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Abstract

Purpose

A survey conducted by Abiomed, Inc. revealed that 10 of 60 patients who received ventricular assistance via the AB5000 ventricular assist device (VAD) experienced hemolysis. The present study was conducted to investigate which factors influence hemolysis under pulsatile-flow VADs such as the AB5000.

Methods

We compared the specificity of the AB5000 and its driving console with those of the NIPRO-VAD and VCT50χ under severe heart failure conditions using a mock circulatory system with glycerol water solution. We used the mock circuit with bovine blood to confirm which pump conditions were most likely to cause hemolysis. In addition, we measured the shear velocity using particle image velocimetry by analyzing the seeding particle motion for both the AB5000 and NIPRO-VAD under the same conditions as those indicated in the initial experiment. Finally, we analyzed the correlation between negative pressure, exposure time, and hemolysis by continuously exposing fixed vacuum pressures for fixed times in a sealed device injected with bovine blood.

Results

Applying higher vacuum pressure to the AB5000 pump yielded a larger minimum inlet pressure and a longer exposure time when the negative pressure was under -10 mmHg. The plasma-free hemoglobin increased as more negative pressure was driven into to the AB5000 pump. Moreover, the negative pressure interacted with the exposure time, inducing hemolysis.

Conclusions

This study revealed that negative pressure and exposure time were both associated with hemolysis.

Key words: hemolysis; ventricular assist device; pulsatile flow; negative pressure; exposure time

Introduction

A ventricular assist device (VAD) is widely used as a bridge to transplantation, bridge to decision, and bridge to bridge therapy. Today, there are an increasing number of patients who want to use a left VAD as the destination therapy [1, 2]. The extracorporeal and pulsatile-flow VADs that are commercially available in Japan are the AB5000 (Abiomed, Inc., Danvers, MA, USA), the NIPRO-VAD (Nipro Corporation, Osaka, Japan) and the EXCOR pediatric VAD (Berlin Heart Inc., Berlin, Germany). A survey conducted by Abiomed, Inc. revealed that 10 of 60 patients who received ventricular support from the AB5000 VAD experienced hemolysis [3]. In continuous-flow VADs, turbulence effects may cause hemolysis owing to red blood cell (RBC) damage. This hemolysis increases when RBCs are exposed to significant fluctuations in shear stress [4, 5, 6]. In the pulsatile pump, although several parameters such as dehydration, aortic valve regurgitation, an increase in vacuum velocity at the inflow site, artificial valve, and the operating mode of the pump have the potential to cause hemolysis, the obvious cause of a high degree of hemolysis has remained unclear [7]. Hemolysis occurs when RBCs rupture and release their contents into the surrounding fluid, which can cause heart failure and renal failure [8]. Therefore, the causes and mechanisms of hemolysis in patients with pulsatile-flow VADs should be adequately analyzed to alleviate the problem of hemolysis in clinical practice. The main factors of hemolysis can be identified from the shear stress, total exposure time to the shear stress, and viscosity using the equation by Giersiepen, et al. [9]. However, on the basis of our clinical experience, including surgery and postoperational management, we hypothesized that negative pressure from pulsatile-flow VADs contributes to hemolysis. Therefore,

this study was conducted to investigate the influence of negative pressure on hemolysis in pulsatile VADs.

Materials and Methods

Characteristics of the AB5000 and its driving system

The AB5000 VAD was developed as a successor to the BVS5000. The AB5000 was used widely in clinical settings in the US after being approved by the Food and Drug Administration in 2003 [3, 10]; however, its sale was discontinued. The AB5000 blood pump is a polyurethane sac-type pump, with a 100-mL maximum loading capacity and 95-mL stroke volume. The length of the driving tube from the AB5000 pump to the driver is 1.8 m, and this length was used in the present study. A polyurethane tricuspid valve is placed in the outflow and inflow orifices of the internal structure. The BVS5000 passively drains patients' blood into the atrial chamber by gravitation; however, the AB5000 works via automatic sucking force, which continues until reaching its full fill capacity for a maximum of 4 seconds. The stroke flow is 3–6 L/min and is autoconfigured except for the negative-drive pressure. The negative pressure is the only monitor setting that can be changed; it can be adjusted every 5 mmHg from -35 mmHg to -100 mmHg.

Characteristics of the NIPRO-VAD and its driving system

The NIPRO-VAD was first implemented in 1982 [11] and remains the most common extracorporeal VAD used in Japan. The NIPRO-VAD is a pneumatically driven diaphragm-type VAD made of antithrombogenic polyurethane. The diaphragm divides the pump into an air chamber and a blood chamber. The entry and exit of the blood chamber contain built-in mechanical valves (Medtronic Hall

valve; Medtronic Inc., Minneapolis, MN, USA) that allow blood to flow in only one direction, preventing regurgitation [12]. The blood pump has a volume of 70 mL and can pump 50–60 mL per beat during normal operations [13]. The length of the driving tube from the NIPRO-VAD to the driver is 5.0 m, and this length was used in the present study. The NIPRO-VAD works by sucking force with a maximum stroke flow of approximately 5 L/min. The settings for the positive pressure (range, 150–300 mmHg on the monitor), negative pressure (range, -100–0 mmHg on the monitor), heart rate, and percent systolic pressure can be changed.

Characteristics of the Laboheart NCVC

The mock circulatory system for a VAD endurance test circuit (Laboheart NCVC; Iwaki & Co., Ltd., Tokyo, Japan; Fig. 1) consists of an industrial pulsatile pump mimicking the left ventricle, with two duckbill valves mimicking the mitral and aortic valves, a reservoir tank mimicking the left atrium, a closed chamber with an air regulator mimicking aortic compliance, and an electromagnetic proportional valve mimicking peripheral resistance.

Particle image velocimetry (PIV)

PIV is an optical method used to visualize the seeding particle motion and flow in fluids, and to measure the shear velocity. The fluid containing small tracer particles is illuminated to show the particle motion. The PIV system (Fig. 2; KLD-V5, Kato Koken Co., Ltd., Kanagawa, Japan) consists of the following components that provide the illumination of the flow field: tracer particles (Diaion HP20SS, Mitsubishi Chemical Corporation, Tokyo, Japan), an image capture system (Phantom V1212, Vision Research Inc., Wayne, NJ, USA), and software (FlowExpert2D2C, Kato Koken Co., Ltd.) that

analyzes the PIV images and computes the flow field parameters. The shear velocity is calculated by space differences in speed measured by direct cross-correlation (shear velocity measurement method), and the shear stress is converted from the shear velocity.

Experiments

Four experiments were performed to investigate the influence of negative pressure on hemolysis when using pulsatile VADs.

Experiment 1 was carried out to determine the differences between the AB5000 and NIPRO-VAD pumps using glycerol water solution. Experiment 2 was designed to confirm that the experiment would yield identical trends to Experiment 1 using bovine blood, which causes hemolysis. Experiment 3 was carried out with PIV to confirm the shear stress reached under the same conditions in which hemolysis occurred in Experiment 2. Experiment 4 was performed to analyze whether the negative pressure and exposure time were associated with hemolysis.

Experiment 1: Differences between the AB5000 and NIPRO-VAD pumps using glycerol water solution

The Laboheart NCVC was used to investigate the specificity of the AB5000 and its console driving system. We compared the specificity of the AB5000 and its console driving system, as well as the specificity of the VCT50χ driving system, with the specificity of the NIPRO-VAD and VCT50χ driving systems. A 40% glycerol water solution, which was maintained at 20°C (viscosity, 3.72 mPa·s), was circulated in the Laboheart. For these comparisons, the negative pressures on the monitors of the AB5000 and NIPRO-VAD were changed to -100 mmHg, -60 mmHg, and -35 mmHg. The positive

pressure (180 mmHg), heart rate (80 beats per minute), and systolic pressure percentage (30%) on the NIPRO-VAD remained at fixed settings. The aperture ratios for the electromagnetic proportional valve in the Laboheart were set at 30%, which represented the peripheral vessels' opening ratios; these ratios represent the most severe heart failure conditions among possible aperture ratios. The other Laboheart settings, including preload and afterload, remained fixed. Inlet pressure, outlet pressure, inlet flow, outlet flow, and time per single pulse exposed to a negative pressure of < -10 mmHg in the inlet minimum pressure were measured using a data acquisition system (Powerlab ML786/ML112, ADInstruments, New South Wales, Australia). The sampling frequency of Powerlab was 100 Hz. Powerlab was set to measure the cumulative time in which the negative pressure was < -10 mmHg during a single pulse. Using the mock circulatory system, exposure time by negative pressure under -10 mmHg per single pulse and minimum negative pressure in an inlet portion of the pump were compared for the AB5000-AB5000 console, the AB5000-VCT50χ, and the NIPRO-VAD-VCT50χ.

Experiment 2: Differences between the AB5000 and NIPRO-VAD pumps using bovine blood

We examined whether the conditions determined in the initial experiment, which yielded different results for the two pumps, caused the hemolysis. The mock circulatory loop (Fig. 3) was connected to either the AB5000 or the NIPRO-VAD, and a heparinized bovine blood sample (1000 mL) was used as working fluid within 3 hours after slaughter. The bovine blood at 40% hematocrit and 37°C was regulated by diluting it with physiological saline. We used a blood reservoir and carefully ensured that the blood and air did not mix because a previous report indicated that air in the blood can induce hemolysis [14]. To apply the same conditions (peak inflow, peak outflow, peak inlet pressure, and

peak outlet pressure) as those indicated in the initial mock circulation experiment, the preload and afterload were controlled by clamping the tubes and altering the reservoir bag height. The inlet minimum pressure and the exposure time to negative pressure under -10 mmHg per single pulse were measured using Powerlab. The plasma-free hemoglobin (PFHb) was measured using a HemoCue (AMCO, Inc., Tokyo, Japan). The data were obtained before and 5 hours after running either the AB5000 or the NIPRO-VAD. Each experiment was repeated five times.

Experiment 3: PIV analysis for the measurement of shear stress

We used PIV to confirm the shear stress reached under the same conditions (peak inflow, peak outflow, peak inlet pressure, and peak outlet pressure) in which hemolysis occurred in Experiment 2. The Laboheart NCVC was used to make the measurement conditions using 40% glycerol water solution at 20℃. The negative pressures on the monitors of the AB5000 and NIPRO-VAD were changed to -100 mmHg, -60 mmHg, and -35 mmHg. The aperture ratios for the electromagnetic proportional valve in the Laboheart were set at 30%. The shear stress around the inlet valve that was the highest shear stress in the pulsatile pump during our preliminary study was compared between the AB5000-AB5000 console, the AB5000-VCT50χ, and the NIPRO-VAD-VCT50χ.

Experiment 4: Analysis of the correlation between negative pressure, exposure time, and hemolysis

To analyze the correlation between the negative pressure, exposure time, and hemolysis, a simple, small device was constructed from a plastic sealable box (Fig. 4). The negative-pressure-driving device was created to easily confirm the correlation between negative pressure, exposure time, and

hemolysis by eliminating other possible hemolysis-related factors. The bovine blood hematocrit was maintained at 40% and 37℃. The fixed negative pressures (-5, -10, -20, -30, -40, and -50 mmHg) were continuously applied to the sealed device for fixed times (1.0, 2.0, 3.0, and 4.0 seconds). One hundred milliliters of heparinized bovine blood was injected each time. Each test was repeated 100 times. Negative pressure in the box was measured using a pressure measurement device (Trucal, 59PXCAL, Edwards, Chiba, Japan). The PFHb was measured via the HemoCue after each procedure. The same procedure was repeated ten times.

Statistical analysis

JMP software (version 12.0, SAS Institute Japan, Inc., Tokyo, Japan) was used for all statistical analyses. The time exposed to negative pressure at less than -10 mmHg per single pulse, the minimum negative pressure on the monitor for each pump-console combination, and the mean value of the gaps between the initial value and the PFHb at 5 hours after running the pumps for each pump-console combination at each negative-pressure setting were compared via analysis of variance (Experiment 2), as were the correlations between negative pressure, exposure time, and hemolysis (Experiment 4). P-values < 0.05 were considered statistically significant.

Results

Experiment 1

Figure 5a and 5b show the negative pressure driven into the inlet portion and the exposure time, while Table 1 shows the VAD flow in each pump-console combination at three negative-pressure settings using glycerol water solution. For the -100 mmHg and -60 mmHg negative-pressure settings on the AB5000-AB5000 console and AB5000-VCT50χ combination, the minimum pressure at the inlet

portion was lower and the exposure time to negative pressure under -10 mmHg was longer than the minimum pressures and exposure times of the NIPRO-VAD-VCT50χ combinations, respectively (Fig. 5a and 5b).

Experiment 2

Figure 6a and 6b show the negative pressure driven into the inlet portion and the exposure time, and Figure 6c shows the result of the hemolysis test in each pump-console combination at each negative-pressure setting. Table 2 shows the VAD flow in each pump-console combination at three negative-pressure settings using bovine blood. Compared with the NIPRO-VAD-VCT50χ, the AB5000-AB5000 console and AB5000-VCT50χ had significantly lower minimum pressure at the inlet portion, and significantly longer exposure time to negative pressure under -10 mmHg at the negative pressures of -100 mmHg and -60 mmHg ($P < 0.05$; Fig. 6a and 6b). These trends were the same as those in the initial experiment using the Laboheart with glycerol water solution. The PFHb at 5 hours after running the pump was significantly increased at -100 mmHg and -60 mmHg for the AB5000-AB5000 console and AB5000-VCT50χ compared with the NIPRO-VAD-VCT50χ ($P < 0.05$; Fig. 6c); however, the PFHb was slightly increased at -35 mmHg. There were no significant differences in the VAD flows among the three pump-console combinations at each negative-pressure setting (Table 2).

Experiment 3

The shear velocity measured with PIV for both the AB5000 and NIPRO-VAD is shown in Fig. 7. Redder hues show a more positive value of the velocity gradient, while bluer hues show a more

negative value of the velocity gradient. The velocity gradient is the rate of change in speed against location. Table 3 shows the maximum shear stress, which was calculated from the maximum shear velocity (shear stress: shear velocity・$3.72・10^{-3}$), in each pump-console combination at three negative-pressure settings using 40% glycerol water solution at 20℃. The maximum shear stresses in the AB5000-AB5000 console were 0.38 Pa (-100 mmHg), 0.35 Pa (-60 mmHg), and 0.3 Pa (-35 mmHg). The maximum shear stresses in the AB5000-VCT50χ were 0.26 Pa (-100 mmHg), 0.24 Pa (-60 mmHg), and 0.19 Pa (-35 mmHg). The maximum shear stresses in the NIPRO-VAD-VCT50χ were 0.22 Pa (-100 mmHg), 0.19 Pa (-60 mmHg), and 0.15 Pa (-35 mmHg).

Experiment 4

Fig. 8a and 8b show the mean PFHb value per second of driven negative pressure from 10 procedures. As shown in Fig. 8a, at a negative pressure of -5 mmHg, the PFHb increased slightly as the exposure time increased. At a negative pressure of -10 mmHg, the PFHb increased significantly with the increase in the exposure time from 2 to 4 sec ($p < 0.05$). At a negative pressure below -20 mmHg, the PFHb increased significantly with the increase in the exposure time from 1 to 4 sec ($p < 0.05$). In addition, as shown in Fig. 8b, when the exposure time was 1 sec, the PFHb increased slightly as the negative pressure decreased. At exposure times of longer than 2 sec, the PFHb increased significantly with the decrease in the negative pressure from -10 to -50 mmHg ($p < 0.05$).

Discussion

Hemolysis is evaluated based on shear stress (τ) and exposure time by shear stress (t) using the equation below [9]. The shear stress was calculated by multiplying the viscosity (μ) by the shear velocity (D): $dHb/Hb = 3.62 \cdot 10^{-5} \cdot \tau^{2.416} \cdot t^{0.785}$, $\tau = \mu \cdot D$

Hemolysis occurs when shear stress exceeds 200–300 Pa [15]. To confirm whether the shear stress influenced hemolysis during this time, shear velocity was measured using the PIV by analyzing the seeding particle motion for both the AB5000 and NIPRO-VAD, and was then converted to the shear stress. The shear stress in each case was observed from 0.15–0.38 Pa according to PIV. Consequently, we confirmed that the shear stress did not reach a level that would cause hemolysis. Furthermore, four factors should be considered. First, no patients who were supported by the BVS5000, which works by gravity instead of sucking force, have reported hemolysis. Second, RBCs are more vulnerable to negative pressure than to positive pressure [16]. Third, the AB5000 system maintains continuous sucking for a maximum of 4 seconds until the pump is full. Fourth, the survey conducted by Abiomed, Inc. revealed that patients assisted by the AB5000 who experienced hemolysis improved after the AB5000 pump was changed to the centrifugal-flow VAD pump. Therefore, we hypothesized that some of the hemolysis was due to the negative pressure at the inlet portion.

In this study, the PIV demonstrated that the shear stress did not reach the level at which hemolysis occurs; therefore, the shear stress was not independently involved in the hemolysis. Moreover, the second experiment revealed that at -100 mmHg and -60 mmHg, the AB5000 pump caused a lower minimum inlet pressure and longer exposure time to negative pressure under -10 mmHg, thus

significantly causing hemolysis compared with the NIPRO-VAD. The higher minimum inlet pressure and shorter exposure time of the NIPRO-VAD did not induce hemolysis. Therefore, significant hemolysis tended to occur when the negative pressure on the AB5000 pump monitor increased. These results were in agreeance with our prediction. In addition, the final experiment indicated that the PFHb increased significantly over the exposure time to negative pressure under -10 mmHg, and as the negative pressure increased, the rate of change in the PFHb over exposure time significantly increased. Hence, hemolysis rarely occurs at > -10 mmHg, and when the negative pressure is low, hemolysis may not occur in the short exposure time. Consequently, negative pressure and exposure time were considered to be involved in the hemolysis independent of the shear stress. We do not have detailed data for all patients who were supported by the AB5000, but the AB5000 has a system that continues automatically sucking until reaching full capacity for a maximum of 4 seconds, and this sucking motion can generate a high degree of hemolysis.

Conclusion

In the present study, the influence of negative pressure on hemolysis with pulsatile VADs was investigated through a mock circulatory study, PIV study, and sealed sucking device study. Our results revealed that although negative pressure alone does not cause hemolysis, negative pressure and exposure time together do cause hemolysis. The outcomes of the present study will help to create criteria for upcoming pulsatile-flow VADs that do not cause hemolysis.

Limitations

In the initial experiment, the NIPRO-VAD was not connected to the AB5000 console because the glycerol water solution was continuously sucked until reaching 100 mL, which fulfilled the AB5000s maximum capacity in contrast to the NIPRO-VADs maximum capacity of 70 mL. Although glycerol water solution does not completely mimic blood, we used it to investigate the trends of the two pumps. One factor that will be critical for the reproducibility of the present study is the differences in bovine blood samples. Although we did not use blood samples from the same bovine throughout the study, the initial PFHb was the same in the control for each test, and the hemolysis test was repeated five times in the hemolysis study using a pulsatile pump, and 10 times using a sealed sucking device. Therefore, the influence of the differences in bovine blood samples was reduced.

Conflict of interest

No conflict of interest to be declared.

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Figure legends

Fig. 1

Image and schematic of the Laboheart NCVC; IWAKI Co., Ltd., Saitama, Japan.

Fig. 2

Image and schematic of the particle image velocimetry (PIV) equipment. PIV is an optical method used to visualize the flow used to obtain the seeding particle motion and shear velocity in fluids. The fluid with small entrained tracer particles is illuminated to show the particle motion.

Fig. 3

Mock circulation loop consisting of 3/8-inch and 1/4-inch Tygon tubes (Hagitec, Inc., Chiba, Japan) and a polyvinyl chloride compressible blood reservoir.

P: pressure gauge; S: sampling port.

Fig. 4 Sealed device used in the experiment 3

Fixed negative pressure was continuously applied for a fixed time in a sealed device injected with 100 mL of heparinized bovine blood. Negative pressure in the box was gaged by a pressure-measuring device.

Fig. 5 Results of experiment 1

Negative pressure driven into the inlet portion and the exposure time in each pump-console combination at three negative-pressure settings using glycerol water solution.

Fig. 6 Results of experiment 2

(a) Negative pressure driven into the inlet portion and (b) exposure time to negative pressure under -10 mmHg in each pump-console combination at three negative-pressure settings using bovine blood.

(c) ΔPFHb: the mean value of the gaps from five procedures between the initial value and the PFHb at 5 hours after running the pump in each pump-console combination at each negative-pressure setting.

PFHb: plasma-free hemoglobin.

Fig. 7

The particle image velocimetry images of the AB5000-VCT50χ, AB5000-AB5000 console, and NIPRO-VAD-VCT50χ.

Shear velocity is shown in each condition.

Fig. 8 Results of experiment 3

(a) Mean PFHb at each second for each negative pressure on the monitor. (b) Mean PFHb per second of exposure to negative pressure under -10 mmHg.

PFHb: plasma-free hemoglobin.