

Comparison of Infiltration Induced in Veins of Rabbit's Ear and Human's Forearm by Using Bioelectrical Impedance: Pilot Study

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Abstract

An early detection of infiltration in veins is essential to minimize the injuries caused during infusion therapy, which is one of the most important tasks for nurses in clinical settings. We report that bioelectrical impedance analysis is useful in the early detection of infiltration at puncture sites. When infiltration was intentionally induced in the vein of a rabbit's ear, impedance parameters showed significant difference before and after infiltration. In particular, the relative resistance at 20 kHz in the vein of rabbit's ear reduced largely at infiltration, decreased slowly, and then stayed at a constant value. This indicates that the vein in the ear of the rabbit is small, and hence the infiltrated intravenous (IV) solution no longer accumulates after 3 minutes of infiltration. However, when infiltration was induced in the vein of a human's forearm, the relative resistance at 20 kHz decreased gradually over time. In the $R-X_C$ graph, the positions in infiltration induced in the rabbit's ear rapidly shifted before and after infiltration whereas the positions in infiltration induced in the human's forearm changed gradually during infiltration. Our findings suggest that bioelectrical impedance analysis is an effective method to detect the infiltration early in a noninvasive and quantitative manners.

Keywords: Intravenous Infiltration, Early Detection, Multifrequency Bioelectrical Impedance Analysis, Equivalent Circuit

1. INTRODUCTION

Infiltration, one of the most frequent complications of infusion therapy performed using peripheral intravenous (PIV) catheters [1], is defined as "careless management of the surrounding subcutaneous tissues" by the Infusion Nurses

Society (INS) [2]. Patients with infiltration often experience pain, and severe cases are left with persistent disability in their arms [3]. Thus, infiltration can be a serious side effect that must be carefully monitored to detect anomalies early during administration [4]. The INS have created an infiltration scale to assess signs and symptoms such as "skin blanched", "edema", "cool to touch", "pain", and "numbness" [1]. Infiltration and extravasation are risks associated with intravenous administration therapy during which unintended leakage of an IV solution into the surrounding subcutaneous tissue can occur [5]. When the intravenous (IV) solution or medications leak from venous blood vessels into the surrounding tissues, infiltration occurs. Infiltration can be caused by improper placement or dislodgment of the catheter. The movement of the patient can cause the catheter to slip out or through the vein [6]. Infiltration events are graded from 1 to 4, with grade 4 events deemed the most severe [7]. Recognizing the early signs and symptoms of infiltration can limit the amount of fluid that leaks from the vein into the subcutaneous tissues. Such signs and symptoms include local edema, skin blanching, cooling of skin, leakage at the puncture site, pain, and feelings of tightness [8]. While immediate action using appropriate measures (i.e., dilution, extraction, antidotes, and supportive treatments) can decrease the need for surgical intervention,

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many injuries may be prevented by following the established policy and procedures. However, timely surgical intervention, when necessary, can prevent more detrimental adverse outcomes [9]. Many studies have been performed for detecting infiltration and extravasation during peripheral venous treatment using optical and electrical methods because early detection of infiltration helps prevent the occurrence of serious injuries, which may require surgical corrections. An optical method that employs fiber optics and algorithms for tissue optics has been developed to facilitate noninvasive monitoring of IV sites [10, 11]. An early detection system (IV watch Model 400) of peripheral IV infiltration and extravasation events through continuous monitoring of IV sites has been developed using near-infrared (NIR) light [12]. Researchers have also attempted to use ultrasound to examine the exogenous fluids injected into cutaneous and subcutaneous tissues. Furthermore, ultrasound could detect small volumes of fluids, such as cosmetic fillers and subcutaneous injections. Therefore, ultrasound could be a potential reference standard for the future evaluation of IV infusion monitoring devices [13]. An early infiltration detection system should be simple, reliable, economical, and capable of monitoring IV infiltration in a noninvasive manner for easy use in nursing and medical practice. The infiltration detection system using bioelectrical impedance analysis (BIA) satisfies these conditions because BIA is a safe, practical, and noninvasive method for measuring the composition of biological tissues and materials [14]. BIA has been employed to diagnose diseases [15] and to assess the hydration status, body composition, muscle-fat ratio, obesity degree, lean balance, edema, and nutritional status of the patients [16, 17]. In this study, infiltration was induced by puncturing the vein wall with a needle in a rabbit's posterior ear. During infiltration, the IV solution accumulating in the subcutaneous tissues was investigated using impedance parameters such as resistance, relative resistance, reactance, and resistance vs. reactance [18]. The impedance parameters showed a significant difference in the vein in the rabbit's ear, but they gradually changed in the vein in the human's forearm. The mechanism of infiltration induced in the veins of the rabbit's posterior ear and the human's forearm was described using an equivalent circuit and impedance analysis.

2. EXPERIMENTAL

2.1 Theory of Bioelectrical Impedance (Z)

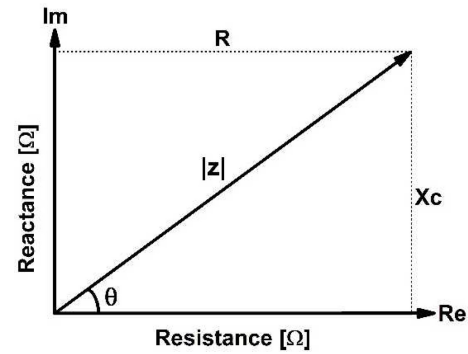


Fig. 1. Impedance (Z) consisting of resistance (R) and reactance (X_C).

Impedance (Z) is the opposition to the flow of an alternating current (AC) and, hence, is dependent on the frequency of the applied AC. Z is defined in terms of impedance magnitude ($|Z|$) and phase angle (θ) as shown in Equations (1)-(3) and Fig. 1. Impedance is a complex quantity composed of resistance (R) of the total body water and reactance (X_C) due to the capacitance of the cell membrane [19]:

$$Z = R + jX_C \quad (1)$$

$$|Z| = \sqrt{R^2 + X_C^2} \quad (2)$$

$$\theta = \tan^{-1} \left(\frac{X_C}{R} \right) \quad (3)$$

The resistance of an object depends on the shape and the material of the object. For a given shape, the resistance depends on the material the object is made from. In other words, different materials provide different resistances to the flow of electric charges. The resistivity ρ of a material is directly proportional to the resistance R of an object. The resistivity ρ is an intrinsic property of a material, and does not depend on its shape or size. The resistance of an object of length L , made of a material having cross-sectional area A and resistivity ρ , is as follows [19].

$$R = \rho \frac{L}{A} \quad (4)$$

The capacitor affects the current, and has the ability to stop the current in a fully charged state. Since an AC voltage is applied, the root mean square (RMS) current is limited by the capacitor. Since the RMS current is regarded as the effective resistance of the capacitor for AC, RMS current I in a circuit containing only capacitor C is given by another version of the Ohm law as follows:

$$I = \frac{V}{X_C} \quad (5)$$

where V is the RMS voltage and X_C is defined to be

$$X_C = \frac{1}{2\pi fC} \quad (6)$$

where X_C , expressed in ohms, is called the capacitive reactance because the capacitor reacts in such a way as to impede the current. X_C is inversely proportional to the capacitance, C ; The larger the capacitance, the more charge the capacitor can store, and more current can flow. The capacitance is also inversely proportional to the frequency f ; the greater the frequency, the less time there is to fully charge the capacitor, and hence it impedes current less [20].

2.2 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 [21], 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. An equivalent electrical circuit model has been used to investigate the response of different tissue components to AC having multifrequency. Our model considers seven electrical components: skin resistance, contact capacitance, fat resistance, fat capacitance, extracellular resistance, intracellular resistance, and cell membrane capacitance [22]. The human body model 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 a resistor and capacitor [23, 24]. Fig. 2 shows the equivalent circuit of a cell in the human body. Table 1 lists the descriptions of symbols represented in Fig. 2.

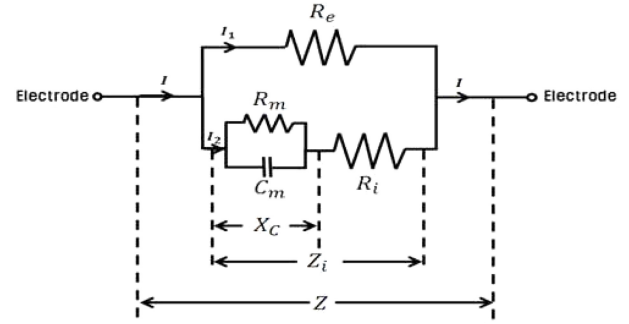


Fig. 2 Human body consists of resistors (R_e, R_m, R_i) and capacitor (C_m) connected in parallel or series. In the parallel model, two or more resistors and capacitors are connected in parallel, with the current passing through the extracellular space at low frequencies and through the intracellular space at high frequencies.

Table 1. Description of symbols represented in Fig. 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	Impedance of cell membrane
Z_i	Impedance of X_C and R_i
Z	Impedance of Z_C 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 impedance (X_C) of the cell membrane in Fig. 1 can be expressed as follows:

$$X_C = \frac{1}{\frac{1}{R_m} + j\omega C_m} = \frac{R_m}{1 + j\omega R_m C_m} \quad (7)$$

The reactance (X_C) of the cell membrane and the resistance (R_m) of the ICF connected in series can be expressed as (8).

$$Z_i(j\omega) = R_i + X_C = R_i + \frac{R_m}{1 + j\omega R_m C_m} \quad (8)$$

Total impedance (Z) of the cell model having a coupling structure in parallel with the ECF and the ICF connected in series with the cell membrane (X_C) can be expressed by Eq. 9.

$$Z = \frac{1}{\frac{1}{R_e} + \frac{1}{Z_i}} = \frac{R_e Z_i}{R_e + Z_i} \quad (9)$$

The reactance (X_C) of the cell membrane depends on the applied frequency. When the frequency of the applied AC is low,

X_C and Z_i increase in Eqs. (7) and (8), so that Z increases. When the frequency of the applied AC is high, the opposite phenomenon occurs and then Z decreases.

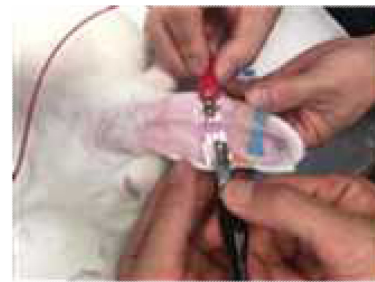
2.3 Peripheral intravenous injection and induced infiltration

Electrodes for applying the current and collecting the voltage were attached to both sides of the IV infusion site. Ag/AgCl electrode (2223H, 3M, Korea) with foam tape and sticky gel was used to minimize the interfacial effects between the electrode and the skin. After inserting the PIV catheter into a vein of a rabbit's posterior ear, impedance parameters (R , X_C) were measured as a function of time and frequency while infusing an IV solution at the rate of 4 gtt. (4 drops per min.) to prevent blood clotting. Then, infiltration was deliberately induced by pushing the needle through the vein wall into the subcutaneous tissue in a rabbit's posterior ear as shown in Fig. 2(a). Fig. 2(b) shows the impedance measurement in the human forearm before and after infiltration while intravenously infusing IV solution at the rate of 60 gtt. (60 drops per min.). Impedance was measured before and after infiltration using multichannel impedance measuring instrument (called a vector impedance analyzer) developed by Kim et al. [25]. AC with 10 different frequencies ranging from 20–1000 kHz was applied to the electrodes to measure Z . This study on animals was approved by the Youngnam University Hospital Animal Care and Use Committee (YUMC-AEC2016-011).

3. RESULTS

3.1 Resistance (R) as a function of time(t)

Fig. 3 shows the resistance (R) as a function of time while infusing the IV solution into the vein in rabbit's posterior ear. An AC was applied to the electrodes attached to both sides of IV infusion site and the frequency varied. The resistance decreased most markedly during infiltration and then slowly decreased with slight fluctuation. When AC having a frequency of 20 kHz was used, the resistance was most significantly reduced at infiltration. Since AC of frequency 20 kHz does not pass through the cell membrane, a sharp decrease in resistance during infiltration indicates that a considerable amount of the IV solution flowing out of the vein is accumulating in the ECF (including the interstitial fluid). A subsequent decrease in the resistance over time indicates that the IV solution still is accumulating in the



(a)



(b)

Fig. 3. (a) Electrodes attached to a rabbit's posterior ear for detecting the infiltration. (b) Circular electrodes used to measure the impedance to detect vein-induced infiltration into the left forearm. Outside band electrodes are used for detecting infiltration with another measuring device.

subcutaneous tissue. A slight increase in resistance after 15 min of infiltration indicates the flow of IV solution due to a rupture of the weak vein in the rabbit's ear owing to the pressure of the fluid. In our previous reported paper that described infiltration in the human forearm [26], when infiltration was intentionally induced in the human's forearm, the resistance gradually decreased over time. This indicates that the IV solution leaking out from a vein in the human's forearm gradually accumulated in the surrounding subcutaneous tissue after infiltration.

3.2 Relative resistance (R/R_{BI}) as a function of time (t)

Fig. 4 shows the relative resistance (white square) measured at 20 kHz in the other veins of a rabbit's posterior ear and human's forearm as a function of time. Compared to the relative resistance before infiltration (BI), the relative resistance was significantly reduced at infiltration (AI), and then slowly decreased and stayed at a constant value. This indicates that the vein in the rabbit's ear was thin so that the infiltrated IV solution no longer accumulated after 3 min of infiltration. At 15 min after infiltration, the venous blood vessel in the rabbit's ear burst and the resistance slightly increased again. The right side in Fig. 4 also shows the relative resistance (dark circle) measured at 20 kHz in the human's

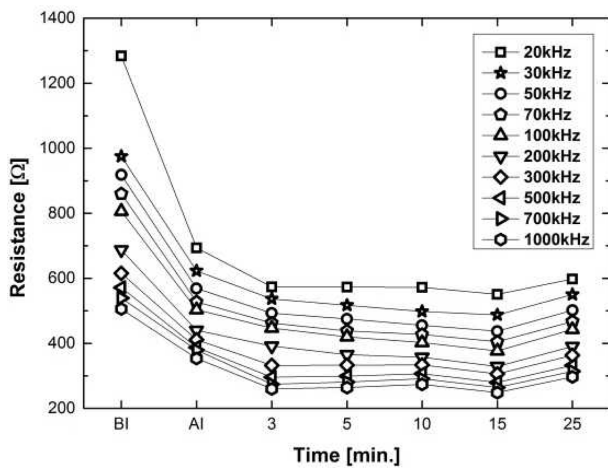


Fig. 4. Resistance as a function of time during infusing IV solution into the vein in a rabbit's posterior ear.

forearm as a function of time. The relative resistance gradually decreased over time. This indicates that the vein in the human's forearm is large and there are many subcutaneous tissues, so that the IV solution is still accumulating in subcutaneous tissues over time. In thin blood vessels, the relative resistance is markedly different before and after infiltration whereas the relative resistance gradually decreases in the vein of the human's forearm since the IV solution continues to accumulate in the thick subcutaneous tissue after infiltration.

3.3 Reactance (X_C) as a function of time (t)

Fig. 5 shows the reactance (X_C) of the cell membrane as a function of time while infusing the IV solution into the vein in

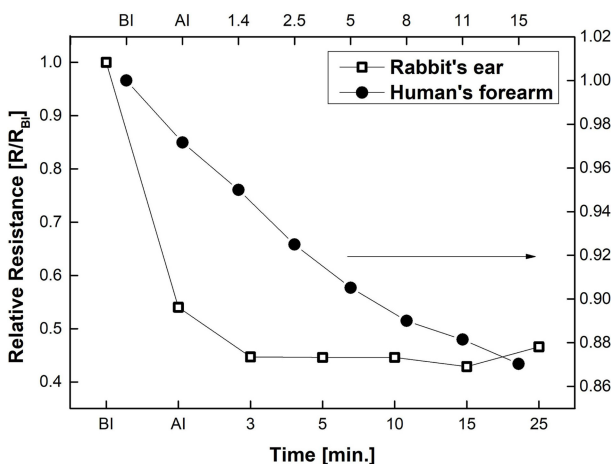


Fig. 5. Relative resistance measured at 20 kHz in the veins of rabbit's ear and human's forearm as a function of time.

the rabbit's ear. The magnitude of the reactance largely decreased at infiltration (AI) and was constant thereafter. The magnitude of the reactance was most dramatically reduced at 20 kHz. This is because the blood components released from the venous blood vessels in the infiltration cause the cell membranes to aggregate in a linear/ parallel manner, so that the capacitance of the cell membrane becomes lower and the reactance increases toward zero. Thus, the magnitude of the reactance decreases sharply at infiltration (AI), as seen in Fig. 5. The IV solution and blood components were adsorbed to the cell membrane due to infiltration, seriously reducing the ability of the cell membrane to slow the electric current. Using this phenomenon, the infiltration can be detected in thin blood vessels such as those in neonates.

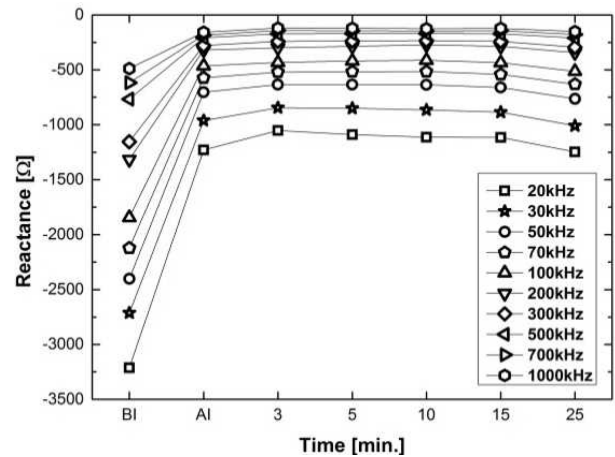


Fig. 6. Reactance as a function of time during IV solution infusion into the vein of rabbit's posterior ear.

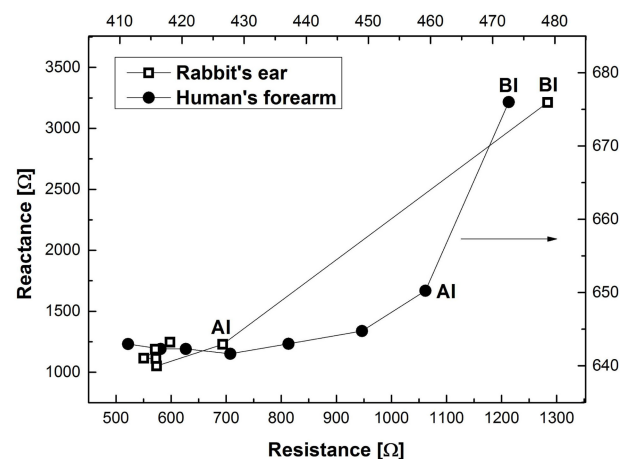


Fig. 7. Reactance versus resistance before and after infiltration during IV solution infusion into the veins of the rabbit's ear and human's forearm. BI indicates the time before infiltration occurs and AI indicates the time at which infiltration occurs.

3.4 Resistance (R) versus reactance (X_C)

Fig. 6 shows the relationship between resistance (R) and reactance (X_C) during the infusion of IV the solution into the veins in the rabbit's ear and the human's forearm. When infiltration was induced in the vein of the rabbit's ear, the position at AI in the R - X_C graph abruptly shifted relative to the position at BI. This indicates that the ear of the rabbit is thin and the surrounding subcutaneous tissues are so small that IV and blood components easily accumulate in the subcutaneous tissues during infiltration and less accumulated after infiltration. On the other hand, when infiltration was induced in the vein of human's forearm, the position in the R - X_C graph gradually changed, revealing that the IV solution and blood components leaking out of the vein continue to accumulate in the surrounding subcutaneous tissues.

4. DISCUSSION

Infiltration is particularly difficult to detect early on. To date, techniques for detecting the infiltration have largely relied on clinical methods, which include visual and tactile examination of the skin and tissues surrounding the IV injection site for factors such as tissue pressure, color, edema, turgor, and temperature [8]. However, these methods have disadvantages in detecting infiltration because infiltration is better identified after tissue damage has already occurred in subcutaneous tissue. In addition, infiltration detection systems were mainly developed using infrared light. Infiltration was recognized to decrease the reflectivity due to the leaked solution when comparing the reflectance of the lights before and after infiltration [12, 26,]. Moreover, these data do not accurately reflect the accumulation of solution/fluid from the vein into the surrounding subcutaneous tissue, because they depend on the partial reflectivity of the IV solution exposed to the skin and the infiltrated IV solution (also blood components) into the subcutaneous tissue.

In this study, BIA was used to investigate the pathophysiological properties of biological tissues to detect infiltration. When infiltration was intentionally induced in the vein of rabbit's ear, impedance parameters showed significant difference before and after infiltration. On the other hand, when infiltration was induced in the vein of the human's forearm, impedance parameters gradually changed because the IV solution accumulates in thick subcutaneous tissue.

Compared to the relative resistance before infiltration (BI), the relative resistance at 20 kHz was largely reduced at infiltration (AI), slowly decreased, and stayed at a constant value. This indicates that the vein in the rabbit's ear was thin so that the infiltrated IV solution no longer accumulated after 3 min of infiltration. In addition, when infiltration was intentionally induced in the vein of a human forearm, the relative resistance at 20 kHz gradually decreased over time. This indicates that the vein in the human's forearm was thick and there are many subcutaneous tissues, so that the IV solution continued to accumulate in subcutaneous tissues over time. Moreover, when infiltration was induced in the vein of the rabbit's ear, the position at AI in the R - X_C graph abruptly shifted to the position at BI. This indicates that the ears of the rabbit are thin and the surrounding subcutaneous tissues are so small that the IV solution and blood components easily accumulated in the subcutaneous tissues during infiltration and accumulated less after infiltration. However, when infiltration was induced in the vein of the human's forearm, the position in the R - X_C graph gradually changes over time, revealing that the IV solution and blood components leaking out of the vein still continue to accumulate in the surrounding subcutaneous tissues. Using multifrequency bioelectrical impedance and an equivalent circuit model of the cell, the IV solution leaking from the vein after infiltration was confirmed to accumulate in the ECF, proposing an indicator for early detection of infiltration.

5. CONCLUSIONS

In this study, impedance parameters were measured as a function of time and frequency during the infusion of IV saline solution into the vein in a rabbit's ear and a human's forearm. Experimental results are summarized as follows. When infiltration was intentionally induced with a needle in the rabbit's ear, impedance parameters (R , R/R_{BI} , X_C , and R vs. X_C , and R vs. X_C) exhibited significant differences before and after infiltration. However, when infiltration was deliberately induced in the vein of the human's forearm, these parameters gradually changed over time. These results indicate that the vein in the ear of a rabbit is thin and there are less subcutaneous tissues such that the infiltrated IV solution no longer accumulates after 3 min of infiltration, and that the vein in the human's forearm is thick and there are more subcutaneous tissues such that the infiltrated IV solution continues to accumulate in subcutaneous tissues

over time. In addition, when infiltration was induced in the rabbit's ear, the relative resistance measured at 20 kHz was reduced largely at infiltration (AI), slowly decreased, and then reached a constant value. However, when infiltration was induced in the human's forearm, the relative resistance decreased gradually over time. Thus, in thin blood vessels, the relative resistance is markedly different before and after infiltration whereas the relative resistance in thick blood vessels gradually decreases over time because the IV solution and blood components continue to accumulate in the surrounding subcutaneous tissues after infiltration. Our findings could be applicable to detect the infiltration early in neonates with narrow veins and severe patients with frequent infiltration.

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