate analysis of systolic dysfunction and association with 30-day and 6-month mortality**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>30-day mortality</th>
<th>6-month mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Survivors</td>
<td>Nonsurvivors</td>
<td>$P$ value</td>
</tr>
<tr>
<td><strong>Strain analysis</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>RV free wall strain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV dysfunction</td>
<td>43/60 (72%)</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>$&lt; -21$</td>
<td>17</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>$-13$ to $-21$</td>
<td>31</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>$&gt; -13$</td>
<td>12</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>GLS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV dysfunction</td>
<td>36/52 (69%)</td>
<td>0.40</td>
<td>0.44</td>
</tr>
<tr>
<td>$&lt; -17$</td>
<td>16</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>$-10$ to $-17$</td>
<td>25</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>$&gt; -10$</td>
<td>11</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td><strong>Standard echocardiographic analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV dysfunction</td>
<td>19/60 (32%)</td>
<td>0.26</td>
<td>0.17</td>
</tr>
<tr>
<td>Mild</td>
<td>12</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Moderate</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Severe</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>LV dysfunction</td>
<td>20/60 (33%)</td>
<td>0.50</td>
<td>0.55</td>
</tr>
<tr>
<td>Mild (EF = 45 to 55%)</td>
<td>8</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Moderate (EF = 35 to 45%)</td>
<td>8</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Severe (EF &lt; 35%)</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Data presented as $n$ (%). Strain is a measure of myocardial deformation and is described in negative values; greater negative numbers indicate better function. EF, ejection fraction; GLS, global longitudinal strain; LV, left ventricle; RV, right ventricle.
Table 5 Odds ratios for subsets of right ventricular free wall strain versus 6-month mortality

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe vs. mild/moderate</td>
<td>15.23</td>
<td>2.5 to 296.27</td>
<td>0.002</td>
</tr>
<tr>
<td>(strain &gt; −13 vs. −13 to −21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe vs. normal (strain &gt; −13 vs. &lt; −21)</td>
<td>26.4</td>
<td>3.7 to 553.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mild/moderate vs. normal</td>
<td>1.73</td>
<td>0.5 to 6.56</td>
<td>0.4</td>
</tr>
<tr>
<td>(strain −13 to −21 vs. &gt; −21)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Discussion

In this observational cohort study of 60 patients with severe sepsis or septic shock we demonstrated: frequent biventricular systolic dysfunction, occasionally severe, occurring within 24 hours of diagnosis; that STE is a more sensitive method of assessing systolic dysfunction than conventional echocardiography; and that severe RV dysfunction assessed by STE (RV free wall strain) is associated with a worse prognosis.

The use of STE in the noncritically ill population is increasing because most modern high-end echocardiography machines have the software capability. These advanced machines are becoming increasingly available in the ICU and it is suggested that STE may unmask systolic dysfunction not seen by standard echocardiographic assessment [11]. Indeed, a greater portion of the patients in our study were identified as having systolic dysfunction of both the RV and LV when assessed by STE as compared with conventional echocardiography.

STE assessment of the LV GLS adds prognostic value in heart failure [22] and myocardial ischemia [20], and RV free wall strain analysis in pulmonary vascular disease trumps all other measures of RV function in the independent prediction of clinical deterioration and mortality and may help guide therapy [21,23-25]. In our septic population, RV free wall strain was the only parameter associated with mortality.

STE is dependent on adequate image quality, and studies in the noncritically ill report a 7 to 9% suboptimal image quality for STE analysis [18,20]. Imaging in the critically ill can be difficult and 13% of our patients were excluded due to poor image quality; however, STE was still feasible in the majority of our patients with adequate images. However, the difficulty in imaging analysis may explain why the interobserver variability in our study was slightly higher compared with others [18].

Myocardial dysfunction in sepsis is caused by a variety of factors, including direct effect by the infectious process (inflammatory mediators, bacterial toxins, and/or myocardial mitochondrial dysfunction), decreased myocardial perfusion, interventricular dependence and raised pulmonary pressures from acute lung injury, hypoxia, hypercarbia and atelectasis. Evaluation of myocardial contractile function by echocardiography is challenging, particularly for the RV due to its complex geometry, which makes volumetric assessment difficult. Several studies have found RV systolic dysfunction early in the course of sepsis to be associated with increased mortality [26-28]. However, other studies have found no significant difference between survivors and nonsurvivors [2,29]. A similar debate exists concerning LV dysfunction and outcomes [30-33]. A recent meta-analysis failed to find any evidence of differences in RV or LV function related to mortality [34].

The association between 6-month mortality and severe RV free wall strain dysfunction highlights the importance of RV function analysis in the prognosis of the critically ill patient, and this supports studies in other populations such as patients with acute respiratory distress syndrome [35]. All of the patients in our study with severe RV strain dysfunction died within 6 months of admission to the ICU with severe sepsis, potentially due to being sicker on admission (higher SOFA scores), being more likely to be on mechanical ventilation, or having worse gas exchange, worse LV GLS function and higher echo-based RV systolic pulmonary pressure estimation than patients without severe RV dysfunction. A myriad of factors are at play, and the RV can be affected by all of them – RV dysfunction is therefore likely to be a marker of disease severity as much as being a factor behind the association with poor outcomes. However, early recognition of RV dysfunction may help in the care of the critically ill patient with sepsis and may place emphasis on limiting factors that are potentially involved, such as fluid overload, high positive end-expiratory pressure levels, atelectasis, hypoxia or hypercarbia, amongst others.

Limitations

This study is observational in nature and has a limited number of patients, and the imaging was not optimized for STE (for example, improved endocardial border definition, RV centric views, and so forth). One cannot exclude that weaker associations may be statistically significant in a cohort with a larger sample size. Repeated imaging and further STE analysis were not performed. Further dysfunction that would be seen by standard echo parameters may have occurred at a later
Figure 3 Association of right ventricle free wall systolic strain with clinical and echocardiography parameters of disease severity and right ventricular dysfunction. Error bars ± standard deviation. LV, left ventricle; PaO$_2$/FiO$_2$, arterial partial pressure of oxygen/fraction of inspired oxygen ratio; RAP, right atrial pressure; RV, right ventricle; SOFA, Sequential Organ Failure Assessment; TV Sm, Tricuspid valve systolic motion velocity.

Figure 4 Kaplan–Meier 1-year survival curves based on right ventricle free wall strain. RV, right ventricle.
stage. Larger, prospective studies with imaging focused for STE optimization and follow-up echocardiography
STE analysis could be considered in future.

There are several drawbacks to current STE analysis that limit its clinical utility in the ICU at this time: STE
requires adequate image quality, which can be challenging
particularly in the mechanically ventilated patient
(10 of the 14 patients excluded due to inadequate image
quality), STE is time consuming to perform, and normal
values have been difficult to elucidate partly due to
vendor differences in the software algorithms [19]. Our
cutoff values between normality, mild and moderate ab-
normality and severe abnormality are similar to recent
studies on large populations of both normal controls
[18,19] and patients with cardiac dysfunction [25]. With
technology advancing and expert groups such as the
American Society of Echocardiography and the
European Association of Echocardiography calling for
concordance on vendor STE software analysis, and as
the use of STE becomes more widespread, perhaps
strain will become a more standard measurement in
the future [17].

Conclusions
STE unmasks systolic dysfunction unrecognized with
conventional echocardiography in patients with severe
sepsis or septic shock. RV dysfunction assessed by strain
appears to be correlated with worse late outcomes, espe-
cially if the dysfunction is severe. LV dysfunction assessed
either by conventional imaging or STE does not appear to
correlate with survival in sepsis.

Key messages

- STE unmasks systolic dysfunction unrecognized with
conventional echocardiography in patients with severe
sepsis or septic shock.
- Severe right ventricular strain dysfunction is
associated with worse prognosis.
- LV dysfunction assessed by standard
echocardiography or STE is not associated with
early or late outcome.

Abbreviations
FAC: fractional area change; GLS: global longitudinal strain; LV: left ventricle; RV: right ventricle; SOFA:
Sequential Organ Failure Assessment; STE: speckle
tracking echocardiography.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
SRQ, JNP, MM, SG, JNS, GCK and JKO contributed to data acquisition and
take responsibility for the integrity and accuracy of the data and analysis.
SRQ, JNP, GCK and JKO had access to the data, and contributed to study
conception and design, statistical analysis and preparation of the manuscript.
MW and SG contributed to study conception and design, and preparation of the manuscript. JNS contributed to data analysis and interpretation, and
drafting of the manuscript. All authors read and approved the final
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Section A: Speckle tracking echocardiography

Chapter 4: Acute right ventricle failure


Diagnostic workup, etiologies and management of acute right ventricle failure

A state-of-the-art paper

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Abstract

Introduction: This is a state-of-the-art article of the diagnostic process, etiologies and management of acute right ventricular (RV) failure in critically ill patients. It is based on a large review of previously published articles in the field, as well as the expertise of the authors.

Results: The authors propose the ten key points and directions for future research in the field. RV failure (RVF) is frequent in the ICU, magnified by the frequent need for positive pressure ventilation. While no universal definition of RVF is accepted, we propose that RVF may be defined as a state in which the right ventricle is unable to meet the demands for blood flow without excessive use of the Frank–Starling mechanism (i.e. increase in stroke volume associated with increased preload). Both echocardiography and hemodynamic monitoring play a central role in the evaluation of RVF in the ICU. Management of RVF includes treatment of the causes, respiratory optimization and hemodynamic support. The administration of fluids is potentially deleterious and unlikely to lead to improvement in cardiac output in the majority of cases. Vasopressors are needed in the setting of shock to restore the systemic pressure and avoid RV ischemia; inotropic drug or inodilator therapies may also be needed. In the most severe cases, recent mechanical circulatory support devices are proposed to unload the RV and improve organ perfusion.

Conclusion: RV function evaluation is key in the critically-ill patients for hemodynamic management, as fluid optimization, vasopressor strategy and respiratory support. RV failure may be diagnosed by the association of different devices and parameters, while echocardiography is crucial.

Keywords: Right ventricle failure, Pulmonary hypertension, Critically ill patients, Echocardiography, Shock

Introduction

For years, the left ventricle (LV) has been considered by cardiologists and intensivists as the essential ventricle for maintenance of effective circulation. The LV, after all, holds the central role in defining arterial pressure, one of the main determinants of organ perfusion with blood flow. However, as better bedside hemodynamic monitoring and advanced imaging techniques have evolved, the linkage between Guytonian physiology and cardiovascular assessment demonstrated the essential role of right ventricular (RV) function in cardiovascular homeostasis. This realization is supported by several parallel lines of evidence. First, many critical care patients receive positive-pressure ventilation. The increasing airway pressure artificially increases right atrial pressure (RAP), the back pressure to venous return [¹], limiting cardiac output, while simultaneously increasing RV afterload [²]. The phasic changes in RV output due to positive-pressure breathing define most of the dynamic changes in LV output, quantified as either arterial pulse pressure...
or LV stroke volume variations [3]. Second, the RV is the main limiting factor of fluid-responsiveness, as shown in pulmonary embolism (PE) [4] and in septic shock [5]. Indeed, its primary function is to optimize systemic venous return by decreasing or keeping RAP as low as possible while simultaneously ejecting its highly varying end-diastolic volume into a highly compliant and low resistance pulmonary circulation. When the RV fails, it cannot achieve these goals and the patient becomes fluid-unresponsive. Third, many situations in the critical care setting may promote RV failure (RVF) by causing increases in pulmonary vascular resistance, as described below.

Thus, it is not surprising that the occurrence of RVF reflects loss of cardiovascular reserve and is strongly associated with a poor prognosis. Worsening RV function is both a marker of adverse outcome and a direct contributor to mortality in a variety of disease states experienced in the critical care settings, as discussed later in acute respiratory distress syndrome (ARDS), RV myocardial infarction (MI) or decompensated pulmonary artery hypertension (PAH). The interplay between the RV and the pulmonary vasculature is a critical component of cardiac performance and patient outcomes while a number of diseases can directly or indirectly alter this interaction.

This state-of-the-art paper is an invited paper for the cardiovascular issue of Intensive Care Medicine. It reports the current definition, epidemiology and etiologies of RVF in the critical care setting, as well as the current recommendations for diagnostic workup and management. This paper is written by recognized experts in the field who also propose 10 key points regarding RVF based on the current knowledge, as well as main uncertainties/controversies in the field (Table 1).

Pathophysiology and definition of acute RV failure
Acute RVF in critically ill patients is sometimes called the “acute right heart syndrome” (ARHS). A commonly used definition for RVF does not exist, while a recent statement defined ARHS as a rapidly progressive syndrome with systemic congestion resulting from impaired RV filling and/or reduced RV flow output [6]. We propose here a universal definition of RVF based on pathophysiology. In critically ill patients, ARHS is usually clinically diagnosed by a combination of systemic hypoperfusion (cool extremities, confusion, chest pain, arrhythmia, ileus, oliguria, lactic acidosis) and systemic congestion (turgescence jugular veins, hepatomegaly, oedema, ascites). Oedema and ascites are only present in patients with pre-existing chronic RVF or dysfunction. If a pulmonary artery catheter (PAC) is present in patients with predominant RVF, it displays a RAP higher than the pulmonary artery occlusion pressure, at which point the patient is usually hemodynamically unstable. In patients with severe biventricular failure, RAP may be elevated without an elevated ratio. Bedside echocardiography shows dilated or remodelled right heart chambers and depressed indices of systolic function most often in the presence of increased pulmonary artery pressures (PAP), as measured directly by the PAC or estimated by echo on the basis of increased velocity of tricuspid regurgitation and shortened acceleration time of RV ejection flow-velocity. A notch on the pulmonary flow signal is often indicative of pulmonary vascular obstruction (proximal or more distal). When a paradoxical intraventricular septal motion is also observed, some authors have also named this pattern cor pulmonale [7].

In situations where pulmonary hypertension (PH) is prominent, the ARHS is basically caused by a failure of RV systolic function adaptation to increased loading conditions (homeometric adaptation, or Anrep mechanism). According to the Anrep mechanism, rapid increase in PAP (within minutes) augments RV contractility (measured by end-systolic elastance, $E_s$) in order to match the afterload (measured by pulmonary arterial elastance, $E_a$). However, homeometric adaptation is often limited in critically-ill patients where pulmonary hypertension is associated with systemic hypotension and systemic inflammation, two factors contributing to RV injury. Optimal RV-arterial coupling relies on an $E_a/E_s$ ratio of 1.5–2 to ensure flow output at minimal energy expenditure. When the $E_a/E_s$ decreases to 1 and below, the RV enlarges to preserve flow output (heterometric adaptation, or Starling mechanism), at the price of increased filling pressures and systemic congestion [8]. The tricuspid valve is an essential part of RV structure and function. Unlike the mitral valve, the tricuspid value can dilate in its lateral dimension over a short time period resulting in acute regurgitation. This is a useful short-term adaptation, as it serves to decompress the acutely overloaded RV chamber preventing further dilatation. This adaptive regurgitation however results in increased venous and hepatic congestion and reduced forward flow.

Accordingly, RVF is defined by a state in which the RV is unable to meet the demands for blood flow without excessive use of the Frank–Starling mechanism (i.e. increase in stroke volume associated with increased preload). This definition was initially proposed by Sagawa and colleagues after having shown that the “laws of the heart” (i.e. Anrep and Starling mechanisms) equally apply to both the RV and the LV [9] in spite of their obvious embryological and structural differences [10]. The evolution of RV functional adaptation to increased loading conditions is non-linear. RV dimensions may markedly increase with moderate increases in preload or afterload.
Table 1 Key points, uncertainties and clinical research recommendations in acute RV failure in critically ill patients

Key points
1. RV function is essential to cardiovascular homeostasis, especially in critically ill patients undergoing mechanical ventilation
2. Phasic changes in RV output define most of the dynamic changes in LV output. This explains that "left" parameters for predicting fluid-responsiveness are less accurate in case of RV failure
3. The RV can maintain an optimal ventriculo-arterial coupling in case of PH (homeometric adaptation or Anrep mechanism), especially when its loading conditions increase occurs progressively and is not severe in nature (unless it occurs early in the post-natal period). This adaptation is limited in ICU because of the frequently associated systemic hypotension and inflammation
4. When the homeometric mechanism is overtaken (acute increase in PH, end-stage chronic PH), the RV enlarges to preserve stroke volume (heterometric adaptation or Frank-Starling mechanism)
5. RV failure may be defined by a state in which the RV is unable to meet the demands for flow without excessive use of the Frank-Starling mechanism
6. RV failure in the ICU usually associates with systemic hypoperfusion and systemic congestion
7. Causes of RV failure (medical or perioperative) are numerous and related to pressure overload, volume overload or decreased contractility, as well as tachyarrhythmias
8. Positive pressure ventilation has a major impact on RV function, either directly (via changes in airway pressures) or indirectly (via changes in PaO2, PaCO2, pH)
9. Echocardiography is crucial for diagnosis, but may be combined with invasive monitoring (increased filling pressure)
10. Management includes optimization of respiratory support and hemodynamic support. The failing RV does not tolerate fluid expansion and significant diuresis may be needed. Vasopressors such as norepinephrine are the primary salvage treatment

Current uncertainties and knowledge gaps
1. A commonly used and proven definition of RV failure does not exist. Which thresholds for CVP and effective stroke volume index should be used?
2. The relation between RV end-diastolic volume and distending pressure can be highly variable over short intervals of time
3. Should a significantly dilated RV that is still meeting the demand for flow qualify as RV failure? Should it be called RV dysfunction (early stage RV failure)?
4. The "true" incidence of RV failure is unknown in the ICU (recognizing that the incidence based on different criteria may vary)
5. Since RV failure is a key mediator of poor prognosis in critically ill patients, should RV be systematically protected?
6. Are new imaging techniques, such as CT-scan, MRI and 3D-Echo useful for diagnostic process in the critically ill?
7. Is fluid removal an appropriate approach to improve RV function? If so, what is the best method and how can therapy be guided?
8. Which parameters are sufficiently accurate and practical to optimize fluid status in RV failure?
9. What is the role of inotropics (e.g., levosimendan) to improve ventriculo-arterial coupling? Are there specific situations in which this should be used (or not be used)?
10. What is the role of dobutamine or milrinone in RV failure? Is one drug superior? Should these drugs be generally used or limited to specific scenarios?

Clinical research priorities
1. To investigate in a large observational multicenter and prospective study, including unselected consecutively admitted patients in the ICU, the incidence of RV failure and its impact on the fluid responsiveness, hemodynamic support, organ failure, and prognosis
2. To investigate the use of non-invasive monitoring of pulmonary vascular compliance, ventricular interdependence and ventriculo-arterial coupling to guide treatment decisions
3. To investigate the role of advanced echo techniques (e.g., strain) or RV end-systolic dimension measurement to early identify RV injury before the onset of failure
4. To investigate the role of portal vein flow and renal flow monitoring as read-outs for RV function in the intensive care setting
5. To investigate in an RCT the impact of applying a systematic RV protective strategy on mortality. A first application could be pursued in ARDS
6. To develop clinical trials in acute HFrEF based on RV phenotypes
7. To investigate the role of PDE5 inhibition in patients with acutely HFrEF or HFpEF and evidence of RV dysfunction and PH
8. To investigate the role of perioperative inhaled prostanoids in patients with RV failure undergoing high-risk surgery
9. To evaluate the value of prolonged mechanical support systems of the acutely failing RV
10. To develop enriched clinical trials based on molecular imaging, or pathway specific phenotyping of the RV

ARDS acute respiratory distress syndrome, CT computed tomography, CVP central venous pressure, HFrEF heart failure with preserved ejection fraction, HFpEF heart failure with reduced ejection fraction, ICU intensive care unit, LV left ventricle, MRI magnetic resonance imaging, PDE5 phosphodiesterase 5, PH pulmonary hypertension, RCT randomized controlled trial, RV right ventricle

even though homeometric adaptation remains [8]. Thus, RV dimensions can be increased above normal limits (defined on healthy control populations), yet flow output remains sufficient without onset of systemic congestion. This intermediate zone may be called RV maladaptation or RV dysfunction, as it may be associated with eventual biological alterations and "pending" RVF. Once RV systolic function becomes uncoupled from the pulmonary circulation and the RV dilates, there is a negative diastolic interaction due to ventricular
competition for space within indistensible pericardium. Associated with RV dilation both LV filling and cardiac output decrease [11]. This decreasing cardiac output eventually manifests as a decreased systemic arterial pressure, decreasing coronary blood flow and its associated negative systolic interaction. The vicious circle is further aggravated by RV ischemia due to decreased coronary perfusion pressure (gradient between diastolic blood pressure and right atrial pressure) [12] and contraction asynchrony [10, 13]. Right heart distension reflexly activates the sympathetic nervous system and the renin–angiotensin–aldosterone sequence which both result in renal salt and water retention aggravating systemic congestion and worsening ventricular interactions by further dilatation of the RV [14, 15].

Understanding these mechanisms, summarized in Fig. 1, helps to identify targets of therapeutic interventions.

Etiologies and epidemiology of RVF in the critical care settings

RVF in medical situations

RVF is a heterogeneous syndrome rather than a single disease. Treatment approaches, therefore, must be individualized based on the underlying etiology and mechanism of dysfunction. Because of differences in methodology and definition of RVF, as well as a paucity of prospective studies, the prevalence of acute RVF in the critical care setting has not been defined precisely. Moreover, the prevalence or incidence of RVF may vary depending on the criteria used.

Acute RVF occurs in many different situations (Fig. 2), which induce the described RV-arterial uncoupling. The most common cause of RVF is PH. Uncoupling of RV systolic function is generally observed with rapid increase of PAP or end-stage PAH, but also occurs with only mild PH in patients with lung inflammatory states (e.g. ARDS), sepsis and LV failure, all conditions also associated with negative inotropic effects. RVF may also develop in patients with PAH, because chronic RV remodelling has already occurred and the clinical presentation and treatments can be different from acute PH, for example, PAH with connective tissue diseases causing marked RV hypertrophy. In many of these acute and chronic situations, high airway pressure and high tidal volume mechanical ventilation intensify or even may cause acute RVF by increasing pulmonary vascular resistance [16]. In ARDS, one of the most common causes of acute RVF in the critical care setting, pulmonary vascular dysfunction is common [17]. Acute cor pulmonale (ACP) occurs in 14–50% of ventilated ARDS, with most studies reporting a prevalence of
around 25% \[18\]. Causes are multiple and usually combined lung inflammation, pulmonary artery injury and the effects of positive pressure ventilation \[19\]. In a large cohort of more than 700 patients with moderate to severe ARDS and ventilated in a “protective” manner (e.g. with a tidal volume around 6 mL/kg and a strict limitation of plateau pressure below 30 cmH₂O), ACP was found in 22% of cases. Four risk factors were identified, i.e. pneumonia, PaO\(_2\)/FiO\(_2\) < 150 mmHg, PaCO\(_2\) ≥ 48 mmHg and driving pressure ≥ 18 mmHg \[20\]. Those patients with ACP are usually more tachycardic, have a lower systolic and mean arterial pressure and are more frequently in shock (86 versus 67%) \[21\]. In acute PE, cardiogenic shock occurs in ~ 4.5% of patients \[22\], and some evidence of RV strain occurs in about one-third of acute PE patients \[23\]. Pulmonary artery thrombosis has also been reported in sickle cell disease during acute chest syndrome in 17% of cases \[24\]. This is associated with an overall 24% incidence of RVF, especially when ARDS is also present \[25\]. RV MI is seen in about one third of cases of inferior wall acute MI \[26\]. Like other causes of acute RVF, RV MI causes uncoupling of RV systolic function and the pulmonary circulation, producing systemic congestion and reduced flow \[6\]. However, unlike most conditions associated with critical illness, in RV MI the lesion resides within the right ventricle, rather than in the pulmonary circulation.

The prevalence of acute RVF in other conditions (e.g. COPD exacerbations, left heart failure, sleep-disordered breathing) is not exactly known. However, many of these conditions are common, and some form of RV dysfunction (acute or chronic) may occur in as many as 80% of these patients \[27, 28\]. RVF is also common in various forms of PAH and may occur as acute-on-chronic RVF or as new-onset RVF. Precipitating factors include infection, volume overload, myocardial ischemia, PE, anaemia, trauma, surgery, arrhythmias, medical non-adherence, and progression of previously undiagnosed PAH \[29, 30\].

A common theme in all these conditions is that the occurrence of RVF is associated with a significantly worse survival. For example, the 90-day mortality rate
for patients with massive PE is 52% [22]; RV MI raises the risk of death more than twofold [31]; severe ACP is associated with increased mortality in ARDS [20]; and ICU mortality for patients admitted with decompensated PAH and RVF is 41% [30].

Lastly, there has been a recent focus on the management of patients who are resuscitated from cardiopulmonary arrest and transferred to a critical care unit. Up to 50% of these patients will need vasopressor support for hemodynamic instability [32]. A study investigating RV function in the first few hours after cardiac arrest showed that around 90% of this group of patients demonstrated both RV structural and functional abnormalities and that increase in the chamber dimensions was associated with increased mortality [33].

Perioperative RVF
RVF is much more likely to complicate cardiac surgery with numerous causes [34], while patients with existing severe PH and undergoing non-cardiac surgery may also have perioperative RVF. Patients with pre-existing PH, impaired RV function and tricuspid valve insufficiency are at increased risk of acute decompensation [35, 36]. RVF may occur following cardiac surgery secondary to acute left sided pathology, including LV failure, ventricular septal defects following MI and acute severe mitral valve regurgitation. Isolated acute right-sided failure may occur because of inadequate intraoperative right-sided cardioplegia administration or complications related to coronary artery graft flow or tricuspid valvuloplasty surgery. Intracoronary air and long cardiopulmonary bypass times may be contributory factors. Surgery involving the pulmonary arteries such as lung transplant and pulmonary endarterectomy can precipitate RVF [37]. An identifiable group of patients at higher risk of acute RVF are those undergoing cardiac transplantation, where RVF has been identified as an important cause of early deaths, and those receiving a LV assist device (LVAD) [38]. Transplant patients can develop acute RV pressure overload as a consequence of myocardial ischemia–reperfusion injury associated with organ preservation combined with either acute or chronically raised pulmonary vascular resistance. In a recent large study of 2988 patients from the European Registry of patients with Mechanical Circulatory Support (EUROMACS), RVF following LVAD implantation occurred in 22% of patients within 30 days of surgery with 7% requiring Mechanical Circulatory Support (MCS). Consistent with other risk stratification models, patients with evidence of RV function impairment were at higher risk [39]. Congenital heart disease and corrective surgeries such as those for Tetralogy of Fallot may result in RVF for a number of reasons and may limit the feasibility of the procedure. Acute cardiogenic shock mimicking RVF may also occur in the presence of pericardial thrombus causing a localized compression and obstruction to RV filling with significantly raised central venous pressure.

Diagnostic workup
Clinical presentation, examination, ECG, biochemical assessment and imaging are involved in the diagnosis of acute RVF and monitoring response to treatment. Signs, symptoms and laboratory tests can elucidate acute RVF etiologies. However, these findings lack sensitivity and specificity [40] and abnormal signs, symptoms and lab results can be from a variety of other pathology causing organ hypoperfusion (Table 2). There is no specific biochemical marker that identifies acute RVF [6, 41]. Diagnostic workup is, therefore, highly dependent on the clinical diagnosis aided by imaging. In particular, echocardiography plays a major diagnostic role [42]. We suggest a possible diagnostic pathway in the Fig. 3.

Best standard of care (for diagnosis and investigation)
A high level of suspicion ensures timely identification of acute RVF, which is essential for appropriate management. Delayed diagnosis and treatment of the underlying cause, as well as failure to prevent further injury to the RV (e.g. through fluid overload or worsening RV afterload) are all associated with worse outcomes. Early signs which should raise concern include hypoxemia, acidosis, hyperlactatemia, troponin rise, minor coagulopathy, and acute renal and liver dysfunction due to increased venous pressure. These are all non-specific findings and should prompt further investigation, particularly a thorough echocardiographic examination.

Initial assessment
Clinical presentation and examination vary with etiology and presence of co-morbidities, especially chronic RV changes. Recognition of pre-existing PAH (e.g. from parenchymal lung disease) is important as it dramatically impacts the patient’s ability to cope with increases in PAP [43] and predisposes to death from acute on chronic RVF [44]. ECG and CXR findings may be normal, however, ECG may identify arrhythmias or RV strain pattern and CXR examination may suggest new parenchymal lung disease or volume overload potentially caused by left-sided heart disease [45].

Echocardiography (Fig. 4, Table 3)
Echocardiography plays an important role in the diagnosis of acute RVF in the ICU, initially by identifying presence of left-sided heart disease. In addition, echocardiography can non-invasively assess RV preload, contractility and afterload. Focused cardiac studies provide a
Where there is reduced inter-observer variability (the RV is normally less than 60% the size of the LV) and function, particularly the apical four-chamber view RV geometry and position can make accurate analysis makes echocardiography highly versatile. Output, filling pressures, RV size and function and PAP rapidly assess response to treatment in terms of cardiac hemodynamic and valvular assessment.

Table 2 History, investigation, laboratory tests and CXR abnormalities associated with acute RVF, all lack sensitivity and specificity and can be caused by other etiologies causing organ hypoperfusion

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<th>History</th>
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<td>Shortness of breath</td>
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<td>Confusion</td>
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<td>Right upper quadrant pain</td>
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<td>History of pulmonary hypertension</td>
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<td>Tricuspid regurgitation murmur</td>
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<td>Hypoaemia</td>
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<td>Hyperlactatemia</td>
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<td>Raised Troponin</td>
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<td>Acute renal failure</td>
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<td>Transaminitis</td>
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<td>Mild coagulopathy</td>
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<td>Mild hypoglycaemia</td>
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<td>Hyperbilirubinemia</td>
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<td>Raised BNP</td>
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<tr>
<th>ECG</th>
<th>V1–V4, II, III, aVF ST changes and/or T wave inversion</th>
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<tr>
<td>Complete or incomplete right bundle branch block</td>
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<td>Low limb lead voltage</td>
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<td>QRS axis &gt; 90°/right axis deviation</td>
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<td>Dominant R wave V1</td>
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<td>RV hypertrophy</td>
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<td>Deep S wave I, Q wave and T wave inversion lead III</td>
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<tr>
<th>CXR</th>
<th>Enlarged heart size</th>
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<td>Right atrial dilation (increased curvature)</td>
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<tr>
<td>Right heart border prominence</td>
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<tr>
<td>Pleural effusions</td>
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<td>Proximal pulmonary artery dilation</td>
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Care should be taken if there is LV enlargement as RV size may be underestimated (dimensions and area should be measured). Moreover, the concept that RV dilation must be present to diagnose RVF is contentious and it would be more accurate to describe a dynamic situation of increasing RV volumes by fluid expansion without changes in cardiac output as a signature of acute RVF. LV and left atrial enlargement point towards postcapillary PH involvement (although other etiologies need to be considered), whereas RVF associated with precapillary PH can be associated with a shift of the interventricular septum towards the left and a relatively under-filled LV. RV function can be assessed with multiple parameters and qualitative, as well as quantitative parameters are important [47]. The majority of echocardiography parameters for assessment of pulmonary hemodynamics in the critically ill have been shown to be accurate. Particular care should be taken with integration of findings into the clinical presentation. Importantly, dynamic measures of RV systolic function, such as speckle tracking, have proven highly sensitive in defining both early RV strain prior to overt RVF and improvements in RV function in response to specific therapies, such as pulmonary vasodilator therapy [48, 49].

In RV MI, a key distinguishing characteristic is that RV systolic pressure, along with related echocardiographic indices such as the tricuspid regurgitation jet velocity, is not significantly elevated. Thus echocardiographic assessment is essential for distinguishing RV MI from other causes of acute RVF. However, some of these patients may also require positive pressure ventilation in case of associated cardiogenic pulmonary edema due to large inferior MI or mitral regurgitation, and the pattern of RVF is closer to that is usually observed in situations with injury of the pulmonary circulation.

Transoesophageal echocardiography (TOE) is the essential diagnostic tool for all RVF following cardiac surgery, transthoracic windows are generally poor in patients following sternotomy. A more recently developed disposable TOE probe has been described that can be used for up to 72 h, and can track RV functional recovery and inform changes in hemodynamic therapy [50, 51].

Computed tomography (CT) (Fig. 4)

CT pulmonary angiography is the imaging method of choice in acute PE and echocardiography should not be used to exclude venous thromboembolism [52]. RV size is assessed, with or without ECG-gating [53], by analysing RV/LV diameter ratio (greater than 1 predicts risk for adverse outcomes in PE); however, there are reports of significant inter-observer variability and volumetric analysis may be better [54]. Increased RV/LV ratio can
also point towards PH that is not related to acute PE, in particular when it is accompanied by pulmonary artery diameters exceeding that of the aorta [55]. RV function can be further assessed by the determination of ejection fraction (assessment requires ECG gating) and the presence of interventricular septal bowing and inferior vena cava contrast reflux [56]. Additionally, CT angiographic determination of the left to right atrial ratio can help to distinguish between pre- and post-capillary forms of PH [57].

**Invasive monitoring**

Pulmonary artery catheter (PAC) use provides continuous monitoring of PAP and may identify those patients with acute RV dysfunction with poor compliance through monitoring of RV pressures (using proximal port in RV) vs PAP (steeper RV diastolic pressure slope) [58]. Since PAC use is still common in cardiac surgical critical care [59] clinicians need to be cognizant of these hemodynamic signatures when following these patients post bypass. Although less used nowadays due to the risks of placement, use of the PAC may help in those at risk of acute RVF (e.g. history of significant PAH) or those not responding to conventional treatment. Still, when available, the estimate of pulmonary vascular compliance (pulmonary arterial pulse pressure to stroke volume ratio) offers more insight into defining RV performance in ARDS patients than doing measures of pulmonary vascular resistance [60, 61]. Combining echocardiography with invasive PAC monitoring seems the ideal method for monitoring this challenging group of patients. Temporal trends in PAP and RAP likely hold more benefit than static measures (e.g. increasing PAP and decreasing RAP may indicate improved RV output into a pulmonary system with high resistance). Thermodilution-based cardiac output estimations should be used with caution in acute RVF as significant acute tricuspid regurgitation may lead to underestimation [62], especially when the severity of the regurgitation is not fixed for beat to beat, as it may occur in mechanically ventilated patients. However, when used very rigorously, it has been suggested to have a good accuracy in a small population of spontaneous ventilated patients with PAH [63]. Transpulmonary thermodilution (PICCO® device), another popular invasive monitoring device, has been reported not to be appropriate in detecting isolated RVF [64].
Fig. 4 Current imaging techniques in acute right ventricle (RV) failure diagnosis and recent advances. Echocardiography: panels a–n. All view needs to be used to assess RV size and RV function, a parasternal long axis view, b parasternal short axis view (including eccentricity index in assessment of ventricular interdependence), c apical four chamber view (dimensions and area may be useful particularly if the LV is dilated), d subcostal view. Preload analysis: e assessment for fluid responsiveness by stroke volume variation with respiration ± passive leg raise, f IVC size variation with respiration (less accurate in presence of RVF and significant tricuspid regurgitation), g presence of pericardial effusion. Contractility assessment: h fractional area change, i subjective analysis, j TAPSE (tricuspid annular plane systolic excursion). Afterload assessment: k tricuspid regurgitation jet used for estimation of peak systolic pulmonary artery pressures ($4\times TRV_{max}^2 + right\ atrial pressure$), where $TRV_{max}$ is the maximal velocity of the tricuspid regurgitation, m RV outflow tract flow analysis (e.g., “flying W sign” in raised pulmonary vascular resistance), n pulmonary regurgitation flow for estimation of diastolic pulmonary artery pressures ($4\times PRV_{end-diastolic}^2 + RAP$), where $PRV$ is the velocity of the pulmonary regurgitation. Computed tomography (CT): panels o–q. o LV/RV diameter ratio, p pulmonary artery size and presence of thrombus, q IVC contrast regurgitation in acute RV failure. Recent advances: panels r–t. r Speckle tracking echocardiography, s 3D echo volumetric analysis, t apical dyskinesia by magnetic resonance imaging (MRI) due to pulmonary embolism. Image courtesy of Dr. Faraz Panthan.
Several novel PH biomarkers are described that relate to heart failure, inflammation, cardiovascular remodelling and endothelial cell-smooth muscle cell interaction [65]. They have predominantly been studied in animals or in small patient numbers, in single centres for risk stratification of PE and chronic PAH cohorts, and never in acutely ill patients [66–68]. Many studies also suffer from publication bias, multiple testing and retrospective analysis which limits their validity [65].

Speckle tracking echocardiography appears to be a promising monitoring approach. Recently developed software can track the movement of the grey-scale pixels relative to each other providing a quantitative measure of

<table>
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<tr>
<th>Echocardiographic variables</th>
<th>Acute RV failure phenotype</th>
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<tr>
<td>General</td>
<td>Features may help differentiate:</td>
</tr>
<tr>
<td></td>
<td>Acute, acute-on-chronic</td>
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<tr>
<td></td>
<td>Predominantly RV failure vs. biventricular failure</td>
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<td></td>
<td>SPECIFIC etiology</td>
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<td></td>
<td>Predictive parameters of response to therapy</td>
</tr>
<tr>
<td>Diagnostic considerations</td>
<td>Suggest either severe acute pressure overload or acute on chronic RV failure</td>
</tr>
<tr>
<td>Severe RV enlargement</td>
<td>Best assessed in the sub-costal view; suggests chronic pressure overload state</td>
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<tr>
<td>RV hypertrophy</td>
<td>This suggest arrhythmogenic RV cardiomyopathy</td>
</tr>
<tr>
<td>Aneurysms</td>
<td>Presence of &quot;hyperdynamic apex&quot; or McConnell sign suggests acute PH</td>
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<td></td>
<td>Preserved apical contraction can also be seen in RV MI. Patients with RV MI may also have preserved infundibular contraction in the presence of separate branch</td>
</tr>
<tr>
<td>Segmental wall motion abnormalities</td>
<td>Very useful to assess ventricular interactions depends on relative dimensions of ventricles, relative pressure and ventricular synergy. Septal flattening suggests pressure overload when occurring at end-systole</td>
</tr>
<tr>
<td>Pulmonary flow</td>
<td>The presence of a pulmonary notch is indicative of pulmonary vascular disease with significant obstruction (proximal or distal)</td>
</tr>
<tr>
<td>Pressure estimates</td>
<td>Evaluation of RVSP or early diastolic pressure flow gradient is useful in estimating pulmonary pressure (cf. Fig. 4)</td>
</tr>
<tr>
<td>Thrombus near right atrium</td>
<td>Careful assessment of local tamponade is essential as may be an important cause of hemodynamic compromise</td>
</tr>
<tr>
<td>LV phenotypes</td>
<td>Presence of LV enlargement suggests chronic LV pathology. LV systolic function may be decreased in the presence of severe RV involvement and indicates low effective stroke volume of the entire system</td>
</tr>
<tr>
<td>Other</td>
<td>Displaced septal position of the tricuspid valve may suggest Epstein’s anomaly; also screen for the presence of shunts</td>
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**Pitfalls in the assessment of acute RV failure**

**Post-operative pitfalls**

Annular indices such as TAPSE and RV longitudinal strain are usually not reliable post-pericardectomy and may remain altered in the long term

**Pressure assessment**

Avoid reporting pressure with sub-optimal signals; ensure consistency with the other markers such as septal curvature

**Estimation of RAP**

The IVC diameter may not be reliable to estimate RAP in intubated patients

**Different definitions CT/echo**

RV strain on CT and echo refer to different concepts: by CT mainly refers to RV enlargement, and echo refers to functional indices

**Management consideration**

**Preload assessment**

Estimating dynamic change in stroke volume or its surrogates using PLR or limited volume load challenge may be useful to assessing potential response to fluid resuscitation. Assessment of septal curvature may also be useful to assess response to preload optimization. Interest in assessing portal vein and renal vein flow is gaining interest to assessing pressure overload

**Response to inotropic therapy**

Assessment of contractile reserve to dobutamine or other agents may help tailor therapy and avoid dangerous escalation of inotropic support

**Ramp echocardiographic protocol**

Assessment of recovery of the right ventricle during weaning of ECMO support and continuous flow LVAD

CT computed tomography, ECMO extracorporeal membrane oxygenation, IVC inferior vena cava, LV left ventricle, LVAD left ventricular assist device, MI myocardial infarction, PH pulmonary hypertension, PLR passive leg raising, RAP right atrial pressure, RV right ventricle, RVSP right ventricular systolic pressure, TAPSE tricuspid annular plane systolic excursion
deformation (known as "strain"), a negative dimensionless value, which describes a relative change in distance between pixels. Strain is used as a surrogate for systolic performance but not contractility; the greater the negative value, the greater the degree of deformation. RV function is classically assessed by tracking the movement of the RV free wall only. Known as RV free wall strain (normal values are more negative than −20 to −25%), it has been shown to describe cardiac dysfunction not elucidated by conventional echocardiographic techniques [69] and is highly prognostic in PAH cohorts [70], as well as in septic patients [71]. Speckle tracking echocardiography requires a reasonably high level of experience and training to perform as erroneous results are easy to acquire if the tracking is inappropriately performed. Measuring RV free wall longitudinal strain using manual tracing of RV end-diastolic and end-systolic length may be more simple and has been shown to be prognostic in patients with PAH [72]. As RVF induces congestion, the role of portal vein flow and renal flow monitoring by simple Doppler method should also be investigated to evaluate RV function.

Three-dimensional echocardiography is emerging with the potential to overcome the limitations of single-plane imaging seen in conventional echocardiography. For the RV this has particularly interest due to the abnormal concentric shape. Widespread use has been limited by imaging difficulties and availability, however its accuracy has been validated against cardiac magnetic resonance imaging (CMR) [73]. Further advances include the development of 3D speckle tracking of the RV in PAH [74]. To date, the use of 3D imaging of the RV has not been well investigated in the critically ill.

CMR is often used as the reference standard in studies investigating accuracy of RV imaging [75, 76]. CMR allows comprehensive evaluation of RV anatomy, volume, function and tissue characterization, with features such as RV dilation, abnormal septal and free wall motion, and tricuspid regurgitation easily recognized [77]. RV functional changes over time are much more accurately assessed by CMR than by echocardiography [78]. Native T1 mapping [79], T2-weighted and late gadolinium enhancement [80] potentially enable characterization of oedema, infarction or inflammation, although the RV free wall is not always easily detected and RV analysis is not well-validated or imprecise. However, CMR studies in the critically ill are currently lacking due to the restricted access, limitations of compatible equipment, patient and staff safety and time needed for imaging. Newer methods, as open-MRI with limited magnetic field [81], or methods aimed to reduce speed of MRI from 45–60 min to potentially 15 min [82] should make CMR increasingly available for critically ill patients.

Management
Treatment of the cause
It is obvious that, when reversible, the priority must be to specifically treat the cause of RVF. For instance, fibrinolysis or even surgical embolectomy may be considered in RVF-related PE [52]. RV MI also presents some unique options for treatment, including percutaneous coronary intervention. Precipitating factors of decompensated chronic RVF have to be controlled (see previous sections for the precipitating factors).

Hemodynamic support (Fig. 5)
The management of acute RVF focuses on stabilizing hemodynamics, optimizing loading conditions and treating potential reversible cause. Prompt treatment of arrhythmias (tachy or brady) is also essential to avoid the vicious circle of hypotension, ischemia and further arrhythmias.

One of the most important misconceptions in managing RVF is assuming that the majority of patients are on the preload dependent zone of the Frank–Starling relationship and would, therefore, benefit from volume loading. However, acute RVF leads to diastolic LV failure [83, 84], wherein both hypovolemia and hypervolemia are poorly tolerated and the optimal RV filling volume is often difficult to define. Even small fluid boluses can be poorly tolerated in acute RVF and ACP. In 13 patients with hemodynamic and radionuclide ventriculographic evidence of RV MI, progressive volume loading has been demonstrated to significantly increase RAP and PAOP but without significant change in cardiac index [85]. In canine model of PE or in the positive pressure ventilated setting, the lack of hemodynamic improvement following fluid challenge has been reported [86, 87]. In a landmark study in the setting of experimental RV MI (pig model), the importance of pericardial constraint was demonstrated, highlighting the importance of ventricular interactions [11]. Experimental studies in RV MI, PE and PAH have all shown that volume loading can increase right cavity size, increase pericardial constraint and further limit LV filling through the mechanisms of ventricular interdependence [88–90]. In a model of acute-on-chronic pulmonary thromboembolic disease, Boulou et al. also recently demonstrated that fluid challenge is not associated with an increase in stroke volume or cardiac output [91]. Taken together, these experimental and clinical studies would argue against routine volume loading in acute RVF unless clear evidence of hypovolemia or stroke volume responsiveness to physiological variation is noted. Patients with RV MI could benefit from volume repletion in the presence of clear evidence of hypovolemia; the usually lower afterload and lower ventricular wall stress compared to patients with chronic pressure...
overload can be placed at a more favourable portion of the Frank–Starling relationship. If fluid is given, starting with low volume repletion of 100–250 mL is often preferred while monitoring stroke volume or blood pressure response (unless active source of rapid volume loss is known to co-exist). Several studies including an excellent comprehensive review by Marik et al. have shown that RAP alone should not be considered a reliable marker of volume status or volume responsiveness \[92]\, while other parameters for fluid responsiveness have been proposed \[93]\, some of them unfortunately limited in RVF. Briefly, echocardiography is key in optimizing fluid loading, while IVC diameter has been recently reported to poorly predict the response to fluids in mechanically ventilated patients \[94]\, and in fact there is no magic parameter to guide the need for fluids \[95]\. Measuring changes in cardiac output in response to a passive leg raise manoeuvre define volume responsiveness and can be used to attempt judicious fluid loading (with assessment of response to the intervention) \[96]\. In fact, the majority of patients with acute RVF associated with chronic PAH, congenital heart disease or biventricular failure would respond more to volume removal than infusion.

Since most RV coronary flow occurs in systole, if PAP increases above systemic arterial pressure, RV ischemia can develop. The primary salvage treatment to sustain cardiovascular function is the infusion of vasopressors (e.g. norepinephrine, vasopressin or terlipressin) to keep systemic arterial pressure greater than pulmonary arterial pressure. In a canine model of acute obstruction of the pulmonary circulation, fluid loading worsened RVF, while in contrast norepinephrine infusion restored mean arterial pressure to baseline, decreased biventricular filling pressure and increased cardiac index \[97]\. Inotropic drugs have also been proposed, while no reasonable study may clearly recommend their use in acute RVF-related

Fig. 5 Physiological consideration during the management of acute RVF. The cardiopulmonary unit is central in tailoring management of RVF. Pulmonary vascular resistance or impedance is influenced by hypoxemia, hypercapnia and acidosis, lung volumes and positive pressure ventilation. Maintenance of blood pressure and coronary pressure is essential in managing RVF. In addition, management of RVF including fluid management has to take into account zone ventricular interactions, pericardial constraint, fluid responsiveness (zone of the Starling curve). Abdomino-thoracic and cardio-thoracic are essential to consider in acute RVF in the ICU setting as these can be overlooked caused of hemodynamic instability.
PH. There is probably no place for isoproterenol in the management of ARF, as in a model of experimental PE, all dogs randomized to receive isoproterenol died [98]. In PE, dobutamine has been reported to improve hemodynamics and reduced pulmonary vascular resistance [99]. In RVF related to ARDS, it makes sense to use inodilator to improve RV-pulmonary circulation coupling, as reported in a pilot study in which levosimendan was infused in 35 patients [100]. In 25 patients with cardiogenic shock related to myocardial infarction not sufficiently improved after percutaneous revascularization and infusion of dobutamine or norepinephrine, RV performance, as well as hemodynamics, was improved by levosimendan infusion [101]. However, at this time, no clear recommendation can be made due to the absence of sufficient data.

An exciting novel direction in the management of RVF is the use of MCS devices. In situations where medical therapy is inadequate, the employment of MCS devices to augment cardiac output, decrease RA and RV preload and improve oxygenation and acidosis can provide a life-saving bridge to either recovery or transplant. Surgically implanted RV assist devices (RVADs) have been used for more than two decades for this purpose. However, their placement via sternotomy or thoracotomy is often not feasible in critically ill patients. More recently, interest has turned to percutaneously placed support devices, which have the potential to revolutionize our approach to this patient population, providing the advantage of rapid deployment without the surgical risk. The Impella RP (Abiomed Inc) can be placed via one venous access site (usually the femoral vein) with delivery of blood from the RA to PA via a 22F impeller mounted on an 11F catheter. In a prospective cohort study including 30 patients with refractory RVF, 18 post LVAD and 12 following cardiac surgery [102]. The overall mortality at 30 days was 73.3%, which compares favourably to previous case series of surgically placed RVADs. Two other percutaneously placed MCS devices also exist, one requiring two venous catheters and the other a dual-lumen cannula for RA inflow and PA outflow [103–105]. Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) can offer both right and left sided circulatory support and is currently the most widely utilized percutaneously deployed MCS for acute or acute on chronic RVF. The creation of mobile “ECMO teams” allows the utilization of this treatment modality throughout the hospital in a rapid response manner, including code situations. The successful use of “awake” ECMO, with placement of the venous and arterial catheters using only conscious sedation, avoiding mechanical ventilation, has garnered recent attention in the management of PH as a bridge to transplant.

**Respiratory strategy**

RVF in the ICU is clearly promoted and worsened by positive-pressure ventilation, either related to respiratory settings or to their consequences, which are blood gases (PaO\(_2\), PaCO\(_2\)). Though especially true in ARDS, it can potentially be seen in any mechanically ventilated patient. In general, plateau pressure and driving pressure have to be limited [20, 106]. As hypercapnia by increasing the hypoxic pulmonary vasoconstriction is deleterious for the right ventricle, especially when inducing acidosis [107], PaCO\(_2\) has to be controlled. This may be achieved by different ways: limiting intrinsic PEEP (PEEP\(_i\)), decreasing respiratory rate (RR) in acute exacerbation of COPD or acute asthma, increasing RR without inducing PEEP, in ARDS, and removing CO\(_2\) by extracorporeal circulation [108]. Hypoxia also contributes slightly to PH [109], thus oxygenation has to be optimized. However, recruitment manoeuvres followed by application of a high PEEP, to “optimize lung aeration and oxygenation”, increase mortality and hemodynamic compromise in ARDS patients [110]. At the opposite, ventilation in prone position has been reported to increase oxygenation, decrease PaCO\(_2\), plateau pressure and driving pressure in ARDS, and finally to correct RVF [111]. Nitric oxide inhalation (iNO) could also be tried in refractory PH with acute RVF, not to improve oxygenation, as it failed to improve prognosis in ARDS [112], but with a goal to decrease PAP and RV afterload and then to improve hemodynamic status. iNO has been suggested to be associated with a lower mortality in patients with PAH at risk of RVF after orthotopic heart or lung transplantation which is not the case after cardiac surgery or in medical patients with hypoxemia [113].

**Conclusion**

We propose in this manuscript a universal definition of RVF, which is defined by a state in which the RV is unable to meet the demands for blood flow without excessive use of the Frank–Starling mechanism. RVF is frequent in the critically ill ICU patient, while studies are lacking to precisely know its incidence in unselected population. It may occur de novo (“acute”) or by decompensation of a pre-existing condition (“acute-on-chronic”). It is associated with worse prognosis. Hemodynamic and respiratory management is mainly based on pathophysiological rationale, as the absence of sufficient clinical studies to compare one direction or the other does not allow doing any formal recommendation. Future research should be based on large database study of admitted unselected patients to evaluate incidence, impact and management.
Compliance with ethical standards

Conflicts of interest

AVB has received Grant from GSK for conducting clinical research and is membership of the scientific advisory board. RN has relationship with drug companies including AOPOrphan Pharmaceuticals, Actelion, Reata, Lung Biotechnology Corporation and United Therapeutics. In addition to being investigator in trials involving these companies, relationships include consultancy service, research Grants, and membership of scientific advisory board. HH declares no conflict of interest with regards to the content of this manuscript. MRP declares no conflict of interest with regards to the content of this manuscript. HJB declares research Grants from Actelion, GSK, Therabell and membership of the scientific advisory board. FH declares no conflict of interest with regards to the content of this manuscript.

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Strain imaging in right ventricle assessment

Abstract

The right ventricle is becoming increasingly recognised as being integral to cardiac mechanics and analysis of its function is an essential part of any echocardiogram performed in the critically ill patient. However, it has a complex triangular, conical shape and is located in a difficult to image retrosternal position. Unlike the LV with its myocardial fibres in many different directions, the RV has a predominance of longitudinal fibres with the majority of its movement being in a basal to apex direction. This makes it sensitive to analysis with speckle tracking echocardiography analysis of longitudinal strain: commonly reported as right ventricle free wall strain.

Strain is a measure of relative myocardial deformation analysed through tracking of the speckles that make up the myocardium on the two dimensional B-mode image. It is a post-processing imaging tool and a reasonable degree of experience in echocardiography is required before tackling this form of assessment. Strain is sensitive, reproducible, angle-independent, not prone to translation error like other conventional echocardiography tools and most importantly can recognise cardiac dysfunction and mechanics that cannot be described by any other non-invasive imaging technique.

There are many echocardiography parameters to assess right ventricle function and none of them are perfect. Neither is right ventricle strain assessment unfortunately. However, its advantages are proven by the fact that it has entered clinical practice (exclusively to cardiology departments at this stage) in many larger centres around the world. In the critically ill the use of right ventricle function strain analysis is limited exclusively to research. With the increasing availability of higher end machines in the ICU the use of speckle tracking echocardiography may grow as will our understanding of right ventricle function.
Section A: Speckle tracking echocardiography

Background
In previous years, right ventricle (RV) function analysis had been largely overshadowed by left ventricle (LV) assessment. Although the RV is only one sixth the mass of the LV it plays an integral role in cardiac function and the prognostic value of RV function has now been shown in multitude cardiovascular diseases: for example heart failure(1), pulmonary hypertension(2), valvular heart disease(3) to name a few. The importance of evaluating the unique RV function and anatomy is gaining momentum, particularly in the critically ill, as an essential component of cardiac mechanics and patient management(4).

One reason the RV has been relatively ignored is potentially due to the challenging imaging. When Mother Nature designed the RV she did not have echocardiography in mind. The RV has a complex triangular, crescent, conical shape (see Figure 1), it is located in a challenging to image retrosternal position, wrapped around the LV and its movement during contraction is complex.

![Figure 1](attachment:image.png)

**Figure 1**: The right ventricle. (a) Lateral view, (b) Inferior view, (c) Medial view and (d) Superior view. TV tricuspid Valve; PV pulmonary valve; IVS interventricular septum

Echocardiography is an essential method to assess RV function in the ICU patient due to its non-invasive nature, repeatability and capability to be done at the bedside in a safe manner. It is far from perfect however. The ‘ideal’ echocardiography measure of RV function should be feasible in routine practice, take a relatively short amount of time to perform and to train in how to do, be highly reproducible and have incremental value over a range of values of
Section A: Speckle tracking echocardiography

dysfunction. There is no current parameter that satisfies all of these variables and each has their own advantages and disadvantages (*Table 1*).

<table>
<thead>
<tr>
<th>Right ventricle assessment method</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Subjective assessment</td>
<td>Quick</td>
<td>Reasonable level of experience required</td>
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<tr>
<td></td>
<td>Global assessment</td>
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<td>TAPSE</td>
<td>Simple</td>
<td>Angle-dependent</td>
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<td></td>
<td>Quick to perform</td>
<td>Prone to translational error</td>
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<td></td>
<td>Easy to learn</td>
<td>Single point assessment of complex structure</td>
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<td></td>
<td>Well validated</td>
<td>Lacks sensitivity</td>
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<td></td>
<td>Specific</td>
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<tr>
<td>Tissue Doppler Imaging</td>
<td>Easy to learn and perform</td>
<td>Angle-dependent</td>
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<tr>
<td>RV S’ (systolic motion)</td>
<td>Relatively load independent</td>
<td>Single point assessment of complex structure</td>
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<td></td>
<td>Part of standard imaging protocol</td>
<td>Lacks sensitivity over range of RV dysfunction</td>
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<td></td>
<td>Well validated in non-critically ill populations</td>
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<td></td>
<td>Not as dependent on image quality as other parameters</td>
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<tr>
<td>Fractional Area Change</td>
<td>Easy to perform</td>
<td>Poor sensitivity</td>
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<td>(FAC)</td>
<td>Can be done on most machines</td>
<td>Time consuming</td>
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<tr>
<td>RV myocardial performance index</td>
<td>Relatively load independent</td>
<td>Requires calculation</td>
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<td>Small time intervals</td>
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<td>Not part of standard imaging</td>
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<td>Lacks repeatability</td>
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<td>Speckle tracking echocardiography</td>
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<td>Learning curve</td>
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<td>Angle independent</td>
<td>Time to perform</td>
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<td></td>
<td>Describes ranges of dysfunction</td>
<td>Entire RV free wall must be seen throughout the cardiac cycle</td>
</tr>
<tr>
<td></td>
<td>Post processing analysis</td>
<td>Image quality dependent</td>
</tr>
<tr>
<td></td>
<td>Normalised for heart size</td>
<td>Requires specific software</td>
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<tr>
<td></td>
<td></td>
<td>Vendor variability</td>
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*Table 1*: Methods of right ventricle function assessment in the critically ill
Section A: Speckle tracking echocardiography

Strain imaging describes ventricular function in a relatively novel and sensitive manner. It can describe subclinical disease and cardiac function that cannot be expressed by conventional echocardiography. It is performed by two principle methods: tissue Doppler imaging and speckle tracking echocardiography. Tissue Doppler was the original method, however it requires high frame rates (typically greater than 150 frames per second), is angle dependent, more time consuming and lacks reproducibility(5). Speckle tracking has essentially taken over as the strain imaging method both in clinical practice and research. It is a post-processing method (ie: analysis is done after images have been stored) done on B-mode images, is angle independent, uses lower frame rates (generally more than 45 frames per second) and is becoming increasingly automated. The focus of this chapter will be speckle tracking echocardiography: principles of analysis, parameters, advantages, limitations and potential utility in the critically ill.

In the ICU, RV failure can have devastating effects: as seen in ARDS (6,7) and severe sepsis cohorts(8) where it is an independent risk factor for mortality. Accurate and early recognition may be important to tailor management to protect the RV(9). Strain analysis may play a role in this recognition and has the potential to help guide therapy and provide accurate prognostication.

Strain

What is strain? Strain (also known as Lagrangian strain) is a dimensionless index of relative myocardial deformation(10) (see Figure 2).

\[ \text{Strain} = \frac{L - L_0}{L_0} \]

Figure 2: The concept of strain. Similar to a piston shortening; initial length = Lo; after contraction = L; strain = (L – Lo) / Lo
Section A: Speckle tracking echocardiography

It is presented as a percentage and is a negative number, the concept being: the more negative a number, the greater the degree of deformation (i.e., the greater degree of contraction) and the better the myocardial function (see Figure 3). One of the first benefits to note is that it is normalized for heart size as is a measure of relative deformation. This reduces the biological variability.

**Figure 3:** Graph to describe change of strain with deformation: the greater the degree of deformation, the greater of strain, the better the systolic function.

The RV has a predominance of longitudinal muscle fibres in its free wall with the majority of motion being in the apical to base direction. Hence longitudinal strain is the value used to describe the RV function (11): RV free wall strain. The majority of research into RV strain comes from pulmonary hypertension cohorts (2,12,13). Studies investigating RV free wall vs septal motion the free wall strain was most closely correlated with RV ejection fraction, invasive mean pulmonary artery pressure, peak systolic pulmonary artery pressure, RV end diastolic volumes by cardiac MRI and exercise tolerance by 6 minute walk-test. The RV septal movement held no association with these RV function parameters (12,14). Current research and clinical practice reports RV free wall strain as the estimate of RV function using...
Section A: Speckle tracking echocardiography

strain imaging(15). Absolute values are yet to be validated(16), but based on current research normal is -25%(15).

A further important strain principle is that it describes ‘active’ movement rather than ‘tethering’. For example, akinetic segments can be pulled and display movement (known as ‘tethering’) despite having no ‘active’ contraction or thickening. Strain imaging is able to distinguish between these. Consider McConnell’s sign, suggested to be specific for acute pulmonary embolism: RV basal and mid segment akinesia with RV apical sparing. Speckle tracking studies suggest the RV apex is not truly spared and may be a visual illusion of preserved contractility due to tethering to a hyperdynamic LV(17).

Speckle tracking echocardiography

Speckle tracking imaging is a relatively novel method of RV function analysis that quantifies the degree of myocardial deformation or strain. It is performed through post-processing analysis of B-mode images (ie: once they have been stored). The software tracks the granulated speckles that make up the image of the myocardium and determines their deformation relative to each other. The speckles are naturally occurring ultrasound artifacts, approximately 20-40 pixels in size(4). They do not represent real physical structures in the myocardium. They are caused by complex ultrasound wave constructive and destructive interference of reflectors in the myocardium that are closer together than the resolution limit of the ultrasound system(18). These speckles are stable and unique for each region of the myocardium, like a fingerprint, known as kernels, and can be tracked relative to each other during the cardiac cycle (see Figure 4).
Section A: Speckle tracking echocardiography

Right ventricle ‘centric’ views = focused on RV free wall clarity

Figure 4: Speckle tracking echocardiography: the software tracks groups of speckles known as ‘kernels’ through the cardiac cycle and determines the degree of deformation (or strain)

\[
\text{Strain} = \frac{L - L_0}{L_0} = \frac{7 - 10}{10} \times 100 = -30\%
\]

The main advantages of this method include: angle-independence, sensitivity over a range of RV dysfunction, reproducible and studies using MRI as the reference standards have shown RV free wall strain to be the best predictor of reduced RV function amongst all transthoracic echocardiography RV assessment techniques(19). It is feasible in the ICU setting in 65-85% of patients(8,18) and is a part of standard imaging in patient cohorts such as pulmonary hypertension in the larger units of the world(2). In the critically ill the use of RV free wall strain is limited to a handful of research projects but they suggest, as has been found in other diseases, that speckle tracking describes cardiac dysfunction not recognised by conventional echocardiography(20).

Other parameters described by strain imaging

Strain is the principle parameter reported in RV analysis: RV free wall strain. Other parameters can be described, although are limited to research work and often require analysis on a dedicated work-station.

Strain rate (SR). SR describes the rate of deformation (ie: change in strain over time). It has potential to describe systolic function that is not described by strain and has been described as being less load dependent(5,21).
Section A: Speckle tracking echocardiography

Strain rate early relaxation (SRe). SRe describes the rate of deformation returning to its original position. It is a surrogate for diastolic function, similar to e’ value with Tissue Doppler Imaging (22). Although reference values have not been describe there are studies suggesting SRe can identify ischaemic areas vs viable myocardium (23).

Timing of contraction. A subtle difference exists in timing of peak systolic strain vs post-systolic strain. Peak systolic strain describes maximal deformation before pulmonary valve closure. Post-systolic strain describes deformation that occurs after pulmonary valve closure and is considered ‘ineffective’. Synchronous contraction is all segments reaching peak strain together. Dyssynchrony occurs if there is a significant difference between individual segments reaching peak strain and is also felt to be a marker of ‘ineffective’ contraction (see Figure 5).

Figure 5: Timing of contraction for individual RV free wall segments: (A) Normal RV free wall strain curve with synchronous contraction (all segments reaching peak strain together). (B) Severe RV dysfunction from severe pulmonary hypertension leading to ‘ineffective’ free wall contraction (post systolic shortening after pulmonary valve closure). (C) Dyssynchronous RV free wall contraction: significant difference in timing between earliest segment to reach
peak strain value and final segment to reach peak strain value. PVC = pulmonary valve closure; S = peak systolic strain prior to pulmonary valve closure (ie: effective contraction); PSS = post-systolic strain (ie: ineffective contraction after pulmonary valve closure)

**Displacement and velocity.** Longitudinal displacement of individual segments can be assessed as well as their speed of movement. The utility of these parameters is not certain.

**How to perform RV speckle tracking**

A degree of experience is required to perform speckle tracking analysis. This should include a sound knowledge in conventional echocardiography, for example Level II ability (American Society of Echocardiography): defined as including a minimum of 6 months of echocardiography education involving 300 studies with a wide variety of abnormalities(25). Essentials for performing RV speckle tracking include: ECG tracing for timing, the RV free wall needs to be seen throughout the cardiac cycle and imaging needs to be optimised for frame rate. The challenging part of speckle tracking comes in the post-processing analysis to ensure accurate values are being obtained.

**Imaging.** Reasonable image quality is required with RV centric views from the apical position with ECG monitoring essential for timing in analysis. Images should be optimised for frame rate: single focal zone (at the base of the tricuspid valve), reduced depth and sector width ensuring the RV free wall and tricuspid annuli are seen throughout the cardiac cycle. RV centric views can be obtained by sliding the probe laterally from the apex using the LV as the acoustic window. Care must be taken not to foreshorten the RV. Three cardiac cycles should be obtained and five if with atrial fibrillation.

**Speckle tracking analysis.** Specific training for speckle tracking analysis is required and may include: practice on at least 25 normal studies with images provided to become familiar with the software being used and images required. Then analyse 25 of your own studies, including abnormal RV function with expert supervision and feedback. Further studies are needed in this area to define competence. Each vendor’s software has slightly different
Section A: Speckle tracking echocardiography

methods to perform speckle tracking analysis (see section: ‘Limitations’) but the principles remain the same.

(a) Choose the reference point. End-diastole is conventionally used as the ‘reference’ point[10]. Software systems often choose the peak of the QRS. Use of mitral valve closure or largest diameter of the LV can help to accurate define end-diastole.

(b) Define the regions of interest. Most speckle tracking software is not specifically designed for the RV and analysis ‘borrows’ the apical four chamber view algorithm. There are variations in the ‘automaticity’ of each vendor’s software but each requires that the user define the myocardium to some degree. The aim is to accurately trace the endocardial border: defined as the inner contour of the myocardium, avoiding the trebeculations. Starting typically at the lateral tricuspid annulus, approximately 7-15 points are placed along the endocardium to the medial tricuspid annulus. Tracking of the interventricular septal segments can be ignored for the RV.

Some software does not required epicardial border measurements and some do. The epicardial border is defined as the outer contour of the myocardium, trying to avoid the pericardium. Once the epicardial border has been traced it should seem as if approximately 85% of the myocardium is selected as the endocardial and epicardial tracings sit just inside each of the borders (see Box ‘Pearl 1’).

Pearl 1

Accurate placement of the regions of interest are essential to ensure accurate speckle tracking of the RV

- Epicardial and endocardial borders should sit just inside the boundaries (~85% of endocardium should be highlighted)
- Myocardial trebeculations and pericardium
- Ensure tracings begin and end at the annulus
- Avoid placing regions of interest too low at the annulus, for example including the right atrial wall, values can be artificially low

(c) Making sense of the curves. Learning to assess and understand the curves produced is essential to using this tool and is by far the most challenging part of the process. Strain curves are usually in the negative portion of the graph (due to the speckles coming closer
**Section A: Speckle tracking echocardiography**

together). The exception is if segments are dyskinetic or aneuysmal. Strain rate curves are usually in the negative portion of the graph for systole and in the positive portion of the graph for diastole (see **Figure 6**).

**Figure 6**: Making sense of the speckle tracking curves. (A) Normal RV strain curve; strain is a negative value as is a measure of relative deformation = (L-Lo)/Lo x 100. The speckles come together during systole and return to their staring position at end of diastole. (B) Strain rate curve; strain rate is a measure of change in strain over time, hence it reaches a peak during mid systole, then slows until the segment starts to relax in diastole and a positive deflection is seen as the speckles are separating.

The following steps are an example of how to ensure accurate tracking:

1. Review RV movement before tracking to estimate RV function, it would be unusual to get grossly abnormal strain if RV function is subjectively normal
2. After tracking review the movement of the regions of interests: does it follow the myocardium well? If not, revision is needed for appropriate tracking (see **Case study 1**)
3. Ensure the annulus regions of interest are tracking well as with some vendors this is the ‘anchor’ for analysis
4. Review strain curves, their time to peak and do they concur with what you were seeing?
5. Review strain rate curves, displacement and velocity curves, do they concur with what you were seeing and appear to make sense? NB: this stage of the process may only be possible if you are performing the post-processing analysis at a reporting computer.
Section A: Speckle tracking echocardiography

Once completed it is advisable to repeat the whole process on the same image or on another similar image to check the result. Once proficient in speckle tracking this process does get faster and more efficient and shouldn’t take longer than 5 minutes maximum.

Limitations of RV speckle tracking assessment

It takes a degree of training and experience to perform RV speckle tracking, analyse the images and the time taken to get results is relatively long compared to other parameters. Image quality must be of a relatively high standard to perform RV speckle tracking. The majority of vendors do not have a specific RV analysis package and the apical four chamber view algorithm is used, ignoring the interventricular septum. The relevance of this is not known.

Vendor variability. There is a degree of vendor variability in speckle tracking results. Each vendor has slightly different algorithms for strain analysis: for example, measuring the epicardial speckles vs taking an average of the entire myocardial segment. At this stage there is currently insufficient evidence to favour one way or another. Task forces have been set up by the American Society of Echocardiography (ASE) and the European Society of Echocardiography (ESE) to try and work with industry to help solve this. The basic recommendation at this stage is to use the same software for repeated analysis or if comparing patient groups.

Clinical applications in the critically ill

The use of RV free wall strain is predominantly limited to cardiology patients in the larger centres where it has been shown to be of use in outcome prediction and treatment response in patient cohorts such as pulmonary hypertension(2). However, as the research base grows and normal ranges are validated(16) its use may increase. Currently, in the critically ill it is purely research based and there is a paucity of studies. We will discuss possible areas where this imaging method may show promise.

Severe sepsis. One of the main advantages of speckle tracking analysis is in recognising cardiac dysfunction that is not described by conventional echocardiography. This may result
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in a greater diagnosis of RV dysfunction in the critically ill with severe sepsis or septic shock where it has been suggested that severe RV dysfunction is associated with worse outcomes(8).

Adverse effects of raised pulmonary vascular resistance. Mechanical ventilation with high driving pressures or positive end expiratory pressure, hypoxia, hypercarbia, severe acidosis, inflammatory response (eg: from ARDS) can result in raised pulmonary vascular resistance which can lead to RV dysfunction and eventually cor pulmonale(6). RV free wall strain has been shown to feasible in detecting RV dysfunction imposed by PEEP(26) and has been shown to be more sensitive than some conventional methods analysis(22). This may improve the earlier recognition of RV dysfunction and treatment can be tailored towards a RV protective approach(9).

Acute pulmonary embolism (PE). Speckle tracking has given insight into the RV response to acute pressure overload in PE. Possible mechanisms include apical and mid RV free wall segments deteriorating first and dyssynchrony appearing before RV dilation(27). RV free wall strain may help with prognostication(28), however this is contentious(29).

Advanced heart failure. RV function has a critical role in severe heart failure in determining clinical outcomes and success of treatments such as mechanical device implantation or transplantation. RV free wall strain assessment has been shown to have the best correlation with RV stroke work index in patients with severe heart failure compared to conventional measures(30).

Future applications

Three dimensional strain. 3D echocardiography has recently emerged and is a promising alternative to the single plane imaging of the RV's complex shape. It has shown good reproducibility and correlation with MRI assessment(31). From the 3D images speckle tracking strain assessment can be performed which may provide further insights into the complex movement of the RV.
Summary

Right ventricle strain analysis performed with speckle tracking echocardiography has potential to describe dysfunction that is not recognised by conventional echocardiography. It is angle independent, sensitive and can be performed with standard 2D imaging. It does however take a degree of training, takes longer than other measures to analyse and there is variability depending on vendor used. Its use in the ICU population is limited to a handful of research studies but their results are enticing in describing non-invasively specific RV dysfunction.
References


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Chapter 5: Effect of cardiac surgery on the right ventricle


*joint first authors
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UNDER REVIEW: ‘Heart, Lung & Circulation’ Journal

Minimally invasive vs standard mitral valve repair effect on right ventricular systolic function assessed by echocardiography

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Section A: Speckle tracking echocardiography

Abstract

Background: Right ventricular (RV) dysfunction can occur after cardiac surgery and persist for years. We compared peri-operative RV systolic function in patients undergoing minimally invasive robotic-assisted mitral valve repair (MIMVr) vs standard ‘open’ mitral valve repair (MVr). Speckle tracking (RV free wall strain [RVS]) was used as a sensitive echocardiography method.

Methods: Retrospective analysis, over 3 years, of consecutive patients (n=158) referred to Mayo Clinic (Minnesota, USA). Pre-operative, pre-discharge and 1 year transthoracic echocardiograms were reviewed. A prospective pilot study was performed for sample size estimation. Primary outcome was RV free wall strain (RVS).

Results: RVS declined after surgery in both MIMVr and MVr groups (-22.2±7% to -16.2±6%; -23.5±8% to -13.4±5% respectively, p<0.001 for both) and at 1 year follow up (-18.9±6% and -15.5±5% respectively, p<0.001 vs pre-op values for both). There were smaller reductions in RVS in MIMVr vs MVr group (-6.0% vs -10.3%, p<0.01), which persisted after adjusting for baseline values (RVS treatment effect 1.5%, p=0.007). There was greater recovery in MIMVr vs MVr group at 1 year follow up vs pre-surgery values (-3.4% vs -8.1% respectively, p<0.001, RVS treatment effect 1.7%, p=0.001). Bypass time was higher in the MIMVr group (80min±22 vs 40min±20, p<0.0001). The echo findings remained significant correcting for age, pulmonary pressures and change in ejection fraction.

Conclusions: RV systolic dysfunction assessed by echo is common after mitral valve repair surgery. Deterioration in RV contraction is less pronounced following MIMVr vs MVr and is associated with enhanced RV functional recovery at 1 year, albeit not to pre-operative levels.

Keywords: right ventricle, strain, mitral valve repair, speckle tracking, echocardiography
Section A: Speckle tracking echocardiography

Introduction

Postoperative right ventricular (RV) dysfunction after cardiac surgery has been recognized for more than 30 years[1], however the mechanism, associated factors and significance are not well understood. This reduction in RV systolic function has been reported to persist for months to years following surgery[2] and has been suggested to be a strong independent predictor for long-term mortality[3]. RV dysfunction is also frequent in those undergoing mitral valve repair surgery[4], and this impairment has been shown to subsequently improve, to some degree, in the long term[5]. Minimally invasive, robotic-assisted, mitral valve repair (MIMVr) is becoming increasingly common and offers reduced blood loss, incision infection, arrhythmias and hospital stay[6]. Recent studies suggest a difference in the effect of MIMVr versus standard ‘open’ sternotomy mitral valve repair (MVr) on RV function peri-operatively[7], but this has only been evaluated in relatively small number of patients and the longer term outcomes have not been well described.

Factors discussed in the literature to be associated with post operative RV dysfunction include: hypoperfusion during cold cardioplegic arrest[8], direct exposure of RV to the atmosphere, rapid increase in temperature after bypass, poor network of collaterals, non-venting of venous blood returning to the RV[9], myocardial hypothermia[10] and size or location pericardial opening[11,12] [7]. The degree of reduction in the RV systolic function has been suggested not to be related to whether surgery is done on-pump or off-pump[13] or even on the type of surgery[12]. Pre-operative RV contractile functional reserve may play a role[14]. Several methods have been used to assess RV systolic function peri-operatively in cardiac surgery including: direct placement of conductance catheters[15], pulmonary artery catheters[3,10] and using echocardiography, both transthoracic[2,9] and transoesophageal[11], assessing RV fractional area change (FAC)[16], Tricuspid annular plane systolic excursion (TAPSE)[4], Tissue Doppler Imaging (TDI)[11,12], RV index of myocardial performance (RIMP) or Tei index[9,16], hepatic vein flow patterns and Speckle tracking echocardiography (STE) to analyze both the left[17] and right ventricle[18].

STE has emerged as a technique for quantifying myocardial systolic deformation [known as Strain (S) and Strain Rate (SR)] in a sensitive manner elucidating cardiac dysfunction not recognized by conventional methods[19]. The RV has a preponderance of longitudinal fibers and therefore a greater proportion of contractility of the RV occurs from
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base to apex. Longitudinal STE can act as both a feasible and sensitive quantitative method of RV function assessment (RV free wall longitudinal Strain [RVS] and RV free wall longitudinal Strain Rate [RVSR]), as has been found in pulmonary vascular disease where it trumps all other measures of RV function in the independent prediction of clinical deterioration and mortality and may help guide therapy[20-23]. We sought to compare RV systolic function, assessed by STE, before and after MIMVr versus MVr surgery, perioperatively and at 1 year follow-up.

Materials and Methods

We performed a retrospective analysis of consecutive patients referred for mitral valve repair surgery (both MIMVr and MVr) over a 3-year period at St. Mary’s Hospital, Mayo Clinic, Rochester, MN, USA. Preoperative, post-operative (pre-discharge) and follow up echocardiograms at approximately one year were reviewed. Exclusion criteria were insufficient image quality for STE, and all other types of surgery. Baseline criteria gathered included medical history. A respiratory history was considered significant if patients had less than 75% predicted FEV1, or chronic inhaled or oral bronchodilator or chronic steroid therapy aimed at lung disease. Patients with asthma or seasonal allergies were not considered to have chronic lung disease. A prospective pilot study was performed to estimate sample size (see Appendix A). The project was approved by the Mayo Institutional Review Board (IRB 13-001619). Patients in the retrospective cohort were included with waiver of consent however, patients gave written informed consent to be involved in the prospective pilot study.

Echocardiography.

Echocardiography was performed with commercially available machines used in our echocardiography laboratory, and images were analyzed for routine echocardiographic parameters and RV systolic function by the staff echo-cardiologist on the same day as images were acquired. RV function and dimensions were assessed according to American Society of Echocardiography (ASE) guidelines for assessment of the right heart in adults[24]. RV systolic function parameters included: peak systolic velocity of the lateral Tricuspid annulus (S’), Tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC)
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and RV index of myocardial performance (RIMP) with abnormal levels considered as less than 10cm/s, 16mm, 35% and more than 0.55 respectively. RV peak systolic pulmonary pressures were estimated from peak tricuspid regurgitation velocities, and right atrial pressures were estimated from an interrogation of the inferior vena cava and pulse wave Doppler of the hepatic vein. All patients had colour Doppler and continuous wave Doppler through the right ventricular outflow tract to exclude obstruction. For the prospective study three beat images were taken of the RV optimizing for off-line STE analysis: optimal endocardial border definition, frame rates higher than 50, single focus, narrow sector widths, reduced depth and utilization of off-axis imaging if needed. LV ejection fraction (EF) and lateral and medial mitral valve TDI were measured to estimate LV systolic function.

Speckle Tracking Echocardiography (STE) analysis.

Three beat, DICOM, two-dimensional clips were transferred to a Syngo Velocity Vector Imaging workstation (Siemens Medical Solutions USA Inc., California): a vendor-agnostic, STE software for analysis by SYC, who was adequately trained in STE analysis before commencing the study. The RV endocardium was traced manually with 8-15 points, starting and finishing at the tricuspid annulus, on images that were optimized for STE analysis if available (frame rate >50fps). Once the accuracy of tracking was ensured, displacement, velocity, S and SR curves were assessed sequentially for appropriate correlation, motion, smoothness, time-to-peak and delay. RV values were an average of the three free wall segments. The same cardiac cycle was taken for the S and SR value. Negative strain values indicate myocardium contraction. Positive strain rate values indicate myocardium relaxation/lengthening. Reproducibility of STE imaging was determined in a random 10% patient subgroup with blinded assessment (by S.O and S-Y.C).

Statistical analysis.

A sample size calculation was performed based on data from the prospective pilot study with RVS as the primary outcome: power 0.8, alpha 0.05, difference to detect 1.5%, standard deviation 3; estimated sample size 128 (finally 158 patients were conservatively included). Data are expressed as mean± standard deviation (SD) or median (interquartile range; IQR) for continuous variables. Normality was assessed using the Shapiro-Wilk test. Pre and post operative values are compared using a paired t-test. Comparison of the effect
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of MIMVr vs MVr on RV function was based on analysis of covariance general linear models (ANCOVA) with adjustment made for baseline values. Categorical variables are expressed as number and percentages with comparisons by Pearson’s Chi-square analysis or Fisher’s exact test. Multiple linear regression analysis was used to form an adjusted model for RVS changes around surgery. Relevant parameters were chosen established by baseline characteristic differences and clinically relevant values. All probability values are 2-sided and a value of ≤0.05 was considered significant. Reproducibility was assessed by Bland-Altman analysis (mean difference and standard deviation). Statistical analysis was performed using JMP version 13.0 (SAS Institute Inc., North Carolina).

Results

188 consecutive patients undergoing MIMVr and MVr surgery were assessed at our institution over a 3 year period. Thirty patients (15%) were excluded based on insufficient imaging quality for STE analysis and 158 patients were included in the study (see Figure 1).

![Figure 1: Flow diagram of patient recruitment](image-url)
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Echocardiograms were performed pre-operatively (median time to operation 46.5 days IQR 24-73), post-operatively/pre-discharge (1 patient had missing data, mean time from operation 3 days ±0.9) and at follow up (4 patients missing, mean time from operation 381 days ±88). Pre-operative echocardiography showed similar RV systolic function (based on TV S’ and RVS), LV systolic function (based on EF and cardiac index), the severity of MV and TV regurgitation. However, baseline clinical heterogeneity was evident: patients undergoing minimally invasive surgery were younger, a higher percentage were male, they had slightly larger LV diastolic dimensions and lower echo-based RV systolic pressure estimates on pre-operative echocardiography and, of note, bypass time was longer, however cross-clamp time, operation time, time intubated and day in hospital were all similar (Table 1).
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<td>Respiratory history, n (%)</td>
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| Medical history Pre-surgical echo findings | | |
|-------------------------------------------|-----------------|-----------------|-------------------|-------------------|
| LV diastolic dimension (mm) | 59 ± 5 | 57 ± 5 | 0.05* |
| LV systolic dimension (mm) | 36 ± 4 | 35 ± 5 | 0.59 |
| LV EF (%) | 66 ± 5 | 64 ± 8 | 0.10 |
| LV cardiac index (L/min/m²) | 2.9 ± 0.6 | 3.1 ± 0.5 | 0.18 |
| MV regurg volume (cc by cont eqt) | 82 ± 38 | 72 ± 19 | 0.29 |
| MV regurg volume (cc by PISA) | 84 ± 31 | 75 ± 23 | 0.13 |
| MV ERO (cm² by cont eqt) | 0.52 ± 0.24 | 0.42 ± 0.12 | 0.09 |
| MV ERO (cm² by PISA) | 0.52 ± 0.22 | 0.48 ± 0.19 | 0.24 |
| Echo RV SPAP (mmHg) | 31 ± 8 | 40 ± 17 | 0.0001* |
| Tricuspid regurgitation | | | | |
| None-mild | 97% | 93% | 0.34 |
| Moderate | 3% | 7% | |
| Severe | 0 | 0 | |
| Lateral TV S' (cm/s) | 15 ± 3 | 15 ± 3 | 0.54 |
| RV free wall S (%) | -22 ± 8 | -23 ± 8 | 0.35 |

| Surgical | | |
|----------|-----------------|-----------------|---------|
| Cross clamp time (mins) | 51 (±17) | 49 (±19) | 0.49 |
| Bypass time (mins) | 80 ±22 | 49 ±20 | <0.0001* |
| Operation time (hrs) | 3.4 (±1) | 3.2 (±1) | 0.39 |
| Time intubated (hrs) | 5.5 (±3) | 8.5 (±11) | 0.26 |
| Days in hospital (days) | 4.1 (±2) | 4.4 (±2) | 0.5 |

**Table 1:** Baseline clinical, echocardiography and surgical characteristics of study population
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After surgery, there was a significant reduction in RV systolic function (RVS, RVSR and lateral TV S') in both the MIMVr and MVr groups: RVS -22.2±7% to -16.2±6 and -23.5±8% to -13.4±5% (p<0.001 for both). The RV systolic function improved by the follow-up scan at approximately 1 year in both the MIMVr and MVr groups: RVS -18.9±6% and -15.5±5% (p<0.001 vs pre-op values for both) (Table 2 and Figure 2), although not significantly with lateral TV S' in the MVr group.

<table>
<thead>
<tr>
<th></th>
<th>Minimally invasive mitral valve repair surgery</th>
<th>Sternotomy mitral valve surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-op</td>
<td>Post-op</td>
</tr>
<tr>
<td>RV free wall S (%)</td>
<td>-22.2±7</td>
<td>-16.2±6</td>
</tr>
<tr>
<td>RV free wall SR (°⁻¹)</td>
<td>-1.5±0.6</td>
<td>-0.8±0.4</td>
</tr>
<tr>
<td>Echo RV SPAP (mmHg)</td>
<td>31±8</td>
<td>33±8</td>
</tr>
<tr>
<td>Lateral TV S', (cm/s)</td>
<td>15±3</td>
<td>11±3</td>
</tr>
<tr>
<td>LV diastolic dimension (mm)</td>
<td>59±5</td>
<td>52±5</td>
</tr>
<tr>
<td>LV systolic dimension (mm)</td>
<td>36±4</td>
<td>36±6</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>66±5</td>
<td>56±8</td>
</tr>
<tr>
<td>LV cardiac index, (L/min/m²)</td>
<td>2.9±0.6</td>
<td>3.5±0.7</td>
</tr>
</tbody>
</table>

**Table 2**: Pre-operative, post-operative/pre-discharge and one year follow-up echocardiography results [RV, right ventricle; S, strain; SR, strain rate'; SPAP, systolic pulmonary artery pressure; TV, tricuspid valve; S', systolic motion; LV, left ventricle; EF, ejection fraction]
Figure 2: Retrospective study comparing right ventricular systolic function as assessed by longitudinal free wall systolic strain, pre-mitral valve repair, post-operation (pre-discharge) and at follow-up in patients who underwent robotically assisted minimally invasive mitral valve surgery vs ‘open’ sternotomy surgery. * p value <0.05 for minimally invasive surgery group post-operative vs pre-operative and follow up vs pre-operative; ** p value <0.05 for ‘open’; # p<0.05 comparing change in RV function after surgery between surgical groups, accounting for baseline values (ANCOVA); Box, mean, standard deviation and whiskers are 95% confidence intervals

The change in RVS was not associated with age, sex, baseline LV diastolic dimension, bypass or cross clamp time, change in EF or change in peak systolic pulmonary artery pressures. In keeping with successful mitral valve repair, there was a significant decrease at one year follow-up, in echo derived RV systolic pulmonary artery pressures (31±8mmHg to 26±5mmHg in the MIMVr group and 40±17mmHg to 30±7mmHg in the MVr group, p<0.001
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in both groups), LV diastolic dimensions (59±5mm to 50±4mm in the MIMVr group and 57±5mm to 49±5mm in the MVr group, p<0.001 in both groups) and LV systolic dimensions (36±4mm to 33±4mm in the MIMVr group, and 35±5mm to 33±6mm in the MVr group, p<0.001 in both groups). Also, cardiac index increased after surgery despite a significant reduction in LV EF (66±5% to 56±8% in the MIMVr group and 64±8% to 54±10% in the MVr group, p<0.001 in both groups), however by one year follow up there was a significant improvement in EF from post-operative levels (59±7% and 57±11% respectively, p<0.001 in both groups).

Comparing the extent of these changes seen after surgery (whilst accounting for baseline values), the MIMVr group vs the MVr group had a significantly smaller reduction in RVS post-surgery (-6±1% vs -10.3±8%, with a treatment effect of 1.5%, p<0.01) and at one year follow-up (-3.4±9 vs -8.1±8, with a treatment effect 1.7%, p<0.001) (see Figure 3).

Figure 3: Retrospective analysis study: Mean percentage change in right ventricular free wall systolic strain comparing pre-operative vs post-operative values and pre-operative vs follow-up values.
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A significant difference was also seen in the extent of the change in lateral TV s’ post-surgery (4.4±4 vs 5.9±4, with a treatment effect 1.2cm/s, p<0.01) but significance was lost at 1 year follow up. All other parameters showed a statistically similar degree of change comparing MIMVr vs MVr groups. There was no significant difference in LV size or function parameters between the groups. Using multiple linear regression, the significance of the difference in RVS based on operation type was retained after adjusting for age, change in EF or systolic pulmonary artery pressure (treatment effect 1.2%, p=0.05) (Table 3).

<table>
<thead>
<tr>
<th></th>
<th>Change in pre vs post surgery values</th>
<th>Change in pre vs 1 year follow-up study values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimally invasive MV surgery</td>
<td>Sternotomy MV surgery</td>
</tr>
<tr>
<td>RV free wall S (%)</td>
<td>-6.0 ±9</td>
<td>-10.3 ±8</td>
</tr>
<tr>
<td>RV free wall SR (1)</td>
<td>0.4 ±0.8</td>
<td>0.7 ±0.8</td>
</tr>
<tr>
<td>Echo RV SPAP (mmHg)</td>
<td>2.2 ±10</td>
<td>3.8 ±13</td>
</tr>
<tr>
<td>Lateral TV S’ (cm/s)</td>
<td>4.4 ±4</td>
<td>5.9 ±4</td>
</tr>
<tr>
<td>LV diastolic dimension (mm)</td>
<td>6.3 ±4</td>
<td>6.5 ±5</td>
</tr>
<tr>
<td>LV systolic dimension (mm)</td>
<td>-0.3 ±4</td>
<td>0.1 ±4</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>9.8 ±8</td>
<td>10.5 ±10</td>
</tr>
<tr>
<td>LV cardiac index (L/min/m²)</td>
<td>-0.6 ±0.7</td>
<td>-0.6 ±0.9</td>
</tr>
</tbody>
</table>

Table 3: Comparison of effect of minimally invasive mitral valve surgery vs standard ‘open’ sternotomy mitral valve repair surgery (ANCOVA analysis of treatment effect, adjusting for baseline values)
**Section A: Speckle tracking echocardiography**

Interrater reproducibility by Bland Altman analysis demonstrated good interobserver agreement: mean difference (standard deviation) 0.8% (±5) for pre-operative RVS, 1.0% (±4) for post-operative RVS and 1.0% (±4) follow up studies RVS.

**Discussion**

The principal findings from our study are that RV systolic function assessed by echocardiography is common after mitral valve repair surgery with both minimally invasive and standard ‘open’ sternotomy approaches. However, the deterioration in RV function is less with the minimally invasive approach and there is an improved recovery in RV function at 1 year follow up, albeit not to pre-operative levels. This effect was seen despite a significantly longer bypass time in the MIMVr group. In support of other studies that have reported similar reductions in RV function across different types of operation[12] and on vs off -bypass[11], the reduction in RV strain function was not associated with cross-clamp, bypass, operation time, intubation time, days in hospital or changes in echo derived peak systolic pulmonary artery pressure estimation or LV EF.

Assessing RV systolic function by echocardiography can be challenging due to the complex geometry and retrosternal position wrapped around the LV. Conventional methods of analyzing RV function by transthoracic echocardiography can be insensitive, angle dependent and affected by translational movement which is important given the predominance of longitudinal fibers in the RV resulting in the majority of RV movement occurring from base to apex. STE assessment of the RV appears both sensitive to RV longitudinal function and is angle independent[22]. Indeed, it was the perioperative strain assessment of RV function that displayed the most significant differences.

Our findings help generate hypotheses for potential reasons behind the smaller reduction in RV systolic function after MIMVr compared to ‘open’ MVr. Firstly, there are many differences between the two surgical groups, as can be seen in their baseline heterogeneity: patients undergoing minimally invasive surgery tend to be younger and have less-comorbidities; potentially being younger and healthier may make the RV more resistant to operative insult. Secondly, from the surgical aspect, both size and location of the pericardial incision are different in minimally invasive surgery and there is no full sternotomy, less instrumentation and the pericardium is partially closed after mitral valve
repair in our institution, whereas in the open procedure no pericardial closure is performed. Possibly the size and site of the pericardial incision may alter LV rotational dynamics or RV motility which may change the RV longitudinal function as has been hypothesized in well performed recent studies[7]. Finally, MIMVr has excellent short and long term successes with similar durability to open repair with reported faster extubation, less postoperative pain, bleeding and transfusion as well as shorter intensive care and hospital stay[6] which may reduce reflex pulmonary vasoconstriction and thereby RV afterload. We did not see some of these findings in our study, yet still a significant difference was seen in RV function between the groups.

Our study has a number of limitations. Firstly, it is a single centre study performed in a group of patients undergoing mitral valve surgery with baseline heterogeneity. However, statistical analysis (using ANCOVA) of echo data used baseline values in the assessment to help each subject act as their own control. Secondly, post-procedural echocardiography is often challenging in these patients, particularly those having ‘open’ sternotomy procedures, and some study images were part of a routine assessment and not optimized for off-line STE examination. Thirdly, approximately 15% of patients were excluded from our study for poor quality of images which made STE difficult, this introduces potential selection bias. Fourthly, we did not assess functional status or clinical outcomes in our patients at follow up. Finally, 2D echocardiography itself is potentially a less than ideal method to assess RV function in this group of patients. There is an argument that RV geometric alterations occur with cardiac surgery rather than functional changes[25,26]. However, other studies suggest RV function after cardiac surgery is a strong independent predictor for long-term mortality. Given the mounting body of evidence on the prognostic importance of acute RV failure, further studies investigating the potential for minimally invasive cardiac surgery minimizing RV dysfunction seem warranted, particularly using more robust methods of assessing RV function such as cardiac MRI. The strengths of our study are the relatively large sample volume compared to other single center studies and the near complete follow up data 1 year after surgery which is often hard to obtain.
Conclusions

Our study demonstrates a significant reduction in RV function assessed by echocardiography after mitral valve surgery. Speckle tracking assessed RV function (RV free wall strain and strain rate) showed significantly less deterioration in the minimally invasive surgery group as compared to the standard ‘open’ sternotomy mitral valve surgery group. Furthermore, this reduction in RV systolic function improved to a greater extent in the minimally invasive surgery group compared to the ‘open’ mitral valve surgery group. Our findings generate interesting mechanistic hypotheses for further study into the etiology of these differences: clinical and physiological differences between patients, pericardial closure post mitral valve repair, sternotomy and instrumentation effect, size and location of the pericardial incision. Whether these physiologic differences result in improved clinical outcomes is unknown and remains to be studied.
Section A: Speckle tracking echocardiography

Acknowledgements: The authors would like to thank the Mayo Clinic (Minnesota, USA) echocardiography department sonographers, reporting doctors and personnel for their assistance in acquiring the echocardiography data.

Competing interests: RD is the inventor of a minimally invasive mitral valve repair device with Neochord Inc., and holds a patent and potential royalties as described by their institution. The rest of the authors declared that they have no relevant competing interests.

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Author contribution: SO, S-YC, JP, RS, JO, GC all made substantial contributions to the conception and design of the study. SO, S-YC, RS, JS, RD made substantial contributions to the acquisition and interpretation of data. SO, S-YC, JP, JO, SP, HM, GC made substantial contributions to analysis and interpretation of data. All authors helped draft and revise the manuscript for intellectual content and approved the final version. All authors agree to be accountable for all aspects of the work.

Data sharing: The datasets generated and analysed during this study are available from the corresponding author on reasonable request.
Section A: Speckle tracking echocardiography

Bibliography


**Section A: Speckle tracking echocardiography**

effect of different cardiothoracic operations on echocardiographic right ventricular long axis velocities, and implications for interpretation of post-operative values. Int J Cardiol. 2011 Sep 1.


**Section A: Speckle tracking echocardiography**


Section A: Speckle tracking echocardiography

Appendix A: prospective study

Objective: A prospective study was performed to examine the difference in RV systolic function peri-operatively in mitral valve repair surgery: minimally invasive robotically assisted, mitral valve repair (MIMVr) vs standard ‘open’ sternotomy mitral valve repair (MVr). Data from this pilot study was used to estimate the sample size required for the main study.

Methods: We examined RV systolic and diastolic function in 32 adult patients undergoing mitral valve repair surgery (16 by MIMVr; 16 by MVr) at St Mary’s Hospital, Mayo Clinic, Rochester, Minnesota. Exclusion criteria were insufficient image quality for STE, previous cardiac surgery, supraventricular tachyarrhythmias, congenital heart disease and procedures which directly affect the right ventricle myocardium (eg: tricuspid valve repair) or off-pump surgery. Patients were imaged shortly before surgery and the morning after surgery; if patient was unavailable, attempts were made on consecutive days thereafter.

Transthoracic echocardiography was performed with a Vivid 7 or Vivid 9 echocardiography machine (GE Medical Systems, Wisconsin) by S.O. RV function and dimensions were assessed according to American Society of Echocardiography (ASE) guidelines. RV systolic and diastolic function parameters were included. 3 beat images were taken of the RV optimizing for endocardial border definition and off-line STE analysis: frame rates greater than 40, single focus, narrow sector widths, reduced depth and utilizing off-axis imaging if needed for RV free wall imaging (for example lateral apical placement using LV as an acoustic window).

Speckle Tracking Echocardiography (STE) analysis. 3 beat two-dimensional clips were transferred to a Syngo Velocity Vector Imaging workstation (Siemens Medical Solutions USA Inc., California) for STE analysis. The endocardium was traced manually from the medial annulus with 7-15 points. Once accuracy of tracking was ensured, displacement, velocity, S and SR curves were assessed sequentially for appropriate correlation, motion, smoothness, time-to-peak and delay. RV values were an average of the three free wall segments. The
Section A: Speckle tracking echocardiography

same cardiac cycle was taken for the S and SR value. All images were analyzed twice by S.O. to ensure accuracy of results.

Results: Baseline characteristics are shown in Table 1. Echocardiographic data before and after surgery is shown in table 2.

<table>
<thead>
<tr>
<th>Baseline variable</th>
<th>Minimally invasive mitral valve repair</th>
<th>‘Open’ mitral valve repair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>16 (3 female)</td>
<td>16 (6 female)</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>62 ±7</td>
<td>69±15</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>25 ±5</td>
<td>27 ±6</td>
</tr>
<tr>
<td>Body Surface Area</td>
<td>2 ±0.2</td>
<td>2 ±0.4</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>5 (31%)</td>
<td>8 (50%)</td>
</tr>
<tr>
<td>Coronary disease, n (%)*</td>
<td>1 (6%)</td>
<td>5 (31%)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>3 (19%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)*</td>
<td>1 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory history, n (%)</td>
<td>2 (13%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Surgical characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross clamp time (hrs)*</td>
<td>48 ±12</td>
<td>38 ±16</td>
</tr>
<tr>
<td>Bypass time (hrs)*</td>
<td>66 ±12</td>
<td>46 ±15</td>
</tr>
<tr>
<td>Operation time (hrs)*</td>
<td>3.5 ±0.6</td>
<td>2.6 ±0.6</td>
</tr>
<tr>
<td>Time intubated (hrs)*</td>
<td>5 ±2</td>
<td>9 ±3</td>
</tr>
<tr>
<td>Days in hospital</td>
<td>5 ±2</td>
<td>5 ±1</td>
</tr>
</tbody>
</table>

Table 1: Clinical characteristics and surgical factors. * Significant difference between groups (p<0.05)
## Section A: Speckle tracking echocardiography

<table>
<thead>
<tr>
<th>Operation</th>
<th>Robotically-assisted mitral valve repair (n = 16)</th>
<th>Open mitral valve repair (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echocardiography values</strong> (mean ±SD)</td>
<td><strong>Pre</strong></td>
<td><strong>Post</strong></td>
</tr>
<tr>
<td>RV free wall longitudinal S (%)</td>
<td>-24.7 ±3</td>
<td>-16.5 ±3</td>
</tr>
<tr>
<td>RV free wall longitudinal SR (°)</td>
<td>-1.6 ±0.2</td>
<td>-1.0 ±0.2</td>
</tr>
<tr>
<td>RV free wall longitudinal SRe (°)</td>
<td>1.3 ±0.3</td>
<td>1.0 ±0.3</td>
</tr>
<tr>
<td>Echo RV SPAP (mmHg)</td>
<td>30 ±7</td>
<td>34 ±9</td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>25 ±4</td>
<td>14 ±3</td>
</tr>
<tr>
<td>Lateral TV S’ (m/s)</td>
<td>0.15 ±0.04</td>
<td>0.1 ±0.09</td>
</tr>
<tr>
<td>RV FAC (%)</td>
<td>44 ±6</td>
<td>40 ±9</td>
</tr>
<tr>
<td>RIMP</td>
<td>0.43 ±0.1</td>
<td>0.55 ±0.1</td>
</tr>
<tr>
<td>Tricuspid E:A ratio</td>
<td>1.2 ±0.5</td>
<td>1.3 ±0.4</td>
</tr>
<tr>
<td>Tricuspid E:e’ ratio</td>
<td>3.8 ±2</td>
<td>7.5 ±3</td>
</tr>
<tr>
<td>RA size (cm²)</td>
<td>16 ±3</td>
<td>18 ±3</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>65 ±4</td>
<td>59 ±5</td>
</tr>
<tr>
<td>Lateral MV S’(m/s)</td>
<td>0.11 ±0.02</td>
<td>0.07 ±0.02</td>
</tr>
<tr>
<td>Medial MV S’ (m/s)</td>
<td>0.09 ±0.02</td>
<td>0.06 ±0.01</td>
</tr>
</tbody>
</table>

*Table 2: Pre and Post-operative echocardiographic data*
**Chapter 6: Effect of PEEP on the right ventricle in an animal model**

Effect of positive end-expiratory pressure on porcine right ventricle function assessed by speckle tracking echocardiography

Sam R Orde1,2*, Atta Behfar1, Paul G Stalboerger1, Sergio Barros-Gomes1, Garvan C Kane1 and Jae K Oh1

Abstract
Background: Right ventricle (RV) dysfunction and hypotension can be induced by high levels of positive end-expiratory pressure (PEEP). We sought to determine in an animal model if a novel ultrasound analysis technique: speckle tracking echocardiography (STE), could determine deterioration in RV function induced by PEEP and to compare this to a conventional method of RV analysis: fractional area change (FAC). STE is a sensitive, angle-independent method for describing cardiac deformation ('strain') and is particularly useful in analyzing RV function as has been shown in pulmonary hypertension cohorts.

Methods: Ten pigs, 40-90 kg, anaesthetized, fully mechanically ventilated at 6 ml/kg were subject to step-wise escalating levels of PEEP at two-minute intervals (0, 5, 10, 15, 20, 25 and 30 cmH2O). Intracardiac echocardiography was used to image the RV as transthoracic and transesophageal echocardiography did not give sufficient image quality or flexibility. Off-line STE analysis was performed using Syngo Velocity Vector Imaging (Siemens Medical Solutions Inc, USA). STE systolic parameters are RV free wall strain (RVfwS) and strain rate (RVfwSR) and the diastolic parameter RV free wall strain rate early relaxation (RVfwSRe).

Results: With escalating levels of PEEP there was a clear trend of reduction in STE parameters (RVfwS, RVfwSR, RVfwSRe) and FAC. Significant hypotension (fall in mean arterial blood pressure of 20 mmHg) occurred at approximately PEEP 15 cmH2O. Comparing RVfwS, RVfwSR and RVfwSRe values at different PEEP levels showed a significant difference at PEEP 0 cmH2O vs PEEP 10 cmH2O and above. FAC only showed a significant difference at PEEP 0 cmH2O vs PEEP 20 cmH2O and above. 30% of pigs displayed dyssynchronous RV free wall contraction at the highest PEEP level reached.

Conclusions: STE is a sensitive method for determining RV dysfunction induced by PEEP and deteriorated ahead of a conventional assessment method: FAC. RVfwS decreased to greater extent compared to baseline than FAC, earlier in the PEEP escalation process and showed a significant decrease before there was a clinical relevant decrease in mean arterial blood pressure. Studies in ICU patients using transthoracic echocardiography are warranted to further investigate the most sensitive echocardiography method for detecting RV dysfunction induced by mechanical ventilation.

Keywords: Speckle tracking echocardiography, Right ventricle, Right ventricle strain, PEEP, Mechanical ventilation

Background
Right ventricle (RV) failure in the critically ill is an independent risk factor for mortality in patients with acute lung injury and acute respiratory distress syndrome (ARDS) [1,2]. It can be challenging to treat and requires accurate and early recognition in order to tailor treatment [3,4]. Echocardiography has a crucial role in the diagnosis of RV failure in the ICU [5]. Interpretation can be difficult however, due to the crescentic shape, retrosternal position and the poor correlation between conventional assessment methods, such as fractional area change (FAC) and intrinsic RV contractile dysfunction [6] as well as translational errors with methods such as tricuspid annular plane systolic excursion and tissue Doppler imaging. Speckle tracking echocardiography (STE) has emerged as a relatively novel, angle-independent technique for...
analyzing the grey-scale ultrasound (B mode) images of the heart [7] and can elucidate cardiac dysfunction not seen with conventional echocardiography techniques [8,9]. STE is particularly useful for assessing RV systolic function: RV free wall strain (RV\textsubscript{fwS}) and RV free wall strain rate (RV\textsubscript{fwSR}) which are suggested to be more robust measures of RV contractility than conventional echocardiography methods in diseases such as pulmonary hypertension [10-13].

Positive end expiratory pressure (PEEP) is an integral component of mechanical ventilation in critically ill patients suffering from acute lung injury and ARDS, yet can have negative consequences on cardiac haemodynamics [14]. ‘Open-lung ventilation’ aims to decrease the cyclic opening and closing of small distal airways and atelectatic alveoli which can lead to ventilator-induced lung injury [15,16] through the use of elevated PEEP levels. Cardiac function can be affected by high PEEP levels in several ways including: biventricular reduced venous return and increased right ventricle (RV) afterload, which is poorly tolerated [17] resulting in RV dysfunction, cor pulmonale and acute hypotension [3].

The aim of this study was to perform a step-wise PEEP escalation maneuver in anesthetized, fully mechanically ventilated pigs and to assess their RV function with STE and a conventional echocardiography measure of RV function analysis: FAC. We sought to 1) Determine if STE could describe changes in RV function induced by escalating levels of PEEP; 2) To compare RV\textsubscript{fwS} to a conventional measure of RV function assessment: FAC; and 3) Determine if RV\textsubscript{fwS} or FAC deterioration occurred prior to PEEP induced hypotension (defined as a fall in mean arterial blood pressure [MAP] of 20 mmHg).

Methods
All animal experiments and protocols were approved and carried out according to the guidelines of the Animal Care and Use Committee of the Mayo Clinic (Rochester, MN, USA). In 10 Yorkshire female swine weighing median 45 kg (41.5 to 60.5 interquartile range [IQR]), after overnight fasting, anesthesia was induced with Telazol (5 mg/kg intramuscularly) and Xylazine (2.0 mg/kg intramuscularly). The animals were intubated with a 7 mm internal diameter endotracheal tube, mechanically ventilated by a Datex-Ohmeda 7100 ventilator (GE Healthcare) with volume control mode at tidal volumes of 6 ml/kg, fraction of inspired oxygen (FiO\textsubscript{2}) started at 0.4 aiming for saturations greater than 92%, inspiratory/expiratory ratio of 1:2, end-inspiratory pause of 10%, respiratory rate of 16 breaths per minute and initial PEEP of 0 cmH\textsubscript{2}O. Anesthesia was maintained with inhaled isoflurane 1.0-3.0%. The pigs were placed in a supine position during the entire experiment.

Percutaneous access was achieved through the femoral artery and both femoral veins for monitoring of arterial pressures (9 F sheath), pulmonary artery pressures (831HF75P, Swan-Ganz 7.5 French, Edwards Life-sciences, Irvine, CA) and for the intracardiac echocardiography (ICE) catheter respectively. Correct positioning of the pulmonary artery catheter in the pulmonary artery was confirmed with fluoroscopy (see Figure 1), waveform analysis and by inflation of the catheter balloon. All intravascular catheters were zeroed to the atmosphere. The mid-point of the anterior and posterior chest was considered the reference point. Electrocardiogram and intravascular pressures were monitored continuously.

Due to the mediastinal anatomy of the swine, trans-thoracic and transoesophageal echocardiography did not provide sufficient image quality or flexibility to sufficiently image the RV free wall. We therefore had to use ICE, performed with an 8 French AcuNav ultrasound catheter connected to an Acuson SC2000 ultrasound machine (Siemens Medical USA, Malvern, Pennsylvania) inserted into the right atrium. Imaging was performed by A.B. (who is appropriately trained in this method) and was optimized for maximal frame rate to enable accurate speckle tracking and focused on the RV free wall in the long axis ensuring the tricuspid annulus was visible throughout the cardiac cycle (see Figure 2). The mean (±SD) frame rate was 113 (±13) frames per second.

Once baseline stability was achieved, PEEP was increased in a stepwise manner every 2 minutes from PEEP 0 cmH\textsubscript{2}O to PEEP 30 cmH\textsubscript{2}O in 5 cmH\textsubscript{2}O increments keeping the tidal volumes constant (see Figure 3). Before

![Figure 1 Fluroscopy images of intracardiac echocardiography (ICE), pulmonary artery and arterial catheters used during the study.](image-url)
each increase in PEEP, recordings were made at end-expiration: intracardiac echocardiography clips of 3 seconds, haemodynamic parameters and saturations. Significant hypotension was considered a decrease in MAP of 20 mmHg. The stepwise PEEP maneuver was ceased at PEEP 30 cmH\textsubscript{2}O and PEEP returned to 0 cmH\textsubscript{2}O. The maneuver was ceased earlier if MAP fell below 25 mmHg, heart rate fell below 40 beats per minute or if oxygen saturation fell below 60% and was unresponsive to FiO2 of 1.0.

Two-dimensional ICE images were transferred to a Syngo Velocity Vector Imaging workstation (Siemens Medical USA, Malvern, Pennsylvania). A single best cardiac cycle was chosen to determine FAC by manually tracing the RV endocardium at end-diastole and end-systole: $FAC = (\text{end diastolic area} - \text{end systolic area})/\text{end-diastolic area}$. 

![Figure 2](image1.png) Representative intracardiac echocardiogram (ICE) images of the right ventricle (RV) at end-expiration and end-diastole. (a) PEEP 0 and (b) PEEP 30. Imaging optimized to assess the RV free wall, including the tricuspid annulus throughout the cardiac cycle, maximizing for frame rate to allow for accurate speckle tracking assessment.

![Figure 3](image2.png) Graphical representation of the step-wise escalating PEEP protocol. Indicates timing of recordings made at end-expiration: physiological data and intracardiac echocardiography (ICE) images for post processing analysis.
area) x 100. One to three beat cardiac cycles were chosen for STE analysis. The endocardium was traced manually at end-systole from the medial to lateral annulus with approximately 7–15 points. RV function values are an average of the three free wall segments. Systolic function parameters are measures of deformation or strain: RVfwS and RVfwSR (change in strain/time) and these are negative values: the more negative the value the better the function. Diastolic function is determined by a positive value: RV free wall strain rate early relaxation (RVfwSRe): the speed that deformation returns to the end-diastolic value. Strain and strain rate curves were chosen based on appropriate tracking as well as assessing displacement, velocity, strain and strain rate curves for appropriate motion, smoothness and segment correlation. The same cardiac cycle was chosen for strain and strain rate values. See Figure 4 for examples of strain and strain rate curves at PEEP 0 cmH\textsubscript{2}O and final PEEP value.

To assess for synchrony of RV free wall segment contraction we used a method proposed by Yu et al. [18] to assess for dyssynchrony of the left ventricle. The Time To Peak (TTP) strain value is determined by comparing the time taken from the onset of the QRS to peak strain value for each segment. TTP delay is the time difference between the segments with the smallest TTP compared to segment with the largest (see Figure 4: Maximal PEEP strain curve). The mean of the TTP delay at PEEP 0 cmH\textsubscript{2}O was used as the reference value and 2 standard

![Figure 4 Examples of strain and strain rate curves of the right ventricle free wall segments.](image-url)
deviations was added to this to obtain the 95th percentile value. We then assessed the TTP delay at the highest PEEP level that was reached for each pig. Dyssynchrony was considered if the TTP delay was above the PEEP 0 cmH2O 95th percentile value.

Statistical analysis was performed with JMP version 10 (SAS Institute Inc., North Carolina). Continuous variables are expressed as mean +/- standard deviation (SD) or median with IQR. Repeated measure analysis at various PEEP levels was done with the one-way ANOVA. If a significant difference was found, post-hoc comparisons between the individual PEEP levels was done using Tukey HSD test with Bonferroni correction for p-value. All probability values are 2-sided and a value of ≤0.05 was considered significant, except for multiple comparisons between the different PEEP levels where, according to Bonferroni correction, p < 0.002 was considered significant.

Results

Physiological data are presented in Table 1. In summary: with escalating levels of PEEP there was a trend of a fall in MAP and a rise in mean pulmonary artery pressure (MPAP), however only with MAP were significant differences seen between individual PEEP levels: at 15 cmH2O and higher vs baseline PEEP 0 cmH2O (see Figure 5). Significant hypotension, defined as a decrease in MAP to a level that was reached for each pig. Dyssynchrony was considered if the TTP delay was above the PEEP 0 cmH2O 95th percentile value.

Comparing TTP delay values at PEEP 0 cmH2O vs final PEEP values, 30% of pigs had dyssynchrony of the RV free wall at the highest PEEP level reached, defined as a delay of >108 msec (as determined by mean TTP at PEEP 0 cmH2O + 95% percentile value) between the earliest contracting segment vs the latest contracting segment.

Measurement variability

Blinded interrater variability for STE analysis was assessed by S.G. on a randomly selected pig at all PEEP levels. Bland-Altman analysis demonstrated good intraobserver and interobserver agreement. The interobserver and intraobserver mean difference (± standard error) were respectively: RVfwS -1.1 (±0.5) and -0.6 (±0.6); RVfwSR -0.1 (±0.1) and -0.1 (±0.1); RVfwSRe 0.1 (±0.1) and 0.1 (±0.1).

Discussion

Our study demonstrates a clear trend of deterioration in RV function with escalating PEEP levels assessed with a conventional echocardiographic method, FAC, and with Speckle Tracking Echocardiography (STE), a novel echocardiography technique. Both RV systolic function parameters measured by STE (RVfwS and RVfwSR) and the diastolic function parameter (RVfwSRe) reduced with elevated PEEP levels. A drop of 20 mmHg in the MAP was considered a clinically relevant end-point and this occurred at approximately PEEP 15 cmH2O. FAC only showed a significant deterioration at PEEP level of 20 cmH2O.

Table 1 Physiological data (values expressed as mean ± SD)

<table>
<thead>
<tr>
<th>PEEP (cmH2O)</th>
<th>PEEP 0</th>
<th>PEEP 5</th>
<th>PEEP 10</th>
<th>PEEP 15</th>
<th>PEEP 20</th>
<th>PEEP 25</th>
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<tbody>
<tr>
<td>Heart rate (bpm)</td>
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<tr>
<td>99 ± 13</td>
<td>104 ± 18</td>
<td>113 ± 26</td>
<td>113 ± 27</td>
<td>109 ± 30</td>
<td>83 ± 39</td>
<td>112 ± 36</td>
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<td>Saturation (%)</td>
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<td>96 ± 4</td>
<td>97 ± 4</td>
<td>91 ± 7</td>
<td>78 ± 16</td>
<td>73 ± 29</td>
<td>90 ± 15</td>
<td>74 ± 40</td>
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<tr>
<td>Fraction inspired oxygen (FiO2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0.4 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.8 ± 0.2</td>
<td>0.8 ± 0.2</td>
<td>0.8 ± 0.2</td>
<td>0.8 ± 0.2</td>
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<tr>
<td>Mean Arterial Pressure (mmHg)</td>
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</tr>
<tr>
<td>86 ± 18</td>
<td>73 ± 15</td>
<td>70 ± 21</td>
<td>48 ± 11*</td>
<td>43 ± 19*</td>
<td>38 ± 15*</td>
<td>39 ± 15*</td>
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<tr>
<td>Mean Pulmonary Artery Pressure (mmHg)</td>
<td></td>
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<tr>
<td>18 ± 4</td>
<td>19 ± 5</td>
<td>21 ± 6</td>
<td>21 ± 5</td>
<td>24 ± 5</td>
<td>27 ± 5</td>
<td>30 ± 7</td>
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</tr>
</tbody>
</table>

*indicates significant difference (p < 0.002) compared with PEEP 0 cmH2O.
However STE values of systolic function (RVfwS and RVfwSR) and diastolic function (RVfwSRe) showed significant deterioration earlier in the PEEP escalation process: at PEEP 10 cmH\textsubscript{2}O. No significant difference was seen between either systolic or diastolic parameters at higher PEEP levels suggesting a plateau effect in the degree of RV functional deterioration. Our findings suggest that RV dysfunction induced by PEEP may be identified earlier and with increased sensitivity with STE than by FAC. The effect of PEEP on RV strain has been demonstrated in a study in critically ill patients undergoing a recruitment maneuver [19] indicating the feasibility of this technique in the ICU population.

Echocardiography is an important means of recognizing RV dysfunction induced by mechanical ventilation [6]. Sonographic imaging of the RV can be challenging due to its shape and position and conventional echocardiographic assessment methods are limited by angle-dependence, translational error and often a qualitative approach to analysis. STE is a relatively novel, angle-independent ultrasound imaging technique, which follow groups of grey-scale pixels which create the image of the myocardium (known as ‘kernels’) and tracks their degree of deformation (strain) and rate of deformation (strain rate) as a surrogate for systolic function [7]. Strain is the most commonly utilized STE value clinically, however animal studies have suggested that strain rate may be a more robust measure of myocardial contractility that is less influence by changes in cardiac load and structure and strain may be influenced in particular by afterload [20]. In our study both RVfwS and RVfwSR were both influenced by PEEP to a similar extent. The initial rate of kernels returning to their end-diastolic position (strain rate early relaxation or RVfwSRe) is a surrogate for diastolic function in much the same way as the e’ value with Tissue Doppler Imaging. Although this has not been validated as a clinical reference value at this stage, a small number of animal and clinical studies have shown SRe can identify ischaemic areas and viable myocardium in studies of coronary artery disease [21] where diastolic as well as systolic dysfunction occurs.

Unlike the LV, which contracts in all planes (longitudinally, radially, circumferentially with twist and torsion [22]) the RV contracts predominantly in the longitudinal direction due to the dominance of longitudinal muscle fibers in the RV free wall [23]. This places RV free wall strain, which assesses motion in the longitudinal direction, as a sensitive, quantifiable and importantly a feasible tool for assessing RV function non-invasively. Indeed RV free

![Figure 5](image_url) Change in physiological parameters with escalating PEEP levels. Mean (+/−95% confidence limits). Mean arterial pressure, mean pulmonary artery pressure, oxygen saturation and fractional inspired oxygen vs PEEP.
wall strain has been investigated in pulmonary hyper- tension cohorts and trumps all other echocardiographic methods in predicting both symptom progression and mortality [10,13].

PEEP is an integral part of mechanical ventilation particularly in the critically ill patient with acute lung injury or ARDS. Counteracting alveolar cycling, collapse, derecruitment and to maintain functional residual capacity PEEP aims to reduce hypoxaemia and ventilator-induced lung injury [16]. High levels of PEEP are often recommended in severe ARDS [24] and can affect biventricular function in a variety of complex methods. The exact physiological effects of PEEP on haemodynamics are not entirely elucidated, however RV dysfunction and reduced cardiac output are of serious concern, with cor pulmonale reported in 20-25% of patients with ARDS [2,25] and is associated with significantly higher mortality [1]. The effect of PEEP on the right ventricle depends on the changes in lung volumes and intrathoracic pressure as well as the underlying pathological state and the physiological response of the pulmonary vasculature [17]. PEEP is reported to predominantly affect RV afterload resulting in

Table 2 Conventional echocardiography and speckle tracking echocardiography data (values expressed as mean ± SD)

<table>
<thead>
<tr>
<th>PEEP (cmH₂O)</th>
<th>PEEP 0</th>
<th>PEEP 5</th>
<th>PEEP 10</th>
<th>PEEP 15</th>
<th>PEEP 20</th>
<th>PEEP 25</th>
<th>PEEP 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV EDA (cm²)</td>
<td>11 ± 3</td>
<td>11 ± 2</td>
<td>11 ± 1</td>
<td>10 ± 2</td>
<td>10 ± 1</td>
<td>13 ± 2</td>
<td>13 ± 1</td>
</tr>
<tr>
<td>RV FAC (%)</td>
<td>44 ± 6</td>
<td>42 ± 7</td>
<td>36 ± 6</td>
<td>32 ± 7</td>
<td>26 ± 7</td>
<td>22 ± 4</td>
<td>20 ± 9</td>
</tr>
<tr>
<td>RVfwS (%)</td>
<td>−21.5 ± 3</td>
<td>−18.2 ± 3</td>
<td>−13.7 ± 4*</td>
<td>−11.3 ± 3*</td>
<td>−9.0 ± 4*</td>
<td>−7.8 ± 4*</td>
<td>−6.9 ± 3*</td>
</tr>
<tr>
<td>RVfwSR (−1)</td>
<td>−1.6 ± 0.3</td>
<td>−1.3 ± 0.2</td>
<td>−1.0 ± 0.2*</td>
<td>−0.9 ± 0.2*</td>
<td>−0.8 ± 0.3*</td>
<td>−0.6 ± 0.3*</td>
<td>−0.7 ± 0.2*</td>
</tr>
<tr>
<td>RVfwSRe (−1)</td>
<td>1.7 ± 0.2</td>
<td>1.3 ± 0.3</td>
<td>1.2 ± 0.3*</td>
<td>0.9 ± 0.3*</td>
<td>0.7 ± 0.3*</td>
<td>0.5 ± 0.2*</td>
<td>0.6 ± 0.2*</td>
</tr>
</tbody>
</table>

RV: right ventricle; EDA: end-diastolic area; FAC: fractional area change; RVfwS: right ventricle free wall longitudinal strain; RVfwSR: right ventricle free wall longitudinal free wall strain rate; RVfwSRe: right ventricle free wall longitudinal early strain rate relaxation. NB: RVfwS and RVfwSR are systolic function parameters and are expressed as negative values: the less negative a value, the better the function. RVfwSRe is a diastolic function parameter and expressed as a positive value: the more positive, the better the relaxation function. *indicates significant difference (p < 0.002) compared with PEEP 0 cmH₂O. † indicates significant difference compared with PEEP 5 cmH₂O. ‡ indicates significant difference compared with PEEP 10 cmH₂O.
a reduced RV stroke volume through increased RV outflow impedance in ARDS patients [26,27] and there are reports of increased RV end-diastolic area [25]. This has led to the concept of a 'RV protection' approach to mechanical ventilation in ARDS patients, which limits PEEP and avoids hypercapnic acidosis [28]. STE potentially may provide a method for identifying RV failure induced by PEEP ahead of conventional methods of RV function assessment. This has the potential to allow the physician to direct therapy earlier at protecting the RV [25].

Limitations

STE, as with conventional echocardiography, is limited by adequate image quality. We utilized ICE in order to maximize the imaging quality of the RV free wall as neither transthoracic or transoesophageal echocardiography could reliably be performed to provide sufficient image quality of the RV free wall for STE analysis. This relates to the mediastinal anatomy of the pig model. The use of STE with ICE has not been validated, however STE analysis is angle-independent, was feasible and each pig acted as its own control. The ultrasound equipment is comparable and the only difference is the transducer. Our data should be translatable to echocardiography images acquire by other transducers. However, the need to use ICE prevented many of the standard echocardiography measures of RV function such as TAPSE and Sm by Tissue Doppler Imaging as these values are angle dependent and require apical imaging. FAC was the most plausible method to assess RV function as recommended by ASE guidelines [29]. Tachycardia can also impair the software’s ability to accurately track the speckles of the image, and heart rates greater than 100 were frequently observed particularly during the escalating PEEP process. We performed the step-wise PEEP escalation process in pigs with healthy lungs, pigs with diseased lung and reduced compliance may affect results.

Conclusion

RV dysfunction in the critically ill is known to be associated with poor outcomes and can be induced by mechanical ventilation and PEEP therapy. Speckle tracking echocardiography is a quantifiable, sensitive and feasible angle-independent method for detecting RV dysfunction induced

Table 3 Right ventricle free wall strain segmental data (values are expressed as mean ± SD)

<table>
<thead>
<tr>
<th>PEER (cmH2O)</th>
<th>PEER 0</th>
<th>PEER 5</th>
<th>PEER 10</th>
<th>PEER 15</th>
<th>PEER 20</th>
<th>PEER 25</th>
<th>PEER 25</th>
<th>PEER 30</th>
<th>Mean difference from PEER 0 to final PEER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal segment S(%)</td>
<td>-19.2 ± 4</td>
<td>-15.8 ± 3</td>
<td>-12.3 ± 5</td>
<td>-8.5 ± 4</td>
<td>-9.1 ± 1</td>
<td>-7.4 ± 1</td>
<td>-6.4 ± 1</td>
<td>14.0 ± 1</td>
<td></td>
</tr>
<tr>
<td>Mid segment S(%)</td>
<td>-23.4 ± 4</td>
<td>-19.7 ± 5</td>
<td>-15.1 ± 5</td>
<td>-11.2 ± 4</td>
<td>-8.6 ± 5</td>
<td>-9.3 ± 6</td>
<td>-8.7 ± 5</td>
<td>15.5 ± 2</td>
<td></td>
</tr>
<tr>
<td>Apical segment S(%)</td>
<td>-22.4 ± 4</td>
<td>-19 ± 4</td>
<td>-12.7 ± 5</td>
<td>-13.3 ± 3</td>
<td>-9.3 ± 3</td>
<td>-7.3 ± 3</td>
<td>-7 ± 3</td>
<td>15.2 ± 1</td>
<td></td>
</tr>
<tr>
<td>TTP delay (msec)</td>
<td>50 ± 29</td>
<td>78 ± 58</td>
<td>72 ± 28</td>
<td>69 ± 43</td>
<td>113 ± 61</td>
<td>118 ± 133</td>
<td>86 ± 70</td>
<td>71.3 ± 31</td>
<td></td>
</tr>
</tbody>
</table>

S: strain; TTP delay: time to peak strain delay between segmental values. *indicates significant difference (p < 0.002) compared with PEER 0 cmH2O. **indicates significant difference compared with PEER 5 cmH2O.
by escalating PEEP levels, and may display dysfunction ahead of conventional echocardiographic methods of assessment. The STE software is available on most current high-end machines, and is becoming increasingly available in intensive care units world-wide. Further studies in the ICU population, particularly with acute lung injury and ARDS, using transthoracic imaging are warranted.

**Acknowledgements**

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**Competition interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

SO, AB, PS, GK and JO contributed to study conception and design, preparation and revision of the manuscript and take responsibility for the integrity and accuracy of the data and analysis. SO, SG, AB and PS contributed to data acquisition. SO, AB, SG, GK and JO contributed to analysis and interpretation of the data and revision of the manuscript. All authors read and approved the final manuscript.

**References**

Chapter 7: Effect of PEEP on right ventricle function in patients with ARDS

Moderate and Severe Acute Respiratory Distress Syndrome: Hemodynamic and Cardiac Effects of an Open Lung Strategy With Recruitment Maneuver Analyzed Using Echocardiography

Pablo Mercado, MD1; Julien Maizel, MD, PhD1,2; Loay Kontar, MD1; Marek Nalos, MD, PhD3; Stephen Huang, MD, PhD2; Sam Orde, MD3; Anthony McLean, MD, PhD3; Michel Slama, MD, PhD1,2

Objectives: Open lung ventilation with a recruitment maneuver could be beneficial for acute respiratory distress syndrome patients. However, the increased airway pressures resulting from the recruitment maneuver may induce cardiac dysfunction, limiting the benefit of this maneuver. We analyzed the effect of a recruitment maneuver and decremented positive end-expiratory pressure titration on cardiac function.

Settings: Medical ICU Amiens, France.

Patients: Twenty patients with moderate to severe acute respiratory distress syndrome

Interventions: Patients underwent a stepwise recruitment maneuver with respiratory evaluation and echocardiography assessment of cardiac function including longitudinal strain at baseline, peak positive end-expiratory pressure of recruitment maneuver (positive end-expiratory pressure 40 cm H2O), and at “optimal” positive end-expiratory pressure. The patients were divided into two groups based on change on the PaO2/Fio2 ratio (nonresponders < 50%; responders ≥ 50%).

Measurements and Main Results: At peak positive end-expiratory pressure during the recruitment maneuver, the arterial pressure, cardiac output, left ventricular size decreased and right ventricular size increased. The left ventricular ejection fraction decreased from 60% ± 13% to 48% ± 18% (p = 0.05). Both left and right ventricular global longitudinal strain were impaired (-15.8% ± 4.5% to -11% ± 4.7% and -19% ± 5% to -14% ± 6% [p = 0.05] respectively). Fifty percent of patients were nonresponders and demonstrated a lower hemodynamic tolerance to the recruitment maneuver than responders. Optimal positive end-expiratory pressure was 14 ± 5 cm H2O (vs 11 ± 4 cm H2O at baseline), and PaO2/Fio2 ratio increased from 111 ± 25 to 197 ± 89 mm Hg (p < 0.0001). All hemodynamic variables returned to their baseline value after the recruitment maneuver despite a higher positive end-expiratory pressure.

Conclusions: An open lung strategy with a stepwise recruitment maneuver permitted a higher positive end-expiratory pressure and improved oxygenation without any cardiac impairment. The recruitment maneuver was associated with mild and transient, cardiac dysfunction, with nonresponders demonstrating poorer tolerance. (Crit Care Med 2018; XX:00–00)

Key Words: acute respiratory distress syndrome; echocardiography; hemodynamics; open lung strategy; recruitment maneuver

A napplication of high positive end-expiratory pressure (PEEP) levels is promoted in acute respiratory distress syndrome (ARDS) patients to recruit the lung and improve oxygenation. However, controversy exists concerning both the ideal level of PEEP and on the necessity to perform a recruitment maneuver (RM) (1-4). Large multicenter studies using high PEEP after incremental titration did not demonstrate a survival advantage over low PEEP strategies (1, 2). Our hypothesis is that improvement in respiratory variables induced by high positive end-expiratory pressure (PEEP) is accompanied by a detrimental hemodynamic effect which may counter the beneficial effect of high PEEP after incremental titration (5, 6). A RM requires application of high airway pressures (7–11)
which may induce hemodynamic compromise (12–16) and therefore a strategy that opens the lung and maintains it open but without any detrimental hemodynamic effect would be preferred.

We hypothesize that an open lung ventilation strategy with a RM employing a decremental PEEP titration to determine optimal PEEP could be beneficial and safe for both the heart and lung (7, 8). This could be explained by the fact that compared with a PEEP setting strategy on the inspiratory limb of the volume/pressure (V/P) curve, a PEEP setting on the expiratory limb of the V/P curve obtained after a maximal recruitment strategy would be less injurious in term of hemodynamics. Therefore, we undertook a study to assess simultaneously both the respiratory and cardiac effects of an open lung strategy, including the application of a relatively novel echocardiographic technique (speckle tracking echocardiography to assess longitudinal strain), to diagnose early ventricular systolic dysfunction (17–20).

METHOD
Mechanically ventilated patients with ARDS admitted to the Amiens Medical ICU were included in a prospective study within the first 72 hours after ARDS was recognized. Intravascular volume was optimized for each patient prior to undertaking a RM with decremental PEEP titration (8). During the procedure, cardiac function was evaluated using advanced echocardiography methods, along with lung function testing at baseline, maximal PEEP level of the RM, and within 1 hour after setting the optimal PEEP.

Patients
All patients who were intubated and on mechanical ventilation were included if they fulfilled the criteria for moderate to severe ARDS as per Berlin definition (21). They were all paralyzed (22). Patients gave their informed consent if they improved or consent was provided by their next of kin. We excluded patients less than 18 years old, pregnant women, moribund patients, patients with severe hemodynamic instability, pneumothorax or at high risk of pneumothorax, high intraabdominal pressure, and very poor echogenicity. In order to decrease mechanical complication risk, we performed prior the RM in all patients a CT scan to rule out any anatomical pathology (emphysema) which may increase this risk. As well, hemodynamics and oxygenation of all patients were stable at least during 1 hour before the inclusion, and hypovolemia was excluded or corrected.

RM
Before starting the RM, all patients underwent a passive leg raise (PLR) maneuver to exclude severe hypovolemia (23–26). A stepwise RM was chosen because this approach has been demonstrated to be better hemodynamically tolerated than other recruitment methods (27, 28). The RM commenced by initially applying a PEEP of 25 cm H₂O and a driving pressure (DP) of 15 cm H₂O (8). PEEP was then incrementally increased by 5 cm H₂O every 2 minutes up to 40 cm H₂O (except at 40 cm H₂O step at which duration was between 3 and 4 minutes in order to record echocardiographic images), while keeping a 15 cm H₂O DP. Following the peak PEEP step, a PEEP of 25 cm H₂O and a DP of 15 cm H₂O was applied, followed by a stepwise reduction of PEEP of 2 cm H₂O every 4 minutes. At each step, the oxygen saturation and dynamic respiratory system compliance were recorded. The reduction in PEEP levels was terminated when either oxygen saturation or compliance decreased by more than 2% or by 2 mL/cm H₂O, respectively. Once this lowest step was reached, and reduced oxygenation recognized, the RM was done again (to reopen the lung), and PEEP was then reduced directly to the previous PEEP level preceding the lowest step, designated the optimal PEEP level, that is, this level would be 2 cm H₂O above the lowest step PEEP level (Fig. 1). Respiratory rate (between 20 and 35/min to have lowest PaCO₂) and inspiratory/expiratory ratio (no lower than 1/1.5) were kept similar during the study (supplementary material, Supplemental Digital Content 1, http://links.lww.com/CCM/D663).

Hemodynamic Assessment
Mean arterial pressure (MAP), diastolic arterial
pressure (DAP), systolic arterial pressure (SAP), heart rate (HR), and central venous pressure (CVP) were recorded at baseline, at the peak of the RM and at the optimal PEEP. As proposed by Sutton et al (29), we calculated the coronary perfusion pressure (CPP) index using DAP–CVP, which corresponds to the coronary perfusion gradient between the pressure in the aorta and the pressure into the venous sinus (29).

**Echocardiography**

At baseline, at peak of the first RM and 1 hour after setting the optimal PEEP, transthoracic echocardiography was performed using a Vivid S6 echocardiograph (GE Medical Systems, Milwaukee, WI). We recorded left ventricular (LV) end-diastolic volume and LV end-systolic volume permitting calculation of the LV ejection fraction (LVEF). The LV end-diastolic area (LVEDA) and the right ventricular end-diastolic area (RVEDA) were measured to assess the RVEDA/LVEDA ratio from the four-apical chamber view. Recorded from the same view, using M-mode, were mitral annulus plane systolic excursion (MAPSE) and tricuspid annulus plane systolic excursion (TAPSE). Inferior vena cava maximal and inferior vena cava minimal diameters were measured from the subcostal view. Cardiac output (CO) was calculated from the area of the aortic annulus and stroke volume (SV) from the aortic outflow tract velocity integral using pulsed wave interrogation of the aortic blood flow. A surrogate of LVEF was calculated using the SV/LVEDA ratio. The mitral inflow maximal velocity of E (E) and A (A) wave velocities were measured. Tissue Doppler imaging of both mitral and tricuspid lateral annulus was performed during diastole to obtain early mitral annulus velocity (E′) and late mitral annulus velocity (A′) and also to obtain systolic mitral annulus velocity and systolic velocity of tricuspid annulus (S′tric). Using speckle tracking analysis (EchoPAC Clinical Workstation Software; GE Vingmed Ultrasound AS, Horten, Norway), we assessed LV longitudinal strain (LVLS) and right ventricular free wall longitudinal strain (RVLS) as previously described (17) (Fig. 2). Reproducibility of these measurements were already published by our group (17).

**Respiratory Evaluation**

FiO₂, SaO₂, tidal volume (TV), respiratory rate, PEEP, total dynamic respiratory system compliance (Crs), plateau pressure (PP), and DP were measured. Arterial and central venous blood gas tests were obtained as well.

**Ethic Committee**

The protocol was approved by the Amiens ethic committee, and informed consent obtained from either family or from the patient after clinical recovery.

**Statistics**

All measurements had normal distribution (this was verified using Shapiro-Wilk test) and then were presented as mean ± SD. We programmed to do a subgroup analysis splitting the patients in responders (for whom the PaO₂/FiO₂ [P/F] increased by > 50% after the RM) and nonresponders in whom the P/F ratio increased less than or equal to 50%. Analysis of covariance and t test were performed to analyze the differences between groups with Bonferroni adjustment. All statistical analyses were performed with MedCalc software (Version 12.0.4.0; MedCalc Software, Mariakerke, Belgium) and SigmaPlot software (Version 11.0; Systat Software, San Jose, CA). The threshold for statistical significance was set to p value of less than 0.05.

**RESULTS**

Between January 2015 and May 2016, a total of 24 patients presented with moderate or severe ARDS. Four were excluded based on uninterpretable imaging. The remaining 20 patients (mean age 54 ± 11 yr old) presented with ARDS primarily resulting from pneumonia. Patient’s...
characteristics are presented in the supplementary material (Supplemental Digital Content 1, http://links.lww.com/CCM/D663). Fifteen were in septic shock requiring noradrenaline (0.7 ± 1.17 µg/kg/min) or dobutamine (5 µg/kg/min) infusion to maintain an adequate MAP. The Simplified Acute Physiology Score 2 was 61 ± 13 with an overall in-hospital mortality rate of 55%. Two patients received 500 mL before the RM maneuver following a positive PLR. Neither the infusion rate of catecholamines nor the FiO₂ were altered during the RM.

**RM Effects**

At the maximum PEEP RM step, oxygenation dramatically improved with an increase in P/F (+64%) (Table 1). From baseline to highest PEEP, the TV and Crs significantly decreased. Hemodynamic impairment was observed between these two PEEP levels with a decrease of SAP (–17%; p = 0.009), DAP (–14%; p = 0.01), MAP (–15%; p = 0.08), SV (–19%; p = 0.01), and CO (–20%; p = 0.04) and an increase of CVP. CPP significantly decreased (–37%; p = 0.01) and returned to the baseline value at optimal PEEP (Table 1). The size of the LV significantly decreased, and LV systolic function was impaired as demonstrated by a significant decrease in ejection fraction and MAPSE (Tables 2 and 3). Speckle tracking identified a decrease in LVLS from –15.8% ± 4.5% to –11% ± 4.7% (p < 0.0001) and was similar for the six analyzed segments (Supplemental Fig. 1, Supplemental Digital Content 2, http://links.lww.com/CCM/D664; legend, Supplemental Digital Content 1, http://links.lww.com/CCM/D663). RVEDA and RVEDA/LVEDA significantly increased (Table 2). Right systolic function was reduced as shown by a decrease in both Stric and RVLS (by 23%; p = 0.01 and 26%; p = 0.01), respectively (Supplemental Fig. 1, Supplemental Digital Content 2, http://links.lww.com/CCM/D664; legend, Supplemental Digital Content 1, http://links.lww.com/CCM/D663). Speckle tracking analysis identified worsened strain in all three RV segments.

**TABLE 1. Oxygenation, Respiratory, and Hemodynamic Variables During the Recruitment Maneuver and at the Best Positive End-Expiratory Pressure**

<table>
<thead>
<tr>
<th>Headings</th>
<th>Baseline, Mean ± SD</th>
<th>Recruitment Maneuver, Mean ± SD</th>
<th>Best Positive End-Expiratory Pressure, Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>FiO₂ (%)</td>
<td>79±20</td>
<td>85±19</td>
<td>82±21</td>
</tr>
<tr>
<td>Tidal volume (mL)</td>
<td>377±61</td>
<td>228±98a</td>
<td>409±116a</td>
</tr>
<tr>
<td>Respiratory rate (/min)</td>
<td>27±5</td>
<td>28±5</td>
<td>27±5</td>
</tr>
<tr>
<td>Positive end-expiratory pressure (cm H₂O)</td>
<td>11±3</td>
<td>39±2b</td>
<td>14±5a</td>
</tr>
<tr>
<td>Plateau pressure (cm H₂O)</td>
<td>27±6</td>
<td>54±1a</td>
<td>29±6a</td>
</tr>
<tr>
<td>Driving pressure (cm H₂O)</td>
<td>16±5</td>
<td>15±0.5</td>
<td>15±2</td>
</tr>
<tr>
<td>Respiratory system compliance (mL/cm H₂O)</td>
<td>29±11</td>
<td>15±6a</td>
<td>31±16a</td>
</tr>
<tr>
<td>Pao₂ (mm H₂O)</td>
<td>86±27</td>
<td>159±105a</td>
<td>162±96a</td>
</tr>
<tr>
<td>Paco₂ (mm Hg)</td>
<td>47±13</td>
<td>62±17a</td>
<td>53±19</td>
</tr>
<tr>
<td>pH</td>
<td>7.3±0.09</td>
<td>7.21±0.09a</td>
<td>7.26±0.11</td>
</tr>
<tr>
<td>O₂ saturation (%)</td>
<td>93±4</td>
<td>95±6</td>
<td>96±4a</td>
</tr>
<tr>
<td>Pao₂/ FiO₂</td>
<td>111±25</td>
<td>182±99a</td>
<td>197±89a</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>80±11</td>
<td>68±16a</td>
<td>81±13a</td>
</tr>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>115±15</td>
<td>95±33a</td>
<td>119±20a</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mm Hg)</td>
<td>63±11</td>
<td>54±11a</td>
<td>64±11a</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>92±12</td>
<td>92±11</td>
<td>97±15</td>
</tr>
<tr>
<td>Central venous pressure (mm Hg)</td>
<td>15±7</td>
<td>22±5a</td>
<td>15±5a</td>
</tr>
<tr>
<td>Central venous O₂ saturation (mm Hg)</td>
<td>76±9</td>
<td>78±3</td>
<td>86±8a</td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td>62±17</td>
<td>48±21a</td>
<td>62±19a</td>
</tr>
<tr>
<td>Cardiac output (L/mn)</td>
<td>5.8±2</td>
<td>4.6±2.3</td>
<td>5.9±2a</td>
</tr>
<tr>
<td>Coronary perfusion pressure (mm Hg)</td>
<td>46±16</td>
<td>29±10a</td>
<td>47±8a</td>
</tr>
</tbody>
</table>

*p < 0.05 vs baseline.

*p < 0.05 vs recruitment maneuver.

n = 20 for all variables.
Optimal PEEP

The optimal PEEP was set at 14 ± 5 cm H₂O (vs 11 ± 4 cm H₂O at baseline) (Table 1). All hemodynamic values returned to the baseline level except the mixed venous oxygen saturation, which increased significantly (Table 1). Left and right ventricular (RV) function variables were identical to baseline levels despite the PEEP increasing by 27% (Table 2).

Responders/Nonresponders

All baseline values were identical between responders (n = 10) and nonresponders (n = 10) except for RVEDA/LVEDA which was slightly higher in nonresponders than in responders and CPP, SAP, and DAP lower (supplementary material, Supplemental Digital Content 1, http://links.lww.com/CCM/D663). At the peak PEEP of the RM, DAP, MAP, CPP, SV, SV/LVEDA, and RVLS were significantly lower in nonresponders than in responders (supplementary material, Supplemental Digital Content 1, http://links.lww.com/CCM/D663). Crs decreased significantly more in nonresponders than in responders as did SV/LVEDA, SV, CO, E', A', E, apical LV longitudinal strain, and medial RV longitudinal strain (supplementary material, Supplemental Digital Content 1, http://links.lww.com/CCM/D663). At optimal PEEP, P/F, oxygen saturation, PaO₂, pH, HR, and CVP were significantly higher in the responder group than in nonresponders, whereas CPP, SV, SV/LVEDA, A, TAPSE were lower (supplementary material, Supplemental Digital Content 1, http://links.lww.com/CCM/D663). In both the responder and nonresponder groups, all the hemodynamic values, LV and RV sizes, and functions returned to baseline values, even though the PEEP was set at 13 cm H₂O in responders and at 15 cm H₂O in nonresponders (Supplemental Tables 1-4, Supplemental Digital Content 4, http://links.lww.com/CCM/D666).

Complications

There were no discernable complications requiring intervention in any patient during the RM (chest radiograph and

### TABLE 2. Left and Right Cardiac Function During the Recruitment Maneuver and at the Best Positive End-Expiratory Pressure

<table>
<thead>
<tr>
<th>Headings</th>
<th>Baseline, Mean ± SD</th>
<th>Recruitment Maneuver, Mean ± SD</th>
<th>Best Positive End-Expiratory Pressure, Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular end-diastolic volume (mL)</td>
<td>90 ± 28</td>
<td>62 ± 27&lt;sup&gt;a&lt;/sup&gt;</td>
<td>81 ± 30&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Left ventricular end-systolic volume (mL)</td>
<td>37 ± 19</td>
<td>32 ± 21&lt;sup&gt;a&lt;/sup&gt;</td>
<td>35 ± 24</td>
</tr>
<tr>
<td>LVEDA (cm&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>30 ± 7</td>
<td>25 ± 6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>29 ± 6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>60 ± 13</td>
<td>48 ± 18&lt;sup&gt;a&lt;/sup&gt;</td>
<td>62 ± 15&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stroke volume/LVEDA</td>
<td>2.16 ± 0.87</td>
<td>1.99 ± 0.69&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.11 ± 0.62</td>
</tr>
<tr>
<td>Mitral annular plane systolic excursion (cm)</td>
<td>1.42 ± 0.6</td>
<td>1.04 ± 0.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.36 ± 0.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>E (m/s)</td>
<td>0.82 ± 0.21</td>
<td>0.66 ± 0.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.85 ± 0.21&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>A (m/s)</td>
<td>0.64 ± 0.17</td>
<td>0.58 ± 0.19</td>
<td>0.65 ± 0.19&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>E' (m/s)</td>
<td>0.1 ± 0.04</td>
<td>0.09 ± 0.04</td>
<td>0.1 ± 0.04</td>
</tr>
<tr>
<td>Late mitral annulus velocity (m/s)</td>
<td>0.12 ± 0.05</td>
<td>0.1 ± 0.05</td>
<td>0.11 ± 0.04</td>
</tr>
<tr>
<td>E/A</td>
<td>1.3 ± 0.4</td>
<td>1.2 ± 0.05</td>
<td>1.3 ± 0.4</td>
</tr>
<tr>
<td>E/E'</td>
<td>10.3 ± 5.5</td>
<td>7.5 ± 3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9.6 ± 4.9&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Systolic mitral annulus velocity (m/s)</td>
<td>0.12 ± 0.05</td>
<td>0.11 ± 0.05</td>
<td>0.12 ± 0.05</td>
</tr>
<tr>
<td>Left ventricular longitudinal strain (%)</td>
<td>-15.8 ± 4.5</td>
<td>-11 ± 4.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-16.4 ± 5.6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>RVEDA (cm&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>1.8 ± 4</td>
<td>2.1 ± 5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.8 ± 4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tricuspid annular systolic excursion (cm)</td>
<td>1.93 ± 0.6</td>
<td>1.51 ± 0.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.9 ± 0.5&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>RVEDA/LVEDA</td>
<td>0.6 ± 0.12</td>
<td>0.86 ± 0.14&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.59 ± 0.13&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Systolic velocity of tricuspid annulus (m/s)</td>
<td>0.13 ± 0.03</td>
<td>0.1 ± 0.04&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.13 ± 0.04&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Inferior vena cava (cm)</td>
<td>2.2 ± 0.5</td>
<td>2.2 ± 0.6</td>
<td>2.2 ± 0.5</td>
</tr>
<tr>
<td>Right ventricular free wall longitudinal strain (%)</td>
<td>-19.5 ± 14 ± 6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-19 ± 6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-19 ± 6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

A = late mitral flow velocity, E = early mitral flow velocity, E' = early mitral annulus velocity, LVEDA = left ventricular end-diastolic area, RVEDA = right ventricular end-diastolic area.

<sup>a</sup>p < 0.05 vs baseline.

<sup>b</sup>p < 0.05 vs recruitment maneuver.

n = 20 for all variables except for right ventricular free wall longitudinal strain. n = 14.
ultrasound examination were systematically performed in order to find a pneumothorax). In four patients (two in the responder and two in the nonresponder group), the RM was stopped at the PEEP of 35 cm H₂O step because of hemodynamic intolerance when the MAP dropped to less than 50 mm Hg on applying a PEEP of 40 cm H₂O (MAP).

DISCUSSION
This study demonstrates that in patients with moderate to severe ARDS, a slow stepwise RM is associated with oxygenation improvement as already demonstrated (3, 30) and transient and reversible right and left cardiac dysfunction. Furthermore, setting a higher PEEP after this RM dramatically improved both oxygenation and lung function without any deterioration in either LV or RV function.

The hemodynamic effects of high PEEP and high PP during RMs have been analyzed using invasive right catherterization, but little information is available concerning cardiac function analyzed using an imaging technique and no data using speckle tracking (31, 32). Although hemodynamic alterations occur, this impairment reverses rapidly after inflation is terminated (31–33). The observed hemodynamic effects resulting from a RM are explained by either a decrease of RV preload and or increase of RV afterload (34–47).

By increasing mediastinal pressure, a high airway pressure reduces transmural pressure of the right atrium and of the superior vena cava, thereby reducing both right atrial and RV preload, with a subsequent reduction in CO. This effect is more pronounced in patients with a low preload or hypovolemia than in normovolemia as previously demonstrated (12).

Another mechanism leading to RV dilatation, dysfunction, and acute cor pulmonale (ACP) is by the high transpulmonary pressure induced by increased airway pressure causing collapse of pulmonary capillaries, thereby increasing RV afterload (16, 18, 19, 48). This effect is particularly observed in patients with previous RV dysfunction or dilation due to the ARDS and/or sepsis.

Although it can be concluded that assessment of fluid status, RV size, and function is critical prior to undertaking any RM (45), it remains unanswered as to whether a fluid infusion in ARDS patients without right heart dysfunction would limit any detrimental effect of high pressure on RV preload, by increasing CO and by decreasing pulmonary resistance via opening pulmonary capillaries, as described by Fougères et al (49). Conversely, in the presence of ACP or RV dysfunction, fluid infusion should be avoided as it may cause a deleterious effect on the RV function (50).

In our study, we used speckle tracking echocardiography, a new and accurate way to assess myocardial systolic function via

| TABLE 3. Difference Between Baseline and Recruitment Maneuver (Δ) and Between Baseline and Best Positive End-Expiratory Pressure (Δ) in Responders and Nonresponders |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| **Headings Baseline vs Recruitment Maneuver (%)** | **Responders, Mean ± SD** | **Nonresponders, Mean ± SD** | **p** |
| Δ Left ventricular end-systolic volume | −31 ± 18 | 7 ± 37 | 0.0006 |
| Δ Early peak velocity of mitral annulus | 1 ± 25 | −33 ± 27 | 0.002 |
| Δ Late peak velocity of mitral annulus | −3 ± 28 | −33 ± 30 | 0.02 |
| Δ Early peak velocity of mitral flow | −12 ± 13 | −24 ± 17 | 0.04 |
| Δ SV | −20 ± 12 | −32 ± 16 | 0.05 |
| Δ Cardiac output | −15 ± 18 | −33 ± 18 | 0.03 |
| Δ Crs | −43 ± 12 | −53 ± 8 | 0.02 |
| Δ Apical left ventricular longitudinal stress | 5 | 30 | 0.05 |
| Δ Right ventricular longitudinal strain med | −26 | −52 | 0.05 |
| Δ SV/LVEDA | 8 ± 23 | −16 ± 18 | 0.02 |

<table>
<thead>
<tr>
<th><strong>Headings Baseline vs Best Positive End-Expiratory Pressure (%)</strong></th>
<th><strong>Responders, Mean ± SD</strong></th>
<th><strong>Nonresponders, Mean ± SD</strong></th>
<th><strong>p</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ Plateau pressure</td>
<td>1 ± 19</td>
<td>19 ± 27</td>
<td>0.05</td>
</tr>
<tr>
<td>Δ Crs</td>
<td>20 ± 26</td>
<td>−4 ± 22</td>
<td>0.02</td>
</tr>
<tr>
<td>Δ Pao₂</td>
<td>153 ± 74</td>
<td>22 ± 19</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Δ O₂ saturation</td>
<td>6 ± 4</td>
<td>2 ± 4</td>
<td>0.03</td>
</tr>
<tr>
<td>Δ Pao₂/Fio₂</td>
<td>143 ± 66</td>
<td>18 ± 22</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Δ SV/LVEDA</td>
<td>14 ± 19</td>
<td>−6 ± 21</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Δ = difference in percentage between best positive end-expiratory pressure and baseline, Crs = total respiratory compliance system, LVEDA = left ventricular end-diastolic area, SV = stroke volume.
a variable known as “strain” (51). We demonstrated using this technique that longitudinal LV strain was significantly altered during the RM. This was associated with decreased LVEF and MAPSE. This LV systolic dysfunction may play a role in the hemodynamic deterioration during the RM. To explore the cause of this dysfunction, we calculated the CPP which grossly represents the difference of the pressure between the coronary artery and the coronary sinus which is an index of coronary perfusion (29). The CPP dramatically decreased during the RM, and the combination of a low MAP and RV overload may induce myocardial ischemia (and/or a myocardial redistribution), explaining in part the observed myocardial dysfunction (52, 53).

At baseline, the PEEP was set at 11 cm H₂O by the attending intensivist. Following the RM, the PEEP was titrated to 14 cm H₂O. Despite this significant PEEP increase, all variables at 14 cm H₂O were like those at 11 cm H₂O. In contrast with our study, other studies have demonstrated that high PEEP may be hemodynamically deleterious by decreasing RV preload as well as increasing RV afterload (18, 19). One of the reasons could be that PEEP was personalized in our study in contrast with other studies in which PEEP was set arbitrarily. Our hypothesis to explain these differences is that the effect of PEEP on the RV is different after incremental PEEP setting compared with when the PEEP is settled after a RM. In the former, applying a high PEEP leads to an alveolar overdistension of the “baby lung” which may squeeze pulmonary capillaries inducing pulmonary hypertension and RV dysfunction. In the latter, the RM opens the lung resulting in the same pressure being distributed to the entire lung without overdistension, avoiding any compression of pulmonary capillaries.

Following the example of Grasso et al (34), our patients were divided into two groups, RM responders and nonresponders. At baseline, nonresponders had a slight higher RV/LV ratio than responders and lower SAP and CPP. A RM was tolerated less well hemodynamically by nonresponders than by responders. This was associated with more pronounced deterioration of the Crs. We submit therefore that in nonresponders, the RM only slightly opened the collapsed lung, inducing higher overdistension with more deleterious effects on cardiac function, compared with responders in whom the lung was opened much more. This instability together with higher RV wall tension and low CPP may reduce the coronary flow more in nonresponders (52, 53). Then, caution should be taken when a RM is performed in ARDS patients high RVEDA/LVEDA.

Limitations

Our study suffers several limitations. First, the study was monocentric and included a small number of patients. Second, our population was heterogeneous, mixing different anatomic-clinical type of ARDS. Mortality rate was as high as 55%; this is due to severe ill patients included in our study with many having immune depression due to lymphoma, leukemia, or cirrhosis. Third, despite increasing the P/F ratio and the total compliance respiratory system, we did not independently evaluate the actual proportion of lung opened by our mechanical ventilation strategy. We expected to have no change or deterioration of the P/F ratio during the RM due to a decreased V/Q ratio, and this was a surprise to have an increased P/F ratio. One explanation is that the decreased V/Q was lower than expected due to a high pulmonary capillary pressure and to a beneficial effect of lung units opening. Fourth, this study analyzed the effect of high PEEP only 1 hour after the RM, and long-term cardiovascular effects were not assessed. Fifth, we did not have any patients with severe ischemic disease, and uncertainty still exists as to whether a RM would induce LV systolic dysfunction in this group of patients. Sixth, lung and chest wall elastance were not assessed to investigate any relationship with cardiac changes during the RM.

Conclusions

In this study, we demonstrated that a slow stepwise RM improves oxygenation and lung function with only mild and transient detrimental hemodynamic and cardiac effects identified. These detrimental effects were completely reversed after the maneuver. Despite the optimal PEEP being higher than baseline PEEP, after the RM, there was improved oxygenation and lung function in the absence of any hemodynamic or cardiac alterations particularly in responder patients. In summary, an open lung strategy achieved by a slow stepwise RM appears to be beneficial for the lung while not resulting in negative effects on the heart.

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Chapter 8: Subjective analysis of the right ventricle in the critically ill

Subjective right ventricle assessment by echo qualified intensive care specialists: assessing agreement with objective measures

Sam Orde1*, Michel Slama2, Konstantin Yastrebov3, Anthony Mclean1, Stephen Huang1 and on behalf of the College of Intensive Care Medicine of Australia and New Zealand [CICM] Ultrasound Special Interest Group [USIG]

Abstract

Background: Right ventricle (RV) size and function assessment by echocardiography (echo) is a standard tool in the ICU. Frequently subjective assessment is performed, and guidelines suggest its utility in adequately trained clinicians. We aimed to compare subjective (visual) assessment of RV size and function by ICU physicians, with advanced qualifications in echocardiography, vs objective measurements.

Methods: ICU specialists with a qualification in advanced echocardiography reviewed 2D echo clips from critically ill patients on mechanical ventilation with PaO2:FiO2 < 300. Subjective assessments of RV size and function were made independently using a three-class categorical scale. Agreement (B-score) and bias (p-value) were analysed using objective echo measurements. RV size assessment included RV end-diastolic area (EDA) and diameters. RV function assessment included fractional area change, S′, TAPSE and RV free wall strain. Binary and ordinal analysis was performed.

Results: Fifty-two clinicians reviewed 2D images from 80 patients. Fair agreement was seen with objective measures vs binary assessment of RV size (RV EDA 0.26 [p < 0.001], RV dimensions 0.29 [p = 0.06]) and function (RV free wall strain 0.27 [p < 0.001], TAPSE 0.27 [p < 0.001], S′ 0.29 [p < 0.001], FAC 0.31 [p = 0.16]). However, ordinal data analysis showed poor agreement with RV dimensions (0.11 [p = 0.06]) and RV free wall strain (0.14 [p = 0.16]). If one-step disagreement was allowed, agreement was good (RV dimensions 0.6 [p = 0.06], RV free wall strain 0.6 [p = 0.16]). Significant overestimation of severity of abnormalities was seen with subjective assessment vs RV EDA, TAPSE, S′ and fractional area change.

Conclusion: Subjective (visual) assessment of RV size and function, by ICU specialists trained in advanced echo, can be fairly reliable for the initial exclusion of significant RV pathology. It seems prudent to avoid subjective RV assessment in isolation.

Keywords: Right ventricle, Subjective assessment, Speckle tracking, Critically ill, ICU
Background

The importance of the right ventricle (RV) in the management of critically ill patients is increasingly recognised [1]. RV dilation and dysfunction are common in the ICU and are associated with worse outcomes in disease states such as ARDS, septic shock and heart failure [2–5]. Echocardiography (echo) plays a crucial role in RV assessment for both diagnosis and monitoring and is an essential tool for the management of these patients in the ICU [1]. The use of echo in the critical care environment is increasing around the world [6] as is research in this area [7]. Echo is well known to be user dependent both in image acquisition and analysis [8]. Leading national echocardiography society guidelines suggest to examine the heart from multiple acoustic windows with overall assessment to be based on subjective assessment in addition to quantitative parameters [9]. Subjective assessment (‘eyeballing’) of the RV is rapid and remains a common method used clinically [10] especially in the ICU. However, the accuracy, inter-observer and intra-observer concordance is not well described, particularly for critical care physicians.

The RV is not always easy to image with ultrasound. It has a crescentic shape, wrapped around the left ventricle with a retrosternal position. There are numerous methods available to measure RV size and function, yet the parameter that is the most accurate in the critically ill is controversial. With regard to RV size, basal, mid and longitudinal dimensions (in the apical four-chamber view) have been validated as well as the end-diastolic area (again from the apical four-chamber view) [9]. However, it is worth noting that these reference values are based on published data obtained from normal adults without any history of heart or pulmonary disease. Multiple measures are also used for the assessment of RV function, including TAPSE (tricuspid annular plane systolic excursion), fractional area change (FAC) and S’ (systolic velocity on tissue Doppler imaging) and the relatively novel and sensitive parameter RVfwS (assessed by speckle tracking).

We sought to compare subjective RV size and function assessment by intensive care specialists with qualifications in critical care echo (CCE) vs quantitative RV echo measurements (using RVfwS as the primary reference method) in critically ill patients. We hypothesised that there would be fair to good agreement.

Methods

Fifty-two currently practising intensive care specialists with a qualification in advanced echocardiography were invited to review, offline and in a blinded fashion, a selection of 2D echo clips of 80 critically ill patients. Participants were asked to subjectively estimate RV size and function based on the following categories: normal, mild/moderate or severely abnormal (see Additional file 1: Appendix 1 for data sheet), which were deemed clinically relevant by the authors. A presentation was provided to the clinicians consisting of 80 slides, one per patient, with three to five video clips on each slide (depending on echo windows available) (see Additional file 2: Appendix 2 for example). All images were obtained from patients at a single-centre, tertiary hospital. Participants were instructed to review in their own time. There was no clinical data provided for individual patients, only the general inclusion criteria.

An intensive care specialist was defined as a clinician who is a Fellow of the College of Intensive Care Medicine (CICM) of Australia and New Zealand, or who had passed their final exams and were in their ‘fellowship’ (final) year of training. Advanced and expert levels of training in CCE were defined in accordance with recommendations on levels of training in CCE by the CICM Ultrasound Special Interest Group (USIG) [11]. The definition of the expert level of training included CCE experience in excess of 7 years of practice; thus, this period was used in sub-group analysis.

The project was approved by the Nepean Blue Mountains Local Health District (LNR/13/NEPEAN/154). Imaging of patients was performed after written consent being provided prospectively by the authorised representative (next of kin) or retrospectively by the patient (deemed reasonable given echo being considered standard of care in our unit and the non-invasive nature of the imaging).

Patients

Inclusion criteria for critically ill patients imaged included adult (>18 years), mechanically ventilated (pressure support or mandatory ventilation) with a ‘significant’ ventilation-perfusion (VQ) mismatch defined as a PaO2:FiO2 ratio < 300. Non-consecutive patients were imaged within 24 h of admission when S.O. was able to review and consent patients. Exclusion criteria included pregnant women, congenital heart disease, previous cardiac surgery, patients undergoing palliative treatment or having inadequate echo imaging to be able to perform STE and assess RVfwS.

Echocardiography

Transthoracic echocardiography images were acquired by S.O. or experienced sonographers (all highly trained and fully qualified in comprehensive critical care echo) using either a Vivid 7 machine (GE Medical systems, Chicago, USA) using a M4S probe, or a Siemens SC2000 using a 4V1c transducer (Siemens Healthineers, Erlangen, Germany). A standard comprehensive study was performed which included conventional 2D (or B-mode images) as per current American Society of Heart Failure, 2019; (AJF) 32(4): 761–767. doi:10.1223/HFPJ.0000000000006020
Echocardiography (ASE) guidelines [9]. In addition, non-standard ‘RV centric’ views optimised for speckle tracking were obtained: three cardiac cycles in sinus rhythm, five in atrial fibrillation, reduced depth and width, frame rate > 50 fps, single focal point and ensuring the RV free wall endocardium was seen throughout the cardiac cycle.

RV dilation was defined by RV long axis greater than 83 mm, RV mid-diameter greater than 35 mm and RV basal diameter greater than 42 mm [9] with categorical data based on two dimensions being abnormal defining mild/moderate dilation and all three dimensions being abnormal defining severe. Categorical RV end-diastolic area (RV EDA) definitions included < 29 cm² being normal, 29–38 cm² being mild/moderately dilated and greater than 38 cm² being severely dilated [12]. RV function by STE was defined as RVfwS more negative than –21% being normal, between –13 and –21% being mild/moderately abnormal and less negative than –13% being severely abnormal. These values have been used in previous studies in critically ill patients [3], normal subjects [13] and pulmonary hypertension patients [14]. TAPSE categorical data was defined as normal greater than 16 mm [9], mild/moderate dysfunction 10–16 mm and severe dysfunction less than 10 mm [15]. Fractional area change and S' were assessed in a binary fashion as per ASE guidelines: cut-off of 35% and 9.5 cm/s² respectively as no published categorical data for severity was found.

Speckle-tracking echocardiography (STE)

RVfwS was assessed by speckle-tracking echocardiography (STE): a relatively novel method increasingly used in critical care echo, however, primarily from a research perspective at this stage. STE is a post-processing software (i.e. a computer program analyses the echo images once they are stored) that tracks the movement of the speckles that make up the myocardium (known as ‘kernels’) throughout the cardiac cycle [16] to determine the ‘strain’ parameter. Systolic strain values are negative, indicating degree of deformation. The more negative a value, the greater the degree of deformation and the greater the systolic function. Although RV systolic function can be assessed by both free wall and ventricular septal strain analysis, using only strain of the free wall (RVfwS) is preferred and has been shown to be sensitive [17], have superior prognostic characteristics over conventional parameters in pulmonary hypertension cohorts [14] and be feasible in the critically ill [18].

The 2D digital clip (3 cycles for sinus rhythm, 5 for atrial fibrillation) RV-centric, apical four-chamber views were transferred to a TomTec system for STE analysis (TomTec Imaging, Edisonstrasse, Germany). STE analysis was performed by S.O (experienced in this form of evaluation) in a manner as previously described [3, 19]. RV-centric views were analysed initially, but if they were unable to be used, then apical four-chamber views were assessed. All three RV free wall segments had to be viewed throughout at least one cardiac cycle and tracking sufficient for a patient to be included. If STE was not able to be performed with either of these views, then the patient was excluded. The endocardium was traced manually, at end-systole, starting at the lateral tricuspid annulus with 7–15 points, finishing at the medial annulus. Drift correction was included in tracking. Only the free wall segments were considered as per guidelines [9]. Once accuracy of tracking was assured, the displacement, velocity, strain and strain rate curves were then assessed for smoothness of fit, dysynchrony, time to peak and correlation. If curves were not acceptable, then tracking was repeated. The same cardiac cycle was chosen for STE values if the patient was in sinus rhythm, but averages were taken if in atrial fibrillation. The digital clips used were analysed three times to ensure consistency of results and the final result chosen was based on the curves with the best smoothness of fit. A 15% random population was assessed for inter-rater (M.S) variability for RVfwS.

Statistical analysis
A sample size of 50 clinicians reviewing 80 cases was calculated using estimates from previous published data [20] as well as an estimated contingency table based on the presumed spread of normal vs mild/moderate vs severe RV dysfunction that we would see (see Additional file 1: Appendix 3). A power of 80% and significance of 0.05 was considered acceptable for the power calculation. Statistical analysis was performed with JMP Pro version 13 (SAS Institute Inc., Cary, NC, USA). Continuous variables are expressed as mean ± standard deviation (SD) if normally distributed and median with interquartile range (IQR) if not normally distributed. Normality was assessed using the Shapiro-Wilk test. Categorical variables are expressed as the number and percentage with comparisons by Pearson’s chi-square analysis or Fisher’s exact test. P values < 0.05 are considered statistically significant. Ordinal categorical analysis (normal vs mild/moderate vs severe) as well as binary analysis (normal vs abnormal) was attempted. Cohen’s kappa and Bangdiwala’s B-statistic were used as a measure of concordance. B-score interpretation was considered poor less than 0.25, fair 0.25 to 0.49, good 0.5 to 0.74, excellent 0.75 to 0.99 and perfect 1. Bias was assessed by Mann-Whitney-Wilcoxon test for marginal distribution. Agreement charts were used to provide a visual impression of the data (an excellent review article on these charts is suggested [21]). Agreement is determined by the size of the box. Black indicates concordance, grey indicates one adjacent level of agreement (e.g. ‘normal’ chosen when quantifiable result ‘mild/moderate’).
The direction of observer bias is reviewed by examining the ‘path of the rectangles’ and how it deviates from the diagonal line (of no bias). Further analysis was done accounting for (a) those with more than 7 years of echo experience (arbitrary level required for ‘significant’ experience in CCE by the CICM USIG), (b) those who felt they practised at a level of a cardiologist and (c) those with DDU vs other qualifications. Intra-rater variability was assessed in eight assessors, who reviewed the same images twice at separate times determined by the assessor. This was analysed by intra-class correlation coefficient.

Results
Fifty-two intensive care specialists reviewed images from the 80 patients (30–120 min reported as time taken to complete study by candidates). An attempt was made to obtain images from apical, parasternal and subcostal windows in all study participants. Screened patients were excluded, when apical views were insufficient for quantification by investigators or when both subcostal and parasternal views were deemed to be of insufficient quality for subjective assessment (see flow diagram in Fig. 1). Feasibility of performing RVfwS in our patient population was 79%. Eighty patients were included: 54% male, median age 68 years (IQR 59 to 73); 91% in sinus rhythm; median P:F ratio 174 (IQR 132 to 208); median PEEP 10 (7 to 12); mean APACHE III 80.5 (± 26); and median time on ventilator 6 days (3 to 9). The right ventricle size and function is displayed in Table 1. Of note, more patients were diagnosed with RV dilation when RV diameters were measured vs end-diastolic area (41% vs 26% respectively [p < 0.001]). No significant difference was seen comparing RVfwS vs $S$’ ([p < 0.01]); RVfwS vs TAPSE (p < 0.001) and $S$’ vs TAPSE (26% and 23% respectively [p < 0.001]). RVfwS defined more patients with severe dysfunction vs TAPSE (18% vs 5% respectively [p < 0.001]).

The characteristics of the intensive care specialist participants are shown in Table 2. Those participating had considerable clinical (median 4.5 yrs, as a specialist) as well as echo experience (median 7 years). The most common echo qualification held by those participating in the study was the DDU (27 of the 52 involved in the study). Table 3 shows the agreement and bias seen with subjective RV size and function assessment. Agreement was fair for binary (normal vs abnormal) assessment of RV size (subjective vs RV EDA = 0.26 [p < 0.001]; vs RV dimensions 0.29 [p = 0.06]) as well as for RV function assessment (subjective vs RVfwS = 0.27 [p = 0.35]; TAPSE = 0.27 [p < 0.001]; vs $S$’ = 0.29 [p < 0.001]). FAC = 0.31 [p < 0.001]) (see Additional file 1: Appendix 4 for agreement plots based on binary data for subjective RV size and function assessment). Agreement was also fair when assessment was for some ordinal data (normal, mild/moderate, severe) for RV size assessment (subjective vs RV EDA = 0.26 [p < 0.001] and RV function assessment (subjective vs TAPSE = 0.28 [p < 0.001]). In regard to ordinal data, if one-step disagreement was allowed for (weighted agreement B-score), good agreement was seen for RV size assessment (subjective vs RV EDA = 0.62 [p < 0.001]; vs RV dimension = 0.59 [p = 0.06]) and RV function assessment (subjective vs RVfwS = 0.60 [p = 0.16]; TAPSE = 0.65 [p < 0.001]) (see Figs. 2 and 3 for agreement plots of subjective RV size and function assessment respectively based on ordinal data). Poor agreement was seen in unweighted ordinal data for subjective assessment vs RV dimension (0.11

![Study flow diagram and echo windows obtained in those included](image-url)
Large positive bias (overestimating severity) was seen in the agreement of RV size when assessed by RV EDA (in both ordinal and binary data) and in RV function when assessed by TAPSE and RV $S'$ in binary data. A small negative (underestimating) bias in assessing RV function was seen when FAC was used as comparator (Additional file 1: Appendix 4).

Using RVfwS and RV dimensions as the reference methods, there was no significant difference seen in agreement when accounting for those with less than more than 7 years of echo experience (see Additional file 1: Appendix 5), whether the participant felt they practised at level of cardiologist (see Additional file 1: Appendix 6) or those with DDU qualification vs others (see Additional file 1: Appendix 7). Fair to excellent correlation was seen in intra-rater agreement of RV size and good to excellent correlation in RV function assessment when they repeated their evaluation (see Fig. 4).

Blinded inter-rater variability for STE analysis was performed on a random 15% of the population (by M.S. and S.O): Bland Altman analysis demonstrated good interrater agreement with mean difference (± standard deviation) 1.1 (± 4.9).

## Discussion

We compared subjective (visual) RV size and function assessment with objective echocardiography measures in 80 critically ill patients by 52 intensive care specialists with qualifications in advanced echocardiography. To our knowledge, this is the largest and most robust analysis of subjective RV assessment vs objective measures performed, particularly in the critically ill. We found fair agreement by clinicians in assessing whether RV size and function was normal vs abnormal compared to conventional echo parameters, as well as the relatively novel and sensitive parameter RVfwS (assessed by speckle tracking). If the categorical data could be assessed in an ordinal manner (normal, mild/moderate, severe), with one-step disagreement allowed, then good agreement was seen. Poor agreement was seen when comparing subjective RV function assessment with RVfwS when unweighted (i.e. concordant) analysis was required. These degrees of agreement remained when accounting for whether or not the clinician had ‘significant’ echocardiography experience (more than 7 years at advanced level), if they felt they practise echo at the level of a cardiologist or for different qualifications.

Subjective assessment was also found to have significantly overestimated severity of RV dilation and dysfunction compared to quantification of RV EDA, TAPSE, $S'$ and RV fractional area change. Interestingly, no bias was seen when compared with RVfwS, which could potentially be due to STE identifying more abnormalities than conventional parameters. This finding is reaffirmed in other critical care echo studies assessing RVfwS [3]. Raters may be relying more on the change in area and wall motion function in subjective RV function assessment as evident from the reduced bias in results with

### Table 1 Right ventricle size and function echocardiography data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (IQR or ±SD)</th>
<th>% patients with abnormal values (n, %)</th>
<th>Categorical data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>End-diastolic area (cm$^2$)</td>
<td>24.2 (18 to 30)</td>
<td>21 (26%)</td>
<td>59 (74%)</td>
</tr>
<tr>
<td>Long axis (mm)</td>
<td>80.8 (± 10)</td>
<td>33 (41%)</td>
<td>27 (34%)</td>
</tr>
<tr>
<td>Mid diameter</td>
<td>31.7 (± 7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal diameter</td>
<td>40.6 (± 8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV size</td>
<td>Fractional area change (%)</td>
<td>32.5 (± 11)</td>
<td>51 (64%)</td>
</tr>
<tr>
<td>RV $S'$</td>
<td>11.3 (± 3)</td>
<td>20 (26%)</td>
<td></td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>18.9 (16 to 21)</td>
<td>18 (23%)</td>
<td>62 (78%)</td>
</tr>
<tr>
<td>RV free wall Strain</td>
<td>– 19.6 (± 6)</td>
<td>46 (58%)</td>
<td>34 (43%)</td>
</tr>
</tbody>
</table>

IQR interquartile range when describing non-normally distributed data, SD standard deviation when describing normally distributed data, RV right ventricle, $S'$ systolic motion

[p < 0.06]) and RVfwS (0.14 [p = 0.16]). Large positive bias (overestimating severity) was seen in the agreement of RV size when assessed by RV EDA (in both ordinal and binary data) and in RV function when assessed by TAPSE and RV $S'$ in binary data. A small negative (underestimating) bias in assessing RV function was seen when FAC was used as comparator (Additional file 1: Appendix 4).

Using RVfwS and RV dimensions as the reference methods, there was no significant difference seen in agreement when accounting for those with less than more than 7 years of echo experience (see Additional file 1: Appendix 5), whether the participant felt they practised at level of cardiologist (see Additional file 1: Appendix 5) or those with DDU qualification vs others (see Additional file 1: Appendix 7). Fair to excellent correlation was seen in intra-rater agreement of RV size and good to excellent correlation in RV function assessment when they repeated their evaluation (see Fig. 4).

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### Table 2 Intensive care specialist characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Values (IQR or %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years performing CCE (years)</td>
<td>7 (5 to 11)</td>
</tr>
<tr>
<td>Approximate number of TTE performed per year (n)</td>
<td>100 (63 to 200)</td>
</tr>
<tr>
<td>Self-reporting performance of CCE at level of cardiologist (%)</td>
<td>40 (77%)</td>
</tr>
<tr>
<td>Years practising as ICU specialist (years)</td>
<td>4.5 (2 to 10)</td>
</tr>
</tbody>
</table>

IQR interquartile range when describing non-normally distributed data, CCE critical care echocardiography
RVfwS and FAC agreement plots. Although there was only fair agreement, the magnitude and direction were fairly consistent with FAC and RVfwS.

We are not aware of any other studies in CCE assessing subjective vs objective analysis of RV or LV size and function, despite how often this is performed. Cardiology previously addressed LV assessment in a study by Blondheim et al. [22] demonstrating reasonable coefficient of variation and a study by McGowan et al. [23], demonstrating good intra- and inter-observer variability of LV visual quantification by echo. However, the applicability to the ICU population is not known. In the critical care setting, echocardiography is the mainstay of bedside assessment of RV function [1]. Although MRI remains the gold standard for RV assessment outside ICU, it is currently not routinely used in the critically ill. Subjective assessment of the RV is quick and simple and is frequently performed by ICU clinicians and cardiologists. RVfwS has been suggested to be the most sensitive echo parameter to quantitatively describe RV dysfunction [24]. It is now recommended that detailed quantification of the RV should be performed using multi-plane set of images, and include RVfwS [25].

### Table 3 Agreement and bias of subjective assessment of RV size and function by Australasian intensive care specialists with advanced and expert level of training in critical care echocardiography

<table>
<thead>
<tr>
<th>Data type</th>
<th>Parameter</th>
<th>Agreement (B-score)</th>
<th>Bias (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Unweighted</td>
<td>Weighted*</td>
</tr>
<tr>
<td>RV size</td>
<td>Binary RV end-diastolic area</td>
<td>0.26</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>RV dimensions</td>
<td>0.29</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Ordinal RV end-diastolic area</td>
<td>0.26</td>
<td>0.6234</td>
</tr>
<tr>
<td></td>
<td>RV dimensions</td>
<td>0.11</td>
<td>0.5870</td>
</tr>
<tr>
<td>RV function</td>
<td>Binary RV free wall strain</td>
<td>0.27</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>TAPSE</td>
<td>0.27</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>S’</td>
<td>0.29</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Ordinal Fractional area change</td>
<td>0.31</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>RV free wall strain</td>
<td>0.14</td>
<td>0.5999</td>
</tr>
<tr>
<td></td>
<td>TAPSE</td>
<td>0.28</td>
<td>0.6499</td>
</tr>
</tbody>
</table>

Interpretation of B-score: poor < 0.25, fair 0.25–0.49, good 0.5–0.75, excellent 0.75 to 0.99 and perfect 1.00

*Weighted agreement allowed for one-step disagreement

---

**Fig. 2** Agreement plot (also called Bangdiwala’s observer agreement chart) of subjective (visual) RV size assessment vs right ventricle end-diastolic area and right ventricle dimensions; please see the ‘Methods’ section or reference [21] for the description of interpretation if needed.
Previous studies assessing the LV using global longitudinal strain demonstrated association with mortality in critically ill patients with sepsis and septic shock, the finding absent using traditional echo quantification of LV\(^26\). Is it possible that subjective RV assessment might be recognising dysfunction not recognised by the standard quantitative parameters and therefore could be used for prognostications in some groups of critically ill? The fair agreement between subjective and objective RV assessment identified in our study suggests that visual assessment could be acceptable for initial rapid and crude bedside qualification of RV size and function by critical care physicians with sufficient level of CCE training. Such approach would be useful, for example, in rapid differentiation of shock. In addition, the intra-rater correlation of subjective assessment of RV size and function was very good in more than 80% of the selected sample, suggesting very good consistency of subjective RV rating performed by advanced and expert level CCE users. However, monitoring of RV function during titration of pharmacological and mechanical interventions requires significantly finer level assessment, thus rendering fair level of agreement insufficient. Therefore for the time being, quantitative RV echocardiographic assessment remains the pragmatic reference standard for ICU bedside RV monitoring and detection of subtle changes.

Further studies in this area may consider which RV measure of size and function is actually the most accurate in the critically ill where RV dysfunction appears to be common. It is likely that cardiac MRI studies still may be needed for this. In addition, as multi-centre studies are being performed using echo as the imaging tool, investigating the agreement between critical care physicians performing the studies and acquiring the data would be extremely interesting and valuable.

**Limitations**

The study suffers from several limitations. No clinical context was supplied to the doctors who performed the assessment, only the inclusion criteria to image the patients. This makes analysis different from genuine assessment in the clinical environment which may have an effect. Objective echo analysis was done predominantly by a single user (S.O) including strain analysis, and this may be a factor in terms of feasibility in larger studies. Finally, it is not known which single quantitative parameter describes RV size or function best in the critically ill. TAPSE or \(S'\) represent a surrogate of global RV performance and thus cannot be used in isolation. Arguably, the most sensitive measure of RV function is RVfwS, hence why this was chosen as the primary outcome. However, using RVfwS in this regard limited inclusion of patients who could have suitable imaging (RV centric apical view) with a feasibility of 79%, suggesting possible selection bias. The strength of our study is the relatively large sample size, both in number of clinicians as well as patients participating in the analysis.
Conclusions
Subjective (visual) assessment of the RV size and function can be fairly reliably used in the critical care setting for initial exclusion of significant RV pathology, when performed by intensivists with advanced and expert CCE level of training. Monitoring of RV size and function or detection of fine abnormalities requires quantitative assessment.

Additional files

**Additional file 1:** Appendix 1. Answer sheet for right ventricle (RV) size and function by subjective assessment. To be filled out by intensive care specialists or fellows with at least one qualification in advanced echocardiography. 2D echo images from 80 patients to be reviewed assessing RV size and function as normal, mild/moderately impaired, and severely impaired. Appendix 3. Contingency table used for sample size estimation based on possible agreement. Appendix 4. Agreement chart (Bangdiwala’s observer agreement chart) for binary data (normal vs abnormal) on right ventricle subjective size and function assessment. Please see the ‘Methods’ section or reference [21] for the description of interpretation if needed. Appendix 5. Agreement chart (Bangdiwala’s observer agreement chart) for categorical data (normal, mild/moderately impaired, severely impaired) for right ventricle subjective size and function assessment based on level of echo experience (less or more than 7 years). Appendix 6. Agreement chart (Bangdiwala’s observer agreement chart) for categorical data (normal, mild/moderately impaired, severely impaired) for right ventricle subjective size and function assessment based on participant qualification (DDU vs other). Appendix 7. Agreement chart (Bangdiwala’s observer agreement chart) for categorical data (normal, mild/moderately impaired, severely impaired) for right ventricle subjective size and function assessment based on participant that they practised at level of cardiologist.

Additional file 2: Appendix 2. Example of 2D echo images to be reviewed in order to assess subjectively right ventricle size and function.

Abbreviations
ASE: American society of echocardiography; CCE: Critical care echocardiography; CICM: College of Intensive Care Medicine of Australia and New Zealand; DDU: Diploma of diagnostic ultrasound; Echo: Echocardiography; EDA: End-diastolic area; FAC: Fractional area change; IQR: Interquartile range; RV: Right ventricle; RVfwS: Right ventricle free wall strain; S′: Systolic velocity on tissue Doppler imaging; SD: Standard deviation; STE: Speckle-tracking echocardiography; TAPSE: Tricuspid annular plane systolic excursion; USIG: Ultrasound Special Interest Group

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Fig. 4 Intra-rater agreement in right ventricle size and function assessment

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Availability of data and materials
The datasets generated and analysed during this study are available from the corresponding author on reasonable request.

Authors’ contributions
SO conceived and designed the study, acquired the data and performed the majority of the echocardiograms, analysis of the data and preparation of the manuscript. MS assisted with the data analysis and interpretation and drafting of the manuscript. AM and SY assisted with the study design, data acquisition and drafting of the manuscript. SH assisted with study design, statistical analysis and drafting of the manuscript. All authors drafted and reviewed the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study was approved by the Nepean Blue Mountains Local Health District Ethics approval and consent to participate manuscript. All authors read and approved the final manuscript.

SO assisted with study design, statistical analysis of the manuscript. SH assisted with design, data acquisition and drafting of the manuscript.

Consent for publication
Consent for use of de-identified images contained in this article was given by the authorized representatives (next of kin) or retrospectively by the patient (LNR/13/NEPEAN/154) and written consent was provided prospectively by the patient given the non-invasive nature of the imaging.

Competing interests
The authors declare that they have no competing interests.

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References
SECTION B:

3D TRANSTHORACIC ECHOCARDIOGRAPHY
Section B: 3D transthoracic echocardiography

Section overview

This section is comprised of 1 manuscript published in a peer reviewed journal: Critical Care.

Chapter 9: Feasibility of 3D transthoracic echocardiography in the critically ill


Assessing ventricular size and function is the foundation for diagnosis of cardiac dysfunction in the critically ill. 3D transthoracic echocardiography (3D TTE) for biventricular volume assessment is semi-automatic and can potentially be time saving, reproducible and provide a great deal of data in a single image acquisition. It is suggested to be accurate vs MRI as a reference standard. We sought to assess the feasibility of performing this imaging technique in the critically ill and compared it to conventional parameters (Eg: Doppler assessed stroke volume) which are suggested to be accurate in the critically ill.
Section B: 3D transthoracic echocardiography

Chapter 9: Feasibility of transthoracic 3D echocardiography in the critically ill

Feasibility of biventricular 3D transthoracic echocardiography in the critically ill and comparison with conventional parameters

Sam Orde1,2*, Michel Slama3, Nicola Stanley4, Stephen Huang1 and Anthony Mclean1

Abstract

Background: Transthoracic 3D cardiac analysis is enticing in its potential simplicity and wealth of data available. It has been suggested to be accurate vs magnetic resonance imaging in relatively stable patients, but feasibility and agreement with conventional echocardiographic assessment of stroke volume (SV) have not been thoroughly assessed in critically ill patients, who are traditionally harder to image. The objectives of this study were to compare 3D transthoracic volumetric analysis vs Doppler assessment of SV (which is suggested to be accurate in the critically ill) and Simpson's biplane assessment in a cohort typical of the intensive care unit (ICU), where accurate assessment is important: mechanically ventilated patients with a significant ventilation/perfusion (V/Q) mismatch. We hypothesised that it would be feasible but might lack agreement.

Methods: Patients were imaged within 24 hours of admission. Inclusion criteria were adult patients, V/Q mismatch present (defined as a ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300), and mechanically ventilated with Doppler SV assessment possible. Biventricular echocardiographic volumetric analysis was performed using Siemens SC2000 along with standard Simpson's biplane and Doppler SV assessment. 3D images were unacceptable if two segments or more were unable to be seen in two volumetric planes. 3D left ventricular (3DLV) and 3D right ventricular (3DRV) analyses were performed with the Tomtec Imaging and Siemens Acuson platforms, respectively.

Results: Ninety-two patients were included (83 in sinus, 9 in atrial fibrillation). 3DLV and 3DRV analyses were feasible in 72% and 55% of patients, respectively; however, they underestimated SV compared with Doppler by 2.6 ml (± 10.4) and 4.1 ml (± 15.4), respectively. Limits of agreement for 2D, 3DLV and 3DRV volumetric analysis techniques were large.

Conclusions: 3DLV and 3DRV volumetric analyses appear feasible (obtainable) in the majority of mechanically ventilated ICU patients. Compared with the Doppler method, 3DLV and 3DRV volumetric analyses underestimate SV. The large limits of agreement between the methods also cast doubt on their comparability. Given the scenarios in which SV analysis is required (e.g., assessment of cardiac performance), our study cautions against the use of 3D SV clinically.

Keywords: 3D, Echocardiography, Stroke volume, Critically ill, ICU

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Background
Assessing ventricular size and function is the foundation for the diagnosis of cardiac dysfunction in the critically ill. Stroke volume (SV), end-diastolic volume (EDV), end-systolic volume (ESV) and ejection fraction (EF) are important when considering management in many circumstances, such as heart failure, fluid administration and effect of treatment. SV and cardiac output estimation using Doppler echocardiography (echo) has been suggested to have sufficient precision to be able to estimate cardiac output in the critically ill [1, 2], and although it is far from perfect, it is a standard method of assessment in many intensive care units (ICUs). Echo technology is advancing, and techniques such as 3D echo are now available which can potentially hold some benefits over conventional echo methods and provide additional data that may be important (e.g., strain, twist and torsion). 3D echo has been suggested to be time-saving, reproducible and accurate vs magnetic resonance imaging (MRI) [1]. This has not been reliably assessed in the critically ill.

3D transthoracic echo has been a feature of most major ultrasound systems since 2008, being used for valvular analysis and volumetric and left ventricular (LV) mass estimation [2]. 3D left ventricular (3DLV) volumetric analysis with echocardiography is touted as more accurate than 2D echo volumetric estimation (using MRI as the gold standard) [3], and structures can be seen in the context of the whole myocardial volume rather than a single plane (see Fig. 1). EF, for example, can be hindered by foreshortening, malrotation or assumptions about ventricular shape, which may lead to inaccuracies. In addition, it is much more automated and may therefore provide rapid image analysis without additional human error or bias and has been shown to be repeatable in the cardiology setting [3].

3D volumetric measurements by echo were originally made by acquiring images over multiple heartbeats, obtaining the full-volume image through stitching together the data. More recently real-time 3D echo has been developed, which allows for the full volume to be recorded in one beat and prevents stitching artefacts, which can occur with respiratory movement or with arrhythmias such as atrial fibrillation. This can be particularly attractive in imaging the critically ill because breath holds can be challenging and arrhythmias are common. With real-time 3D transthoracic echo, there is reduced temporal and spatial resolution [4], and there is a need for specialised knowledge and equipment and importantly dependency on image quality.

We sought to assess if SV obtained by different methods, namely pulsed-wave Doppler, Simpson’s bi-plane and 3D echocardiography, is comparable and to assess if 3DLV and 3D right ventricular (3DRV) echo are feasible in an ICU population who were mechanically ventilated. We assumed that the SV of the LV would equal the SV of the right ventricle (RV). We chose a cohort of patients who would be considered typical ICU patients in whom volumetric analysis was important: mechanically ventilated critically ill patients with a significant ventilation/perfusion (V/Q) mismatch (defined by ratio of arterial oxygen partial pressure to fractional inspired oxygen [P/F], < 300).

Methods
Adult patients admitted to the ICU of Nepean Hospital, Sydney, Australia, over an 18-month period were considered in this study. The project was approved by the Nepean Blue Mountains Local Health District (LNR/13/NEPEAN/154), and written consent was provided prospectively by the authorised representatives (next of kin) or retrospectively by the patient, given the non-invasive nature of the imaging. Patients were included if they were over the age of 18 years, were mechanically ventilated with a P/F ratio < 300 and were able to have SV assessed by Doppler echo. Patients were excluded if they had intracardiac shunts, previous cardiac surgery or congenital heart disease or were pregnant. We did not include consecutive patients, because SO was the sole investigator performing the 3D analysis and the majority of 2D studies (see Fig. 2 for study flowchart).

Standard echocardiography
2D transthoracic echocardiography was performed by SO or research sonographers (all highly trained, fully...
qualified sonographers) using either a Vivid 7 machine (GE Medical systems, Chicago, IL, USA) with an M45 probe or a Siemens SC2000 with a 4V1c transducer (Siemens Healthineers, Erlangen, Germany). Accurate SV was ensured by estimating the left ventricular outflow tract (LVOT) diameter in a zoomed view of the LVOT and averaging LVOT velocity time integral measures with pulsed-wave Doppler (three cycles were averaged for patients in sinus rhythm and five for those in atrial fibrillation), with a closing click present and ensuring optimal Doppler angle and Doppler trace [5]. An LV centric apical four- and two-chamber view with minimised depth and optimal focal points was used to accurately estimate EF and volumes by Simpson’s biplane.

### 3D echocardiography

Real-time 3DLV and 3DRV assessment was performed using the 4Z1c full-volume 1.5–3.5-MHz matrix array transducer on the SC2000 echo machine by an experienced 3D operator (SO). The apical view was used, with the ventricle being analysed placed in the middle of the sector and the depth, sector size and angle adjusted to ensure maximal volumes per second (minimum acceptable 20 vol/s, range 20–45). Three cardiac cycles were recorded for sinus rhythm and five for atrial fibrillation. Images were analysed at stand-alone stations: LV images were transferred to a Tomtec system (TomTec Imaging, Unterschleissheim, Germany), and RV images were transferred to the SC2000 workstation using the RV analysis application; both systems use similar voxel analysis techniques and hence were felt to be comparable. Analysis was performed by clinicians with experience in 3D echo (SO and MS) using the automated analysis packages. SO completed all the offline 3D RV analyses, and MS completed all the offline 3D LV analyses. A 10% random population was assessed by both for inter- and intra-rater variability. Image quality was assessed in a manner similar to that in recent studies by reviewing the three planes that are provided. If two consecutive segments or more in any two views were not visualised, then the image was considered poor and unsuitable [6].

The automated analysis packages were used to estimate volumes for both the LV and RV. LV volumes were estimated in end-diastole (ED) and end-systole (ES) by the software tracing the endocardium in three planes: apical four-, two- and three-chamber cut planes (see Fig. 3). The operator can perform changes to ensure accurate border identification in the images provided. The software then creates models of the LV cavity at ED and ES, from which the volumes (and other data) are estimated without making geometric assumptions. RV volumes use a similar principle of reviewing endocardial borders, but they need to be manually traced in the apical four-chamber, short-axis and coronal views in ED and ES, and volume change is then presented in an active 3D model (see Fig. 4).

A method was considered feasible if it could be performed in the majority of patients included in the study.

### Statistics

Statistical analysis was performed with JMP Pro version 13 (SAS Institute Inc., Cary, NC, USA). Continuous variables are expressed as mean ± SD if normally distributed and as median with IQR if not normally distributed. Normality was assessed using the Shapiro-Wilk test. P values < 0.05 were considered statistically significant. Bias (mean of difference), precision (SD of difference) and limits of agreement (95% CI of the bias) statistics were performed using methods described by Bland and Altman [7]. To correct for magnitude-dependent variability, the bias was divided by mean SV and expressed as a percentage [8]. Thirty percent limits of agreement have been considered acceptable in previous meta-analysis data [9]. However, it should be noted that this ‘acceptable’ limit of agreement is based on the premise that both the reference method and the new method being investigated have percentage errors < 20%, whereas some recent evidence may suggest that both Doppler and 3D volumetric analysis may be greater [10, 11]. Feasibility for each analysis in this study was defined as the proportion of patients in whom the operator(s) could obtain optimal images for the respective
analysis. Inter- and intra-rater variability was assessed by the absolute difference between 3D SV assessment methods vs Doppler and expressed as a percentage of their mean.

**Results**

Ninety-nine patients were imaged, but seven patients were excluded because Doppler SV estimation could not be obtained reliably (7%). The characteristics of the 92 patients included in the study, along with ventilation data, are shown in Table 1. The majority of patients were in sinus rhythm and received mandatory mechanical ventilation. The patient group was critically unwell with a mean Acute Physiology and Chronic Health Evaluation III score of 84 (IQR 61–100) and were intubated for a median of 6 days. The most common reason for intubation was pneumonia (both community- and hospital-acquired). Median positive end-expiratory pressure...
levels were 8, with mean P/F ratios being in the moderate category by the Berlin definition of acute respiratory distress syndrome [12].

The echo data are shown in Table 2 and include feasibility of each technique. Most patients were able to have Simpson’s biplane assessment with 2D imaging performed (85%), and the majority could have 3DLV assessment performed (72%); however, in only 55% of the patients included could 3DRV assessment be performed. 3DLV analysis took approximately 2–4 minutes, and 3DRV analysis 5–10 minutes, to perform per patient; these values are estimates only and were not formally timed.

### Stroke volume assessment

Using Doppler as the reference method, 2D Simpson’s biplane, 3DLV and 3DRV analysis all underestimated

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, n</td>
<td>92</td>
</tr>
<tr>
<td>Age, years, median (IQR)</td>
<td>67 (57 to 73)</td>
</tr>
<tr>
<td>Sex, female, n (%)</td>
<td>42 (46%)</td>
</tr>
<tr>
<td>Rhythm, sinus rhythm, n (%)</td>
<td>83 (92%)</td>
</tr>
<tr>
<td>APACHE III score, mean (SD)</td>
<td>84 (61 to 100)</td>
</tr>
<tr>
<td>Ventilation time, days, median (IQR)</td>
<td>6 (3 to 9)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Volume</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>63 (68%)</td>
</tr>
<tr>
<td>Aspiration</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>21 (23%)</td>
</tr>
<tr>
<td>Abdominal sepsis (any source) with respiratory compromise</td>
<td>175.5 (± 57)</td>
</tr>
<tr>
<td>Exacerbation of COPD</td>
<td>8 (6.25 to 12)</td>
</tr>
<tr>
<td>Neutropaenic sepsis</td>
<td>96 (91 to 97)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Ventilation mode</td>
<td>Pressure</td>
</tr>
<tr>
<td>Mandatory</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Pressure support</td>
<td>175.5 (± 57)</td>
</tr>
<tr>
<td>P/F ratio, mean (SD)</td>
<td>8 (6.25 to 12)</td>
</tr>
<tr>
<td>PEEP, cmH$_2$O, median (IQR)</td>
<td>96 (91 to 97)</td>
</tr>
<tr>
<td>Arterial oxygen saturation, %, median (IQR)</td>
<td>96 (91 to 97)</td>
</tr>
</tbody>
</table>

**Abbreviations:** APACHE III, Acute Physiology and Chronic Health Evaluation III, COPD, Chronic obstructive pulmonary disease, P/F, Ratio of arterial oxygen partial pressure to fractional inspired oxygen, PEEP, Positive end-expiratory pressure.
SV (positive bias seen in Table 3), with 2D Simpson’s biplane assessment showing the smallest bias (0.2 ml) and 3DRV the greatest (4.1 ml). All three methods of SV assessment had wide ranges of limits of agreement (−23 to 23 ml, −18 to 23 ml, and −26 to 34 ml for 2D Simpson’s biplane, 3DLV, and 3DRV, respectively, and corrected percentage errors of 50%, 51%, and 74%, respectively). Comparing 3DLV with 3DRV SV estimation, 3DRV analysis underestimated SV compared with 3DLV (bias 3 ml), again with wide limits of agreement (−27 to 32 ml), and lacked agreement: The corrected percentage error was 40% (see Fig. 5).

**Left ventricle assessment**
Comparing 2D Simpson’s biplane and 3DLV assessments, 3DLV seemed to underestimate SV, LV end-diastolic and LV end-systolic volumes, and EF (bias 2.8 ml, 5.7 ml, 2.8 ml and 0.7%, respectively) with relatively wide ranges of limits of agreement (−20 to 25 ml, −33 to 44 ml, −31 to 36 ml, and −20 to 22%, respectively). The corrected percentage error was greatest for LV end-systolic volumes (75%) and was the smallest when comparing SV and EF (40%); however, it was still considered to lack clinical comparison.

**Repeatability**
A random ten patients were selected for blinded variability analysis of the offline 3DLV and 3DRV SV assessments (i.e., analysis of the images). Inter-rater variability was reasonable for (1) 3DLV with mean absolute difference (±SD) of 3.6 ml (± 8.6) and expressed as percentage of the mean 8% (± 19) and (2) 3DRV with mean absolute difference (±SD) of −2.1 (± 7.3) and expressed as percentage of the mean 10% (± 22). Intra-rater variability also showed reasonable repeatability for (1) 3DLV with mean absolute difference (±SD) of −3.6 ml (± 8.8) and expressed as percentage of mean 7% (± 19) and (2) 3DRV with mean absolute difference (SD) of −1.6 (10) and expressed as percentage of the mean difference of 4% (± 27).

**Discussion**
We found real-time 3DLV and 3DRV transthoracic echo analysis of SV to be possible in a majority of critically ill patients, defined as patients on mechanical ventilation

---

**Table 3** Bias, precision, limits of agreement and corrected percentage error between Doppler, 2D and 3D volumetric data

<table>
<thead>
<tr>
<th>Techniques being compared</th>
<th>Value</th>
<th>Bias</th>
<th>Precision</th>
<th>Limits of agreement</th>
<th>Corrected Percentage error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doppler vs 2D Simpson's biplane</td>
<td>Stroke volume, ml</td>
<td>0.2</td>
<td>119</td>
<td>−23.1 to 23.5</td>
<td>50.2%</td>
</tr>
<tr>
<td>Doppler vs 3D LV</td>
<td>Stroke volume, ml</td>
<td>2.6</td>
<td>104</td>
<td>−17.8 to 23.0</td>
<td>51.3%</td>
</tr>
<tr>
<td>Doppler vs 3D RV</td>
<td>Stroke volume, ml</td>
<td>4.1</td>
<td>154</td>
<td>−26.2 to 34.3</td>
<td>73.5%</td>
</tr>
<tr>
<td>3D LV vs 3D RV</td>
<td>Stroke volume, ml</td>
<td>2.7</td>
<td>149</td>
<td>−26.5 to 31.9</td>
<td>67.6%</td>
</tr>
<tr>
<td>2D Simpson’s biplane vs 3D LV</td>
<td>Stroke volume, ml</td>
<td>2.8</td>
<td>115</td>
<td>−19.7 to 25.4</td>
<td>40.1%</td>
</tr>
<tr>
<td></td>
<td>LV end-diastolic volume, ml</td>
<td>5.7</td>
<td>19.7</td>
<td>−33.0 to 44.3</td>
<td>37.0%</td>
</tr>
<tr>
<td></td>
<td>LV end-systolic volume, ml</td>
<td>2.8</td>
<td>17.0</td>
<td>−30.6 to 36.2</td>
<td>74.6%</td>
</tr>
<tr>
<td></td>
<td>Ejection fraction, %</td>
<td>0.7</td>
<td>10.7</td>
<td>−20.4 to 21.7</td>
<td>40.4%</td>
</tr>
</tbody>
</table>

Abbreviations: LV Left ventricular, RV Right ventricular
with significant V/Q mismatch; however, it did not have sufficient agreement with Doppler echo assessment to be considered clinically or statistically acceptable. In the intensive care clinical setting, cardiac volume analysis needs to be feasible, but low variability and high precision are key. We found that 3D transthoracic echo did not have sufficient agreement to be either statistically or clinically satisfactory for SV estimation in this study. 2D Simpson’s biplane analysis of SV was also assessed (because use of Doppler is considered to require higher levels of training [13]), and this also did not have sufficient precision to be considered acceptable vs Doppler analysis.

The ability to accurately measure SV in the critically ill plays an important role in analysis of cardiac function and haemodynamics, which are often abnormal in the ICU setting. Doppler echocardiography has been shown to be an accurate and precise method for estimating cardiac output and SV in the critically ill patient [10] and is the method of choice for many intensivists in cardiac assessment for fluid administration [14], evaluation of shock [15] and RV analysis [16]. 3D transthoracic echo transducers have become increasingly available and are described in the cardiology literature as having better accuracy and precision in measuring LV volumes than 2D transthoracic echo by methods such as Simpson’s biplane [17]. 3D echo may offer an advantage over conventional 2D echocardiography in a number of areas. In particular, the fact that the entire ventricle can be assessed rapidly, in a relatively automated fashion, means that errors such as angle dependence, as well as assumptions about the ventricle size or regional wall motion abnormalities, can be avoided. Imaging faults, such as foreshortening, which are reported to occur in approximately 50% of standard 2D imaging by sonographers, are avoided [18]. Compared with cardiac MRI, both 3D and 2D echo underestimate LV volumes. However, 3D under-represents values approximately 50% less than 2D and with approximately half the 95% CIs [17]. In addition, 3D transthoracic equipment is costly and requires significant training, and parameters such as diastolic function are not assessed.

There are several limitations to our study. It is a single-centre study performed by echocardiography enthusiasts. The 3D volumetric data were acquired on a single platform by a single operator, and data were analysed by the same operator, and therefore we cannot exclude bias. We attempted to limit bias by ignoring Doppler data prior to analysis of 3D volumes; however, a more structured blinding of data, or random assessment, would have meant greater scientific rigour. Data were analysed by a second experienced user and inter-rater variability was small and not statistically significant. The lack of consecutive assessment of patients indicates selection bias, but pragmatically, performing the study meant only one operator was regularly available for 3D imaging. The use of Doppler echo as the reference standard for SV estimation is controversial [19]. Basic evaluation of the errors of Doppler SV estimation vs thermodilution to guide sample size prior to starting the study would be ideal. In this regard, further studies using thermodilution, or ideally MRI, as the reference standard are warranted. In addition, we did not assess the trending ability of 3D transthoracic echo or the repeatability of the 3D data acquisition itself, and this may be a useful addition to future studies. Indeed, we postulate that the greatest source of variability in SV assessment using 3D transthoracic echo may be image acquisition itself.

Finally, the reporting of limits of agreement may be considered controversial because larger limits of agreement may be considered statistically satisfactory due to previous evidence that both Doppler SV assessment and 3D volumetric analysis may have percentage errors > 20% vs a gold standard (thermodilution and MRI, respectively) [10, 11]. However, from a clinical perspective, tighter limits of agreement were felt to be more relevant.

Further studies are warranted in this area for analysis of precision (vs robust reference standards such as thermodilution of MRI), as well as in assessing the change in SV. In addition, comparison among groups of physicians with different levels of experience may be useful to confirm these results. RV volumes in particular are not easily assessed by 2D echo, and given the complex shape of this ventricle and the extent of RV dysfunction in the critically ill, 3D RV analysis is enticing. 3D transoesophageal echo for volumetric analysis in the critically ill has been studied, particularly in the peri-operative setting, and has been suggested to be both feasible and as accurate as other forms of echocardiography [20]. Cardiac volumes and SV analysis play an important role in the care of the critically ill. Therefore, it is important to find a feasible, user-independent, repeatable, non-invasive, accurate technique in the critically ill.

**Conclusions**

3DLV and 3DRV echo imaging in the critically ill is feasible and reproducible, but SV estimation by real-time 3D echo analysis did not have sufficient statistical or clinical agreement with Doppler evaluation of SV in this study.

**Abbreviations**

2Ch: Two-chamber view; 3Ch: Three-chamber view; 3DLV: 3D left ventricular; 3DRV: 3D right ventricular; 4Ch: Four-chamber view; APACHE III: Acute Physiology and Chronic Health Evaluation III; COPD: Chronic obstructive pulmonary disease; ED: End-diastolic; ESV: End-systolic volume; EF: Ejection fraction; ES: End-systolic; ETV: End-diastolic; VGS: Global circumferential strain; GCS: Global longitudinal strain; ICU: Intensive care unit; LV: Left ventricle; LVEF: Left ventricular ejection fraction; MRI: Magnetic resonance imaging; P/F: PaO2/FiO2: Ratio of arterial oxygen partial pressure to fractional inspired oxygen; PEEP: Positive end-expiratory pressure; RVOT: Right ventricular outflow tract; V/Q: Ventilation/perfusion
Acknowledgements
The authors thank Iris Ting, Louise Smith, Euguenia Khodolishi and Keren Mowbray of the Nepean Intensive Care Cardiovascular Ultrasound Laboratory for their expertise and skill in assisting with acquiring conventional echocardiographic studies.

Availability of data materials
The datasets generated and analysed during this study are available from the corresponding author on reasonable request.

Authors’ contributions
SO conceived of and designed the study, acquired data including performing the majority of the echocardiograms, analysed the data and prepared the manuscript. MS and NS assisted with data analysis, interpretation, and drafting of the manuscript. SH assisted with study design, statistical analysis and drafting of the manuscript. AM assisted with study design and drafting of the manuscript. All authors drafted and reviewed the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study was approved by the Nepean Blue Mountains Local Health District (LNR/13/NEPEAN/154), and written consent was provided prospectively by the authorised representatives (next of kin) or retrospectively by the patient, given the non-invasive nature of the imaging.

Consent for publication
Consent for use of de-identified images contained in this article was given by the individuals involved.

Competing interests
The authors declare that they have no competing interests.

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SECTION C:

MYOCARDIAL CONTRAST PERFUSION ECHOCARDIOGRAPHY
Section C: Myocardial contrast perfusion echocardiography

**Section overview**

This section is comprised of two manuscripts and one textbook chapter. The literature review contains one manuscript published in a peer reviewed journal ‘Critical Care’ and an invited textbook chapter in the ‘Oxford textbook of Advanced echocardiography’. The feasibility study performed in the critically ill is under peer review in ‘Critical Care’.

**Chapter 10: Explanation of technique and literature review**


The textbook chapter discusses the use of echocardiography contrast in the ICU and highlights the potential clinical role MCPE may have in the critically ill. The review article then considers the technique of MCPE in detail, as well as potential limitations and advantages. We suggest, MCPE may play a role in recognising acute coronary artery occlusion in the ICU patient. This can be challenging as Troponin elevation with or without acute ECG changes and regional wall motion abnormalities is common (eg: LAD territory ischaemia vs stress induced cardiomyopathy or Takotsubo’s syndrome).

**Chapter 11: Myocardial contrast perfusion echocardiography in the critically ill**


This study assesses the feasibility of MCPE in the critically ill and analyses its ability to recognise acute coronary artery occlusion in critically ill patients with Troponin elevations being considered for angiographic intervention. This is the first time MCPE has been assessed for this manner and it appears to hold promise.
Section C: Myocardial contrast perfusion echocardiography

Chapter 10: Explanation of technique and literature review


REVIEW

Bedside myocardial perfusion assessment with contrast echocardiography

Sam Orde1* and Anthony McLean1,2

Abstract
This article is one of ten reviews selected from the Annual Update in Intensive Care and Emergency Medicine 2016. Other selected articles can be found online at http://www.biomedcentral.com/collections/annualupdate2016. Further information about the Annual Update in Intensive Care and Emergency Medicine is available from http://www.springer.com/series/8901.

Background
Myocardial perfusion can be safely assessed at the bedside using contrast echocardiography. The contrast agents consist of tiny microbubbles (approximately 1–8 μm in diameter), which remain in the systemic circulation for ~3–5 min after venous injection. Low intensity ultrasound imaging is required to prevent the microbubbles from being destroyed. Myocardial perfusion is assessed by destroying the microbubbles with a ‘flash’ of higher intensity ultrasound and then analyzing the replenishment rate as the microbubbles seep back into the myocardial circulation.

There is reasonable evidence that myocardial contrast perfusion echocardiography (MCPE) can help in the detection of coronary artery disease as well as having prognostic value over regional wall motion analysis. However, there are challenges in bringing it into everyday clinical use: the imaging is challenging and relatively complicated compared to standard echocardiography; the sensitivity and specificity are not 100%; it remains an ‘off-label’ use of contrast echocardiography; and there are safety issues to consider. It has been investigated for more than 25 years and yet still has not made it into main-stream cardiac evaluation.

One area of considerable interest and future potential is in critically ill patients who have raised cardiac enzymes, especially troponins, with or without electrocardiogram (EKG) abnormalities or regional wall motion abnormalities, in whom the diagnosis of ischemia needs to be addressed. Examples include Takotsubo’s or septic cardiomyopathy. Investigation with angiography or further imaging may be detrimental in patients with acute renal failure or bleeding risk and there are dangers associated with unnecessary transfer. It is not suggested that MCPE would take the place of angiography or other investigations assessing myocardial perfusion, but potentially MCPE could identify patients (or at least triage them) who have normal myocardial perfusion yet abnormal troponins, EKGs and have regional wall motion abnormalities. In addition, there are exciting implications for the future use of microbubble contrast in terms of drug and gene delivery.

Contrast echocardiography agents
Echocardiography imaging in the critically ill can be frustratingly difficult at times. Contrast echocardiography agents were originally designed to help improve endocardial border definition, known as left ventricle opacification, as well as to enhance Doppler signals. Their use can prevent non-diagnostic studies from being inconclusive, particularly in the critically ill [1]. These contrast agents were originally described in the 1960s [2] and further development in the 1980s and ’90s saw specific contrast agents designed to remain in the systemic circulation after venous injection, as well as ultrasound imaging enhancement techniques developed (such as harmonic imaging) to enhance left ventricular opacification [3–5].

The contrast agents consist of microbubbles containing a hemodynamically inert gaseous core (e.g., octafluoropropane, sulfur hexafluoride) and a stabilizing outer shell (e.g., lipid, albumin or biopolymer), which oscillate under the influence of ultrasound waves [6].
Similar to agitated saline, now in use for over 35 years to determine cardiac and intrapulmonary shunts, these contrast echocardiography microbubbles form multiple small liquid-air interfaces whose boundaries have a high acoustic impedance mismatch resulting in enhanced ultrasound reflection. A major difference of contrast microbubbles compared to saline bubbles is the size, with the bubbles small enough (1–8 μm) to traverse the pulmonary capillaries in order to enter the systemic circulation. Saline bubbles are typically 50–90 μm diameter and are destroyed as they pass into the pulmonary capillaries.

Microbubbles require specific ‘activation’ to be effective (different methods are required for different agents). Injected intravenously, they cross the pulmonary circulation into the system circulation. With similar behavior and rheology to red blood cells (RBCs) [7], they remain entirely within the vascular compartment and last in the circulation for approximately 3–5 min before they burst and lose their ability to produce ultrasound backscatter. Once the microbubbles are destroyed, the shell is metabolized by fatty acid metabolism if made of lipid (such as with Definity [BMS, Billerica, MA]), or by the reticuloendothelial system. The inert gas is not metabolized and simply escapes from the lungs [8].

There are various contrast agents available, each having slightly different compositions and gas cores (Table 1). Different countries have different agents available. The first generation contrast agents, developed at the end of the 20th century, have a lipid shell with an air core, are soluble and are able to pass through the pulmonary circulation but lose their echogenicity and dissolve rapidly. The second generation contrast agents were then developed and have high-molecular weight gaseous cores, are less soluble than air, with stabilizing lipid or biopolymer shells and remain more stable under the ultrasound field and, therefore, have an increased lifespan in the circulation [9]. These preparations include the standard contrast agents used today: Definity, Optison (GE healthcare, Chalfont St Giles, UK) and Sonovue (Bracca, Milan, Italy). Third generation agents include those specifically used for research-based activities, specialized imaging or therapeutic purposes [8].

### Effect of ultrasound on contrast agents

Specific imaging techniques and software are required to perform MCPE to take advantage of the different ultrasound reflection properties of the contrast microspheres versus soft tissue. When ultrasound interacts with the microbubbles they oscillate and this effect is dependent on the ultrasound acoustic pressure as well as the shell and core gas properties of the agent. Ultrasound acoustic pressure is described as the ‘mechanical index’ and corresponds to the power output of the scanner [10]. With standard 2D echocardiography imaging the mechanical index is ~1.4; however, at this level the microspheres would oscillate to such a degree that they would burst and be destroyed. Therefore low mechanical index (<0.2) imaging is used with contrast imaging.

The oscillation effect of contrast echocardiography under low mechanical index ultrasound means the ultrasound reflections are different for microbubbles compared to soft tissue. This difference can be harnessed to enhance contrast versus tissue differentiation when imaging: microbubbles reflect ultrasound in a non-linear format compared to tissue, which reflects ultrasound in a linear manner. Non-linear reflection means the sound waves are reflected not only at the frequency of the original ultrasound wave but also at higher, harmonic frequencies. Soft tissue, however, produces fewer harmonics, hence reflection of the ultrasound waves in a more linear fashion. There are different methods used

### Table 1 Contrast echocardiography agents

<table>
<thead>
<tr>
<th>Classification</th>
<th>Gas core</th>
<th>Shell</th>
<th>Trade name</th>
<th>Bubble size (μm)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>First generation</td>
<td>Air</td>
<td>Albumin</td>
<td>Albunex</td>
<td>2–8</td>
<td>No longer made</td>
</tr>
<tr>
<td>Air</td>
<td>Palmitic acid/galactose</td>
<td>Levovist (Schering, Kelinhworth, NJ)</td>
<td>2–8</td>
<td>Non-cardiac use mainly</td>
<td></td>
</tr>
<tr>
<td>Air</td>
<td>D-galactose</td>
<td>Echovist (Berlex, Lachine, Quebec City, Canada)</td>
<td>2–8</td>
<td>First commercially available agent</td>
<td></td>
</tr>
<tr>
<td>Second generation</td>
<td>Octafluoropropane (C₈F₈)</td>
<td>Albumin</td>
<td>Optison (GE healthcare, Chalfont St Giles, UK)</td>
<td>1–10</td>
<td>Available in USA, Europe, South America</td>
</tr>
<tr>
<td>Octafluoropropane (C₈F₈)</td>
<td>Lipid</td>
<td>Definity (BMS, Billerica, MA)</td>
<td>1–10</td>
<td>Available in USA, Europe, South America, Canada, Australasia</td>
<td></td>
</tr>
<tr>
<td>Sulfur hexafluoride (SF₆)</td>
<td>Lipid</td>
<td>Sonovue (Bracca, Milan, Italy)</td>
<td>1–10</td>
<td>Available in Europe and USA (known as Lumason)</td>
<td></td>
</tr>
</tbody>
</table>

NB: The list does not include every available contrast agent worldwide and the accuracy of the ‘comments’ section may change but is up to date at time of writing to the best of the authors’ knowledge.
by various vendors to take advantage of the specific reflection properties for tissue vs contrast microbubbles, including: pulse inversion, power modulation and coherent contrast imaging to reduce the soft tissue linear reflections of the fundamental frequency [11].

Myocardial perfusion imaging
In the 1990s, initial studies in animals, subsequently validated in humans, investigated the hypothesis that myocardial blood flow could be assessed with contrast echocardiography by destroying the contrast microbubbles with a ‘flash’ of high diagnostic intensity ultrasound and then assessing the rate of replenishment of the microbubbles into the myocardium [12–14]. The replenishment is assessed by the change in intensity or brightness in a ‘region of interest’ (ROI). The microbubbles behave like RBCs, hence the theory that any change in signal intensity represents a change in myocardial blood flow.

With normal myocardial blood flow, 90 % of the coronary circulation resides within the myocardial capillaries and RBCs travel at approximately 1 mm/s at rest. After destruction of the contrast the signal intensity is anticipated to return to normal after approximately 5–7 cardiac cycles [13] (Fig. 1). During stress or exercise where vasodilation and increased capillary blood flow are present, the rate of return of signal intensity is faster: approximately 2–3 cardiac cycles. The rate of microbubble replenishment can be assessed qualitatively (as seen in Fig. 1), but also quantitatively by reviewing the change in signal intensity over time in a specific ROI (Fig. 2). Myocardial blood flow is considered the product of plateau signal intensity and rate of replenishment (Fig. 3). The concept being that the slower the rate of replenishment and lower the plateau signal intensity, the poorer the myocardial blood flow.

Safety profile
The use of contrast echocardiography, extensively investigated in several large multicenter trials [15–17], has been found to be well-tolerated and safe in both non-critically ill and critically ill patients [18]. ‘Black-box’ warnings were issued by the US Food and Drug Administration (FDA) in 2007 but these were downgraded within 12 months. The current FDA recommendations state that if a patient has an unstable cardiopulmonary condition or pulmonary hypertension (the severity is not stated), the patient should have cardiorespiratory monitoring for 30 min after contrast agent administration [19]. In the United States, echocardiography laboratories are not accredited unless they have the ability to perform contrast echocardiography [20].

Side effects are rare and include headache, flushing or back pain. These symptoms are usually relieved on cessation of contrast agent administration. There is a 1:10,000 chance of an anaphylaxis type reaction (considered secondary to the microbubble shell and possibly non-IgE related) [9]. Contraindications include previous hypersensitivity to contrast agents or to blood products (e.g., albumin), severe pulmonary hypertension and cardiac right-to-left or bidirectional shunts. These last two contraindications are under debate and evidence exists of the safety in these conditions, whereas there are only case reports of harm with recent use of ultrasound contrast [16, 21].

We consider an individualized approach of risk versus benefit is required for MCPE. Important requirements
include expertise to perform and interpret the procedure, and the study should be performed in an environment with appropriate monitoring and resuscitation facilities.

Applications in the critically ill
Recognition of acute coronary artery disease
The diagnosis of acute coronary syndromes (ACS) in the intensive care unit (ICU) can be challenging. Critically ill patients with ischemic heart disease are at greater risk during times of stress and the classic history of central crushing chest pain can be absent as a result of acute illness, sedation and/or mechanical ventilation. Troponin elevation, EKG and regional wall motion abnormalities (RWMA) are frequently seen in conditions other than myocardial infarction [22], for example Takotsubo’s and septic cardiomyopathy amongst many other causes [23]. In addition, investigating for possible ACS with angiography or single photon emission computed tomography (SPECT) can be dangerous due to the inherent risks of patient transport, contrast-induced nephropathy, radiation, access issues, anticoagulation, and delays in diagnosis. Cost and access to suitable angiographic facilities may be issues in some ICUs. Potentially, MCPE could help identify patients with ACS at the bedside in the ICU, not to replace further imaging, but rather as a triage tool or simply to add confidence to the physician’s clinical acumen [24].

MCPE has been compared to SPECT, the most widely used perfusion technique for assessment of coronary artery disease. In several studies for detection of coronary artery disease, MCPE has shown excellent concordance (81 % [76.4–85.6]) [25]. A meta-analysis indicated a higher sensitivity for MCPE than for SPECT and no difference was found for specificity [26]. Various clinical studies have used MCPE to quantify myocardial blood flow, trying to differentiate coronary artery ischemia from not significantly occluded coronary arteries. Senior et al. reported that MCPE could differentiate ischemic from non-ischemic cardiomyopathy (defined as < 50 % coronary artery stenosis) with a specificity of 89 % and sensitivity of 91 % [27].

Microvascular versus macrovascular function assessment
Microvascular dysfunction has been proposed in a number of cardiac conditions such as Takotsubo’s [28] and septic cardiomyopathy [29] amongst others. Whether the microvascular dysfunction is a primary cause of secondary phenomena is not known. Abdelmoneim et al
performed MCPE in 9 patients with angiographically confirmed Takotsubo’s syndrome and were able to show reduced perfusion in the myocardium with a 71% concordance with areas of RWMA [28]. It is suggested that the microvasculature in the endocardial regional has the lowest flow reserve and is more susceptible to ischemia than the epicardium possibly due to the larger epicardially placed coronary arteries [30]. Therefore, with microvascular disorders there may be a reduction in the endocardial myocardium to a greater extent than in the epicardial myocardium (Fig. 4).

Possible future roles for contrast echocardiography
Advances in contrast microbubble formulations, imaging and post-processing analysis, indicate that the future for contrast echocardiography may include imaging of macro and microvasculature elsewhere in the body as well as targeted drug and/or gene delivery.

Contrast-enhanced ultrasound
Using contrast agents in a similar manner to MCPE, non-invasive and bedside perfusion assessment of organs may be possible. Schneider et al. suggested that assessing renal cortical perfusion with contrast is feasible and well-tolerated in the ICU population and that possibly a decrease in renal perfusion may occur within 24 h of surgery in patients at risk of acute kidney injury (AKI) [31]. These techniques are relatively unexplored at this time and although they hold promise, do demonstrate significant heterogeneity and the results remain unpredictable [32]. Further investigation is certainly warranted.

Targeted drug delivery
The property of contrast microbubbles bursting under the effect of ultrasound can be used to target drug delivery. Drugs can be attached to microbubbles by a variety of methods [10] and as long as the site is accessible to ultrasound, a burst of high mechanical index ultrasound may be able to locally deliver the drug, such as thrombolysis. Transfer of genetic material has also been suggested and has been shown to be safe and more specific than viral vectors for cDNA delivery [33].

Conclusion
The use of contrast echocardiography in the critically ill is safe compared to other contrast agents, feasible at the bedside and has the potential to rescue undiagnostic echocardiograms. Although the agents are only indicated for left ventricular opacification, the off-label use of MCPE holds promise as being a potential method to assess myocardial perfusion at the bedside. The technology has been available for over two decades and is yet to find a place in regular clinical practice, but as a result of ever evolving sophistication of microbubble agents, software and hardware still holds considerable promise. The utility of MCPE in the ICU has not been extensively considered to date but potentially may have a role in the challenging arena of accurate and timely diagnosis of ACS in the critically ill.

![Fig. 4](image)

Takotsubo’s cardiomyopathy with microvascular dysfunction (arrows). Endocardial perfusion defect shown at 5 beats post flash in the apical region where transient apical hypokinesis was visualized. Coronary angiography confirmed normal vasculature and left ventriculography demonstrated apical ballooning.
Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
Both authors read and approved the final manuscript.

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References
Abstract
Echocardiography in the ICU is notorious for being difficult to perform leading to frustratingly non-diagnostic studies with a lack of confidence in findings. The use of ultrasound contrast to enhance these images has the potential to salvage inconclusive studies and change management in critically ill patients.

Ultrasound contrast, once ‘activated’, produces tiny microspheres containing an inert gas with a stabilising shell with a diameter of approximately 1-5µm. They are injected intravenously and pass through the pulmonary microcirculation into the systemic circulation. They last approximately 3-5 minutes and remain entirely in the vascular space. The gas is released unchanged by the lungs and the stabilising shell is typically metabolised by the reticulo-endothelial system or by fatty acid metabolism.

These agents are essentially safe in the critically ill. Minor side effects can occur in 1-2% and is alleviated by ceasing administration. There is a 1 in 10,000 chance of an anaphylaxis type reaction and hence cardiopulmonary monitoring for at least 30 minutes after administration is recommended and processes in place to deal with this unlikely occurrence.

Contrast enhanced echocardiography can help to accurately detect the endocardial border, ventricular dysfunction, regional wall motion abnormalities, left ventricle thrombi, abnormal masses, enhance Doppler signals amongst other potential benefits. In addition, the use of contrast can prevent further investigations and transfer which may be detrimental to the critically ill patient.
**Introduction**

Transthoracic echocardiography (TTE) in the critically ill patient can be technically challenging. Patients are often suboptimally positioned, mechanical ventilation inflates the lung fields (particularly with high levels of positive end expiratory pressure) and surgical drains and dressings are often in the way. Even with technical refinements that improve image quality, such as harmonic imaging, more than 65% of critically ill patients have at least one view that is non-diagnostic\(^1\) even in expert hands.

Contrast enhanced transthoracic echocardiography has the potential to overcome some of the imaging limitations that hinder TTE and can at least salvage a non-diagnostic study through improved endocardial border definition, (see section: ‘Contrast applications in critically ill’). The benefit of contrast has been reported to be particularly advantageous in ICU patients\(^2,3\).

The use of contrast is not without its problems. There are safety concerns that need to be considered.\(^4\) However, the safety profile of ultrasound contrast is amongst the safest of any non-invasive imaging technique that requires a contrast agent\(^5\). There is a cost burden for the contrast itself, imaging hardware, an imaging software (see section: ‘How to perform contrast enhanced ultrasound’). The use of contrast has been shown to be a cost effective strategy. However, this is reported predominantly in the US health system where reimbursement for ultrasound contrast use is possible\(^6\). More importantly the use of contrast enhanced echocardiography may prevent the need for more invasive or dangerous investigations like transoesophageal echo\(^2\).

**Contrast agents**

Intravenous injection of agitated saline is an ultrasound contrast technique that has been used for over 35 years\(^7\). The saline/air bubbles enhance ultrasound backscatter by forming multiple small, liquid-air interfaces (typically bubbles are 50-90µm diameter) with their high acoustic impedance mismatch boundaries. This technique utilises normal B-mode imaging and is often used for determining right to left cardiac shunts, intra-pulmonary shunts or to enhance tricuspid regurgitation Doppler signals.
Commercially available microsphere contrast agents contain microscopic bubbles that consist of a gaseous core with a stabilising outer shell. These bubbles oscillate under the influence of ultrasound waves\(^{(8)}\). There are various contrast agents available worldwide. Selective ones are available in different countries\(^{(9)}\). The composition of each contrast agent differs in terms of the gas used in the core and the structure of the outer shell (\textit{Table 1}), which leads to variations in their response to ultrasound and their clinical utility\(^{(10)}\).

The first-generation commercially available contrast agents, developed in the 1990s, consisted of an air core with a lipid shell and included: Echovist (Berliex, Lachine, Quebec City, Canada), Levovist (Bayer Shering, Berlin, Germany) and Albunex (Mallinckrodt, St Louis, Missouri)\(^{(11)}\). They were able to pass through the microcirculation, however they dissolved and lost their echogenicity rapidly. This led to the development of the second-generation agents, which are among the standard agents used today, including (not exclusively): Optison (GE Healthcare, Chalfont St Giles, UK), Definity (BMS, Billerica, Massachusetts) and Sonovue (Bracca, Milan, Italy). Third generation agents are also available and are considered novel, custom-made agents which are used for specialised imaging or therapeutic purposes\(^{(2)}\).

<table>
<thead>
<tr>
<th>Classification</th>
<th>Shell</th>
<th>Gaseous core</th>
<th>Trade name</th>
<th>Bubble size ((\mu m)), mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First generation</td>
<td>Albumin</td>
<td>Air</td>
<td>Albunex</td>
<td>2-3 (2-8)</td>
</tr>
<tr>
<td></td>
<td>Galactose / Palmitic acid</td>
<td>Air</td>
<td>Levovist</td>
<td>2-3 (2-8)</td>
</tr>
<tr>
<td></td>
<td>D-Galactose</td>
<td>Air</td>
<td>Echovist</td>
<td>2-3 (2-8)</td>
</tr>
<tr>
<td>Second generation</td>
<td>Albumin</td>
<td>Octafluoropropane (C(_3)F(_8))</td>
<td>Optison</td>
<td>4-5 (1-10)</td>
</tr>
<tr>
<td></td>
<td>Lipid</td>
<td>Octafluoropropane (C(_3)F(_8))</td>
<td>Definity</td>
<td>1-2 (1-10)</td>
</tr>
<tr>
<td></td>
<td>Lipid</td>
<td>Sulfur hexafluoride (SF(_6))</td>
<td>Sonovue</td>
<td>2-3 (1-10)</td>
</tr>
</tbody>
</table>

\textit{Table 1:} First- and second-generation contrast agent NB: This table is not inclusive of every available contrast agent

In general, ultrasound contrast agents in current use contain microscopic bubbles (typically \(<5\mu m\)) of high-molecular weight inert gases with a stabilising lipid, bipolymer or protein shells\(^{(5)}\). which result in small bubbles with increased lifespan in the circulation. They do not aggregate in the microcirculation and are biologically safe\(^{(4,11)}\). They remain entirely...
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in the vascular circulation and behave in a similar manner to red blood cells(12). After the microsphere bubbles burst, the gas is not metabolised and escapes from the lungs. The microsphere shell is typically eliminated by the reticulo-endothelial system or, in the case of Definity with its lipid shell, is metabolised by the usual process of fatty acid metabolism(2).

Due to the small bubble size and stability, following intravenous injection they pass through the pulmonary circulation into the systemic system lasting approximately 3-5 minutes. Similar to agitated saline contrast agents are injected into a vein, however they differ from agitated saline in that some microsphere contrast bubbles require specific ‘activation’ to be effective, they are smaller (<8µm) and there are some higher safety concerns. The agents available, their pharmacodynamics, indications, contraindications, safety profile, how to perform contrast enhanced ultrasound, interpret images, applications in the critically ill as well as possible further applications will be discussed.

Relationship of ultrasound with contrast agents

Understanding the relationship of ultrasound with contrast agents is important in order to optimise imaging settings for contrast specific imaging. Due to the size of the gas-filled microspheres of contrast agents being smaller than the ultrasound wavelengths, the bubbles oscillate expanding and contracting with the effect of ultrasound(13). Their behaviour is highly dependent on the acoustic pressure of the ultrasound wave as well as the density of the microsphere gas core and shell. Acoustic pressure is measured as “Mechanical Index” [MI] on ultrasound machines, a unit-less indication of the non-thermal bioeffects of ultrasound waves. With conventional 2D B-mode imaging the MI is typically approximately 1.4. At this pressure the microspheres would be destroyed, therefore low MI imaging is utilised in contrast specific imaging (typically 0.1-0.2)(2,5).

At low MI, contrast specific imaging also takes advantage of the different effect that the ultrasound has on tissue vs the microspheres. At low MI, tissue has a linear backscatter behaviour to the ultrasound energy, with symmetrical compression and rarefaction sound wave reflections. However, the microspheres oscillate and have a non-linear reflection
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Behaviour producing asymmetrical reflections with different phases and harmonics to the original signal (known as the ‘fundamental frequency’) that was sent out (13).

Individual ultrasound vendors employ specific imaging phasing or amplitude variation to exploit the linear vs non-linear differences in ultrasound wave reflection. This leads to improved contrast vs tissue differentiation on imaging (see Figure 1). These techniques include pulse inversion (14) and power modulation (5): the concept of sending out multiple pulses down each scan line, which are either directly out of phase with each other or half the amplitude respectively. Reflections from tissue vs contrast microspheres can then be determined on the basis of being linear reflections (which are suppressed) vs non-linear (which are enhanced) leading to improved endocardial border definition.

Safety profile in the critically ill and contraindications

The use of contrast-enhanced ultrasound is a safe procedure and is very well tolerated in the critically ill as well as the non-critically ill population (15). Indeed, in the United States, the ability for an echocardiography laboratory to perform contrast echocardiography is necessary to be formally accredited (16). The safety profile of these agents has been extensively investigate in several very large studies in a wide range of medical conditions including the acutely ill (17-20). Previous ‘black-box’ warnings for ultrasound contrast agents in 2007 issued by the FDA were subsequently significantly downgraded within the year. Current FDA recommendations state that if a patient has an unstable cardiopulmonary condition or pulmonary hypertension (the severity is not stated), the patient should have cardiorespiratory monitoring for 30 minutes after administration of the contrast agent (21).

Possible adverse events to ultrasound contrast include headache (2%), back pain or flushing (1%), which are alleviated by ceasing the administration of the contrast agent. There is a 1 in 10,000 chance of an anaphylaxis type reaction, likely secondary to the microsphere shell (2) and is thought to be non-IgE-related (5). In this regard, it is important that any
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centre that performs contrast echocardiography should have policies, appropriate staff and equipment available whilst performing these studies(16).

Current contra-indications include previous hypersensitivity to ultrasound contrast, cardiac right-to-left, bidirectional or transient shunts as well as severe pulmonary hypertension. SonoVue has further contraindications including uncontrolled severe hypertension and adult respiratory distress syndrome(22). There is current debate regarding several of these contraindications, in particular intracardiac shunts and pulmonary hypertension, with evidence of no harm in these settings(18,23).

As with most procedures in the critically ill, the relative risks and benefits need to be considered and the use of contrast enhance echocardiography is no different. An individualised approach is required, adequate expertise to perform and interpret the study, and procedures in place if adverse events (albeit rare) occur.

How to perform contrast enhanced echocardiography

‘Activation’ and preparation of the contrast agent.

Specific instructions to each agent should be reviewed. Most contrast agents are presented in a glass vial, require refrigeration (~4°C), and have an expiration date to be checked prior to use. Contrast agents require ‘activation’ to produce the bubbles and must be suspended or reconstituted in a specific solution prior to administration.

In the case of Definity, high-speed oscillation (4500 oscillations/min for 45 seconds) is required in a VialMix device (Lantheus Medical Imaging, Billerica, Mass, USA) to generate 1.3ml of activated contrast agent (see Figure 2), which can then be drawn up into 10-20ml of normal saline or sterile water for bolus administration or 50ml for continuous infusion. Optison and Sonovue are reconstituted with normal saline, and then hand agitated for 20 seconds.(2) Care should be taken when drawing up the agents to avoid exposing to excessive low or high pressure which may result in microbubble destruction(5).

Administration.
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Contrast agents can be administered either by bolus injection or by continuous infusion. Bolus injection is easier but requires careful administration to avoid artefacts: 1-2ml bolus of contrast agent at 0.5-1ml/sec, followed by a 2-3ml saline flush over 3-5seconds or when contrast agent is seen in the right ventricle. Further boluses are then given as required. Continuous infusion can be done either by slow ‘hand-push’ (0.5-1ml every 2-3 mins) or by an infusion pump (150-200ml/hr for a 50ml solution), which is more reliable(16). If the vial has been left unattended for a short while sediment can appear. Resuspension by gentle rolling the syringe or moving the infusion bag is all that is required.

**Contrast specific imaging and settings.**

As discussed previously (see section ‘Relationship of ultrasound with contrast agents’) low MI imaging is required to real-time imaging with ultrasound contrast to avoid destruction of the microbubbles. It is preferable to use vendor specific software for contrast enhanced ultrasound imaging, which is available with most systems and has pre-adjusted settings and imaging specifications that require minimal adjustment. The following settings should be optimised(16):

- MI should be 0.1-0.3
- Gain and Time Gain Compensation (TGC), adjusted to minimize near field gain
- Transmit focus level should be at the mitral valve level
- Persistence or frame averaging should be low
- Compression or dynamic range should be mid-way
- Depth should be 10-14cm approximately to focus on the left ventricle (see Figure 1)
- Sector width should include the entire LV
- Image colour tint adjustment (chroma map): user preference, however some experts suggest an orange or sunset hue can help with endocardial border enhancement

Imaging is predominantly performed from apical views. Ideally the patient should be in a left lateral position if possible. Cardiopulmonary monitoring is required (see section ‘Safety profile in the critically ill and contraindications’) and monitor for potential side effects up to 30 minutes post procedure. Shadowing from ribs should be avoided.

**Contrast enhanced ultrasound difficulties and artefacts.**
Various pitfalls can arise with the use of ultrasound contrast such as poor filling of the ventricle, basal attenuation and artefacts such as swirling and blooming (see Figure and movie 3)(2,16). All of these difficulties, like many in ultrasound, are more easily conquered with experience and do not take too many studies before reasonable images are achieved. The American Society of Echocardiography recommend that a minimum level of echocardiography experience is required to perform contrast enhanced echocardiography: Level 2, defined as including a minimum of 6 months of echocardiography education involving 300 studies with a wide variety of abnormalities(16,24).

Under-filling of contrast in the ventricle can occur if insufficient amount of contrast is administered, not enough flush used (bolus injection), the MI is too high or significant attenuation is occurring from rib artefacts. Basal ventricle attenuation can occur with a hyperechoic contrast load in the apex and is caused by too much contrast being administered leading to an attenuation artefact. Either simply wait for contrast to dissipate, transiently increase the MI or use a brief high MI impulse (for example with the use of a colour Doppler box) to destroy some bubbles. Contrast swirling is caused by the MI being too high leading to bubble destruction or insufficient contrast being administered. Finally, blooming can be seen both on 2D and Doppler imaging with too much contrast being administered leading to indistinct definition of the endocardial border and spectral Doppler profile respectively (see Box ‘Pitfalls in contrast enhanced ultrasound imaging’).

Applications in the critically ill

The utility of ultrasound contrast in left ventricle opacification (LVO) in rescuing potentially non-diagnostic studies (often defined as more than two LV segments being unable to be imaged) is well reported(2,25). Its potential in the critically ill is to enhance the diagnostic utility of TTE and to prevent the need for more invasive, costly imaging and transfer or sedation required for further procedures (eg: transoesophageal echocardiography [TOE] in a non-ventilated patient)(15). Furthermore, contrast enhanced ultrasound can lead to a significant change in management and this has been reported to be most evident in the critically ill population(3).
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Volume quantification and regional wall motion analysis. LVO enhances the endocardial border, which makes assessment of ejection fraction and regional wall motion analysis more accurate (see Figure 4) and diagnosed with a greater degree of confidence(26).

Cardiac anatomy. Intra-cardiac structures as well as the endocardial border can be defined with increased quality with contrast enhanced echocardiography (see Figure and movie 5), for example: LV thrombi, LV non-compaction (non-compaction cardiomyopathy), cardiac masses, LV pseudoaneurysm, myocardial rupture, apical hypertrophy, LV apical ballooning (Takotsubo’s cardiomyopathy) (see Box ‘Pearl 1’).

Doppler enhancement. The use of contrast can improve the Doppler signal if it is suboptimal on standard TTE. For example, peak velocities may be more easily determined in aortic valve stenosis(27). Agitated saline has also been used for improved tricuspid valve regurgitation velocity interrogation(16). Care should be taken not to overestimated the Doppler profile secondary to a blooming artefact.

Extracardiac / vascular anatomy. Pathologies such as aortic dissection(28), atherosclerotic plaque(29) and true vs false lumen identification in aortic dissections can be detected with increased accuracy(16).

Off-label uses: The property of contrast microsphere bubbles being able to pass through the pulmonary circulation into the systemic circulation can be used to estimate regional myocardial blood flow(5). This is known as real-time myocardial contrast echocardiography. By applying a burst of high MI ultrasound to destroy bubbles the rate and extent to which the contrast reappears in the myocardium can be determined qualitatively as well as quantitatively using specific software. Although sensitivity, specificity and reproducibility can be poor, contrast perfusion imaging can potentially help guide diagnosis and therapy in critically ill patients with troponin elevation to determine if ischaemia is present or not(30,31). There is potential that this technology may also be able to be taken beyond the myocardium with assessment of muscle perfusion (eg: in critical illness myopathy), carotid artery plaque blood flow (eg: in risk analysis of plaque rupture) and other microvascular blood flow areas. This is a wonderful area of potential research in the ICU population in years to come.

Further applications
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Research is the use of ultrasound contrast is growing exponentially with some truly remarkable concepts and potential applications. Outside of the field of diagnostic echocardiography, contrast microspheres have been promoted for transport and delivery of various bioactive substances such as DNA, thus potentially providing a technique for non-invasive gene delivery or organ specific drug delivery such as thrombolysis(32). Further imaging developments tracking the movement of individual microspheres in the ventricle have described the vortex formation of blood in the ventricle(33). This has been used to describe possible ‘ineffective’ blood movement in heart failure and have been hypothesised to provide a mechanism of accurate placement of pacing wires. The possibilities for describing cardiovascular physiology and function in the critically ill population are intriguing.

Summary

Contrast enhanced echocardiography has the potential to rescue undiagnostic transthoracic echocardiograms, which are common in the ICU. This can help direct therapy and increase confidence in findings and reduce the need for unnecessary and potentially harmful investigations or transfer. Ultrasound contrast is one of the safest non-invasive contrast agents in the critically ill and significant side effects are rare, but they need to be known about and appropriately management and protocols need to be in place.
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Boxes

Pearl 1
Contrast enhanced echocardiography can be considered in any patient in whom standard imaging does not lead to diagnostic information when any of the following are being considered: LV thrombi, LV non-compaction (non-compaction cardiomyopathy), cardiac masses, LV pseudoaneurysm, myocardial rupture, apical hypertrophy, LV apical ballooning (Takotsubo’s cardiomyopathy).

Pearl 2
Contrast enhanced echocardiography can salvage a non-diagnostic study in the critically ill patient and prevent the need for more invasive, costly investigations, the need for transport or sedation.

Pitfall 1: Contrast enhanced echocardiography imaging

| Underfilled left ventricle Swirling artefact | Increase contrast being administered |
| Basal attenuation Blooming | Increase flush being administered |
| | Reduce MI |
| | Improve imaging position |
| | Wait for contrast to dissipate |
| | Transiently increase the MI |
| | Use brief high MI impulse (eg: colour Doppler box) |
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**Figure legends**

**Figure & movie 1:** (A) Typical B-mode non-diagnostic image seen in critically ill patient; (B) Contrast specific imaging before contrast administered; (C) Contrast specific imaging with contrast administered demonstrating the endocardial border with clarity (in particular the lateral wall).

**Figure 2:** (A) Unactivated ultrasound contrast agent (Definity), (B) VialMix device used for activating Definity agent, (C) VialMix device in use shaking the Definity vial for activation, (D) Activated Definity agent

**Figure and movie 3:** Pitfalls in contrast enhanced ultrasound imaging: (A) Poor left ventricle filling with ultrasound contrast, (B) Basal attenuation, (C) Swirling artefact, (D) Doppler trace blooming artefact

**Figure 4:** (A) Conventional imaging of a left ventricle in a critically ill patient with the entire endocardial border unable appropriately visualised in the apical four chamber view at end-systole. (B) Contrast enhanced ultrasound in the same patient. The ejection fraction could now be accurately estimated as the endocardiac border is seen with clarity.

**Figure and movie 5:** (A) Conventional imaging in a patient with severely reduced left ventricle systolic function with an echo density seen at the apex suggestive of an apical thrombus. (B) Left ventricle opacification imaging in the same patient clearly showing there is no thrombus present and there is simply heavy trebeculation.
Section C: Myocardial contrast perfusion echocardiography

Bibliography


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Chapter 11: Myocardial contrast perfusion echocardiography in the critically ill

Feasibility of myocardial perfusion assessment with contrast echocardiography: can it improve recognition of acute coronary artery occlusion in the ICU?

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Abstract

**Background:** Diagnosis of acute myocardial infarction (MI) caused by coronary artery occlusion in ICU can be difficult and inappropriate intervention is potentially harmful. Myocardial contrast perfusion echo (MCPE) examines ultrasound contrast intensity replenishment curves in individual myocardial segments measuring peak contrast intensity and slope of return as an index of myocardial blood flow (units = intensity of ultrasound per sec [dB/sec]). MCPE could possibly serve as a triage tool to invasive angiography by estimating blood flow in the myocardium. We sought to assess feasibility in the critically ill and if MCPE could add incremental value to clinical acumen in predicting acute MI from coronary artery occlusion.

**Methods:** Single centre, prospective, observational study. Inclusion criteria were: adult ICU patients with Troponin I >50ng/L and cardiology referral being made for consideration of acute MI. Exclusion criteria: poor echo windows (2pts), known ischaemic heart disease, contrast contraindications. Medical history, ECG, troponin and 2D echo images used to estimate likelihood of MI (clinical acumen) were assessed by 7 cardiologists and 6 intensivists blinded from the MCPE results. Clinical acumen, quantitative MCPE and subjective (visual) MCPE assessment were assessed in their ability to predict acute MI from coronary artery occlusion.

**Results:** 40 patients underwent MCPE analysis; 6 (15%) had acute coronary artery occlusion; median 11 of 16 segments (IQR 8-13) could be imaged (68.8% [IQR 50-81]). No adverse events occurred. A significant difference was found in overall MCPE blood flow estimation between those diagnosed with acute coronary artery occlusion and those without (3.3 vs 2.4dB/s, p=0.050). A MCPE value of 2.8dB/s had 67% sensitivity and 88% specificity in detecting acute coronary artery occlusion. Clinical acumen showed no significant association in prediction of acute coronary artery occlusion (OR 0.6, p=0.09), however if quantitative or visual MCPE analysis was included significant association occurred (OR 17.1, p=0.01; OR 23.0, p=0.01 respectively).
**Section C: Myocardial contrast perfusion echocardiography**

**Conclusions:** MCPE is feasible in the critically ill and shows better association with predicting acute coronary artery occlusion vs clinical acumen alone. MCPE adds incremental value to initial assessment of presence of acute coronary artery occlusion which may help guide those who require angiography.

**Keywords:** critically ill, contrast, echocardiography, perfusion
Section C: Myocardial contrast perfusion echocardiography

Background

Acute myocardial ischaemia (MI) from acute coronary artery occlusion can be challenging to diagnose in the critically ill[1]. Accurate diagnosis is important as unnecessary angiographic intervention or anti-thrombotic therapy can be harmful, particularly in those with multi-organ dysfunction. Medical history, examination, ECG analysis, echo and other investigations are all important for diagnosis but can lack precision in the ICU. Troponin levels, in particular, can be elevated in critically ill patients reflecting myocardial damage, but this may occur through several mechanisms other than acute coronary artery occlusion[1].

Myocardial perfusion assessment with echo contrast (known as myocardial contrast perfusion echocardiography [MCPE]) is a technique used predominantly in stress echo studies for simultaneous assessment of myocardial perfusion and regional wall motion abnormality. It has been shown to improve the detection of coronary artery disease, in a safe manner and can have prognostic value over regional wall motion detection [2,3]. Echo contrast agents (eg: Definity) are microbubbles of inert gas surrounded by a stabilizing shell (eg: perflutren carbon) typically 1-8µm in diameter. These bubbles are injected into the venous system and are small enough to pass through the pulmonary microvasculature to then pass into the systemic circulation. This allows for the labelled use of this agent for left ventricle (LV) opacification to improve detection of thrombus, regional wall motion abnormalities, accurate ejection fraction estimation etc... [4]. Low intensity ultrasound waves are needed when imaging with echo contrast to prevent destruction of the fragile bubbles. However, this feature can be used to advantage by applying a burst of high intensity ultrasound for a short period of time, bubbles are destroyed, and through analyzing the ‘replenishment’ rate, as contrast bubbles trickle back in to the myocardial circulation, perfusion can then be assessed[5] (see Figure 1).
Echo contrast agents have been shown to be safe in the critically ill for LV opacification[6]. This study sought to assess the feasibility of MCPE in ICU patients with raised troponin levels being referred for coronary angiography for suspected acute coronary artery occlusion. Furthermore, we pursued if quantitative or subjective (ie: visual) assessment with MCPE could aid in the diagnosis of acute coronary artery occlusion. It was hypothesised that MCPE would be feasible, improve recognition and add incremental value to clinical acumen.

**Methods**

**Study design**

We performed a prospective, observational study in the ICU at Nepean Hospital, Sydney, Australia between May 2014 and January 2017 on non-consecutive patients (S.O sole MCPE operator in unit, hence dependent on availability). All patients or authorized representatives (next of kin) gave written consent to be involved in the study which was
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approved by the Nepean Blue Mountains Local Health District human research and ethics committee (study 15/17-LNR/15/NEPEAN/37). Inclusion criteria were: adult (>18 years), raised (high sensitivity) troponin I levels (greater than 50 ng/L), acute coronary artery occlusion being considered, and a request made for consideration of coronary angiography. Patients were excluded if they had urgent angiography already performed due to STEMI criteria being met, were unable to have apical echo imaging performed (2 patients), past medical history of ischaemic heart disease, contraindications to echo contrast (allergies, known significant intracardiac shunts, severe pulmonary hypertension), significant valvular abnormalities, pregnant, study refusal.

Six Intensive Care specialists with a high level of echo experience (ie: DDU qualification or equivalent) as well as 7 Cardiologists were invited to review all relevant patient data and echo imaging to provide an estimate, based on clinical acumen, of likelihood of acute coronary artery occlusion on a Likert scale. Data included: admission history, ECG, serum troponin levels, past medical history (particularly including history of hypertension, diabetes, smoking, family history). In addition, time of admission, imaging and Troponin, APACHE III, SOFA score and haemodynamic data was recorded. The presence of acute coronary artery occlusion was assessed by coronary angiography, nuclear imaging, MRI, CTCA or normal repeat echocardiography shortly after initial imaging in patients with stress induced cardiomyopathy diagnosis.

Echocardiography and myocardial contrast perfusion echocardiography (MCPE) imaging

A full comprehensive echo was performed initially by S.O or trained sonographers with either a Vivid 9 or Vivid I echo machine (General Electric, Boston, Massachusetts). The studies and analysis were performed in accordance with leading echo organization guidelines [7] [8] to obtain LV size, ejection fraction and regional wall motion abnormalities to gain a wall motion severity index score: average of 16 segment model score based on normal thickening = 1, hypokinesis = 2, akinesis = 3, dyskinesis = 4. In addition, speckle tracking echocardiography (STE) analysis was also performed to determine global longitudinal strain. STE analysis was completed in manner as previously described [9] [10] by S.O (who has performed over 1000 analysis) in accordance with a consensus document from leading organisations [11]. S.O. then performed the MCPE examination with a Vivid 9
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echo machine with a M3S matrix array transducer, at the earliest time frame possible from inclusion criteria being met.

The contrast agent Definity® was used for MCPE analysis. The microspheres have a mean bubble size 1-10µm enabling passage through the pulmonary vasculature[4]. Definity was drawn up into a 20ml syringe with normal saline and injected in 1-2ml increments to enable a homogenous contrast enhancement in the myocardium with no attenuation. Once imaging was optimized a flash of higher intensity ultrasound (MI ~1.0) for 30 frames (to cover at least one systolic period) timed to coincide with systole on the ECG, was manually triggered. Images were recorded for 2-5 beats prior to the flash, and 8-15 beats after the flash to adequately assess for replenishment.

MCPE image analysis

Images were transferred to an EchoPACS reporting station (General Electric, Boston, Massachusetts) for off-line quantitative analysis for each segment that was able to be visualised. Analysis was attempted to be performed in a blinded fashion to outcome results in a manner as previously described in other studies [12,13]. Subjective (visual) analysis was performed with a simple scoring system: 0 normal, 1 contrast perfusion deficit. Quantitative analysis was performed by measuring ultrasound signal intensity in the ‘region of interest’ (ROI) at each myocardial segment following a standard 16 cardiac segment model (see Figure 2). The ROI size was optimized to include as much of the myocardial segment as possible while avoiding the low intensity signals from the pericardium or high intensity signals from the LV cavity. The first end-systolic frame after the ‘flash’ was considered $t_0$ and signal intensity (SI) was calculated for each ROI at each end-systolic frame and plotted against time and fitted to the exponential function: $y(t) = A(1-e^{-\beta(t-t_0)}) + C$. $Y$ is the SI in the ROI at the end-systolic frame, $A$ is the plateau SI corresponding to myocardial blood volume, $\beta$ is the exponential decay function (decay constant) representing the rate of SI rise and $C$ is the intercept at the origin reflecting the background intensity level. $A \times \beta$ provides an estimate of the initial rate of contrast replenishment and this provides a surrogate of myocardial blood flow[14].
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**Figure 2:** Segmental coronary artery territory vascular supply used for feasibility assessment of myocardial contrast perfusion echocardiography (MCPE) and 2D echo analysis.

Feasibility of both subjective and quantitative analysis was assessed at segmental and coronary artery territory distribution (see Figure 2) as well as apex vs mid vs basal level. Segments were excluded from analysis if the myocardium vasculature lacked opacification on visual and quantitative analysis. Coronary artery territories were considered ischaemic if a third (or more) of the segments in that territory had impaired contrast filling. The left anterior descending (LAD) and right coronary artery (RCA) territories were considered unable to be assessed if 2 segments were unable to be examined. The left circumflex coronary artery (LCx) territory was considered unable to be assessed if 1 segment could not be examined.

**Statistical analysis**

Due to the exploratory nature of the study a sample size was not formally calculated and a number of 40 patients was felt suitable to make an initial assessment and guide future research. Statistical analysis was performed with JMP Pro version 13 (SAS Institute Inc., Cary, NC, USA). Continuous variables are expressed as mean +/- standard deviation (SD) if normally distributed, median with interquartile range (IQR) if not normally distributed. Normality was assessed using the Shapiro-Wilk test. Feasibility was defined as the number
of segments where analysis was possible compared to total segments from all included patients. Between group comparison for continuous data was performed by Student t-test and non-parametric or non-normally distributed data by Wilcoxon signed-rank/Kruskal-Wallis (rank sum) test. Categorical data was compared by Pearson’s chi-squared analysis or Fisher’s exact test. All probability values are two-sided and P values <0.05 are considered statistically significant. Logistic regression was used to assess the association between the presence of acute coronary artery occlusion and clinical acumen and/or subjective or visual MCPE analysis. Receiver operating curves were analysis to determine optimal MCPE values for presence or absence of acute coronary artery occlusion. Inter-rater variability was performed on a random 15% of patients for myocardial blood flow estimation by MCPE and assessed by absolute difference and expressed as a percentage of their mean.

Results
40 patients, 70% female, mean age 59.8 (±17), were included in the study of which 6 were confirmed to have acute coronary artery occlusion (15%), all by coronary angiography: 2 patients with right coronary artery ischaemia, 1 patient with left circumflex coronary artery and 3 with both the left anterior descending and left circumflex coronary artery occluded. No adverse reactions to echocardiography contrast were seen. Acute coronary artery occlusion was assessed by angiography in 22 patients (55%). Normal non-invasive studies led to the decision not to proceed with angiography in the remaining 18 patients: normal follow up echo in 11 (28%), normal CT coronary angiogram in 3 (8%) and normal MRI perfusion study in 4 (10%). Demographic, clinical and initial investigation data is presented in Table 1. No major baseline differences were seen between patients with no acute coronary artery occlusion found vs those with occlusive disease, except diabetes was more prevalent in the acute coronary artery occlusion group (p=0.001). Patients were critically ill as demonstrated by a mean SOFA score of 7 (equating to a 15-25% risk of ICU death[15]) and a mean APACHE III score of 73 (estimated risk of hospital death approximately 25-35%[16]), with 43% requiring catecholamine support and 53% mechanically ventilated. Risk factors for coronary artery disease were commonly seen in both groups (particularly hypertension and smoking, seen in 40% and 35% respectively).
## Section C: Myocardial contrast perfusion echocardiography

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall</th>
<th>No significant coronary artery disease diagnosed</th>
<th>Acute coronary artery occlusion</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Number (n, %)</td>
<td>40</td>
<td>34 (85%)</td>
<td>6 (15%)</td>
<td>-</td>
</tr>
<tr>
<td>Female (%)</td>
<td>28 (70%)</td>
<td>25 (74%)</td>
<td>3 (50%)</td>
<td>0.25</td>
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<tr>
<td>Age (years)</td>
<td>59.8 (+17)</td>
<td>58.1 (+17)</td>
<td>69.4 (+18)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>16 (40%)</td>
<td>13 (38%)</td>
<td>3 (50%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>9 (22%)</td>
<td>4 (12%)</td>
<td>5 (83%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>14 (35%)</td>
<td>11 (32%)</td>
<td>3 (50%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Family history (%)</td>
<td>4 (10%)</td>
<td>3 (9%)</td>
<td>1 (17%)</td>
<td>0.55</td>
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<td>Systolic (mmHg)</td>
<td>117 (102-127)</td>
<td>114 (101-128)</td>
<td>122 (+10)</td>
<td>0.9</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>64 (+13)</td>
<td>65 (+14)</td>
<td>60 (+13)</td>
<td>0.39</td>
</tr>
<tr>
<td>Mean (mmHg)</td>
<td>79 (68-94)</td>
<td>83 (+16)</td>
<td>80 (+10)</td>
<td>0.57</td>
</tr>
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<td>Sinus rhythm (n, %)</td>
<td>38 (95%)</td>
<td>32 (94%)</td>
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<tr>
<td>Heart rate (beats per min)</td>
<td>86 (18)</td>
<td>87 (+19)</td>
<td>78 (+8)</td>
<td>0.07</td>
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<td>Weight (kg)</td>
<td>80.4 (+24)</td>
<td>79.9 (+25)</td>
<td>83.7 (+18)</td>
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<td>GCS</td>
<td>11 (3-15)</td>
<td>11 (3-15)</td>
<td>11 (5-15)</td>
<td>0.5</td>
</tr>
<tr>
<td>Catecholamines required (n, %)</td>
<td>17 (43%)</td>
<td>16 (47%)</td>
<td>1 (17%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Dose (mcg/kg/min)</td>
<td>15.1 (+10)</td>
<td>15.1 (+10)</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>Mechanical ventilation (n, %)</td>
<td>21 (53%)</td>
<td>18 (53%)</td>
<td>3 (50%)</td>
<td>1.0</td>
</tr>
<tr>
<td>PaO2 (mmHg)</td>
<td>78 (68-89)</td>
<td>75 (66-88)</td>
<td>88 (+20)</td>
<td>0.5</td>
</tr>
<tr>
<td>Platelets (ng/dL)</td>
<td>231 (+102)</td>
<td>230 (+103)</td>
<td>239 (+106)</td>
<td>0.9</td>
</tr>
<tr>
<td>Creatinine (ng/dL)</td>
<td>91 (61-170)</td>
<td>89 (61-171)</td>
<td>122 (+64)</td>
<td>0.8</td>
</tr>
<tr>
<td>Bilirubin (ng/dL)</td>
<td>6.5 (5-15)</td>
<td>8 (5-15)</td>
<td>5 (4.5-17)</td>
<td>0.3</td>
</tr>
<tr>
<td>SOFA score</td>
<td>7 (5)</td>
<td>7 (5)</td>
<td>6 (5)</td>
<td>0.6</td>
</tr>
<tr>
<td>APACHE III</td>
<td>73 (32)</td>
<td>72 (34)</td>
<td>82 (7)</td>
<td>0.3</td>
</tr>
<tr>
<td>ST elevation, n(%)</td>
<td>5 (13%)</td>
<td>5 (15%)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>T wave inversion or flattening, n(%)</td>
<td>29 (73%)</td>
<td>24 (71%)</td>
<td>5 (83%)</td>
<td>1.0</td>
</tr>
<tr>
<td>ST depression, n(%)</td>
<td>6 (15%)</td>
<td>4 (12%)</td>
<td>2 (33%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Troponin I (ng/mL)</td>
<td>1987 (400-4384)</td>
<td>1943 (357-4182)</td>
<td>3016 (1255-8630)</td>
<td>0.28</td>
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<td>LV end diastolic diameter (mm)</td>
<td>49.0 (8)</td>
<td>48.6 (8)</td>
<td>50.7 (7)</td>
<td>0.54</td>
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<td>LV ejection fraction (%)</td>
<td>45.7 (15)</td>
<td>46.1 (15)</td>
<td>43.2 (16)</td>
<td>0.69</td>
</tr>
<tr>
<td>Wall motion score index</td>
<td>2.0 (1.4-2.4)</td>
<td>2.0 (1.5-2.4)</td>
<td>1.8 (0.5)</td>
<td>0.95</td>
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<td>Global longitudinal strain (%)</td>
<td>-9.2 (5)</td>
<td>-9 (-11 to -6)</td>
<td>-7 (-16 to -7)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

**Table 1:** Baseline patient demographics, clinical parameters and initial investigations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>APACHE III</td>
<td>73 (32)</td>
</tr>
<tr>
<td>SOFA score</td>
<td>7 (5)</td>
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<tr>
<td>Global longitudinal strain (%)</td>
<td>-9.2 (5)</td>
</tr>
<tr>
<td>No significant coronary artery disease diagnosed</td>
<td>34 (85%)</td>
</tr>
<tr>
<td>Acute coronary artery occlusion</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
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</tr>
<tr>
<td>Diabetes (%)</td>
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</tr>
<tr>
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<td>Catecholamines required (n, %)</td>
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</tr>
<tr>
<td>Platelets (ng/dL)</td>
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</tr>
<tr>
<td>Creatinine (ng/dL)</td>
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</tr>
<tr>
<td>Bilirubin (ng/dL)</td>
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</tr>
<tr>
<td>ST elevation, n(%)</td>
<td>5 (13%)</td>
</tr>
<tr>
<td>T wave inversion or flattening, n(%)</td>
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<td>ST depression, n(%)</td>
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<tr>
<td>Wall motion score index</td>
<td>2.0 (1.4-2.4)</td>
</tr>
<tr>
<td>Global longitudinal strain (%)</td>
<td>-9.2 (5)</td>
</tr>
</tbody>
</table>
Section C: Myocardial contrast perfusion echocardiography

No significant differences were seen between the groups in terms of investigations performed assessing for possible ischaemia: including ECG, Troponin I blood tests and echo. The most common ECG finding was T wave inversion or flattening (seen in 73%). Troponin I levels were severely raised in both groups (median 1943 [357-4182] vs 3016 [1255-8630] for those with no acute coronary artery occlusion vs those with respectively). Echo was performed within median 8hours (3-22) from when Troponin levels were taken. Echo data displayed predominantly normal LV size: mean end diastolic diameter 49mm (8); with mildly reduced LV systolic function measured by conventional ejection fraction: mean 45.7% (15); but with global longitudinal strain analysis by speckle tracking more severe dysfunction was elucidated: mean -9.2% (5). Substantial regional wall motion abnormalities were common (median wall motion score index 2 [1.4-1.8]).

Feasibility analysis: Feasibility and values for each myocardial segment analysis technique is are shown in Table 2. Quantitative analysis was estimated to be performed 24hours – 3weeks from time of echo. 2D segmental thickening analysis showed the greatest feasibility (in 90-100% of patients) and subjective MCPE analysis the least (20-53% of patients).

Despite both 2D segmental thickening assessment and longitudinal strain analysis by STE being feasible in the majority of segments assessed, there were no significant differences seen in wall motion score index or longitudinal strain analysis values between groups with acute coronary artery occlusion and those with no coronary artery disease diagnosed. However, in both subjective as well as quantitative MCPE assessment significant differences were seen (except in the right coronary artery territory in quantitative assessment).

Quantitative MCPE analysis had better feasibility than subjective MCPE assessment. The LAD territory was the most feasible to be assessed (65% by quantitative MCPE and 53% by subjective MCPE analysis) and the LCx the least (20% by quantitative MCPE and 33% by subjective MCPE analysis). The feasibility of MCPE subjective and qualitative analysis was greatest at the apical level (89% and 90% respectively). The mid level was easier to analyse (66% and 68% respectively) than the basal level (39% and 48% respectively).
Table 2: Feasibility and results (overall and for individual coronary artery territories) for segmental wall motion assessment with conventional echocardiography as well as myocardial contrast perfusion echocardiography. LAD: left anterior descending coronary artery; LCx: left circumflex coronary artery; RCA: right coronary artery.

Detection of acute coronary artery occlusion: Based on ROC curve analysis, the optimal MCPE cut-off value for presence vs absence of acute coronary artery occlusion is 2.9 dB/s (see Figure 3) which had 67% sensitivity and 88% specificity.
**Figure 3:** Receiver operating curve for myocardial contrast perfusion echocardiography (MCPE) for determining presence vs absence of acute type 1 myocardial infarction (value of 2.9dB/s had 67% sensitivity and 88% specificity).

We found a positive predictive value of 50% and a negative predictive value of 91%. Of the 3 patients who were found to have perfusion deficits on MCPE, 2 had angiography and the other an MRI. Association between clinical acumen and quantitative MCPE or subjective MCPE analysis in predicting acute coronary artery occlusion is shown in *Table 3*.

<table>
<thead>
<tr>
<th>Model</th>
<th>Covariates</th>
<th>Odds Ratio [Confidence intervals]</th>
<th>P value</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Clinical acumen</td>
<td>0.64 [0.37-1.10]</td>
<td>0.091</td>
<td>0.09</td>
</tr>
<tr>
<td>2</td>
<td>Quantitative MCPE analysis</td>
<td>10.3 [1.41-75.7]</td>
<td>0.022</td>
<td>0.15</td>
</tr>
<tr>
<td>3</td>
<td>Subjective MCPE analysis</td>
<td>33.0 [2.57-424.0]</td>
<td>0.003</td>
<td>0.26</td>
</tr>
<tr>
<td>4</td>
<td>Clinical acumen</td>
<td>0.57 [1.03-1.75]</td>
<td>0.049</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>Quantitative MCPE analysis</td>
<td>17.15 [1.61-183.1]</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Clinical acumen</td>
<td>0.74 [0.38-1.40]</td>
<td>0.352</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>Subjective MCPE analysis</td>
<td>23.05 [1.69-313.6]</td>
<td>0.010</td>
<td></td>
</tr>
</tbody>
</table>

*Table 3:* Logistic regression analysis of association between clinical acumen, quantitative or subjective myocardial contrast perfusion echocardiography (MCPE) analysis in predicting presence of acute myocardial infarction. MCPE; myocardial contrast perfusion echocardiography
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Clinical acumen showed no significant association in predicting presence of acute coronary artery occlusion (OR 0.64, p=0.091), however if quantitative or subjective MCPE analysis was included in the model incremental improvement and significant association was seen (OR 17.15, p=0.013; OR 23.05, p=0.010 respectively). The best association was seen with subjective MCPE analysis alone (OR 33.0, p=0.003).

Inter rater variability was assessed by M.S vs S.O in a random 6 patients (15%). Inter-rater variability was reasonable with mean absolute difference in estimated blood flow (+/-SD) of 0.31dB/s (+/-1.5) and expressed as percentage of the mean 9% (+/-36).

Discussion

We found myocardial contrast perfusion echocardiography (MCPE) to be feasible to perform in critically ill patients, with no significant adverse reactions were seen. Importantly, clinical acumen alone (using clinical history, ECG, echo and Troponin I levels) did not have significant association with predicting the presence of acute coronary artery occlusion. However, if quantitative or subjective MCPE analysis was included in the assessment then significant association was seen.

Troponin I levels are frequently elevated in the ICU population, however only a minority of patients have acute coronary artery occlusion (eg: from thrombus or acute plaque rupture). Ko et al found only 30% of ICU patients with raised Troponin levels and ECG changes suggestive of coronary artery disease ended up with a diagnosis of acute ischaemia on coronary angiography [1]. Neither conventional segmental myocardial thickening analysis on 2D echo images or longitudinal strain analysis by STE could distinguish acute ischaemia either. This is mirrored in the fact that both specialists in ICU and cardiology were unable to reliably predict acute coronary artery occlusion based on convention means. The diagnosis of acute coronary artery occlusion can be extremely difficult in the critically ill and this is potentially dangerous given the risk of sending a patient for angiography (including radiographic contrast administration) or prophylactic use of anti-platelet and anticoagulation agents. Our study indicates that MCPE use can aid in making the correct diagnosis.
Wei et al pioneered the method of using echo contrast to estimate myocardial blood flow, and it appeared to correlated well with radiolabeled microsphere myocardial blood flow [17]. This technique has been used in the cardiology sphere for decades and large safety studies have been performed on the use of contrast [18], but to our knowledge there is little information of the utility of MCPE in the critically ill. We see this analysis technique not to replace angiography or other imaging modalities, but to help reduce some of the variation seen in clinical assessment with conventional means and may help direct decision making. It is far from perfect but may be a useful addition to the critical care physician armamentarium.

We found MCPE much better at assessing the apical than the basal segments, which may mean that this method may be more efficient at assessing left anterior descending coronary artery territory ischaemia than the other coronary arteries. Indeed feasibility was much better in the LAD territory than the LCx or RCA. This is disappointing given that posterior ischaemia may be more difficult to diagnose in critically ill patients, however other studies have reported similar results [19].

**Limitations:** There are several limitations to our small, single center, observational study. The primary issue is the lack of a recognized reference standard to exclude acute coronary artery occlusion (angiography or cardiac MRI) in a significant portion of our patients (eg: 28% of our patients a simple normal follow up echo). However, often once an acute event had settled the risk of angiography may outweigh the benefit (eg: likely stress induced cardiomyopathy in a patient with subarachnoid haemorrhage). It is not excluded that those with an initial abnormal echo and then normalized findings at a later date still had coronary artery disease similar to those having exercise stress tests, however we did find a high specificity and negative predictive value in those with acute coronary artery disease. In addition, the analysis was performed by a single operator (S.O) who was at times the treating clinician. The blinding of the analysis was therefore, at times, not possible. Patients were not consecutive as S.O was the sole MCPE operator in the unit and patient inclusion was based on other clinicians highlighting potential subjects, during work hours. Several patients are likely to have been missed and this suggests selection bias. However, this was...
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primarily a feasibility study and information may be useful as pilot data to guide future studies. The analysis of our data into coronary artery territories may also be inaccurate as individual patient coronary artery blood flow does not always follow the standard anatomical boundaries.

**Future research:** The use of MCPE in determining large defects in myocardial blood flow useful in the ICU environment and further research should be done in this area to try and help improve our early recognition of acute coronary artery occlusion. Studies should focus on true blinded assessment, multi-operator analysis and objective MCPE analysis performed immediately after the study has taken place. Additional studies may assess the significant variation seen in clinicians estimating the likelihood of acute coronary artery occlusion being present and if MCPE analysis could help reduce some of this variation.

**Conclusion:** We found MCPE estimation of myocardial blood flow to be feasible in critically ill patients and found no adverse events. Clinical correlation alone is extremely variable and unable to reliably determine the presence or absence of acute coronary artery occlusion, yet we know that unnecessary intervention or treatment can be harmful. MCPE may be able to improve our recognition in predicting acute coronary artery occlusion in the critically ill.
List of abbreviations:

Echo; echocardiography
LAD; left anterior descending coronary artery
LCx; left circumflex coronary artery
LV; left ventricle
MCPE; myocardial contrast perfusion echocardiography
MI; myocardial infarction
RCA; right coronary artery
ROI; region of interest
SI; signal intensity
Declarations:

Ethics approval and consent to participate: The study was approved by the Nepean Blue Mountains Local Health District (study 15/17-LNR/15/NEPEAN/37) and written consent was provided prospectively by the patient or authorized representative (next of kin) prior to imaging.

Consent for publication: Consent for use of de-identified images contained in this article was given by the individuals involved.

Availability of data material: The datasets generated and analysed during this study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: Not applicable.

Author contributions: SO conceived and designed the study, acquired data including performing the echocardiograms, analysis of the data and preparation of the manuscript. MS and FP assisted with data analysis, interpretation and drafting of the manuscript. AM assisted with study design, data analysis and drafting of the manuscript. SH assisted with study design, data analysis, statistical analysis and drafting of the manuscript. All authors drafted and reviewed the manuscript and approved the final draft.

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CONCLUSIONS
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The aim of this thesis was to determine the feasibility and potential clinical use of advanced echocardiography techniques, particularly (a) speckle tracking echocardiography (STE), (b) 3D transthoracic echocardiography (3D TTE) and (c) myocardial contrast perfusion echocardiography (MCPE). I have addressed these questions in 3 sections relating to each technique and I will conclude discussions in turn.

(a) Speckle tracking echocardiography (STE)

This promising technique for elucidating cardiac dysfunction was found to be feasible in the majority of critically ill patients: LV STE analysis (global longitudinal strain) could be performed in 80% of patients and RV free wall strain in 79-85% of patients examined in the 5 research studies included in this section. STE was also found to have practical utility: in all studies more LV and RV dysfunction was found using STE compared to conventional analysis. Indeed, after showing it to be feasible in the initial studies, we used RVfwS as a reference standard in a multi-centre study assessing subjective RV analysis in critically ill patients. In particular, RV dysfunction assessed by RV free wall stain (RVfwS) held significant prognostic relevance in those with septic shock and highlighted subtle dysfunction induced by mechanical ventilation (both in animal and human studies) in critically ill patients.

(b) 3D transthoracic echocardiography (3D TTE)

The ability to accurately measure LV and RV volumes in the critically ill plays an important role in analysis of cardiac function and haemodynamics, which are often abnormal in the ICU setting. Hence, 3D TTE analysis of cardiac volumes seems enticing: with its semi-
Conclusions

automatic nature and wealth of information provided with one acquired loop. Despite finding 3D TTE feasible in the majority of mechanically ventilated ICU patients for volumetric analysis (more so LV than RV, 72% and 55% respectively), it lacked the necessary low variability and high precision vs standard measures used in the ICU environment to conclude it is suitable for clinical use at this stage. Further studies are needed in this area, particularly using a robust reference standard, analysing the change in SV and 3D TOE analysis.

(c) Myocardial contrast perfusion echocardiography (MCPE)

Current minimally invasive methods to assess for acute coronary artery occlusion in the critically ill lack sensitivity and specificity. Troponin elevation, acute ECG changes, regional wall motion analysis on echo and overall clinical acumen often lack diagnostic capabilities. MCPE was found to be feasible in the critically ill in our small single centre study and showed better association with predicting acute coronary artery occlusion vs clinical acumen alone. As mentioned, we do not suggest MCPE should take the place of diagnostic angiography, but merely may help triage patients who may need the service. Again, robust reference methods for analysis other than angiography would be beneficial, as well as larger studies, with multiple imaging clinicians involved to assess feasibility in a more clinically realistic manner.

Ongoing research

Broad conclusions from our thesis suggest both STE and MCPE are feasible in the critically ill and may have clinically relevant uses. Significant limitations in all of our studies were the lack of a suitable reference standard and that the majority of imaging and analysis were often performed by a single operator. For these techniques to hold true clinical significance, multi-centre assessment by typical critical care physicians with advanced echo skills vs a gold standard (eg: MRI) is required.