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RESEARCH ARTICLE

MEDICAL PHYSICS

Study of flow effects on temperature-controlled radiofrequency ablation using phantom experiments and forward simulations

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Abstract

Purpose: Blood flow is known to add variability to hepatic radiofrequency ablation (RFA) treatment outcomes. However, few studies exist on its impact on temperature-controlled RFA. Hence, we investigate large-scale blood flow effects on temperature-controlled RFA in flow channel experiments and numerical simulations.

Methods: Ablation zones were induced in tissue-mimicking, thermochromic phantoms with a single flow channel, using an RF generator with temperature-controlled power delivery and a monopolar needle electrode. Channels were generated by molding the phantom around a removable rod. Channel radius and saline flow rate were varied to study the impact of flow on (i) the ablated cross-sectional area, (ii) the delivered generator power, and (iii) the occurrence of directional effects on the thermal lesion. Finite volume simulations reproducing the experimental geometry, flow conditions, and generator power input were conducted and compared to the experimental ablation outcomes.

Results: Vessels of different channel radii r affected the ablation outcome in different ways. For $r = 0.275$ mm, the ablated area decreased with increasing flow rate while the energy input was hardly affected. For $r = 0.9$ mm and $r = 2.3$ mm, the energy input increased toward larger flow rates; for these radii, the ablated area decreased and increased toward larger flow rates, respectively, while still being reduced overall as compared to the reference experiment without flow. Directional effects, that is, local shrinking of the lesion upstream of the needle and an extension thereof downstream, were observed only for the smallest radius. The simulations qualitatively confirmed these observations. As compared to performing the simulations without flow, including flow effects in the simulations reduced the mean absolute error between experimental and simulated ablated areas from 0.23 to 0.12.

Teresa Nolte and Nikhil Vaidya contributed equally to this work.

Volkmar Schulz and Karen Veroy contributed equally to this work.

A single reference experiment, that is, not using a flow channel, and the image in the upper left corner of Figure 5 were included into a publication submitted to Int. J. Hyperthermia for model validation purposes.

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Conclusion: While the temperature control mechanism did not detect the heat sink effect in the case of the smallest channel radius, it counteracted the heat sink effect in the case of the larger channel radii with an increased energy input; this explains the increase in ablated area toward high flow rates (for $r = 2.3$ mm). The experiments in a simple phantom setup, thus, contribute to a good understanding of the phenomenon and are suitable for model validation.

KEYWORDS

directional effects, flow effects, forward simulation, phantom experiments, temperature-controlled radiofrequency ablation

1 | INTRODUCTION

Percutaneous thermal ablation techniques can treat both primary and secondary focal liver tumors in a minimally invasive manner.¹ Compared to other clinically established ablation techniques such as microwave ablation, RFA is preferred for treatments near adjacent sensitive structures, where a slower heating process may be required (e.g., for the ablation of subcapsular nodules).^{2,3} However, RFA outcomes in the liver are not easily predictable due to the cooling effect of blood flow, complexity of the vessel architecture, and variable liver properties.^{4,5} Numerical simulations can help to understand the various contributions of such effects.⁶ Ultimately, simulation-based treatment planning frameworks will be able to suggest optimal treatment parameters to the clinician to ensure complete ablations while limiting damage to adjacent structures, thereby reducing tumor recurrence.⁷⁻¹⁰ This article focuses on the study of large vessel blood flow effects that cause localized heat transport.¹¹ Considering both fine-scale and large vessels, the perfusion-induced heat sink effect has been shown to reduce coagulation necrosis. Lu et al.⁴ found the presence of large peritumoral vessels to be the dominant predictor of tumor recurrence in a retrospective clinical study of 105 RFA cases. By performing RFA under portal vein occlusion or even after interrupting all hepatic perfusion, significantly increased lesion volumes were recorded as compared to normal blood flow conditions in both preclinical and clinical procedures.^{12,13} In Ref. [9] clinically significant over- or under-treatment has been reported in the vicinity of large blood vessels. Depending on the vessel radius and the blood flow rate, size reduction and deformation of the ablation zone and/or stretching of the thermal lesion in the flow direction may occur.^{11,14} The latter will be referred to as directional effect throughout this paper. Understanding the occurrence of large vessel flow effects is important when planning an intervention next to major vessels.

As far as numerical simulations are concerned, modeling blood-flow effects is complicated due to the diversity in blood vessel diameters and network topologies. Pennes¹⁵ modeled small, densely packed blood

vessels using a volumetric heat sink term. Nakayama and Kuwahara¹⁶ derived a more realistic description for the heat sink effect of small blood vessels. This two-equation model treats blood temperature and tissue temperature as coupled variables. However, it is unclear where to place the radius cutoff to distinguish between large and small vessels. Generally, blood vessels are considered thermally significant if (i) the total length of the vessel is comparable to the vessel thermal equilibrium length and (ii) the local surrounding tissue temperature is not close to the vessel outlet temperature.¹⁷⁻¹⁹ The aforementioned conditions assume that the blood interacts with tissue of a uniform temperature. This assumption is not satisfied for non-uniformly heated tissue.²⁰ Shrivastava et al. found that the thermal significance of a blood vessel does not depend on its diameter or the heat transfer coefficient; instead, the thermal significance strongly depends on the inlet vessel temperature and surrounding tissue temperatures.²¹ To our knowledge, the directional effect of individual blood vessels has not been studied in detail. Huang et al. investigated the directional effect of blood vessels through simulations.¹⁴ The blood velocity was assumed to be a function of vessel diameter. Vessel diameters of 1 and 2 mm were studied, and directional effects were only observed for 1 mm. We have, in the past, performed a simulation study on the directional effect of blood vessels in RFA.²² While assuming a dependence of flow rate on the vessel radius as suggested by Murray's law,²³ directional effects were found to occur below vessel radii of 0.5 mm and, if considering blood coagulation effects, above 0.4 mm for the blood vessel parameters considered. Kim et al.²⁴ have reported that a safety margin greater than 3 mm induced in clinical treatment is associated with a lower rate of local tumour progression. It may hence be important to determine whether any directional effects interfere with this margin.

Experimental studies of the combined impact of large vessel and background perfusion effects can be realized as retrospective evaluation of clinical treatments,^{4,25} in the preclinical setting,²⁶ as well as by using machine-perfused ex-vivo liver setups.^{11,27-29} Yet, most studies so far have used impedance-controlled RF generators. For example, Bitsch et al.¹¹ observed both size reductions and

deformations of ablation zones under perfusion in comparison to non-perfused controls using an impedance-controlled system with constant power input in perfused bovine livers. Temperature-controlled RF generators have so far been less investigated but may react differently to blood flow effects. Pillai et al.²⁹ found reduced volume and mass of the ablated lesions in the vicinity of major hepatic vessels despite employing longer ablation times. Non-perfused ex-vivo liver setups including one or more flow channels permit to study large vessel flow effects in an isolated fashion, as they lack background perfusion. For example, Poch et al.³⁰ examined flow through a perfused glass tube using an impedance-controlled RF generator with automatically modulated power and found incomplete ablation at different vessel-to-applicator distances as well as changes in shape. Welp et al.³¹ compared ablation experiments with a perfused glass vessel and constant power input to a finite element model. Blood flow did not affect the lesion diameter for large distances between electrode and vessel, although shape deformations occurred. Also among ex-vivo flow studies, temperature-controlled systems are underrepresented. Ablation phantoms, as for example tissue-mimicking thermochromic phantoms (TMTCP), constitute even more controlled experimental environments.^{32,33} Known material properties make them especially suitable for model validation purposes.

The present study investigates large vessel flow effects on temperature-controlled RFA in TMTCP equipped with a single flow channel. For different vessel radii and saline flow rates, we assess the resulting ablation zone areas, the impact of flow on the generator feedback algorithm, and the occurrence of directional effects. We compare the experimental results to numerical simulations and use them for model validation, thereby increasing confidence in further simulation-only results. Likewise, our study increases the fundamental understanding of how blood vessels affect temperature-controlled RFA treatment outcomes.

2 | MATERIALS AND METHODS

2.1 | Experimental setup

2.1.1 | Fabrication of TMTCP

Tissue-mimicking thermochromic phantoms for RFA consist of a polyacrylamide gel formulation, to which a

thermochromic ink and sodium chloride are added. The ink changes color irreversibly from white to magenta above a threshold temperature while NaCl enhances electrical conductivity. Thermal conductivity, thermal diffusivity, and mass density of the phantom mimic human liver tissue, and discoloring has been described as proportional to the maximum achieved temperature value.^{32,34} For phantom preparation, 671 g of deionized water was mixed with 175 g of a 40% (Bis-)Acrylamide 19:1 solution. 50 g of irreversible change ink concentrate and 7 g of sodium chloride (Sigma Aldrich, USA) were added to the solution and mixed under continuous stirring. The sodium chloride ensures that the phantom mimics the electrical conductivity of liver tissue. 1.4 g of N,N,N',N'-tetramethylethylenediamine was added before 1.4 g of ammonium persulfate (both from Sigma Aldrich, USA), which initialized polymerization. The mixture was poured in a cube-shaped container and allowed to polymerize at room temperature. The different gel-ink combinations used are shown in Table 1. The gel-ink combination used for each of the experiments is shown in Table 2. The Kromagen Magenta MB60-NH and 60-NH inks will be referred to as ink I and ink II, respectively.

The custom-fabricated sample container (Figure 1) allowed to insert rods of different radii through the center of the cube before pouring in the liquid phantom material. The inner dimensions of the sample container were 10 cm × 10 cm × 10 cm. After polymerization, the rod was removed without damaging the now solidified phantom, leaving a flow channel of known position and dimensions. Moreover, the cuboid container provided an insertion channel for the monopolar RFA needle to position it parallel to the flow channel at a wall-to-wall distance of 3 mm. The ground pad (Angiodynamics, New York, USA), cut to a size of 10 cm × 10 cm, was located on the bottom face of the sample container. Figure 2 shows a coronal cross-section through needle and flow channel as well as a 3D view of the geometry.

2.1.2 | RFA experiments including flow

Table 2 lists the RFA experiments performed. Three flow channel radii and four distinct flow rates per channel were considered. Figure 1 depicts the experimental setup. RFA experiments were carried out using a RITA 1500X RF generator and a Uniblatch ablation needle

TABLE 1 Different gel-ink combinations used in the study and their respective volumetric heat capacities

Combination	(Bis-)Acrylamide	Ink	Volumetric heat capacity (J · m ⁻³ · K ⁻¹)
1	NationalDiagnostics, USA	Kromagen Magenta MB60-NH, TMC Hallcrest, UK	4.069e6 ³⁴
2	FischerSci, The Netherlands	Kromagen Magenta MB60-NH, TMC Hallcrest, UK	2.529e6
3	NationalDiagnostics, USA	Kromagen Magenta 60-NH, TMC Hallcrest, UK	2.475e6

TABLE 2 Vessel radius, saline flow rates, and gel–ink combinations used for the experiments performed

Experiment no.	Vessel radius (mm)	Saline flow rate ($\text{ml} \cdot \text{min}^{-1}$)	Gel–ink combination
1	0.275	0.157 (=ML prediction)	1
2	0.9	5.50 (=ML prediction)	2
3	2.3	91.7 (=ML prediction)	3
4	0.275	0.0784 (<ML prediction)	2
5	0.9	1.68 (<ML prediction)	2
6	2.3	11.0 (<ML prediction)	3
7	0.275	0.428 (>ML prediction)	1
8	0.9	4.58 (>ML prediction)	1
9	2.3	29.9 (>ML prediction)	3
10	0.275	0.713 (>ML prediction)	1
11	0.9	7.63 (>ML prediction)	2
12	2.3	49.9 (>ML prediction)	3

Note: Experiments 1–3 used the physiological flow rates for a given vessel radius according to Murray's Law (ML).²³

FIGURE 1 Photograph of experimental setup showing the (i) sample container with tissue-mimicking thermo-chromic phantoms containing a flow channel; (ii) the radiofrequency generator with data logging and needle electrode installed within the phantom; and (iii) flow circuitry including a peristaltic pump, pulsation dampener, and tubing. Saline outflow from the phantom occurred on the needle side [Color figure can be viewed at wileyonlinelibrary.com]

(both by Angiodynamics, New York, USA). The RF generator has an internal power control algorithm which uses the temperature measured in the tip of the ablation

needle as feedback. The power control algorithm adjusts the delivered power over time to follow a prescribed temperature curve defined by an end temperature of 103°C and an ablation time of 10 min. A maximum power of 35 W was fixed as an upper limit for power delivery. It should be noted that the actually delivered power during an ablation experiment stays well below this limit. The active electrode length was set to 3 cm. Saline solution (0.1% (w/w) in deionized water) was prepared and flow through the channel was established using either a Multi-Phaser™ NE-1000 syringe pump (ProSense, Oosterhout, The Netherlands) or a Masterflex L/S peristaltic pump (Cole-Parmer, Wertheim, Germany) depending on the required flow rate. A pulsation dampener was inserted into the flow circuit when using the peristaltic pump. Saline flow was turned on prior to ablation and stopped after the generator's cool-down cycle. During each RFA experiment, delivered power and the temperature at the needle tip were logged from the generator every second. Reference RFA experiments were also conducted, omitting the flow channel during phantom preparation and conducting the experiment with identical settings otherwise. After each experiment, the ablation needle was removed and the phantom material was cut in half along the central plane passing through both needle canal and flow channel. The resulting discolored zone was photographed with a custom-made camera setup including a CCD camera (IDS Imaging Development Systems, Obersulm, Germany) and reproducible lighting conditions.

2.2 | Choice of channel radii and saline flow rates

In the present study, the objective was to study the effect of varying flow rate and radius independently. The smallest channel radius of 0.275 mm was chosen since it is small enough to guarantee directional effects (based on our previous simulation results²²). The larger radii of 0.9 and 2.3 mm were arbitrarily chosen within the range of vein radii observed in human livers³⁵ to investigate the effect of increasing radius. Flow rates equal to, larger, or smaller than the ones predicted by Murray's law were chosen for the experiments. If a network of flow channels (e.g., vascular system) which delivers a certain flow rate is considered, the viscous resistance against which the pump has to work increases as the channel diameter decreases. Hence, the pump mass increases with decreasing channel diameter. At the same time, the mass of tubing and fluid rises as the channel diameter increases. The form of Murray's Law used in this work to compute “physiological” flow rates gives the relationship between flow rate and channel diameter such that the sum of pump mass, tubing mass, and fluid mass is minimized for that flow rate assuming laminar flow.²³ It is given by

FIGURE 2 (a) Top view of geometry showing plane containing the ablation needle and saline flow channel axes; (b) three-dimensional view of tissue-mimicking thermochromic phantoms cube, ablation needle, and saline flow channel [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 3 Enlarged view of the ablation needle geometry [Color figure can be viewed at wileyonlinelibrary.com]

$$Q = \left(\frac{1024\mu}{d_i^6 \pi^2 \xi [\rho_{\text{tube}} (c^2 + 2c) + \rho_{\text{fluid}}]} \right)^{-1/2} \quad (1)$$

Here d_i , Q , μ , ξ , and c are the vessel diameter, volume flow rate, dynamic viscosity of the fluid, power-to-mass ratio of the pumping system, and a constant material property of the tube, respectively. The constants ρ_{tube} and ρ_{fluid} are the tube material density and fluid density, respectively. The material constant $\xi [\rho_{\text{tube}} (c^2 + 2c) + \rho_{\text{fluid}}]$ is independent of the vessel diameter, and its value was derived back from Equation (1) using the known values of $Q = 1.57e - 5 \text{ m}^3 \cdot \text{s}^{-1}$ and $\mu = 0.00365 \text{ Pa} \cdot \text{s}$ for hepatic vessels with $d_i = 10 \text{ mm}$.³⁶ The constant $\xi [\rho_{\text{tube}} (c^2 + 2c) + \rho_{\text{fluid}}]$ was estimated at $93.44 \text{ kg} \cdot \text{s}^{-3} \cdot \text{m}^{-1}$. Table 2 shows the relation between Murray's law and the saline flow rates used in this study.

2.3 | Analysis of ablation zones

Photographs of the discolored ablation zones were analyzed using the open-source software GIMP. For both ink I and ink II, the photographs mentioned above were transformed to gray values and the discolored zone was selected by a threshold. For phantoms prepared with ink I, preliminary calibration experiments showed that full discoloring was achieved after heating the material above 70°C . For phantoms prepared with ink II, discoloring was mostly, but not yet fully completed at the lower temperature of 65°C . To still assess the $T > 70^\circ\text{C}$ zone, we used the gray value of the 70°C calibration experiment as a threshold. The area of the $T > 70^\circ\text{C}$ zone was computed using GIMP's histogram

tool. The simulated $T > 70^\circ\text{C}$ zone was overlaid with the photographs by aligning needle canal, flow channel, and outer border of the phantom cube.

2.4 | Simulation setup

2.4.1 | Simulation geometry

The simulation geometry consisted of three subdomains: (i) TMTCP, (ii) ablation needle, and (iii) saline flow channel. The Uniblade ablation needle, which has an inhomogeneous internal structure, was modeled as a homogeneous material with volume-averaged thermal and electrical properties used in its interior. The outer dimensions of the ablation needle were modeled exactly. Figure 3 shows a close-up of the ablation needle subdomain. The needle active region was represented as a separate boundary surface which allows electric current to pass while the two insulated surfaces do not. The top surface of the needle was used to apply the input voltage which induces tissue heating.

2.4.2 | Mathematical model

In this work, heat transfer in solid TMTCP was described by the diffusion equation while that in saline was described by advection–diffusion. Since the TMTCP does not contain the fine-scale vessels present in the human liver, Pennes' perfusion term¹⁵ does not appear in the heat equation. The governing equations for TMTCP (p), saline (s), and ablation needle (n) subdomains are given by

TABLE 3 Convection coefficient values for external boundaries of the simulation geometry.³⁷

Boundary	Convection coefficient h ($W \cdot m^{-2} \cdot K^{-1}$)
Top TMTCP Face (air interface)	12
Bottom TMTCP Face (resting on table)	9
TMTCP Side Faces (parallel to ablation needle and flow channel)	12
TMTCP Side Faces (perpendicular to ablation needle and flow channel)	10
Ablation needle–Air Interface	12

$$\begin{aligned}
 \rho_p C_p \frac{\partial T_p}{\partial t} &= \nabla \cdot k_p \nabla T_p + \sigma_p |\nabla \phi_p|^2, \\
 \rho_s C_s \left(\frac{\partial T_s}{\partial t} + \vec{u}_s \cdot \nabla T_s \right) &= \nabla \cdot k_s \nabla T_s + \sigma_s |\nabla \phi_s|^2, \quad (2) \\
 \rho_n C_n \frac{\partial T_n}{\partial t} &= \nabla \cdot k_n \nabla T_n + \sigma_n |\nabla \phi_n|^2.
 \end{aligned}$$

where ρ_i , C_i , T_i , k_i , σ_i , and ϕ_i are the density, specific heat, temperature, thermal conductivity, electrical conductivity, and electric potential, respectively, for $i \in \{p, s, n\}$. Similarly, the expressions $\sigma_i |\nabla \phi_i|^2$ are the RF heat source densities in the three subdomains. The saline velocity $\vec{u}_s$ was assumed to have a laminar and steady profile. All interfaces between TMTCP, saline, and ablation needle subdomains are thermally conducting with negligible contact resistance. Hence, temperature and heat flux are continuous across these interfaces. Saline inflow and outflow boundaries were kept at room temperature (21°C). All external boundaries of the TMTCP had the thermal boundary condition $-k_p \nabla T_p \cdot \hat{n} = h(T_p - T_{\text{ref}})$ $W \cdot m^{-2} \cdot K^{-1}$, where T_{ref} is the room temperature and $\hat{n}$ is the surface normal. The needle surface exposed to air also had a convection boundary condition. The associated convection coefficients are given in Table 3. The initial temperature was 21°C.

The electric potential in all subdomains is governed by the quasi-static approximation

$$\nabla \cdot \sigma_i \nabla \phi_i = 0 \quad (3)$$

where $i \in \{p, s, n\}$. A time-dependent voltage $\phi_{\text{top}} = \frac{P_{\text{in}}}{\int_{\Gamma_{\text{AS}}} \vec{J}(t) \cdot \hat{n} dS}$ was applied at the top boundary of the

ablation needle, where Γ_{AS} is the active surface of the needle, and $\vec{J}(t) = \sigma \nabla \phi(t)$ is the electric current density. The functions ϕ and $\vec{J}$ are continuous across the vessel-tissue boundary and the active surface of the needle. The input power, $P_{\text{in}}(t)$, was taken from the RF generator logging data. The ground pad, located at the bottom surface of the phantom, was set to 0 V, while all other boundaries were electrically insulated.

The density, specific heat capacity, and thermal conductivity of the TMTCP for the gel–ink combination 1 were taken from Ref. [34]. To the best of our knowledge, the temperature dependence of these properties does not appear in literature. The gel–ink combinations 2 and 3 have different heat capacities, which were estimated from their cooling behavior, and are given in Table 1. The complex dielectric properties of the gel were measured and a conductivity value of $1 \text{ S} \cdot \text{m}^{-1}$ was obtained at the generator frequency (460 MHz). The saline density and specific heat capacity values used were $\rho_s = 970 \text{ kg} \cdot \text{m}^{-3}$, $C_s = 4200 \text{ J} \cdot \text{K}^{-1} \cdot \text{m}^{-3}$. The following temperature-dependent expression was used for the saline thermal conductivity

$$k_s(T) = 10^{-0.62 + (0.999 - 150.7/T) \sqrt{(1-T/650.3)}} \text{ W} \cdot \text{m}^{-1} \cdot \text{K}^{-1},$$

where T is the temperature in K. All these values were taken from Refs. [38,39] and median values from the temperature range of interest were used for ρ_s and C_s . The value of $\sigma_s = 0.15 \text{ S} \cdot \text{m}^{-1}$ was used for the saline electrical conductivity.⁴⁰ The average material properties used for the needle were as follows: $\rho_n = 1 \text{ kg} \cdot \text{m}^{-3}$, $C_n = 1000 \text{ J} \cdot \text{kg}^{-1} \cdot \text{K}^{-1}$, $k_n = 0.02 \text{ W} \cdot \text{m}^{-1} \cdot \text{K}^{-1}$, and $\sigma_n = 1.0e7 \text{ S} \cdot \text{m}^{-1}$.

The governing equations were solved using the commercial finite volume simulation package, Simcenter STAR-CCM+. The finite volume method (FVM) is used to solve systems of partial differential equations (which model conservation laws) in *integral form*. The spatial domain is subdivided into small volumes (the “finite volumes”) and the flux of the modeled variable through each face of the finite volume approximated.⁴¹ The geometry was discretized using a combination of polyhedral cells in most regions and hexahedral prismatic layers in regions with high temperature/potential gradients, in particular, at the ablation needle–TMTCP interface and vessel–TMTCP interface. A mesh convergence analysis revealed that appropriate mesh sizes were 0.3 mm at the ablation needle surface and 1 cm at the phantom outer boundary (figures and analysis not shown). For the vessel subdomain, an intermediate mesh size dependent on the vessel radius was chosen. These settings led to ~100,000 cells (DoFs) in the mesh. Furthermore, a time step of 0.5 s (determined from the mesh convergence analysis) was used in the simulation. The second-order implicit Backward Differentiation Formula (or BDF-2) scheme was used to discretize the time derivatives.⁴²

2.5 | Directional effect metric

In RFA, the directional effect of blood flow on the thermal lesion is characterized by the stretching of the lesion in the direction of blood flow. Figure 4 shows a schematic of directional effects on the thermal lesion

in RFA. The average lesion boundary displacement Δ_A (%)²² was used to quantify the directional effect and is given by,

$$\Delta_A = \frac{\Delta_{up} + \Delta_{down}}{2l_{ref}} \quad (4)$$

where Δ_{up} , Δ_{down} , and l_{ref} are defined as shown in Figure 4. The displacements Δ_{up} and Δ_{down} are positive in the direction of flow and negative otherwise. The displacement Δ_A represents stretching of the thermal lesion in the direction of blood flow as a percentage of reference lesion length. A large positive Δ_A corresponds to a large directional effect and vice versa. The Δ_A metric was computed on the $T > 52^\circ\text{C}$ zones which were used to analyse directional effects (reported in Section 3.3).

3 | RESULTS

3.1 | Influence of flow conditions on ablated areas (Experiments and Simulations)

Figure 5 gives an overview of all ablation results obtained for different channel radii and flow rates as well as for the reference cases. Below the corresponding reference experiment without flow channel, all experiments with saline flow are depicted. Around the needle, the magenta-colored zone is visible, indicating where tissue temperatures over 70°C or 65°C were reached for ink I or II, respectively. The experimental $T > 70^\circ\text{C}$ zones, obtained by gray-value based thresholding, are marked in blue, whereas the simulated $T > 70^\circ\text{C}$ zones are marked in black. Without flow, the ablated areas are symmetric with respect to the needle. For a radius of 0.275 mm and the two smallest flow rates of $0.078 \text{ ml} \cdot \text{min}^{-1}$ and $0.157 \text{ ml} \cdot \text{min}^{-1}$, the $T > 70^\circ\text{C}$ zones are distorted along the saline flow direction. These directional effects will be further discussed in Section 3.3. For all experiments with flow, the $T > 70^\circ\text{C}$ zones are narrower on the flow channel side than on the opposite one. For larger flow rates, the 70°C zones do not cover the flow channel region anymore, which reveals heat transport by saline away from the ablation site. The simulated $T > 70^\circ\text{C}$ zones show a close correspondence with the discolored areas in general. However, in four experiments (1, 5, 7, and 10), the experimentally obtained 70°C zone area unexpectedly exceeds the simulated area toward the top end of the needle. Throughout the rest of this article, we will refer to this feature as the “bump structure.” Figure 6 shows the experimental and simulated normalized ablated areas, determined by the $T > 70^\circ\text{C}$ zone, for the different flow experiments. Normalization was performed with respect

FIGURE 4 Schematic of the directional effect (green line) of a blood vessel on a thermal lesion. The directional effect causes stretching in the flow direction. Definitions of Δ_{up} , Δ_{down} , and l_{ref} used to define the Δ_A directional effect metric are shown. The cross-section is the one containing the vessel axis and the shortest line segment connecting the vessel axis and the radiofrequency-needle axis. This figure is based on a figure from Ref. [22] (Vaidya et al., 2021), licensed under the Creative Commons Attribution-NonCommercial license [Color figure can be viewed at wileyonlinelibrary.com]

to the experimental or simulated area of the corresponding reference experiment. For the smallest radius of 0.275 mm, both normalized areas are found to decrease with flow rate apart from one outlier. In contrast, both simulated and experimental ablated areas increase toward higher flow rates for the largest channel radius of 2.3 mm despite the increased heat transport away from the ablation site. For the intermediate channel radius of 0.9 mm, the experimental ablation area slightly decreases with flow rate while the simulated ablation area slightly increases.

The simulated temperature plots and the saline velocity fields are shown in the supporting information as Figures S1-S3, respectively.

3.2 | Comparison between simulation and experiment

The experimental and simulated $T > 70^\circ\text{C}$ zone areas are compared by means of the correlation plot in Figure 7 to assess whether the simulations agree with the experimental outcome. The plot shows that most simulated $T > 70^\circ\text{C}$ zones are close to the experimental

FIGURE 5 Experimentally obtained ablation zones for all radiofrequency ablation experiments and the corresponding reference experiments. The experimental and simulated 70°C temperature contours are marked by a blue and a black line, respectively. The ablation needle was inserted from the left side. Saline flow was established from right to left through the flow channel, which is located below the ablation area. Radius and flow rate for each experiment were as specified within the figure below the ablation zones. In four experiments, the experimental ablation zone shows an unexpected “bump” structure, which we marked by white arrows. The numbering of the experiments refers to Table 2 [Color figure can be viewed at wileyonlinelibrary.com]

ones. Some simulated zone areas underestimate the experimental ones, among which are the ones exhibiting the bump structure toward the top end of the

ablation zone, cf. Figure 5. The R -squared value for the data points was found to be 0.12. If the data points with the bumps in the experimental $T > 70^{\circ}\text{C}$ zone are

FIGURE 6 Experimental and simulated ablation zone areas from the flow experiments, normalized to the corresponding reference experiments, for the different investigated flow channel radii. The term $A_{\text{flow}}/A_{\text{ref}}$ is the ratio of experimental/simulated flow-affected $T > 70^\circ\text{C}$ zones to the respective reference $T > 70^\circ\text{C}$ zones

ignored, the R -squared value goes up to 0.65. The R -squared value is computed in the following way

$$\begin{aligned}\bar{A}_{\text{exp}} &= \frac{1}{N_{\text{flow}} + N_{\text{ref}}} \left(\sum_{i=1}^{N_{\text{flow}}} A_{\text{flow,exp}}^i + \sum_{i=1}^{N_{\text{ref}}} A_{\text{ref,exp}}^i \right) \\ SS_{\text{tot}} &= \sum_{i=1}^{N_{\text{flow}}} (A_{\text{flow,exp}}^i - \bar{A}_{\text{exp}})^2 + \sum_{i=1}^{N_{\text{ref}}} (A_{\text{ref,exp}}^i - \bar{A}_{\text{exp}})^2 \\ SS_{\text{res}} &= \sum_{i=1}^{N_{\text{flow}}} (A_{\text{flow,exp}}^i - A_{\text{flow,sim}}^i)^2 + \sum_{i=1}^{N_{\text{ref}}} (A_{\text{ref,exp}}^i - A_{\text{ref,sim}}^i)^2 \\ R^2 &= 1 - \frac{SS_{\text{res}}}{SS_{\text{tot}}}.\end{aligned}\quad (5)$$

The value of the Pearson correlation coefficient, ρ , was found to be 0.66 considering all data points.⁴³ Ignoring the data points with bumps, $\rho = 0.86$ was obtained.

The deviation of our experimentally obtained normalized ablation areas, $a_{\text{exp}} = A_{\text{flow,exp}}/A_{\text{ref,exp}}$, from a prediction a_{pred} , was further quantified by mean absolute error (MAE) calculations, defined as

$$\text{MAE} = \frac{\sum_{i=1}^N |a_{\text{exp}}^i - a_{\text{pred}}^i|}{N}.\quad (6)$$

Here, $N = 12$ is the number of experiments including flow channels. When using the simulated normalized areas to predict the ablation outcomes, that is, setting a_{pred} to $a_{\text{sim}} = A_{\text{flow,sim}}/A_{\text{ref,sim}}$, thereby quantifying the mean difference between the experimental

FIGURE 7 Correlation plot comparing the experimental and simulated $T > 70^\circ\text{C}$ zone areas A_{exp} and A_{sim} . The simulations underestimate the experimental areas for the smallest channel radius. These are the experiments with the bump structure in the $T > 70^\circ\text{C}$ zone

and simulated data points in Figure 6, $\text{MAE} = 0.12$ is obtained. When neglecting flow effects from the prediction and assuming the outcome equals the outcome of the reference experiment without any flow, that is, when setting $a_{\text{pred}} = 1$, a twofold higher $\text{MAE} = 0.23$ is obtained. It should be noted that a direct comparison of the experimental results to the vendor prediction was unfortunately not possible, as the electrode manual does not comment on the extent of the $T > 70^\circ\text{C}$ zones.

FIGURE 8 Simulations to further investigate the directional effect: The reference $T > 52^\circ\text{C}$ zone (blue) and the flow-affected $T > 52^\circ\text{C}$ zone (red) for channel radius 0.275 mm with increasing saline flow rate (Subfigures (a)–(d)) and for channel radius 0.9 mm with the lowest flow rate of 1.679 $\text{ml} \cdot \text{min}^{-1}$ (Subfigure (e)). The black arrow indicates the saline flow direction. These results are “Simulation-only.” [Color figure can be viewed at wileyonlinelibrary.com]

3.3 | Directional effects (Experiments and Simulations)

The directional effect of saline flow can be seen as a stretching of the $T > 70^\circ\text{C}$ region along the flow direction. In Figure 5, this phenomenon is visible only for experiments 1 and 4. According to our simulation experience, the thermal lesion in liver tissue typically coincides with a boundary temperature of around 52°C . The study by Huang¹⁴ showed that lower temperature contours are stretched more by blood flow, so the $T > 52^\circ\text{C}$ zones were also obtained from the simulations. The simulation

results for the 52°C contour show directional effects in experiments 1, 4, and 7 from Table 2. Figure 8a through e shows cross-sections of the $T > 52^\circ\text{C}$ zones obtained in the simulations. The red outline shows the flow-affected $T > 52^\circ\text{C}$ zone while the blue outline shows the reference $T > 52^\circ\text{C}$ zone. In Figure 8a–c, there is a distinct “tail” on the $T > 52^\circ\text{C}$ zone which stretches in the flow direction. For the channel radius of 0.275 mm and flow rate 0.0784 $\text{ml} \cdot \text{min}^{-1}$, a small directional effect occurs in the $T > 52^\circ\text{C}$ zone. The directional effect is larger when the flow rate rises to 0.157 $\text{ml} \cdot \text{min}^{-1}$. Near the inflow end, there is a shrinking of the $T > 52^\circ\text{C}$

FIGURE 9 (a) Example power curve that was obtained from the generator logging. (b)–(d) Normalized energy input for the radiofrequency ablation experiments with different radii and flow rates. E_{flow} is the total energy supplied in the experiments with flow, and E_{ref} is the total energy input in the respective reference experiment

zone of the order of 4 mm. Similarly, near the outflow end, there is tail region of 9 mm in length. For the flow rate of $0.428 \text{ ml} \cdot \text{min}^{-1}$, the directional effect decreases. Finally, for the flow rate of $0.713 \text{ ml} \cdot \text{min}^{-1}$, the directional effect is negligible. The tail structure due to the blood flow was not seen for any other channel radius. In all the figures, the vessel-affected and reference lesions differ only on the vessel side of the ablation needle, and directional effects occur mostly near the entry and exit points of the flow. The Δ_A values were 7.02%, 10.83%, 3.8%, 1.25%, and 1.14%, respectively, for the $T > 52^\circ\text{C}$ zones in Figure 8a–e.

3.4 | Analysis of generator power input (Experiments Only)

From the logged generator power curves $P(t)$, the total energy input was calculated as $E = \int P(t) dt$ for all ablation experiments and normalized to the energy input of the corresponding reference experiment. An example for a power curve $P(t)$ is shown in Figure 9a. Power curves for all experiments can be found in the Supporting Information (Figure S4). Oscillations in the curves probably originate from the generator feedback loop, as the device constantly adjusts the power to follow a prescribed temperature curve which it monitors at the tip of the ablation needle.⁴⁴ According to Figure 9b–d, for the larger radii, that is, 2.3 and 0.9 mm, the energy input increases with flow speed, whereas a decreasing energy input is observed for the smallest radius.

4 | DISCUSSION

In this study, ablation experiments were performed in TMTCPs with a flow channel to investigate temperature-controlled RF ablations. With this novel experimental setup, we were able to investigate the characteristics of large-vessel flow effects on temperature-controlled RF ablations, that is, the variation of lesion area, lesion shape, and power deposition with flow rate and channel radius. A clinically approved RF generator was employed for the experiments. For $r = 0.275$ mm, the measured $T > 70^\circ\text{C}$ zone area first oscillated and then decreased with increasing flow rate. This initial oscillation (for the flow rate of $0.157 \text{ ml} \cdot \text{min}^{-1}$) can be attributed to the large anomalous “bump” from Figure 5. The measured $T > 70^\circ\text{C}$ zone areas reduced with increasing flow rate for $r = 0.9$ mm, but an increase in area and energy input with flow rate was observed for the largest flow channel radius. This finding seemed surprising at first sight, as larger flow rates should result in an increased heat transport away from the ablation zone and hence in smaller $T > 70^\circ\text{C}$ zone areas, but can be understood by taking into account the temperature-based feedback algorithm. The RF generator uses the temperature measured by a probe in the needle tip as feedback in the power control algorithm. A blood vessel of small radius may still draw away heat from the ablation site; however, this heat loss is not detected by the temperature sensor in the needle tip. Larger vessels, on the contrary, draw higher amounts of heat away from the ablation site so that the overall tissue

heating is reduced. Consequently, a lower temperature is measured at the needle tip, which the RF generator compensates for with an increased power input. The increased energy delivery into the tissue then leads to an overall increasing $T > 70^\circ\text{C}$ zone area, which is however asymmetric with respect to the needle axis. The results underline that it is not always straightforward to predict the resulting ablation zone size by looking at nearby larger vessels before the start of a treatment—at least not in the case of feedback-controlled RF generators, which deliver variable power to the tissue depending on input variables such as the tissue temperature. Only in two experiments, directional effects of the flow were observed, that is, at the two smallest flow rates tested with the 0.275 mm channel radius. The polyacrylamide gel phantoms proved suitable for the flow channel experiments, since a flow channel could be molded directly into it without the need for a glass tube. This resembles the in-vivo situation more closely, as glass vessels were reported to locally change the electric fields.¹⁰ It should be emphasized that temperature-controlled systems differ from impedance-controlled ones by the shape of their delivered power-over-time curve. While the impedance-controlled devices typically provide a constant or stepwise increasing power⁴⁵ over a variable amount of time until a sudden rise in impedance indicates tissue coagulation, temperature-controlled devices use a fixed ablation time during which they try to follow the prescribed temperature curve, typically with an initial increase in deposited power which gradually adjusts to lower values (e.g., Ref. [33]). For example, Bitsch et al. observed both increased energy deposition and exposure time in a machine perfused setup with an impedance controlled system when perfusion was turned on.¹¹ Despite these fundamental differences, retrospective clinical studies have not been able to attribute differences in treatment outcome to the device type,^{4,46} which may be due to the large variability in experimental parameters.

Next to the experiments, simulations were performed based on the experimental settings, that is, geometry, material properties, and experimentally measured power curve. By comparing the simulated and experimental $T > 70^\circ\text{C}$ zone areas, confidence in the simulation model was gained. In Figure 7, the deviation of the data points for $r = 0.275$ mm from the $A_{\text{sim}} = A_{\text{exp}}$ line varies according to the size of the anomalous “bump” structure visible in Figure 5. The size of the bump is largest for the flow rate of $0.157 \text{ ml} \cdot \text{min}^{-1}$ (Experiment 1), and this data point has the largest deviation from the $A_{\text{exp}} = A_{\text{sim}}$ line in Figure 7. The size of the bump decreases successively for the flow rates of $0.428 \text{ ml} \cdot \text{min}^{-1}$ (Experiment 7) and $0.713 \text{ ml} \cdot \text{min}^{-1}$ (Experiment 10). The data points corresponding to those flow rates are successively closer to the $A_{\text{exp}} = A_{\text{sim}}$ line in Figure 7. For the flow rate of $0.0784 \text{ ml} \cdot \text{min}^{-1}$, for which there was no bump, the deviation of the data point from the

$A_{\text{exp}} = A_{\text{sim}}$ line in Figure 7 is smallest. Including flow in the simulations reduced the MAE between simulation and experiment from 0.23 to 0.12. This was considered acceptable, especially as the MAE is still dominated to some extent by the unexpected bump structure that caused high deviations in 4 out of the 15 ablation experiments. The proposed phantom setup proved to be useful for model validation, as it permitted to isolate the large vessel flow effects from other perfusion effects and because the material properties of the phantom are known.

Following this validation step, the simulation model was employed to further investigate the directional effects in the clinically relevant $T > 52^\circ\text{C}$ region (which is inaccessible to our experimental setup). At this lower temperature, the directional effect was observed for the three lowest flow rates at 0.275 mm channel radius. The simulation results suggest that the directional effect first increases, reaches a maximum, and then decreases as flow rate is increased for a constant channel radius. For $r = 0.275$ mm, the directional effect metric, Δ_A , first increases from 7.02% to 10.83% when the flow rate increases from $0.0784 \text{ ml} \cdot \text{min}^{-1}$ to $0.157 \text{ ml} \cdot \text{min}^{-1}$, and then decreases to 3.8% and 1.25% for flow rates of $0.428 \text{ ml} \cdot \text{min}^{-1}$ and $0.713 \text{ ml} \cdot \text{min}^{-1}$, respectively. This is because, for flow rates lower than $0.157 \text{ ml} \cdot \text{min}^{-1}$, heat diffusion is strong due to low flow velocities. This causes only limited heat advection downstream of the ablation needle before the saline cools due to diffusion. For flow rates larger than $0.157 \text{ ml} \cdot \text{min}^{-1}$, the flow velocity is too high for the phantom to be heated locally downstream of the ablation needle. For the case with the largest directional effect, there was a shrinkage of the $T > 52^\circ\text{C}$ region at the location of saline inflow, affecting the the ablation safety margin locally. On the other hand, a local extension of the $T > 52^\circ\text{C}$ region was present at the saline outflow, posing a potential threat to sensitive structures. In other regions, the shape of the $T > 52^\circ\text{C}$ region did not differ from the reference $T > 52^\circ\text{C}$ region. A study by Debbaut et al. estimated that there are about 10 times more meso-scale blood vessels of radius below 0.3 mm in the liver than of radius above 3 mm, which are vulnerable to thermal damage depending on their distance from the ablation needle.³⁵

Our study has some important limitations. First of all, the discoloring of the thermochromic ink marks the region where $T > 70^\circ\text{C}$ for ink I (or $T > 65^\circ\text{C}$ for ink II, respectively). Note that this region should not be confounded with the zone of coagulated tissue, which is the clinically relevant outcome of an ablation treatment. The zone of coagulated tissue would have a larger extent, as (i) coagulation also happens at lower temperature and (ii) depends on the thermal dose.⁴⁷ Despite this limitation, the presented setup still allowed to perform model validation at $T > 70^\circ\text{C}$ before extending the simulation results to lower temperatures. Second,

the presented experimental setup is much more simple than the situation faced during an in-vivo liver RFA treatment. For instance, phantom, needle and flow channel geometry, and the saline flow rate are known with high accuracy and can be fed into the simulation framework without any need for medical imaging beforehand. Besides this, the experiments performed ignore micro-vascular perfusion since a phantom is used, and the simulations do not consider the temperature dependence of the phantom properties. Despite their reduced complexity with respect to the in-vivo situation, the experiments still allow to investigate large vessel blood flow effects on temperature-controlled RFA in a fundamental fashion. Similar studies have been performed previously for impedance-controlled generators.^{30,48} Moreover, a well-controlled environment of known properties can be considered advantageous for model validation. In the flow experiments, saline solution was used as a perfusion fluid due to simplified handling in comparison to blood. This means, however, that our experiments and simulations were not suitable to investigate heat-induced coagulation effects in blood. Pulsatility of blood flow was also not considered. However, pulsatility of flow was minimized experimentally using a pulsation dampener with the peristaltic pump and appropriate syringe sizes with the syringe pump, respectively. Furthermore, simulation studies on the potential impact of pulsatility on thermal therapy have so far shown only a minor effect on average heat transfer through the vessel wall.^{14,49,50} As mentioned above, 4 out of 15 experimental ablation zones exhibited a bump structure of unknown origin. Three different possible causes for this deviation were explored by performing additional simulations (data not shown). Neither a local inhomogeneity in phantom thermal conductivity, current leakage from the insulated ablation needle surface, nor a local contact resistance on the ablation needle active surface produced a similar feature in the simulated results.

Future work could comprise experimental geometries of more complicated nature, for example, the molding of more than one flow channel or even more complicated vessel structures. A similar study using blood as a perfusate could be set up to investigate the effects of thermal coagulation of blood.⁵¹ Admittedly, a thermochromic ink that changes its color at a lower temperature would constitute an important improvement for future experiments. A potential future improvement for clinical RFA interventions that use an RF generator with temperature-controlled feedback could be to monitor the delivered power in real time and to provide, based on simulations with a simplified vessel model, an updated prediction of the ablation zone size. Such a simplified vessel model could be obtained by segmenting needle and nearby vessels from the pre-interventional contrast-enhanced CT. Importantly, approximating the radius-dependent flow rates via Murray's law does not

require actual flow measurements such as by Color Doppler ultrasound. However, the validity of this approximation needs to be verified in vivo, as our study showed a dependency of the ablated region on the flow rate.

5 | CONCLUSION

In this study, RFA was performed in TMTCPs with a single flow channel using a temperature-controlled RF generator. Likewise, large-vessel flow effects on temperature-controlled RFA outcomes were studied, revealing influence of flow on the temperature-feedback loop. The measured $T > 70^{\circ}\text{C}$ zone areas (i) were asymmetric about the RF needle axis for all radii; (ii) decreased with increasing flow rate for $r = 0.275$ mm and $r = 0.9$ mm; and (iii) increased with increasing flow rate for $r = 2.3$ mm. The energy input of the temperature-controlled generator (i) fluctuated about the reference energy input with increasing flow rate for $r = 0.275$ mm; (ii) increased with increasing flow rate for $r = 0.9$ mm and $r = 2.3$ mm. The flow influenced the temperature control algorithm for the two larger channels, but not for the smallest channel. The experimental setup was suitable for validating the simulation model, which enhanced confidence in the simulation-only results. The simulation model was then used to study the directional effects on the thermal lesion. The directional effect on the 55°C contour (which roughly corresponds to the thermal lesion in the human liver) was observed only for $r = 0.275$ mm, and it first increased and then decreased with increasing flow rate. Furthermore, the directional effects can either locally decrease or increase the ablation margin. The interventional radiologist would have to be aware that in some cases more flow effects may lead to larger lesions than cases with fewer flow effects, whereas in others the lesion could shift downstream because of directional effects. Thus, our study contributes to the understanding of temperature-controlled ablation outcomes in vivo in the vicinity of large blood vessels.

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CONFLICT OF INTEREST

Marco Baragona, Valentina Lavezzo, Aaldert Elevelt, and Ralph Maessen are currently employed by Philips

Research Europe. Volkmar Schulz is a CEO of Hyperion Hybrid Imaging Systems GmbH.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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