In Silico and in Vitro Development of a New Bipolar Radiofrequency Ablation Device for Renal Denervation

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Technical Advance

***In silico* and *in vitro* development of a new bipolar radiofrequency ablation device for renal denervation**

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Running head: A new RFA device for renal denervation

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Abstract

Background: Renal denervation with radiofrequency ablation has become an accepted treatment for drug-resistant hypertension. However, there is a continuing need to develop new catheters for high-accuracy, targeted ablation. We, therefore, developed a radiofrequency ablation device with a basket catheter and bipolar electrodes for controlled, targeted ablation through Joule heating induction between 60°C and 100°C.

Methods: Finite element modeling was used to determine the optimum catheter design to deliver a minimum ablation zone of 4 mm (W) x 10 mm (L) x 4 mm (H) within 60 seconds with a 500 kHz, 60 Vp-p signal, and 0.9 W maximum. The computational model was validated using in vitro phantom tissue impregnated with a color-changing thermochromic pigment.

Results: The *in vitro* ablation zone closely matched the size and shape of the simulated area. The new electrode design directs the current density towards the artery walls and tissue, reducing unwanted blood temperature increases by focusing energy on the ablation zone. In contrast, the basket catheter design does not block renal flow during renal denervation.

Conclusions: This computational model of radiofrequency ablation can be used to estimate renal artery ablation zones for highly targeted renal denervation in patients with resistant hypertension. Furthermore, this innovative catheter has short ablation times and the lowest power requirement of existing designs to perform the ablation.

Keywords: Basket catheter, high blood pressure, hypertension, radiofrequency ablation, renal denervation, resistant hypertension

Background

Hypertension is extremely common and, if inadequately treated, significantly increases the risk of heart disease, stroke, and death. A 12-13 mmHg reduction in systolic blood pressure in hypertensive patients equates to at least a 21% reduction in stroke, coronary heart disease, and death from cardiovascular disease [1]. In 2020, the American Heart Association (AHA) reported that 31.9% of the American population (~75 million people) have hypertension, resulting in ~90,000 deaths from hypertension annually and an annual healthcare expenditure of \$55.9 billion [2].

48 AHA/American College of Cardiology guidelines define resistant hypertension (RH) as
49 hypertension resistant to three or more medications resulting in a blood pressure higher
50 than a target of $\geq 130/80$ mmHg or a blood pressure $< 130/80$ mmHg in a patient taking $\geq$
51 four antihypertensive drugs. RH affects 12-15% of patients treated for hypertension and
52 remains a clinical management challenge [3].

53 Hypertension is, at least in part, caused by chronic activation of the sympathetic
54 nervous system. As early as 1889, experiments with dogs showed that stimulation of renal
55 or splanchnic nerves caused changes in blood pressure [4]. In 1925, Adson performed
56 surgical sympathectomy (disconnection of the sympathetic nerves at the trunk) to treat
57 hypertension [5]. For the subsequent two decades, surgical sympathectomy (thoracolumbar
58 splanchnicectomy) became the procedure of choice for patients with HT who did not
59 respond to diet or the then limited available pharmacological therapy [6]. Indeed, between
60 1938 and 1947, approximately 2,400 patients with hypertension were treated by surgical
61 sympathectomy [7]. Although blood pressure reductions after the operation were often
62 significant, patients were seriously affected by intolerable post-operative postural
63 hypotension [8]. When the first effective antihypertensive drugs (diuretics) became
64 available in the mid-1950s, pharmacological therapy became the standard of care for
65 patients with hypertension [9].

66 Since stimulation of the renal nerves raises blood pressure through vasoconstriction
67 and volume and sodium retention [10-12], ablating renal nerve activity (renal denervation;
68 RD) effectively lowers blood pressure [13]. The highest density of renal sympathetic nerves
69 is within 12 to 15 mm of the abdominal aorta and within 4 mm radially from the renal artery
70 inner lumen [14]. RD's goal is to "open circuit" the efferent and afferent renal sympathetic
71 nerves between the kidneys and the central nervous system to reduce blood pressure.

Indeed, the first bilateral RDs for hypertension were performed in 1934 and 1935, establishing the procedure's safety with no adverse effect on renal function [15, 16]. The last ten years have seen a surge in the minimally-invasive, catheter-based delivery of radiofrequency, chemicals, or ultrasound to achieve RD in hypertensive patients [13]. Although early trial results from the SYMPPLICITY HTN-3 trial of RD were disappointing, with the primary efficacy endpoint not met [17], subsequent trials using next-generation multielectrode radiofrequency (RF) and ultrasound renal nerve ablation systems have shown consistent blood-pressure-lowering effects of RD [11, 12]. Furthermore, the SYMPPLICITY HTN-3 trial results led to the improvement and redesign of the ablation catheter from a single point unipolar ablation electrode to a four-quadrant unipolar device. In addition to the RF electrode design or means of ablation, recent data suggest that the efficacy of RD depends on the successful ablation of renal fibers associated with arterial branches and polar arteries [18], necessitating the development of effective, small-diameter catheters.

To date, no RD device has been cleared by the Food and Drug Administration (FDA) in the USA except for investigational purposes [19]. Here, we report *in vitro* RF ablation using bipolar electrodes on thermochromic phantom tissue to validate a targeted RD computational model for human use. Our new catheter design does not block renal blood flow, does not require cooling, and has low power consumption due to the bipolar electrode design.

Methods

Computational modeling

The finite-element method (FEM) has previously been used to model RF tumor or cardiac ablation [20-22]. Here we also used FEM to solve electromagnetic equations coupled with bioheat equations for bipolar electrodes in contact with tissue design to deliver a minimum ablation zone of 4 mm (W) x 10 mm (L) x 4 mm (H) within 60 seconds with a 500 kHz, 60 Vp-p signal and 0.9 W maximum.

COMSOL version 5.5 (COMSOL, Stockholm, Sweden) was used to generate geometric models, assign material properties and boundary conditions, define infinite element domains, generate meshes, and perform the coupled electromagnetic heating calculations. A coupled analysis was required since the electrical properties of tissue change with temperature and, therefore, the electric field profile must be recalculated at each time step. All analyses were performed on a PC equipped with an Intel® Core™ i7-9700 CPU @ 3GHz, 64 GB of memory, and Windows 10 Home OS.

Model geometry

We developed a 3D FEM model geometry of bipolar cylindrical electrodes inside a renal artery surrounded by connective tissue (**Figure 1A**). The renal artery internal diameter was 4.1 mm [14], the wall (tunica intima and media) thickness was 0.5 mm [23], and the surrounding connective tissue was modeled to a radius of 10 mm. An infinite element domain was defined around the geometric model for approximating an infinitely large domain (**Figure 1A**). The electrode dimensions were 0.61 mm outside diameter, 0.1 mm thickness, and 3 mm long assembled over a Pellethane® tube. The electrodes were designed to be in contact with the renal artery's inner wall through an exposed window of 1 mm x 2.5 mm, as shown in **Figure 1B** (patent pending).

Figure 1. (A) 3D model geometry for FEM analysis of the bipolar electrodes in contact with phantom tissue to mimic placement inside the renal artery. Electrode dimensions: diameter 0.61 mm, length 3 mm with a 1.5 mm separation. (B) Innovative bipolar electrode design (patent pending) to focus current density towards the artery wall and surrounding tissue. Electrodes (red and black) dimensions as per (A).

Electrical and thermal properties

Table 1 shows the material properties at 500 kHz used in the computational model to describe the blood, artery wall, connective tissue, thermoplastic catheter material (Pebax®), and electrode components.

Table 1. Electrical and thermal properties at 500 kHz for components in the FEM model.

Component	Relative Permittivity (ϵ_r)	Electrical Conductivity σ (S/m)	Density (kg/m ³)	Heat Capacity at Constant Pressure J/(kg·°C)	Thermal Conductivity W/(m·°C)
Blood ^a	4,190	0.748	1,050	3,617	0.52
Artery Wall ^a	312	0.324	1,102	3,306	0.46
Connective Tissue ^a	201	0.391	1,027	2,372	0.39
Pebax® 7233 ^b	4	1.25E-12	1,010	1,700	0.26
Electrodes (PtIr 90/10) ^{c,d}	1	1.00E+09	7,950	502	14

^a Dielectric Properties » IT'IS Foundation. <https://itis.swiss/virtual-population/tissue-properties/database/dielectric-properties/>

^b <https://www.materialdatacenter.com/ms/en/tradenames/Pebax/ARKEMA/Pebax%C2%AE+7233+SP+01/f21dd478/264>

^c https://www.engineersedge.com/properties_of_metals.htm

^d <https://www.azom.com/properties.aspx?ArticleID=965>

Temperature changes result in electrical conductivity changes in biological tissues (artery walls and connective tissue) [24] and, during RF ablation, the temperature of tissues increases. The changes to the electrical conductivity in tissues included in the model were described using:

$$\sigma(T) = \sigma_0[1 + k_1\Delta T] \quad (1)$$

where σ_0 is the initial electrical conductivity at the reference temperature, k^1 is the temperature coefficient, and $\Delta T[^\circ\text{C}]$ is the temperature difference from the initial reference temperature. We set $k^1 = 2.05\%/^\circ\text{C}$, and the linear electrical conductivity in the model was determined by

$$\sigma(T) = 0.324[1 + 0.0205\Delta T] \quad (2)$$

For the artery wall and connective tissue, the equation was

$$\sigma(T) = 0.391[1 + 0.0205\Delta T] \quad (3)$$

Both equations are bounded within the experimental data of 30-80°C [25].

Multi-physics computation

Electric field

When electric fields are applied to tissue, the temperature in the zone between the bipolar electrodes increases due to Joule heating through tissue conduction and dielectric loss. For the tissues in the model at 500 kHz, dielectric losses are negligible, so only the resistive loss (i.e., Joule heating) was considered in this simulation [26]. The electric field $\mathbf{E}$ (V/m) profile was calculated from the negative gradient of the voltage using the equation

$$\mathbf{E} = -\nabla V \quad (4)$$

where ∇ is the *del* operator that turns the scalar voltage V (V) to a vector field. Then, current density $\mathbf{J}$ (A/m²) was computed from

$$J = \frac{E}{\rho_e} \quad (5)$$

where ρ_e is the electrical resistivity of the material ($\Omega\cdot m$). Then, the average power dissipated in the tissue between the electrodes was determined by

$$P_{av} = \frac{1}{2} \Re (J^* \cdot E) \quad (6)$$

where $\Re$ is the real part from the vector dot product of conjugate J and E .

Bioheat equation

Penne's bioheat equation describes the temperature distribution increase surrounding the bipolar electrodes during the Joule heating process and incorporates the convective heat transfer from blood perfusion within the tissue

$$\rho C_p \frac{\partial T}{\partial t} - \nabla \cdot k \nabla T = \frac{1}{2} \Re (J^* \cdot E) + \rho_b C_{p,b} \omega_b (T_b - T) + Q_{met} \quad (7)$$

where ρ is the tissue density (kg/m^3), C_p is the tissue-specific heat ($J/kg\cdot K$), and k is the tissue thermal conductivity ($W/m\cdot K$) of the components in the model. T_b is the blood temperature (assumed to be $37^\circ C$), ρ_b is blood density (kg/m^3), $C_{p,b}$ the specific heat of the blood ($J/kg\cdot K$), and ω_b is the blood perfusion ($1/s$). Q_{met} is the energy generated by metabolic processes (W/m^3) and is negligible for the renal artery model. The blood temperature in large surrounding vessels has minimal impact on the thermal field between the bipolar electrodes due to their distance from the renal artery and was therefore not included in the model.

Boundary conditions

Artery walls and surrounding tissue with Dirichlet boundary conditions: temp = normal body temperature ($37^\circ C$) and voltage = 0 V.

185

186 Ablated tissue

187 To determine the ablation zone (i.e., where cell death occurs), the Thermal Damage
188 transformation model was included in the COMSOL model with a temperature threshold.
189 The isothermal surfaces were plotted using the following parameters to determine the
190 ablation zone: damage temperature 60°C, damage time 1 s, necrosis temperature 90°C, and
191 enthalpy change 0 J/kg.

192

193 *In vitro experiments*

194 We prepared a thermochromic tissue phantom (TCP) for direct visualization of ablation and
195 comparison with the simulated isothermal ablation zones. The TCP mimicked the tissue's
196 electrical properties and was prepared using polyacrylamide gel with a thermochromic ink
197 additive that permanently changes color from white to magenta when heated over 60°C.
198 The TCP was formulated as described by Mikhail et al. [27] and contained: deionized water
199 76.1 (v/v), 40% acrylamide/bis-acrylamide 17.5 (v/v), magenta MB60°C concentrate 5.0 (v/v)
200 sodium chloride (NaCl) 0.9 (w/v), ammonium persulfate (APS) 0.14 (w/v), and N, N, N', N'-
201 tetramethylethylenediamine (TEMED) 0.14 (v/v). The electrical conductivity was adjusted to
202 match the connective tissue since this is the most relevant parameter for the thermal Joule
203 heating effect.

204 The TCP was ablated with a bipolar electrode connected to a waveform generator
205 and linear amplifier, as shown in **Figure 2**. The exposed surface of the electrodes was in
206 contact with the TCP and impregnated with saline solution, which mimics the conductivity
207 of blood. An ablation signal of 3.0 V_{p-p} and 500 kHz was generated with an Agilent 33220A
208 waveform generator (Agilent, Santa Clara, CA, USA) and amplified to 60 V_{p-p} with a

Pendulum F20A fixed-gain linear amplifier (Pendulum, Stockholm, Sweden). A Tektronix TDS2001C oscilloscope (Tektronix, Beaverton, OR, USA) and a Fluke 8846A Precision Multimeter (Fortive, Everett, WA, USA) were connected to monitor and confirm that the appropriate ablation signal was applied to the TCP through the electrodes (not shown in **Figure 2** for simplification).

Figure 2. Thermochromic tissue phantom (TCP) ablation experimental setup. 1) Signal generator (3 Vp-p, 500 kHz) was amplified by 2) 20 gain linear power amplifier (60 Vp-p, 500 kHz) and 3) applied to TCP with a bipolar electrode and an insulating plate to maintain its position. 4) Top view of the TCP ablated by the bipolar electrodes in 60 seconds.

Oscilloscope and precision meter not shown for clarity.

Results

RF ablation catheter design

The bipolar electrode design in this study (**Figure 1**) can be assembled in a 6 Fr catheter with four splines carrying either 2 or 4 electrodes per spline. Each spline is made of thermoplastic

(Pebax®) extrusions with their inner lumen containing a pre-shaped nickel-titanium (Nitinol) and electrical wires (**Figure 3**). The Nitinol provides a collapsible basket to be delivered through femoral access to the renal artery. It expands to the pre-shaped form creating firm connectivity between the electrodes and the artery inner walls. Each bipolar electrode can be independently selected for ablation of each quadrant in contact with the splines inside the artery (patent pending).

Figure 3. Graphical model of the basket catheter with four splines and four electrodes per splines. Note: two splines have a fifth, non-active radio-opaque electrode for position orientation during fluoroscopy.

In silico and in vitro comparisons

The isothermal plot from the computer model (**Figure 4A**) predicted the tissue volume that reached an ablation temperature of $\geq 60^{\circ}\text{C}$ after 60 seconds of ablation due to the induced

Joule heating. The ablated area consisted of two elongated lobes with an approximate maximum dimension of 4 mm × 10 mm × 4 mm (length × width × height).

The ablated TCP tissue (**Figure 4B**) was measured and compared with the isothermal plot from the computer model (**Figure 4A**) and is shown in **Figure 4C**. Note the excellent correlation between simulated and experimentally defined areas (4 mm x 10 mm x 4 mm vs. 3 mm × 8.5 mm × 3.5 mm), indicating that the computer model accurately predicted the RF ablation zone *in vitro*.

Figure 4. (A) Computer simulation of the isothermal ablation zone for a 500 kHz input signal with an amplitude of 60 Vp-p at 60 seconds of ablation. The computer model predicted an ablation zone of 4 mm x 10 mm x 4 mm (length x width x height) over the bipolar electrodes. (B) Thermochromic tissue phantom (TCP) after an ablation signal (500 kHz, 60 Vp-p) was applied for 60 seconds. The dark pink color change corresponds to the area

where the temperature exceeded 60°C. Note the similarities with the computer model in (A). (C) Ablation zone comparison between computer model (A) and TCP tissue experiment (B). The ablation zone was 3 mm × 8.5 mm × 3.5 mm. Note the very close correlation between the experimental and simulated ablation volumes.

Discussion

Resistant hypertension remains common and a clinical management challenge [1]. After initially disappointing clinical trial results, the technique's refinement has now resulted in the inconsistent demonstration of RD efficacy for patients with treatment-resistant hypertension [11, 12]. However, the Food and Drug Administration (FDA) has not approved any device for RD except for investigational purposes, despite the many ongoing clinical trials for RD and suggesting a need for further catheter refinement.

Several RF ablation catheter devices with the CE mark are authorized for use in the European Union (EU) (**Table 2**). All are single electrode devices except for the Vessix™ (Boston Scientific, Marlborough, MA), incorporating a balloon with bipolar electrodes [19]. This has the consequent disadvantage that once inflated, the balloon blocks renal blood flow during ablation. Our electrode design based on a basket catheter does not require a balloon, so it has the advantage of no renal blockage during ablation. Furthermore, there is no need for cooling, and the catheter has short ablation times and the lowest power requirement of existing designs to perform the ablation.

Table 2. A comparison of CE-marked renal denervation catheters and our catheter. Adapted from [19].

Catheter	Energy	Configuration	Electrode	Balloon	Cooling	Delivery	Ablation time (s/artery)	Max. power (W)	Vascular access (Fr)
Simplicity™ (Medtronic)	RF	Unipolar	Single	No	Blood	Deflectable tip	540	8	6
Spyral™ (Medtronic)	RF	Unipolar	Multiple	No	Blood	Monorail	60	8	6
Vessix™ (Boston Scientific)	RF	Bipolar	Multiple	Yes	None	Over-the- wire	30	1	8
EnligHTN™ (St Jude)	RF	Unipolar	Multiple	No	Blood	Delectable tip	90	6	8
Iberis™ (Terumo)	RF	Unipolar	Single	No	Blood	Delectable tip	540	8	4
Paradise™ (Recor)	US	Unipolar	Single	Yes	Close irrigated	Over-the- wire	50-150	30	6
Our design	RF	Bipolar	Multiple (8 or 16)	No	Not required	Guided sheet	60	0.9	6

279

280

RF ablation devices have evolved from single unipolar electrodes (the original

281

Symplicity HT1™, Medtronic, Santa Clara, CA, USA) to multi-electrode unipolar systems

282

(Spyral™).[28] Here we designed a bipolar electrode for RF ablation with the electrode

283

design, dimensions, geometry, and ablation area simulated and optimized via FEM *in silico*.

284

The simulation included the surrounding artery and connective tissue's electrical properties

285

to predict the ablation zone dimensions to achieve renal nerve ablation. A TCP was used to

286

compare the *in vitro* ablation zone with simulations. While the TCP starts changing color at

287

60°C, there is considerable variability to determine the exact location where the TCP starts

288

to display temperature color transition. Nevertheless, the TCP allows visual and quantitative

289

comparison of the geometry, shape, and form of ablation, which in this case very closely

290

matched the computational simulation. Therefore, this model will be helpful for further

optimizing catheter design for accurate renal nerve ablation in animal models *in vivo* to pave the way for clinical validation.

This computational model of RF ablation can be used to estimate ablation zones in the renal artery for RD in patients with hypertension. The model provides an efficient iterative platform to design and refine RF ablation electrodes for targeted ablation geometries and dimensions. The model can be extended to other anatomical landmarks to predict the RF ablation pattern in the targeted zone. This model is complemented by the TCP to provide a relatively simple and cost-effective *in vitro* medium for quick feedback to the computational model from RF ablation experiments, allowing short iteration times during catheter development compared to traditional, costly, and time-consuming animal and human trials.

Conclusions

Our bipolar RF ablation electrode deserves further study and development as a potential RD device. The bipolar configuration and innovative electrode design ensure that the current density is focused on the target tissue, reducing the energy transferred to renal blood, reducing the need for cooling. Furthermore, the electrode window can be modified in shape and dimensions based on the intended location and geometry desired for ablation. This model and TCP can be used to investigate other ablation applications, e.g., tumor ablation, to design an electrode for the specifically intended zone. Further *ex vivo* and *in vivo* studies are warranted to further validate this new bipolar catheter system.

Abbreviations

AHA, American Heart Association

315 FDA, Food and Drug Administration

316 FEM, finite element modeling

317 RD, renal denervation

318 RF, radiofrequency

319 RH, resistant hypertension

320 TCP, thermochromic tissue phantom

321 HT, Hypertension

322

323 **Ethics approval and consent to participate**

324 Not applicable

325 **Consent for publication**

326 Not applicable

327 **Availability of data and materials**

328 All data generated or analyzed during this study are included in this published article

329 **Competing interests**

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331 Palm Harbor, Florida, USA

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334 Palm Harbor, Florida, USA

335 **Authors' contributions**

336 N.P. conducted the experiments and wrote the manuscript; K.M. and S.E.S. advised on the

337 experiments' design. All authors reviewed the manuscript.

338

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419

Figures

Figure 1

(A) 3D model geometry for FEM analysis of the bipolar electrodes in contact with phantom tissue to mimic placement inside the renal artery. Electrode dimensions: diameter 0.61 mm, length 3 mm with a 1.5 mm separation. (B) Innovative bipolar electrode design (patent pending) to focus current density towards the artery wall and surrounding tissue. Electrodes (red and black) dimensions as per (A).

Figure 2

Thermochromic tissue phantom (TCP) ablation experimental setup. 1) Signal generator (3 V_{p-p}, 500 kHz) was amplified by 2) 20 gain linear power amplifier (60 V_{p-p}, 500 kHz) and 3) applied to TCP with a bipolar electrode and an insulating plate to maintain its position. 4) Top view of the TCP ablated by the bipolar electrodes in 60 seconds. Oscilloscope and precision meter not shown for clarity.

Figure 3

Graphical model of the basket catheter with four splines and four electrodes per splines. Note: two splines have a fifth, non-active radio-opaque electrode for position orientation during fluoroscopy.

Figure 4

(A) Computer simulation of the isothermal ablation zone for a 500 kHz input signal with an amplitude of 60 Vp-p at 60 seconds of ablation. The computer model predicted an ablation zone of 4 mm x 10 mm x 4 mm (length x width x height) over the bipolar electrodes. (B) Thermo-chromic tissue phantom (TCP) after an ablation signal (500 kHz, 60 Vp-p) was applied for 60 seconds. The dark pink color change corresponds to the area where the temperature exceeded 60°C. Note the similarities with the computer model in (A). (C) Ablation zone comparison between computer model (A) and TCP tissue experiment (B). The ablation zone was 3 mm × 8.5 mm × 3.5 mm. Note the very close correlation between the experimental and simulated ablation volumes.