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Preliminary Study of Fibrotic Cardiac Tissues Characterization Using Impedance Spectroscopy

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Abstract— This paper presents a preliminary study of impedance spectroscopy using cardiac pacing leads for tissue characterization. The results highlight the possibility to discriminate the tissue nature via a statistical analysis of the impedance model parameters.

Keywords— Bioimpedance spectroscopy; impedance modelling; electrode-tissue interface; cardiac fibrosis

I. INTRODUCTION

Long-term efficiency of implantable devices is affected by fibrosis, an inflammatory response that encapsulates over time the implant [1]. In the case of cardiac active implants, this phenomenon has several consequences: fibrotic adherences, higher stimulation thresholds, lower battery lifespan. A major breakthrough occurred in the 1980’s, with the development of steroid-eluting leads that increased compatibility between the electrode and the tissue [2]. Despite this technical advance, fibrosis remains an issue for the cardiac leads, especially for the latest implants such as leadless pacemakers and resynchronization devices. Electrical impedance spectroscopy (EIS) is a well-known technique for characterizing living tissues [3] and fibrosis is a tissue remodeling that should have a signature in EIS spectrum. Preliminary studies showed that *in situ* impedance measurements in myocardium or epicardium allowed discriminating healthy and infarcted tissue [4], [5].

Our long-term objective is to take advantage of the already implanted pacing device, to investigate electrode-induced cardiac fibrosis by local impedance measurement. We present here a preliminary study conducted with human cardiac leads on *ex vivo* swine cardiac tissue. In this first step, the goal is to obtain a reference database of bioimpedance measurements to better choose the frequency range of interest for further characterization and to analyze the impedance differences between normal tissue and tissue containing more collagen. Indeed, collagen is one of the main components of the extracellular matrix which is abundantly produced in the fibrosis development [6]. To analyze the results, we fitted the data with an electrical equivalent model and highlighted significant differences in the statistical analysis.

II. BIOIMPEDANCE MEASUREMENTS

A. Material

The measurements were performed with the lab instrument Solartron 1260 (Ametek, USA), an impedance spectrometer largely used for bioimpedance measurements, and a human cardiac lead, Sprint Quattro Secure 6947M (Medtronic, USA), which is a pacing/defibrillating lead. We focused on the pacing termination. We used *ex vivo* left ventricles of young swine (Large White, 40±5kg) to perform the measurements (Figure 1).

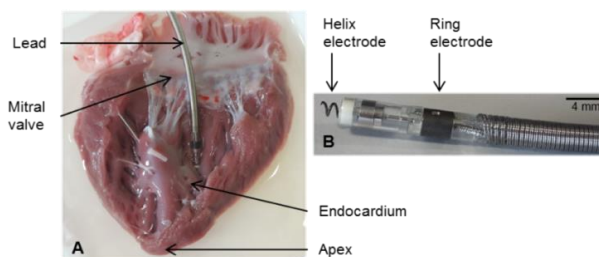


Fig. 1. A) Photograph of a swine left ventricle with the Sprint Quattro Secure 6947M lead placed for the measurements in ‘healthy’ tissue, B) Photograph of the extremity of the Sprint Quattro Secure 6947M lead.

B. Protocol

The measurements were done at a 100 mV voltage level, with a logarithmic frequency sweep from 1MHz to 0,1Hz, with 10 points per decade. Each measurement was repeated five times and the mean of these five measurements is calculated. The ventricle was immersed in a cardioplegic solution (in mM: 110 NaCl, 1,2 CaCl₂, 16 KCl, 16 MgCl₂, 10 NaHCO₃, 10 glucose) and placed on ice during the measurements. We performed these *ex vivo* measurements in two different endocardial regions of the ventricle: the ‘healthy’ lateral wall and a more ‘collagen’ rich region near the basal region and auriculo-ventricular ring. The first region is where the lead is placed in Figure 1, and the second one is the white region just above the mitral valve in Figure 1.

C. Results

The impedance magnitude and phase graphs for the ‘healthy’ and the ‘collagen’ regions are shown in Figure 2.

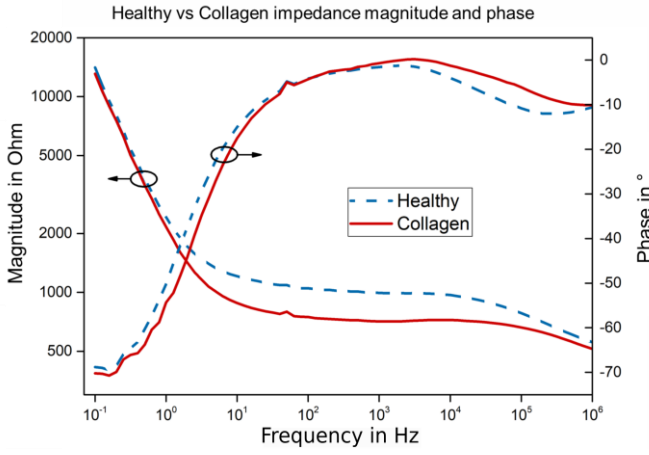


Fig. 2. Magnitude and phase of impedance. Each curve is the mean of $N = 6$ measurements (red for ‘healthy’ region, green for ‘collagen’ region). The standard deviation error bars are represented at 1 kHz for the magnitude and at 100kHz for the phase.

As we could expect, the curves exhibit the electrode-tissue pseudo-capacitive behavior of the double-layer effect below 10 Hz, a resistive plateau in the central region [10 Hz-10 kHz], and a second cut-off region around 10 kHz. In the resistive region, a significant shift the impedance magnitude is observe, indicating a higher conductivity of the ‘collagen’ region, compared with the ‘healthy’ tissue. Such a difference has already been observed between healthy and ischemic cardiac tissues [5]. The phase presents also a significant difference in the 100 kHz region.

III. MODELLING AND ANALYSIS

A. Impedance model

As we carried out the two-point measurement technique on a wide frequency range, the impedance equivalent model can be considered as the electrode-tissue impedance (Z_{elec}) in series with the tissue impedance (Z_{tissue}). Z_{elec} is dominant at low frequencies, Z_{tissue} at higher frequencies. Each component could be represented the Cole equation or an equivalent model with CPE elements (Constant-Phase elements) [7][8]. Different models have been considered for the fitting, and, in our frequency range that excludes extremely low and high frequencies, the model that provided always the best fit is described in equation (1). R characterizes the tissue resistance, (f_{α} , α) the CPE of the electrode-tissue interface and (f_{β} , β) the CPE of the extracellular-intracellular interface.

$$Z = R \cdot \frac{1 + \left(\frac{jf}{f_{\alpha}}\right)^{\alpha}}{\left(\frac{jf}{f_{\alpha}}\right)^{\alpha}} \cdot \frac{1}{1 + \left(\frac{jf}{f_{\beta}}\right)^{\beta}} \quad (1)$$

B. Identification method

The model was identified using Non-Linear-Least-Square method on experimental data. In case of no convergence, a second identification using a gradient-descend was used. For both methods, the objective function was set to the Root-Mean-Square error of the distance between measured and modeled data. Finally, the NRMSE (Normalized Root Mean Square Error) did not exceed 2%.

C. Statistical analysis

We used the Wilcoxon-Mann-Whitney to compare the five model parameters of the ‘healthy’ and ‘collagen’ conditions. Statistical analysis was performed using R (R Core Team, 2017). The result is presented in Figure 3.

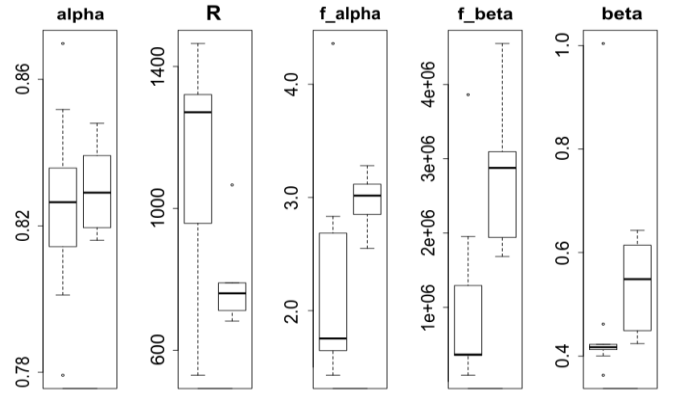


Fig. 3. Statistical analysis results presented using whisker box diagrams, for each diagram the left box represents the healthy data and the right one the collagen data. A p-value < 0.05 was considered statistically significant.

No difference can be observed in the distribution of the parameter α , which median value is 0.83. This result is not surprising as α is mainly related to the surface roughness of the electrode [8]. Distribution of parameter R is significantly different between the both conditions, with a p value of 0.03, a result consistent with the decrease in impedance magnitude observed in Figure 2 around 1 kHz; this implies the significant difference observed in distribution of parameter f_{α} . The parameters β and f_{β} also exhibit a significant difference between the both conditions that requires extending the frequency band of the measurement to be further analyzed.

IV. CONCLUSION

This preliminary investigation demonstrates that EIS reveals clear differences between normal myocardium and tissue containing more collagen, measured with human cardiac pacing leads. The next steps will be to characterize more realistic fibrotic tissue as well as perform EIS measurements in perfused cardiac tissue, a condition mimicking the *in vivo* beating behavior.

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