NON-INVASIVE BLOOD CLOTTING DETECTION FOR EXTRACORPOREAL CIRCULATION USING AN OPTICAL SENSOR

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ABSTRACT

Appropriate anticoagulants and real-time monitoring of blood clotting are essential to provide patients with safe extracorporeal circulation. However, in actual clinical practice, only visual monitoring is performed, and automatic real-time monitoring of blood coagulation is not implemented. In this study, we investigated whether blood coagulation could be detected automatically by using the change in blood color with blood coagulation. A reflective color sensor was used as the optical sensor. Bovine blood was used in this study, and calcium chloride was added to neutralize the anticoagulant. The RGB (R: red, G: green, B: blue) values of blood color were recorded every three minutes for 30 minutes until the bovine blood coagulated. The data were recorded on a personal computer with a sampling frequency of 1 Hz and a recording time of 15 seconds. In the measurement results, it was difficult to visually distinguish the change of blood color with the blood clotting process. However, the recorded R value could represent the stage of blood coagulation. The R value and elapsed time had a very strong negative correlation (r = -0.983, $p < 0.001$). Moreover, the change in R value was observed to decrease by approximately 3% ($p < 0.01$) after 9-12 minutes, 5% ($p < 0.001$) after 15-18 minutes, and 10% ($p < 0.001$) after 21-24 minutes compared with the 0-minute time point. The decrease in R value gradually decreased with blood clotting, reaching about 15% at the 27-30 minutes points. No changes were observed in the G or B values with blood clotting. This study found that blood clotting can be detected by the R value. The R value detected by color sensor depended on blood clotting, thus suggesting that a color sensor may be available for real-time monitoring of blood clotting in the blood circuit during extracorporeal circulation.

Keywords: Color sensor, Blood color, Blood clotting.

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1. INTRODUCTION

Evaluation of blood clotting is necessary for patients during extracorporeal circulation, anticoagulant therapy, and coagulopathy. Coagulation analysis can not only be used to detect coagulation failure associated with disease, but also to monitor the effects of drugs such as anticoagulants [1]. In extracorporeal circulation devices like hemodialysis and mechanical circulation support, blood clotting is promoted by contact of the blood with the non-physiological substances (e.g., the dialysis membranes and blood lines). This is attributed to the intrinsic coagulation mechanism and activation of platelets. In the extracorporeal circulation, such as dialysis, blood clotting was incurred by the functioning of intrinsic and extrinsic coagulation [2]. In addition, patients with chronic renal failure tend to bleed [3], [4] and have blood hypercoagulability [5], [6]. The bleeding tendency is thought to be caused by a decline in platelet function from uremia [7]. Chronic renal disease patients may already have cardiac disease before the start of dialysis, but dialysis patients have a risk for developing cardiovascular disease, such as cardiac arrest, acute myocardial infarction, and cerebrovascular disease [1], [2], [8-14]. Therefore, anticoagulants for patients in extracorporeal circulation avoid the generation of blood clots, and it is necessary to pay attention to bleeding. Generally, anticoagulants for dialysis patients are administered by systemic coagulation and local coagulation. Local anticoagulants are applied to patients who have a high risk of bleeding, while systemic anticoagulants are applied to patients with low risk of bleeding. Therefore, the use of appropriate anticoagulants is required to perform safe and effective dialysis for patients. For efficient dialysis, anticoagulants are needed to secure the openness of dialysis membranes and lines without blood clotting. Thus, anticoagulants in hemodialysis are intended to prevent the occurrence of the blood clotting in the blood circuit during this process. However, the prescription of anticoagulants is determined by the specific clinical condition of the patient [15]. Furthermore, the anticoagulants should be carefully administered when the dialysis patient has a high risk of bleeding. Anticoagulants have different half-lives depending on the type. When anticoagulants with a long

half-life are being administered to patients with bleeding tendency, concern must be given to the risk of complications such as cerebral hemorrhage and gastrointestinal hemorrhage [10], [16]. Conversely, anticoagulants with a short half-life are at risk of coagulation in the extracorporeal circulation circuit. If blood clotting occurs in the blood circuit during extracorporeal circulation, the blood circuit must be replaced. The blood in the circuit is then lost. This will place a burden on medical staff and result in increased medical expenses. Therefore, real-time monitoring is required to reduce the risk of blood clotting in the extracorporeal circulation circuit. However, real-time monitoring of blood clotting during hemodialysis has not been performed [17]. In the blood coagulation detector, technological methods of whole blood clotting analysis measurement have already been established. Blood clotting detection using mechanical, optical, and electromagnetic methods is a common technology [18]. In this study, we focus on optical sensors that have achieved dramatic development in recent years and investigate whether real-time monitoring of blood clotting in extracorporeal circulation is possible with an optical sensor.

2. METHODS

2.1 Blood coagulation monitoring system

In this study, a measurement system was constructed to detect changes in blood color associated with blood clotting. Figure 1 shows a block diagram of the experiment used for measuring blood clotting. The measurement system consists of a color sensor (TCS3200, amsAG, Premstätten, Austria) that detects RGB (R: red, G: green, B: blue) values and a control box (Arduino UNO Rev3) that transmits the outputs from the color sensor to the computer. The TCS3200 of the color sensors is Arduino compatible that converts visible color intensity to frequency with the array of red, green, and blue optical detectors. The blood is injected into a clear glass beaker. The color sensor for identifying blood color is mounted on the bottom of a clear glass beaker. The bottom of the beaker containing blood is illuminated by a white LED, and the light reflected by the blood is detected by a color sensor. The detected data are entered in the control box, which outputs the RGB value of each 8 bits for blood color. These RGB color data are recorded on the computer. The beaker containing the blood and the color sensor were shielded by corrugated carton to exclude the effects of external light.

2.2 Blood

Bovine blood (10 mL; Lot No. HNEGA-015, Japan Bio Serum Co. Ltd, Tokyo, Japan) was used. The bovine blood was returned to room temperature (25°C) before starting measurements. Anticoagulants (Alsever) were used in bovine blood for the purpose of preservation. Then, 15 mL of neutralizer ($CaCl_2$: 0.025 mol/L, Lot No. U2840, Sigma-Aldrich Japan, Tokyo, Japan) was added to the bovine blood (bovine blood + $CaCl_2$), immediately before the measurement. As a control, 10 mL of bovine blood containing no $CaCl_2$ was prepared for comparison. Both the bovine blood + $CaCl_2$ and the control were measured under the same conditions.

2.3 Measurement conditions

The data output from the control box was recorded on the computer with a 1 Hz sampling frequency and a recording time of 15 seconds. In this study, the changes in blood color with blood clotting were measured for both the bovine blood + $CaCl_2$ and the control. The blood color standard (reference value) was set to observe any change in blood color over time. This was the RGB value of each blood sample at the start of the measurement

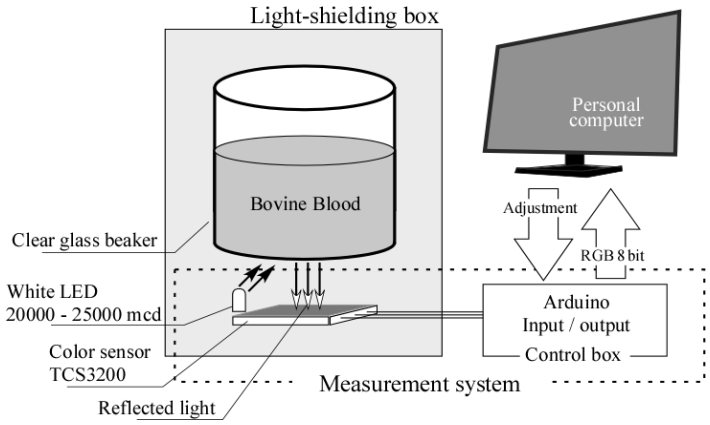

Figure 1. Block diagram of the blood coagulation monitoring system. Bovine blood was added to a clear glass beaker, which was left unsealed. A color sensor was mounted on the bottom of the beaker, assuming the detection of non-invasive blood coagulation. White LED with a luminous intensity of 20,000 – 25,000 mcd was used as the light to irradiate the bottom of the beaker.

period (0 minutes). RGB values were recorded every 3 minutes for 30 minutes.

3. RESULTS

RGB values of the bovine blood + $CaCl_2$ were detected by color sensor every 3 minutes, and each blood condition was visually confirmed after recording the RGB values. Figure 2 shows the bovine blood + $CaCl_2$ condition at the 0, 3, 12, 18, 24 and 30-minute time points. Blood clotting was not confirmed visually from the start of measurement until 9 minutes. Changes to the blood were slightly recognized at the 12-minute point, the blood clotting state was confirmed after 15 minutes, and the blood clot was completely formed after 21 minutes. Table 1 (control bovine blood) and Table 2 (bovine blood + $CaCl_2$) show the changes of RGB value over time from the 0 to 30-minute time points. The G value was zero in both the control bovine blood and the bovine blood + $CaCl_2$. The B value change was only slight, and no significant difference was observed in compare with reference. However, significant changes were obtained in R or B value of the control bovine blood and the bovine blood + $CaCl_2$ at 0 min ($p < 0.001$). A positive correlation was observed between blood color and elapsed time (r = 0.569, p = 0.0862) for the B value of the control bovine blood. In contrast, a negative correlation was observed (r = -0.584, p = 0.076) for the bovine blood + $CaCl_2$. Similarly, a positive correlation (r = 0.406, p = 0.245) was observed for the R value of the control bovine blood. However, a strong negative correlation (r = -0.983, $p <$ 0.001) was observed for the R value of the bovine blood + $CaCl_2$. Therefore, we focused on the R value for the analysis of detecting blood clotting. However, a difference appeared when comparing the R values of the control bovine blood with the bovine blood + $CaCl_2$, with

Figure 2. The blood coagulation stage of the bovine blood + $CaCl_2$ at the 0, 3, 12, 18, 24, and 30-minute time points.

Table 1. RGB values (average ± standard deviation) of bovine blood

Time (min)	Bovine blood (Control)		
	R-value	*G-value*	*B-value*
0 (reference)	184.67 ± 3.50	0.00 ± 0.00	11.80 ± 3.10
3	182.20 ± 1.52	0.00 ± 0.00	9.60 ± 3.91
6	186.93 ± 4.61	0.00 ± 0.00	13.47 ± 5.40
9	186.87 ± 3.36	0.00 ± 0.00	11.00 ± 0.00
12	186.87 ± 3.36	0.00 ± 0.00	11.13 ± 0.00
15	186.87 ± 3.36	0.00 ± 0.00	13.00 ± 5.28
18	186.00 ± 0.00	0.00 ± 0.00	12.27 ± 3.86
21	186.87 ± 3.36	0.00 ± 0.00	12.00 ± 3.87
24	186.87 ± 3.36	0.00 ± 0.00	13.00 ± 5.28
27	186.00 ± 0.00	0.00 ± 0.00	13.00 ± 5.28
30	185.73 ± 0.70	0.00 ± 0.00	13.20 ± 6.26

Table 2. RGB values (average ± standard deviation) of bovine blood + $CaCl_2$

Time (min)	Bovine + $CaCl_2$		
	R-value	*G-value*	*B-value*
0 (reference)	160.47 ± 3.62	0.00 ± 0.00	0.20 ± 0.77
3	161.87 ± 4.55	0.00 ± 0.00	1.27 ± 3.39
6	158.60 ± 1.55	0.00 ± 0.00	0.73 ± 2.84
9	157.20 ± 2.57	0.00 ± 0.00	0.53 ± 2.07
12	155.87 ± 3.36	0.00 ± 0.00	1.60 ± 2.75
15	151.80 ± 1.01	0.00 ± 0.00	0.20 ± 0.77
18	149.07 ± 3.79	0.00 ± 0.00	0.20 ± 0.77
21	145.07 ± 3.39	0.00 ± 0.00	0.00 ± 0.00
24	142.80 ± 4.66	0.00 ± 0.00	0.00 ± 0.00
27	138.13 ± 0.52	0.00 ± 0.00	0.00 ± 0.00
30	135.87 ± 1.55	0.00 ± 0.00	0.00 ± 0.00

the R value of the blood + $CaCl_2$ being lower. Therefore, each R value was normalized to the average of the reference data to compare the two samples. Figure 3 shows the changes in each normalized R value for the control bovine blood and the bovine blood + $CaCl_2$ over time. A significant decrease in R value after 3 minutes was observed compared with the reference data ($p < 0.05$) in the control bovine blood. Significant differences were not observed in the R values between the reference and the other data. The rate of change of the R value was 0.58-1.34%, and the maximum value was at the 3 minutes time point. In the bovine blood + $CaCl_2$ sample, no significant difference was observed compared with the reference data in the R value after 3-6 minutes. However, the R values were significantly different at the 9 and 12-minute time points ($p < 0.01$), and even more so at the 15 and 30-minute time points ($p < 0.001$), where the values decreased dramatically compared with the reference data. The rate of change in the R value was approximately 1% until the 6 minutes point. The rate of change then increased to approximately 3% at 9-12 minutes, 7% at 15-18 minutes, 11% at 21-24 minutes, and 15% at 27-30 minutes. Comparing the top part (control bovine blood) with the lower part color bar (bovine blood + $CaCl_2$) in the Fig. 3, the change in blood color was observable in the lower part color bar over time, but it was difficult to confirm in the top part color bar.

4. DISCUSSION

Anticoagulants were added to the bovine blood used in this study, which inhibit the coagulation action of calcium ions. Therefore, calcium chloride was added to bovine blood to activate the coagulation action. This study required blood coagulation within 30 minutes and rapid color change, surely. However, RGB values show incomplete coagulation of blood with recordings for less than 30 minutes. For 30 minutes over, the blood was complete of coagulation, therefore, there is no change in the RGB values. In this study, data were acquired at every 3-minutes for 30 minutes until blood clotting, and the data recording interval was gradual, which is not effects on the recording. Therefore, we adopted $CaCl_2$, which seems to be more than usual. The ratio of calcium chloride and the blood used in this study was prepared to complete the blood coagulation in 30 minutes. Our results revealed that the R and B value may be indicating the blood color changed with blood clotting. In particular, the R value showed a large change. Generally, as the RGB values increase, the color becomes more vivid. In contrast, as RGB values decrease, each color loses its vividness and approaches black. In this study, the decreased R value of the bovine blood + $CaCl_2$ suggested that the blood color changed from red to black, indicating the occurrence of blood clots. Thus, in these results, a decrease in R value indicates that a blood clot has

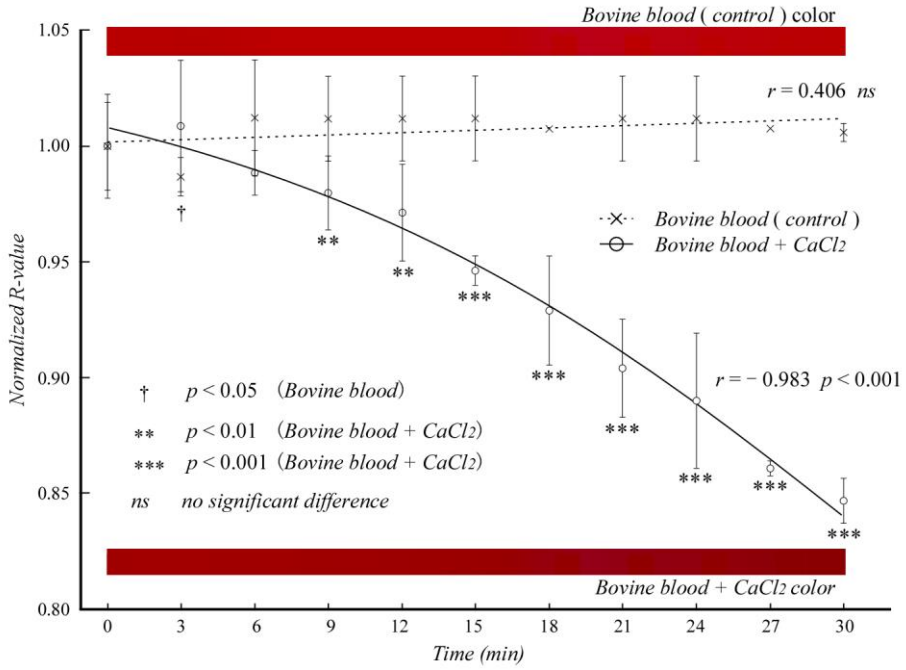

Figure 3. R value (blood color) over time. The cross mark and top color bar show the change in the R value of the control bovine blood, and the open circle mark and lower color bar show the change in the R value of the bovine blood + $CaCl_2$. R values with the control and bovine blood + $CaCl_2$ were analyzed by the correlation and the *t*-test. From the color bar, it seems difficult to clearly and quickly recognize that the blood color has changed compared with the reference blood color (0 minutes).

progressed over time. However, it is difficult for human vision to recognize the significant change of R value that can be detected by color sensors. Recognizing blood color in a blood clot can depend on an individual's color sense and clinical experience. Therefore, using this device may make it possible to detect blood clots in the blood circuit during extracorporeal circulation. A change in blood color was not observed in the bovine blood other than at the 3 minutes point. The R value was observed 1.34% ($p < 0.05$) lower than the reference data after 3 minutes. If this R value is low, it is inferred that it a blood clot is present. However, a change in the blood color was not observed for 30 minutes, and blood clotting was not observed in the control bovine blood. Furthermore, the change of R value was not observed in the blood color until after 6 minutes in the bovine blood + $CaCl_2$. Therefore, the observed decrease in the R value 3 minutes later may be an error from the measurement environment or an erroneous detection in the bovine blood. There was no significant change in R value of the control bovine blood, as it was suggested that the blood would not coagulate for 30 minutes. As a countermeasure against this error, it is conceivable to use a high sampling frequency, short-time measurement, and cut-off filter. The R value decreased significantly from the 9-minute point in the bovine blood + $CaCl_2$. The bovine blood may be occurred immediately the clotting reaction after added the $CaCl_2$. However, the bovine blood + $CaCl_2$ had not change blood color for 6 minutes. It thinks that low-temperature blood [19, 20], no flowing blood, and large amount of the $CaCl_2$ may affect the blood clotting mechanism. The no flowing blood compared with flowing blood may affect regulation of the blood clotting [21]. In addition, Ca^{2+} is the blood clotting factor, thus, the blood clotting was inhibited by low concentration of Ca^{2+} [22, 23], even high of Ca^{2+} may be slow the blood clotting [24]. Thus, these indicate that optimal Ca^{2+} concentration may promote the blood coagulation. In these results, it was estimated that blood clotting began to appear within 6-9 minutes, which was enhanced. The decrease in the R value observed in the bovine blood + $CaCl_2$ suggested that the blood clotting ability was activated by the addition of calcium chloride. It was difficult to visually confirm the blood clotting from the start of measurement until approximately 12 minutes later, but the blood clotting was confirmed at approximately 15-18 minutes later. However, the confirmation of clotting was not visually recognized by blood color. Therefore, if the blood is coagulated and grown, then blood clotting is visually confirmed. Yet, it was difficult to distinguish blood clotting by using blood color. Thus, it seems difficult that clinical staff can find or estimate blood coagulation in the extracorporeal circulation circuit by blood color only in early stage of the clotting process. In contrast, it was easy to detect the change in blood color using a color sensor. Moreover, this study indicates that the change of the R value depended on the progress of blood clotting, and the color sensor was able to detect the gradually changing blood color. Our results suggest that real-time monitoring of blood clotting in the blood circuit during extracorporeal circulation may be realized by using a color sensor.

5. CONCLUSION

In this study, we investigated whether blood clotting could be detected using a color sensor. Our analysis revealed a correlation between the R value measurement with the color sensor and blood clotting progress. In contrast, the G value measured by the color sensor was not related to blood clotting. Therefore, the R value detected by slightly 15 seconds (measurement time) may be suitable for monitoring the blood clotting stage. Moreover, using a color sensor may be useful for real-time detection of blood clotting changes over time. Our findings here suggest that optical sensors can non-invasively detect blood clotting in the blood circuit during extracorporeal circulation and allow the generation of caution and warning alarms that depend on the stage of blood coagulation. Therefore, the application of the system used in this study may contribute to providing safe extracorporeal circulation to the patients. However, this study did not use flowing blood. The next step will be performed with flowing blood using circulation circuit and pump. Moreover, B value and blood clotting progress were not analyzed detailly, this will be considered in the future. We will use a spectral camera to analyze blood color and compare with color model such as RGB and CMYK. Therefore, it is necessary to validate the experiment with multiple protocols and repeat the experiment.

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