Radiofrequency ablation combined with conductive fluid-based dopants (saline normal and colloidal gold): Computer modeling and ex vivo experiments

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Abstract

Background: The coagulation zone volume created during radiofrequency ablation (RFA) is limited by the appearance of roll-off. Doping the tissue with conductive fluids, e.g. gold nanoparticles (AuNPs) could enlarge the coagulation zones by delaying the roll-off. Our goal was to characterize the electrical conductivity of a substrate doped with AuNPs and to study by computer modeling and ex vivo experiments the effect on coagulation zone volumes.

Methods: The electrical conductivity of substrates doped with normal saline or AuNPs was assessed experimentally using agar phantoms. The computer models, built and solved on COMSOL Multiphysics, consisted of a cylindrical domain mimicking liver tissue and a
spherical domain mimicking a doped zone with diameters of 2, 3 and 4 cm. Ex vivo
experiments were conducted on bovine liver fragments and under three different doping
conditions: 1) non-doped tissue (ND Group), 2 mL of 0.9% NaCl (NaCl Group), and 2 mL
of AuNPs 0.1 wt% (AuNPs Group).

**Results:** The theoretical analysis showed that adding normal saline or colloidal gold in
concentrations lower than 10% only modify the electrical conductivity of the doped substrate
with practically no change of the thermal characteristics. The computer results showed a
relationship between doped zone size and electrode length regarding the created coagulation
zone. We observed a good agreement between ex vivo and computational results in terms of
transverse diameter of the coagulation zone.

**Conclusions:** Both computer and ex vivo experiments showed that doping with AuNPs can
enlarge the coagulation zone, specially the transverse diameter, hence achieving more
spherical coagulation zones.

**Keywords:** Gold nanoparticles, nanofluid, saline solution, radiofrequency ablation

**Background**

Radiofrequency (RF) ablation (RFA) is a minimally invasive procedure used to thermally
destroy tumors. During the procedure a needle-like ablation electrode is inserted into the
tumor and electrical current (~500 kHz) is conducted between this electrode and a large-
surface dispersive electrode placed on the patient’s skin. The electrical power is converted
into heat by the Joule effect and causes cell death by coagulative necrosis when tissue
temperature exceeds 50 °C for several minutes. The thermally damaged tissue is called the \textit{coagulation zone}. The therapeutic goal is to cover the tumor with this zone. Unfortunately, the coagulation zone size is strongly limited by the appearance of a phenomenon called \textit{roll-off}, which consists of the cessation of RF power due to a sudden increase in electrical impedance, which is caused by the fact that the desiccated tissue (i.e. that reaching \textasciitilde100 °C) completely encircles the active electrode [1].

In order to ensure that the coagulation zone covers the entire tumor, some studies demonstrated that injecting conductive fluids (such as saline solutions) at the target site before RFA can enlarge the coagulation zone [2,3]. The idea behind this ‘fluid-modulated RFA’ is to increase the electrical conductivity of the fluid-doped tissue and hence increase the deposited RF power at the target site. In practical terms, the improvement lies in delaying roll-off as long as possible, so that RF power is applied for the maximum possible time. This is crucial, since it is known that coagulation zone volume is not greatly affected by power reapplications after the first roll-off [4]. It is assumed that saline infusion increases the tissue electrical conductivity due to the large number of ions in the solution, and in fact there is a direct relation between saline concentration and electrical conductivity [5]. However, increasing infusion volume does not always lead to a larger coagulation zone volume [6].

Magnetic and metallic nanoparticles (NPs) have recently been targeted in the tumor area under the hypothesis that the NP-doped region concentrates the power deposition and focuses the heating while better preserving the surrounding area [7]. NPs have been also used in hyperthermia treatment for targeting procedures, principally involving magnetic fluid hyperthermia, which means that significant heat can be generated by applying a high intensity alternating magnetic field to iron oxide NPs previously located in the tumor area [7–9]. Gold
NPs (AuNPs) combined with RF heating have also been studied to heat tumors [10,11], concluding that the RF-targeting AuNP combination could represent an effective therapy for treating several types of diseases [12].

Although the experimental results so far seem promising, there is a lack of information on the electrical and thermal effect of AuNPs–based fluids during RFA, and their differences regarding the use of saline. To fill this gap, we conducted a study with two objectives: 1) to characterize the changes in electrical conductivity of a substrate doped with two solutions: 0.9% NaCl (normal saline) and 0.01 wt% colloidal gold (colloidal suspension of AuNPs in deionized water); and 2) to carry out a computer modeling study and ex vivo experiments on the effect of both dopants on coagulation zone volumes created during RFA. While the numerical model provided information on the effect of RFA on different dopant concentrations and doped zone size, the ex vivo experiments were performed with a reduced set of parameters to verify the conclusions of the simulation study.

Results

Electrical characterization of doped phantoms

Table 1 shows the results of impedance and electrical conductivities measured on the agar phantom samples. As expected, the single agar samples had the lowest conductivity, which increased after doping the sphere with NaCl or AuNPs solution. The highest conductivity was obtained from 1.5 wt% of NaCl solution (0.145 S/m), followed by 1 wt% of AuNPs solution (0.138 S/m) and 1.0 wt% of NaCl solution (0.113 S/m). Analysis of variance confirmed that there were significant differences in the $Z$ values between the groups. The amount by which each dopant (NaCl or AuNPs) raised the electrical conductivity of the
substrate (agar gel) can be estimated from the results in Table 1. In the case of NaCl, Bennett [5] experimentally found the following frequency-independent (up to 100 kHz) linear relation between NaCl concentration and electrical conductivity of agar phantoms doped with NaCl:

\[
\sigma (S/m) = 215 \cdot \frac{\text{(grams of NaCl)}}{\text{(solution volume, mL)}} + 0.0529
\]  

(1)

The residual value found by us when NaCl was not added (0.067 S/m) is more or less in agreement with the offset reported by Bennett [5] in Eq. (1) and is possibly associated with the component of the agar phantoms that is not soluble at room temperature (since deionized water has extremely low electrical conductivity, < 0.2 mS/m). When Eq. (1) was used to estimate the electrical conductivities in our cases of NaCl doping, we obtained values smaller than those estimated experimentally (e.g. 0.09 S/m instead of 0.113 S/m for NaCl 1 wt%; and 0.1 S/m instead of 0.145 S/m for NaCl 1.5 wt%). This disagreement could be due to the errors accumulated in the experimental measurement of Z and in the subsequent estimation of \(\sigma\) from computer modeling. Eq. (1) encouraged us to propose an equation that relates the electrical conductivity of a substrate doped with 0.01 % AuNPs with its concentration in the substrate. From the experimental data obtained (1 wt%, 0.138 S/m) this would be:

\[
\sigma (S/m) = 0.071 \cdot (\text{wt%}) + \sigma_S
\]  

(2)

where \(\sigma_S\) is the electrical conductivity of the non-doped substrate. It should be emphasized that this expression is only approximate, since it is based on a single concentration value. It is not easy to theoretically estimate the electrical conductivity of AuNPs colloidal solutions or substrates doped with this solution, since it depends on many factors, such as measurement frequency or NP size [13]. In this respect, expression (2) would be limited to a frequency of 500 kHz and NPs size of 10 nm.
Computational results

As the results showed that doped zone has a crucial effect on the temperature distributions and the size of the coagulation zone, we give the results for each doped zone size separately.

For the 2-cm doped zone, Table 2 shows the results for 50, 70 and 90 V RFA until roll-off, and Figure 1 shows the related temperature distributions. As expected, initial impedance declined slightly as dopant concentration increased, with generally lower values in the case of AuNPs. Time to roll-off ($t_{\text{100-}}$) showed relatively similar values at 50 V (450–479 s), with the highest value for AuNPs at 10%. The delay in roll-off implied a longer ablation time and hence a greater amount of delivered energy. In terms of coagulation zone size, transverse diameter values increased as dopant concentration augmented, from 2.6 cm for ND to 4.4 cm for AuNPs at 10%. In this case the coagulation volume tended to be more spherical (see Fig. 1). When applied voltage was increased to 70 and 90 V, roll-off occurred earlier and produced smaller coagulation zones, especially due to the reduced transverse diameter, since the axial diameter was almost unaffected by the applied voltage.

Table 3 shows the results of the 3-cm doped zone for 50, 70 and 90 V RFA up to roll-off, with the associated temperature distributions in Figure 2. Initial impedance declined as dopant concentration increased and reached lower values than the 2-cm doped zone, with shorter roll-off times. Table 4 shows the results of the 4-cm doped zone at 50, 70 and 90 V RFA up to roll-off, with the associated temperature distributions in Figure 3. Initial impedance was even lower than in 3-cm doped zone and declined as dopant concentration increased. Times to roll-off were even shorter than in the 3-cm doped zone and the axial and
transverse diameters were smaller, especially at 50 V. Overall, we observed that as the
diameter of the doping zone increased, the diameter of the coagulation zone decreased.

Ex-vivo results

Table 5 gives the results of the ex vivo experiments and Figure 4 shows examples of the
coaagulations in each group up to roll off, which occurred earlier in the ND (281 ± 31 s) than
the AuNPs Group (432 ± 36 s). There was a direct relationship between time to roll-off (t_{100-}
o) and coagulation zone size, with the smallest diameters in the ND Group (2.4 ± 0.2 cm)
and the largest in the AuNPs Group (3.7 ± 0.3 cm). There were no significant differences in
the initial impedance of the groups: 70.7 ± 6.3 Ω, 73.2 ± 4.0 Ω and 74.4 ± 2.4 Ω, for ND,
NaCl and AuNPs Groups, respectively, which could be due to the low precision of the RF
generator (±10%). When the coagulation zone reached the tissue surface, the transverse
diameter was assessed by the radius of the deepest zone (i.e. not in contact with the surface).

Additionally we conducted computer simulations mimicking the same applied voltage that
used during ex vivo experiments (57 V). When a 2-cm doped zone was assumed, the
transverse diameter of the coagulation zone was 2.2 cm for ND, while that it ranged from 2.4
to 2.9 cm for NaCl, and from 2.6 to 3.8 cm for AuNPs (both dopants for concentrations
varying from 1 to 10%). These values were very similar to those observed in the experiments.
In contrast, the times until roll-off predicted by the computer model (222–289 s) were in
general shorter than measured during ex vivo experiments (281–432 s). When we considered
a greater extension of the doped zone (3- and 4-cm diameters) transverse diameters predicted
by the model were smaller than those obtained in the ex vivo experiments.
Discussion

The first step was to assess how the properties of the doped substrate change with dopant type and concentration. We considered two fluid-based dopants: normal saline and colloidal gold. While saline infusion has been clinically used at different concentrations to dope RFA target tissue [6,14], colloidal gold is little used in clinical practice [15]. The use of a fluid-based dopant before and during RFA is associated with the following two phenomena: 1) higher substrate electrical conductivity, especially if hypertonic saline (> 3%) is used instead of normal saline (0.9%); and 2) roll-off delay due to rehydration of the desiccated tissue (only with continuous infusion or periodic administration of bolus during RFA [14]). Only the first phenomenon was considered for the present study, since we assumed that the doping was by infusion before RFA (i.e. by preinjection), in which case the dopant is expected to only alter the properties of the affected substrate.

Although some authors [16] have suggested that the use of NPs could significantly raise the thermal conductivity of the substrate (up to ~23%), this would only be true at very high concentrations (e.g. 4% volume fraction [16]). In fact, our theoretical estimates (see Table 6) showed that the volume fraction occupied by the NPs is much smaller, e.g. 5×10⁻⁵ % when 10% colloidal gold (0.01 wt%) is infused in the substrate. Our estimates (see Section 2.2) therefore showed that only the electrical conductivity is substantially modified by the effect of saline and colloidal gold-based dopants, at least at the concentrations considered (less than 10 wt%). This is in agreement with previous estimates of the properties of saline-mixed tissue, when electrical conductivity was seen to change drastically with the saline:tissue mixing ratio while the thermal conductivity hardly changed [17].
While the electrical properties of colloidal gold have been previously evaluated [18], no study has evaluated the electrical conductivity of AuNPs-substrate mixtures. Our data shown in Table 6 provide guiding values on how the electrical conductivity of a substrate doped with colloidal gold could change at different weight concentrations (between 1 and 10%). It is reasonable to assume that a higher concentration of doping agent in the substrate (> 10%) and other more conductive types of dopants (e.g. hypertonic saline or >0.01 wt% colloidal gold) will offer higher electrical conductivity values.

Once it was found that the addition of nanofluid (normal saline or colloidal gold 0.01 wt%) to a substrate at concentrations between 1 and 10% only modified its electrical conductivity, we explored how this could alter the electrical and thermal performance of a spherical doped zone during RFA. To achieve this, we built a numerical model based on a doped zone surrounded by non doped tissue, i.e. similar to a two-compartment model, as proposed in [19,20]. These models have already shown that the presence of a tumor with higher electrical conductivity than the surrounding tissue provides very different temperature distributions than models based on homogeneous tissue (one-compartment model) [19,20]. They also suggested that the maximum voltage applied without roll-off occurrence is different for tumors of different sizes and reduces as tumor diameter increases [20]. None of the previous models considered different tissue doping conditions or assessed the effect of doped zone size in relation to electrode length.

Our computational results showed that in the non doped (ND) tissue model the relationship between doped zone diameter and electrode length determines RFA electrical and thermal performance. As the doped zone size exceeds the electrode length (i.e. the electrode is completely inside the doped zone, as in the case of the 4-cm), the temperature distribution is more similar to the case of homogeneous tissue RFA, i.e. electrical power
deposition (or current density) and heating mainly occurs at the edges of the electrode (see Fig. 3). This is known as the *edge effect* and greatly limits the growth of the transverse diameter of the coagulation zone and therefore its sphericity.

On the other hand, we found that if the electrode length exceeds the doped zone diameter and the edges of the electrode are outside the doped zone (as in the 2-cm case), the *edge effect* is in some way compensated by the high electrical conductivity of the doped zone, which means that the current density is higher in the central zone than at the edges, where independent heating zones can be seen in the first few seconds (see Fig. 1). This behavior was amplified by the presence of a highly conductive dopant, insofar as the current density is greater than in the non doped tissue case. As a result, the computational results shown in Fig. 1–3 suggest that an effective way of ablating a spherical tumor could involve the following procedure: 1) use an electrode of greater length than the tumor diameter (e.g. 1 cm longer), 2) locate the tumor in the central area of the electrode, i.e. leaving the distal and proximal edges surrounded by healthy tissue, and 3) dope the tumor with a sufficiently high concentration of conductive agents (for example, 10% AuNPs 0.01 wt%). This would create relatively spherical coagulation zones capable of destroying the tumor, plus a safety margin (see Fig 1). From an oncological point of view, we recognize that traversing the tumor with the sharp tip of the electrode and exceeding its limits would imply a clear risk of needle track seeding prior to RFA (i.e. tumor cell spread [21]). However, it is also true that the tissue adjacent to the tip will most certainly be ablated, greatly reducing this risk.

Our results also suggest that when RFA is conducted on substrates with high electrical conductivity (note that this may be valid both for tumors doped with conductive substance and for non doped tumors with much higher conductivity than the surrounding tissue), larger
Coagulation zone volumes can be created at low voltages (50 V). However, moderate and high voltages (70 and 90 V) can quickly heat the tissue with the risk of an early roll-off, which notably limits the growth of the coagulation zone transverse diameter (see Fig. 1–3). This fast RFA heating on a highly conductive substrate was demonstrated by Ji et al [22] in an ex vivo study in which the evolution of tissue temperature at 1 and 2 cm from the electrode was recorded. Both our computer and experimental results (see Table 1 and Fig. 4) suggest that when the electrical conductivity of the dopant increases, the transverse diameter enlarges more than the axial diameter so that the coagulation zone is more spherical, which is in agreement with Ji et al’s results [22]. However, their experimental setup and ours share the uncertainty about the exact distribution of the dopant around the electrode. For this reason, our computer results suggest that in both experimental models the dopant possibly concentrated in the central electrode zone, thus achieving preferential heating in said zone, plus a more spherical coagulation zone.

Our conclusion on the recommended use of low voltage instead of high voltage goes in the opposite direction to the impedance-controlled pulsed protocol, which employs high voltage pulses and is broadly used in clinical practice. This protocol was demonstrated to be optimal versus a low-voltage continuous protocol in a classical work by Goldberg et al [23], later improved by Solazzo et al [24]. However, these studies used a homogenous tissue, i.e. a non-doped target. Other experimental studies on RFA combined with saline infusion could deliver RF power at a high voltage with few roll-offs [25]. In fact, our clinical experience of ablating tumors smaller than 2 cm with a 3-cm electrode with hypertonic saline infusion only in the central electrode zone showed that it was possible to deliver power without roll-offs when an extra bolus is infused after 4 min [14]. The discrepancy of these results with those
from our model is that the dopant fluid possibly provides an extra hydration effect which
could be the partial cause of the roll-off delay, as we modeled in [26]. Our computer results
call attention to the need to explore optimized protocols for the case of substrates doped with
highly conductive fluids and suggest that in these cases the relationship between electrode
length and tumor size could condition the result in terms of coagulation zone volume.

By comparing our computer and ex vivo results, we observed a good agreement in terms
of transverse diameter of the coagulation zone when we assumed a 2-cm diameter doped
zone, which suggests that during ex vivo experiments the dopant possibly extended in an area
of that size. The times until roll-off predicted by the computer model were shorter than those
observed during ex vivo experiments. This could be due to the fact that the computer model
did not include the possible rehydration effect of the presence of the doping fluid, which has
been shown to slightly delay the appearance of the roll-off [26].

Finally, although there are still no data available on the advantages of nanofluids over
saline to dope targets, it should not be forgotten that there are serious risks associated with
infusing large amounts of fluid in RFA [27], and it seems reasonable to suggest that electrical
conductivity increase should be achieved with the smallest possible amount of fluid.

Limitations

Some limitations have to be pointed out. First, our theoretical estimations showed that the
presence of either dopant (NaCl or AuNPs) at the concentrations considered only had an
impact on the electrical characteristics of the substrate. This might not be valid with fluids at
higher concentrations (i.e. >0.9% in case of NaCl, and >0.01 wt% in case of colloidal gold)
or when the substrate is doped with higher concentrations of dopant fluid (i.e. >10%). It is
also important to point out that the theoretical estimates of density, volumetric heat specific
and thermal conductivity of the doped substrate were based on expressions that have been proposed to study tissues with variable water content [28]. Second, our modeling study assumed that the dopant is spherically distributed around the electrode. This should be seen as a first approximation to the real situation, which could be different in the case of a heterogeneous tissue where the presence of blood vessels could preferentially evacuate the dopant agent [29]. And third, our model considered that electrical conductivity of doped substrates dropped 2 orders of magnitude once temperature reached 100 °C. However, there are no experimental data on electrical conduction through desiccated tissues previously doped with AuNPs, i.e. we do not yet know if the ‘dry residue’ formed by the NPs themselves can conduct the RF current in any way.

Conclusions

The theoretical analysis showed that the addition of normal saline or colloidal gold (0.01 wt%) at concentrations lower than 10% only modify the electrical conductivity of the doped substrate and have very little effect on the thermal characteristics. The computer results showed a relationship between doped zone size and electrode length regarding the created coagulation zone, and that highly conductive doped substrates possibly require low voltages to obtain large spherical coagulation zones. Both computer and ex vivo experiments showed that doping with AuNPs can enlarge the coagulation zone, especially the transverse diameter, hence achieving more spherical coagulation zones.
Methods

Electrical characterization of the doped substrates

In order to quantify changes in electrical conductivity of a substrate doped with a small amount of normal saline or AuNPs colloidal solution we built tissue-mimicking phantoms based on agar gel (constituted by deionized water and 2 gr/mL agar-agar powder). The phantoms had two compartments: a sphere mimicking a 4-cm doped zone, and a cylinder enclosing said sphere and mimicking non-doped tissue (see Figure 5a). The sphere was located in the center of the cylinder. To prepare the phantom, after the solidification of the outer cylinder, the spherical piece was inserted into it and allowed to solidify at room temperature. Once solidified, the entire phantom was kept in refrigeration at 10 °C at least 12 hours before experiments.

While the cylinder was always made of agar gel, the spherical compartment was doped with one of two solutions: either 0.9% NaCl (Pisa Pharmaceutics, Guadalajara, Mexico) or 0.01 wt% colloidal AuNPs solution (10 nm average diameter) provided by the Physics Institute of UASLP (San Luis Potosí, Mexico). We built four different spherical pieces to model four different conditions of the doped zone: 1) identical to the rest of the phantom (i.e. non doped tissue, using a 33.5 cm³ agar gel volume); 2) spherical zone doped with 1 wt% of NaCl (using a mixture with 0.83 g of agar power and 0.3 cm³ of 0.9% NaCl); 3) spherical zone doped with 1.5 wt% of NaCl (using a mixture with 0.8 g of agar power and 0.5 cm³ of 0.9% NaCl); and 4) spherical zone doped with 1 wt% of AuNPs solution (using a mixture with 0.83 g of agar power and 0.01 wt% AuNPs solution).

To estimate the electrical conductivity ($\sigma$) of the doped zone, we measured the impedance $Z$ between a 3-cm active electrode model Cool-Tip (Medtronic, Minneapolis, MN, USA)
inserted in the center of the spherical piece and a 2-mm thick aluminum foil entirely surrounding the phantom and acting as a dispersive electrode (Figure 5b). Z measurements were conducted by applying a sine voltage of 2 V amplitude and 500 kHz frequency. Voltage and current were measured by a digital oscilloscope TDS 3034B and a current probe mode A622, both from Tektronix (Beaverton, OR, USA). As expected, at RF frequencies the phantoms behaved electrically as pure resistors (no phase shift between current and voltage was observed), so that Z was inversely related to \( \sigma \). Once Z measurements were obtained, we built a theoretical model and conducted computer simulations by changing \( \sigma \) values until we obtained the same Z values (i.e. a trial and error approach was used to estimate \( \sigma \)). The geometry, size and electrical boundary conditions of the theoretical model exactly mimicked the experimental conditions. Figure 6a shows the boundary conditions used. One-way analysis of variance was performed by the Fisher test (P = 0.05) to compare the Z values obtained with the four groups.

**Computer modeling of RFA in a doped zone**

Computer modeling was used to study the effects of doping a tissue zone with NaCl and AuNPs on RFA electrical and thermal performance. Computer models were built and solved by Finite Element Method using COMSOL Multiphysics software (Burlington, MA, USA). The problem represented a 2D axis symmetric model (see Figure 6b) and consisted of a cylindrical domain mimicking non doped liver tissue and a spherical domain mimicking a doped zone with variable diameter (2, 3 and 4 cm). This sensitivity analysis was motivated by the fact that the spatial distribution of the doping agent around the electrode was not really known. It also included an RF applicator identical to the Cool-Tip applicator used in the agar.
and ex vivo experiments. The dispersive electrode was modeled as an electrical boundary condition \( V = 0 \) on all the outer boundaries. The properties of the materials are shown in Table 7 [14]. The model was based on a coupled electric-thermal in which the governing equation for thermal problem was:

\[
\frac{\partial (\rho h)}{\partial t} = \nabla \cdot (k \nabla T) + q + Q_p
\]  

(3)

where \( \rho \) (kg/m\(^3\)) is tissue density, \( h \) (J/kg·K) enthalpy, \( k \) (W/m·K) thermal conductivity, \( T \) (°C) temperature, \( t \) (s) time, \( q \) the heat source and \( Q_p \) heat loss by blood perfusion (which is ignored since we are modeling ex vivo conditions). For biological tissues enthalpy is related to tissue temperature by the following expression [30]:

\[
\frac{\partial (\rho h)}{\partial t} = \frac{\partial T}{\partial t} \begin{cases} 
\rho_i c_i, & 0 < T \leq 99^\circ C \\
h_{fg} C, & 99 < T \leq 100^\circ C \\
\rho_g c_g, & T > 100^\circ C
\end{cases}
\]  

(4)

where \( \rho_i \) and \( c_i \) are density and specific heat of tissue respectively at temperatures below 100 °C \((i=l)\) and at temperatures above 100 °C \((i=g)\), \( h_{fg} \) is the product of water latent heat of vaporization and water density at 100 °C, and \( C \) is tissue water content inside the liver (68%) [31]. Equation (3) was applied to each region of the model by substitution of the appropriate properties. To calculate \( Q_{RF} \) we solved the electrical problem, which for RFA can be calculated by:

\[
Q_{RF} = \mathbf{J} \cdot \mathbf{E} = \sigma \cdot |\mathbf{E}|^2 = \sigma \cdot \left|(-\nabla V)\right|^2
\]  

(5)

where \( \mathbf{J} \) is current density (A/m\(^2\)), \( \mathbf{E} \) electrical field (V/m), \( \sigma \) electrical conductivity (S/m) and \( V \) voltage (V). We used quasi-static approximation to solve the electromagnetic problem, where conduction currents were assumed to dominate compared to displacement currents. The electric voltage was computed by solving the equation [19]
\[ \nabla \cdot (\sigma \nabla V) = 0 \quad (6) \]

We assumed that the temperature dependence of electrical conductivity for both doped zone and for non doped tissue was determined by:

\[ \sigma(T) = \sigma_0 e^{0.15(T - T_b)} \quad (7) \]

where sub index \( o \), indicates properties measured at \( T_b \) (37 °C). Damage to tissue is the effect of exposing it to a high temperature for a prolonged time. A traditional way to predict the probability of irreversible thermal damage is the Arrhenius reaction rate model:

\[ \Omega(t) = A \int_0^t \exp[-E_a/RT(\tau)]d\tau \quad (8) \]

where \( \Omega(t) \) is the degree of tissue death, \( A \) is the frequency factor (7.39·10^39 s\(^{-1}\)), \( E_a \) is the activation energy for the irreversible damage reaction (2.557·10^5 J/mol), and \( R \) is the universal gas constant (8.314 J/mol·K). The kinetic parameters (\( A \) and \( E_a \)) that accounts for the morphological changes in tissue related to the thermal degradation of proteins were taken from [19]. A value \( \Omega = 4.6 \) (which corresponds to 99% of cell death probability) was used to compute the coagulation zone boundary.

To determine how dopant solution within the tissue modifies the temperature distributions in the tissue during RFA, NaCl and AuNPs were assumed to change the properties of the tissue they came into contact with. The doped substrate was always assumed to coincide with the volume of a spherical zone around the electrode. To estimate the electrical conductivities for tissue doped with NaCl or AuNPs we used Equations (1) and (2), which were obtained from the results of the experiments on the agar model (see Results section), and where \( \sigma_S \) (electrical conductivity of the non-doped substrate) was that of the non doped tissue (0.2 S/m in Table 7). Electrical impedance was assumed to increase by +1.5%/°C until 100 °C. To
model the tissue desiccation associated with the vaporization, when temperature reached 100ºC we assumed that electrical conductivity dropped 2 orders of magnitude.

The other properties (density, volumetric heat specific and thermal conductivity) were estimated theoretically using the expression proposed in [28] for tissue characteristics according to the water content. Firstly, density of the doped tissue ($\rho_{DT}$) can be determined as:

$$\rho_{DT} = (1 - \Phi_D)\rho + \Phi_D \rho_D$$  \hspace{1cm} (9)

where $\rho$ is the density of the non-doped tissue (see Table 7), $\rho_D$ the density of dopant (NaCl solution or solid AuNPs (19,300 kg/m$^3$)) and $\Phi_D$ denotes the volume fraction of dopant within the doped tissue. In the case of AuNPs, due to the extremely low value of $\Phi_D$ (e.g. $\sim 50 \cdot 10^{-9}$ in the case of 0.01 wt% of AuNPs occupying 1% by weight of doped tissue), $\rho_{DT} \approx \rho$, i.e. doped tissue density is hardly affected by the addition of the NPs. Likewise, in the case of NaCl solution, due to the similarity between its density ($\sim 1000$ kg/m$^3$) and that of the tissue (1080 kg/m$^3$), $\rho_{DT} \approx \rho$, i.e. the doped tissue density is little affected by the NaCl solution.

Volumetric specific heat of doped tissue $(\rho c)_{DT}$ can be similarly determined by:

$$(\rho c)_{DT} = (1 - \Phi_D)(\rho c) + \Phi_D (\rho c)_D$$  \hspace{1cm} (10)

where $\rho c$ is the volumetric specific heat of the non doped tissue, and $c\rho_D$ the volumetric specific heat of dopant. In the case of AuNPS, although the solid NPs have a much lower value (129 J/K·m$^3$) than tissue (3455 J/kg·K), the extremely low value of $\Phi_D$ implies that the volumetric specific heat of the doped tissue is not greatly affected by the AuNPs. Likewise, due to the similarity between the volumetric specific heat of the NaCl solution ($\sim 4090$ J/kg·K
and the NaCl solution has little effect on the volumetric specific heat of the doped tissue.

To determine the thermal conductivity in the doped tissue we used the Maxwell-Eucken model [33] applied to suspension of particles:

$$k_{DT} = k \cdot \frac{k_D + 2k - 2\phi_D(k - k_D)}{k_D + 2k + \phi_D(k - k_D)}$$ (11)

where \(k_{DT}\) is a mixture of two phases, a continuous phase (the suspending liquid, non-doped tissue in our case) of conductivity \(k\) is the thermal conductivity of the non-doped tissue, and a disperse phase of dopant (NaCl solution or gold spherical NPs of conductivity \(k_D = 317\) W/m·K), and the volume fraction \(\phi_D\) of dispersal phase [34]. Once more, the extremely low value of \(\phi_D\) means that the thermal conductivity of the doped tissue is not much affected by the AuNPs, while the similarity between the thermal conductivity of the NaCl solution (~0.63 W/m·K [32]) and the tissue (0.502 W/m·K) showed that that thermal conductivity of the doped tissue was not affected by the NaCl solution.

We assessed the effect doping the tissue with different concentrations \(C\) of 0.01% AuNPs colloidal solution, ranging from 0% (non-doped tissue) to 10%. Each concentration value was a value of a volume fraction of solid AuNPs in the doped tissue (\(\phi_D\)). Table 6 summarizes the estimated characteristics of the doped tissue for different 0.9% NaCl solution and Au colloidal (0.01 wt%) concentration values distributed in the tissue (from 0% to 10%). Note that only the electrical characteristics were significantly modified by the dopants while the thermal properties remain unchanged.

To study the effects of the dopants on the coagulation zone created during RFA, we simulated three values of applied voltage: 50, 70 and 90 V. While the first (low voltage) is expected to avoid roll-offs for at least 10 min, the third (high voltage) is the standard value
used in clinical practice for pulsed protocols [35]. All three values were expected to provide a preliminary insight into the effect of the dopant in terms of delaying roll off, which was assumed to occur when impedance reached 100 Ω (initial impedance was always lower than this value). After computing the coagulation zone boundary by the Ω = 4.6 isoline, we computed the axial (A) and transverse (B) diameters (see Fig. 6b). Coagulation zone sphericity was assessed as A/B (values close to 1 are associated with spherical coagulation zones, while values greater than 1 are associated with ellipsoids).

Ex vivo experimental setup

The experimental setup was based on an ex vivo model at room temperature (20 ºC), which consisted of samples (8 ×10 × 5 cm ± 2 cm) of bovine liver acquired locally. The samples were placed on a metal plate which acted as a dispersive electrode. An active electrode model Cool-tip (Medtronic, Minneapolis, MN, USA) with 1.5 mm outside diameter and 3 cm long active tip was horizontally inserted ~1 cm into each sample (see Figure 7). The electrode was internally cooled with circulating water (at 8 ± 2 ºC) using a Masterflex L/S peristaltic pump (Cole-Parmer, Vernon Hills, IL, USA) at a rate of 40 mL/min. The pump was started at least 2 min before RFA to ensure effective cooling. Ablations were conducted by an RFG 3E-RF generator (Radionics, Burlington, MA, USA). Since the simulation results presented before suggested that highly conductive doped substrates possibly require moderate voltages, the RF generator set to ~57 V constant voltage was applied until roll-off (a variation of ± 2 V occurred between applications, due to the imprecision of the generator itself).

Three RFA protocols were tested: 1) non doped tissue (ND Group), 2) previous infusion of 2 mL of 0.9% NaCl (NaCl Group), and 3) previous infusion of 2 mL of AuNPs 0.1 wt%
(AuNPs Group). Note that a colloid with a higher concentration of AuNPs was used in the ex vivo experiments in case of higher differences than those suggested by the computer results. Each protocol was run on \( n = 4 \) samples. The infusion took around 1 min and was distributed at three points spaced 1 cm apart (\(~20\) s each) located along the electrode length and at the same depth as the electrode. This was done to achieve a more or less homogeneous distribution of the dopant around the electrode (see Figure 7) and was similar to the method used in [22]. RFA started immediately after infusion.

**Declarations**

**Ethics approval and consent to participate**

This article does not contain any studies with human participants or animals performed by any of the authors.

**Consent for publication**

Consent for publication was obtained for every individual person’s data included in the study.

**Availability of data and materials**

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

**Competing interests**

The authors declare that they have no competing interests.
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**Authors’ contributions**

EB contributed with the planning of experiments and numerical models performed in this work. RR-M supervised the experimental work regarding electrical properties of doped tissues and ex-vivo experiments, and also contributed in building numerical models. DLC-L is the graduate student who built and performed numerical simulations and experiments, helping also to analyze the results obtained. All contributed equally in this work. All authors read and approved the final manuscript.

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Captions for tables, figures and additional files

Tables

Table 1. Impedance measured from phantoms samples (n = 10) and σ values (estimated from computer simulations) of the agar-gel cylinder and of sphere.

Table 2. Results of the RFA for different values of applied voltage on a 2-cm spherical zone in case of non doped tissue (ND) and two types of dopants: saline solution (0.9% NaCl) and AuNPs (0.01 wt%).

Table 3. Results of the RFA for different values of applied voltage on a 3-cm spherical zone in case of non doped tissue (ND) and two types of dopants: saline solution (0.9% NaCl) and AuNPs (0.01 wt%).

Table 4. Results of the RFA for different values of applied voltage on a 4-cm spherical zone in case of non doped tissue (ND) and two types of dopants: saline solution (0.9% NaCl) and AuNPs (0.01 wt%).

Table 5. Results of the ex vivo experiments for the three considered groups (n=4, mean ± standard deviation).
Table 6. Estimation of the characteristics of the tissue doped with different concentration (C, volume fraction) of a solution of 0.01% (wt) AuNPs and a solution 0.9% NaCl.

Table 7. Characteristics of the materials used in the computational model [14].

**Figures**

**Figure 1** Temperature distributions computed at roll-off time for different values of applied voltage on a 2-cm spherical zone doped with NaCl and AuNPs solutions at 10%. ND: non doped tissue case (scale in ºC between 106 ºC and 5 ºC).

**Figure 2** Temperature distributions computed at roll-off time for different values of applied voltage on a 3-cm spherical zone doped with NaCl and AuNPs solutions at 10%. ND: non doped tissue case (scale in ºC between 112 ºC and 5 ºC).

**Figure 3** Temperature distributions computed at roll-off time for different values of applied voltage on a 4-cm spherical zone doped with NaCl and AuNPs solutions at 10%. ND: non doped tissue case (scale in ºC between 116 ºC and 5 ºC).

**Figure 4** Examples of coagulations created with RFA on non doped (ND) liver samples and on samples doped with 2 mL of 0.9% NaCl (NaCl) and 2 mL of 0.1 wt% AuNPs. Constant voltage of ~57 V was applied until roll-off (scale in mm, measurements in cm).
Figure 5  
A: Agar phantoms were based on a sphere of radius $r = 2$ cm located at the center of a cylinder of diameter $d = 10$ cm and height $H = 11$ cm. B: Experimental setup used to electrically characterize each phantom, including an RF applicator (active electrode) inserted into the center of the sphere doped with NaCl or AuNPs. The entire phantom was surrounded by a 2 mm thick aluminum foil that acted as a dispersive electrode.

Figure 6  
a) Geometry and boundary conditions of the theoretical model used to estimate the values of electrical conductivity associated with the doped zone in the agar phantoms. Dimensions: $r_0 = 50$ mm, $z_0 = 110$ mm, $r_1 = 0.75$ mm, $z_1 = 40$ mm, $z_2 = 70$ mm. $V_i = 2$ V. b) 2D axisymmetric model used to study the temperature distributions during RF ablation of a doped zone with different dopants. It consisted of a cylinder of non doped liver tissue (radius $r_0 = 10$ cm and height $r_h = 16$ cm) surrounding a spherical doped zone of variable radius (dashed red line, $r_t = 2$, 3 and 4 cm). The active electrode ($r_e = 0.75$ mm) is inserted into the center of the doped zone. Solid blue line represents the contour of the coagulation zone, and A and B are the axial and transverse diameters, respectively.

Figure 7  
Cross-section view of tissue sample used in the ex vivo experiments. The ablation electrode was inserted 1 cm below the tissue surface. A, B, and C indicate the dopant infusion points (saline solution or Au colloidal). Solid blue line would represent the contour of the coagulation zone, while dashed red line would represent the contour of the doped zone.