Rend. Lincei Mat. Appl. 25 (2014), 301–307
DOI 10.4171/RLM/680

Mathematical Biology — *Mathematics helps assessing the risks of esophageal thermal lesions in pulmonary veins isolation by means of cryoablation*, by Antonio Fasano, Luca Anfuso and Iacopo Borsi, communicated on 9 May 2014.

Abstract. — Cryoablation of the pulmonary veins ostia in the left atrium is a procedure often used to cure drug resistant atrial fibrillation. Among the possible complications esophageal thermal lesions can be induced, which in some case turn out to be lethal. Hence the importance of predicting the thermal field created around the heart during the procedure. This goal is achieved here by utilizing a suitably simplified geometry and assuming that heat propagation is governed by the bioheat equation with temperature dependent blood perfusion rate.

Key words: Cryoablation, bioheat equation, body temperature.

Mathematics Subject Classification: 80A20, 92C50, 92–04.

1. Introduction

Drug resistant atrial fibrillation is treated by ablating the nerves running along the four Pulmonary Veins (PVs) at the sites (ostia) in which they empty in the Left Atrium (LA). Such nerves are responsible for sending signals deregulating the heart beat. Ablation can be performed either by heat, using a Radio Frequency (RF) probe, or by dramatically lowering the temperature (cryoablation). In the latter case a catheter with an inflatable balloon is inserted through the septum in the LA and nitric oxide (NO_2) is circulated at a temperature as low as $-70°$C. The inflated balloon touches the complete ostium circumference and is kept there for 4–5 *min*. Both RF and cryoablation can produce lesions in the esophagus, which happens to run close to the LA (Esophageal Thermal Lesions, or ETLs). In some cases these ulcerations can develop into fistulae with lethal consequences. Trials have been performed to assess the risks of RF (see [3, 4]). Cryoablation, which became available more recently, has been considered safer, but some clinical trials have shown that risks are actually comparable ([1, 5]). Many papers dealt specifically with the complications connected to cryoablation. We just quote [6, 8], which point out the importance of measuring the Luminal Esophageal Temperature (LET) and to establish a safe threshold to prevent the insurgence of ETLs. An advantage of using the balloon is that isolating one PV may require just one application, while the lesions produced by a probe are so small that many of them are necessary for each ostium, implying a much longer procedure. Another risk associated to cryoablation is the Phrenic Nerve (PN) palsy, impeding breathing (fortunately it is reversible in most cases). This sce-

nario makes it clear how important is to know the evolution of the thermal field which accompanies an ablation procedure.

LET is measurable by means of probes equipped with thermal sensors to be introduced in the esophagus. It is important, however, to predict the thermal field in the whole region including the interested organs. For RF-ablation a mathematical model has been proposed and implemented in [2]. Here we present a model based (likewise [2]) on a simplified geometry and on the assumption that heat propagation is governed by the so-called bioheat equation, in which blood perfusion rate in the interested organs is temperature dependent. This is a preliminary note aimed at showing the main results. The full paper will be published elsewhere.

2. The mathematical model

An important feature to be emphasized is that there is a large variability in patients' reaction to cryoablation. Normally LET decreases from the baseline temperature by only a few degrees, but in some cases even negative temperatures have been reported. Such a phenomenon may have several causes, but the most important is certainly how the esophagus is located with respect to the heart. While the two organs are normally separated by a distance of the order of 1 *cm*, in some extreme cases they are in direct contact. Therefore a mathematical model can only refer to an average geometry and for this reason not a great accuracy is required. This circumstance suggests to use a simplified geometry, with an idealized shape of the organs, respecting the main features influencing the evolution of the thermal field. We also note that the duration of each application of the balloon includes two or three hundred heart beats, thus pulsations can be averaged out and we can suppose that blood flow is stationary. That said, we consider the domain described in Fig. 1.

The esophagus E is a straight cylinder. The heart H is represented as the union of two cylinders H1 (atria), H2 (ventricles) of different thickness with a septum (not shown) of negligible thickness, not permeable to blood and perfectly pervious to heat. Each atrium is directly connected with the respective ventricle. We bypass the fluid dynamical problem in H by assuming that blood has a uniform velocity v_B in each cross section, determined by the discharge of 5 *l/min* in each direction. The heart is surrounded by a fat layer F. The afferent and efferent vessels are represented by just two identical ducts VA, VB, each with an upper and a lower segment. The whole system is contained in a cubic box of connective tissue.

To save space we do not list all the geometrical details. We just remark that the cylinder E (practically closed at rest) has been given an internal diameter of 2 *mm* because it contains the probe measuring LET. It is assumed that its thickness is 3 *mm*. The external radius of H is 40 *mm*. H1 is 5 *mm* thick and 50 *mm* high, H2 is 15 *mm* thick and 70 *mm* high. Vessels VA1, VA2, VB1, VB2 have an external radius of 14 *mm* and are 2 *mm* thick, 40 *mm* high. The fat layer F around H is taken 3 *mm* thick. The distance between E and H is 6 *mm*. The thermal properties of the tissues are shown in Table 1.

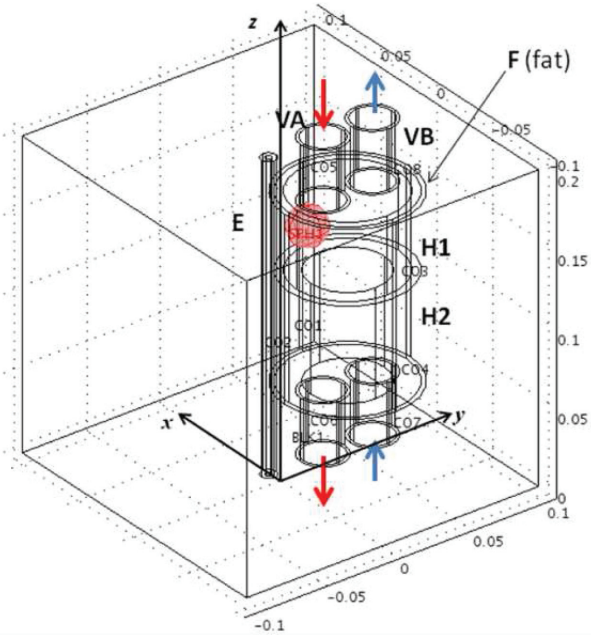

Figure 1: The idealized geometry used in the model. The balloon is placed in the "atrium" facing the esophagus. All afferent and all efferent vessels are merged in one single duct. Septum is not shown. The fat layer is visualized as a rim around three cross sections in order to make the figure readable. Length unit is meter.

Table 1. Tissues thermal properties (from [2]). ρ density, c specific heat, k thermal conductivity.

	$\rho\ (kg\ m^{-3})$	$c\ (Jkg^{-1}K^{-1})$	$k\ (Wm^{-1}K^{-1})$
Esophagus	1000	3700	0.4
Connective	1000	3200	0.4
Fat	900	2200	0.2
Hearth	1200	3200	0.7
VA, VB	1000	3200	0.4
Blood	1000	4180	0.54

The cryoballoon is a sphere 25 *mm* of diameter (the one used have diameters of 23 *mm* or 28 *mm*), tangent to the horizontal and to the vertical wall of H1, as close as possible to E.

Table 2. Perfusion rate (sec^{-1}) in various organs at baseline temperature ([7]).

Heart	1.7×10^{-2}
Fat	5.5×10^{-4}
Connective	6.0×10^{-4}
Esophagus	3.0×10^{-3}

We assume that the governing equation for the temperature T in the solid tissues is the bioheat equation (where metabolic heat production is neglected)[1],

$$\rho c \frac{\partial T}{\partial t} - k\Delta T = -\omega(T)\rho_B c_B (T - T_B) \tag{1}$$

where T_B is the blood temperature (37°C) and $\omega(T)$ is the blood perfusion rate (sec^{-1}) that here we take in the form

$$\omega(T) = \left[\omega_0 + \omega_1 \frac{T - T_B}{T_B}\right]_+,$$

selecting $\omega_1/\omega_0 = 1$ (a large value, so to take less advantage of blood perfusion and underestimate the temperature). ω_0 has different values in the various organs (Tab. 2).

For the blood flowing through VA, VB, H we just take the advection-diffusion equation. Heat flux is continuous everywhere. The initial temperature is T_B and a no flux condition is taken at the boundary of the box (consistently with the fact that metabolic heat has been neglected).

On the balloon boundary temperature is prescribed to drop to −70°C in 3 *sec*.

3. Results and comments

We present the results of just two simulations. In the first one we follow the thermal evolution for 5 *min* (a time not exceeded for a single application) in the following points:

(A) a group of points in the horizontal plane through the balloon center (Fig. 2)
(B) the point P_{H1} vertically aligned with P_H at the upper H/F interface.

Fig. 3 shows that LET reaches the value 32°C, while the minimum external esophageal temperature is 4°C less. The temperature in P_M is a plausible value

[1] The order of magnitude of metabolic heat production for a person at rest is 1 W/kg. The bioheat equation, first formulated by H. H. Pennes in 1948 [10] has been generalized in various ways (see the review paper [9]). The form (1) is sufficient for our purposes.

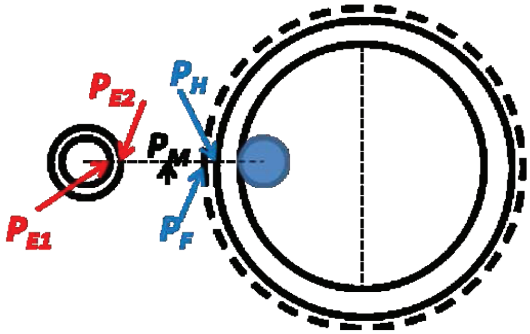

Figure 2: The set of points in group A.

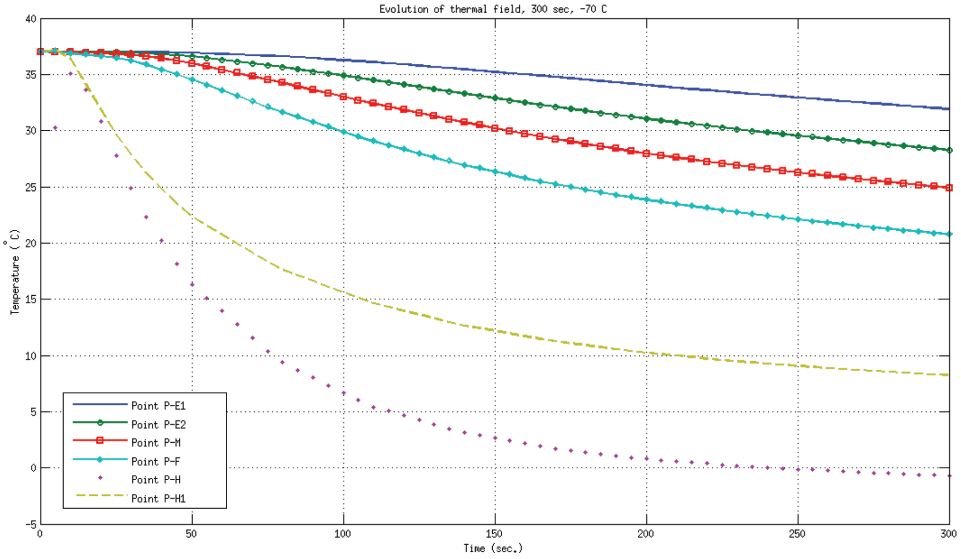

Figure 3: Cooling curves, balloon temperature $-70°$C, duration of cooling 300 *sec*.

for the phrenic nerve, which however can be as low as the temperature in P_F, depending on the actual nerve location. The temperature in P_H, which goes down to $-1°$C, represents a limit value attainable by LET if the esophagus happens to be in contact with the LA. Actually, even lower values of LET have been recorded (down to $-14°$C, [6]), which can be the result of various concurrent phenomena (abnormal positioning of the balloon, atrium and esophagus thinner than normal, reduced perfusion, etc.). Since connective tissue and esophagus heat diffusivities are not very different, it is easy to infer the difference between external and internal esophageal temperature for different values of the esophagus thickness and distance from the heart by simple extrapolation.

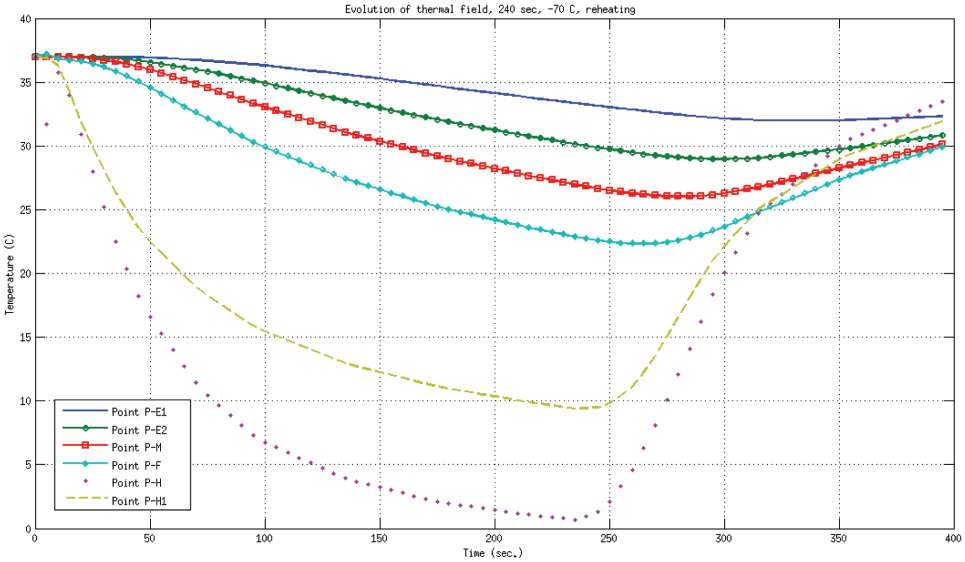

Figure 4: Cooling at $-70°C$ for 240 *sec*. Then return of the balloon temperature to $37°C$ in 30 *sec*. Temperature of distal organs keep decreasing for several seconds.

The second simulation deals with a case in which the gas supply to the balloon is suspended after 4 *min*. This is simulated by taking the balloon temperature back to $37°C$ in 30 *sec* (Fig. 4).

The main feature to be emphasized here is that, while the temperature in P_H reacts immediately, the temperature in other points keeps decreasing for a time which increases with the distance from the balloon. For instance LET is still decreasing after 6 *min*. This is an important information to be kept into account when it is decided to interrupt the procedure, since both LET and other relevant temperatures will go down by some more degrees despite the suspension of gas supply.

In conclusion, the model presented allows to effectively predict the thermal field during a cryoablation procedure, pointing out some important features of clinical relevance.

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Received 14 March 2014,
and in revised form 21 April 2014.

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