Considerations for Thermal Injury Analysis for RF Ablation Devices

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Abstract: *Background*: The estimation of lesion size is an integral part of treatment planning for the clinical applications of radiofrequency ablation. However, to date, studies have not directly evaluated the impact of different computational estimation techniques for predicting lesion size. In this study, we focus on three common methods used for predicting tissue injury: (1) iso-temperature contours, (2) Cumulative equivalent minutes, (3) Arrhenius based thermal injury. *Methods*: We created a geometric model of a multi-tyne ablation electrode and simulated thermal and tissue injury profiles that result from three calculation methods after 15 minutes exposure to a constant RF voltage source. A hybrid finite element technique was used to calculate temperature and tissue injury. Time-temperature curves were used in the assessment of iso-temperature thresholds and the method of cumulative equivalent minutes. An Arrhenius-based formulation was used to calculate sequential and recursive thermal injury to tissues. *Results*: The data demonstrate that while iso-temperature and cumulative equivalent minute contours are similar in shape, these two methodologies grossly over-estimate the amount of tissue injury when compared to recursive thermal injury calculations, which have previously been shown to correlate closely with *in vitro* pathologic lesion volume measurement. In addition, Arrhenius calculations that do not use a recursive algorithm result in a significant underestimation of lesion volume. The data also demonstrate that lesion width and depth are inadequate means of characterizing treatment volume for multi-tine ablation devices. *Conclusions*: Recursive thermal injury remains the most physiologically relevant means of computationally estimating lesion size for hepatic tumor applications. Iso-thermal and cumulative equivalent minute approaches may produce significant errors in the estimation of lesion size.

INTRODUCTION

Radiofrequency Ablation (RFA) has become the standard of care for the treatment of primary and metastatic tumors. The goal of these treatments is to produce necrosis by raising local tissue temperatures, while limiting the collateral damage to adjacent healthy tissues. Ablation probes are positioned in the vicinity of aberrant tissues and high frequency alternating current (450-550 kHz) is delivered through an un-insulated electrode into the surrounding tissue to a dispersive ground electrode that is applied to the patient. The deposited electromagnetic energy is converted to heat which raises the temperature of the tissue and results in thermal necrosis.

While the use of radiofrequency ablation devices is well established, there is debate as to which computational method works best in estimating lesion size. Since necrosed volumes are not readily assessed under *in vivo* conditions, a variety of approaches are used to estimate the size of the lesion based upon temperature and exposure time. Iso-temperature contours that are derived from calculated temperature profiles, for example, have been used to estimate the tissue lesion boundary. The temperature thresholds that have been used to predict lesion size and define thermal injury are well documented in the literature [1-21]. The most common temperatures used are 43°C [22, 23], 48°C [24,25], 50°C [9,13,14], and 59°C [12]. While some of this variation is attributable to differences in tissue type (i.e. heart, liver, etc.), the literature shows broad inter-tissue variability.

Other strategies better approximate tissue injury by accounting for both exposure temperature and time [25-30]. The most common of these is the method of cumulative equivalent minutes. Several investigators have noted that for each degree increase above 43°C in temperature, there is approximately a two-fold decrease in the time required to achieve the same biological effect [28-33]. The equivalent time for each second of exposure to temperatures greater than 43°C is calculated by the isoeffect equation [33]:

$$t_{\exp} = t_{critical} * 2^{(T_{\exp}-43)} \quad \text{Eq. 1}$$

where T_{exp} and t_{exp} represent the tissue exposure temperature (in Celsius) and time, respectively. Integrating the equivalent time (t_{exp}) over the entire exposure time, gives the cumulative equivalent time at 43°C (CEM_{43}). When the CEM_{43} value exceeds a critical threshold, the tissue is considered to be thermally necrosed. Thresholds for CEM_{43} have been tabulated in the literature for several types of tissue based upon experimental observation of tissue injury at 43°C [34-37].

Another approach for approximating tissue injury utilizes the Arrhenius equation. This method establishes a first-order exponential relationship between tissue exposure temperature, exposure time, and tissue injury based upon experimental cell survivability studies. For a specified exposure temperature and time, the Arrhenius fit parameters determine the probability of cell damage. Arrhenius parameters have been determined in several body tissues, including the liver at high temperatures [31-33,38]. In the

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majority of studies, temperature and tissue injury profiles are calculated sequentially, meaning that Arrhenius calculations are not made until temperature calculations are completed [29-30]. A more physiologically based approach used by a few investigators has employed analytical solutions where temperature and tissue injury are calculated simultaneously [34-35]. When calculated in this manner, increased temperature causes local thermal injury which results in the localized cessation of blood flow. As a tissue lesion grows, the envelope of tissue where tissue perfusion is absent grows.

METHODS

At 450-550 kHz, the wavelength of electromagnetic energy is several orders of magnitude larger than the size of the ablation-tines. Therefore, a quasi-static approximation can be used to solve the electrical and heat conduction problems. The electric field is solved by using the generalized Laplace equation,

$$\nabla \cdot \left[\sigma(T) \nabla V \right] = 0 \qquad \text{Eq. 2}$$

where ∇ is the gradient operator, $\sigma(T)$ is the temperature-dependent conductivity (Siemens/meter), and V is the electric potential (Volts). The temperature is solved by using a modified Pennes bioheat equation [36],

$$\rho C \frac{dT}{dt} = \nabla \cdot (k \nabla T) + \sigma(T) |\nabla V|^2 - \alpha \rho_b C_b \omega (T - T_{amb}) + Q_m \qquad \text{Eq. 3}$$

where ρ is the density, C is the heat capacity of tissues, k is the heat conduction coefficient, ρ_b is the density of blood, C_b is the heat capacity of blood, ω is the perfusion coefficient, and α is the tissue state coefficient which varies between 0-1 depending on the normalized value of local tissue perfusion.

Iso-Temperature Contours

For this methodology, tissue damage was assumed to occur once tissue exceeded a specific temperature. Equations 2 and 3 were solved simultaneously assuming that α=1 for temperature. Iso-temperature contours at 42°C (IT42), 47°C (IT47), and 60°C (IT60) were compared.

Cumulative Equivalent Minutes (Thermal Dose)

Using the calculation method specified by Saparato and Dewey [28], the CEM_{43} the thermal dose is defined [33] as

$$CEM_{43} = \int R^{43 - T(t)} dt \qquad \text{Eq. 4}$$

For most biological tissues, the value of *R* is 0.5 for temperatures exceeding 43°C. For exposure temperatures below 43°C, the value of *R* is 0.25. The critical thermal dose for liver tissue is CEM_{43} = 340 minutes [39]. Equations 2 and 3 were solved simultaneously assuming that α=1. Once the temperature was determined at each time step, the CEM_{43} was calculated. The tissue was considered to be necrosed when the CEM_{43} exceeded 340 minutes (C340).

Arrhenius Based Recursive Thermal Injury

Thermal injury and cell necrosis can be assessed directly by using the Arrhenius equation [34]. Although it is widely recognized that tissue injury is the result of several complex mechanisms, the progression of thermal injury can be reasonably approximated by a single process that is described by a first order kinetics expression

$$\Omega(t) = \ln\left(\frac{c(0)}{c(t)} \right) = \int_0^t A \cdot e^{\frac{-\Delta E}{RT}} dt \qquad \text{Eq. 5}$$

where $\Omega(t)$ is the degree of tissue injury, c(t) is the concentration of living cells, c(0) is the initial concentration of living cells, R is the universal gas constant, A is a "frequency" factor for the kinetic expression (s^{-1}), and ΔE is the activation energy for the irreversible damage reaction ($J\text{-}mol^{-1}$) [37]. The kinetic parameters account for morphologic changes in tissue relating to the thermal degradation of proteins [35]. The tissue injury integral increases as the time of exposure is increased. The critical value, Ω=1, signifies the point when thermal necrosis occurs. This corresponds to a viable cell concentration of 37%, which indicates a 63% cell necrosis volume. In its original formulation, the Arrhenius equation was associated with the percent of a volume of cells surviving a uniform exposure to temperature for a length of time. However, when the volume constitutes a single cell, the Arrhenius equation reflects the percent probability of cell survivability [34].

A known phenomenon that occurs with necrosed tissues is the transient cessation of localized blood flow during tissue heating. To adequately capture this behavior, the effective model geometry must continually change to correctly assess the level of tissue perfusion for each location in the model at each time step [40]. This significantly increases computation time and is the primary reason that simultaneous calculations have not been performed much to date. A recursive algorithm such as Gauss-Seidel, must be employed at each time step to insure that electromagnetics-thermal results change consistently with the local level of tissue perfusion. For purposes of this study, equations 2-4 were solved simultaneously using a Gauss-Seidel method. The results of the approach were previously compared directly to lesion sizes generated experimentally in liver tissue and were found to agree within 5%. In the present study, we assume that comparable levels of accuracy to experimental measurement exist. Comparisons were made assuming thermal injury thresholds of 63% (D63) and 99.99% (D100) tissue damage.

Model Geometry

In this study, we created a model geometry similar to several commercially available multi-tine ablation electrode (Fig. **1**). The model consists of 8 flexible tines that are spaced evenly at 45° angles. An additional electrode protrudes from the center of the tyne arrangement. Each tyne is 0.5 mm in diameter and 38 mm in length. When fully deployed, the 8 outer tines expand 2.41 centimeters from the center. Fig. (**1**) depicts the tines in a fully deployed configuration. Therapeutic treatment is achieved by applying a source voltage to the conducting tip. A conducting surface, applied to the patient skin clinically, serves as an electrical ground return.

Fig. (**2**) depicts the model geometry used in this study. The model geometry represents a quarter of the ablation probe. Source voltage ($\mathbf{V_o}$) is applied to all of the tines and the tip of the cannulating needle (red). The proximal portion of the electrode (blue) is electrically insulated with the

Fig. (6). Lesion Volume with No Tissue Perfusion for a 15 Minute Ablation with a Constant 22.5 Volt Source. Graph shows the total volume of tissue necroses calculated for a 15 minute ablation using a constant 22.5 volt source, using cell damage thresholds (D), isothermal temperatures (IT), and thermal dosing (C) with no tissue perfusion. Although the lesion growth rate calculated for 340 cumulative equivalent minutes at 43°C (C340) and for an isothermal temperature of 47°C (IT47) are very similar, they grossly overestimate the rate of lesion growth. The graph shows that the IT60 curve is a better approximation of modeled cell damage calculated using either the 63% or 100% iso-damage contours methods.

Fig. (7). Lesion Volume with 100% Normal Tissue Perfusion (6.4×10^{-3} $m_b^3/m_t^3/s$) for a 15 Minute Ablation with a Constant 22.5 Volt Source. Graph shows the total volume of tissue necroses calculated for a 15 minute ablation using a constant 22.5 volt source, using cell damage thresholds (D), isothermal temperatures (IT), and thermal dosing (C) with 100% normal tissue perfusion (6.4×10^{-3} $m_b^3/m_t^3/s$). The data demonstrate that volumes calculated using traditional isothermal temperatures of 42°C and 47°C grossly overestimate the rate of lesion growth. Likewise, the volume calculated using cumulative equivalent minutes at 43°C also overestimates the rate of lesion growth. The graph shows that the IT60 curve is a better approximation of cell damage calculated using either the 63% or 100% iso-damage contours methods.

comparison for a 15 minute perfused ablation using a constant 22.5 volt source. The figures demonstrate that although the lesion growth rate calculated for 340 cumulative equivalent at 43°C (C340) and for an isothermal temperature of 47°C (IT47) are very similar, they grossly overestimate the rate of lesion growth. The graph shows that the isothermal temperature of 60°C (IT60) is a better approximation of modeled cell damage calculated using either the 63% (D63) or 100% (D100) recursive tissue injury contours.

Tables **1** and **2** show the total volume of tissue necroses calculated for different source voltages for unperfused and perfused tissues ablation, respectively. The data shows that lesion volume for the unperfused simulation is grossly overestimated when calculated using isothermal temperature (97-169%) and thermal dosing (114%) descriptions. For perfused tissue, the data show more pronounced overestimations of 905-1751% for isothermal temperatures and 1165% for thermal dosing. The large discrepancy in lesion size is attributable to several mechanistic differences

Table 1. Lesion Volume with No Tissue Perfusion

Source Voltage (Volts)	D=63% (mm^3)	D=100% (mm^3)	IT=42°C (mm^3)[1]	IT=47°C (mm^3)[1]	IT=60°C (mm^3)	C_{43}=340 min (mm^3)
0.0	0	0	0	0	0	0
2.5	0	0	0	0	0	0
5.0	0	0	0	0	0	0
7.5	0	0	32	0	0	0
10.0	0	0	6312	0	0	104
12.5	0	0	13790	2432	0	6704
15.0	48	32	20550	9632	32	12920
17.5	2124	744	26500	15520	1244	18530
20.0	8264	6972	31540	21060	7588	23780
22.5	13320	11950	35890	26300	12710	28560

[1]The 42°C and 47°C isothermal volumes were chosen specifically because they are frequently used to establish damage thresholds in hyperthermia and radiofrequency ablation, respectively.

Values represent the total volume of tissue necroses calculated over the course of the simulated ablation using various cell damage thresholds (D), isothermal temperatures (IT), and thermal dosing times (C_{43}) with no tissue perfusion. The data show that lesion volume is grossly overestimated when calculated using isothermal temperatures (97-169%) and thermal dosing (114%) descriptions. Thermal dosing volume is calculated as the region of tissue where the cumulative equivalent minutes exceed known tissue damage at 43°C. Since tissue damage is calculated using a first order rate law, the 63% tissue damage limit is used as a comparison to all values in the table.

Table 2. Lesion Volume with 100% Normal Tissue Perfusion

Source Voltage (Volts)	D=63% (mm^3)	D=100% (mm^3)	IT=42°C (mm^3)[1]	IT=47°C (mm^3)[1]	IT=60°C (mm^3)	C_{43}=340 min (mm^3)
0	0	0	0	0	0	0
2.5	0	0	0	0	0	0
5.0	0	0	0	0	0	0
7.5	0	0	0	0	0	0
10.0	0	0	64	0	0	0
12.5	0	0	1592	32	0	132
15.0	0	0	7404	268	0	1488
17.5	48	32	11890	2104	24	6576
20.0	236	164	16360	7144	88	10480
22.5	1136	760	21030	11420	700	14380

[1]The 42°C and 47°C isothermal volumes were chosen specifically because they are frequently used to establish damage thresholds in hyperthermia and radiofrequency ablation, respectively.

Values represent the total volume of tissue necroses calculated over the course of the simulated ablation using various cell damage thresholds (D), isothermal temperatures (IT), and thermal dosing times (C_{43}) with 100% normal tissue perfusion (6.4×10^{-3} $m_b^3/m_t^3/s$). The data show that lesion volume is grossly overestimated when calculated using isothermal temperatures (905-1751%) and thermal dosing (1165%) descriptions. Thermal dosing volume is calculated as the region of tissue where the cumulative equivalent minutes exceed known tissue damage at 43°C. Since tissue damage is calculated using a first order rate law, the 63% tissue damage limit is used as a comparison to all values in the table.

Table 3. Lesion Dimensions with no Tissue Perfusion

	Width (mm)						Depth (mm)					
Source Voltage (Volts)	**D = 63%**	**D = 100%**	**IT = 42°C[1]**	**IT = 47°C[1]**	**IT = 60°C**	**C_{43} = 340 min**	**D = 63%**	**D = 100%**	**IT = 42°C[1]**	**IT = 47°C[1]**	**IT = 60°C**	**C_{43} = 340 min**
0	0	0	0	0	0	0	0	0	0	0	0	0
2.5	0	0	0	0	0	0	0	0	0	0	0	0
5.0	0	0	0	0	0	0	0	0	0	0	0	0
7.5	0	0	26	0	0	0	0	0	20	0	0	0
10.0	0	0	28	0	0	26	0	0	26	0	0	20
12.5	0	0	32	26	0	28	0	0	29	23	0	26
15.0	26	26	34	30	26	30	20	20	31	27	20	28
17.5	26	26	36	32	26	34	22	22	33	30	22	31
20.0	28	28	38	34	28	36	26	26	33	31	26	33
22.5	32	30	38	36	32	38	29	28	35	33	29	33

[1]The 42°C and 47°C isothermal volumes were chosen specifically because they are frequently used to establish damage thresholds in hyperthermia and radiofrequency ablation, respectively.

Values represent the maximum lesion width and depth calculated over the course of the simulated ablation using various cell damage thresholds (D), isothermal temperatures (IT), and thermal dosing times (C_{43}) with no tissue perfusion. The data show overestimations in lesion dimensions calculated using traditional isothermal temperatures of 42°C and 47°C. Similar overestimation of lesion dimensions are found with the thermal dosing method. The data demonstrate that lesion width and depth are relatively insensitive methods of reporting lesion growth for a multi-tine probe geometry, since the extent of the lesion may reflect the development of several smaller lesion areas. This explains why there is virtually no transition between the absence and presence of a lesion.

Table 4. Lesion Volume with 100% Normal Tissue Perfusion

	Width (mm)						Depth (mm)					
Source Voltage (Volts)	**D= 63%**	**D= 100%**	**IT= 42°C[1]**	**IT= 47°C[1]**	**IT= 60°C**	**C_{43}= 340 min**	**D= 63%**	**D= 100%**	**IT= 42°C[1]**	**IT= 47°C[1]**	**IT= 60°C**	**C_{43}= 340 min**
0	0	0	0	0	0	0	0	0	0	0	0	0
2.5	0	0	0	0	0	0	0	0	0	0	0	0
5.0	0	0	0	0	0	0	0	0	0	0	0	0
7.5	0	0	0	0	0	0	0	0	0	0	0	0
10.0	0	0	26	0	0	0	0	0	20	0	0	0
12.5	0	0	28	26	0	26	0	0	25	20	0	20
15.0	0	0	30	26	0	28	0	0	28	22	0	25
17.5	26	26	32	28	6	30	20	20	30	26	20	26
20.0	26	26	34	30	26	32	22	21	31	28	20	28
22.5	28	28	36	32	28	34	26	22	33	30	22	30

[1]The 42°C and 47°C isothermal volumes were chosen specifically because they are frequently used to establish damage thresholds in hyperthermia and radiofrequency ablation, respectively.

Values represent the maximum lesion width and depth calculated over the course of the simulated ablation using various cell damage thresholds (D), isothermal temperatures (IT), and thermal dosing times (C_{43}) with 100% normal tissue perfusion(6.4×10^{-3} $m_b^3/m_t^3/s$). The data show overestimations in lesion dimensions calculated using traditional isothermal temperatures of 42°C and 47°C. Similar overestimation of lesion dimensions are found with the thermal dosing method. The data demonstrate that lesion width and depth are relatively insensitive methods of reporting lesion growth for a multi-tyne probe geometries, since the extent of the lesion may reflect the development of several smaller lesion areas. This explains why there is virtually no transition between the absence and presence of a lesion.

that are not accounted for in the isothermal and thermal dosing methods. Thus, the overestimation in lesion size is not a systematic error and a simple correction cannot be made to account for the characteristic behavior. Thermal dosing volume is calculated as the region of tissue where the cumulative equivalent minutes exceed known tissue damage at 43°C. The 63% tissue damage limit was used as a comparison to all values in the table since this approach was previously validated experimentally and found to agree within 5%. Tables **3** and **4** show the maximum lesion width and depth calculated for different source voltages for unperfused and perfused tissue ablation, respectively. The data demonstrate that lesion width and depth are relatively insensitive methods of reporting lesion growth for a multi-tyne probe geometry, since the extent of the lesion may reflect the development of several smaller lesion areas. This explains why there is virtually no transition between the absence and presence of lesions.

DISCUSSION AND CONCLUSION

Several studies have been conducted to describe lesion growth for radiofrequency ablation devices [2,9-12,21,24,29-30,34-35]. In the majority of these cases, markers such as temperature isotherms and thermal dosing are used as the primary measure for lesion size. Only a few studies have used the Arrhenius formulation of tissue damage. Most of these, sequentially calculate the tissue damage from temperature data. Only a handful of studies calculate tissue injury simultaneously with temperature and account for physiologic change in the local perfusion due to cell necrosis [34,35,40,44]. To date, a side-by-side comparison of the effects of these calculations schemes has not been assessed. In this paper, we compare the most common methods used to computationally estimate lesions.

Our results demonstrate that sequential calculation of tissue injury following the calculation of temperature produces results that are inaccurate, regardless of whether iso-temperature contours, thermal does (cumulative equivalent minutes), or Arrhenius approaches are used. The data show that iso-temperature and thermal dosing approaches tend to overestimate lesion size. Arrhenius methods, when calculated sequentially, tend to underestimate lesion size. While it is possible to select more representative iso-temperature curves (i.e. IT60), the selection is not usually based on physiological changes but empirical observation.

The data also demonstrate that lesion width and depth are inadequate means of characterizing treatment volume for multi-tine ablation devices. Figs. (**4** and **5**) demonstrate that the contiguous volume seen in fully developed ablation profiles is the result of the merging of several smaller lesions that develop first at the distal end of each tine. For a multi-tine ablation device at shorter ablation times and lower source voltage, it may be difficult to assess the uniformity of lesion size by simply measuring the lesion width and depth.

DISCLAIMER

The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the Department of Health and Human Services.

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