Adrenal ablation as a treatment for hypertension: analyzing the dielectric properties of adrenal glands for microwave ablation technologies

Bilal Amin¹,²,³, Grazia Cappiello¹,³, Martin J. Krašny¹,³, Eoghan Dunne¹,³, Aoife Lowery⁴, Michael Conall Dennedy², Punit Prakash⁵, Adnan Elahi¹,² and Martin O'Halloran¹,²,³

¹Translational Medical Device Laboratory, University of Galway, Galway, Ireland; ²Electrical and Electronic Engineering, University of Galway, Galway, Ireland; ³School of Medicine, University of Galway, Galway, Ireland; ⁴Discipline of Surgery, Lambe Institute for Translational Research, University of Galway, Galway, Ireland and ⁵Department of Electrical and Computer Engineering, Kansas State University, Manhattan, KS, USA

Abstract

Adrenal gland-induced hypertension, also known as secondary hypertension, is a medical condition caused by an underlying adrenal pathology, most typically adrenocortical adenomas. Current clinical practices involve pharmacotherapy or surgical resection to treat adrenal gland diseases that cause hypertension. However, due to the limitations of these treatment options, microwave ablation (MWA) has emerged as a promising minimally invasive alternative. An accurate understanding of the dielectric properties of adrenal glands would support the further development and optimization of MWA technology for treating adrenal tumors. Only a few studies have examined the dielectric properties of both human and animal adrenal glands, and the sample sizes of these studies have been relatively small. Therefore, further dielectric data of human and animal adrenal glands are warranted. This paper presents the ex vivo dielectric properties of the ovine adrenal glands (medulla and cortex) and summarizes the published literature on dielectric data of adrenal glands from porcine, bovine, ovine, and human samples in the microwave frequency range to analyze the consistency and reliability of the reported data. The dielectric properties of the ovine adrenal glands (N = 8) were measured using an open-ended coaxial probe measurement technique at frequencies ranging from 0.5 to 8.5 GHz. This study also investigated the temperature-dependent dielectric properties of the ovine adrenal medulla ranging from 37 to 64°C at frequencies ranging from 0.5 to 8.5 GHz. The dielectric properties of the ovine adrenal medulla measured in this study were consistent with the literature. Moreover, the review suggests that variations exist in the dielectric properties of the adrenal medulla and cortex among species. The study also found that the dielectric properties of the adrenal medulla decrease with increasing temperature, similar to other tissues for which temperature-dependent dielectric data have been reported. This summary of dielectric data of adrenal glands and the temperature-dependent dielectric properties of the ovine adrenal medulla will accelerate the development of MWA technologies for hypertension treatment.

Introduction

Hypertension is a common chronic medical condition characterized by high blood pressure [1]. The adrenal glands are located on the top of the kidneys and play a crucial role in regulating blood pressure by secreting hormones such as aldosterone and cortisol. In some cases, overactive adrenal glands can lead to hypertension, also known as secondary hypertension [2, 3]. Secondary hypertension accounts for about 10% of all hypertension cases, and adrenal gland-related hypertension, also known as primary aldosteronism, is the most common form of secondary hypertension [4]. The prevalence of hypertension and the associated morbidity and mortality with the condition are significant public health concerns worldwide. According to the World Health Organization, hypertension affects approximately one billion people globally and is a leading cause of cardiovascular disease, stroke, and kidney failure [5]. The economic burden of hypertension is also substantial, with estimates suggesting that hypertension-related healthcare costs in the United States alone exceed $50 billion annually [3, 6]. Current clinical practices for the treatment of hypertension include lifestyle modifications, such as diet,
exercise, and medication. However, these treatments are not always effective, and some patients may require additional interventions [2]. Adrenalectomy, the surgical removal of the adrenal gland, is currently the most effective treatment for adrenal gland-related hypertension [2]. However, this procedure is invasive and costly and carries a risk of complications [7]. Thus, safer, less invasive, and more effective treatment for secondary hypertension is urgently needed.

Over the past 10 years, minimally invasive technologies have been increasingly used to thermally ablate solid tumors within large organs, including cryoablation, radiofrequency ablation (RFA), and microwave ablation (MWA) [8]. Cryoablation is associated with significant procedural pain and may not be suitable for larger adenomas. Moreover, cryoablation is found to carry a risk of hypertensive crisis during the thawing phase [9]. RFA is a minimally invasive procedure that uses radiofrequency current (~500 kHz) to heat and destroy adrenal tumors. Although RFA offers several benefits over traditional adrenalectomy, such as a less invasive approach resulting in reduced pain, scarring, and recovery time, the long-term safety and efficacy of RFA still require further investigation [10]. One of the main challenges of RFA is maintaining the ablation zone while avoiding thermal damage to surrounding tissues [10]. To address these limitations, MWA has emerged as a promising alternative for treating adrenal diseases. MWA uses a needle or stiff catheter to deliver microwave energy to the target area, causing coagulation necrosis by heating the surrounding tissue to temperatures above 50–60 °C [11, 12]. MWA offers several theoretical advantages over RFA, such as more precise targeting, efficient ablation, and a reduced risk of complications. Clinical studies have demonstrated the efficacy of MWA in treating tumors in various organs, including the liver, lung, kidney, and breast [13]. MWA systems operate at frequencies of 915 MHz, 2.45 GHz, or 5.8 GHz, with the latter frequency providing faster heating and shorter antenna lengths [11, 14]. Further research is needed to determine the long-term safety and efficacy of MWA for adrenal tumors.

The dielectric properties are crucial in determining the potential efficacy and effectiveness of MWA treatment for adrenal tumors [11, 15–17]. Furthermore, these properties determine the way tissues interact with the microwave energy emitted by the ablation antenna, influencing the amount of energy absorbed and resulting in heating [18]. The tissues around the adrenal glands, including blood vessels and muscle, have higher dielectric properties and can act as barriers to microwave energy transmission, decreasing the amount of energy reaching the tumor [14]. This can lead to ineffective ablation and require higher energy levels and extended treatment durations. Therefore, understanding the dielectric properties of adrenal glands and surrounding tissues is vital to plan and execute effective MWA procedures [16, 19, 20].

Extensive experimental research has been conducted to investigate the dielectric properties of various biological tissues, such as the breast, lung, skin, kidney, bone, and heart [20–23]. Despite the large number of experimental studies that have characterized the dielectric properties of various biological tissues, only three studies to date have reported the dielectric properties of adrenal glands [11, 15, 24]. Peyman et al. [24] reported the in vivo dielectric properties of the outer layer of the porcine adrenal gland, also known as the adrenal cortex, for a frequency range of 50 MHz–20 GHz. However, the authors did not report the dielectric properties of the adrenal medulla, which is the other distinct tissue layer in the adrenal gland. Shahzad et al. [15] reported the ex vivo dielectric properties of bovine adrenal glands for a frequency range of 0.5–20 GHz and distinguished between the adrenal cortex and medulla. Bottiglieri et al. [11] reported the ex vivo dielectric properties of ovine and human adrenal glands for a frequency range of 0.5–8.5 GHz. However, due to the design of their study, the authors were unable to access the inner parts of the human adrenal glands, specifically the adrenal medulla. Consequently, their findings only pertain to the normal adrenal cortex of human glands. Regarding the choice of an animal model for preclinical testing of MWA devices, Bottiglieri et al. [11] suggested that ovine is a feasible model for testing the safety and performance of MWA devices.

This study first presents the dielectric properties of the ovine adrenal glands (medulla and cortex). Ovine tissue has been chosen for this study as it has been reported to be a feasible model for the preclinical testing of MWA devices in the literature [11]. In this study, the ex vivo dielectric properties of eight ovine adrenal gland samples were measured using an open-ended coaxial (OECL) probe across the microwave frequency range of 0.5–8.5 GHz. The results were compared with the dielectric properties of the ovine adrenal glands reported in the literature. Second, this study also provides a summary of the dielectric properties of adrenal glands reported in the literature and examines the consistency and reliability of the reported adrenal gland dielectric data. This study is the first to document a summary of the dielectric properties of the adrenal medulla and cortex in the literature. The analysis and comparison provided in this study can aid in the development and optimization of MWA-based technologies for hypertension treatment. Third, this study provides a Debye model for the ex vivo dielectric properties of ovine adrenal glands measured in this study. The Debye model is useful for representing the frequency-dependent dielectric properties and is suitable for use with electromagnetic (EM) computer models that are used to optimize the device design. Finally, this study examined the temperature-dependent dielectric properties of the ovine adrenal medulla across 37–64 °C. The temperature-dependent dielectric properties contribute to improved modeling of ablation devices, providing a means to assess how dynamic intra-procedural changes in tissue dielectric properties impact the transient evolution of the ablation zone. Temperature-dependent dielectric properties can also inform the development of EM-based approaches for monitoring the progression of tissue ablation zones [25]. The findings of this study can be used to improve the accuracy of MWA-based technologies for hypertension treatment and facilitate the development of new EM-based, cost-effective therapeutic alternative medical devices for treating hypertension.

The remainder of this paper is structured as follows: the “Materials and methods” section discusses the source of ovine adrenal gland samples, the methodology used to measure the dielectric properties of adrenal glands, the measurement protocol and system uncertainty analysis of the dielectric properties measurement equipment, the fitting model used on dielectric properties data, the experimental procedure for measuring the temperature-dependent dielectric properties, and finally the literature review strategy. The “Results and discussion” section presents the results and discussion on the dielectric properties measurement of ex vivo ovine adrenal glands, including the adrenal medulla and cortex, interspecies comparison of dielectric properties of adrenal glands from the literature, and findings on temperature-dependent dielectric properties. Finally, conclusions are drawn in the “Conclusions” section.
Materials and methods

Source of tissues

In this study, a total of eight ovine adrenal gland samples (N = 8) were dissected from slaughtered animals in a local abattoir. After excision, the glands were sealed in closed plastic containers within their fat capsule to prevent tissue dehydration. Samples were transported to our lab within 24 h. Since the adrenal glands were obtained from animals slaughtered for human consumption within a regulated abattoir, therefore, no ethical approval was necessary. Once the samples were received in the laboratory, the adrenal glands were separated from the surrounding structures, such as the kidney and fat. The size of the samples varied, with lengths ranging between 25.0 ± 7 mm, widths of 10.6 ± 2 mm, and thicknesses of 5.4 ± 0.9 mm. The adrenal glands were sectioned to provide access to both the adrenal cortex and the medulla layers, and measurements were performed on the internal surface of the tissue to minimize the effect of surface dehydration. Figure 1 shows the photograph of one of the adrenal gland samples and the measurement sites on the adrenal cortex and medulla tissues.

Dielectric properties measurements

The dielectric properties were measured using a slim-form OECL probe (Keysight 85070E, Santa Rosa, CA, USA). The reflection coefficient (S11) at the calibration plane of the probe was recorded using a vector network analyzer (VNA) (Keysight VNA E5063A, Santa Rosa, CA, USA). The data were recorded in the frequency range of 0.5–8.5 GHz over 101 linearly spaced frequency points. A commercially available software suite (Keysight N1500A, Santa Rosa, CA, USA) was used to convert the S11 parameters to real (ε’ (ω)) and imaginary (ε’’ (ω)) parts of the complex permittivity [11, 20, 26]. The dielectric properties were recorded by precisely placing the probe on the tissue sample as shown in Fig. 2. The slim-form probe was firmly attached to the VNA to minimize the measurement inaccuracies caused by repositioning the probe. A lift stand as shown in Fig. 2 was used to place the tissue samples during the measurements to avoid sample movement and to ensure proper contact of the probe with the tissue sample. The temperature of each sample was recorded using a digital infrared thermometer with dual-laser targeting (Precision Gold, N85FR). The experimental setup for measuring the dielectric properties is shown in Fig. 2. The temperature of the samples varied between 22.80 ± 0.70°C. At each measurement location of the sample, a total of five measurements were performed. Accordingly, for the eight ovine adrenal glands, a total of 335 dielectric measurements were recorded and analyzed (total measurement points = 67; adrenal cortex measurement points = 35; and adrenal medulla measurement points = 32). The probe was cleaned with an alcohol wipe before each measurement.

Temperature-dependent dielectric properties

In this study, the temperature-dependent dielectric properties of one of the adrenal glands were measured using the Fisher Isotemp Water Baths (Fisher Scientific 154626Q, Hampton, NH, USA). The temperature-dependent dielectric properties were measured only for the adrenal medulla. Due to the shrinking width of the adrenal cortex tissue with increasing temperature, it was challenging to achieve proper contact between the OECL probe and the adrenal cortex tissue. Therefore, the temperature-dependent dielectric properties of the adrenal cortex were not taken into consideration. The water-filled bath was placed on the lift table. The adrenal gland was placed in a plastic container to prevent direct contact with the water. The temperature of the water bath was raised to predetermined values of 37°C, 46°C, 53°C, and 64°C, and the dielectric properties of the adrenal gland were measured at each temperature using the measurement setup illustrated in Fig. 3. These temperatures represent an important spectrum of temperatures commonly used in clinical practice for effective MWA. The time to reach the sample to the desired temperatures was not recorded in this particular experiment. Furthermore, the sample
Temperature-dependent dielectric properties measurement setup.

is the permittivity of free space. The relaxation constant

represents the mean of the measured dielectric properties of 0.1 M NaCl solution at 24.90°C. The uncertainty related to repeatability (UCREP) provides a measure of the random errors affecting the measurement process. The repeatability is expressed as the standard deviation of the dielectric properties data that are repeatedly acquired under the same measurement condition. The uncertainty in repeatability of measurements in terms of percentage is defined as follows:

\[
UC_{REP}(f) = \left( \frac{DP_{mean}(f) - DP_{ref}(f)}{DP_{mean}(f)} \right) \times 100, \tag{2}
\]

where \(DP_{mean}(f)\) represents the mean of the measured dielectric properties of 0.1 M NaCl solution at a specific frequency point \(f\). In this study, the uncertainty due to the cable movement was not considered as the probe was directly connected to the VNA. Moreover, the probe was not moved during the dielectric properties measurement sessions. The combined uncertainty (UCCOM) was computed by using the standard uncertainty (UCSTD) values of each of the uncertainty components (UCACC and UCREP). The expanded uncertainty (UCEXP) was calculated by considering a 95% confidence interval, according to the guidelines of the National Institute of Standard and Technology [30]. In this study, the expanded uncertainty of the measurement equipment was found to be 0.78% and 5.08% for relative permittivity and conductivity, respectively. All the uncertainty components computed in this study are reported in Table 1. The uncertainty components are computed separately for both the relative permittivity and conductivity of 0.1 M NaCl for a frequency range of 0.5–8.5 GHz.

Fitting model on ex vivo ovine dielectric properties data

The dielectric properties of biological tissues are highly frequency-dependent [31]. The two most commonly used parametric models of dielectric properties are the Cole–Cole model and the Debye model [21, 32]. The Cole–Cole model is computationally expensive and cannot be easily expressed in the time domain [21]. However, the Debye model can be easily expressed in both the time and frequency domains and is not computationally expensive [21, 33]. Therefore, this study has employed the Debye model as a fitting model for the ovine dielectric properties measured in this study. The Debye model is defined as follows:

\[
\hat{\varepsilon} = \varepsilon_{\infty} + \sum_{p=1}^{n} \frac{\Delta \varepsilon_p}{1 + j\omega\tau_p} + \frac{\sigma_{\infty}}{j\omega\varepsilon_0}, \tag{3}
\]

where \(\hat{\varepsilon}\) is the complex permittivity of the material, \(\varepsilon_{\infty}\) is the permittivity at the highest frequency, \(\Delta \varepsilon_p\) is the change in the permittivity at the \(p\)th dispersion, \(\tau_p\) is the relaxation constant at the \(p\)th dispersion, \(\sigma_{\infty}\) is the static ionic conductivity, \(\omega\) is the angular frequency, and \(\varepsilon_0\) is the permittivity of free space. The Debye parameters were optimized by using the algorithm. In this study, a weighted least squares method (W-LSM) was developed in MATLAB (R2017b, The MathWorks, Inc., Natick, MA, USA) to fit the two-pole Debye model [21]. The W-LSM was proposed by Fujii.
Table 1. Uncertainty in accuracy and repeatability components for measured relative permittivity and conductivity of 0.1 M NaCl for a frequency range of 0.5–8.5 GHz

| Parameter | Value | Probability distribution | Divisor (DIV) | Standard uncertainty (%)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$UC_{ACC}$</td>
<td>0.60</td>
<td>R</td>
<td>$\sqrt{3}$</td>
<td>0.34</td>
</tr>
<tr>
<td>$UC_{REP}$</td>
<td>0.20</td>
<td>N</td>
<td>1</td>
<td>0.20</td>
</tr>
<tr>
<td>$UC_{COM}$</td>
<td>0.39</td>
<td>$\sqrt{\sum UC_{STD}^2}$</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$UC_{EXT} (\lambda = 2)$</td>
<td>0.78</td>
<td>$UC_{COM} \times \lambda$</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$UC_{ACC}$</td>
<td>4.20</td>
<td>R</td>
<td>$\sqrt{3}$</td>
<td>2.42</td>
</tr>
<tr>
<td>$UC_{REP}$</td>
<td>0.80</td>
<td>N</td>
<td>1</td>
<td>0.80</td>
</tr>
<tr>
<td>$UC_{COM}$</td>
<td>2.54</td>
<td>$\sqrt{\sum UC_{STD}^2}$</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$UC_{REP} (\lambda = 2)$</td>
<td>5.08</td>
<td>$UC_{COM} \times \lambda$</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

$\lambda$ = multiplying factor for computing the expanded uncertainty, $R$ = rectangular distribution, $N$ = normal distribution.

[33] as a numerical fitting technique. The W-LSM assigns weights to the data points being fitted. These weights are used to emphasize or de-emphasize certain points in the fitting process, depending on their relative importance or reliability [33]. A complex weight factor $\gamma$ was introduced to facilitate the control and thus enhance the accuracy of the fit on the measured dielectric properties data. The error was chosen to be dependent on the permittivity itself and is modeled as follows:

$$\hat{E}_i \approx \{\hat{\varepsilon}(\omega)\}^\gamma, \quad (4)$$

where $\hat{\varepsilon}(\omega)$ is the measured complex permittivity at the frequency $\omega$. The weight factor in this study was kept at 1 to assign equal weight to all permittivity values. The nonlinear least squared method was used with the Newton iterative method to minimize the total weighted and the squared error as follows [21]:

$$E^2 = \sum_{i=1}^{N_f} \left[ \frac{\{C_r(\omega) - M_r(\omega)\}^2}{E_r(\omega)} + \frac{\{C_i(\omega) - M_i(\omega)\}^2}{E_i(\omega)} \right], \quad (5)$$

where $N_f$ denotes the number of frequency points, $C_r(\omega)$ and $C_i(\omega)$ are the real and imaginary parts of the calculated complex permittivity, respectively, $M_r(\omega)$ and $M_i(\omega)$ are the real and imaginary parts of the measured complex permittivity, respectively, and $E_r(\omega)$ and $E_i(\omega)$ are the real and imaginary parts of the allowable error $E_i$, respectively. The two-pole Debye model was fitted to the mean dielectric properties of the ovine adrenal medulla and cortex tissues over the measured frequency range (0.5–8.5 GHz). The mean square error (MSE) was calculated between the mean measured dielectric properties and the dielectric properties resulting from the two-pole Debye model. The MSE is a commonly used metric to evaluate the performance of a model by measuring the difference between the predicted and actual values. It represents the average of the squared differences between the predicted and actual values and therefore indicates how well the model fits the data. The MSE can be calculated as follows:

$$MSE = \frac{1}{n} \times \left( \sum (\varepsilon_i - \hat{\varepsilon}_i)^2 \right), \quad (6)$$

where $n$ denotes the number of data points, $\varepsilon_i$ is the $i$th actual value, $\hat{\varepsilon}_i$ is the $i$th predicted value, and $\Sigma$ denotes the sum of the squared differences between predicted and actual values.

Literature review methodology

A systematic review of the literature was conducted to collate the dielectric properties of adrenal glands published in previous studies. The databases including PubMed, Scopus, and Web of Science were included to search for studies that reported the dielectric properties of adrenal glands. The search was conducted using the keywords “adrenal gland”, “dielectric properties”, and “microwave ablation”. After screening the titles and abstracts of the identified studies, the full texts of the studies that met the inclusion criteria were retrieved. Only the studies that reported the dielectric properties of adrenal glands are included, and studies that did not provide sufficient information about the dielectric properties are excluded. All studies that reported the dielectric properties of other tissues or organs were also excluded.

Results and discussion

This section presents the ex vivo dielectric properties of the ovine adrenal glands. First, the measured dielectric properties of the adrenal glands in the current study are compared with the existing literature. The dielectric properties of the adrenal medulla and cortex are separately presented. This separated analysis will facilitate an intra-tissue comparison of the dielectric properties of the adrenal medulla and cortex obtained from different studies. Furthermore, the two-pole Debye model parameters for the mean dielectric properties of the adrenal medulla and cortex measured in this study are presented and compared with the existing literature. Finally, the temperature-dependent dielectric properties of the ovine adrenal medulla measured in this study are presented.

Dielectric properties of adrenal medulla

The relative permittivity and conductivity of the ovine adrenal medulla measured in this study are shown in Fig. 4(a) and (b), respectively. The measured dielectric properties are compared with the dielectric properties of the adrenal medulla from bovine and ovine reported by Shahzad et al. [15] and Bottiglieri et al. [11], respectively. The solid lines in Fig. 4 show the mean dielectric properties of the adrenal medulla from each study, while the error bars
Comparison of ex vivo dielectric properties (a) relative permittivity and (b) conductivity for the adrenal medulla from reported studies. The dielectric properties of the adrenal medulla from ovine, bovine, and porcine do not exhibit significant variation in results.

on the solid lines of dielectric properties of the adrenal medulla measured in this study indicate the range of variation in dielectric properties observed among the measured samples. The comparative analysis indicates the following:

1. Differences in dielectric properties of the adrenal medulla are observed for samples acquired from different species: bovine and ovine.
2. The mean relative permittivity and conductivity of the ovine adrenal medulla measured in this study were compared to those reported by Bottiglieri et al. [11]. The results show an average percentage difference of 1.60% and 1.55% for relative permittivity and conductivity, respectively.
3. There is a notable difference between the dielectric properties of the bovine and ovine adrenal medulla measured in this study. The results show an average percentage difference of 5.19% and 1.80% for relative permittivity and conductivity, respectively.

Dielectric properties of adrenal cortex

The relative permittivity and conductivity of the ovine adrenal cortex measured in this study are shown in Fig. 5(a) and (b), respectively. The measured dielectric properties are compared with the dielectric properties of the adrenal cortex from porcine, bovine, ovine, and human reported by Peyman and Gabriel [24], Shahzad et al. [15], and Bottiglieri et al. [11], respectively. The solid lines in Fig. 5 show the mean dielectric properties of the adrenal cortex from each study, while the error bars on the solid lines of dielectric properties of the adrenal cortex measured in this study indicate the range of variation in dielectric properties observed among the measured samples. The comparative analysis indicates the following:

1. Differences in dielectric properties of the adrenal cortex are observed for samples acquired from different species: porcine, bovine, ovine, and human.
2. The mean relative permittivity and conductivity of the ovine adrenal cortex measured in this study were compared to those reported by Bottiglieri et al. [11]. The results show an average percentage difference of 6.12% and 3.35% for relative permittivity and conductivity, respectively.
3. The relative permittivity of the human adrenal cortex is found to be higher than the relative permittivity of ovine, bovine, and porcine samples.
4. There is a notable difference between the dielectric properties of the bovine and ovine adrenal cortex measured in this study. The results show an average percentage difference of 8.76% and 13.83% for relative permittivity and conductivity, respectively.
5. There is a notable difference between the dielectric properties of the porcine and ovine adrenal cortex measured in this study.
study. The results show an average percentage difference of 10.75% and 12.83% for relative permittivity and conductivity, respectively.

6. The dielectric properties of the bovine and porcine adrenal cortex did not exhibit significant differences. The results show an average percentage difference of 2.04% and 4.40% for relative permittivity and conductivity, respectively.

Ovine, bovine, porcine, and human adrenal glands showed interspecies differences in their dielectric properties, which can be attributed to several factors. One major factor in these differences is the difference in tissue composition. Ovine, bovine, and human adrenal glands differ in the relative amounts of various components such as water content, proteins, lipids, and ions [34, 35]. These differences can affect the dielectric properties of the tissue, as each component has a unique response to an electric field. Another factor is the difference in tissue structure. The arrangement of cells, extracellular matrix, and blood vessels can vary across species, which can affect how the tissue responds to an electric field [7, 36, 37]. For example, the size and shape of cells influence their orientation in an electric field, and the presence of blood vessels can alter the conductivity of the tissue. Moreover, Meo et al. [35] reported interspecies differences between porcine, ovine, bovine, and human for liver and kidney tissues. The authors found that the differences in dielectric properties between the two organs in animals compared to the two organs in the human cadaver are relatively high. Salahuddin et al. [38] reported that there is more than 25% variation between the dielectric properties of the same tissue for different species [38]. Finally, the methodology for characterizing the dielectric properties of bovine and ovine by Shahzad et al. [15] and Bottiglieri et al. [11], respectively, is the same compared to this study, and therefore, all studies would have reported temperature and sample preparation so these factors can be discounted and differences in dielectric properties can be attributed to samples. As we show in the later section, the temperature at which samples are measured plays a significant role in the obtained dielectric properties values. Thus, we recommend always reporting the sample temperature for future analysis and better comparison between studies. Understanding these differences is important for the development of diagnostic and therapeutic tools for adrenal gland-related diseases in different animal models and human patients.

**Fitting model on ex vivo dielectric properties data of adrenal glands**

This study collated the Cole–Cole models of porcine, bovine, and ovine adrenal glands published in previous studies. All the reported studies utilized the two-pole Cole–Cole model to fit their respective ex vivo dielectric properties data. The models generally showed similar trends in the dielectric properties of adrenal glands, such as the frequency dependence of complex permittivity and conductivity. The collation of the Cole–Cole models is important for developing a robust model for analyzing the ex vivo dielectric properties data of adrenal glands and for understanding their physiological...
Table 2. Summary of the parameters of the two-pole Cole–Cole model fitted to the measured adrenal data (cortex and medulla) in the frequency range 0.5–8.5 GHz from the literature

<table>
<thead>
<tr>
<th>Study</th>
<th>Species</th>
<th>Tissue</th>
<th>$\varepsilon_\infty$</th>
<th>$\sigma_s (S/m)$</th>
<th>$\Delta \varepsilon_1$</th>
<th>$\tau_1$ (ps)</th>
<th>$\alpha_1$</th>
<th>$\Delta \varepsilon_2$</th>
<th>$\tau_2$</th>
<th>$\alpha_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peyman and Gabriel [24]</td>
<td>Porcine</td>
<td>Cortex</td>
<td>3</td>
<td>0.62</td>
<td>48.2</td>
<td>7.06</td>
<td>0.18</td>
<td>52.1</td>
<td>1.95</td>
<td>0</td>
</tr>
<tr>
<td>Shahzad et al. [15]</td>
<td>Bovine</td>
<td>Medulla</td>
<td>3.88</td>
<td>0.62</td>
<td>52.95</td>
<td>7.01</td>
<td>0.17</td>
<td>62.05</td>
<td>4.28</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cortex</td>
<td>3.57</td>
<td>0.46</td>
<td>47.08</td>
<td>8.33</td>
<td>0.16</td>
<td>52.31</td>
<td>1.69</td>
<td>0.03</td>
</tr>
<tr>
<td>Bottiglieri et al. [11]</td>
<td>Ovine</td>
<td>Medulla</td>
<td>1.80</td>
<td>0.40</td>
<td>51.10</td>
<td>7.10</td>
<td>0.10</td>
<td>60.5</td>
<td>1.30</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cortex</td>
<td>1.00</td>
<td>0.40</td>
<td>45.30</td>
<td>6.40</td>
<td>0.10</td>
<td>54.60</td>
<td>1.7</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Figure 6. Two-pole Debye model parameters of adrenal medulla and cortex over 0.5–8.5 GHz frequency band: (a) relative permittivity and (b) conductivity. The measured dielectric data of the adrenal medulla and cortex (dotted lines) are compared with calculated data from the two-pole Debye model (solid lines).

and pathological characteristics. The Cole–Cole models from the previous studies are tabulated in Table 2.

In this study, the two-pole Debye model was fitted to the mean dielectric properties of the ovine adrenal medulla and cortex. Figure 6(a) and (b) shows the measured and calculated dielectric properties from the two-pole Debye model of the adrenal medulla and cortex over a frequency range of 0.5–8.5 GHz. The measured dielectric data of the adrenal medulla and cortex are shown as dotted lines, while the calculated data from the two-pole Debye model are shown as solid lines. The comparison between the measured and calculated dielectric properties data provides an assessment of the accuracy of the two-pole Debye model in describing the dielectric properties of the tissue. In this case, the two-pole Debye model appears to provide a good fit to the measured data, with the calculated data closely following the trends of the experimental data. The relative permittivity of the adrenal medulla and cortex both increase with frequency, while the conductivity of the adrenal medulla is higher than that of the adrenal cortex at all frequencies.

The parameters of the two-pole Debye model fitted to the mean dielectric properties of the adrenal medulla and cortex are presented in Table 3. The results showed that the two-pole Debye model was able to accurately capture the complex dielectric behavior of adrenal tissues. These parameters will aid in broadband EM simulations of adrenal gland tissues for the development of EM diagnostic tools, such as imaging techniques or other applications.

In this study, the MSE was used to quantify the difference between the measured dielectric properties and the calculated values by the two-pole Debye model across all frequency points. The MSE values are tabulated in Table 4. The MSE was calculated for both the relative permittivity and conductivity values of the adrenal medulla and cortex. It can be observed from Table 4 that the MSE values vary depending on the tissue type. Moreover, it can be observed from Table 4 that the model was found to have a good fit for the experimental data of the adrenal cortex compared to the medulla, with low MSE values for both the relative permittivity and conductivity.

Table 3. Two-pole Debye model parameters fitted to the measured adrenal data (medulla and cortex) in the frequency range 0.5–8.5 GHz

<table>
<thead>
<tr>
<th>Tissue</th>
<th>$\varepsilon_\infty$</th>
<th>$\sigma_s (S/m)$</th>
<th>$\Delta \varepsilon_1$</th>
<th>$\tau_1$ (ps)</th>
<th>$\Delta \varepsilon_2$</th>
<th>$\tau_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medulla</td>
<td>14.15</td>
<td>0.73</td>
<td>37.11</td>
<td>10.33</td>
<td>7.70</td>
<td>186.85</td>
</tr>
<tr>
<td>Cortex</td>
<td>14.82</td>
<td>0.63</td>
<td>28.22</td>
<td>10.94</td>
<td>6.66</td>
<td>172.14</td>
</tr>
</tbody>
</table>

Table 4. Mean-squared error value of the fit error. The error values for the fit of each adrenal tissue type (medulla and cortex) are calculated as the mean value across all frequency points

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Mean-squared error (MSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medulla</td>
<td>0.0552</td>
</tr>
<tr>
<td>Cortex</td>
<td>0.0463</td>
</tr>
</tbody>
</table>

https://doi.org/10.1017/S1759078723001447 Published online by Cambridge University Press
and show the mean dielectric properties of the adrenal tissue when exposed to microwaves. This behavior can lead to faster heating of the tissue and more efficient ablation. The observed temperature-dependent changes in the dielectric properties of the ovine adrenal medulla have important implications for the development of MWA technologies for hypertension treatment. The findings suggest that careful consideration of the temperature-dependent dielectric properties of the tissue is necessary to achieve an efficient and safe MWA.

Choice of animal model for preclinical testing of microwave ablation devices for adrenal ablation – a perspective from dielectric properties

The choice of an animal model for preclinical testing of MWA devices for adrenal ablation is crucial as it can greatly affect the accuracy and reliability of the results obtained. When selecting an animal model for this purpose, one important consideration is the dielectric properties of the adrenal gland and surrounding tissues. Different tissues have different dielectric properties, which can affect the way they interact with EM fields, such as those produced by MWA devices [41, 42]. Therefore, selecting an animal model that closely mimics the dielectric properties of human adrenal tissue is important for accurate preclinical testing.

Based on the comparison of dielectric properties of the adrenal medulla and cortex in Figs. 4 and 5, respectively, the dielectric properties of human adrenal glands showed notable differences compared to ovine, bovine, and porcine adrenal glands. The relative permittivity of the human adrenal cortex from a Pheochromocytoma patient was found to be in agreement with the relative permittivity of the bovine adrenal cortex. Therefore, from the perspective of dielectric properties, it can be concluded that no animal model can fully replicate the dielectric properties of human adrenal glands. To this end, factors such as the size and dielectric properties of the adrenal gland in the chosen animal model must be carefully considered to ensure that the results of the testing are relevant to the human application of the device. Moreover, while preclinical testing in animal models can provide valuable insights into the safety and efficacy of MWA devices for adrenal ablation, it is essential to confirm the results in human clinical trials.

Conclusions

First, this paper presented the ex vivo dielectric properties of the ovine adrenal glands (medulla and cortex). The dielectric properties were characterized for a frequency range of 0.5–8.5 GHz by using an OECL probe technique. A two-pole Debye model was fitted on the dielectric properties of the ovine adrenal medulla measured in this study. Second, a first comprehensive review of the dielectric properties of the adrenal glands over the microwave frequency range is presented in this study. Finally, to analyze the variations of dielectric properties of adrenal glands as a function of temperature, this study has presented the temperature-dependent dielectric properties of ovine adrenal glands.

The study found that the dielectric properties of the ovine adrenal medulla measured in this study were consistent with the literature. The study also found variations in the dielectric properties of the adrenal medulla and cortex among species. Furthermore,
based on the interspecies comparison of the adrenal gland dielectric properties, it was found that no animal model can fully replicate the dielectric properties of human adrenal glands.

Overall, this paper contributes to the growing body of research on MWA as a promising alternative to existing treatment options for adrenal gland-induced hypertension. The accurate characterization of the dielectric properties of adrenal glands, as presented in this paper, is crucial for the development and optimization of MWA technology. Future studies should address the need for further research on the temperature-dependent dielectric properties of adrenal glands for a bigger sample size, particularly in humans, to inform the development of effective MWA treatment protocols.

Acknowledgements. This publication has emanated from research conducted with the financial support of the Science Foundation Ireland, the European Regional Development Fund under grant number 13/R3/2073, and the National Institutes of Health (NIH) under grant number R01EB028848. The authors would like to extend their sincere gratitude to Dr Simone Fezzi and Dr Barry McDermott who dissected the adrenal glands included in this study.

Competing interests. The authors declare that there is no conflict of interest regarding the publication of this article.

References
Dr Grazia Cappiello received a bachelor's and master's degree in Biomedical Engineering from the University of Bologna (Italy) and a PhD in Medical Engineering from the University of Galway (Ireland). She has worked as a postdoctoral researcher in the Translational Medical Device Lab at the University of Galway. Her research was focused on the development of treatment planning for microwave hyperthermia and thermal ablation therapy, computational modeling, and applied electromagnetics. She is currently working as an R&D Engineer at Boston Scientific Corporation, Galway. Her focus is on aortic valve development.

Dr Marcin J. Krasny is an engineer with expertise in electronics and communication, specifically in embedded systems. He completed his PhD at the University of Bath, researching piezoelectric materials for energy harvesting applications. He has since worked at the University of Galway, focusing on the electrical characterization of tissues. In his previous post, he worked on an ablation assessment system for the improved treatment of atrial fibrillation. Currently, he is a research fellow at the Translational Medical Device Lab at the Lambe Institute, University of Galway, working on a project related to the assessment of catheter ablation procedures. Marcin has supervised and co-supervised several bachelor's and master's students and has authored multiple peer-reviewed scientific publications and conference proceedings in the fields of medical and bio-electronics. His interests lie in the development of medical electronic devices, including medical instrumentation, wearable devices, bio-sensors, signal conditioning, and RF data transmission of bio-signals.

Dr Eoghan Dunne is a Postdoctoral Researcher in the School of Medicine at the University of Galway and is a part of the Translational Medical Device Lab. He received a BEng in Electronic & Computer Engineering (2016) and a PhD in Electrical and Electronic Engineering (2021) from the University of Galway. His PhD was focused on using machine learning and electrical impedance tomography for monitoring bladder fullness. Since then, he has been working on a Government of Ireland Disruptive Technologies Innovation Fund (DTIF)-funded project to help design a pulsed field ablation device to treat atrial fibrillation with AuriGen Medical. In the past, he has contributed to international projects including OpenWorm c302 and the European-funded project Si Elegans. His research interests relate to electrical impedance, dielectric, and thermal properties, as well as the application of electromagnetic-based ablation and electrical impedance imaging.

Prof. Aoife Lowery is a Consultant Breast and Endocrine Surgeon at Galway University Hospital and a Professor in Surgery at the University of Galway. As a medical graduate of the University of Galway, Aoife completed her specialist surgical training on the Royal College of Surgeons in Ireland Higher Surgical Training Programme and an International Surgical Fellowship in Endocrine Surgery AP-HM (Hôpitaux Universitaires de Marseille), France. She was one of the first Clinician Scientist Fellows funded by Molecular Medicine Ireland and completed her PhD investigating microRNA expression and function in breast cancer at the University of Galway. Aoife is currently a recipient of the Irish Cancer Society Clinical Research Leadership Award and a principal investigator in the Women’s Health Initiative cancer survivorship programme co-funded by the Irish Cancer Society and the National Breast Cancer Research Institute. She is an associate director of the Irish Clinical Academic Training (ICAT) PhD programme, a clinical advisor and mentor on the BioInnovate Ireland fellowship programme and a clinical lead for the Clinical Research Facility at the University of Galway.

Dr Bilal Amin is a Postdoctoral Researcher at the School of Medicine, University of Galway, Ireland. He received his PhD in Electrical and Electronics Engineering from the University of Galway, Ireland. He did his BS in 2013, securing First Class, in Electrical Engineering from COMSATS University Lahore, Pakistan, under the auspices of the National ICT Scholarship Program. In 2015, he earned his master’s degree with distinction in Electrical Engineering from COMSATS University Islamabad, Pakistan. His current research interests are compressive sampling, microwave imaging, medical signal processing, dielectric metrology, bone health monitoring, and electromagnetic medical systems.
Dr Michael Conall Dennedy is a Consultant Endocrinologist at Galway University Hospital and a Senior Lecturer in Therapeutics at University of Ireland, Galway. He is a Galway graduate, having completed a BSc in Pharmacology in 2000, MB, BAO, and BCh in 2002, MD in Obstetrics in 2007, and PhD in Medicine in 2013. He trained through the HSE/HRB National SpR Academic Fellowship Programme, an integrated academic clinician scientist program. Following this, he completed a fellowship in endocrinology at the University of Cambridge and Addenbrooke's Hospital. He assumed his current post in February 2014. His research interests center on the pathogenesis and treatment of functional adrenal tumors, both benign and malignant. He is a member of the European Network for the Study of Adrenal Tumour Working Groups for Adrenocortical Carcinoma, Aldosterone Producing Adenomas, Phaeochromocytoma and Non Aldosterone Producing Adrenocortical Adenomas. He retains links with the Institute of Metabolic Science, University of Cambridge, and has forged collaborations with the Centre for Endocrinology, Diabetes and Metabolism, University of Birmingham. He is also affiliated with the CURAM program at NUI, Galway, and the Translational Medical Device Laboratory. He is the NUI, Galway, director for the Wellcome/HRB Irish Clinical Academic Training (ICAT) Programme and a co-recipient of this award. He is also the director of the undergraduate MB/PhD program at NUI, Galway. He is the Specialty Director for Endocrinology for the Royal College of Physicians of Ireland's, International Clinical Fellows Programme.

Prof. Punit Prakash received the BS degree in Electrical and Computer Engineering from Worcester Polytechnic Institute in 2004 and the PhD in Biomedical Engineering from the University of Wisconsin-Madison in 2008. Since 2012, he has been with the Department of Electrical and Computer Engineering at Kansas State University, where he is currently a professor and holder of the Paul L. Spanihow Professorship in Electrical Engineering. His research interests are centered on electromagnetic energy interactions with tissue, energy-based medical devices, and computational modeling. He serves as Secretary/Treasurer of the Society for Thermal Medicine, co-chair of the IEEE EMBS Summer School on Computer Modeling in Medicine, a charter member of the NIH Imaging-guided Interventions and Surgery Study section, and is past chair of the IEEE EMBS Technical Committee on Therapeutic Systems and Technologies.

Dr Adnan Elahi is a Lecturer in Medical Electronics at the University of Galway, Ireland. He holds a PhD in Electronic Engineering from the University of Galway, an MSc in Embedded Digital Systems from the University of Sussex, United Kingdom, and a BS in Computer Engineering from COMSATS University, Lahore, Pakistan. His PhD research was focused on the investigation and development of novel signal processing algorithms to improve microwave imaging of the breast. He has over 8 years of research experience in medical device development. He has previously worked as a lecturer at COMSATS University Lahore, Pakistan, and as a research associate at Computer Vision Research Group (COMVIS), Lahore, Pakistan.

Prof. Martin O’Halloran received a BE degree in Electronic and Computer Engineering from the University of Galway in 2004 and a PhD in Electrical Engineering from the University of Galway in 2009. He is currently a full Professor of Medical Electronics at the University of Galway, with a research focus on applied medical device development. In parallel, he leads Ireland’s BioInnovate program, a sister program of Stanford's BioDesign. Finally, he is a seven-time recipient of funding from the European Research Council (ERC).