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Electrical Properties of Prostatic Tissues: II. Spectral Admittivity Properties

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Abstract

Purpose—The electrical properties of prostate tissues gauged at discrete frequencies provide sufficient contrast to discriminate malignant from benign prostatic tissues. The frequency dependence of these properties is also a function of tissue morphology. We evaluated the potential of this spectral dependence to provide additional diagnostic information for prostate cancer detection.

Materials and Methods—Electrical conductivity and permittivity were recorded from 50 ex vivo prostates at 31 logarithmically spaced frequencies of 100 Hz to 100 kHz. We used a well established, 4 parameter (σ_∞ , $\Delta\sigma$, f_c and α) model to describe individual spectra with each model parameter influenced by tissue morphology. We evaluated these parameters in terms of discriminatory power using ROC curves.

Results—Of the 4 spectral parameters σ_∞ and f_c were significantly greater in cancer than in benign tissues and $\Delta\sigma$ was significantly more negative in cancer than in benign tissues (each $p < 0.0001$). f_c provided the maximum discriminating power with an ROC AUC of 0.821 and 81.5% specificity at 70% sensitivity. Also, σ_∞ and $\Delta\sigma$ provided high levels of discrimination with an AUC of 0.770 and 0.782, respectively.

Conclusions—Spectral electrical admittivity properties provide sufficient levels of ex vivo cancer discrimination that may potentially enhance disease localization when prostate cancer is suspected. The development of novel technologies gauging these properties in vivo has the potential to provide new tissue characterizing tools for prostate cancer detection and identification.

Keywords

prostate; prostatic neoplasms; prostatic hyperplasia; electric impedance; spectrum analysis

We previously reported the clinical potential of using prostate tissue electrical properties for cancer detection and identification.¹ These properties, which are a function of tissue morphology, are gauged by applying a small electric current of a particular frequency between a pair of electrodes and recording the established voltage potential between another pair of electrodes. The ratio of this current and voltage represents tissue admittivity (electrical properties), which comprises conductivity (σ) and permittivity (ϵ) terms, with conductivity defined as how easily electric current passes through the medium and permittivity defined as how rapidly electric charges accumulate at membranous boundaries. In tissue these admittivity properties vary as a function of the applied frequency. In part I of our study we noted that electrical admittivity gauged at discrete frequencies provides

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sufficient contrast to discriminate malignant from benign prostatic tissues and we assessed which of these discrete frequencies would provide optimal cancer discrimination over the 100 Hz to 100 kHz spectrum.¹ However, the frequency dependence of these properties is also a function of tissue morphology. This spectral dependence, which has the potential to provide additional diagnostic information, is the basis of the current report.

A way of quantifying frequency dependence is by fitting spectral data to a parametric model of individual admittivity spectra. We report this approach using a well established 4-parameter model describing tissue frequency dependent electrical properties. We used an estimation algorithm to extract the 4 model parameters from each electrical property spectrum recorded from a cohort of 50 prostates removed after radical prostatectomy. We evaluated how well these properties discriminate cancer from noncancer tissues, compared these spectral parameters to those collected at a single discrete frequency and discuss the clinical potential of these spectral parameters.

Materials and Methods

Data Acquisition and Study Group

A custom designed probe was used to gauge electrical conductivity and permittivity from 50 ex vivo prostates at 31 logarithmically spaced frequencies of 100 Hz to 100 kHz.¹ Each prostate was sectioned into serial tissue slices at about 3 mm and approximately 2.5 mm diameter circular regions from each of 4 quadrants per slice were probed according to a systematic sampling approach. Each circular area probed was marked with pinholes to provide precise colocalization between histological assessment and recorded admittivity spectra. In all cases measurements were begun within 30 minutes after prostate removal. From the 62 data points (31 frequencies $\times$ the 2 property values σ and ϵ) gauged at each location 4 spectral parameters (σ_∞ , $\Delta\sigma$, f_c and α) were extracted using a Cole model^{2,3} to describe the recorded admittivity spectra. These spectral parameters are typically thought to represent a measure of cumulative intracellular and extracellular fluid conductivity (σ_∞), a measure of the intracellular and extracellular volume ($\Delta\sigma$), a measure of cell membrane quantity and viability (f_c) and a measure of tissue heterogeneity (α). The study protocol received institutional review board approval and informed consent was obtained from the participating subjects.

Data Modeling

Cole and Cole observed that when the permittivity of tissue is plotted as a function of the tissue conductivity, there is a characteristic arc in the complex plane that can be described by the equation, $\sigma_f + j\epsilon_f = \sigma_\infty + [\Delta\sigma/(1 + (jf/f_c)^\alpha)]$, where σ_∞ represents the conductivity at infinite frequency, $\Delta\sigma$ represents the conductivity change between high and low frequencies, f represents the applied signal frequency, f_c represents a characteristic frequency occurring at the apex of the arc, α represents how much the arc is depressed from the horizontal axis and j represents the imaginary number $\sqrt{-1}$.² σ_f and ϵ_f are the conductivity and permittivity values recorded at a particular discrete frequency, respectively. The 31 σ_f and ϵ_f values recorded at each location probed served as inputs to an estimation algorithm developed to extract the spectral parameter set, σ_∞ , $\Delta\sigma$, f_c and α . These parameter sets were extracted for each location probed using a constrained least squares minimization algorithm, similar to that previously described.⁴ Constraints were σ_∞ greater than 0 mS/m, $\Delta\sigma$ less than 0 mS/m, $0 < f_c < 1 \times 10^7$ Hz and $0 < \alpha < 1$, which represent physically realizable values. Quality of fit (q) was specified using the average distance between the fitted $(\sigma_f, \epsilon_f)_{\text{fit}}$ pair and the

measured $(\sigma_f, \epsilon_f)_{\text{meas}}$ pair using the equation, $\left(q = \frac{1}{31} \sum_{f=1}^{31} |(\sigma_f, \epsilon_f)_{\text{fit}} - (\sigma_f, \epsilon_f)_{\text{meas}}| \right)$, with q presented in mS/m.

Statistical Analysis

Tissue types composing the circular regions probed were identified by a single pathologist (AS). Regions consisting of greater than 50% of 1 tissue type were selected for analysis. In these cases each admittivity spectrum was assigned the predominant tissue type. Estimated spectral parameters were analyzed descriptively for each different tissue type and differences were evaluated by paired testing with differences considered significant at $p < 0.05$. We assessed the ROCs associated with discriminating cancer from all benign tissues grouped together by comparing AUCs. This analysis was done for each of the 4 spectral parameters to determine the discriminatory power of these properties. All tests were 2-tailed and statistical analysis was done with Stata®/IC 10.0 for Windows®.

Results

The 4 spectral parameters were extracted from the same 536 admittivity histology data sets assessed in study part I, consisting of 71 ACa, 165 BPH, 148 GI and 152 Str tissue types. Mean $\pm$ SD quality of fit was 1.08 ± 0.94 mS/m for ACa, 1.06 ± 0.52 mS/m for BPH, 0.91 ± 0.45 mS/m for GI and 1.04 ± 0.76 mS/m for Str. No significant differences were noted between any pairings ($p > 0.05$), suggesting that the model fit each different tissue type similarly.

Table 1 and figure 1 list estimated spectral parameters of each tissue type. The range of f_c for each tissue type spanned 5 orders of magnitude (0.1 to 1,000 kHz), skewing mean values toward higher frequencies. Median f_c values were approximately an order of magnitude less than the mean values and may be more representative of the true characteristic frequencies expected. The exception to this was in the ACa group, in which the mean was only twice that of the median. The upper and lower quartile ranges also showed the broader spectrum of f_c values for ACa with the inner quartile range spanning 1,172 kHz for ACa but only 93, 44 and 91 kHz for BPH, GI and Str tissues, respectively. Despite this variation the f_c of ACa was greater than that of the other tissue types in all descriptive categories.

Significant differences were noted between ACa and the other tissue types for all spectral parameters except α ($p < 0.05$, table 2). These relationships were consistent when ACa was compared to all benign tissues grouped together, and when compared to each benign tissue type individually. Specifically σ_∞ and f_c were significantly greater in ACa than in benign tissues, while $\Delta\sigma$ was significantly more negative in ACa.

The influence of Gleason score on spectral parameters in the ACa group was assessed by testing the significance of difference in mean spectral properties when primary, secondary and combined Gleason scores were assigned as the discriminating factor. Paired tests were done between a primary Gleason grade of 3 in 44 preparations and 4 in 27, a secondary grade of 3 in 40 and 4 in 29, and combined scores of 6 in 28 and 7 in 28, 6 in 28 and 8 in 13, and 7 in 28 and 8 in 13. Two secondary grade 5 and 2 combined grade 9 data sets were not included in analysis because of the small number of samples at these Gleason scores. No significant differences were noted for any parameters when the primary Gleason score was used for discrimination ($p > 0.05$). However, significant differences were observed when the secondary and combined Gleason scores were assessed. The dispersion factor α for a secondary Gleason score of 3 was significantly less than that for a secondary Gleason score of 4 ($p = 0.023$). For a combined Gleason score of 6 α was significantly less than that for a combined Gleason score of 8 ($p = 0.044$). The high frequency conductivity σ_∞ for a combined Gleason score of 6 was significantly less than that for a combined Gleason score of 8 ($p = 0.033$). The conductivity change $\Delta\sigma$ for a combined Gleason score of 6 was significantly greater than that for a combined Gleason score of 8 ($p = 0.039$).

The effectiveness of discriminating cancer from other tissue types was evaluated using ROC curves. Because similar significant relationships were observed between ACa and all benign tissue types, the spectral admittivity properties of ACa in 71 preparations were compared to those of all benign tissues together (465). Figure 2 shows ROC curves for each spectral parameter. In order of decreasing AUC f_c had an AUC of 0.821 (95% CI 0.768–0.874), $\Delta\sigma$ had an AUC of 0.782 (95% CI 0.714–0.850), σ_∞ had an AUC of 0.770 (95% CI 0.703–0.838) and α had an AUC of 0.552 (95% CI 0.483–0.621). Table 3 lists SP and property thresholds for these spectral parameters stratified by discrete SN levels. For σ_∞ and f_c threshold values represent the lower limits for obtaining the associated levels of SN and SP, while for $\Delta\sigma$ and α these thresholds represent the upper limits (fig. 1).

When high grade ACa (Gleason sum greater than 6 in 43 preparations) was compared to benign tissues, the AUC of f_c , $\Delta\sigma$ and σ_∞ increased to 0.834 (95% CI 0.769–0.898), 0.805 (95% CI 0.722–0.887) and 0.800 (95% CI 0.719–0.881), respectively, while the AUC of α decreased to 0.519 (95% CI 0.430–0.608). Conversely low grade ACa (Gleason sum less than 7 in 28 preparations) had an AUC of 0.801 (95% CI 0.717–0.885) for f_c , 0.746 (95% CI 0.634–0.859) for $\Delta\sigma$, 0.724 (95% CI 0.610–0.838) for σ_∞ and 0.603 (95% CI 0.507–0.699) for α .

Discussion

Previous investigations performed by our group^{5,6} and others^{7,8} demonstrated significant electrical property differences between ACa and benign prostatic tissues. These differences were observed at multiple discrete frequencies of 1 kHz⁵ to 80 MHz.⁸ We posed the question of whether there is more discriminatory power when spectral admittivity parameters are used instead of discrete single frequency admittivity properties. Except for the depression factor α all ACa extracted spectral parameters were significantly different from those of benign tissues, suggesting that these parameters provide a potentially high level of discriminatory power.

The most prominent spectral parameter differences were observed in characteristic frequency with a mean f_c of ACa that was 4.4 times higher than that of benign tissues. Likewise $\Delta\sigma$ was 2.2 times more negative and σ_∞ was 1.5 times more positive in ACa than in benign tissues. While it was not significant, the α of ACa and BPH appeared to be lower than that of Gl and Str tissues. These relationships stem from different morphological structures present in each identified tissue type. We have suggested that low frequency current flow is typically confined to tissue extracellular spaces because it cannot penetrate the large capacitive impedance of cell membranes.^{5,6} At higher frequencies current overcomes these membrane impedances and passes directly through the cells. The high rate of cellular proliferation in malignant prostatic tissues increases cell density, thereby increasing the volume of intracellular spaces. The increased σ_∞ in ACa suggests that intracellular conductivity may be greater than extracellular conductivity. This finding is similar to that reported by Brown et al, who observed intracellular conductivity 9.4 times higher than extracellular conductivity in cervical tissues.⁹ Conversely the decreased extracellular space in malignant tissues limits current flow at lower frequencies and leads to smaller conductivity. This coupled with a high σ_∞ potentially explains the significantly wider $\Delta\sigma$ observed in ACa. The significant contrasts in f_c arise primarily from the vastly different quantity and viability of cell membranes present in the various tissue types probed (fig. 21). Finally, α is considered a function of feature size variability, including cell size and lumen size, and approaches unity as feature size becomes more homogenous throughout the interrogated domain. Variability in cell and luminal sizes is more prominent in ACa and BPH than in Gl and Str, which potentially explains the higher α values of these normal tissues.

The observed contrasts in these spectral parameters were larger in magnitude than those observed at discrete frequencies.¹ At 90% SN the maximum SP was 49.5% for ε at 100 kHz. In this case f_c provided an 11.2% increase in SP to 60.7% at the same 90% SN, suggesting that incorporating information gauged at multiple frequencies enhances the discriminatory power of using electrical properties for ACa detection. A drawback to using these spectral parameters is that electrical properties must be gauged at a number of frequencies. This requires more complicated instrumentation that can operate over a wide bandwidth and a longer acquisition time for probing tissue. A single 31-frequency admittivity spectrum collected from a specific tissue region requires approximately 18 seconds with the impedance analyzer that we used, whereas a single frequency measurement can be acquired in less than a second. For certain clinical applications, such as needle based sensors, acquisition time may be a concern.

In a preclinical trial of the clinical usefulness of these frequency based electrical parameters to detect cervical cancer the University of Sheffield group reported an AUC of 0.652 for distinguishing CIN from normal cervical tissue.¹⁰ Despite the morphological differences between cervical and prostatic tissues we similarly suggest that these properties potentially provide a highly sensitive and specific contrast mechanism to detect ACa. In fact, the reported AUCs of f_c , σ_∞ and $\Delta\sigma$ exceed those found in CIN detection.¹⁰ Also, reported SN and SP for CIN detection are 60% and 60%, respectively. Our data suggest that at 60% SN the SP (threshold) for discriminating cancer from all benign prostatic tissues using f_c is 87.1% (206 kHz).

Also, the SN and SP for these spectral parameters exceed those reported by Thompson et al to detect any ACa in a PSA based screening population.¹¹ Even at a low PSA thresholds of 1.1 ng/ml they found 83.4% SN and only 38.9% SP. At similar 80% SN f_c provided 71.6% SP at a frequency threshold of 66.7 kHz. For clinically accepted threshold levels of 4.1 ng/ml they observed 20.5% SN and 93.8% SP. At 20% SN the SP (threshold) of σ_∞ was 98.1% (0.362 mS/m), of $\Delta\sigma$ was 98.7% (−0.302 mS/m) and of f_c was 95.3% (1.37 MHz).

The limitations of this study are similar to those discussed in detail in study part I, that is 1) in vivo and ex vivo tissues are expected to have different electrical properties due to temperature variations and lack of blood flow in ex vivo samples, and 2) in some cases the properties gauged were sampled in specimens with multiple tissue types, which influenced spectral properties.¹ Also, the current analysis was based on parameters extracted from a specific model describing the frequency dependence of electrical properties in biological tissues. Correlations between these spectral parameters and morphological features in tissue have been suggested but the relationships are complex with multiple morphological features likely influencing individual spectral parameters. Furthermore, a number of different models have been proposed to describe the dispersive features of these electrical properties.¹² While they are related to the Cole model parameters that we used, these models use a different set of parameters to describe the spectra. Despite these caveats the Cole model is well established and has been successful for describing the electrical properties of tissues other than the prostate.¹³ Also, the multifrequency electrical properties (σ_f and ε_f) used to drive parameter estimation are based on the same raw measures and provide similar discriminatory power regardless of the model used.

Conclusions

Enhanced discriminatory power was observed when spectral admittivity parameters were used instead of discrete single frequency admittivity properties to discriminate malignant and benign prostate tissues. The time to collect this multifrequency property set is longer than that required for single frequency measurements but the increased SN and SP may

warrant these longer acquisition periods. The discrete frequency and spectral admittivity properties provide levels of cancer discrimination that may potentially enhance disease localization when ACa is suspected based on current PSA based screening practices. While the data reported are based on ex vivo tissues, technology development is under way to design clinical tools to gauge these properties in vivo.^{14–16} Development of these novel technologies has the potential to provide new tissue characterization tools for ACa detection and identification.

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Abbreviations and Acronyms

ACa prostate cancer

BPH	benign prostatic hyperplasia
CIN	cervical intraepithelial neoplasia
GI	nonhyperplastic glandular tissue
PSA	prostate specific antigen
SN	sensitivity
SP	specificity
Str	stroma

Figure 1.
Mean spectral admittivity parameters. Whiskers represent SE

Figure 2.
ROC curves for 4 spectral admittance parameters

Table 1
Spectral parameter statistics

	σ_{∞} (mS/m)	$\Delta\sigma$ (mS/m)	f_c (kHz)	α
ACa:				
Minimum	96	−756	3	0.26
25th Percentile	190	−288	88	0.41
Median	248	−156	425	0.48
75th Percentile	351	−96.6	1,260	0.57
Max	925	−37	5,100	0.81
Mean	280	−194	833	0.49
SD	135	133	1,091	0.11
SE	16	16	129	0.01
95% CI	248–312	−225—−162	575–1,092	0.46–0.51
BPH:				
Minimum	84	−591	1	0.22
25th Percentile	146	−116	16	0.40
Median	168	−91	30	0.48
75th Percentile	203	−68	109	0.55
Max	667	−13	4,510	0.78
Mean	183	−106	261	0.47
SD	70	69	690	0.10
SE	5	5	54	0.01
95% CI	172–194	−117—−95	155–367	0.46–0.49
GI:				
Minimum	97	−496	1	0.31
25th Percentile	154	−106	18	0.46
Median	182	−84	31	0.53
75th Percentile	205	−67	62	0.59
Max	571	−15	2,740	0.70
Mean	190	−98	146	0.52
SD	63	62	382	0.10
SE	5	5	31	0.04
95% CI	179–200	−108—−97	84–208	0.51–0.54
Str:				
Minimum	77	−265	0.1	0.04
25th Percentile	145	−81	10	0.42
Median	175	−55	23	0.52
75th Percentile	202	−33	101	0.61
Max	354	−5	4,690	1.00
Mean	177	−64	165	0.53
SD	49	49	489	0.18
SE	4	4	40	0.01

	σ_{∞} (mS/m)	$\Delta\sigma$ (mS/m)	f_c (kHz)	α
95% CI	169–185	–72––56	87–244	0.51–0.57

Table 2
Significance of mean spectral parameter differences in ACa vs benign tissue

Parameter	ACa p Value (paired t test equal variances) [*]			
	Vs Benign	Vs BPH	Vs GI	Vs Str
$\sigma_{\infty}^{\dagger, \ddagger}$	<0.0001	<0.0001	<0.0001	<0.0001
$\Delta\sigma^{\ddagger, \$}$	<0.0001	<0.0001	<0.0001	<0.0001
$f_c^{\dagger, \ddagger}$	<0.0001	<0.0001	<0.0001	<0.0001
α	0.0886 [‡]	0.1826 ^{\$}	0.087 [‡]	0.1072 [‡]

* In 536 data sets with histologically confirmed, greater than 50% individual tissue concentration.

[‡] Mean ACa less than mean tissue type.

[‡] Significant (p <0.05).

^{\$} Mean ACa greater than mean tissue type.

Table 3
SP and thresholds to differentiate ACa from benign tissue at stratified SN

ACa vs Benign	% SN			
	90	80	70	60
σ_{∞} :				
% SP	27.7	58.7	73.8	85.2
Threshold (mS/m)	151	183	202	222
$\Delta\sigma$:				
% SP	28.8	63.7	81.3	86.0
Threshold (mS/m)	-61	-92	-114	-133
f_c :				
% SP	60.7	71.6	81.5	87.1
Threshold (kHz)	41.3	66.7	139	206
α :				
% SP	15.1	28.6	38.1	52.9
Threshold	0.62	0.57	0.55	0.50