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Basic Research on Blood Coagulation Measurement of Extracorporeal Circulation Circuit Using Photoacoustic Imaging of LED Light Source

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Abstract: In extracorporeal circulation devices such as ECMO, blood coagulation occurs due to various factors. Blood coagulation in the extracorporeal circulation circuit is detected ex post facto by existing pressure sensors. Subsequent detection of blood clots leads to the destruction of blood in the circuit, which is detrimental to the patient. Therefore, for the purpose of preliminary measurement in the extracorporeal circulation circuit, we will conduct basic research on measurement using photoacoustic imaging using LEDs as a light source and report it (AcousticX). As a result of measuring the blood in the extracorporeal circulation circuit circulated using the extracorporeal circulation device by photoacoustic imaging over time, it was found that the wave number and intensity of the photoacoustic wave increased with the passage of time. It has been shown that it is possible to measure the temporal change of blood coagulation circulating in the circuit.

Keywords: Blood coagulation, Photoacoustic imaging, LED, Circuit in an extracorporeal device, Temporal observation, Predictive maintenance.

1. Introduction

ECMO (Extracorporeal membrane oxygenation) is said to be the last bastion for the treatment of severely infected COVID-19 infections. When COVID-19 becomes severe, it is difficult to breathe on its own, and an oxygen mask is insufficient. A ventilator inserts a resin tube through the mouth or throat to deliver oxygen to the lungs and help breathe. In other words, it assists the function of the lungs. After that, when it becomes more serious, the ECMO is connected to the patient. It can also deal with respiratory failure and circulatory failure. The ECMO removes blood from the body, supplies oxygen, excretes carbon dioxide, and returns it to the body. It is a treatment that replaces respiratory and circulatory functions until the patient heals and recovers. In other words, it replaces the function of the lungs, so it is not a radical cure. The configuration of ECMO is shown in Fig. 1.

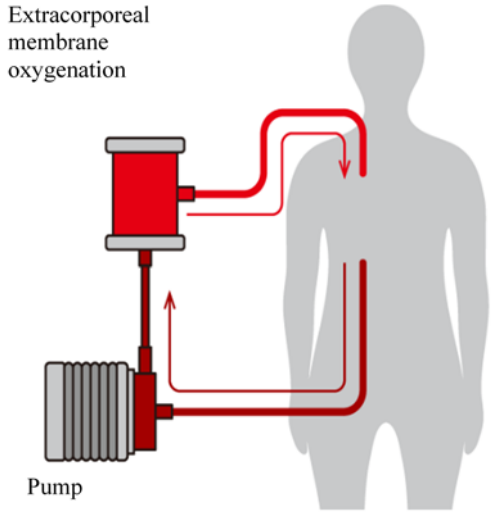


Fig. 1. The configuration of ECMO.

Respiratory failure is the most common cause of death for COVID-19, but the following can also be the cause of death. Causes of death are coagulation activation with excessive immune / inflammatory reactions, so-called cytokine storms, thrombosis, disseminated intravascular coagulation (DIC), and progression to multiple organ failure. [1-5]. In particular, thrombosis and DIC can lead to a rapid deterioration of the condition. Of course, even within the extracorporeal circulation circuit of ECMO, if blood coagulation progresses, it will become clogged and ECMO will not function. Extracorporeal circulation therapy such as ECMO is used in various fields such as heart-lung machines and acute blood purification devices. In the circuit that circulates blood outside the body, blood coagulation occurs due to various factors as described above [6-8]. Various attempts have been made to prevent blood coagulation, and preventive measures using anticoagulants (such as heparin) are currently the mainstream [9-12]. Heparin coatings are used in extracorporeal circulation circuits to suppress coagulation caused by the reaction of blood with foreign bodies [13, 14]. However, since heparin also acts as a foreign substance, it is difficult to completely prevent blood coagulation on the circuit surface. When the circuit is clogged, it is detected by a pressure sensor inside the extracorporeal circuit. However, the detection will be ex post facto because it will be detected after the blood flow in the circuit becomes extremely slow or the circuit is clogged. Subsequent detection of blood coagulation leads to forcing medical staff to take immediate action such as discarding blood in the circuit or replacing the circuit, which is disadvantageous for patients and hospital staff. However, in order to observe changes in blood coagulation status in the extracorporeal circulation circuit in advance, a method with higher sensitivity than the conventional method is required. Therefore, a photoacoustic method was tried as a new measurement method. For the specifications and usage of the photoacoustic method, we referred to the reports of our predecessors. [15-17]. Basic research reports using photoacoustic imaging using LEDs as a light source were conducted at SEIA' 2019 and SEIA' 2020 [18, 19]. In photoacoustic imaging, the measurement target undergoes volume expansion due to the heat generated by the light source, and elastic waves are generated. Elastic waves are received and imaged by ultrasonic probes. The aim of this study is to observe the time course of blood coagulation that occurs in the extracorporeal circulation circuit during blood purification therapy. Since this experiment is a basic experiment, an inexpensive dialysis circuit was used as a circuit measurement target without using an expensive extracorporeal circulation circuit represented by ECMO. Since the dialysis circuit is the same closed circuit as the ECMO circuit, it is considered that there is no difference in measurement. The measurement targets were an air trap to prevent air embolism and a drip chamber equipped with a mesh filter to prevent the generated blood clots from flowing into the body from the extracorporeal circulation circuit. Fig. 2 shows how the blood flow is almost stationary. A drip chamber with slow blood flow is the most suitable measurement target in the circuit because blood coagulates most easily.

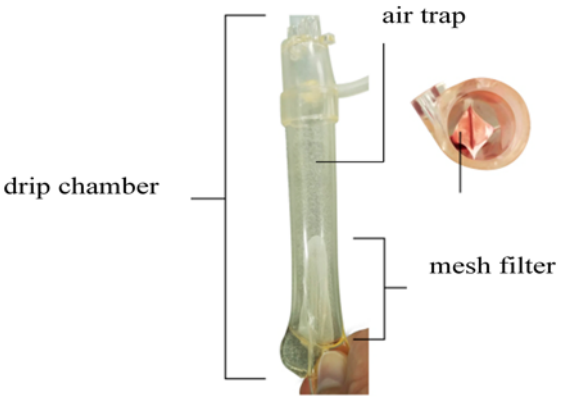


Fig. 2. Drip chamber (overview and cross section).

In a previous research report, blood in a microtube simulating an extracorporeal circulation circuit was measured by photoacoustic imaging with an LED light source. In this paper, we used an extracorporeal circulation device to more practically advance the basic research conducted with microtubes. Using an extracorporeal circulation device, sheep's blood was circulated in the extracorporeal circulation circuit, and the drip chamber was measured by photoacoustic imaging using an LED as a light source.

2. Method

2.1. A-mode Measurement of Solidification Process by Photoacoustic Wave using LED as a Light Source

Fig. 3 shows a schematic diagram of the experimental equipment used in this study. We

examined the measurement of the blood coagulation process in A mode using AcousticX (CYBERDYNE, INC.). Approximately 80 mL of blood was injected into the circulation circuit used in acute extracorporeal circulation therapy. Blood is pumped out by a roller pump and circulates in the circuit. Blood circulates in the circuit at a flow rate of 60 ml/min. The blood temperature was set to 37 °C, which is commonly used in blood purification therapy. The ultrasonic probe used for photoacoustic imaging measurements and the two LED arrays are fixed at about 40 degrees using a jig. The ultrasonic probe and LED were held by hand in the drip chamber to be measured. Regarding the installation of measuring instruments, we refer to the research so far. [18, 20]. The light energy was about 200 μJ/pulse, and the wavelength was 850 nm. There were two types of ultrasonic probes, 10 MHz and 7 MHz. At 10 MHz, the distance resolution improved to some extent, but at 7 MHz, the depth sensitivity increased 4 to 5 times. Therefore, we chose an ultrasonic probe frequency of 7 MHz.

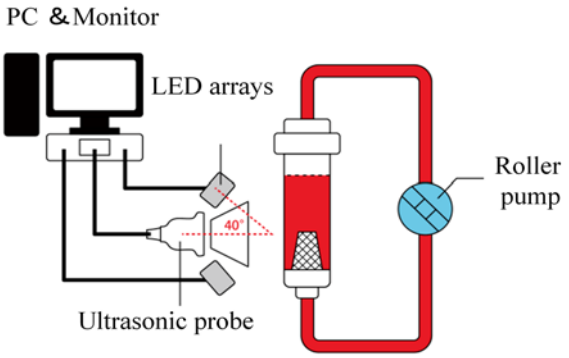


Fig. 3. Configuration diagram of this experiment.

When considering the possibility of a predictive maintenance system, it costs money to use a large amount of blood, and it also takes labor and budget to dispose of it after the experiment. Since a large amount of blood cannot be used at the initial research stage on a budget, I wanted to reduce the amount of blood used as much as possible and increase the number of measurements so that the reproduction of blood coagulation would not be affected. Therefore, in this experiment, the blood used was changed to commercially available sheep blood. Details of the sheep blood used are as follows. Shown in Table 1.

The commercially available blood used is anticoagulant-treated with the anticoagulant ALSEVER'S SOLUTION for transportation. In order to promote blood coagulation, calcium required for blood coagulation is required. By the way, coagulation factors and phospholipids are already contained in blood, so there is no need to add them to commercially available sheep blood. Therefore, we used calcium gluconate as a coagulation accelerator. The upper limit solubility of calcium gluconate is 3.3 g per 100 ml. Infuse 50 ml of blood with 1.1 g of calcium gluconate dissolved in 33 ml of saline.

Table 1. Details of the sheep blood used.

Blood	Aseptic storage blood of sheep
Capacity	100 ml / container
Model number	12070210 Kojin Bio Co., Ltd.
Anticoagulant	Contains anticoagulant (Arsever solution)

2.2. Judgment Criteria When Coagulation Occurs in the Extracorporeal Circulation Circuit

Next, the criteria for determining the occurrence of blood coagulation in the extracorporeal circulation circuit will be described. Since it is difficult to measure the degree of blood coagulation in the circuit during extracorporeal circulation in real time, we observed the following three points where signs of blood coagulation appear in the extracorporeal circulation circuit. These three points are the points used in the medical field to empirically judge the coagulation in the circuit:

1) The blood liquid level in the air trap chamber drops;

2) The venous pressure measured by the pressure sensor decreases;

3) Small bubbles are generated around the roller pump.

2.3. Multidimensional Analysis Based on Photoacoustic Waveform Measurement Modes

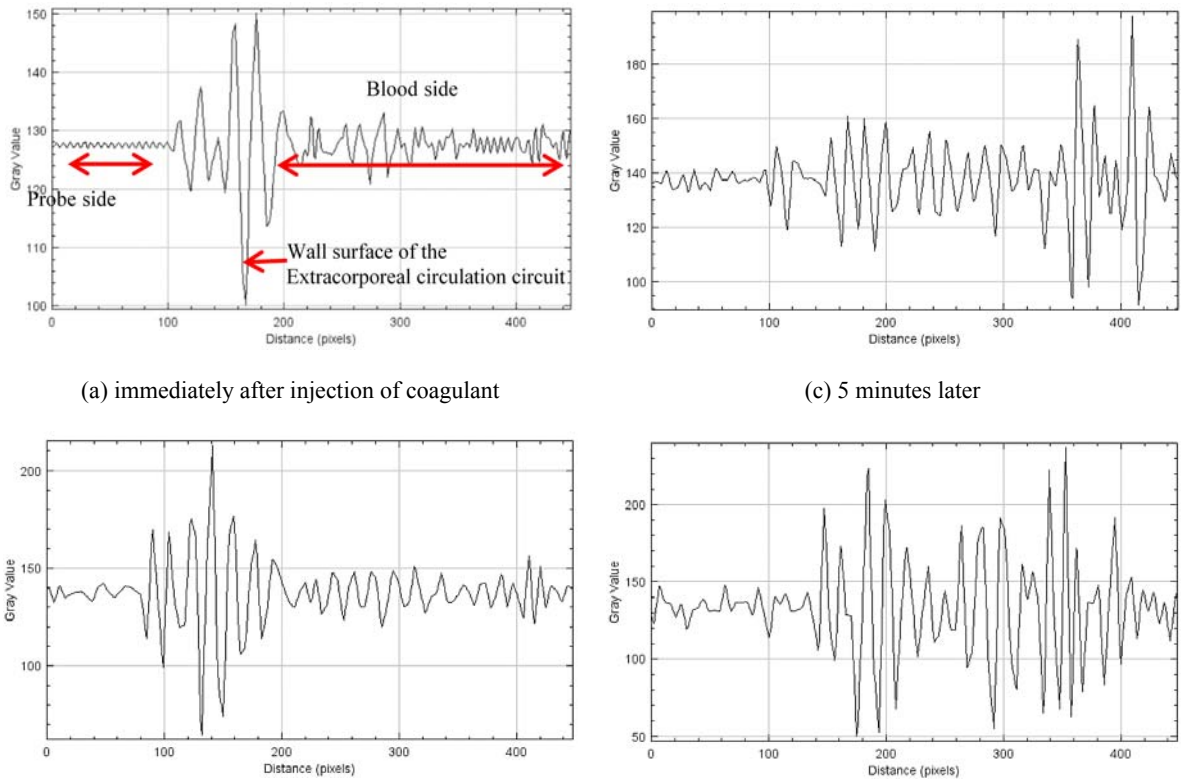
Based on the measurement result of A mode measured in 2.1 above, an image is created and the change over time is analyzed. The waveform of A mode measured in the drip chamber is synthesized, and the image of the elastic wave in the entire drip chamber (B mode) is shown. We also converted the B-mode image into 3D and analyzed the photoacoustic waves that occur over time. ImageJ, a free software, was used for both imaging and analysis.

3. Result

3.1. A Mode Measurement

The photoacoustic wave generated from the drip chamber was measured with an ultrasonic probe, and the result of A mode measurement at the point where the intensity of the photoacoustic phenomenon is shown by the red dashed line in Fig. 3 is shown in Fig. 4. The vertical axis represents the intensity of elastic waves generated from photoacoustic phenomena, and the horizontal axis represents the distance from the ultrasonic probe. The part showing the maximum amplitude of the graph is the wall

surface of the drip chamber, the left side is the ultrasonic probe, and the right side is the inside of the drip chamber (blood). In order to measure the time course of the blood coagulation process, immediately after injecting the coagulant into the drip chamber (Fig. 4 (a)), 2 minutes (b), 5 minutes (c), and 10 minutes later (d), the photoacoustic phenomenon of blood was measured separately.



(a) immediately after injection of coagulant

(c) 5 minutes later

(b) 2 minutes later

(d) 10 minutes later

Fig. 4. Measurement of photoacoustic phenomenon using A mode ultrasonic imaging.

3.2. Judgment Criteria When Coagulation Occurs in the Extracorporeal Circulation Circuit

The experimental results are as follows. A slight change was observed about 7 minutes after injecting 1.1 g of calcium gluconate and 33 ml of physiological saline. After 10 minutes, there was a clear change (confirmed the developmental criteria shown in (4)), and after 15 minutes, there was complete blood flow loss. Fig. 5 shows the state around the roller pump after 15 minutes. From the photograph in Fig. 5, the entire circuit becomes negative pressure and is slightly dented. In addition, bubbles can be confirmed in the circuit. Based on these facts, in this study, 10 minutes after injection of calcium gluconate and physiological saline, which is considered to cause the extracorporeal circulation therapy to stop functioning, was set as the time required for blood coagulation in the extracorporeal circulation therapy. The situation at 3 points 10 minutes after injection of calcium gluconate and saline is as follows:

1) Drop of 1.8 cm from the liquid level at the start of the blood level in drip chamber;

2) Negative pressure state (-1 to -10 mmHg) at the start of the experiment: about 60 mmHg;

3) Generation of bubbles (Many bubbles are generated in the red arrow part).

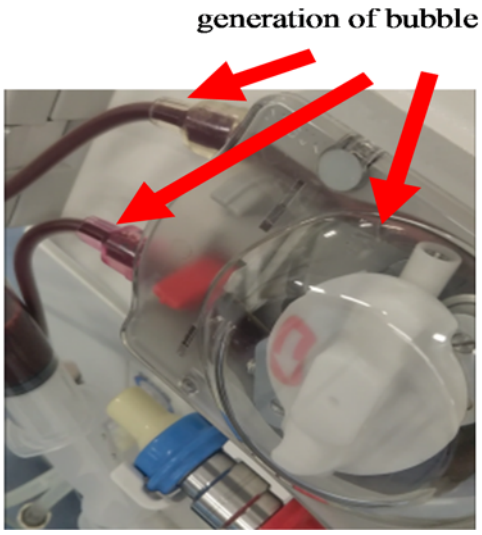


Fig. 5. Bubbles on the pump pull-in side when severe blood coagulation occurs.

3.3. B-mode Measurement and 3D Analysis

3.3.1. B mode

In the drip chamber shown in Fig. 6, the left side of the wall surface is the ultrasonic probe side, and the right side is the blood. The white color (The white color parts) in Fig. 6 indicates that blood obtains light energy and a strong elastic wave is generated by a photoacoustic phenomenon. On the contrary, black (low brightness) indicates that the photoacoustic phenomenon has not occurred or is extremely low. In addition, Fig. 7 shows the measurement results (B mode) reported at SEIA 2019 in order to compare with the time course of blood coagulation in a microtube without blood flow.

3.3.2. 3D Imaging

In order to show the change of blood coagulation over time in Fig. 6 more prominently, the gray scale image in Fig. 6 was converted into a 3D color scale graph as shown in Fig. 8 using the free software ImageJ. Fig. 8 shows the black dotted line points to the wall of the drip chamber.

The right side of the drip chamber wall surface is the blood side (inside the drip chamber), and the left side of the wall surface is the ultrasonic probe side. The x-axis represents the horizontal distance (1 cm from the ultrasonic probe to the blood side), the y-axis represents the vertical distance, and the z-axis represents the pixel brightness (256 levels). The brightness is expressed in 256 steps from 0 to 255. In addition, the low brightness becomes purple, and as the brightness becomes high, it becomes white through orange and yellow. It is considered that the higher the value of the z-axis, the stronger the photoacoustic phenomenon.

4. Consideration

With the passage of time, the position and amplitude of the vibration wave measured by the ultrasonic probe changed. It is considered that the possibility of time-dependent changes due to blood coagulation was shown in the extracorporeal circulation circuit. Comparing to Fig. 6 and Fig. 7, it can be seen that the thick black line is not shown like the microtube wall surface of the B mode image (measurement target: microtube) shown in SEIA2019, and there are ripples. From Fig. 6, the width of the ripples is about 0.2 to 0.3 cm, which is the same as the thickness of the wall surface of the air trap chamber, and from the measurement position, it is considered that the ripples with this width are the wall surface of the air trap chamber. Compared to the micro tube, the wall of the tube is soft and then impedance was almost same as that of the ultrasonic probe gel spacer.

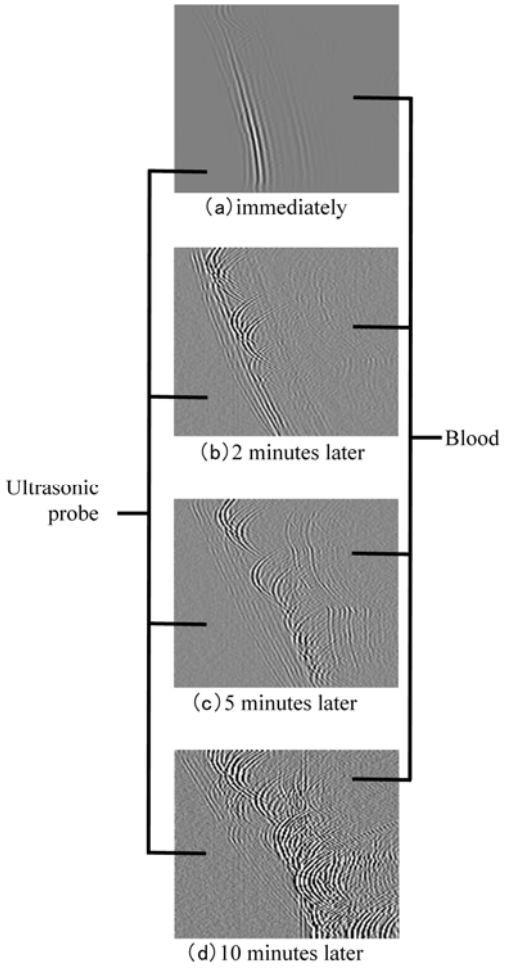
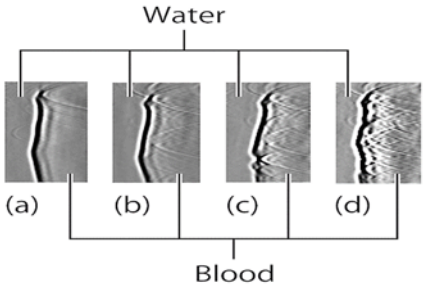


Fig. 6. B mode image by photoacoustic.

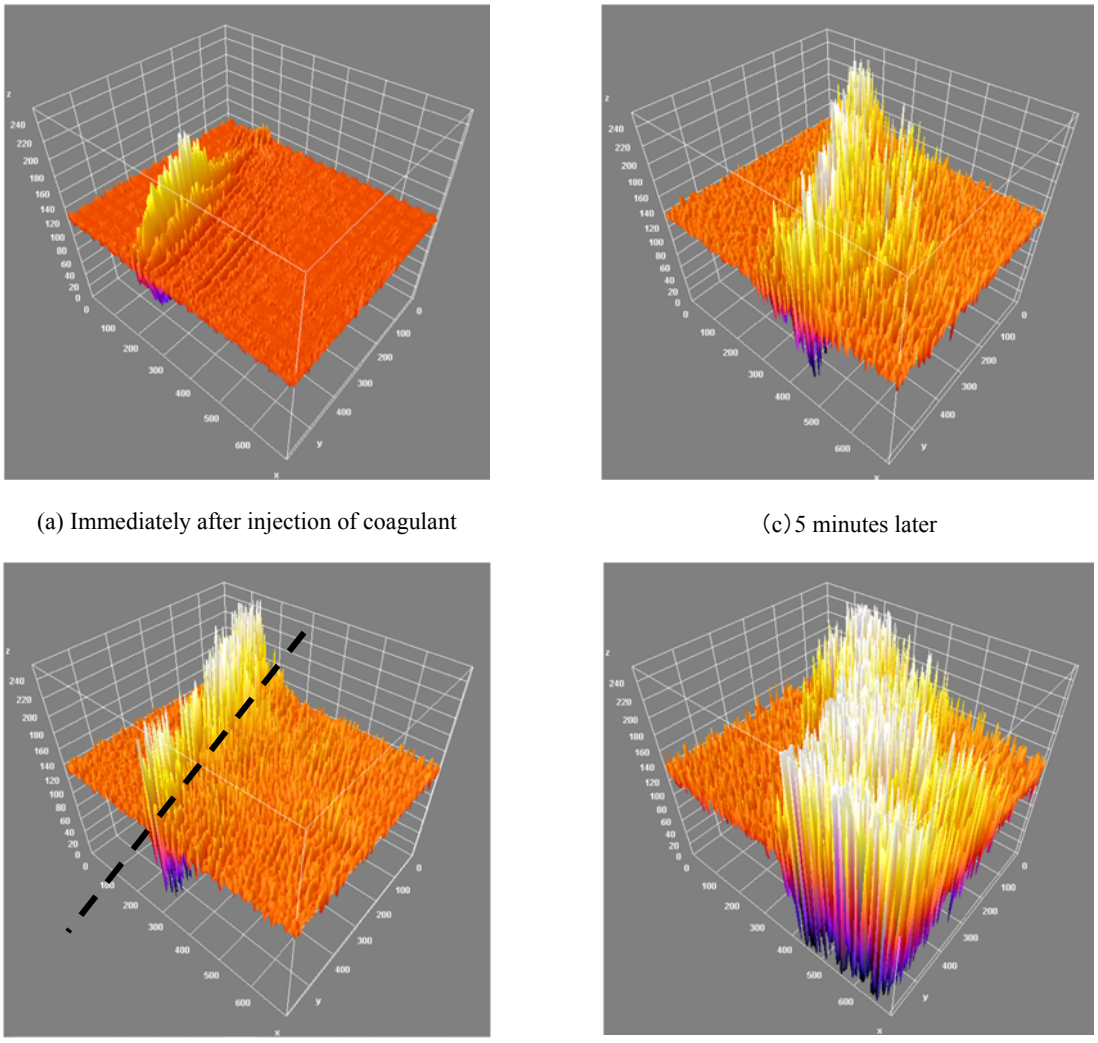


(a) Immediately; (b) 2 minutes later; (c) 5 minutes later; (d) 10 minutes later

Fig. 7. Photoacoustic imaging measurement results reported at SEIA' 2019 (blood coagulation in microtubes).

So it is considered that it was not observed as a thick black line due to wall. Also, the entire B-mode image is slanted. This is because the ultrasonic probe and LED light source do not use a jig and are held and measured by hand. When force was applied to improve the adhesion between the transparent gel spacer and the air trap chamber, the gel spacer was deformed because the transparent gel spacer was soft. From these, it was concluded that the positional relationship between the ultrasonic probe and the object to be

measured was slanted (Fig. 9). Similar results were obtained even if the measurement was repeated while changing the measurer. From the results of this experiment we found that it is important to devise jigs and other devices to apply uniform force.



(a) Immediately after injection of coagulant

(c) 5 minutes later

(b) 2 minutes later

(d) 10 minutes later

Fig. 8. 3D diagram of luminance part by ImageJ.

Fig. 9. Measurement diagram of drip chamber.

From Fig. 8 (a) to (d), it can be seen that the brightness (photoacoustic wave) is high centering on the wall surface of the drip chamber. From Fig. 8, it is considered that the increase in blood coagulation could be confirmed from the inner wall where blood reacted with foreign matter and the mesh filter because the parts where the photoacoustic wave changes strongly are on the wall surface and around the mesh filter.

The anticoagulant Alsever was injected into the blood in the drip chamber and the progress was compared. Fig. 10 (a) shows the results of this experiment, Fig. 8 (d), and Fig. 10 (b) shows photoacoustic imaging 10 minutes after injecting Alsever. It was found that even in the presence of blood flow, no photoacoustic wave is generated when the blood is not coagulated.

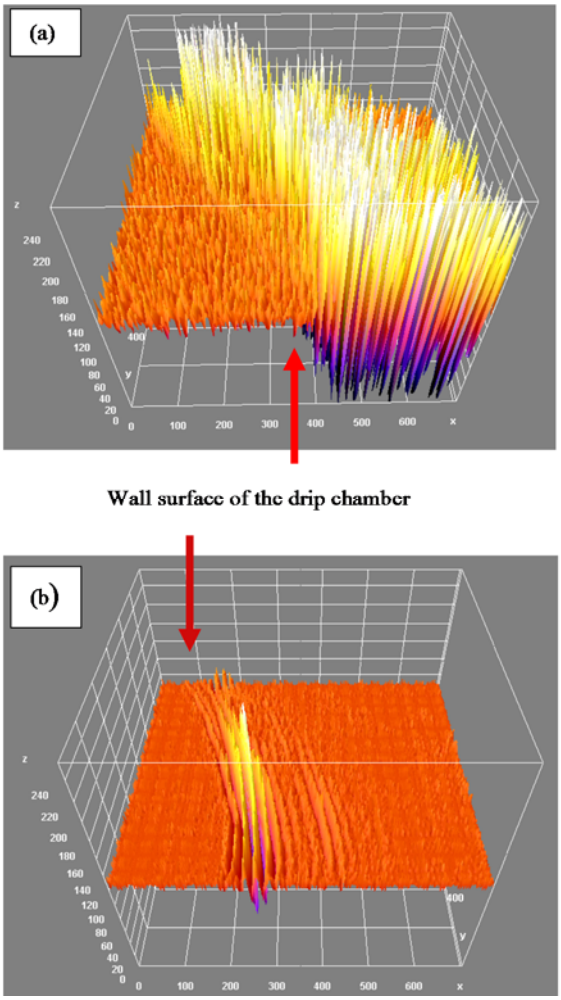


Fig. 10. Comparison of blood coagulation in the drip chamber and blood containing anticoagulant: (a) 10 minutes after blood coagulation begins, (b) 10 minutes after injecting the anticoagulant.

5. Conclusions

We measured the blood coagulation as the changes of the whole extracorporeal circulation circuit, using photoacoustic imaging, instead of measuring individual blood clots. As with the measurement results of changes in blood coagulation in microtubes in SEIA 2019 over time, changes in blood coagulation in the extracorporeal circulation circuit can be measured using the extracorporeal circulation circuit, and demonstrated the possibility of predictive maintenance in extracorporeal circulation therapy. In addition by using LED photoacoustic imaging. We showed the possibility of simple measure machine with a small sensor.

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