Abnormal Aortic Distensibility in Well Controlled Diabetes

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This is to certify that the content of this thesis is my own work. This thesis has not been submitted for any other degree or purpose.

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

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I designed the study with Professor Rajesh Puranik, analysed the data, and wrote the drafts of the manuscript.

In addition to the authorship attribution statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

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As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Lead Supervisor: Professor Rajesh Puranik 30 September 2025

Abstract

Cardiovascular Magnetic Resonance Evaluation of Aortic Distensibility in well controlled Diabetics

Background:

Diabetes mellitus is strongly associated with cardiovascular disease. Specifically, aortopathy can directly contribute to adverse outcomes in diabetic patients but where the precise mechanism of such disease remains unknown. Cardiac MRI (CMR) provides an opportunity to assess aortopathy by quantitating regional aortic distensibility (AoD).

Aims:

Using CMR at 1.5 T, we compared AoD in individuals with well controlled diabetes and no definite coronary artery disease with healthy controls. Early detection of AoD changes could improve clinical surveillance strategies by identifying individuals with “at risk” phenotype for aortic and vascular complications relating to diabetes.

Methods:

CMR generated cine b-SSFP imaging was acquired in the mid ascending aorta and retrospectively gated throughout the entire cardiac cycle. AoD was then calculated via the following equation.

Aomax – Aomin / Aomin * central pulse pressure in subjects with diabetes attending the RPA Diabetes Centre and matched control subjects. Patient demographics and blood pressure was collected.

Results:

Patients with type 2 Diabetes Miletus (T2DM) (n=49, age 59±5years, 63% male, HbA1c 7.4±1.8%, systolic blood pressure 127±9mmHg) had a mean AoD of 2.32±1.34 mmgh-1 * 10-3 compared to controls (n=23, age 57±7, systolic blood pressure 137±13) mean AoD of 4.05 +/- 2.00 mmgh-1 * 10-3 (p=0.046).

Conclusions:

We have demonstrated reduced AoD in well controlled diabetics using CMR. This finding contributes to our understanding of how diabetes leads to the development of aortopathy and warrants longitudinal monitoring for the development of complications.

Introduction:

Diabetes Mellitus (DM) prevalence is increasing. In 2021, the International Diabetes Federation reported that more than 500 million people (10.5% of the world's population) were affected by DM (1). In the same year, 1.3 million Australians were living with DM according to the Australian Institute of Health and Welfare which is a 2.8-fold increase compared to the number of patients in the year 2000 resulting in a 2.5% contribution to the total disease burden in Australia (2).

The link between diabetes and ischaemic heart disease and stroke is strong and well-established (3). Diabetes patients have an approximately two-fold increase in cardiovascular risk (4). Both type 1 and type 2 diabetes, are increasingly recognized as a driver of cardiovascular dysfunction through mechanisms involving arterial stiffness and left ventricular (LV) remodelling (5). Even when adjusting for other risk factors of cardiac disease, such as blood pressure and ischaemic heart disease, type 2 diabetes duration remained an independent risk factor for LV diastolic dysfunction (6). This suggests a direct link between diabetic cardiomyopathy and metabolic derangement which is identified in diabetes.

Furthermore, in diabetic patients, the risk of peripheral vascular disease (PVD) is higher, occurring earlier and is often more severe and diffuse (7). Endothelial dysfunction, vascular smooth muscle cell dysfunction, hyper-coagulability and inflammation are the key factors in diabetic arteriopathy which may cause "aortopathy" leading to various complications along the entire arterial tree.

Multiple inherited and acquired conditions predispose patients to aortopathy including Marfan syndrome, bicuspid aortic valve, and hypertension. However, the relationship between DM and disease of the aorta is complex and not well understood. For example, aortic stenosis (AS) is the most common heart valve disorder in developed countries (8). Dysglycaemia, including glucose levels below the diabetic range, is associated with a higher risk of aortic stenosis (9) and diabetes not only predisposes to degenerative AS but may also contribute to faster disease progression (10). Furthermore, having diabetes is a well-established risk factor for micro and macro vascular disease (11) which are the principle causes of mortality and morbidity in diabetes (12). At the same time, counter-intuitively, in a large-scale study performed by the UK Prospective Diabetes Study (UKPDS) group, the intensive control of diabetes was not associated with reduced macrovascular complications (13).

Further, in a study conducted within our group, we found that the major risk factors for fatal aortic dissection development to be the presence of aortic atherosclerosis and hypertension (14) both of which commonly develop in DM due to complex biochemical pathways related to prolonged exposure to hyperglycaemia and insulin resistance (15). Counter intuitively, however, numerous studies revealed decreased incidence of aortic aneurysms and aortic dissection in patients with DM (16, 17). A nationwide case-control study in the United States found that diabetes was independently associated with decreased rate of hospitalization due to thoracic aortic aneurysm and dissection (17). And a systematic review suggested a protective role for DM on the development of abdominal aortic aneurysms (16). The explanation for these contradictory findings remains uncertain. Hence, the lack of understanding of

the relationship between diabetes and macrovascular complications including aortopathy provides an important avenue of investigation amongst the diabetic cohort using new and emerging imaging techniques to better delineate cardiovascular risk and/or predicting events.

Our group has reported the use of cardiovascular magnetic resonance (CMR) to identify biomarkers of cardiomyopathy in patients with well controlled T2DM and without significant coronary disease. In these patients we have shown frequent occurrence of focal and diffuse myocardial fibrosis that reduces left ventricular compliance leading to development of diabetic cardiomyopathy and possibly resulting in adverse effects on the aorta (18).

Aortic distensibility (AoD) is aorta's ability to change its diameter, area, and pressure during the cardiac cycle to facilitate changing pulsatile flow, in the more "central vasculature," into a steadier or laminar flow which protects the smaller peripheral arteries from severe changes in blood pressure. When AoD is abnormal, it is a strong predictor of future cardiovascular events and all-cause mortality (19).

AoD can be calculated using pulse wave velocity recorded during invasive pressure catheterization. However, in clinical practice, this technique is only used in technical validation studies due to its complexity, cost and Cath-Lab access limitations (20).

With recent advances in technology, various non-invasive imaging modalities can be used to assess AoD including cardiovascular CT, echocardiography, and cardiovascular MRI (CMR).

Computed tomography (CT) gated to the cardiac cycle (cardiac CT) is able to produce tomographic images of the aorta at different phases in the cardiac cycle allowing for assessment of AoD (the maximum and minimum cross-sectional areas of the aorta at an anatomical region of interest are measured), where the distensibility is calculated using the pulse pressure). This technique provides exceptional spatial but often less than ideal temporal resolution unless increasing radiation doses are used. This may lead to underestimation of distensibility if the time point of maximal aortic distention is not captured. It also exposes the patient to iodinated contrast and ionizing radiation, as it requires continuous CT imaging during the entire cardiac cycle (21).

Echocardiography is cheap and widely available modality for vascular characterisation. Compared to cardiac CT, it provides excellent temporal resolution. However, it remains operator dependant and various patient factors may hinder acquiring necessary ‘acoustic windows’ for accurate assessment of deep vessels (22). The spatial resolution for the proximal aorta on echocardiography may be insufficient to reliably calculate AoD.

Cardiac cine Magnetic Resonance Imaging (CMR) is a non-invasive technique that utilizes strong magnetic fields and nonionizing radiation to enable accurate

measurements of both central and peripheral arteries with high special and temporal resolution (22, 23). This allows robust assessment of AoD and may help identify a relationship between AoD and DM. When echocardiography is compared to CMR for measuring AoD in the abdominal aorta, better reproducibility was demonstrated with CMR than with the ultrasound (24).

Furthermore, using CMR with extracellular paramagnetic contrast agents enables measurement of subclinical changes in extracellular volume (ECV), left ventricular end diastolic volume (LV EDV), LV mass, left ventricular ejection fraction (LV EF) and late gadolinium enhancement (LGE). All of which may have utility in understanding mechanisms of disease. Of note, despite the valuable information CMR can provide, this technology is still under-utilised in diabetes due to limited access and relatively higher cost.

Aim:

In this study, we investigated whether adverse aortic phenotype could be established in diabetic subjects and develop independent predictors of reduced AoD. These findings could then assist in improving the vascular surveillance strategy used in diabetic patients prior to the development of established vascular disease and its often severe associated complications in the aorta.

Specifically, we aimed to use CMR to examine the correlation between DM and AoD and identify predictors for the development of abnormal AoD in diabetics.

Methods

Study design:

This is a prospective case control study in which we used the data of previously recruited patients in the DiCOM study (18). During the recruitment period, all patients who attend the diabetes outpatient clinic were invited to participate in the study.

215 patients with Type 2 Diabetes Miletus from the outpatient diabetes clinic service at the Royal Prince Alfred Hospital (RPAH) were screened. 159/215 were excluded for the following reasons: Ninety-two were not contactable by phone, forty-nine declined to participate and eighteen met one of the exclusion criteria.

Inclusion Criteria

1. Patients with type 2 diabetes under active follow up at the Royal Prince Alfred Hospital Diabetes Centre.

The exclusion criteria were:

a. Pre-existing significant coronary artery disease (defined as invasive angiography or cardiac computed tomography coronary angiography evidence of >75% stenosis in epicardial coronary arteries or > 50% in the left main coronary artery.
b. Transthoracic echocardiography evidence of pulmonary hypertension defined as estimated peak systolic pulmonary artery pressure of > 45 mmHg.

c. Patient reported history of excess alcohol intake of >80 g per day.

d. Known inheritable non-ischaemic cardiomyopathy in a first degree relative.
e. Creatinine-based estimated glomerular filtration rate (eGFR) <45 ml/ min/1.73m2.
f. Transthoracic echocardiography (TTE) evidence of a moderate valvular heart disease or greater.
g. Uncontrolled high blood pressure defined as a systolic blood pressure average of > 160 mmHg despite treatment with at least 3 antihypertensive medications.

The remaining fifty-six patients were prospectively recruited to undergo cardiac MRI. 6/56 patients dropped out for the following reasons: Four patients due to claustrophobia, one patient due to low eGFR on the day of CMR scan eGFR <45ml/min and one patient dropped due to body habitus.

Fifty patients completed CMR. One patient who completed CMR dropped out because CMR was suggestive of hypertrophic obstructive cardiomyopathy. The remaining forty-nine patients with CMR were included in this analysis.

The comparison group included 23 otherwise healthy non-diabetic volunteers who did not meet any of the exclusion criteria. Comparison group subjects were recruited through advertisement.

Clinical data and assessment**:**

The recruited diabetic patients received at least annual assessment of their diabetes including a clinical and biochemical assessment and monitoring for complications (microvascular and macrovascular) as per guidelines (25).

Participants' medical history was assessed in detail to ensure they do not meet any exclusion criteria. During their visits to the diabetes clinic, they were screened for symptoms suggestive of coronary artery disease and underwent a comprehensive clinical examination including assessment using the Borg Dyspnoea Scale (26). Healthy volunteers had DM ruled out. A median HBA1c was calculated using values from a minimum of three clinical visits. Blood pressure was measured at the brachial artery as part of the CMR process. Patients' weight and height were also recorded during their CMR visit.

Current medications for diabetes patients:

During participants' pre-study assessment visit, thirty-nine diabetes patients (80%) were taking metformin. SGLT-2 (sodium glucose transporter – 2) was used by fifteen diabetic patients (31%). Fourteen diabetics were on insulin (29%) and 19 (39%) were taking an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB). Thirty-six diabetics were being treated with a statin (73%).

CMR imaging protocol:

All participants had haemoglobin and haematocrit measured using the hospital pathology lab or iSTAT point of care analyser prior to the CMR scans.

Participants were then scanned using a 1.5 T CMR scanner (Achieve, Philips healthcare, Best, The Netherlands) with an 8-channel cardiac chest coil and retrospective ECG gating during breath-hold.

Using Balanced steady-state free precession sequences, we acquired short axis Cine images of the heart between the mitral valve and the apex, and long axis images of the left ventricle in standard 4-chamber, 3-chamber, and 2-chamber views.

Typical parameters were repetition time (TR) <4 ms; echo time (TE) 1.5 ms; flip angle 60; slice thickness 8–10 mm; matrix 192 × 256; field of view 300–380 mm; and temporal resolution 40 ms.

Late gadolinium enhancement:

Entire study cohort received 0.2mmol/kg Gadobutrol as an intravenous gadolinium contrast bolus, followed by a flush with 20 ml saline. Both injected at 2 ml/s. We obtained CMR late gadolinium enhancement images 10 minutes after contrast administration using a phase-sensitive inversion recovery pulse sequence. The null point within the myocardium was guided by a Look Locker sequence.

T1 mapping:

In two matching positions we acquired two ECG gated native T1 values at mid left ventricle. First native T1 measurement acquired before contrast and the second value was obtained 15 minutes after contrast administration. Native T1 was measured using an ECG gated MOLLI (modified Look-Locker inversion) recovery sequence.

The sampling scheme we used for pre-contrast MOLLI sequence was a 5 s (3 s)3 s sampling scheme and the post-contrast sampling scheme we used was a 4 s (1 s)3 s (1 s)2 s.

T2 mapping:

Before giving contrast, we acquired T2 values in short axis at mid left ventricle using a multi echo GraSE black blood sequence with ECG gating.

MRI analysis for Aortic Distensibility:

We used Cine CMR images to measure the maximum and minimum cross-sectional area of the ascending aorta during the cardiac cycle. The ascending aorta was imaged just above the sino-tubular junction and in its short axis, which was derived by aligning two perpendicular LVOT views to ensure reproducibility. Short axis ascending aorta circumference was traced to determine the maximum (in systole, figures 1 and 1a) and minimum (in diastole, figures 2 and 2a) cross section area using Osirix software and Aortic distensibility was determined using the following equation: AoD = $\frac{AoMax - AoMin}{AoMin\ x\ central\ pulse\ pressure.}$

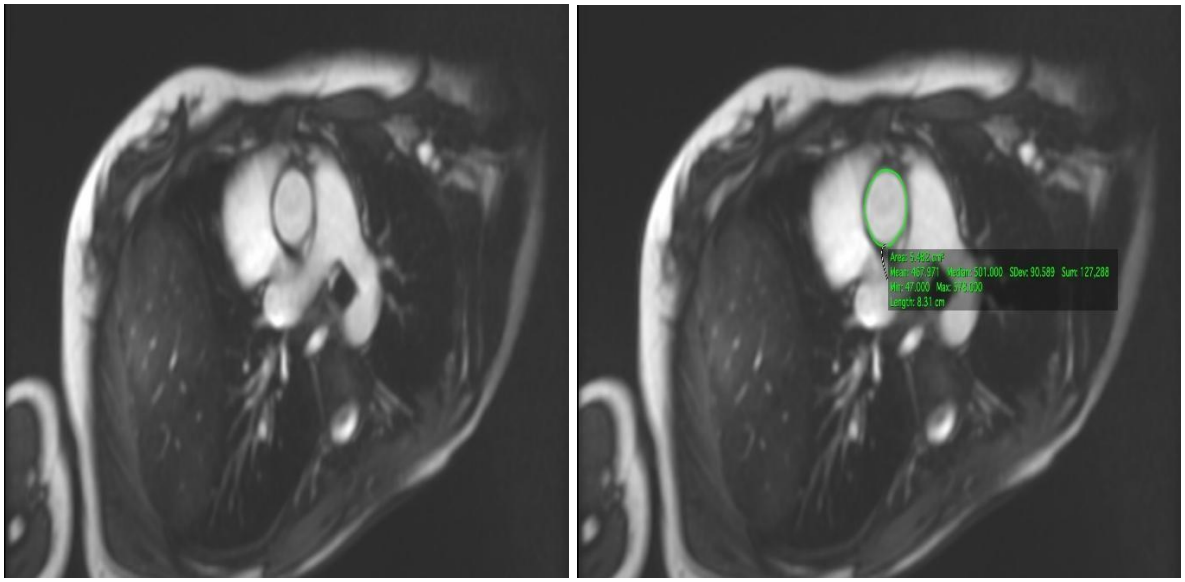

Figure1 (left): cardiac MRI axial image of the ascending aorta during systole and figure 1a (right): traced aortic circumference to obtain area and calculate aortic distensibility.

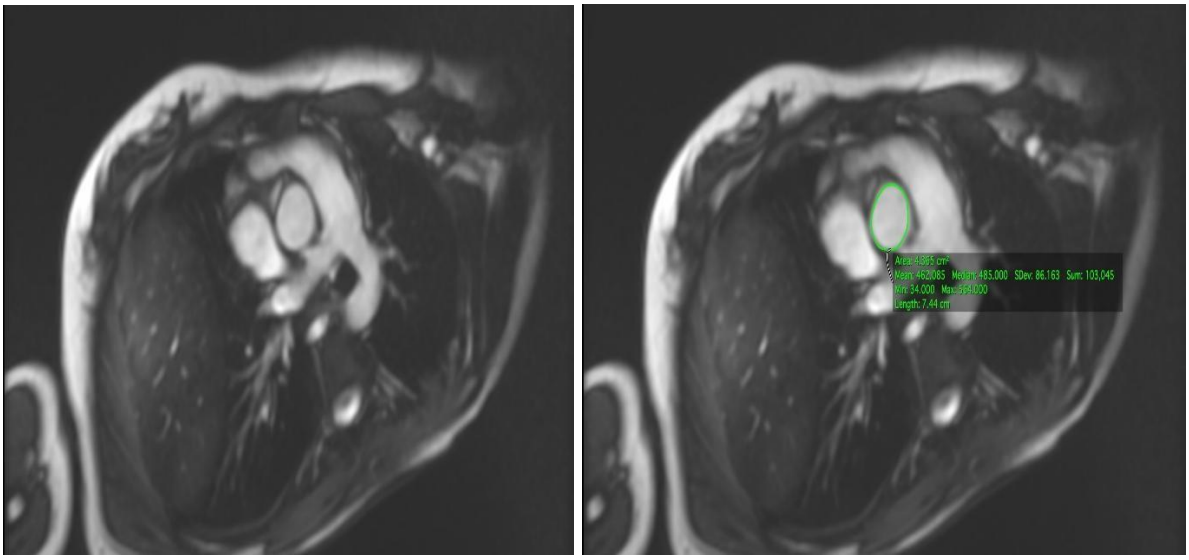

Figure 2 (left): cardiac MRI axial image of ascending aorta of the same patient during diastole and figure 2a (right): traced aortic circumference showing smaller area.

The AoD calculation was confirmed by two investigators who were blinded to the patients' diabetes status and one investigator is a Society of Cardiovascular Magnetic Resonance (SCMR) Level III accredited reporter (RP).

Cine CMR images were also used to measure cardiac chambers volumes. We manually traced the end systolic and end diastolic endothelial borders in each slice of the short axis stack to obtain left ventricle volumetrics, LV mass, and LV ejection fraction.

We obtained patients' weight and height during their cardiac MRI procedure to calculate body surface area (BSA). We then obtained BSA indexed left ventricular mass for each participant.

Using the region of interest tool (ROI) in the Osirix MD software (Pixmeo, Bernex, Switzerland), we obtained T1 maps grey scale and used the results to calculate Extra cellular volume (ECV). This process is recommended by the society of cardiovascular magnetic resonance (SCMR) (27).

A single ROI was determined by conservatively drawing a region on the short axis greyscale maps images of the mid cavity septum. When calculating ECV, any regions of the myocardium demonstrating late gadolinium enhancement were excluded.

To determine LGE presence, we reviewed the LGE image corresponding to the T1 maps. T1 for the blood pool was measured after exclusion of papillary muscles.

ECV was calculated using the following formula. ECV = λ (100 - haematocrit)

$$\lambda = \frac{(1 / \text{Postcontrast Myocardial T1}) - (1 / \text{Postcontrast Myocardial T1})}{(1 / \text{postcontrast blood pool T1}) - (1 / \text{postcontrast blood pool T1})}$$

We followed the same process to assess T2 greyscale maps as recommended by SCMR guidelines. A single ROI was determined by drawing on short axis maps of the septum at the mid cavity level. Any regions of the myocardium demonstrating late gadolinium enhancement were excluded.

Consent and Ethics:

Prospective consent was gained for all patients participating in the study.

The study was reviewed and approved by the Sydney Local Health Districts ethics committee. Protocol Number X18–0245 & HREC/18/RPAH/333.

Statistical analysis

Baseline comparisons were performed using chi-square or Fisher's exact test for dichotomous variables, Student t-tests for normally distributed continuous variables and Mann-U Whitney tests otherwise. We reported results as means with a range of +/- 1 standard deviation or as a median with interquartile range.

This is a cross-section study in which we analysed cardiac MRI data of 72 participants including patients with the presence of Type 2 diabetes mellitus (n=49) and a control group (n=23).

Various multivariant regression analyses were completed for numerous potential predictors of aortic distensibility. We did not hypothesis predictors of aortic distensibility prior to conducting MRI. However, after MRI analysis we included variables that were significantly different between the two groups in these analyses to identify any significant coefficient with aortic distensibility. We evaluated Rsquared and adjusted R-squared in all linear regression models and adjusted the P value accordingly to the number of variables.

In all statistical analyses in this study, a two-sided p-value of <0.05 was considered statistically significant after adjustment of the primary P value by the number of variants included in the analysis as per Bonferroni correction (28).

We used IBM SPSS statistics version 29.0.1.0 for all statistical analyses in this study.

Results:

Seventy-two participants were included in the study. Forty-nine patients with type 2 diabetes with a mean age of 59 years [54 – 64], thirty-one of these patients were males (63%), and twenty-three matched controls with a mean age of 57 years [50 – 64] fourteen subjects of the control group were males (54%). There were no significant baseline demographics differences between T2DM patients and normal controls (table 1). T2DM patients were diagnosed with the disease for an average of 11.2 years [7 – 20]. Average HbA1c was 7.4% (57 mmol/mol) [5.7 – 9.2]. There was no statistically significant difference in systolic or diastolic blood pressure between the two groups. Average systolic blood pressure in diabetics was 127 mmHg [118 – 136] and 137 mmHg [124 – 150] in controls. Average diastolic blood pressure was 82.9 mmHg (73 – 92.8) in diabetics and 78 mmHg (67 – 89) in controls. Heart rate (HR) was mildly increased in the diabetics seventy-one beats per minute (59 – 83) compared to controls 65 (55 – 75).

None of the participants had alcohol consumption in excess of four standard drinks per day. BMI was identical between the two groups (28 [26–32] vs 28 [23–28] kg/m2, P = 0.07).

Table 1: Patient demographics:

Variable	T2DM (n49)	Controls (n23)	P Value
Age (years)	59 (54 – 64)	57 (50 – 64)	0.59
Male %	63%	54%	0.87
HbA1c %	7.4% (5.6 – 9.2)	n.a	
Systolic BP mmHg	127 (118 – 136)	137 (124 – 150)	0.26
Diastolic BP mmHg	82.9 (73 – 92.8)	78 (67 – 89)	0.073

HR	71	65	0.031
BSA	1.98	1.87	0.087
BMI	28	28	0.07

Cardiac MRI results:

Left ventricle volumetrics were significantly lower in the diabetes cohort including left ventricle end diastolic volume (LV EDV) 112 ml (86 – 139) in diabetics versus 128 ml (98 – 160) in controls ($p < 0.001$) and left ventricle end systolic volume (LV ESV) 37ml (22 – 52) in diabetics versus 45 ml (26 – 64) in controls ($P = 0.005$).

Diabetic patients had significantly higher extra cellular volume 28% (21 – 35) compared to controls 25% (21 – 29) $P = 0.02$ and longer native T1 1033 milliseconds (990 – 1076) vs 1010 milliseconds (990 – 1030) in the controls cohort $P < 0.001$.

Left ventricular posterior wall thickness was lower in diabetics 6.6 mm (4.7 – 8.5) compared to controls 9 mm (7.5 – 10.5) $P < 0.001$.

Eleven out of 49 (22%) T2DM patients had late gadolinium enhancement (LGE) but none of the controls did.

Stroke volume (SV), absolute left ventricular mass and indexed LV mass to participants' body surface area were all similar between the two groups with no statistically significant difference.

The anatomical characteristics of the aorta were almost identical between the two groups including aortic root, ascending aorta, and the aorta maximum and minimum dimensions during the cardiac cycle. However, despite these remarkably similar measurements, the aortic distensibility (AoD) was significantly reduced in patients

with T2DM 2.32 $mmHg^{-1}*10^{-3}$ (0.98 – 3.66) vs 4.05 $mmHg^{-1}*10^{-3}$ (1.95 – 6.05) P = 0.046.

Cardiac MRI results are summarized in table 2.

Table 2: Cardiac MRI results:

Variable	T2DM (n49)	Controls (n23)	P Value
LV EDV (ml)	112 (86 – 139)	128 (98 – 160)	<0.001
LV ESV (ml)	37 (22 – 52)	45 (26 – 64)	0.005
LV SV (ml)	72 (57 – 87)	78 (59 – 97)	0.191
LV EF (%)	67 (60 – 74)	65 (59 – 71)	0.218
LV mass (g)	146 (104 – 188)	139 (89 – 189)	0.564
LV mass index (g/m^2)	73 (54 – 91)	76 (56 – 96)	0.426
LV posterior wall thickness (mm)	6.6 (4.7 – 8.5)	9 (7.5 – 10.5)	<0.001
LGE present (%)	11 (22%)	Nil	<0.001
Native T1 (LAX milliseconds)	1033 (990 – 1076)	1010 (990 – 1030)	<0.001
T2 (milliseconds)	55.6 (43 – 68)	60 (39 – 81)	0.361
ECV (LAX %)	28 (21 – 35)	25 (21 – 29)	0.02
Aortic root (mm)	32.8 (28.4 – 37.2)	32.8 (28.7 – 36.9)	1
Ascending aorta (mm)	31.7 (28.2 – 35.2)	31.8 (28 – 35.5)	1
Ao Max	8.5 (7.2 – 9.8)	8.3 (6.7 – 9.9)	0.604
Ao Min	7.2 (6 – 8.4)	7 (5.3 – 8.7)	0.615
AoD $mmhg^{-1} * 10^{-3}$	2.32 (0.98 – 3.66)	4.05 (1.95 – 6.05)	0.046

Multivariate analyses of Predictors of aortic distensibility:

We ran multiple analyses to identify predictors of abnormal aortic distensibility in diabetics. When LV ejection fraction (LV EF), LV end diastolic volume (LV EDV) and ascending aorta stroke volume were considered continuous variables indexed LV mass (ind LV mass) was associated with significantly reduced aortic distensibility (coefficient = -0.037, P = 0.006). There was no significant association between these two values when we ran the same analysis in controls (coefficient = -0.007) P = 0.896 (Table 3 and table 4 respectively).

Table 3: Multivariate analysis of predictors of AoD in Diabetics

Variables	**Coefficient**	**P Value**	**CI 95%**
Ind LV mass	- 0.037	0.006	- 0.063 to - 0.011
LVEF	- 0.004	0.895	- 0.073 to 0.064
LV EDV	0.018	0.229	- 0.012 to 0.047
AAo-SV	0.009	0.682	- 0.037 to 0.055

Aao-SV = ascending aorta stroke volume.

Table 4: Multivariate analyses of Predictors of AoD in controls:

Variables	**Coefficient**	**P Value**	**CI 95%**
Ind LV mass	- 0.007	0.896	- 0.123 to 0.110
LVEF	- 0.008	0.957	- 0.327 to 0.311
LV EDV	- 0.054	0.544	- 0.249 to 0.140
AAo-SV	0.064	0.585	- 0.193 to 0.322

Discussion:

In this study, we identified lower aortic distensibility in a population of well controlled type 2 diabetic patients (n = 49) without significant coronary disease when compared to healthy non-diabetic population (n = 23). Importantly, lower aortic distensibility was correlated with increased indexed LV mass which may, in part via reduced LV compliance, explain the mechanism of reduced aortic distensibility in these patients. These observations can form the basis for future studies aimed at early detection and prevention of vascular disease in patients with diabetes.

Idiopathic vascular abnormalities are well known in patients with diabetes with no identifiable significant pathology (29). Discovering the pathophysiology behind these changes is important for early disease detection, provision of adequate surveillance and to develop future therapeutic strategies that can prevent disease progression. Aortic distensibility is a robust and reproducible parameter that can be readily measured using cardiac MRI and can serve as subclinical biomarker to identify an early abnormal vascular phenotype even when “clinical control of diabetes” is said to be adequate or meeting guideline directed targets. Because compared to nondiabetics, cardiovascular disease develops earlier (30) and remains the leading cause of morbidity and mortality in patients with T2DM (29). The EpiDREAM international cohort study found that even a 1 mmol/l increase in fasting blood glucose corresponded to a 17% higher risk of future cardiovascular events or death (31), highlighting the critical link between dysglycemia and heart health (31).

Additionally, insulin resistance in diabetes, characterized by impaired insulin signalling, hyperinsulinemia, and hyperglycaemia, plays a pivotal role in endothelial

dysfunction and inflammation, accelerating plaque formation and leading to atherosclerotic cardiovascular disease which is driven by this complex interplay of cellular and molecular pathophysiologic factors.

In healthy individuals, left ventricular ejection generates a pressure pulse with a relatively slow pulse wave velocity of 5–7 m/s (32). During diastole, this pulse wave is reflected at distal arteries, particularly at the branching points of arterioles, where it interacts with the recoil waveform to produce the characteristic dicrotic notch. The final shape of the aortic pressure waveform is determined by the summation of these two pressure waves (33).

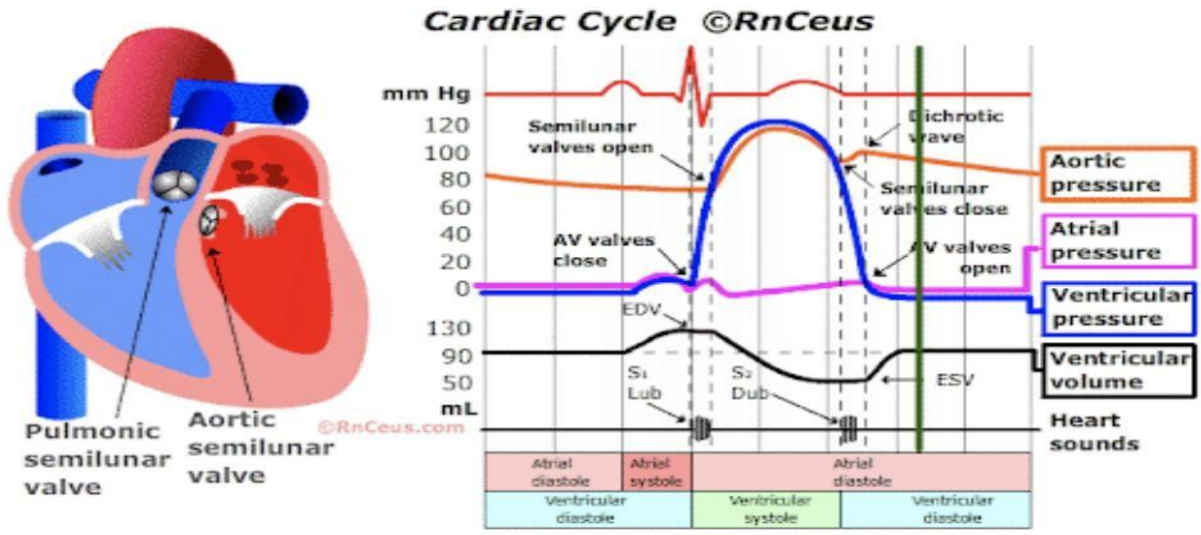

Figure 3: Normal pressure waveforms in the aorta and left cardiac chambers during one cardiac cycle.

In young, compliant vessels, the reflected wave returns during diastole, resulting in a higher pulse pressure in the peripheral arteries compared to the central arteries. However, as vascular stiffness increases with age, pulse wave velocity accelerates, causing the reflected wave to reach the central arteries during systole. This early arrival elevates systolic blood pressure, increasing mechanical stress on the aortic

wall. Over time, these pressures induce elastin deposition within the wall leading to increased aortic stiffness (34).

Greater aortic stiffness raises cardiac afterload, driving concentric remodelling of the left ventricle. In the MESA study (35), investigators observed a positive correlation between aortic arch pulse wave velocity (PWV) and both left ventricular mass and the LV mass-to-volume ratio independent of blood pressure and other cardiovascular risk factors. This increased mass to volume ratio elevates diastolic pressures, further exacerbating wave reflection abnormalities and perpetuating a cycle of progressive aortic stiffness.

In our previous study (18), we identified a significantly elevated occurrence of myocardial fibrosis and increased extra-cellular volume among patients with diabetes, despite good clinical control, which leads to increased mass to volume ratio and reduced left ventricular (LV) compliance. These results were redemonstrated in this analysis. This impairs myocardial compliance causes the transferral of abnormal wave reflections to the aorta, contributing to aortic dilatation and fibrosis, which likely explains this study findings of impaired aortic distensibility in patients with diabetes and the reproducible significant correlation between aortic distensibility and indexed left ventricular mass independent of left ventricular ejection fraction, left ventricular end diastolic volume and stroke volume.

The resultant abnormal wave reflection and impaired distensibility is likely to exacerbate atheroma formation and when coupled with pathological cellular and molecular changes in diabetes, it may contribute to the early development and increased severity of atherosclerotic cardiovascular disease. Furthermore, the interplay between left ventricular fibrosis, increased arterial stiffness and abnormal

wave reflection can further destabilize atherosclerotic plaques, increasing the risk of macrovascular events such as stroke and acute coronary syndrome. These disruptions can also extend to the microvasculature, exacerbating the progression of diabetic microvascular disease.

In this study, we showed the valuable information that a non-invasive cardiac MRI can provide in identifying early predictors of adverse aortic changes in patients with diabetes. Its ability to provide an accurate 3D image of the aortic anatomy and its transit times (phase-contrast sequences) can be used as a non-invasive screening technique to establish early changes in aortic distensibility and indexed left ventricular volume and use these values as independent predictors of vascular complications risk or as a surveillance strategy to monitor treatment efficacy.

Currently, cardiac MRI use as a screening tool in clinical practice remains limited due to the relatively increased cost and logistical complexities. With the recent technological advances, artificial intelligence may play a role in reducing cost and improving access.

Limitations:

Both groups included small number of patients and diabetics group may represent a selection bias because all patients were recruited from a tertiary diabetes centre. Although there was no significant difference in blood pressure between controls and T2DM patients, we cannot completely exclude hypertension as a contributary factor to fibrosis detected by CMR.

A longitudinal study, rather than a cross sectional, following patients over time is needed to better understand the early pathophysiological changes in diabetic cardiomyopathy and resolve whether abnormal aortic distensibility causes myocardial fibrosis or myocardial fibrosis causes abnormal aortic distensibility. Access to MRI remains limited due to the relatively increased cost and logistical complexities compared to a cheaper and easily accessible portable echocardiogram.

Conclusion:

In a cohort of patients with well-controlled type 2 diabetes, aortic distensibility is reduced compared to non-diabetics and significantly correlates negatively with left ventricular mass indexed to body surface area.

Diabetes patients have diffuse myocardial fibrosis and reduced left ventricular volumetrics. These findings may serve as a screening tool for early detection of adverse aortic changes in diabetes and warrant more focused research in the future.

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