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Risk Analysis and Detection of Thrombosis by Measurement of Electrical Resistivity of Blood*

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Abstract— **Monitoring of thrombogenic process is very important in ventricular assistance devices (VADs) used as temporary or permanent measures in patients with advanced heart failure. Currently, there is a lack of a system which can perform a real-time monitoring of thrombogenic activity. Electrical signals vary according to the change in concentration of coagulation factors as well as the distribution of blood cells, and thus have potential to detect the thrombogenic process in an early stage. In the present work, we have made an assessment of an instrumentation system exploiting the electrical properties of blood. The experiments were conducted using bovine blood. Electrical resistance tomography with eight-electrode sensor was used to monitor the spatio-temporal change in electrical resistivity of blood in thrombogenic and non-thrombogenic condition. Under non-thrombogenic condition, the resistivity was uniform across the cross-section and average resistivity monotonically decreased with time before remaining almost flat. In contrary, under thrombogenic condition, there was non-uniform distribution across the cross-section, and average resistivity fluctuated with time.**

I. INTRODUCTION

The emergence of implantable ventricular assistance devices (VAD) has brought a better quality of life to the patients with advanced heart failure, and has allowed them to leave the hospitals and return to their homes [1]–[3]. When blood comes in contact with artificial surface, unlike the natural system of the body, it tends to clot more than normal [4], [5]. The designers of artificial heart pumps, including some of the present authors, have paid maximum attention to minimize the compatibility problem due to design [6]–[9]. In spite of those efforts, there is always a risk of thrombosis. Due to this, regular anti-coagulation medication is inevitable for LVAD implanted patients [3], [10], [11]. But, consistent use of anticoagulants can be dangerous too. For example, it can cause increased bleeding after injury. Such a complication could be minimized if optimum amount of an anticoagulant could be administered [12]. For optimum administration of anticoagulant, the real-time risk analysis of thrombosis is necessary. Most of the current coagulation tests to determine the risk of thrombosis are offline tests. It is not practical, technically as well as economically, to carry out such tests easily on a regular basis.

In this context, Yasuda et al. [13] and Oshima et al. [14] proposed some optical techniques for the monitoring of prethrombus blood. These works were focused on the study of the behavior of erythrocytes and resulting optical response of clotting blood. The works were better than earlier works based on ultrasonography [15], [16] which were mainly able to detect the stage of embolism. However, none of these methods can detect the change in blood protein concentration which trigger the thrombosis. Moreover, the bio-compatible coatings, which block the optical passage, make the practical realization of such a sensor difficult. Additionally, the use of optical source and corresponding signal conversion system add the burden to the size of implantable VADs. In such a situation, the authors believe that the electrical method can be a suitable alternative. Electrical methods, which can even sense the change in protein concentration, make the early detection possible. The existing LVADs, which are operated by electrical energy and controlled by various electronic circuits, can accommodate an electrical sensor easily. The electrical properties of the blood are successfully exploited in some clinical applications [17], [18], and thus have potential to reveal the important clinical properties in relation to risk of thrombosis. In the presented work, we have made an assessment of the change in electrical resistivity of blood in thrombogenic and non-thrombogenic conditions.

II. THEORETICAL REPRESENTATION

The electrical properties of the blood are broadly defined by the electrical properties of the plasma and red blood cells (RBCs). Plasma can be considered as a resistive component while RBC membrane acts as a capacitor. Similarly, intracellular space of the RBC acts as a resistive component. These components can be represented as parts of a electrical circuit as shown in figure 1 [19]. In the very low frequency alternating electrical field (< 1 MHz), where electrical conductivity of the membrane is very low, the equivalent resistivity of the blood can be represented by equation 1 based on Maxwell-Fricke formulation of electrical behavior of the suspension of ellipsoidal particles [19], [20].

$$\rho_b = \rho_p \frac{1 + KV_{con}}{1 - V_{con}} \quad (1)$$

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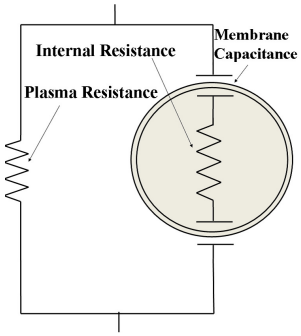


Fig. 1. Electrical Representation of Blood

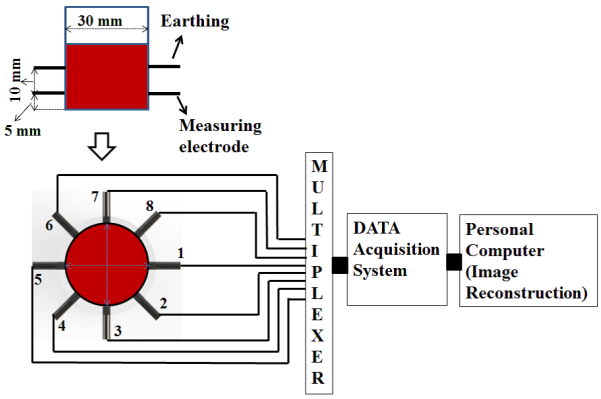


Fig. 2. Experimental Setup

In the equation, ρ_b and ρ_p represent the resistivities of the whole blood and plasma respectively. V_{con} is concentration of red blood cells and K is a variable that depends upon geometry and orientations of RBCs.

During thrombosis, the change in resistivity of plasma is expected due to change in the concentration of coagulation factors. For example, an earlier study has shown important relationship between fibrinogen (a prominent coagulation factor) and electrical resistivity of blood [21]. The change in resistivity which is triggered by change in coagulation factors is very important to analyze the risk and detect the thrombogenic process in an early stage. Similarly, thrombogenic process results in the change in distribution of blood cells which ultimately affects the volume concentration (i.e. V_{con} in the above equation) at particular location. Hence, spatio-temporal visualization of the resistivity change in the blood can reveal the risk and state of thrombogenic process. The objective of this work is to monitor the spatio-temporal change in the electrical resistivity of blood under thrombogenic condition. These changes are visualized by using electrical resistance tomography technique (ERT) [22], [23]. An ERT technique produces a cross-sectional image showing the distribution of electrical resistivity of the contents in the channel/container from measurements taken at the boundary of the channel/container.

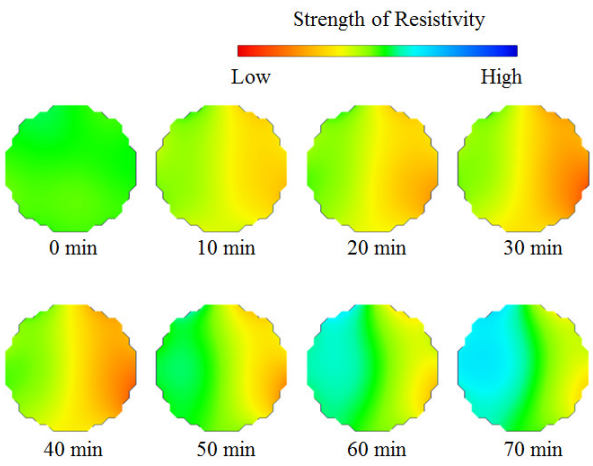
III. Experiments and Results

A. Experimental Setup

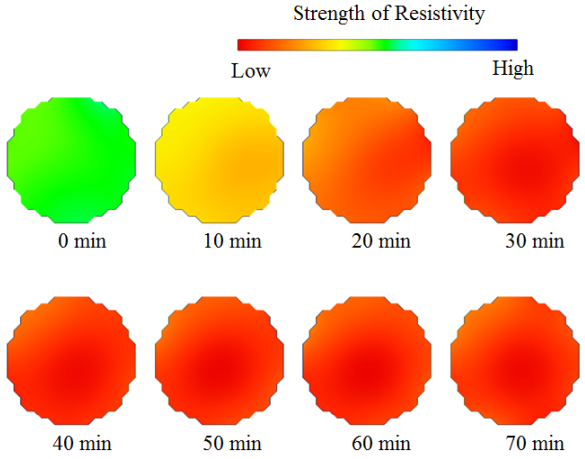
The experiments were conducted in a setup shown in figure 2. An acrylic cylinder (Poly(methyl methacrylate); Height: 80 mm; Inner Diameter: 30mm) was used as a blood container. There are two distinct planes, each having eight stainless steel electrodes (SUS304; Diameter: 2mm; Length: 10mm), in the cylinder for tomographic measurement. Among those two planes, the lower plane, at a height of 5mm from the bottom of the cylinder, was used as measurement plane. Another plane, located 10 mm above the measurement plane, was grounded to provide a uniform reference to the electrodes in the measurement plane. A composite multiplexer and data acquisition system (ITS P2000, Industrial Tomography Systems plc, UK) injects alternating current to the electrodes and scans the resulting voltages. These voltage values were fed to the PC where cross-sectional resistivity distribution was obtained using back-propagation algorithm of tomographic reconstruction [22], [23]. The system was setup in such a way that, in each instance, two of the electrodes were used for the injection (electrodes 1-2) of the current while resulting voltage was measured in two of the remaining electrodes (electrodes 3-4). The resulting voltages between other remaining electrode pairs (4-5, 5-6, 6-7 and 7-8) were then measured keeping current injection pair unchanged. The current injection pair was then switched to 2-3, and voltage was measured between remaining five neighboring electrode pairs. Since the reversal of voltage and current electrode pairs would reflect the same electrical resistivity, the number of voltage measurement pairs gradually decreased when the current injection pair was changed further. In this way, there were 20 independent voltage measurements for 8-electrode system. On the basis of this one complete measurement set, a resistivity distribution of one instance was estimated in the form of a resistivity tomogram.

B. Experimental Conditions

In one set of experiments, acrylic container was filled with 15ml of bovine blood (Shibaura Zouki KK, Tokyo, Japan) treated with sodium citrate solution as an anticoagulant. Before starting the measurements, 3.75ml of calcium chloride solution (0.02M CaCl2, Sysmex Corporation) was added to stimulate the thrombosis. In another set of experiments, nothing was added in the citrated blood so that there would be no thrombogenic process. The voltage measurement, in each case, was carried out for the injection current of 15mA at 9600 Hz frequency. The time required for a single pair of voltage measurement was 8.33 milliseconds, and thus required 167 milliseconds for a set of voltage measurements needed to reconstruct one tomographic image of the cross-section. The experiments were conducted in room temperature. No special measure was taken to control the temperature as the primary objective was to monitor the difference of resistivity change in thrombogenic and non-thrombogenic conditions.

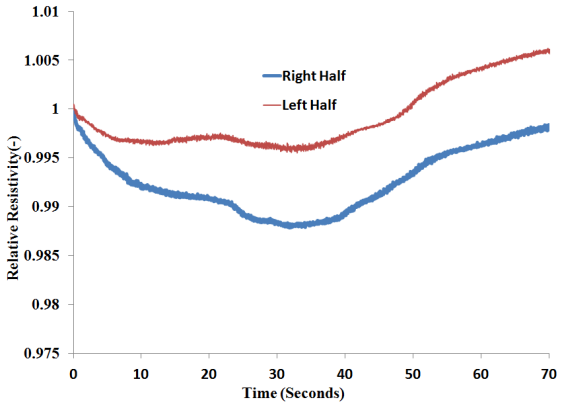


(a) Under thrombogenic condition

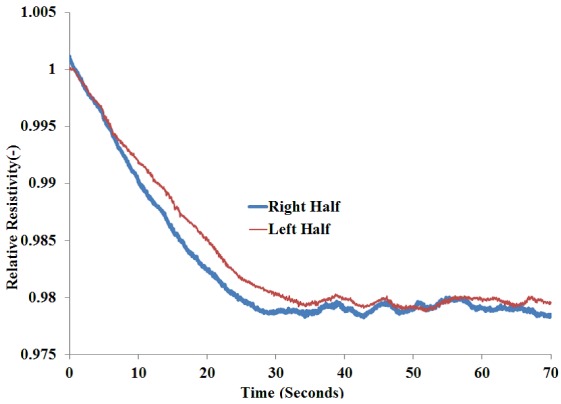


(b) Under non-thrombogenic condition

Fig. 3. Results of tomographic reconstructions



(a) Under thrombogenic condition



(b) Under non-thrombogenic condition

Fig. 4. Change in cross-sectional average resistivity with time

C. Results and Discussions

As expected, significant clotting was detected in the first case when checked after completing the experiments. No clot was observed in the second case indicating that acrylic cylinder and electrodes didn't act as catalysts to thrombosis under given anticoagulant treatment. The tomographic images shown in figure 3 represent the cross-sectional relative resistivity under thrombogenic and non-thrombogenic conditions. The strength of the relative resistivity is represented by the color gradation from red (low resistivity) to blue (high resistivity). The change in resistivity with time in each half of the measurement area are shown in figure 4.

As can be seen from figures 3(a) and 4(a), the relative resistivity in the left half of the cross-section is higher in comparison to the right-half of the cross-section under thrombogenic condition. The pattern of change in average resistivity is also different. In the left half part, the resistivity first decreases slightly. Then it increases slightly before decreasing slightly again. After around 30 minutes, there is monotonous increase in the resistivity. In the right half part, the resistivity first decreases monotonically for around thirty minutes before increasing monotonically. In contrary, the resistivity across the cross-section is almost uniform in non-thrombogenic condition as shown in figures 3(b) and 4(b). In this case, in either half of the container, the resistivity decreased monotonically before remaining flat.

The change in resistivity under non-thrombogenic condition can be partly attributed to erythrocytes sedimentation as the experiments were conducted under static condition. Erythrocytes sedimentation causes change in volume concentration of RBCs in measurement plane, and also their orientation in some degree. These factors effectively change the resistivity as formulated in equation 1. Another factor that may change the resistivity is temperature. As our objective was to observe the difference in thrombogenic and non-thrombogenic condition, we didn't control the temperature assuming that its influence remain same under both conditions as experiments were conducted in identical laboratory environments and blood. The effect of hemolysis is also considered identical as the comparisons were made for the blood drawn from same samples.

Taking the reference of non-thrombogenic condition, the behavior shown by the right half section in thrombogenic condition is somewhat normal for first half an hour. In the other hand, the change in the left side, is distinct which may

be due to undergoing thrombogenic process. The change in electrical resistance under thrombogenic condition can be attributed to the change in protein concentration and red blood cells distribution as mentioned in section II. Though it is difficult to say the exact reason for the transient rise and fall of the resistivity in the left side of the cross-section, this is unique and seems to be an early stage of the clot formation. Similarly, the monotonic rise after that may be the result of gradually concentrating blood cells due to thrombosis. As can be visualized from the tomograms in figure 3(a), the area of higher resistivity is progressing from left to right resulting the increase in resistivity in right half section.

The contribution of the protein concentration and blood cells distribution in each instance of change can't be understood from the current experimental setup, and thus the exact reasons behind the changes mentioned above remain unclear. Still, the major difference under thrombogenic and non-thrombogenic condition lies in the uniformity and pattern of change in the resistivity across the cross-section in measurement plane. And, this difference was reproducible. Such a qualitative difference in spatio-temporal domain facilitates the understanding of the thrombogenic risk which is otherwise difficult to be analyzed in absolute quantitative term.

The obvious limitation of the present experiment is the measurement in the static condition. Thorough investigation considering fluid-dynamic properties in flowing blood is necessary. Similarly, one of the future extensions of this work is to conduct the tomographic experiments under varying ac frequencies. In such a case, the capacitive behavior and internal resistance of the RBCs can be exploited to understand their concentration in the specified region which may shed light on the contribution of the individual parameters (plasma proteins and blood cells) in each instance of spatio-temporal resistivity change.

IV. CONCLUSIONS

Thrombogenic process in blood was visualized using the electrical resistance tomography method. The thrombogenic condition was characterized by non-uniform and fluctuated spatio-temporal distribution of the resistivity across the measurement cross-section in contrast to the uniform distribution of the resistivity in non-thrombogenic condition. Though the thorough quantitative reasoning behind these changes require further investigations, the findings are the first step in the development of the instrumentation system where differences in spatio-temporal domain can reveal the risk or presence of thrombogenic effect.

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