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Four-Point Electrode Measurement of Impedance in the Vicinity of Bovine Aorta for Quasi-Static Frequencies

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Results are presented here of experimental measurements using a four-point electrode technique to measure the complex impedance of bovine aorta submerged in Ringer's solution. Impedance measurements were taken at 250 μm intervals, ranging from 0 (the electrode directly on the surface of the tissue) to 10 mm. Frequencies ranged from 1 kHz to 10 MHz. Throughout this range, the measured impedance changed by an average of 400% when the electrode was 10 mm from the tissue as compared to when the electrode was in direct contact with the tissue. The change in impedance made it possible to determine when the electrode made contact with the arterial wall. Bioelectromagnetics 26:54–58, 2005.

Key words: conductivity; coronary heart disease; ischemia; sensor

INTRODUCTION

Coronary heart disease (CHD) is the deadliest disease in the United States, causing nearly one of five deaths. This year, approximately 1.1 million people in the US will have a new or recurrent coronary attack, and 45% of these people will eventually die as a consequence [American Heart Association, 2001]. The primary cause of CHD is the presence of atherosclerotic lesions. These lesions restrict blood flow to the myocardial tissue, causing localized ischemia, which can lead to the disruption of the heart's action potential, causing ventricular fibrillation. Ischemia can also lead to rupture of the ventricle wall or a fatal decrease in the amount of cardiac output.

There have been a number of tools developed to characterize CHD. Most of the diagnostic tools available, such as electron beam computed tomography (ECT), trans-thoracic and trans-esophogeal ultrasound, and positron emission tomography (PET), noninvasively assess the damage caused by CHD. They do not characterize the type of lesions within the arterial system. There are two invasive procedures, angiography and intra-vascular ultrasound (IVUS) that can, to a limited extent, characterize lesions in situ. Though these procedures can assist the diagnosis, they can only generally characterize morphology. It is very difficult to draw conclusions as to the type and stability of the lesion from the data these procedures provide. Although there are great strides being made to determine the extent of CHD, there is still an urgent need for tools that can be used to aid the cardiologist in the diagnosis and treatment of CHD.

The search for methods to better characterize cardiovascular lesions lies at the forefront of modern cardiovascular research. Extensive research has been conducted measuring the electrical impedance of ischemic tissue [Casas et al., 1999; Schwartzman et al., 1999; Cascio et al., 2001; Howie et al., 2001; Cao et al., 2002; Semenov et al., 2002]. This research has allowed for the development of techniques that aid in characterization of ischemic tissue and cardiac ablation, techniques, which have been included in a number of medical devices (i.e., inventions described in US patent numbers 6501983 and 6604000).

Surprisingly, however, little work has been done to characterize electrical parameters, such as conductivity and permittivity, of cardiovascular lesions [Slager et al., 1992; Konings et al., 1997]. Knowledge of lesion

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parameters and how they vary as a function of frequency, lesion type and proximity to an electrode could assist greatly in the development of a technique that could identify the source of ischemic tissue. In addition to characterizing diseased tissue, impedance measurements could be used to detect normal arterial tissue. This type of measurement would, for example, be invaluable in measuring the lumen diameter of undiseased tissue. Used in conjuction with angiography and as part of an angioplasty procedure, bioimpedance measurements could be used to help properly size stents for placement near lesions.

The research described in this article found that impedance measurements varied significantly as a probe approached the intima of undiseased arterial tissue and that, using this characteristic, it may be possible to use a catheter to detect the intimal boundary of an artery in situ.

MATERIALS AND METHODS

The measurements were conducted using bovine aortic tissue submerged in a Ringer's solution (137 mM NaCl, 5.6 mM KCl, and 2.25 mM $CaCl_2$). For purposes of comparison, two types of electrode were used for this study. The body of the first electrode, known hereafter as electrode 1, consisted of a Teflon^{TM} rod; four pure platinum wires were exposed as points on the bottom of the rod. The two outer current source points were 8 mm apart and the inner voltage measurement points were 5 mm apart. The exposed portion of the wires was 6 mm in length and 0.5 mm in diameter. The second electrode, known hereafter as electrode 2, consisted of four 0.5 mm platinum wires completely submerged in a long cylinder of epoxy, with each wire separated by a distance identical to the first electrode. To expose the wires, approximately 1 mm of the bottom face of the epoxy cylinder was machined off, revealing 4 ''dots'' of platinum flush with the bottom surface.

The impedance measurements were performed by connecting the electrode to an Agilent 4294A Impedance Analyzer via a front-end differential amplifier. The amplifier used for this application was an Analog Devices 8130 amplifier, shown integrated into the measurement circuit in Figure 1. By setting the gain of the amplifier to 1, the differential voltage V_{IN} was equal to the amplifier's V_{OUT}. The input impedance of V_{IN} was 1 MΩ. The current was injected into the samples by the 4294A through the outer points of the electrodes, and the voltage measuring inner points of the electrodes were connected to the 4294A via the front-end [Gersing, 1991]. The apparatus was calibrated to minimize the effect of stray capacitance and inductance by measuring the complex impedance of three calibration resistors.

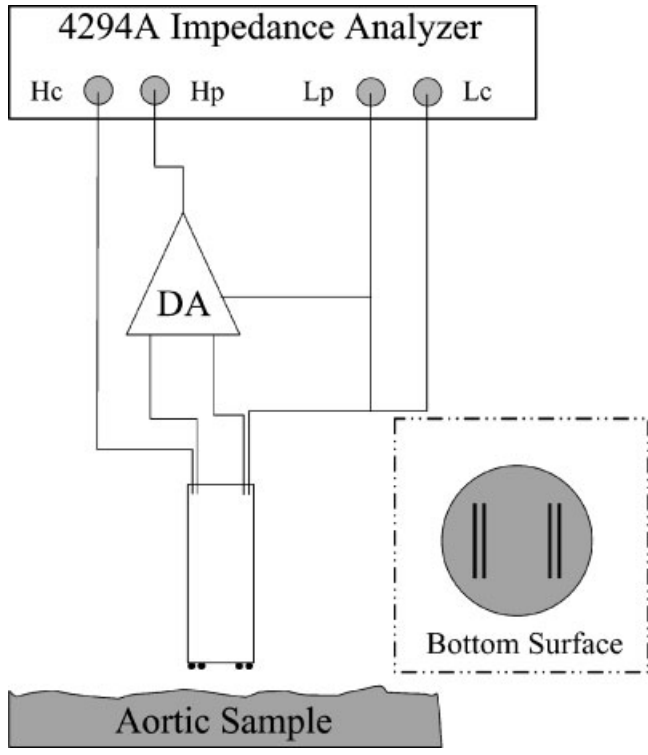

Fig. 1. Schematic of the measurement apparatus. When the electrode was in contact with the sample, a known current went through the sample via the "Hc" terminal. The resulting differential voltage was then transmitted through an Analog Device 8130 high impedance differential amplifier (DA) and measured by the "Hp" terminal. The "Lp" and "Lc" terminals were maintained at virtual ground by the 4294A autobalancing bridge, which was the reference voltage used for the DA. The inset shows the placement of the points on electrode 1 (see text).

The resistors were chosen to approximate zero impedance, infinite impedance, and impedance in the range of the measurements [Torrents and Pallàs-Areny, 2002].

Six fresh aortic samples were obtained from Wolverine Packing Company (Detroit, MI) and the impedance of each sample was measured within 10 h of sacrifice. Prior to measurement, the samples were stored in the Ringer's solution at 4 °C. The samples were prepared for measurement by making an incision on one side along the length of the sample. When the samples were measured, they were brought to room temperature and laid flat in a Teflon holder, with the intima side up. The samples were covered with Ringer's solution to a depth of 3 cm. Finally, the electrode was placed such that the platinum wire just touched the surface of the tissue. The complex impedance, $R + \mathbf{j}X$, was measured between 1 kHz and 10 MHz. The electrode was subsequently moved away from the sample in increments of approximately 250 μm, and the complex impedance was measured at each point.

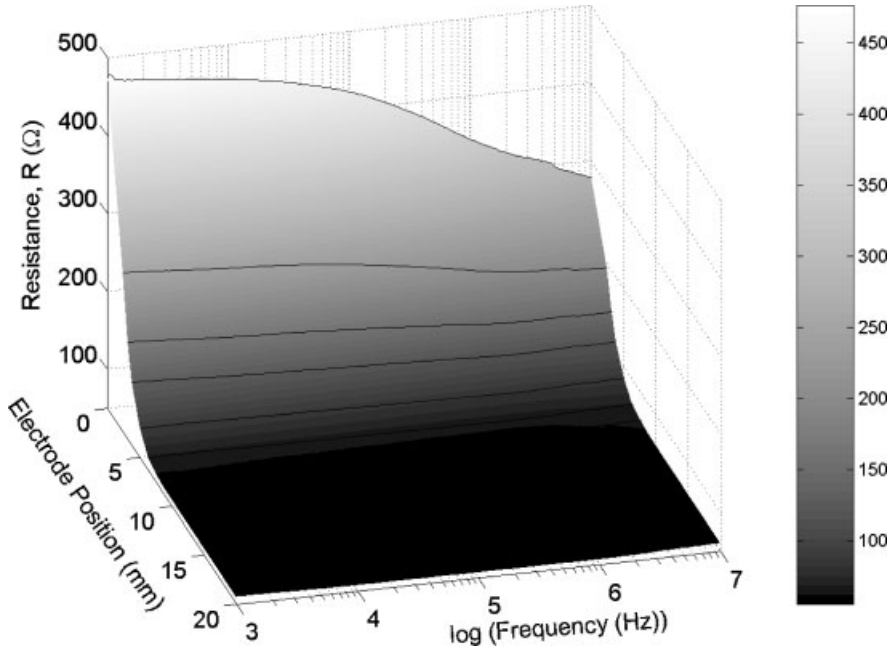

Fig. 2. Resistance measured by the four-point electrode as a function of frequency and position. The black lines represent the measurement taken at each electrode position. The zero electrode position represents direct contact with the intima of the aorta.

RESULTS

Figure 2 shows the results of the resistance measurements for a typical sample, as measured by electrode 1. The surface plot shows the resistance measured by the electrode as a function of frequency and position. When the electrodes were far away from the sample, the impedance measured by the electrode was that of the Ringer's solution only. The measured resistance of the solution was 54 Ω and the measured reactance was negligible. As the electrode was moved closer to the sample, more of the electric field generated by the outer points of the electrode impinged upon the sample, causing an increase in the impedance measured. When the electrode assembly actually touched the tissue, a portion of the surface area of the wire points was in contact with the tissue, while the other portion was in contact with the saline. The average resistance of the samples measured by electrode 1 for the condition when the electrode first made contact with the tissue is shown in Figure 3. The resistance of the sample is shown as a function of frequency, as well as the upper and lower sample standard deviation. The deviation in the measured impedance can be attributed to both the aortic tissue and the surrounding Ringer's solution. The variation between various samples may be attributed to slightly varying contact conditions, as well as sample-to-sample variations in histological structure.

Of primary interest in this study is how the resistance changes as a function of the electrode position. Figure 4 shows a scatter plot of the resistance measured by electrode 1 as a function of position at 1 MHz for each of the six samples. The solid line represents a cubic curve fit of the samples for measurement values less that 6 mm. As the curve reveals, the resistance increases slowly in the range of 4–6 mm, but changes sharply as

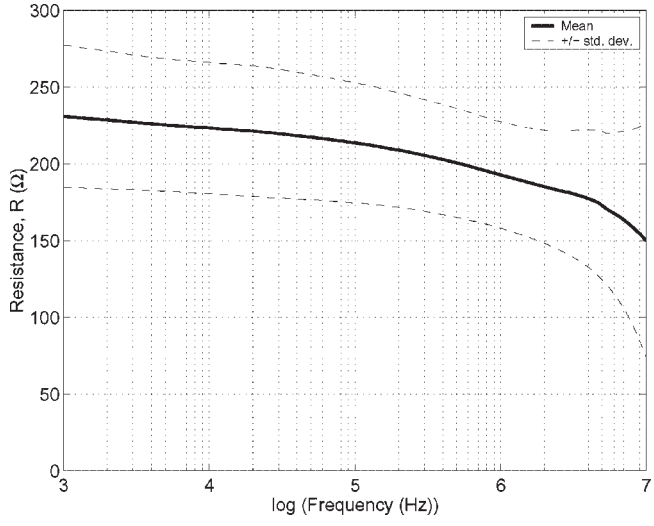

Fig. 3. Average of the measured resistance of the six samples, when electrode 1 is in contact with the aortic tissue.

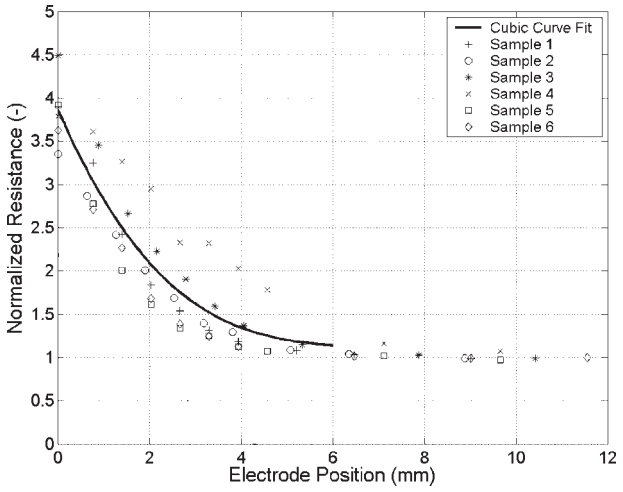

Fig. 4. Resistance as measured by electrode 1 at 1 MHz. In this case, the resistance is normalized to the resistance measured in the far field of the apparatus, 52.4 Ω. The data are fit with a third degree polynomial.

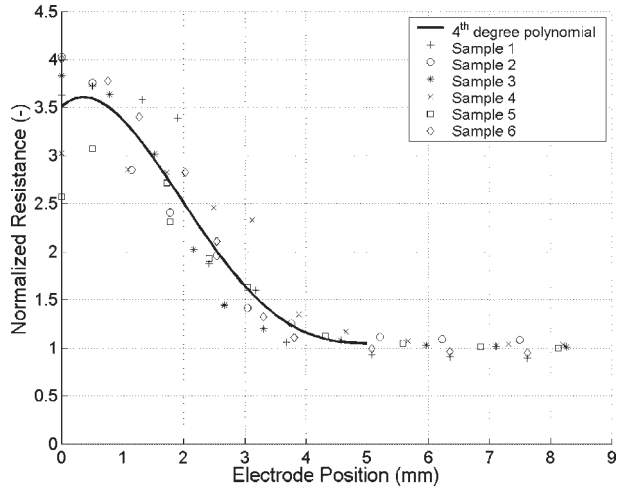

Fig. 5. Resistance as measured by electrode 2 at 1 MHz. In this case, the resistance is normalized to the resistance measured in the far field of the apparatus, 227.55 Ω. The data are fit with a fourth degree polynomial.

the electrode draws closer to the tissue. The trend seen in this figure, for 1 MHz, is similar for all frequency measurements between 1 kHz and 10 MHz. The trend was not as prominent in the reactance measurements because the values were quite small.

The results show a clear change in the measured impedance, as the four-point electrode draws closer to arterial tissue. The measured resistance changes by nearly 400%, as the electrode moves from being purely immersed in the saline to a point where it touches the aortic tissue. The change in reactance is not as large, but is still significant. It may be possible to use the change in resistance in vivo to determine the proximity of a four-point electrode with respect to an artery wall. Moreover, the change in resistance could also be used to determine whether the electrode has made contact with the wall or, possibly, with a lesion.

Even though the impedance measured changes sharply with electrode position, the electrode geometry used for this experiment would probably be inadequate to definitively determine that contact has been made. Ideal electrode geometry would elicit a ''step-change'' in response to contact with the arterial wall; that is, the electrode would only measure a significant change in impedance when making contact with the wall. The impedance would then remain approximately constant as the arterial wall deformed. With this type of electrode response, the point of contact could be made with much greater precision.

Electrode 2 was constructed for the purpose of creating this step-change characteristic. The electrode dots were flush with the surface, such that when the electrode was in contact with the intima, the electrode was completely surrounded by the tissue. Figure 5 shows the resistance measured by electrode 2, as it approaches the intima of the bovine aorta. When considering the measurement by electrode 2, the resistance ceases to change at a point approximately 0.5 mm from the intima, indicating a contact condition. Between 0 and 0.5 mm, the tissue is likely being compressed by the electrode, causing the electrode to measure the same approximate values.

DISCUSSION

The absolute values measured by electrodes 1 and 2 are quite different due primarily to the different geometry of the electrodes, but the percent change in resistance between measurements taken far away from the sample as compared to those taken in contact with the intima is similar for the two electrodes. In Figure 6, the curve fit of the normalized data for both electrodes changes about 400% from the far field measurement to contact with the intima. However, there are important distinctions between the two measurements. First, the measured resistance of electrode 1 begins to change before electrode 2 (6 mm vs. 5 mm away from the intima). Second, electrode 2 shows more of a step-change than electrode 1. For half of the samples measured by electrode 2, the impedance generally decreases or remains the same as the electrode moves further into the intimal wall (from 0.5 to 0 mm). For the remaining samples, the impedance does seem to increase monotonically. The fourth order polynomial fitted to the data was not motivated by a theoretical development, but rather to highlight the general trend of

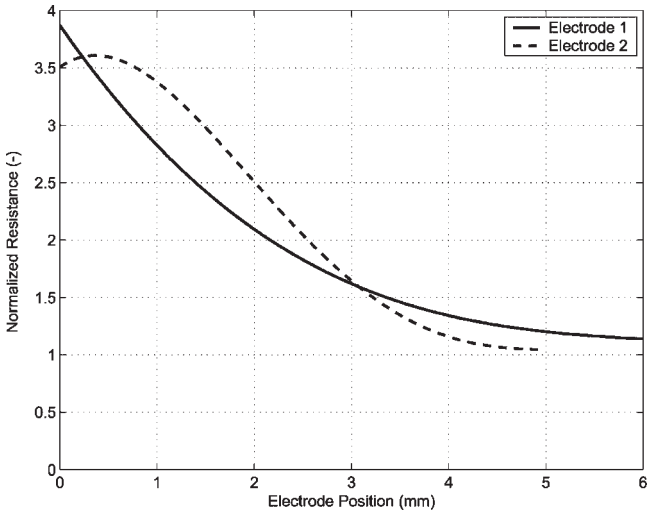

Fig. 6. Comparison of the measurements of electrode 1 and 2. The curves represent the curve fits of the normalized data for each electrode, at 1 MHz.

a ''plateau'' after the electrode makes contact with the intima. In realistic physiological conditions, without the presence of the Teflon backing, the measured impedance would probably not continue to increase, as the electrode would be surrounded by biological tissue. In the current experiment, the measured impedance may continue to increase as the electrode approaches the higher impedance Teflon.

The polynomial curves fitted to the data would seem to indicate that electrode 2 is, in general, more suited for determining contact with the intima. Further improvements could be realized if the electrode spacing was made much smaller, perhaps by utilizing microfabrication techniques. Smaller electrode spacing would allow for greater resolution as the current density, which affects the measured resistance, would not extend out as far from the surface of the electrode [Stiles and Oakley, 2003].

The research shown here represents the first step towards a technique that could be used to measure the coronary artery diameter proximal to the lesion. The technique would involve the use of multiple four-point electrodes mounted on the outer circumference of an angioplasty balloon. The diameter could be determined by continuously measuring the impedance at each electrode on an expanding balloon in the artery. Contact would be confirmed when the impedance increases sharply. In addition to measuring the diameter of a coronary artery, an electrode could be placed in contact with a lesion. Once in contact, the lesion could be characterized by measuring its complex impedance. The constituents comprising the lesion (lipids, collagen, smooth muscle cells, calcium) vary [Stary et al., 1995], as do the permittivity and conductivity of each constituent [Gabriel et al., 1996]. The constituents comprising the lesion would, depending on the morphology, alter the resistance and capacitance of the lesion and thus, would also alter the measured complex impedance by a four-point electrode.

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