Using Daily Plasma-Free Hemoglobin Levels for Diagnosis of Critical Pump Thrombus in Patients Undergoing ECMO or VAD Support

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Abstract: Patients supported with extracorporeal membrane oxygenation (ECMO) or short-term centrifugal ventricular assist devices (VADs) are at risk for potential elevation of plasma-free hemoglobin (pfHb) during treatment. The use of pfHb testing allows detection of subclinical events with avoidance of propagating injury. Among 146 patients undergoing ECMO and VAD from 2009 to 2014, five patients experienced rapid increases in pfHb levels over 100 mg/dL. These patients were supported with CardioHelp, Centrimag, or Pedimag centrifugal pumps. Revolutions per minute of the pump head and flow in the circuit in three of the patients did not change, to maintain patient flow during the period that pfHb level spiked. Two patients had unusual vibrations originating from the pump head during the pfHb spike. Four patients had pump head replacement. Following intervention, trending pfHb levels demonstrated a rapid decline over the next 12 hours, returning to baseline within 48 hours. Two of the three patients who survived to discharge also experienced acute kidney injury, which was attributed to pfHb elevations. The kidney injury resolved over time. The architecture of centrifugal pumps may have indirectly contributed to red blood cell damage due to thrombus, originally from the venous line or venous cannula, being snared in the pump fins or pump head. Keywords: extracorporeal membrane oxygenation, ventricular assist device, plasma-free hemoglobin, hemolysis.

Evolution in centrifugal pump technology and increased adoption of extracorporeal membrane oxygenation (ECMO) and short-term temporary centrifugal ventricular assist device (VAD) has improved patient outcomes (1,2). With extended length of mechanical support, mechanical trauma to blood components is more apparent (3). Animal and in vivo model studies have demonstrated very low generation of plasma-free hemoglobin (pfHb) with the use of new pumps (4–6). In clinical practice, the recognition of hemolysis during artificial circulation is increasingly recognized as a potential complication (3,7,8). Some contributions have addressed the mechanism of pfHb elevation involving vortexing or general clot buildup in the circuit (7,9). Most of these in vitro or in vivo studies involved previous generation pumps and technology.

The high levels of pfHb are thought to have secondary effects in the kidneys causing acute kidney injury (10). This is caused by the buildup of the pfHb structures in the kidney’s glomerular filtration apparatus. Some of the pfHb can be excreted in the urine, known as hemoglobinuria, not be confused with hematuria or intact red blood cells found in the urine. There is limited data on the behavior of pfHb levels after interruption of the mechanism originally leading to hemolysis (7).

METHODS

After receiving institutional review board (IRB) approval, a review of patients from 2009 to 2014 at our institution was completed, including patients with elevation of pfHb that increased above 100 mg/dL. Out of 146 patients, 134 were ECMO patients and 12 were short-term temporary centrifugal VAD patients; five met this criterion for excessive pfHb elevation. In addition, no patients were reviewed or included that had long-term or destination VAD therapy. The pumps used in VAD patients were either Centrimag (Thoratec, Pleasanton, CA) or Pedimag (Thoratec). A
review of these five patients' clinical and laboratory data was performed including the pfHb levels before, during, and after the spike. In addition, the patients' creatinine and blood urea nitrogen (BUN) levels were also reviewed in similar fashion. Interventions performed on the circuit to attempt to reduce the pfHb levels were also reviewed.

The use of ECMO or VAD on these patients was within our institution's standard protocols. Heparin was used as the first-line anticoagulant in all patients, once bleeding was controlled. Anticoagulation therapy was evaluated to be started, in postcardiomyopathy patients, once bleeding reached a minimal level of 1 mL/kg/h from the patient's chest tube drainage. In nonsternotomy patients, anticoagulation therapy was evaluated at the onset of mechanical support. During mechanical support, ECMO patients had an activated partial thromboplastin time (aPTT) maintained at 50–90 seconds, and for the VAD patient, an aPTT was maintained at 45–60 seconds. The patients also had thrombelastograph (TEG) (Haemonetics, Braintree, MA)-guided management of their heparin dosing. In addition, for patients having long-term ECMO therapy, where recovery or bridge to transplant was going to be greater than a week, argatroban was also considered and used as an additional anticoagulant, in some patients.

If bleeding was in excess of 2–3 mL/kg/h, then correction of coagulation was accomplished through reduction or cessation of anticoagulation therapy. This was in addition to considerations of blood product and surgical re-exploration. When bleeding required a reduction of anticoagulation, flow from the mechanical support device was increased to reduce incidence of fibrin or thrombus buildup occurring in the circuit, guided by patient volume status and hemodynamics. Blood products on adults and elder pediatric patients were always administered into the patients' central or peripheral venous lines. In neonate or younger pediatric patients, packed red blood cells were administered into the ECMO circuit and all other blood products were administered into the patients' central or peripheral venous lines.

If a patient on mechanical support was going to have a procedure that had a high likelihood of bleeding, then anticoagulation would be stopped in preparation for that procedure and restarted after bleeding or risk of bleeding had passed. These procedures would include tracheostomies, sternotomies for conversion to central venoarterial (VA) ECMO, placement of additional chest tubes, and additional noncardiac surgeries.

For patients on ECMO and VAD, standard monitoring included pfHb testing once daily. This laboratory test was performed around 5 am with results reported in the same day in the early to mid-afternoon. This approach allowed for another test to be run emergently if needed in the late afternoon to recheck the pfHb value. All pfHb testing were performed on a BioTek Eon spectrophotometer (BioTek Instruments Inc., Winooski, VT). The method calculates both total pfHb and plasma-free oxyhemoglobin by measuring at the following wavelengths: 415, 450, 562, 578, and 598 nm (11). Reference ranges for both total and oxyhemoglobin are reported. Historically and before patient 4, the pfHb values greater than 250 mg/dL were simply reported as a relative value (>250 mg/dL). After patient 3, the linear range was extended to increase the reportable limit of pfHb to 3000 mg/dL. This was done by dilution of samples and all subsequent pfHb results could be reported as absolute values.

RESULTS

The centrifugal pumps used in the five patients were three CardioHelp (Maquet, Wayne, NJ), one Pedimag, and one Centrimag. The spikes in pfHb occurred at various times during mechanical support (Table 1). In addition, patient 1’s current ECMO pump and oxygenator had been in place for only 30 hours at the time of the pfHb spike due to a change out for poor oxygen transfer. Patient 5’s pump and oxygenator had been in use for 15 days at time of pfHb spike, and the venous line had been in use for

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Indication for Support</th>
<th>Type of Mechanical Support</th>
<th>Length of Time on Support before pfHb Spike</th>
<th>First Intervention that did not Decrease pfHb</th>
<th>Event That Decreased pfHb Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16 years</td>
<td>Severe ARDS</td>
<td>VA ECMO</td>
<td>21 days</td>
<td>Venous cannula change</td>
<td>Change out of Cardiohelp</td>
</tr>
<tr>
<td>2</td>
<td>50 years</td>
<td>Myocardium stun after MI and CABG</td>
<td>VA ECMO with LV vent</td>
<td>5 days</td>
<td>Change out of Cardiohelp</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>65 years</td>
<td>Bridge to Heartmate II</td>
<td>Bi VADs</td>
<td>9 days</td>
<td>Thrombus removal from inlet of pumphead</td>
<td>Inspecting and reseating of Bi VADs</td>
</tr>
<tr>
<td>4</td>
<td>6 days</td>
<td>Myocardium stun after Norwood Procedure</td>
<td>VA ECMO</td>
<td>Less than a day</td>
<td>Pumpehead check and reseating</td>
<td>Change out of Pedimag</td>
</tr>
<tr>
<td>5</td>
<td>13 years</td>
<td>Severe ARDS</td>
<td>VA ECMO</td>
<td>93 days</td>
<td></td>
<td>Change out of Cardiohelp</td>
</tr>
</tbody>
</table>

CABG, Coronary artery bypass grafting; VA ECMO, venoarterial extracorporeal membrane oxygenation; VADs, ventricular assist devices; LV, left ventricle; ARDS, Acute Respiratory Distress Syndrome; MI, myocardial infarction.
50 days. Every patient that had a spike in pfHb had time points before the spike where the anticoagulation had been reduced or turned off for a prolonged period. This time the anticoagulation was discontinued varied from 6 to 23 hours, to reduce bleeding. All of these patients had normalization of their coagulation values, ACT, aPTT, and kaolin TEG during this period (Table 2). Majority of the 146 patients also had a cessation or reduction in heparin and normalization of coagulation values that did not lead to pfHb spikes at some point during their ECMO or VAD support.

In those patients without pfHb elevation above 100 mg/dL, the daily pfHb levels were ranging from 12 to 60 mg/dL. In our experience, the revolutions per minute of the pump head in three of the patients did not change to maintain flow during the period in which pfHb level spiked. In the other two patients, the revolutions per minute were increased by approximately 600 rpm (patients 2 and 3). In patient 2, despite the revolutions per minute increase, the ECMO flow was 1.5 L less despite no change in systemic vascular resistance or increased pressure drop in oxygenator. In patient 3, the increase in revolutions per minute on the left VAD maintained the flow. In addition, only two patients (4,5) had unusual vibrations originating from the pump head during the pfHb level spike. In those patients on ECMO, none of the patients had unusual pressure drops or unusual thrombus formations in their oxygenators at the time of pfHb elevation. Following intervention, trending pfHb levels showed a rapid decline over the next 12–24 hours, returning to baseline within 24–48 hours (Figure 1).

Of the five patients, patients 2 and 3 had support withdrawn and later died after the resolution of the pfHb spikes. In both cases, the events leading to withdrawal was not directly

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**Table 2.** Cessation of anticoagulation for pfHb elevation patients, including the periods without anticoagulation, reason for cessation, lowest aPTT, and kaolin TEG R time during period of cessation.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mechanical Support Day</th>
<th>Days Before pfHb Spike</th>
<th>Reason for Anticoagulation Turned Off</th>
<th>Hours off Anticoagulation</th>
<th>Lowest aPTT in Sec</th>
<th>Lowest Kaolin TEG R Time</th>
<th>Surgical Re-Exploration Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>13</td>
<td>Bleeding from chest tube site</td>
<td>6</td>
<td>48</td>
<td>48</td>
<td>Yes</td>
</tr>
<tr>
<td>1</td>
<td>16</td>
<td>7</td>
<td>tracheostomy</td>
<td>7</td>
<td>33</td>
<td>9.2</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>5</td>
<td>Insertion and chest bleeding</td>
<td>2</td>
<td>28</td>
<td>7.8</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>2</td>
<td>Chest bleeding</td>
<td>16</td>
<td>37</td>
<td>10.7</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1</td>
<td>Insertion and chest bleeding</td>
<td>10</td>
<td>33</td>
<td>3.8</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>5</td>
<td>Insertion and chest bleeding</td>
<td>23</td>
<td>38</td>
<td>4.3</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>1</td>
<td>Bleeding chest</td>
<td>16</td>
<td>37</td>
<td>10.7</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>63</td>
<td>tracheostomy</td>
<td>6</td>
<td>24</td>
<td>7.2</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>53</td>
<td>40</td>
<td>Conversion to central VA ECMO and sternotomy</td>
<td>16</td>
<td>31</td>
<td>5.2</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>54</td>
<td>39</td>
<td>Chest bleeding</td>
<td>8</td>
<td>31</td>
<td>5</td>
<td>Yes</td>
</tr>
</tbody>
</table>

aTTP, activated thromboplastin time; TEG, thrombelastograph; R, reaction.

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**Figure 1.** PfHb spikes with days recorded starting at day 0 for the first day of a pfHb spike; interventions are represented by downward pointing arrows at day of intervention. Also an asterisk above the arrow represents an intervention where a component was exchanged out.
related to the pfHb spike, but the inability to offer the patients and their families any additional options for meaningful survival due to underlying cardiac disease. The other three patients (1, 4, and 5) were discharged with acceptable quality of life at discharge and continue to do well (Table 3).

Dialysis was used on four of the five patients, with the two patients who were discharged from the hospital both having complete resolution of their acute kidney injury. The last patient in the series did not require dialysis. A BUN and creatinine followed the spike in pfHb in all patients. The BUN and creatinine levels returned to baseline following the intervention that stopped the hemolysis, and with patients 1, 2, 3, and 4 dialysis was also used to supplement kidney function (Figures 2 and 3).

**DISCUSSION**

Although the basic principles of centrifugal pumps function have stayed the same over the years, the technology of the pumps has improved. Solid plate surfaces have been replaced with designs that allow for more uniform movement of the blood in and out of the pump. The use of bearings has been reduced or eliminated. In one type of pump used in these patients, the Centrimag and Pedimag, the pumps are both entirely magnetically levitated. Given previous studies, these are some of the lowest pfHb-generating pumps available (6). We still had two patients in this series that developed high pfHb levels during their mechanical support period with these pumps. The other pump used in these patients was the CardioHelp. This integrated pump and oxygenator system was used for the other three patients in the series. It contains one bearing on the back of the pump.

While hemolysis over 100 mg/dL occurred only in five out of 146 patients, the causative mechanism is not found and alleviated implications can be significant. With these components in the ECMO and VAD circuits costing thousands of dollars, changing out devices without direct evidence of need is prohibitive. In some of our patients in this series, when possible, the pump head was checked by coming off mechanical support and displacing the blood in the circuit with clear sterile saline. This was done to inspect for signs of thrombus in the pump heads. In pediatric patients, the blood was then displaced into syringes on the postpump side of the circuit. In adults, the blood was displaced back into the patient. This allowed a brief period to see if there was any visible thrombus in the pump head. This step was not done if the patient could not tolerate being off support for 4 minutes.

The design of the CardioHelp pump seems to lend itself to the potential to trap larger thrombus in the pump head. The design of this pump has the normal single inlet tube
seen in all centrifugal pumps, but instead of having a large single outlet, this pump has four smaller veins in the back of the pump head that lead to four larger outlet tubes that go directly into the oxygenator. Although this design seems to be very functional in the development of a compact ECMO circuit, it leaves the pump head susceptible to clot buildup from the venous line or cannula. The clot formation can dislodge and then due to the smaller veins of this circuit, are unable to exit the pump head. With most other pump designs the propulsion fins in the heads do not trap the thrombus and it can exit the single large outlet tube and with patients on ECMO, be caught in the oxygenator (Figure 4). The oxygenator component of the CardioHelp appeared to be within normal ranges of appearance upon inspection after the change out in patients 1, 2, and 5. There were no masses of unusual thrombus in the separate oxygenator in patient 4.

Mechanical support is widely recognized to be fraught with major risks, with one of the greatest risks being excessive bleeding, often requiring excessive blood transfusions (12,13). Transfusions alone increase the mortality of mechanical support patients (14). In the attempt to reduce bleeding risk, anticoagulation management is a balancing act. In this case series, all but one of these patients had a sternotomy, which itself can increase bleeding risk. In addition, all of these patients had periods of bleeding that required the anticoagulation, usually heparin, to be turned off to achieve control of bleeding. While bleeding was controlled with this action, the risk to the circuit is increased, especially with regard to development of thrombus that could cause pump head concerns. In some instances only a minimal amount of thrombus on the pump head or fin can lead to hemolysis. At least in the patients with the Centrimag or Pedimag, the thrombus, even though the fin is spinning at 3,000–4,000 rpm, seemed capable of maintaining its position on the pump fin. In the CardioHelp patients, even though the pump head is spinning between 2,500 and 3,500 rpm, the thrombus did not break down into small segments and pass through the small back veins of the pump. It appears in patient 2 that some of the thrombus actually became lodged in one of the small veins.

Some of these patients did not have flow decreases leading to the need to increase revolutions per minute of the pump to maintain flow with thrombus in the pump head or fins. Whether the need for the revolutions per minute increase is due to a drag on the pump head from the thrombus, or an inefficiency of the fins to effectively propel blood, it is important to make note of any unusual revolutions per minute changes. Also of interest is that only two of the patients had noticeable vibrations from the thrombus being in the pump head or pump fin. At the time of pfHb spike, the circuits had a varying length of days of use from less than a day to 15 days of support before spikes in pfHb, as did days of support from less than a day to 93 days.

From our results with continued monitoring of pfHb levels, these levels should decline noticeably 12 hours or less after an intervention to a half or a third of the peak pfHb level. One previous study also showed similar results at 24 hours after intervention (7). If this drop does not occur, our experience demonstrates that the mechanism of hemolysis has not been addressed and further investigation is warranted. Prompt reporting of pfHb levels over 250 mg/dL in absolute values to the clinician helps to make sure that the clinicians managing the patient understand the pfHb trend for their patients. These absolute values became critical to the management of patient 4 in this study. Downward absolute trends reassured practitioners that the intervention resolved the issue. Plasmapheresis was considered for this patient but due to patient size and improving heart function, the use of plasmapheresis was thought to impede weaning this patient off ECMO in the coming days. No patients in this study received plasmapheresis to reduce the pfHb levels during their mechanical support.

Care must also be taken during sample collection and testing for the pfHb. Creating too large of a negative force on the patient’s sampling line during access for a blood draw can create hemolysis itself leading to a falsely high pfHb in the blood test. Another patient parameter that can be helpful in addition to the pfHb test is the appearance of the patient’s urine. Since pfHb testing is normally run just
once a day, sometimes the first sign of hemolysis is a rose tint to the urine. However, one must be careful to rule out hematuria caused by unrelated problems instead of hemoglobinuria due to hemolysis. Also, it is known that hyperbilirubinemia can lead to interference with pfHb testing (15,16). The measurement for total hemoglobin pigments (oxyhemoglobin, deoxyhemoglobin, methemoglobin) relies primarily on the measurement of the Soret band absorbance at 415 nm, which is very near the absorbance maximum of bilirubin (450 nm). One previous study recommended the use of bilirubin oxidase to eliminate this interference (15). Although this technique was not used at our center there is a concern about monitoring pfHb on all of our patients. Our center has adopted the practice of reporting and monitoring plasma-free oxyhemoglobin levels in hyperbilirubinemia patients, instead of total pfHb levels. The laboratory reports a value just for oxyhemoglobin in patients with total bilirubin levels over 5 mg/dL. The interference from bilirubin is minimal at the maximum absorption wavelength for oxyhemoglobin (578 nm).

The centrifugal pump used in these patients did not seem to directly cause, but indirectly caused blood damage due to thrombus originating from the venous line or venous cannula, with thrombus subsequently becoming snared in the pump fins or trapped in the pump head. Perhaps thrombus or fibrin strands may additionally originate in the pump head as well on the fins or bearings. Regardless of ordination location, pfHb testing provides the opportunity to monitor trends, giving warning when this event is occurring, and enabling timely intervention. If the pfHb levels did not drop in the next 12 hours or less then the issue causing the blood trauma had not been fixed.

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