Title:

Re-evaluation of Pre-pump Arterial Pressure to Avoid Inadequate Dialysis and Hemolysis: Importance of Pre-pump Arterial Pressure Monitoring in Hemodialysis Patients

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Short Title: Importance of pre-pump arterial pressure monitoring in hemodialysis patients

Abstract: Pre-pump arterial pressure (PreAP) is monitored to avoid generating excessive negative pressure. National Kidney Foundation K/DOQI clinical practice guidelines for vascular access recommend that PreAP should not fall below -250 mmHg because excessive negative PreAP can lead to a decrease in the delivery of blood flow, inadequate dialysis, and hemolysis. Nonetheless, these recommendations are consistently disregarded in clinical practice and pressure sensors are often removed from the dialysis circuit. Thus far, delivered blood flow has been reported to decrease at values more negative than -150 mmHg of PreAP. These values have been analyzed by an ultrasonic flowmeter and not directly measured. Furthermore, no known group has evaluated whether PreAP-induced hemolysis occurs at a particular threshold. Therefore, the aim of this study was to clarify the importance of PreAP in the prediction of inadequate dialysis and hemolysis. By using different diameter needles, human blood samples from healthy volunteers were circulated in a closed dialysis circuit. The relationship between PreAP and delivered blood flow or PreAP and hemolysis was investigated. We also investigated the optimal value for PreAP using

several empirical monitoring methods, such as a pressure pillow. Our investigation indicated that PreAP is a critical factor in the determination of delivered blood flow and hemolysis, both of which occured at pressure values more negative than -150 mmHg. With the exception of direct pressure monitoring, commonly used monitoring methods for PreAP were determined to be ineffective. We propose that the use of a vacuum monitor would permit regular measurement of PreAP. **Key words:** Pre-pump arterial pressure – Hemolysis – Blood flow – Pressure pillow – Vacuum monitor – Dialysis

Pre-pump arterial pressure (PreAP) is used to determine whether a prescribed dialyzer blood flow can be delivered without generating excessive negative pressure (1). National Kidney Foundation K/DOQI clinical practice guidelines for vascular access recommend that PreAP should not fall below -250 mmHg because excessive negative PreAP can lead to a decrease in delivered blood flow, inadequate dialysis, and hemolysis (2).

Nonetheless, even moderate negative pressure has been shown to result in a

difference between the blood pump flow rate setting and delivered blood flow (3). Depner TA *et al* reported that neither hematocrit from 21% to 38% nor blood tubing affected delivered blood flow. Rather, PreAP was the primary determining factor for delivered blood flow and there was a demonstrated decrease in blood flow at values more negative than -150 mmHg (4). In this study, the delivered flow was investigated using the same type of ultrasonic flowmeter as reported in prior studies (5,6). However, the exact amount of delivered blood was not formally weighed.

PreAP monitoring has also been shown to be useful in the avoidance of harmful negative pressure which could give rise to blood damage. Blood damage is one of the primary complications in hemodialysis (HD). Any damage to red blood cells can decrease the cellular life span and contribute to anemia. Several factors contribute to hemolysis including shear stresses, blood/air interface and blood attachment to foreign surfaces. Among these, shear stress has been reported to be the primary source of hemolysis in HD. The highest shear stress is expected to occur in the dialysis needle, where the diameter of the tube is the

smallest in the dialysis circuit (7). To our knowledge, the PreAP threshold at which hemolysis occurs has yet to be fully examined.

Despite K/DOQI recommendations, measurement of PreAP has not yet emerged as a clinical standard in worldwide practice (8). For example, in Japan, a collapsible pressure pillow has been used as a sensor for detecting PreAP. However, more cost effective systems including automatic priming and reinfusion systems using dialysate have become commonplace due to the efficiencies in time, labor and saline solution for priming. The dialysis circuit in the automatic reinfusion system eliminates a pillow because it can lead to the formation of clots of blood, that can be returned to patients using autotransfusion. Therefore, the oscillating movement of pulsating blood flow into the arterial chamber is currently the only way to estimate sufficient arterial blood supply. However, the reliability of this movement has yet to be studied as a measure to ensure adequate blood flow.

Therefore, the aim of this study was to re-evaluate the importance of PreAP monitoring in regards to the difference between the blood pump flow rate setting

and delivered blood flow, and hemolysis. Furthermore, a secondary goal was to determine a useful method to monitor PreAP. We investigated the reliability of several candidates such as a pressure pillow.

PATIENTS AND METHODS

Ethics Statement

All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki and individuals' data were analyzed anonymously. All patients and volunteers gave their informed, written consent. This study was approved by the Research Ethics Committee of Tokushima University.

Design and subjects

This study included eight healthy volunteers and five patients with maintenance dialysis at Tokushima University Hospital. All of the volunteers were men aged 26 to 43 years (mean ± SD, 31.8 ± 5.8 years). Patients were aged 50 to 77 years (61.4 ± 11.6 years), and there were two men and three women. The duration of renal replacement therapy ranged from 1 to 120 months

(52.0 ± 55.2 months). Two patients (40%) had diabetes mellitus. Dialysis modality for patients at Tokushima University Hospital was HD. Polyethersulfone membrane dialyzers were used. Every patient received 4-hour dialysis three times per week. Blood samples for biochemical data were obtained from arteriovenous shunt just at the start of the first HD session in this study (9). Hemoglobin and hematocrit values ranged from 8.1 to 10.6 mg/dL (9.6 ± 1.3 mg/dL), and 25.8 to 34.2% (30.2 ± 3.9%), respectively.

Measurement of PreAP, a decrease in blood flow with an ultrasonic flowmeter, hemolysis, and the length of pulsating movement (LPM) *in vitro*.

PreAP, detection of a decrease in blood flow with an ultrasonic flowmeter**,** hemolysis, and pulsating movement were assessed using the dialysis circuit shown in Supplementary figure 1A. The circuit used a PES-13Sα dialyzer (NIPRO, Osaka, Japan) and was primed with saline solution. Approximately 200 mL of saline was filled in the circuit. Then, human blood from a healthy volunteer was drained at a speed of 25 mL/min for 12 minutes with a 16-gauge (16G) (outer diameter: 16G, 1.6 mm, inner diameter: 18G, 1.2 mm, length : 38 mm ,

NIPRO) needle from the arterial line and collected through the dialyzer and venous line with a 15G/16G (outer diameter : 15G/16G, 1.8/1.6 mm, inner diameter : 17G/18G, 1.4/1.2 mm, length : 38 mm, NIPRO) needle into a saline bag. Ten thousand units of heparin were administered initially, and 500 units/hour was continued during the experiment. After blood collection was finished, the same size 15G/16G needle was attached to the arterial line and inserted into the blood collection bag. The blood/saline solution was inverted gently several times and circulated for 10 minutes at a speed of 50 mL/min to mix completely. The final hemoglobin and hematocrit ranges were 8.0 to 9.3 mg/dL (8.8 ± 0.5 mg/dL), and 23.6 to 27.7% (26.2 ± 1.4%), respectively. Next, the blood pump flow rate was set to 100 mL/min and then increased by 50 mL/min every 20 minutes. PreAP was analyzed with a vacuum monitor (Nagano Keiki, Nagano, Japan), delivered blood flow was detected with a Transonic HD02 monitor (Transonic systems Inc., Ithaca, NY, USA) (5,6) and LPM (Supplementary figure 2) was measured three minutes after the blood pump flow rate setting increase. Just before the subsequent flow increase, a 3 mL sample

was passively collected in a 5 ml syringe. It was immediately transferred to a 2.7 mL centrifuge tube with anticoagulant, spun down in the centrifuge and the resulting plasma was pipetted off into a 1.5 mL tube. Tubes with plasma were stored at -80℃ for further analysis. The cyanide-free method was used to measure plasma free hemoglobin (10). A standard curve of human hemoglobin was prepared using hemolysed human blood of known concentration. The plasma samples were then analyzed. Δplasma free hemoglobin was defined as the measured value minus initial plasma free hemoglobin. The maximum blood pump flow rate setting was 400 mL/min. After this first experiment, the needles used in the saline bag were exchanged with the alternate diameter needles (15G→16G or 16G→15G). Again, PreAP, delivered blood flow detected with a Transonic HD02 monitor, and LPM were measured.

Quantification of a decrease in blood flow by weighing the blood *in vitro*.

Following the analysis described above, the venous line 15G/16G needle was stuck into the other saline bag (Supplementary figure 1B). The blood delivered per minute was weighed and corrected to volume by the density. Blood density

was determined by a pycnometer method (11).

Investigation of PreAP and LPM in HD patients.

One hour after the HD session started, PreAP, delivered blood flow and LPM were measured as described above at a blood pump flow rate setting of 250 or 200 mL/min. This procedure was performed during three serial HD sessions performed with 16G needles. Except patient number 1, the puncture site and the direction of the arterial needle (toward or against anastomosis) were nearly identical between each session. All of the three data sets were recorded. For patient number 1, we performed the experiment with the needle punctured both toward and against anastomosis. At the same time, we confirmed that the percentage decrease in delivered blood flow was less than 5% compared to the blood pump flow rate setting by using a Transonic HD02 monitor.

Statistical analysis

All values are expressed as mean ± SD. Results were analyzed using paired t-tests. Statistical significance was defined by P less than 0.05.

RESULTS

Initially, we investigated the significance of PreAP on the difference between the blood pump flow rate setting and delivered blood flow. The recorded difference occurred at values more negative than -150 mmHg regardless of needle diameter (Figure 1E). In this experiment, measured delivered blood flow (Figure 1A,B) was examined using the widely accepted ultrasonic flowmeter technique (5,6). Nonetheless, the accuracy of the machine is ± (blood pump flow rate setting × 0.06 + 8) mL/min according to the manufacturer's instructions. For example, at a flow rate setting of 300 mL/min, the machine accuracy would be ± 26 mL/min or ± 8.7 %. In order to mitigate this potential error, delivered blood flow per minute was weighed and, regardless of needle diameter, the actual blood volume started to decrease at approximately -150 mmHg (Figure 2E).

Next, we measured hemolysis with different needles and flow rates. Hemolysis occurred if PreAP fell below -150 mmHg with both needle diameters (Figure 3E). These results confirm that hemolysis started at comparable PreAP as that in the

previous experiment, which was the primary determinant of the difference between the blood pump flow rate setting and delivered blood flow (Figure 2E). In summary, in this i*n vitro* setting, both a decrease in delivered blood flow and hemolysis were not time or needle-dependent, but PreAP dependent.

Furthermore, we investigated the reliability of two alternate methods to detect a PreAP of -150 mmHg; degree of pulsating movement and collapse of a pressure pillow. LPM is an easy indicator of sufficient blood supply. In the same *in vitro* system, we measured LPM and determined that it increased in relation to PreAP. However, with the same PreAP, LPM was statistically different between both needle types (4.7 ± 0.5 cm at -201 mmHg with 16G vs. 5.4 ± 0.6 cm at -197 mmHg of PreAP with 15G, Figure 4). Moreover, if PreAP was constant but the circuit tube was exchanged for one with a narrower lumen, LPM increased (data not shown). Therefore, LPM was correlated with PreAP, but also affected by needle diameter and other circuit equipment even in this simple *in vitro* setting.

The detection of PreAP was also attempted by touching a pressure pillow. However, all of six experienced clinical engineers and two doctors failed to

detect the objective PreAP (-150 mmHg) blindly, despite advanced training in the collapse of the pillow with the PreAP. In fact, the pillow was far from collapsed at -150 mmHg of PreAP. The values detected varied among individuals and within trials of the same individual, ranging from -150 to -300 mmHg. Thus, the pillow was only useful to detect an extreme decrease in blood flow and not reliable to determine the optimal PreAP.

In vivo, the relationship among blood flow, PreAP and LPM was evaluated in five HD patients. Initially, all PreAP data from every patient were less negative than -200 mmHg. Regardless of condition of puncture point, needle direction, and blood flow, PreAP was variable and LPM was not correlated with PreAP (Figure 5). These results imply that LPM was dependent not only on PreAP but also on other factors such as the direction of the needle or the interface of the needle opening and vessel wall.

Discussion

In this study, we have demonstrated that PreAP is an important factor that

affects both delivered blood flow and hemolysis. The threshold of PreAP that contributes to these problems was -150 mmHg. PreAP monitoring methods such as pulsating movement and a pressure pillow were not effective in the detection of optimal PreAP.

Excessive negative pressure has been demonstrated to be the primary cause of the difference between the blood pump flow rate setting and delivered blood flow (3). PreAP pressures more negative than -150 mmHg have been shown to cause a reduction in delivered blood flow in previous studies, which was supported by our data (4). We confirmed the effect of PreAP more negative than -150 mmHg on blood flow by using different gauge needles and quantifying the delivered blood by weighing directly. This suggests, at least in part, that PreAP is a critical factor in the delivery of actual blood flow in our experiment condition. The ultimate concern with actual blood flow rate not matching the blood pump flow rate setting is the concomitant decrease in blood clearance and delivered dialysis. Teruel JL et al. showed that the difference between the blood pump flow rate setting and delivered blood flow was related to PreAP, regardless of the

needle gauge or blood pump flow rate setting from 300 to 400 mL/min. In this study, an ultrasonic sensor measured the decrease in blood flow to be approximately 10%,15%, and 20% at approximately -150,-200, and -250 mmHg of PreAP, respectively (3). Of note, this study did not measure small solute clearance. However, a 15% decrease in blood flow from 400 to 340 mL/min using a dialyzer with a mass transfer area coefficient of urea of 700 mL/min and a dialysate flow rate of 800 mL/min would be expected to result in an 8% decrease in urea clearance (12). Mehta HK et al. observed the impact of an increase in needle gauge in 22 HD patients. In this study, mean delivered blood flow measured by an ultrasonic sensor increased from 379 mL/min to 402 mL/min. Mean PreAP became less negative from -230 mmHg to -172 mmHg. The percentage of reduction in urea (PRU) level increased from a mean of 63.7% to 68.7% (13). According to the US Renal Data System database (14), a 5% increase in PRU is associated with an 11% decrease in overall mortality up to a PRU of 70%. Therefore, the relationship between PreAP and actual delivered blood flow is quite important to the maintenance of adequate dialysis

(15).

Blood flow also causes shear stress, which is one of the primary causes of hemolysis. Peripheral dialysis needles are expected to have the highest shear stresses within a dialysis circuit. Shear stress in the needle depends on the rate of blood flow (7). Blood flow rates are correlated with PreAP (3,4). Even in more complicated systems such as cardiopulmonary bypass, a combination of negative pressure and air interface had the largest rate of damage. Hemolysis was caused at pressures more negative than -120 mmHg (16). In our mock dialysis experiment, hemolysis was dependent on PreAP regardless of needle diameter. The optimal PreAP to prevent hemolysis was less negative than -150 mmHg, which can also prevent a decrease in blood flow. Hemolysis can be subclinical in a short period at moderate PreAP. However, considering the long life span of HD patients and low incidence of kidney transplantation in Japan, any injury to red blood cells should be averted (17). Thus, PreAP detection is critically important.

Even in our simplified setting, in which blood was abundant and static,

pulsating movement was not decisive in the prediction of PreAP. A pressure pillow was only useful to detect extremely low PreAP, as well as roller pump tubing collapse (4). These results imply that direct PreAP monitoring by a vacuum monitor is the only way to avoid harmful, but not extreme, negative pressure.

Limitations of this study should be noted. Hemolysis in HD patients was not monitored. In Japan, blood flow rates are prescribed at or less than 250 mL/min using 16G needles in most HD patients. In this context, PreAP does not generally fall below -200 mmHg, as was evidenced in this study (Figure 5). PreAP of -200 mmHg caused minimal hemolysis in the approximately 500 mL pool of blood/saline in our *in vitro* experiment (Figure 3). Therefore, we did not endeavor to detect hemolysis at PreAP less negative than -200 mmHg *in vivo* according to the previous report (18). For ethical reasons, we could not prescribe a higher flow rate to induce more negative pressure in HD patients due to the potential complication of inadequate dialysis and hemolysis, given our results.

CONCLUSION

To avoid inadequate dialysis *in vivo*, arteriovenous shunt flow or delivered blood flow serial monitoring have become relatively easy using either an ultrasound technique (19-21) or an ultrasonic flowmeter such as HD02. However, detection of subclinical hemolysis remains difficult. Lactate dehydrogenase is nonspecific and affected by other factors such as liver dysfunction, and plasma free hemoglobin is not regularly analyzed. PreAP is definitely an important factor in the prediction of hemolysis. It is difficult to determine the optimal PreAP threshold by monitoring methods currently available. Therefore, we strongly emphasize the importance of PreAP monitoring to prevent hemolysis.

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FIGURE LEGENDS

FIG. 1. The relationship among pre-pump arterial pressure, blood pump flow rate setting and blood flow measured by an ultrasonic flowmeter.

PreAP, detection of a decrease in blood flow with an ultrasonic flowmeter were assessed using the dialysis circuit shown in Supplementary figure 1A. The

dotted line in figure 1A,B represents the line of identity. All values are expressed as means ± SD (N=8).

FIG. 2. The relationship among pre-pump arterial pressure, blood pump flow rate setting and directly measured blood flow.

PreAP, detection of a decrease in blood flow were assessed using the dialysis circuit shown in Supplementary figure 1B. The blood delivered per minute was weighed and corrected to volume by blood density. The dotted line in figure 2A,B represents the line of identity. All values are expressed as mean ± SD (N=4).

FIG. 3. The relationship among pre-pump arterial pressure, blood pump flow rate setting and hemolysis.

PreAP, hemolysis were assessed using the dialysis circuit shown in Supplementary figure 1A. A 3 mL sample was passively collected in a 5 ml syringe. It was immediately transferred to a 2.7 mL centrifuge tube with anticoagulant, spun down in the centrifuge and the resulting plasma was pipetted off into a 1.5 mL tube. The cyanide-free method was used to measure plasma free hemoglobin. All values are expressed as mean ± SD (N=3 for 15G

and N=5 for 16G).

FIG. 4. The relationship between pre-pump arterial pressure and the length of pulsating movement.

PreAP, the length of pulsating movement were assessed using the dialysis circuit shown in Supplementary figure 1A. All values are expressed as mean ± SD (N=8). *P < 0.01.

FIG. 5. The relationship between pre-pump arterial pressure and the length of pulsating movement in HD patients.

At a blood pump flow rate setting of 250 (A,B) or 200 (C,D) mL/min, PreAP, the length of pulsating movement were assessed in HD patients. The arterial 16G needle was inserted toward anastomosis (A,C) or against anastomosis (B,D). The percentage of decrease in delivered blood flow was less than 5% compared to the blood pump flow rate setting. All of the three data sets from serial HD session were recorded. The number attached to each value shows the patient number.

SUPPLEMENTARY FIGURE LEGENDS

Supplementary FIG.1. Schematic of the mock dialysis circuit used in hemolysis detection (A) and used to quantify actual blood flow (B).

Supplemantary FIG.2. The length of pulasating movement. The amplitude of blood flow surface movement shown in this figure was measured.