




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

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Review Paper

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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 found to be 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,

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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.

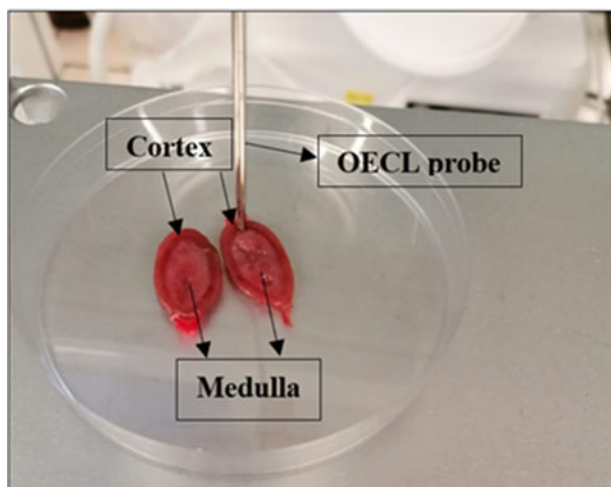


Figure 1. Photograph of ex vivo ovine adrenal gland showing adrenal cortex and medulla. The open-ended coaxial (OECL) probe is in contact with the adrenal cortex. The measurement points are labeled.

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 gland samples 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 (S_{11}) 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 S_{11} parameters to real ($\epsilon'(\omega)$) and imaginary ($\epsilon''(\omega)$) 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

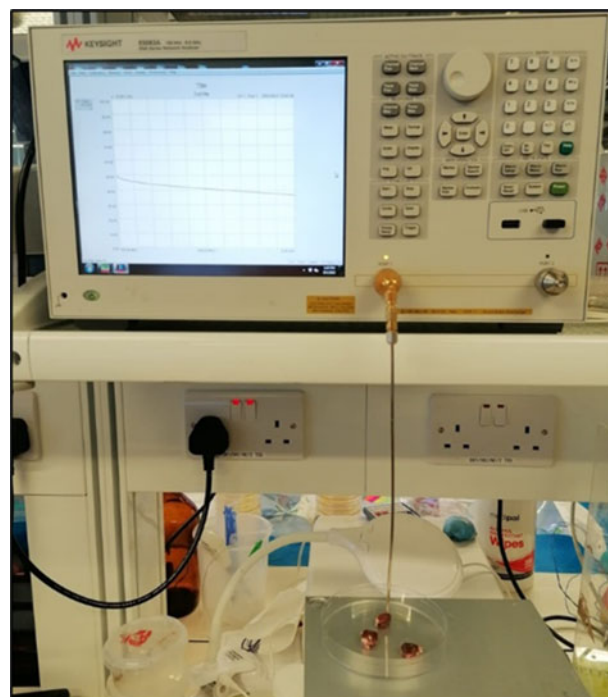


Figure 2. Dielectric properties measurement setup.

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 $22.80 \pm 0.70^\circ\text{C}$. 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

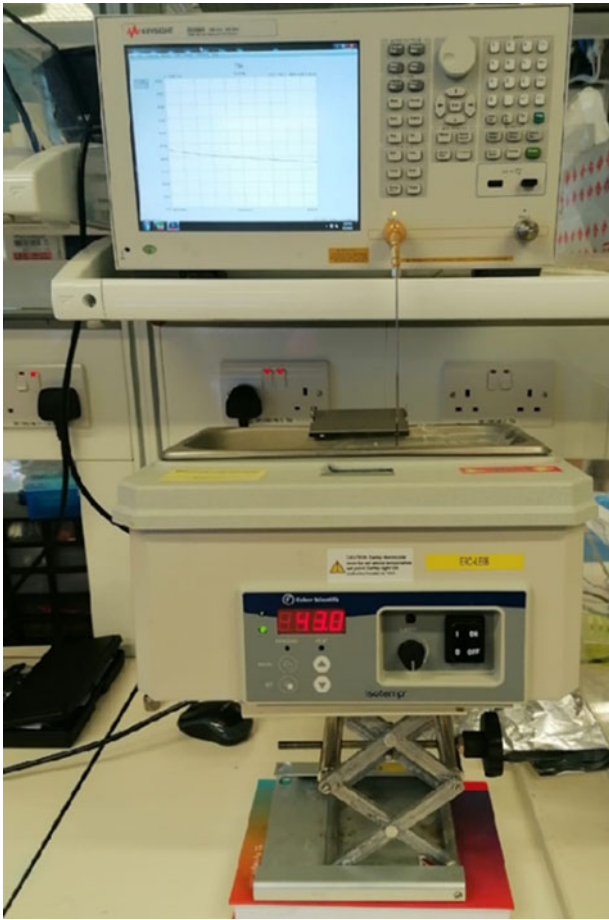


Figure 3. Temperature-dependent dielectric properties measurement setup.

was not covered during the heating process. This may have an impact on the heating rate, as covering or not covering a sample can affect how it interacts with the heating source. Moreover, the experimental conditions were kept consistent to ensure reliable results.

Measurement protocol and system uncertainty analysis

The dielectric properties measurement equipment was calibrated before each measurement session. The slim-form probe was connected directly to the VNA to avoid any errors caused by the movement of the cable. The calibration of the equipment was performed on three standard loads, including open (air), short (shorting block), and load (deionized water) [26, 27]. The mean value of the temperature of the deionized water used for calibration during the dielectric properties measurement session was $24.45 \pm 0.35^\circ\text{C}$. Once the equipment was calibrated, a validation measurement was performed by verifying the dielectric properties of 0.1 M NaCl (saline) solution at 24.90°C [26, 28]. A total of six validation measurements were performed. An estimation of the uncertainty components related to the accuracy and repeatability of the measurement system was performed for each frequency point and then averaged over the frequency range of the measurement (0.5–8.5 GHz). The uncertainty about the accuracy (UC_{ACC}) of the measurements is expressed as the average percentage difference between the measured and reference dielectric properties

data. The uncertainty in accuracy in terms of percentage is defined as follows:

$$UC_{ACC}(f) = \left(\frac{DP_{meas}(f) - DP_{ref}(f)}{DP_{ref}(f)} \right) \times 100, \quad (1)$$

where $DP_{meas}(f)$ represents the measured dielectric properties of 0.1 M NaCl solution at a specific frequency point f and $DP_{ref}(f)$ represents the reference dielectric properties of 0.1 M NaCl solution at the measured temperature as outlined by Gabriel and Peyman [29]. The uncertainty related to repeatability (UC_{REP}) 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:

$$UC_{REP}(f) = \left(\frac{DP_{meas}(f) - DP_{mean}(f)}{DP_{mean}(f)} \right) \times 100, \quad (2)$$

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 (UC_{COM}) was computed by using the standard uncertainty (UC_{STD}) values of each of the uncertainty components (UC_{ACC} and UC_{REP}). The expanded uncertainty (UC_{EXP}) 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:

$$\hat{\epsilon} = \epsilon_\infty + \sum_{p=1}^n \frac{\Delta\epsilon_p}{1 + j\omega\tau_p} + \frac{\sigma_s}{j\omega\epsilon_o}, \quad (3)$$

where $\hat{\epsilon}$ is the complex permittivity of the material, ϵ_∞ is the permittivity at the highest frequency, $\Delta\epsilon_p$ is the change in the permittivity at the p th dispersion, τ_p is the relaxation constant at the p th dispersion, σ_s is the static ionic conductivity, ω is the angular frequency, and ϵ_o 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	Uncertainty (UC) (%)				Standard uncertainty (%) $UC_{STD} = \frac{UC_{(ACC/REP)}}{DIV}$
	Parameter	Value	Probability distribution	Divisor (DIV)	
Relative Permittivity	UC_{ACC}	0.60	R	$\sqrt{3}$	0.34
	UC_{REP}	0.20	N	1	0.20
	UC_{COM}	0.39	$\sqrt{\sum UC_{STD}^2}$	-	-
	$UC_{EXT} (\lambda = 2)$	0.78	$UC_{COM} \times \lambda$	-	-
Conductivity	UC_{ACC}	4.20	R	$\sqrt{3}$	2.42
	UC_{REP}	0.80	N	1	0.80
	UC_{COM}	2.54	$\sqrt{\sum UC_{STD}^2}$	-	-
	$UC_{EXP} (\lambda = 2)$	5.08	$UC_{COM} \times \lambda$	-	-

λ = 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 γ 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:

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

where $\hat{\varepsilon}(\omega_i)$ is the measured complex permittivity at the frequency ω_i . 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]:

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

where N_f denotes the number of frequency points, $C_r(\omega_i)$ and $C_i(\omega_i)$ are the real and imaginary parts of the calculated complex permittivity, respectively, $M_r(\omega_i)$ and $M_i(\omega_i)$ are the real and imaginary parts of the measured complex permittivity, respectively, and $E_r(\omega_i)$ and $E_i(\omega_i)$ are the real and imaginary parts of the allowable error \dot{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, ε_i is the i th actual value, $\hat{\varepsilon}_i$ is the i th predicted value, and Σ 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

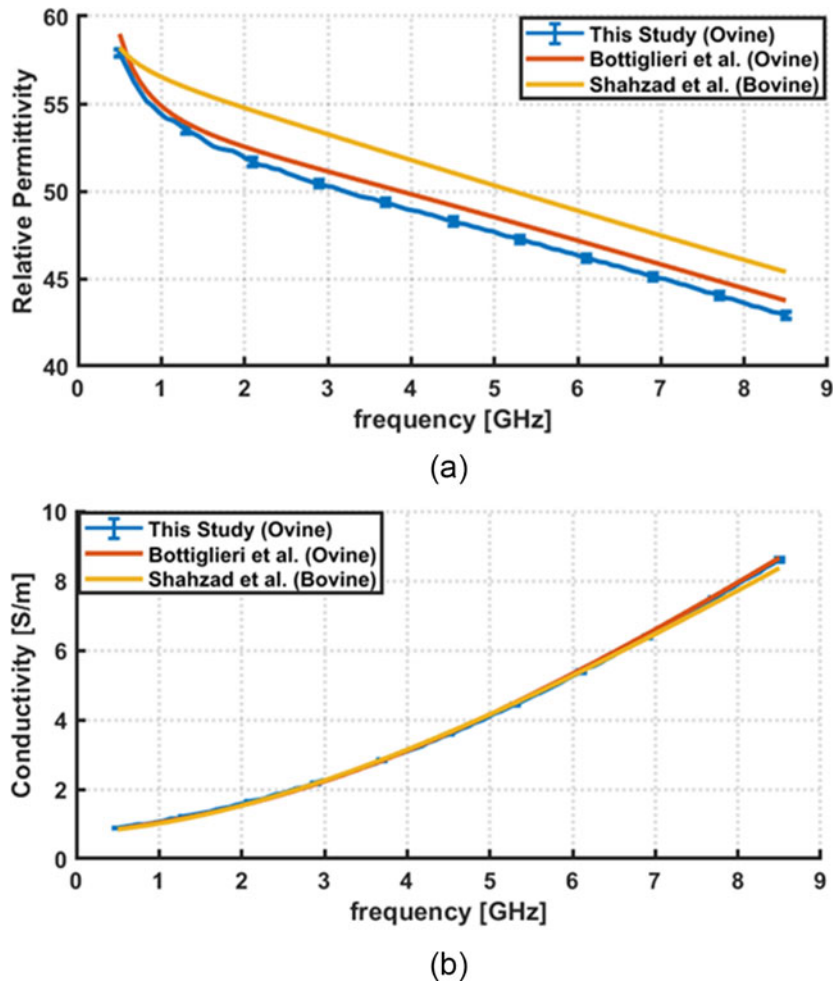


Figure 4. Comparison of ex vivo dielectric properties (a) relative permittivity and (b) conductivity for the adrenal medulla from reported studies. The dielectric properties of the adrenal medulla from ovine, bovine, and porcine do not exhibit significant variation in results.

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

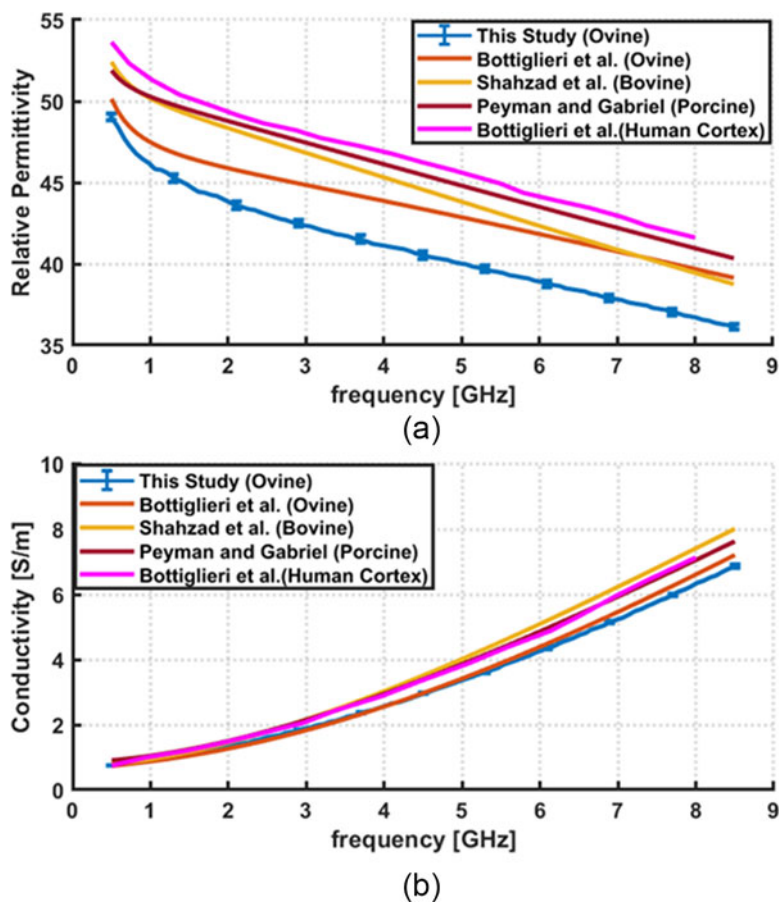


Figure 5. Comparison of ex vivo dielectric properties (a) relative permittivity and (b) conductivity for the adrenal cortex from reported studies. The dielectric properties of the adrenal cortex in human (Pheochromocytoma), ovine, bovine, and porcine do not exhibit significant variation in results.

study. The results show an average percentage difference of 10.75% and 12.83% for relative permittivity and conductivity, respectively.

- 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

Study	Species	Tissue	ϵ_∞	σ_s (S/m)	$\Delta\epsilon_1$	τ_1 (ps)	α_1	$\Delta\epsilon_2$	τ_2	α_2
Peyman and Gabriel [24]	Porcine	Cortex	3	0.62	48.2	7.06	0.18	52.1	1.95 (ps)	0
Shahzad et al. [15]	Bovine	Medulla	3.88	0.62	52.95	7.01	0.17	62.05	4.28 (ns)	0.14
		Cortex	3.57	0.46	47.08	8.33	0.16	52.31	1.69 (ns)	0.03
Bottiglieri et al. [11]	Ovine	Medulla	1.80	0.40	51.10	7.10	0.10	60.5	1.30 (ns)	0.10
		Cortex	1.00	0.40	45.30	6.40	0.10	54.60	1.7 (ns)	0.10

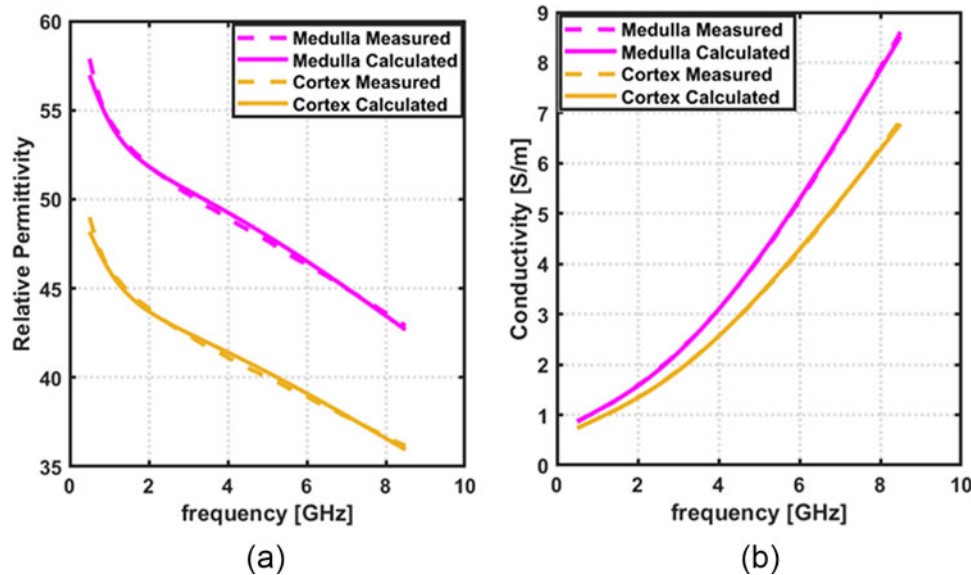


Figure 6. Two-pole Debye model parameters of adrenal medulla and cortex over 0.5–8.5 GHz frequency band: (a) relative permittivity and (b) conductivity. The measured dielectric data of the adrenal medulla and cortex (dotted lines) are compared with calculated data from the two-pole Debye model (solid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

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

Tissue	ϵ_∞	σ_s (S/m)	$\Delta\epsilon_1$	τ_1 (ps)	$\Delta\epsilon_2$	τ_2 (ps)
Medulla	14.15	0.73	37.11	10.33	7.70	186.85
Cortex	14.82	0.63	28.22	10.94	6.66	172.14

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

Tissue	Mean-squared error (MSE)	
	ϵ_r	σ
Medulla	0.0552	6.7018×10^{-4}
Cortex	0.0463	4.5789×10^{-4}

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.

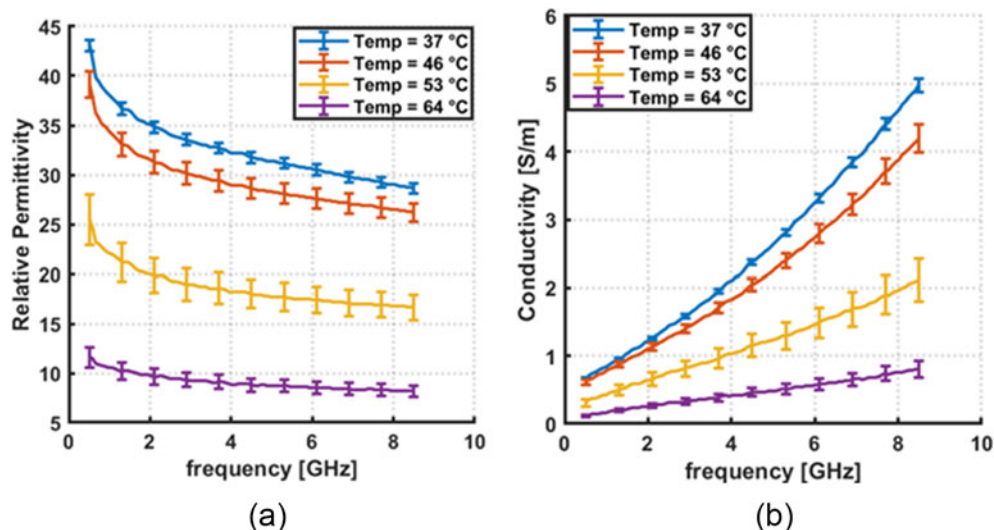


Figure 7. Temperature-dependent dielectric properties (a) relative permittivity and (b) conductivity for the adrenal medulla over 0.5–8.5 GHz frequency band. The temperature of the adrenal gland sample was raised to 37°C, 46°C, 53°C, and 64°C.

Temperature-dependent dielectric properties of adrenal medulla

This study has also investigated the temperature-dependent dielectric properties of the ovine adrenal medulla for temperatures ranging from 37°C to 64°C. 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. Fig. 7(a) and (b) shows the temperature-dependent relative permittivity and conductivity of the ovine adrenal medulla over a frequency range of 0.5–8.5 GHz, respectively. The dielectric properties were recorded at 37°C, 46°C, 53°C, and 64°C. The solid lines in Fig. 7 show the mean dielectric properties of the adrenal medulla at each temperature, while the error bars indicate the range of variation in dielectric properties. It can be observed from Fig. 7 that the dielectric properties of the ovine adrenal medulla decrease with increasing temperature. The dielectric properties tend to drop quickly after 46°C and continue to drop as the temperature is increased further and the tissue becomes more dehydrated [39, 40]. Moreover, at low temperatures, the dielectric properties of the tissue are higher, which means that more energy is absorbed by the 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 glands 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.

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

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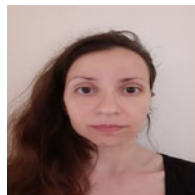
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