Analysis and optimisation of cryoablation with regard to transmurality

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***Abstract*—*Objective*: Permanent isolation of the pulmonary veins is the goal of all atrial fibrillation ablation. However, invasive re-mapping data show that pulmonary vein conduction has recovered in patients with recurrences. For this reason, stable transmurality of the ablation lesions is required to ensure durable pulmonary vein isolation. Currently, the optimal freezing dose of cryoablation is still under debate, which is why this paper aims to examine time-course temperature changes in the tissue and identify influencing factors of coolloop catheter ablation.**
***Methods*: Cryoablation is performed in vitro using a tissue-like phantom with attached thermocouples in a moving water bath. The experiments vary in tissue phantom materials, applied forces as well as freezing duration. Temperatures at the tissue surface and at depths of 1 mm, 2 mm, and 3 mm are continuously recorded during the freezing process.**
***Results*: An average nadir temperature of -51 °C was achieved at the tissue surface, -30 °C, -17 °C, and -12 °C at the tissue depths, respectively. The temperature curves showed significant delays in tissue depth and severe position-dependent differences were identified along the ablation line. No notable difference with regard to change in force was observed.**
***Conclusions*: The current system is expected to achieve long-term cell damage of almost 2 mm tissue depth. Shortening the freezing duration is not recommended due to delayed cooling at depth; a prolongation might be deliberated. The position-dependent differences can be attributed to insufficient enclosure by the current catheter design, which also diminishes the force exerted on the tissue.**

***Index Terms*—Atrial fibrillation, cryoablation, transmurality**

I. Introduction

ATRIAL fibrillation (AF) is the most common cardiac arrhythmia with a significantly increased risk of stroke and immense effects on morbidity [1]. Treatment options include drug therapy and minimally invasive treatment. Usually, drug therapy is the first choice, however, it seems to be less effective and can lead to severe side effects [2]. Special catheters are used for minimally invasive treatment. Besides the use of other forms of energy, cryoablation involves the targeted hypothermia of the affected tissue, thus suppressing its electrical conductivity [3].

Permanent isolation of the pulmonary veins (PVs) is the goal of all AF ablation. However, treated tissue has been observed to recover in patients with AF recurrences. For this reason, stable transmurality of the ablation lesions is required to ensure durable PV isolation. In this regard, the penetration of the entire transmural thickness of the atrial wall, but the avoidance of a too high freezing dose and thus collateral damage play an important role. Currently, the optimal freezing dose of cryoablation is still under debate [4].

There is a huge amount of data available on the effectiveness and safety of AF cryoablation as well as comparisons with the well-established radiofrequency ablation. Several studies have integrated temperature measurements in or on the ablation catheter, but there is currently few information on contact and depth temperature progression in the tissue especially due to the difficulty of implementation in vivo [5]. All existing studies used either a cryoballoon or tip catheter, which differ from the coolloop catheter in design and target temperatures. For this reason, this thesis intends to examine the time-course temperature changes and the minimally achieved temperatures, the nadir temperatures, at the tissue surface and at tissue depth, using the novel cryoablation catheter coolloop. Influencing factors are identified and analysed and conclusions on tissue necrosis and potential optimisation of the procedure are drawn.

II. Methods

The afreeze cryoablation system consists of the catheter and a console from where the physician can initiate and modify the treatment and receives feedback. The console contains a gas bottle, which provides the cooling agent nitrous oxide for the freezing process. Thermocouples are integrated into the catheter to measure internal distal, proximal and shaft temperatures and detect abnormalities, which are then displayed by the console. The target temperature inside the loop is -85 °C.
The experiments are performed in vitro in a simple water bath. The construction including all components can be seen in Figure 1. To simulate the human body temperature, water temperature is set between 33 – 40 °C, which is continuously monitored by a digital thermometer and maintained by an immersion heater with a thermostat. By means of a pump, the thermal load of the blood flow is simulated. The pump is activated when the water reaches a certain level and electrical contact is made by a float. The catheter is placed in the water bath and attached to a designated holder for positioning and fixation to the phantom tissue during the freezing process.

For temperature recordings, thermocouples are attached to the catheter respectively the tissue phantom. Type T

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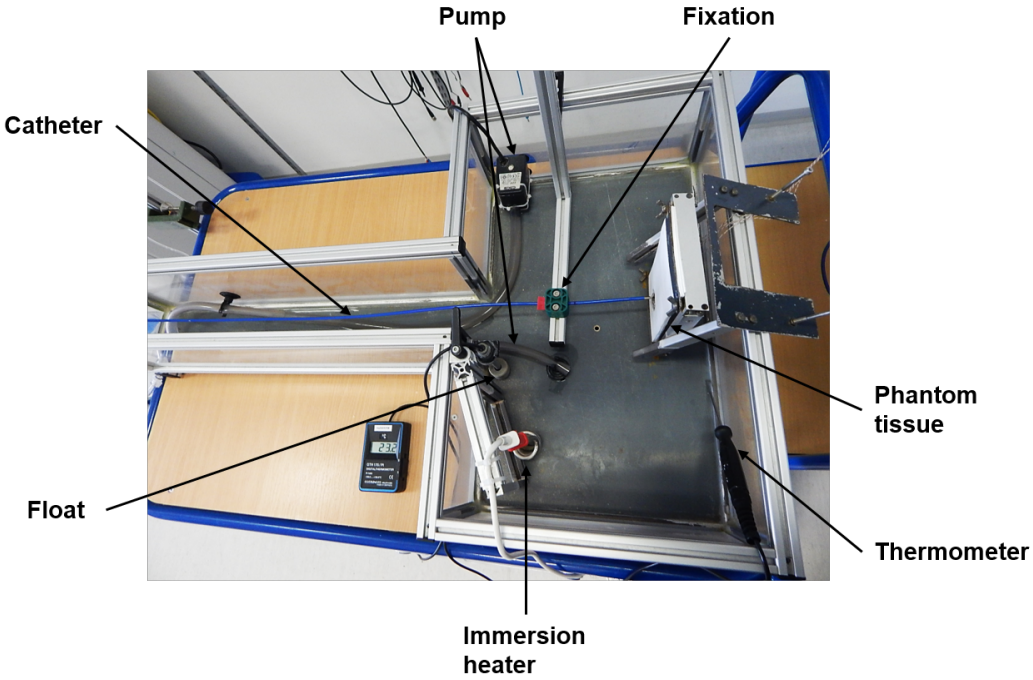

Fig. 1. Experimental setup and description of the components.

thermocouples are used for all measurements because they are resistant to moisture and they can be used at extremely low temperatures [6], which makes them suitable for cryoablation experiments. With regard to accuracy in these specific measurements, standard "tip" sensing devices are used. The two wires of the tip thermocouples are soldered together at one end and attached to the catheter respectively the phantom tissue. Measurements are taken at three different positions: Distally, centrally and proximally specified by the physician's point of view, as illustrated in Figure 2. The second end of the thermocouple is connected to the PicoLog device via a connector. This device is used to read and record the temperature progression and is connected via a USB port to the PicoLog software on the laptop. The software GNU Octave is used to evaluate the measured values.

Five different approaches are chosen for the temperature measurements. In the first approach, the measurements are performed directly on the loop of the catheter with thermocouples glued on distally, centrally and proximally, as shown in Figure 2. The other models are used for contact temperature measurements at the surface of the phantom tissue and at tissue depth. The model structures show an indentation in the top layer for positioning and fixation of the loop as well as for, to a small extent, shielding the thermal load. Thus, the penetration of the loop into the soft cardiac tissue is simulated. The thermocouples are attached along the ablation line onto the foam rubber or silicone, which is used for contact temperature measurements. Measurements are also taken with an unwound loop. Tissue depth measurement is performed with a layer model of adhesive foils. It consists of 0.13 mm thick foils that are adhesive on both sides. The exact thicknesses have been determined after layering using a digital calliper. For the adhesive pads, a thermal conductivity of $0.6\,\mathrm{W\,m^{-1}\,K^{-1}}$ was specified by the manufacturer, which corresponds quite closely to that of the cardiac tissue with $0.587\,\mathrm{W\,m^{-1}\,K^{-1}}$ [7]. Here, the temperatures are recorded exclusively at distal position, at the tissue surface and at 1 mm, 2 mm and 3 mm tissue depth. The measurement range down to a depth of 3 mm is justified by detailed research on the transmural thickness of the left atrial wall, which is highly relevant for effective cryoablation. Due to intra- and inter-patient variability and various approaches, different studies obtained diverging results [8], [9], [10]. Therefore, an average atrial thickness of 3 mm is assumed throughout this work [8], [11], [12], [13].

The experiments are performed with the best possible contact in a laboratory environment and a freezing time of 120 s. The thermal load of the water pump is set as low as possible and as high as necessary for the console as it terminates the freezing process if the thermal load is too low. Currently, there is no possibility for accurate measurement of the flow velocity.
In terms of contact temperature measurement, the goal is to receive rough temperature values on the tissue surface and to compare the different models. Thus, first conclusions about the representativeness of the models and value range shall be drawn. In the tissue depth measurement, it is focused on the duration to reach certain isotherms, on overall nadir temperatures and thawing parameters. It is also observed how the temperature curves and the nadir temperatures alter due to short successive freezing processes meaning the absence of thawing to ambient temperature. Furthermore, the impact

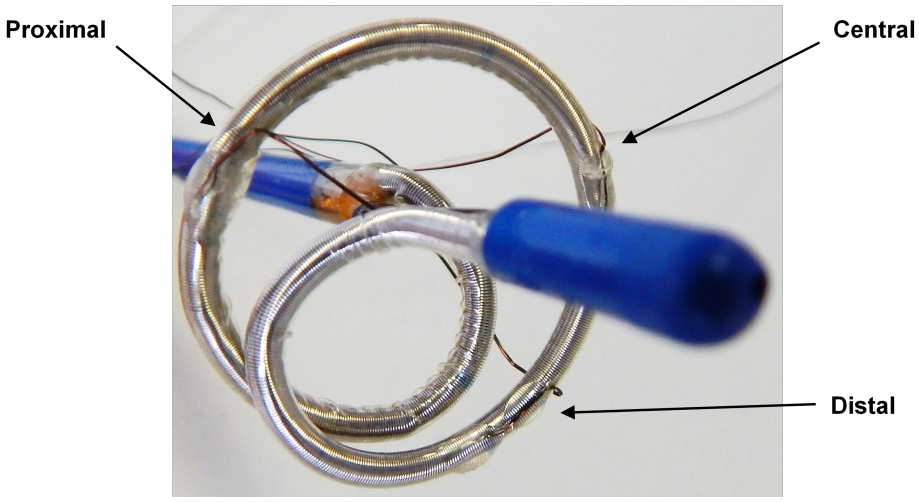

Fig. 2. Positioning of the thermocouples on the catheter distal, central and proximal.

of two different downward forces by the catheter applied to the phantom tissue is regarded. Therefore, the catheter was positioned depending on the fixture and marks were made on the shaft of the catheter, as shown in Figure 3. The applied forces were then measured separately with a tension/compression machine. In the experiments, a distinction is made between 0.04 N respectively 4 g, and 0.55 N respectively 56 g. Finally, the freezing duration is increased from 120 s, which is usual for the laboratory experiments, to standard clinical coolloop ablation duration of 180 s and temperature progression is observed.

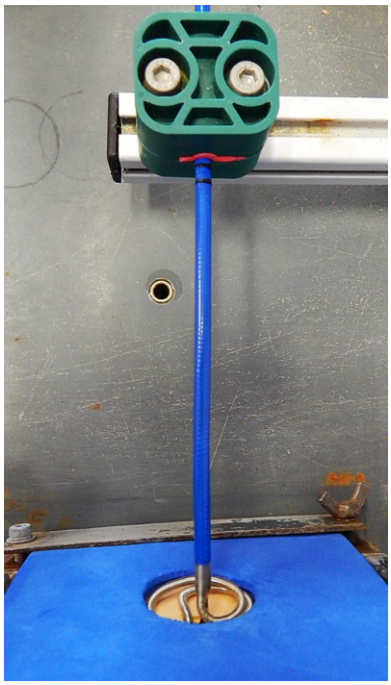

Fig. 3. Fixation of the catheter and markings on the shaft for the force tests.

III. Results

Table 1 shows the average surface nadir temperatures of three trials per approach and thermocouple position. Regarding the similar temperatures of the foam rubber model, silicone model and layer model, the representativeness of the models and values was concluded. In all experimental models, the measurement position showed a great impact on the nadir temperatures. Significantly lower values were achieved distally than centrally and proximally. The measurements with the unwound loop showed not as low average temperatures distally and proximally.

Based on the findings of the depth measurements, average nadir temperatures of -51 °C were achieved at the tissue surface, -30 °C at 1 mm tissue depth, -17 °C at 2 mm depth and -12 °C at 3 mm depth during coolloop ablation with a freezing time of 180 s, which is common in the clinical setting. The time-course temperature change is presented in Figure 4.

A general delay in cooling and thawing was observed in the depth of the tissue. The lowest temperatures at the surface were reached at the end of the freezing cycle; depending on the tissue depth, they were reached with a time delay after the freezing was completed. During the cooling and thawing process, a temporary stagnation or even an increase of the temperature progression occurred around the 0 °C isotherm. Furthermore, large differences between the temperature curves of the outer layers of the tissue phantom were present, while these discrepancies were less pronounced deeper in the tissue. Short successive freezing did not create any significant differences with regard to reached nadir temperatures. Likewise, the change in force by the coolloop catheter had only slight impact, as shown by the nadir temperatures listed in Table 2. Contact temperatures hardly dropped any further after 120 s, but the prolonged freezing cycle of 180 s showed an influence on the temperature progression in the tissue

TABLE I
OVERVIEW OF THE AVERAGE SURFACE NADIR TEMPERATURES ACHIEVED PER POSITION ON THE VARIOUS TISSUE PHANTOM MODELS.

	Distal	**Central**	**Proximal**
	Min *T*/°C	**Min *T*/°C**	**Min *T*/°C**
Measurement at the catheter	-63.6	-44.2	-12.6
Foam rubber model	-55.1	-50.2	-22.8
Silicone model	-52.4	-35.7	-18.1
Open-loop model	-18.9	-34.1	-6.2
Layer model	-51.4	-	-

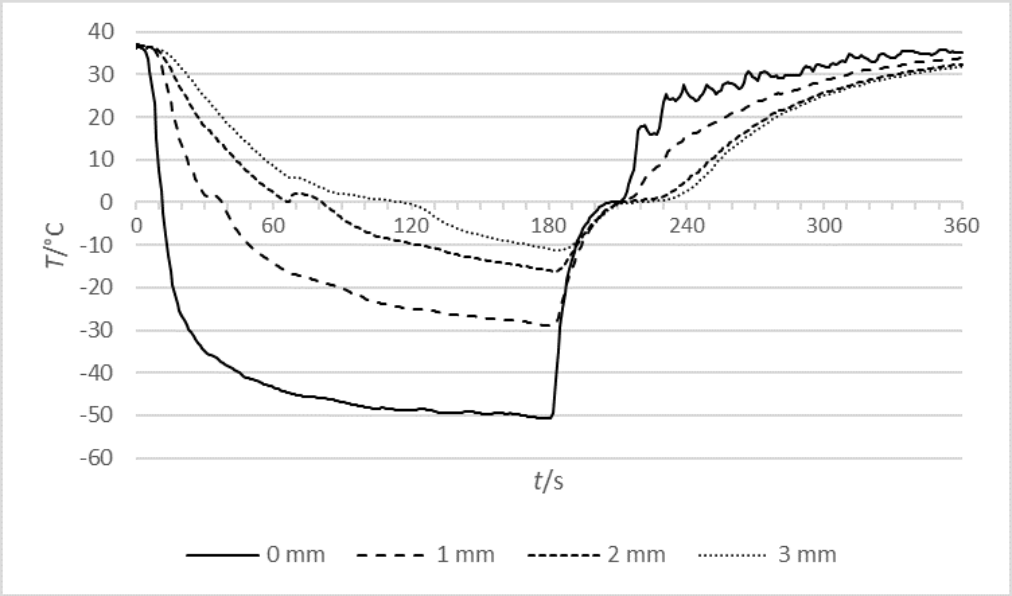

Fig. 4. Temperature progression in the tissue depth of a 180 s freezing cycle.

depth, like Figure 4 and Table 3 indicate.

IV. CONCLUSION

During the freezing process, initial ice formation with subsequent rapid propagation was clearly visible at the positions with complete catheter-tissue contact. The resulting adhesion also provides fixation for the loop during the procedure. For ice formation, complete circumferential catheter-tissue contact, also known as enclosure of the phantom tissue, is fundamental. As can be seen by the design of the loop, which causes an overlap in the distal position and a slight bulge towards the shaft on the proximal side, hardly any ice was formed proximally. By the increased thermal load of the water between this gap, this effect was promoted. The phenomenon appeared likewise in the experiment with the unwound loop. Due to the hereby altered geometry of the loop, both the distal and the proximal side bent up with the application of minimal force, which explains the comparatively low and non-constant values. The contact surface of the catheter in combination with the thermal load, therefore, has a very strong influence on the nadir temperatures to be achieved at the tissue and the resulting effectiveness of the cryoablation. It can be assumed that due to the design of the catheter these parameters further lead to the observed disparities of different positions.

The considerable effect of enclosure was confirmed by various studies [4], [14], [15], [16]. The computer simulation of cryoablation by Handler et al. as well as the conducted in vitro experiments by Giaretto et al. have proven a clear impairment of the freezing process by the thermal load [17], [18]. Wood et al. determined a 72% reduction in lesion size due to convective warming under superfusate flow compared to a no thermal load status [19]. Position-dependent differences in the temperature profiles and nadir temperatures have also been documented several times in the literature. A study of cryoballoon ablations in dogs by Takami et al. has shown clear deviations in the temperature measurements at different positions on the cryoballoon [4]. The same phenomenon was recognised by Weimar et al. Here, the proximal end of the

tip catheter reached considerably lower temperatures than the distal end. [20]

At the surface of the coolloop catheter, an average nadir temperature of -64 °C was measured distally, -44 °C centrally and -13 °C proximally. However, the isolation of the adhesive layer towards the cooling effect of the catheter and also towards the thermal load of the surrounding water, which is given by the design of the experiment, should be noted in this regard.
In comparison, Takami et al. obtained -43.0 °C, -25.8 °C, -18.0 °C, and -15.1 °C at four different positions at the surface of the cryoballoon in a 3-minute ablation [4]. Weimar et al. recorded nadir temperatures of -58.9 °C for the Cryo1 and -61.2 °C for the Maze Linear 3011 catheter on the surfaces of the two tip catheters in their in vitro tests. The values were averaged of the measurements of different positions on the catheters [20].

At tissue site, average nadir temperatures of -51 °C were achieved with the coolloop catheter ablation at the surface, -30 °C at 1 mm tissue depth, -17 °C at 2 mm, and -12 °C at 3 mm depth.
Wood et al. achieved -32 °C in 1 mm, -9 °C in 2 mm, and 6 °C in 3 mm tissue depth in their study with the Freezor 5 tip catheter from CryoCath [19]. Medtronic's Arctic Front Advance cryoballoon reached -33 °C at the tissue surface and -14 °C at a depth of 2 mm and Boston Scientific's POLARx -35 °C and -16 °C, respectively [21]. Because of the variations in design and internal catheter temperatures as well as different setups of the experiments carried out, it is difficult to make direct comparisons. For instance, the cryoballoons tend to have considerably lower internal catheter temperatures than the coolloop catheter [16], [22], [23], [24]. However, the geometry of the inflated balloon interrupts the blood flow through the vein meanwhile the freezing process, making the thermal load at site a much less interfering influence.

The delays of the temperature progression in the tissue depth during the freezing and thawing processes can be ascribed to the weakening cooling effect of the interstitial tissue depending on its thermal conductivity. Consequently, cryoablation has a significantly lower effect on deeper tissue layers. The temporal increase or the stagnation around 0 °C during freezing and thawing is induced by the phase transition of the water. During cooling, this was particularly pronounced in the temperature curves of the tissue depths. During thawing, the temperature curves of all depths approached the 0 °C isotherm asymptotically. When liquid transitions to solid and conversely, which happens at the melting point, all energy supplied is used to strengthen respectively resolve the bonds between the molecules, which is why the temperature at the time of the phase change remains constant. Temporary rising temperatures are the result of a super-cooling effect due to a high cooling rate and hence a super-cooled melt which contains a lot of energy. [25] Takami et al. and Handler et al. described a comparable effect in their studies [4], [17].

The application of higher force by the coolloop catheter to the tissue, 56 g vs. 4 g, resulted in lower nadir temperatures in the tissue, as shown in Table 2, but the temperature differences were minor with regard to the large range between the two forces.
Parvez et al. and Wood et al. evaluated the effect of the change in force at 6 g and 20 g with tip catheters on porcine cadavers and concluded a greater lesion size the greater the contact force [19], [26]. Presumably, due to the design of the coolloop catheter, not all of the applied force can be transferred from the shaft to the tissue. Because of the flexibility of the loop, the force transfer is diminished. In contrast to the experiments with the tip catheters, where no loss of force is expected due to the stability of its structure, no significant added value could be perceived by increasing the contact force in coolloop catheter ablation.

TABLE II
ACHIEVED NADIR TEMPERATURES PER TISSUE DEPTH FOR DIFFERENT FORCE APPLICATIONS.

Tissue depth	56 g	4 g
	Min *T*/°C	Min *T*/°C
0 mm	-51.3	-47.2
1 mm	-26.4	-23.1
2 mm	-11.1	-8.3
3 mm	-4.8	-0.6

In literature, there are widely differing opinions regarding the optimal freezing time. Well-known studies such as the STOP AF trial and the CIRCA-DOSE study defined a standard ablation time of 240 s with the cryoballoon [22], [27]. Various studies observed a plateau phase after a certain freezing duration, at which the lesion size in the tissue hardly increased any further. Regarding tip catheter treatment, Tse et al. mentioned a limited benefit after an ablation time of 5 minutes [28] and Andrade et al. referred to the onset of the plateau phase after 4 minutes [27]. Takami et al. and Ciconte et al. spoke of progressive lesion growth for 3 minutes in the treatment with a cryoballoon catheter. After this time, there is an increased risk of collateral damage. [4], [29] As the optimal ablation duration is accordingly still unclear, often additional circular mapping catheters are used to verify the isolation of the tissue by recording electrical signals [14].
It is assumed that the ideal freezing duration strongly depends on the type of the catheter. As a result of different catheter designs and inner temperatures, the cold transmission between the catheter and the tissue takes place at different speeds and over different contact surfaces. The coolloop catheter is characterised by a high cooling rate and a favourable almost circular contact surface, which is why freezing time is generally shorter than with other cryoablation catheters. However, as previously described, the impairment of the

thermal load is significantly higher in coolloop cryoablation than with a cryoballoon as the blood flow is not interrupted. Although the temperatures at the tissue surface hardly seemed to drop after 120 s, a so-called plateau phase occurred [29], the temperatures in the tissue depth continued to fall significantly after 120 s, as the values in Table 3 indicate.

TABLE III
ACHIEVED NADIR TEMPERATURES PER TISSUE DEPTH FOR THE 120 S AND THE 180 S FREEZING CYCLE.

Tissue depth	**120 s freeze** Min *T*/°C	**180 s freeze** Min *T*/°C
0 mm	-51.4	-51.4
1 mm	-27.2	-29.6
2 mm	-13.5	-17.0
3 mm	-7.5	-12.4

The aim of cryoablation for the treatment of AF is to destroy the tissue, that generates the deceptive signals, through systematic hypothermia. In order to draw conclusions about the extent of tissue isolation based on the recorded temperature progression, the required temperature for suppression of the electrical conductivity of the tissue must be considered. Several studies assumed cell necrosis and thus permanent damage at below -20 °C [5], [17], [20], [30], [31]. Based on a required temperature of -20 °C for long-term cell damage and the current handling of the coolloop catheter, it is expected that tissue gets durable isolated down to a depth of almost 2 mm.

With regard to the assumed average thickness of the atrial wall with 3 mm, a shortening of the standard freezing duration of 180 s is not advisable. In order to achieve sufficient transmural penetration, a prolongation of the ablation time could be considered, also taking into account the risk to the surrounding organs. In addition, more emphasis should be placed on exact precise positioning of the catheter before freezing, as it was confirmed that the quality of ablation has a higher influence than the quantity [32], [33]. Further potential for optimisation lies in modifying the catheter design through improved geometry. A completely circular loop for uniform circular cooling around the PVs is therefore essential. With a re-design of the loop, distal, central and proximal differences shall be avoided and multiple freeze cycles per PV with rotation of the catheter would no longer be necessary. The treatment duration and fluoroscopy time would therefore be shortened and the radiation exposure for the patient minimised. A coolant tube with a directional design would be a further conceivable option. The tube needs good thermal conductivity towards the tissue and insulation against the blood flow to make the treatment as efficient as possible. Therefore, different materials are required.

With regard to all cryoablations, a further consideration would be to determine the individual transmural thickness of the atrial wall in advance using, e.g. by CT scans. Since the freezing time should be sufficient to penetrate the transmural thickness but as short as possible to avoid collateral damage, an individual ablation time suitable for the patient could be determined using algorithms based on the measured thick-ness.

Limitations

Limitations are given particularly by the in vitro experimental setup, which does not exactly reflect the characteristics of an in vivo catheter ablation. In the experiments carried out, no real cardiac tissue was used because of the increased effort required, especially due to the simulation of the thermal load within the organ and the necessity of implanting the thermocouples. Phantom tissue of different materials with diverging thermal conductivity and deformability was used instead of cardiac tissue and no perfusion with blood was given. In the bench test, water was used instead of blood, which also differs in various properties. A wide range of water bath temperatures was accepted allowing a slight variation of the thermal load. The thermal load by the moving water was directed at the right side of the tissue phantom, which was thus deviating from the anatomy; opposite through the opening of the PVs. Due to hand-made tissue phantom models, inaccuracies in this respect cannot be excluded, which refers primarily to the manufacturing methods such as cutting, glueing and soldering. In the case of depth measurement, it cannot be ensured if the catheter was located exactly above the thermocouples or whether there were slightly greater distances between than specified.
In the present experimental model, it is not possible to consider variable PV anatomies, even though the individual shape and tissue thickness represent an important influencing factor in reality. Likewise, it is not feasible to investigate acute and long-term insulation based on tissue phantoms.

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