Comparison of new-generation renal artery denervation systems: assessing lesion size and thermodynamics using a thermochromic liquid crystal phantom model

Sara I. Al Raisi1,2, MB Bch, FRACP; Michael T. Barry1,2, B.Sc; Pierre Qian1,2, MBBS, FRACP; Abhishek Bhaskaran2, MBBS, FRACP; Jim Poulipoulos1,2, PhD; Pramesh Kovoor1,2*, MBBS, PhD

1. Department of Cardiology, Westmead Hospital, Sydney, NSW, Australia; 2. University of Sydney, Sydney, NSW, Australia

Abstract

Aims: The aim of this study was to evaluate and compare lesion dimensions and thermodynamics of the new-generation multi-electrode Symplicity Spyral and the new-generation EnligHTN renal artery denervation systems, using a thermochromic liquid crystal phantom model.

Methods and results: A previously described renal artery phantom model was used as a platform for radiofrequency ablation. A total of 32 radiofrequency ablations were performed using the multi-electrode Symplicity Spyral (n=16) and the new-generation EnligHTN systems (n=16). Both systems were used as clinically recommended by their respective manufacturer. Lesion borders were defined by the 51°C isotherm. Lesion size (depth and width) was measured and compared between the two systems. Mean lesion depth was 2.15±0.02 mm for the Symplicity Spyral and 2.32±0.02 mm for the new-generation EnligHTN (p-value <0.001). Mean lesion width was 3.64±0.08 mm and 3.59±0.05 mm (p-value=0.61) for the Symplicity Spyral and the new-generation EnligHTN, respectively.

Conclusions: The new-generation EnligHTN system produced lesions of greater depth compared to the Symplicity Spyral under the same experimental conditions. Lesion width was similar between both systems. Achieving greater lesion depth by use of the new-generation EnligHTN may result in better efficacy of renal artery denervation.
Abbreviations
BP  blood pressure
RAD  renal artery denervation
RF  radiofrequency
TLC  thermochromic liquid crystal
SS  Symplicity Spyral
NGE  new-generation EnligHTN

Introduction
Following the encouraging results of the Symplicity HTN-1 and Symplicity HTN-2 trials, which demonstrated significant blood pressure (BP) reduction after renal artery denervation (RAD), endovascular radiofrequency (RF) ablation of the renal arteries was considered an acceptable treatment for drug refractory hypertension\(^1,2\). Later, the randomised controlled SYMPLICITY HTN-3 trial failed to show a significant difference in BP reduction between the RAD treatment arm and the sham control arm\(^3\). Nevertheless, the implication of renal sympathetic nerves in the pathogenesis of resistant hypertension has been well described and demonstrated in previous animal and human studies\(^4-8\). Several factors have been proposed that may have limited the denervation efficacy in SYMPLICITY HTN-3\(^9\). A better understanding of the basic mechanisms of denervation and factors affecting procedural success including patient selection, renal nerve anatomy and the biophysics of the various renal denervation systems through further preclinical studies is pivotal to achieving the desired results.

Previously, we developed a thermochromic liquid crystal (TLC) model and validated it in vivo for cardiac RF ablation\(^10\). Subsequently, we modified this model for renal denervation. In our previous study, we assessed and compared lesion size and thermodynamic properties of the single-electrode Symplicity (Flex) renal denervation system (Medtronic, Minneapolis, MN, USA) versus the first-generation multi-electrode EnligHTN system (St. Jude Medical, St. Paul, MN, USA) using the TLC renal artery phantom model\(^11\). Recently, in the new-generation systems, several modifications have been applied to both the EnligHTN and Symplicity renal denervation systems in order to overcome some of the technical procedural challenges, and to reduce overall procedural duration, either of which could ultimately impact on ablation efficacy. Therefore, in this study we aimed to evaluate and assess the performance of the new-generation Symplicity Spyral (SS) and the new-generation EnligHTN (NGE) renal denervation systems using the previously described renal artery phantom model. Table 1 summarises the differences between the old and the new Symplicity and EnligHTN systems.

Methods
Radiofrequency ablations for both the SS and NGE systems were performed in the renal artery phantom model using clinically recommended ablation settings (Table 1). Temporal changes in lesion dimensions (depth and width) for the two systems were measured and compared.

| Table 1. Summary of the technical specifications and a comparison between the new and old Symplicity and EnligHTN renal denervation systems. |
|-----------------|-----------------|-----------------|-----------------|
| **System**      | **Old systems** | **New systems** | **Old systems** |
|                 | Symplicity (Flex) | EnligHTN old generation | Symplicity (Spyral) | EnligHTN new generation |
| **Generator**   | Symplicity G2 | 1st generation | Symplicity G3 | 2nd generation |
| **Number of electrodes** | 1 | 4 | 4 | 4 |
| **Ablation duration (sec)** | 120 | 90 | 60 | 60 |
| **Maximum power per electrode (W)** | 8 | 6 | 6.5 | 8 |
| **Electrode surface area (mm²)*** | 6.39 | 3.7 | 5.9 | 3.7 |

* Measured in-house.
a flow rate of 500 ml/min through the phantom renal artery, and an ablation duration of 60 sec. The gel was allowed to cool down for five minutes between RF ablations and the catheter was moved to a new position after four runs of ablation.

**LESION MEASUREMENTS AND ANALYSIS**

A digital camera (Canon EOS 5D Mark II; Canon Inc., Tokyo, Japan) with a light source (Canon Speedlite 580EX; Canon) was placed in front of the phantom model to capture images at different ablation time points (at baseline, 20 sec, 30 sec, 40 sec, 50 sec and 60 sec). Heating of the gel at the TLC surface produced a colour gradient on the TLC sheet (Figure 1A), which was utilised to calculate the isotherms following thermochromic calibration using in-house developed software (Figure 1B). The 51°C isotherm was used as an arbitrary measure to define lesion borders, as irreversible neural tissue injury occurs at temperatures greater than 45-50°C\(^\text{11}\). Lesion depth \((d)\) was measured as the length of a line between the electrode/gel interface and the 51°C isotherm perpendicular to the electrode tip. Lesion width \((w)\) was defined as the maximum width of the 51°C isotherm perpendicular to \(d\) (Figure 1B).

**STATISTICAL ANALYSIS**

Based on previous work in the same phantom model, RF ablation in replicates of three per catheter were required to detect a significant difference in lesion size, with a power of 95% and \(\alpha=0.05\) (two-tailed), for each parameter tested\(^\text{11}\). Mean lesion depth and width for each system were compared using an unpaired two-tailed Student’s t-test. Data were expressed as mean\(\pm\)standard deviation. The relationship between lesion growth (depth and width) and time was assessed using Spearman’s correlation. Values of \(p<0.05\) were considered significant. Data analysis was performed with GraphPad Prism software 6.0 (GraphPad Software Inc., La Jolla, CA, USA) and SPSS, Version 24 (IBM Corp., Armonk, NY, USA).

**Results**

A total of 32 RF ablations (16 ablations per system) were performed on the phantom renal artery model. All ablations were carried out under similar phantom conditions whereby parameters, including phantom vessel diameter, flow rate and gel temperature, were adjusted to within normal physiological ranges of 5 mm, 500 ml/min and 37°C, respectively. Table 2 summarises the ablation parameters for both systems.

**Table 2. Ablation parameters for Symplicity Spyral and new-generation EnligHTN systems.**

<table>
<thead>
<tr>
<th>System</th>
<th>Symplicity Spyral</th>
<th>New-generation EnligHTN</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ablation number</td>
<td>16</td>
<td>16</td>
<td>–</td>
</tr>
<tr>
<td>Mean power (V)</td>
<td>6.5\pm0.00 (max)</td>
<td>5.3\pm0.07 (ave)</td>
<td>–</td>
</tr>
<tr>
<td>Mean baseline impedance (Ω)</td>
<td>174.3\pm0.88</td>
<td>199.1\pm0.88 &lt;0.001</td>
<td>–</td>
</tr>
<tr>
<td>Mean electrode tip temperature (°C)</td>
<td>45.56\pm0.66 (max)</td>
<td>52.50\pm0.98 (ave)</td>
<td>–</td>
</tr>
<tr>
<td>Ablation duration (sec)</td>
<td>60</td>
<td>60</td>
<td>–</td>
</tr>
</tbody>
</table>

**LESION SIZE AND GROWTH**

Thirty-one RF ablation lesions (16 for SS and 15 for NGE) were analysed at 60 sec to determine final lesion size. A single data point for the NGE group was unavailable due to photographic aberration. Immediately prior to termination of RF ablation (60 sec), mean lesion depth for SS was 2.15\pm0.02 mm versus 2.32\pm0.02 mm for NGE (\(p\)-value <0.001) (Figure 2A). Mean lesion width was 3.64\pm0.08 mm and 3.59\pm0.04 mm (\(p\)-value=0.61) for SS and NGE, respectively (Figure 2B).

In addition, temporal analysis of lesion dimensions was performed to demonstrate the thermodynamics of each ablation system (Figure 3). A Spearman correlation test demonstrated a strong positive correlation between the duration of RF ablation and lesion size (depth and width), which was statistically significant for both systems. The correlation coefficient (\(r_s\)) for ablation duration versus lesion depth was 0.91 (\(p<0.001\)) for SS and 0.86 (\(p<0.001\)) for NGE. The correlation coefficient (\(r_s\)) for ablation duration versus lesion width was 0.606 (\(p<0.001\)) and 0.726 (\(p<0.001\)) for SS and NGE, respectively.

**Figure 1.** Image taken during radiofrequency ablation on the phantom renal artery model at 60 sec using the Symplicity Spyral system in this case. A) Colour gradient on the TLC sheet during RF ablation. B) Lesion post analysis with superimposed isotherms. Yellow line highlights the 51°C isotherm. C) Colour gradient with the corresponding temperature in °C. d: lesion depth; w: lesion width; TLC: thermochromic liquid crystal

**Figure 2.** Scatter plots comparing lesion depth and width for the Symplicity Spyral and new-generation EnligHTN systems at end of radiofrequency ablation (60 sec). A) Lesion depth. B) Lesion width. NGE: new-generation EnligHTN; SS: Symplicity Spyral
Graphs of lesion depth and width over time (Figure 3) suggest that prolonging the ablation duration could potentially increase lesion size, as a plateau phase has not been reached. Nonetheless, analysis of lesion size at different ablation time points demonstrated that about 70-80% of lesion growth occurred within the first 20 sec of RF delivery with a lesion growth rate of 0.076 mm/sec for depth and 0.147 mm/sec for width with SS, and 0.094 mm/sec for depth and 0.124 mm/sec for width with NGE during the initial 20 sec ablation phase. Lesion growth rate slows down thereafter to 0.012 mm/sec for depth and 0.01 mm/sec for width with SS and 0.009 mm/sec for depth and 0.008 mm/sec for width with NGE in the last 20 sec of RF ablation. Thus, increasing ablation time beyond 60 sec may result in only a small increase in lesion size. Table 3 summarises lesion dimensions at 20, 40 and 60 seconds of RF ablation and the percentage of lesion growth (depth and width) at each time point.

**Table 3.** Lesion size and the percentage of growth at 20, 40 and 60 sec during radiofrequency ablation for Symplicity Spyral and new-generation EnligHTN.  

<table>
<thead>
<tr>
<th>Ablation time (sec)</th>
<th>Depth (mm)</th>
<th>p-value</th>
<th>Width (mm)</th>
<th>p-value</th>
<th>% Depth:width of maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SS</td>
<td>NGE</td>
<td></td>
<td>SS</td>
<td>NGE</td>
</tr>
<tr>
<td>20</td>
<td>1.52±0.03</td>
<td>1.87±0.02</td>
<td>&lt;0.001</td>
<td>2.93±0.07</td>
<td>3.08±0.04</td>
</tr>
<tr>
<td>40</td>
<td>1.92±0.03</td>
<td>2.14±0.03</td>
<td>&lt;0.001</td>
<td>3.45±0.08</td>
<td>3.44±0.04</td>
</tr>
<tr>
<td>60</td>
<td>2.15±0.02</td>
<td>2.32±0.02</td>
<td>&lt;0.001</td>
<td>3.63±0.08</td>
<td>3.59±0.05</td>
</tr>
</tbody>
</table>

NGE: new-generation EnligHTN; SS: Symplicity Spyral

**Discussion**

Using the TLC renal artery phantom model, the NGE renal denervation system achieved greater lesion depth compared to the multi-electrode SS system. However, there was no difference in lesion width between the two systems. RF ablation with both systems was performed under consistent experimental settings (i.e., consistent gel impedance, gel temperature, vessel diameter and flow rate) and optimal electrode/gel contact as confirmed by direct visualisation. Our phantom model allows direct comparison due to the ability to control variables, which is difficult to achieve clinically.

In our previous study, we compared the lesion dimensions and thermal properties of the single-electrode Symplicity Flex versus the first-generation multi-electrode EnligHTN renal artery denervation system, utilising the same renal artery phantom model. The present study is the first to compare the new-generation multi-electrode Sypral system to the new-generation EnligHTN system using the TLC/gel phantom model. In RF ablation, only about 1 mm of tissue adjacent to the electrode (area of resistive heating) is heated directly. Deeper tissue is heated by conduction of thermal energy from the resistive heating zone.

Therefore, increased heating at the electrode tissue interface leads to more heat being conducted through the tissue and subsequently larger lesions. This is affected by several factors including ablation power, electrode size, electrode area in contact with tissue, contact force, convective cooling and ablation duration. Whilst the SS electrode surface area is larger compared to the NGE, lesions produced by the SS were comparatively smaller in depth. It has been demonstrated that increased electrode surface area results in larger lesions. Nonetheless, electrodes with a larger surface area usually require higher power delivery to maintain the same current density at the electrode tissue interface. The maximum power generated by the SS and NGE is 6.5 W and 8 W, respectively. Conversely, a larger electrode area leads to more heat loss in the blood pool by convection and, therefore, reduces heating efficiency. Power lost in the blood pool is even greater when electrode-tissue contact is reduced. It is possible that the greater contact force produced by the EnligHTN catheter upon deployment results in more optimal and stable gel contact, and therefore deeper lesions. It is important to note that for all ablations careful placement of the electrode tip against the TLC/gel surface was consistent and confirmed. Haines demonstrated in an in vitro model that greater contact pressure produced deeper lesions as long as electrode-tissue contact was maintained and electrode-tissue temperature kept constant by adjusting power. In his study, lesion width showed no significant difference with increased contact force. Consistent with this finding, we found no difference in width between the two systems. Although not directly measured, it is likely to be the design of the EnligHTN catheter that has the advantage of producing more consistent contact force. This could also explain the lower electrode tip temperature achieved by the SS (Table 2).

Of note, when the old-generation systems were used in the same model, the lesions produced were deeper (3.8 mm and 3.4 mm for Symplicity and EnligHTN, respectively). A recent animal study also suggested a thermal injury depth of 3.9 mm when the Symplicity...
cal denervation, reported on lesion depth of 5-8 mm. However, native energy modalities, including microwave ablation and chemi-ablation systems to reach deeper targets may also be beneficial, if nerve distribution highlight the importance of distal segment ablation. This was demonstrated in a porcine model study by Mahfoud et al, where the addition of ablation distal to the bifurcation using the currently available denervation systems. In distal segments (before the bifurcation), the 50th percentile of nerves was found to be at 1.81 mm from the lumen; 79% of nerves found distal to the bifurcation are located within 2 mm from the lumen.

The limited depth of heating and the current knowledge of renal nerve distribution highlight the importance of distal segment ablation. This was demonstrated in a porcine model study by Mahfoud et al, where the addition of ablation distal to the bifurcation using the SS system resulted in more effective denervation as measured by a reduction in cortical norepinephrine content and axonal density compared to main vessel ablation only. While the focus now has been directed towards more distal denervation (distal segment and distal to the bifurcation), improving ablation systems to reach deeper targets may also be beneficial, if this could be attained safely. Initial experimental studies using alternative energy modalities, including microwave ablation and chemical denervation, reported on lesion depth of 5-8 mm. However, until additional research is conducted to evaluate the efficacy and safety of such modalities further, their use remains experimental.

**Conclusions**

Increased lesion depth was achieved using the NGE renal denervation system compared to the SS system for ablation on the TLC phantom model, with no difference in lesion width. Whilst the difference in depth is small, it may have an impact on denervation efficacy.

**Impact on daily practice**

The relationship between the renal nerves as a target for radiofrequency ablation and ablation depth is one of several factors affecting denervation success. Information on different devices and technologies available with regard to their thermal properties and biophysics can guide clinicians as well as help us to understand the limitations of currently available systems and possible areas for improvement.

**Funding**

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**Conflict of interest statement**

P. Qian and M. Barry are inventors of a microwave catheter for renal artery denervation. The intellectual property is owned by the University of Sydney and Westmead Hospital, Australian Patent AU2015902225, issued 12-06-2015. The other authors have no conflicts of interest to declare.

**References**


