Detection of Intravenous Infiltration in the Posterior Ear of the Rabbit Using Bioelectrical Impedance: Pilot Study

Jaehyung Kim, Beumjoo Shin, Mansup Lee, Yongjin Kim, Ihnsook Jeong, Gyerok Jeon

***Abstract*— Early detection of infiltration is essential to minimize the injuries caused by infiltration. This is one of the most important tasks for nurses infusing intravenous (IV) solution or medications into the blood vessels. In this paper, infiltration phenomena were studied as a function of frequency and time using a bioelectrical impedance analyzer. When IV solution was properly infused into the vein on the back of rabbit, the impedance parameters (impedance, resistance, reactance, and capacitance) measured at five injection sites showed almost similar behavior with very slight standard deviations. On the other hand, the impedance parameters were significantly different before and after infiltration during infusing IV saline solution at the rate of 4 drops per minute into the small vein in the posterior ear of the rabbit. This is because the ears of the rabbit are thin and the vein is narrow so that IV solution temperately penetrates into the skin or subcutaneous tissue at infiltration and does not accumulate well thereafter. These studies may be applicable to infiltration studies in neonates with very small blood vessels.**

***Index Terms*—Intravenous Infiltration, Impedance measurement, Early detection, Equivalent Circuit of Cell Membrane**

I. INTRODUCTION

Insertion of an intravascular catheter is one of the most common invasive procedures in hospitals worldwide. Intravenous (IV) infusion and drug infusion into a blood vessel through a catheter are very common medical procedures for hospitalized patients. However, even in the most rigorous studies, the overall IV catheter failure rate at medical and nursing practices is between 35% and 50% [1, 2]. Failure occurs in the form of phlebitis, infiltration, occlusion / mechanical failure, dislocation, and infection, either alone or in combination with removal of the catheter before or after 72-96 hours of scheduled dwelling time [3, 4]. Infiltration and extravasation are risks of intravenous administration therapy involving unintended leakage of solution into the surrounding tissue [5]. Infiltration and extravasation are complications that can occur during the intravenous therapy administrated via either peripheral or central venous access devices. Both can result in problems such as difficulty in siting of future venous access device, nerve damage, infection, and tissue necrosis [6]. Infiltration occurs when IV solution or medications leak into the surrounding tissue. Infiltration can be caused by improper placement or dislodgment of the catheter. The movement of the patient may cause the catheter to slip or pass through the lumen [7]. Extravasation is a vascular drug leak into the surrounding tissue. Extravasation can lead to fatal local tissue damage resulting in delayed healing, infection, tissue necrosis, disfigurement, loss of function, and amputation. To minimize complications associated with peripheral catheterization, the insertion site should be checked during each shift change and the catheter should be removed if there is inflammation, infiltration, or blockage [8]. Infiltration events are graded from 1 to 4, with grade 4 being the most severe [9]. Early recognition of premature signs and symptoms of infiltration can minimize the amount of fluid and drug that escape into the tissue. Such signs and symptoms include local edema, skin blanching, skin cooling, leakage from the puncture site, pain, and feeling of tightness (pressure) [10]. Immediate measures using appropriate measures (ie., dilution, extraction, antidote and adjuvant treatment) may reduce the need for surgical intervention, but many injuries can be prevented according to established policies and procedures. However, if necessary, timely surgical intervention can prevent serious adverse outcomes [6]. As a study to reduce the infiltration of pediatric patients in the clinical settings, the IV infiltration was reduced to less than 1% due to the IV infusion management program in pediatric patients undergoing peripheral IV infusion in a pediatric hospital [11]. The safety event response team at Cincinnati Children's Hospital Center developed an improvement plan to reduce peripheral intravenous (PIV) infiltration and extravasation. The improvement activities included development of a touch-look-compare method for hourly PIV site assessment, staff education and mandatory demonstration of PIV site assessment, and performance monitoring and sharing of compliance results [12]. Nevertheless, the methods used by medical staff to detect current infiltration are fairly subjective and potentially prone to fail. The infiltration is an even larger concern for pediatric patients who have smaller veins than adults and are more difficult to communicate to the doctor about pain or other discomfort associated with pediatric infiltration.

For this reason, attaching an automated IV infiltration detector to high-risk patients associated with infiltration can potentially reduce the risk associated with damage condition [13]. In addition, studies were performed using optical and electrical methods to detect infiltration and extravasation

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during peripheral IV infusion since early detection of infiltration can help prevent the serious injuries that may require surgical correction. IV infiltration detection devices combined with fiber optics and algorithm were proposed to detect the infiltration around IV injection site noninvasively [13-14]. An IV watch Model 400 was developed for the detection of peripheral IV infiltration and outflow events through continuous monitoring of the IV site using near infrared (NIR) [15]. In addition, researchers have attempted to use ultrasound to examine exogenous fluids injected into the skin and subcutaneous tissue. Ultrasound could detect small amount fluids such as cosmetic fillers and subcutaneous injections. Their study suggested that ultrasound could be a potential reference standard for the future evaluation of IV monitoring devices [16]. However, early infiltration detection system should be simple, reliable, economical, and monitor IV infiltration in a non-invasive manner for ease of use in the nursing and medical practice. Infiltration detection systems using bioelectrical impedance analysis (BIA) satisfy these requirements well because they are safe, practical and non-invasive methods for measuring the composition of biological tissues and substances [17]. BIA has been currently used to diagnose disease and to assess hydration status, body composition, muscle-fat ratio, obesity, lean mass balance, edema, and nutritional status of patients [18, 19]. In this study, bioelectrical impedance (BI) was measured as a function of frequency during infusing IV solution into the vein on the posterior ear of rabbit. In order to investigate any change in BI due to infiltration, BI was measured as a function of time before and after infiltration. Infiltration was deliberately induced by puncturing the vein wall in the posterior ear of rabbit with needle. During infiltration, IV solution accumulated in the subcutaneous tissue was investigated using an equivalent circuit model of the human cell and the impedance parameters such as impedance resistance, reactance, and capacitance of cell membrane [20, 21].

II. METHOD

2.1 Equivalent Circuit of ECF, ICF, and Cell Membrane

A basic understanding of normal body fluid physiology is required to appreciate the nuances of fluid therapy. Total body water (TBW) accounts for approximately 60% of the total body weight. TBW is distributed between the intracellular fluid (ICF) compartment (approximately 66%) and the extracellular fluid (ECF) compartment (approximately 33%). These two spaces are separated by cell membranes. The ECF compartment is further subdivided into intravascular (8% TBW) and interstitial (25% TBW) spaces [22], and these compartments are separated by the capillary wall. The cell membranes between the fluid compartments have different permeability to different solutes based on size, charge, and conformation. The human body consists of resistances (R_e, R_m, R_i) and capacitance (C_m) connected in parallel or in series. In the parallel model, two or more resistors and capacitors are connected in parallel, with the current passing through the extracellular space at low frequencies and through the intracellular space at high frequencies. Cells constituting human organs consist of ECF and ICF that behave as electrical conductors, whereas the cell membrane acts as an electrical resistor and capacitor [23, 24]. Figure 1 indicates an equivalent circuit of a cell in the human body. Table 1 lists the descriptions of the indicated symbols in Fig. 1.

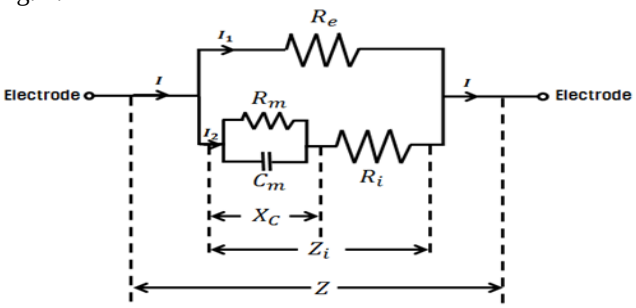


Fig. 1. The human body consists of resistors (R_e, R_m, R_i) and Capacitor (C_m) connected in parallel or in series. In the parallel model, two or more resistors and capacitors are connected in parallel, with the current passing through the extracellular space at low frequencies and through the intracellular space at high frequencies.

Table 1. Description of symbols represented in Figure 1

Symbol	Description
C_m	Capacitance of cell membrane
R_m	Resistance of cell membrane
R_e	Resistance of ECF
R_i	Resistance of ICF
X_c	Reactance of cell membrane
Z_i	Impedance of X_c and R_i
Z	Impedance of Z_i and R_e
I	Current through both ECF and ICF
I_1	Current through only ECF
I_2	Current through both cell membrane and ECF

Since the resistance (R_m) and the capacitance (C_m) of cell membrane are connected in parallel, the reactance (X_C) of cell membrane in Fig. 1 can be expressed as follows:

$$X_C = \frac{1}{\frac{1}{R_m} + j\omega C_m} = \frac{R_m}{1 + j\omega R_m C_m} \quad (1)$$

The reactance (X_C) of cell membrane and the resistance (R_i) of ICF connected in series can be expressed as (2)

$$Z_i(j\omega) = R_i + X_C = R_i + \frac{1}{\frac{1}{R_m} + j\omega C_m} + R_i + \frac{R_m}{1 + j\omega R_m C_m} \quad (2)$$

Total impedance (Z) having a coupling structure in parallel with the extracellular fluid (ECF) with the intracellular fluid (ICF) in series with the cell membrane (X_c) can be expressed by Eq. (3):

$$Z = R + iX_C \quad (3)$$

Total impedance (Z) of cell model can be also represented as (4)

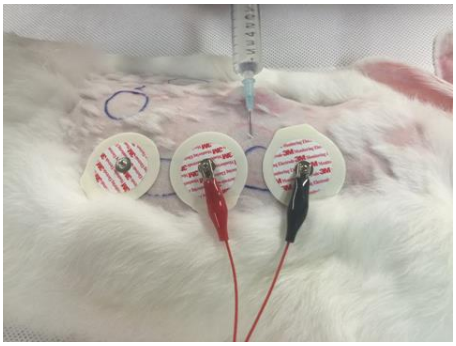
$$Z = \frac{1}{\frac{1}{R_e} + \frac{1}{Z_i}} = \frac{R_e Z_i}{R_e + Z_i} \quad (4)$$

The reactance (X_C) of cell membrane depends on the applied frequency. When the frequency of the applied alternating current is low, X_C and Z_i increase in the equations

(1) and (2), so that Z increases. When the frequency of the applied alternating current is high, the opposite phenomenon occurs and Z is lowered.

2.2 Peripheral intravenous injection and induced infiltration

Electrodes (with a separation of 5cm) for applying the current and collecting the voltage were attached to both sides of IV infusion site. Ag/AgCl electrode (2223H, 3M, Korea) with foam tape and sticky gel was used to minimize interfacial effect between electrode and the skin. Experimental animals were male New Zealand White Rabbit aged 6 months and weighing 2.5-3 kg. After inserting peripheral intravenous (PIV) catheter into a vein on the back of rabbit in figure 2(a), impedance (Z) was measured as a function of frequency during infusing saline IV solution at the rate of 4 drops per minute. Impedance measurement was performed by selecting five places on the back of the rabbit. Saline solution was injected with the minimum amount that would not cause clotting. In addition, the infiltration was deliberately induced by pushing the needle through the vein wall into the subcutaneous tissue in posterior ear of rabbit as shown in figure 2(b). Impedance was measured as a function of frequency before and after infiltration, using multi-channel impedance measuring instrument (called Vector Impedance Analyzer) developed by Kim [25]. AC having eleven frequencies (10, 20, 30, 50, 70, 100, 200, 300, 500, 700, and 1000 kHz) was applied to the electrodes to measure Z. This study was approved by the Youngnam University Hospital Animal Care and Use Committee (YUMC-AEC2016-011).



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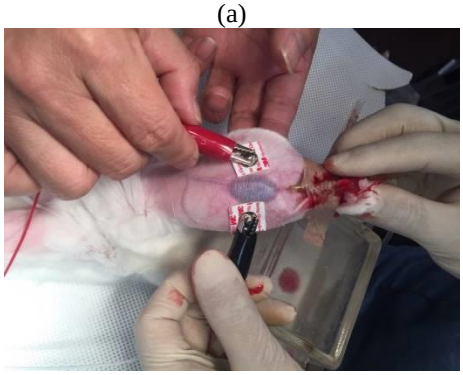

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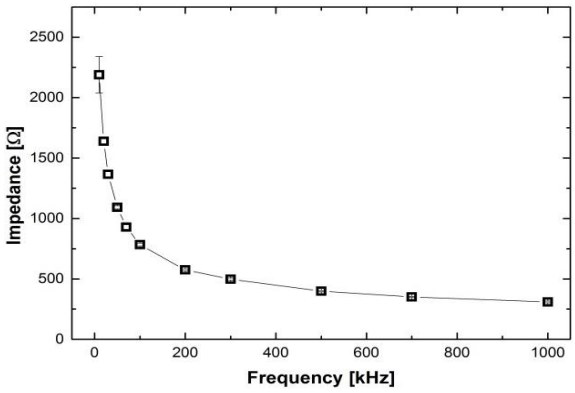
Fig. 2 (a) The locations of the electrodes on the back of the rabbit for impedance measurement. (b) A photograph of impedance measurement after inducing infiltration of vein in posterior ear of a rabbit.

III. RESULT

A. Impedance (Z) as a function of frequency (f)

Impedance of the human body is a major factor affecting the intensity of the current flowing through the human body when the applied voltage is constant. Assuming that the human body is an electrical conductor, impedance is measured differently depending on morphological and structural characteristics of various components such as tissues and cells, moisture in the body, and blood constituting various organ systems. The impedance varies depending on the path of the current applied to the human body, the applied frequency, the cross-sectional area of the measurement site, and the structural characteristics.

Figure 3(a) shows the impedance (Z) as a function of frequency while IV solution was being infused into the vein on the back of rabbit. An alternating current (AC) with eleven frequencies (10, 20, 30, 50, 70, 100, 200, 300, 500, 700, 1000 kHz) was applied to the electrodes attached to the both sides of IV site during infusing IV solution into the vein. Impedance decreased nearly inversely with increasing frequencies of applied AC. In particular, the impedance decreased significantly in low frequency region (10-100 kHz) and gradually decreased at frequencies above 100 kHz. In addition, the standard deviations ($\pm$SD) obtained with Vector Impedance Analyzer were measured largely at 10 kHz and thereafter decreased with increasing frequency. Figure 3(b) shows the impedance measured as a function of frequency when infiltration occurred during infusing IV solution into the vein in the posterior ear of rabbit. Infiltration was induced by intentionally puncturing a small vein in the rabbit's ear with an injection needle. BI (before infiltration) indicates the time when IV solution was properly infused into the vein. BI (at infiltration) indicates the time when infiltration occurred while IV solution was being infused into the vein. Before the infiltration, the impedance was measured relatively high. However, the impedance decreased remarkably after infiltration. Compared to figure 3(a), the impedance was measured very high because the vein in the ear of the rabbit was very small and the ears were thin. In our previously published paper [26], impedance decreased quantitatively where vein in the human's forearm was infiltrated. On the other hand, when infiltration was induced in the posterior ear of rabbit, the impedance decreased significantly during infiltration and thereafter did not decrease any more. This indicates that the ears of the rabbit are thin and the veins in the ear are thin, so that IV solution no longer accumulates in the subcutaneous tissue. The slight increase in impedance at 25 minutes after infiltration was due to that the vein of the rabbit burst out and IV solution that had accumulated in the vein and subcutaneous tissue leaked out.



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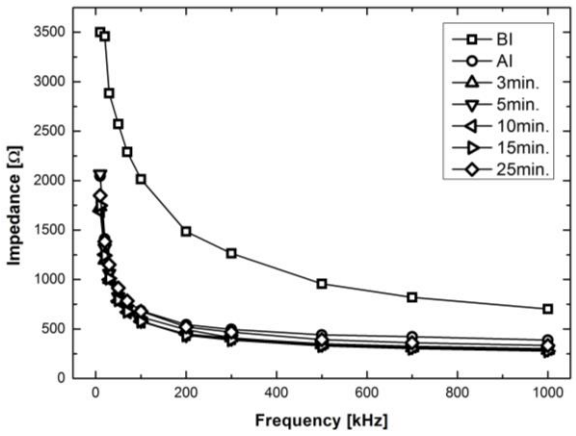


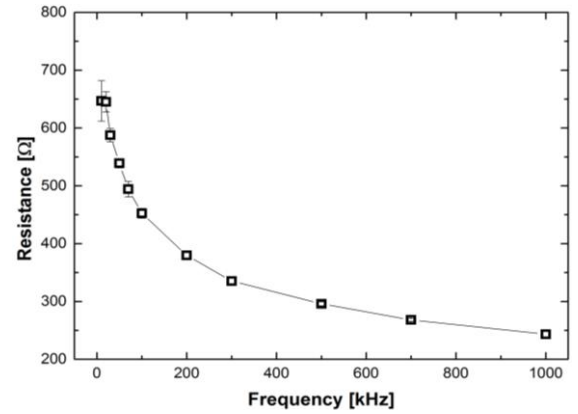
(b)

Fig. 3 (a) Impedance as a function of frequency during infusing saline solution into the vein on the back of a rabbit. (b) Impedance as a function of frequency before and after infiltration during infusing IV solution into the vein in the posterior ear of a rabbit.

B. Resistance (R) as a function of frequency (f)

Whether a cell membrane behaves as a resistor or a capacitor depends on the frequency of the applied AC. When AC with a frequency lower than 50 kHz ($2.1\times10^{-11}eV$) is applied to IV site, the resistance is relatively high because the current primarily flows into narrow ECF, which is composed of adipose tissue. Only a small amount of current finds "the path of least resistance" through a capillary [27]. Hence, the decreasing resistance at 10 kHz (0.41×10^{-11}eV) over time reflects IV solution accumulating in ECF after infiltration. On the other hand, when AC with a frequency higher than 50 kHz is applied to IV site, the current has sufficient energy to pass through the cell membrane; therefore, the current flows into ICF with a larger internal cross-sectional area. Thus, the current flows through both ECF and ICF. As the frequency increases, more current flows into ICF, further lowering the resistance.

Figure 4(a) shows the resistance (R) measured as a function of frequency while IV saline solution was being infused into the vein on the backs of a rabbit. AC having eleven frequencies was applied to the electrodes attached to both sides of IV site during infusing IV solution into the vein. Resistance decreased approximately inversely with increasing frequencies of applied AC during infusing IV solution. In particular, R decreased significantly in low frequency region (10-100 kHz) and gradually decreased at frequencies above 100 kHz. The standard deviation (±SD) of resistance was high at low frequencies (10-100 kHz) and relatively low at high frequencies (≥100 kHz). Figure 4(b) shows the resistance as a function of frequency before and after the infiltration during infusing IV solution into the vein in the posterior ear of the rabbit. Compared with R before infiltration as shown in figure 4(a), the resistance was significantly reduced at infiltration and thereafter decreased further as IV solution was injected into the rabbit ear. At each frequency, the resistance gradually decreased over time, proportional to the amount of IV solution leaking from the vein due to infiltration, indicating IV solution (and blood products) accumulated in ECF including interstitial fluid. This can be a useful parameter for the early detection of infiltration. The increasing R in 25 minutes after infiltration was due to that the vein in the posterior ear of the rabbit burst out and IV solution that had accumulated in the vein and subcutaneous tissue leaked out. When AC having a frequency of 10 kHz (0.41×10^{-10} eV) was applied to IV site, R was significantly large because the current primarily flowed into ECF. The decreasing impedance at 20 kHz over time reflects IV solution being accumulated in the skin and subcutaneous tissue during infiltration. On the other hand, when AC having a frequency higher than 50 kHz (2.07×10^{-10} eV) was applied to IV site, the applied AC was strong enough to penetrate the cell membrane and then flowed into both ECF and ICF. Thus, the decreasing R at AI can be interpreted as an infiltration. Then the decreasing R over time can be considered as gradual accumulation of IV solution and blood leaking from the vein into surrounding tissues. R increased at 25 minutes after infiltration, indicating that the vein in the posterior ear of the rabbit burst out and IV solution accumulated in the vein and subcutaneous tissue leaked out.



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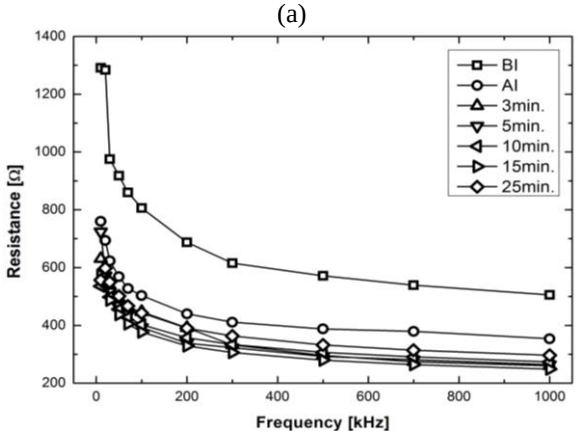


(b)

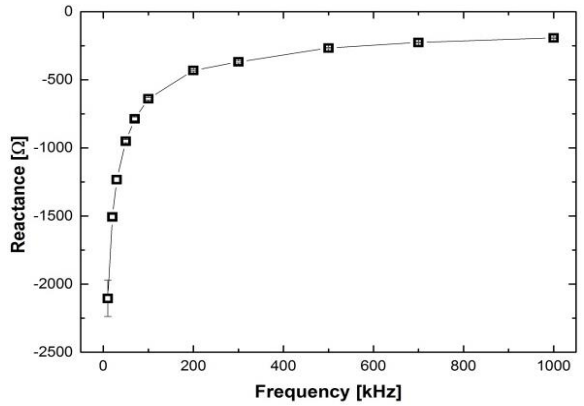
Fig. 4 (a) Resistance as a function of frequency during infusing IV saline solution into the vein on the back of a rabbit. The resistance decreased nearly inversely with increasing frequency. (b) Resistance as a function of frequency before and after infiltration during infusing IV solution into the vein in the posterior ear of rabbit. Resistance was measured high before infiltration, but gradually decreased after infiltration. This indicates that IV solution is accumulating in the vein in the posterior ear of the rabbit due to infiltration.

C. Reactance (X_C) as a function of frequency (f)

The reactance (X_C) of cell membrane is a measure of the function of the cell membrane [27]. The cell membrane can store charge for a short period of time and slow down the current flow. The cell membrane acts as a resistor when the

frequency of the applied current is low and as a capacitor when the frequency of the applied current is high. At a low frequency below 50 kHz, the current cannot flow through the cell membrane. At these frequencies, the cell membrane acts as resistor because current cannot pass through the cell membrane. Therefore, at low frequencies, any current conducting through the body primarily passes through ECF. On the other hand, currents having a frequency higher than 50 kHz can pass through the cell membranes and flow through both ICF and ECF.

Figure 5(a) shows the reactance (X_C) of cell membrane as a function of frequency during infusing IV solution into the vein on the back of a rabbit. The magnitude of the reactance decreased inversely with increasing frequency. Figure 5(b) shows the reactance (X_C) of cell membrane as a function of frequency before and after infiltration during infusing IV solution into the vein in the posterior ear of a rabbit. As the frequency of the applied AC increased, the ability of the cell membrane to slow down the flowing AC was significantly reduced, and hence, X_C decreased. In comparison with figure 5 (a) in which saline solution was properly infused into the vein on the back of the rabbit, the magnitude of X_C was significantly decreased when infiltration occurred. X_C of cell membrane was most evidently reduced at 10 kHz during infiltration. IV solution and blood components were adsorbed to the cell membrane due to infiltration, seriously reducing the ability of the cell membrane to slow AC. This indicates that the infiltration detection is possible when infiltration occurs in thin blood vessels, as in neonates.



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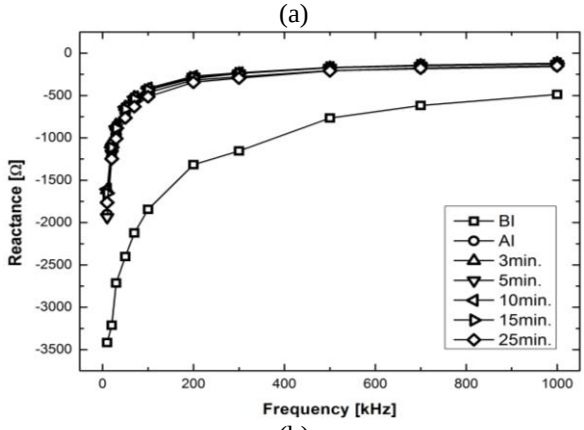


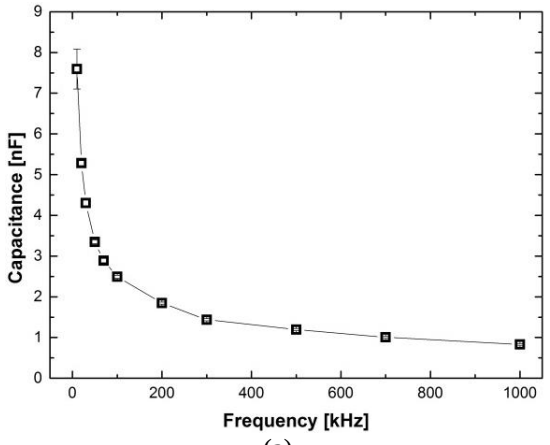
(b)

Fig. 5 (a) Reactance as a function of frequency during infusing IV saline solution into the vein on the back of a rabbit. The reactance decreased approximately inversely with increasing frequency. (b) Reactance as a function of frequency before and after infiltration during infusing IV solution into the vein in posterior ear of the rabbit. The magnitude of reactance decreased at infiltration (AI). This indicates that IV solution and blood components are adsorbed to call membrane, reducing the ability of cell membrane to store electric charges passing through membrane.

D. Capacitance (C_m) of cell membrane as a function of frequency (f)

Capacitance is the absolute amount of energy storage of the body due to intact cellular membranes. A high capacitance indicates that body stores energy effectively. A low capacitance would suggest that cells have trouble in storing energy. The cell membrane acts as a capacitor when a current having a high frequency is applied to the body. The capacitance is inversely proportional to the applied frequency and the reactance as follows: $C_m=1/2\pi f X_C$.

Figure 6(a) shows the capacitance (C_m) of cell membrane as a function of frequency during infusing IV solution into the vein on the back of a rabbit. The capacitance is inversely proportional to the frequency of the applied AC. Figure 6(b) shows the capacitance of cell membrane as a function of frequency before and after infiltration. Capacitance decreases inversely with increasing frequency. Compared with C_m at BI, the capacitance of cell membrane increased significantly at AI and thereafter. After infiltration, infused IV solution and blood components (red blood cells, white blood cells, platelets, etc.) were adsorbed to the cell membrane in the surrounding tissues in the vein of the rabbit's ear, gradually increase the capacitance of cell membrane. At 25 minutes after infiltration, the venous blood vessels ruptured and IV solution and blood components flowed out from the vein into surrounding tissues, slightly decreasing the capacitance of cell membrane.



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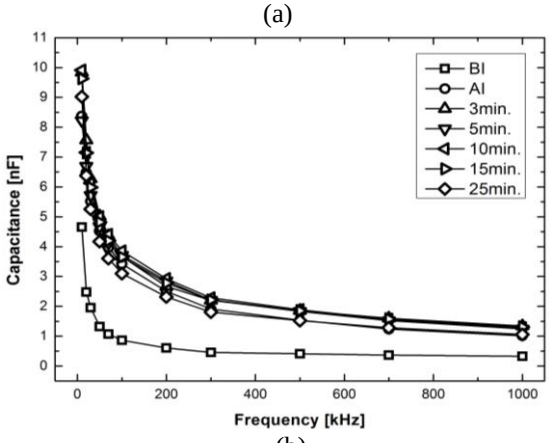

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Fig. 6(a) Capacitance of cell membrane as a function of time during infusing IV saline solution into the vein on the back of a rabbit. The capacitance decreased nearly inversely with increasing frequency. (b) Capacitance of cell membrane as a function of frequency before and after infiltration during infusing IV solution into the vein in the posterior ear of a rabbit. Capacitance increased after infiltration indicating that IV solution and blood components were accumulating to the cell membranes in the vein in the left ear of the rabbit.

IV. DISCUSSION

Infiltration is difficult to detect, especially at an early stage of infiltration. To date, the techniques to detect the infiltration primarily relied on clinical methods, which include visual and tactile examination of the skin and tissue surrounding IV injection site for factors such as tissue pressure, color, edema, turgor and temperature [10]. However, the visual and tactile examination technique is ineffective in detecting the infiltration since tissue damage has already occurred when infiltration is checked. In addition, infiltration detection systems was developed using infrared light as a light source. Infiltration was recognized to decrease the reflectivity due to the leaked solution when comparing the reflectance of the lights before and after infiltration [14, 28]. However, these data do not accurately reflect accumulation of solution/fluid from the vein into skin and subcutaneous tissue because they depends on the partial reflectivity of IV solution exposed to the skin and infiltrated Iv solution (also blood components) into subcutaneous tissue.

In this study, BIA was used to investigate the pathophysiological properties of biological tissues to detect infiltration. When IV solution was properly infused into the vein on the back of rabbit, there were no apparent changes in impedance parameters (Z, R, X_C, C_m) as a function of frequency. On the other hand, when infiltration occurred in a small vein in the rabbit's thin ear, impedance parameters exhibited the apparent differences before and after infiltration. Using multi-frequency bioelectrical impedance and an equivalent circuit model, IV saline solution leaking from the vein after infiltration was confirmed to be accumulated in ECF of surrounding subcutaneous tissue, proposing an indicator for early detection of infiltration. Unlike infiltration in adults with thick veins, newborn infants with thin veins may have similar behavior to infiltration in the veins of the rabbit ear.

V. CONCLUSION

In this study, the impedance was measured as a function of time and frequency when IV solution was infiltrated into the vein in the back or posterior ear of the rabbit. Experimental results can be described as following. First, when infiltration was induced by puncturing the vein wall in the rabbit's ear, the impedance (Z) decreased significantly during infiltration and thereafter did not decrease any more. This indicates that the ears of the rabbit are thin and the veins in the ear are small, so that IV solution no longer accumulates in the skin and subcutaneous tissue. Second, the resistance (R) was significantly reduced at infiltration and thereafter decreased further as IV solution was injected into the rabbit's ear. At each frequency, the resistance gradually decreased over time, proportional to the amount of IV solution leaking from the vein due to infiltration, indicating IV solution (and blood products) accumulated in ECF (including interstitial fluid). This can be a useful parameter for the early detection of infiltration. Third, the magnitude of reactance (X_C) was significantly decreased when infiltration occurred. X_C of cell membrane was most evidently reduced at 10 kHz during the infiltration. IV solution and blood components were adsorbed to the cell membrane due to infiltration, seriously reducing the ability of the cell membrane to slow AC. Fourth, Capacitance (C_m) decreases inversely with increasing frequency. Compared with C_m at BI, the capacitance of cell membrane increased significantly at AI and thereafter. After infiltration, infused IV solution and blood components (red blood cells, white blood cells, platelets, etc.) were adsorbed to the cell membrane in the surrounding subcutaneous tissues of the posterior ear of a rabbit, gradually increasing the capacitance of cell membrane. Unlike infiltration in human veins, infiltration in small venous vessels in rabbit ears exhibited different impedance behaviors. These studies could be extended to infiltration studies in neonates with very thin veins.

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