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ORIGINAL RESEARCH

Carboxyhemoglobin and methemoglobin levels to diagnose hemolysis in patients supported with mechanical circulatory support devices

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BACKGROUND: Decreased systemic oxygen delivery derived from gas exchange abnormalities in severe hemolysis complicates patients requiring mechanical circulatory support devices. Severe hemolysis releases free hemoglobin in plasma causing elevation of carboxyhemoglobin and methemoglobin levels. Hemolysis-induced decline in hemoglobin and oxyhemoglobin saturation significantly reduces the arterial oxygen content in blood, reducing systemic oxygen delivery. These patients develop hypoxemia with misleadingly normal oxygen saturation measured by standard pulse oximetry.

METHODS: Retrospective review of 2 clinical cases reaching carboxyhemoglobin and methemoglobin levels > 2% while supported with an Impella device.

RESULTS: Case 1. Patient with cardiogenic shock refractory to maximal medical therapy required insertion of Impella device achieving improvement in cardiac output, pulse oximetry, arterial oxygen saturation and systemic oxygen delivery. The device caused significant hemolytic anemia with severe decline in hemoglobin and arterial oxygen saturation with elevation of carboxyhemoglobin and methemoglobin levels, causing drastic reduction in systemic oxygen delivery despite adequate cardiac output. Device removal reversed severe hemolytic anemia, causing increased arterial oxygen saturation and systemic oxygen delivery despite borderline cardiac output.

Case 2. Patient with refractory cardiogenic shock improved after insertion of Impella device. Initial improvement cardiac output and systemic oxygen delivery was negated by hemolytic anemia associated with elevation of carboxyhemoglobin and methemoglobin levels. Hemolysis decreased by reducing the Impella power output. Carboxyhemoglobin and methemoglobin levels correlated precisely with degree of hemolysis allowing to titrate therapy to best systemic oxygen delivery.

CONCLUSIONS: Monitoring carboxyhemoglobin and methemoglobin levels readily identifies patients with ongoing hemolysis secondary to invasive supportive devices.

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Background

Many patients admitted to critical care units present with a diverse group of cardiac, valvular, and pericardial diseases that may progress to a hemodynamic state characterized by clinical and biochemical evidence of tissue hypoperfusion, recognized as cardiogenic shock (CS). If persistent, CS can evolve into multisystem organ failure.[1] The most common cause of CS is left ventricular dysfunction from acute myocardial infarction.[2] Although once associated with high mortality (> 80%),[3] the prognosis of CS has improved with modern therapies. Best care standards for managing complex CS require availability of mechanical circulatory support devices (MCSD)[2] that can be inserted percutaneously via central vessels and positioned across the aortic valve and into the left ventricle, as is the case with Impella devices (Abiomed Inc, Danvers, MA).[4] A device like this delivers blood from the inlet area (left ventricle) to the outlet opening (ascending aorta). Depending on the model used, the Impella can generate between 2.5 and 5.5 liter/min of forward flow to unload the left ventricle, increase cardiac output (CO), and reduce myocardial workload and oxygen consumption, resulting in increased coronary and peripheral perfusion.[5] Other similar devices used include the Tandem Heart device (Cardiac Assist Inc, Pittsburg, PA), centrifugal pumps that require surgical implantation such as the CentriMag pump (Thoratec Corporation, Pleasanton, CA), the Biomedicus pump (Medtronic, Northridge, CA), as well as extracorporeal membrane oxygenation (ECMO) devices.[5] Complications associated with the use of these devices include major events such as bleeding, hemolysis, anemia, embolism, valvular dysfunction, and device failure.

Hemolysis is more likely to occur with prolonged device use with an incidence described as high as 62.5%[6] and may cause worsening multiorgan failure. Intravascular hemolytic anemia may occur due to the structural damage caused to the red blood cells (RBCs) by high-velocity jets, damage induced by centrifugal pumps, or shear stress in the devices' tubing. As RBC destruction occurs, free serum hemoglobin (Hb) is released into the circulation. Free serum hemoglobin binds to the plasma-binding protein haptoglobin, thereby reducing unbound plasma haptoglobin levels. The haptoglobin-hemoglobin complex is cleared by the liver.[7]

The enzyme lactic dehydrogenase (LDH) present in RBCs is released into plasma. When intravascular hemolysis is severe, the serum becomes pink in the presence of oxyhemoglobin which may become brownish by the oxidized form methemoglobin (MetHb). Urine becomes dark with free hemoglobin present.[8]

Damaged RBCs are primarily destroyed by the liver. Abnormal or deformed RBCs are destroyed in the spleen, releasing free hemoglobin. Heme oxygenase-1 catabolizes free hemoglobin into biliverdin, iron, and carbon monoxide. Biliverdin is reduced and released into plasma as unconjugated bilirubin, iron is released into plasma and transported to the bone marrow, and carbon monoxide binds to hemoglobin from intact RBCs to produce carboxyhemoglobin (COHb)[7,8].

Hemolytic anemia will induce the kidneys to increase erythropoietin production to stimulate new accelerated RBC production by the bone marrow, manifested by increased count of immature RBCs or reticulocytes.[7,8]

Therefore, when managing critically ill patients supported with MCSD, the presence of anemia associated with elevated free plasma hemoglobin, reticulocytosis, high LDH, and rising unconjugated bilirubin levels combined with low haptoglobin levels should suggest the presence of ongoing hemolysis caused by the device itself.[6] The presence of elevated COHb and MetHb levels remains an under-recognized and under-utilized tool to rapidly identify ongoing hemolysis in critically ill patient supported with MCSD, even when the rate of endogenous production of carbon monoxide has long been reported to correlate with the rate of blood heme destruction in hemolytic anemia.[9] The routine assessment of critically ill patients includes sequential evaluation of arterial and mixed venous blood gases (ABGs, VBGs) to appraise acid-base, ventilation, and oxygenation status by directly measured and derived/calculated variables. ABGs and VBGs samples also routinely display COHb and MetHb levels when measured on a blood gas analyzer that contains a Co-oximeter. COHb and MetHB levels are usually dismissed in the decision-making process managing patients, nor are they usually given consideration as parameters that may correlate with ongoing hemolysis.

The objective of this manuscript is to discuss 2 clinical cases supported with Impella devices that developed hemolysis, highlighting the value of COHb and MetHb levels as reliable biological markers of ongoing hemolysis and therefore helpful for making rapid management decisions that may alter the course of the critically ill patient.

Materials and methods

Retrospective chart review of 2 clinical cases managed in our intensive care unit (ICU) reaching COHb and MetHb levels $\geq$2% while supported with an Impella device. This retrospective study was approved by our Institutional Review Board (IRB application # 17-006784).

Results

Pertinent results from each case are described in the 2 case reports as follows:

Case 1

A teenage patient diagnosed with refractory CS and multiorgan failure from nonischemic idiopathic dilated cardiomyopathy and biventricular failure required admission to the critical care unit. Despite medical management with a vasopressor (norepinephrine), inotropes (dopamine, dobutamine), diuretics (bumetanide), and inhaled nitric oxide, there was worsening dyspnea, progressive elevation of central venous pressures up to 28 mm Hg, and progressive hypoxemia,

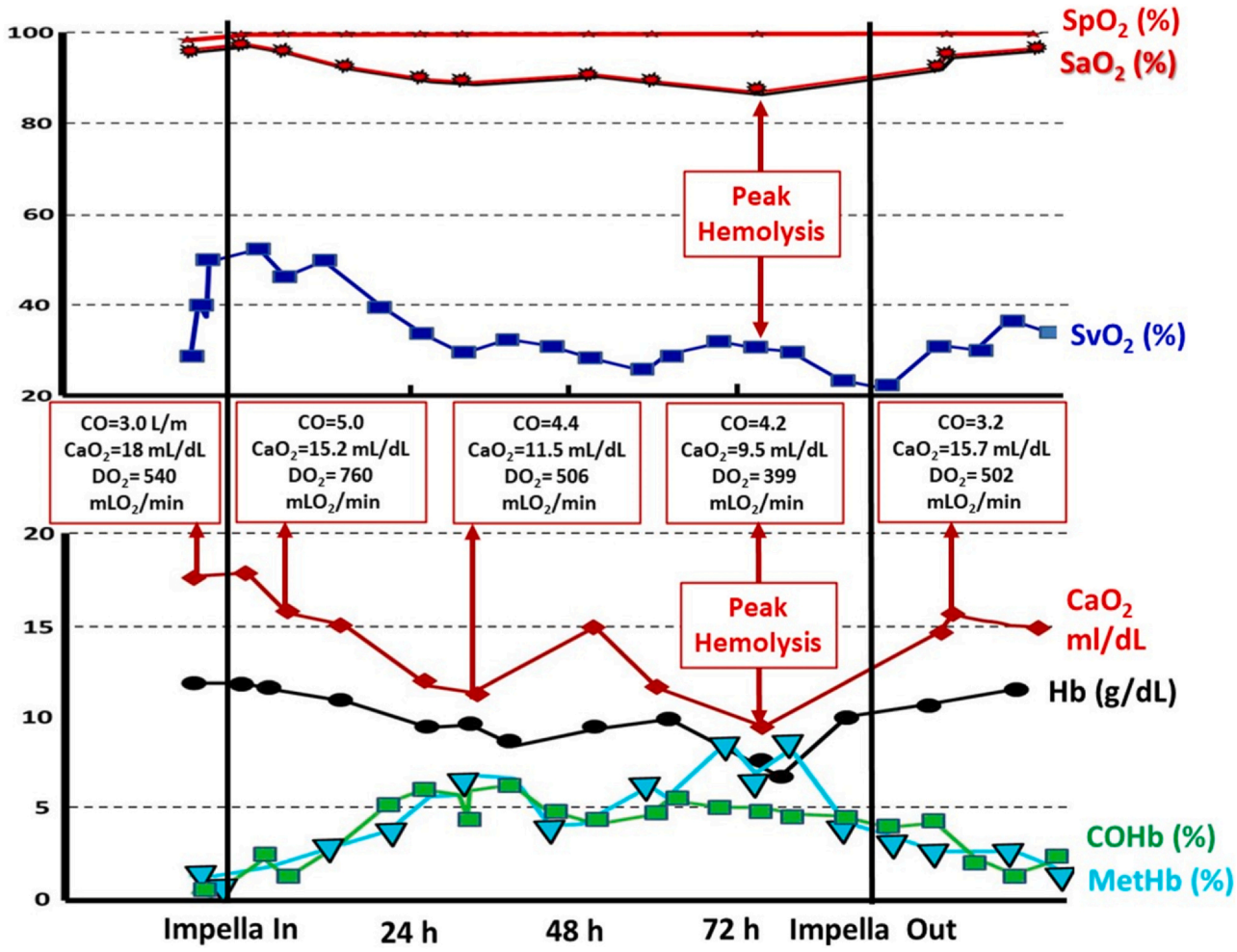

Figure 1 Case 1. Hemodynamic and gas exchange before and after Impella insertion. SpO_2, oxygen saturation measured by pulse oximetry (%); SaO_2, oxyhemoglobin measured by arterial blood gases (ABG) (%); SvO_2, mixed venous oxygen saturation (%); CO, cardiac output (liter/m); CaO_2, arterial oxygen content (ml/dl); DO_2, systemic oxygen delivery (mlO_2/min); Hb, hemoglobin (g/dl); COHb, carboxyhemoglobin (%); MetHb, methemoglobin (%). Black vertical lines on the figure show time of insertion and removal of Impella device. Insertion of Impella device achieved initially an increase in CO with stable CaO_2, therefore improving $DO_2 = (CO \times CaO_2 \times 10)$. This improvement is also shown by increased SvO_2 levels consistent with better tissue perfusion. Impella insertion was associated with progressive drop in hemoglobin due to hemolysis as shown by standard laboratories. The progressive drop in Hb due to hemolysis matches the progressive increment in COHb and MetHb, also associated with reduced SaO_2. SpO_2 is misleadingly normal because it senses the summation of SaO_2 + COHb + MetHb, therefore is not a reliable parameter to follow in these patients. During peak hemolysis, the benefits of increased CO were outweighed by the drastically reduced CaO_2 with a net reduction in DO_2. Impella removal was associated with rapid resolution of hemolysis as shown by COHb and MetHb rapidly returning to normal levels.

causing decreased mixed venous oxygen saturation (SvO_2) down to 27% as evidence of hypoperfusion and increased brain natriuretic peptide levels (up to 1730 pg/ml).

The patient required intubation and placement on positive pressure ventilation, received increased vasopressor support, and had an Impella CP device inserted, with an initial power level of 8 generating flows between 3.1 and 3.5 liter/min. Following insertion, the fraction of inspired oxygen (FiO_2) and positive end-expiratory pressure were adjusted to maintain partial pressures of arterial oxygen (Pao_2) of at least 100 mm Hg. The CO initially improved (from 3.0 to 5.0 liter/min), and oxygen saturation as measured by pulse oximetry (SpO_2) improved from 97% to 100%, with corresponding improvements in arterial oxygen saturation (SaO_2) measured by ABGs from 96% to 98% (see Figure 1).

Hb levels started to decline shortly after Impella device insertion (from 11.9 g/dl reaching as low as 6.8 g/dl), requiring multiple blood transfusions. Despite decreases in SaO_2 levels reaching as low as 87%, the SpO_2 remained misleadingly constant at 100%. Hemolysis was diagnosed and confirmed by the association of progressive anemia requiring blood transfusions, increasing LDH levels reaching 6770 U/liter, increasing total bilirubin levels reaching 42.8 mg/dl (conjugated 37.0-unconjugated 5.8 mg/dL), and raising reticulocyte count (53 nucleated RBC/100 white blood cell which continued to rise to a peak of 124).

The course of his hemolytic anemia correlated precisely with rapidly increasing COHb and MetHb levels (from 0.2% and 0.9%, respectively, prior Impella insertion to a peak of 5.9% and 6.6% during peak hemolysis after

Impella). The reduced levels of Hb and SaO_2 caused a decline in arterial oxygen content (CaO_2) from 18 down to 9.5 ml O_2/dl, and a consequent decline in mixed venous oxygen content (CvO_2) from 8.2 to as low as 3.2 ml O_2/dl. The improved CO following Impella insertion correlated with an initial increase in the calculated systemic oxygen delivery (DO_2), from a baseline of 540 up to 750 ml O_2/min. This initial gain, however, was eventually outweighed by the extreme drop in Hb caused by hemolysis. The anemia plus the reduced SaO_2 caused by rising levels of COHb and MetHb produced a drastic reduction in CaO_2 and consequently poor oxygen delivery to tissues (DO_2), the lowest calculated 399 ml O_2/min, resulting in elevated lactic acidosis (peak, 4.4 mmol/liter).

The severe hemodynamic consequences of hemolysis on gas exchange prompted to wean the Impella power level to 2 decreasing the flow to 1.2 liter/min, followed by a removal of the device. After its removal, hemolysis rapidly resolved, Hb levels climbed, with subsequent improvements in SaO_2 and Cao_2, followed by improved Do_2, and decreased metabolic acidosis, which correlated well with a return of COHb and MetHB down to normal levels (< 2%).

Case 2

After a transient period of unresponsiveness at home, a mentally alert middle-aged patient with a history of nonischemic cardiomyopathy was admitted to the ICU with acute CS after cardiac arrest resulting from ventricular tachycardia (VT) and ventricular fibrillation (VF). Inotropic support with dobutamine was initiated. During placement of central venous catheters, the patient developed a VT/VF arrest requiring multiple attempts at external cardioversion in addition to shocks by an automatic internal cardioverter defibrillator, chest compression for about 10 minutes, and medications for advanced cardiac life support (epinephrine, sodium bicarbonate, magnesium, amiodarone). The cardiac rhythm corrected to perfusing, but given the low pulse pressure, recent VT, and high lactate concentration (peak, 6.8 mmol/liter), the patient was intubated and received positive pressure ventilation with continued inotropic support. An Impella CP device was inserted with an initial power level of 8, generating a flow of 3.0 liter/min.

Following Impella placement, FiO_2 and positive end-expiratory pressure settings were adjusted to maintain PaO_2 levels of at least 100 mm Hg. After Impella insertion, hemodynamic parameters and gas exchange improved: CO increased (from 1.6 up to 5.7 liter/min), SpO_2 changed from 94% to 100%, SaO_2 increased from 96% to 98%, and calculated DO_2 improved from 331 to 741 ml O_2/min (Figure 2).

Although his CO and DO_2 initially improved, reaching normal lactic acid levels (1.8 mmol/liter), hemolysis caused a decrease in Hb levels to as low as 7.1 g/dl, requiring blood transfusions. His ABG levels and calculated DO_2 showed a pattern like the one previously described (increased MetHb and COHb levels associated with decreased SaO_2 despite SpO_2 reading 100%, reduced CaO_2, poor DO_2 levels which were calculated as low as 488 ml O_2/min at the lowest levels of Hb and CaO_2 with rising lactic acid levels to 2.5 mmol/liter). It was decided to intervene before the hemolysis diagnostic panel resulted, based on COHb and MetHb levels.

As soon as hemolysis was suggested by the elevation of COHb and MetHb levels, the Impella power level was turned down from 8 to 5, which reduced the revolutions per minute on the device from 50,000 to 35,000 with consequent flow reduction from 3 to 2 liter/min.

Although lower flows decreased the CO from 5.2 down to 4.3 liter/min, the overall DO_2 increased (from 488 to 657 ml O_2/min) due to improved Hb, SaO_2, and CaO_2. Standard testing later confirmed the presence of hemolysis with elevated LDH (835 U/liter) and free plasma hemoglobin (70.5 mg/dl) levels and low haptoglobin (< 14 mg/dl). Reducing the CO augmentation resolved the hemolytic process, and Impella support was maintained thereon until the patient was stable for final device weaning without further observed episodes of hemolysis.

Discussion

In general, critically ill patients admitted to ICUs are at risk of developing hemolysis, as typically they have multiple invasive lines placed. Those ICU patients requiring MCSD have a considerably higher risk. Patients supported by MCSD who develop hemolysis have worse prognosis than those without hemolysis, as plasma-free hemoglobin may induce kidney damage and multiorgan failure, and these patients may be adversely affected by the need for increased blood transfusions.[10] The recognition and diagnosis of ongoing hemolysis, particularly when it is in low degree, is challenging since usual biological markers of hemolysis such as LDH, bilirubin, and haptoglobin levels are nonspecific and can be abnormal in many conditions other than hemolysis. Plasma-free hemoglobin is another marker of hemolysis, but its values can be spuriously elevated by red cells breaking during the blood draw or in the presence of acute hyperbilirubinemia from liver disease.[11]

COHb levels will be elevated in heavy smokers and those with other environmental carbon monoxide exposure.[12] Normal values of COHb admission should rule out the presence of these conditions, and therefore subsequent elevations in these values should alert to the possibility of ongoing hemolysis. Hemolysis is an underrecognized cause of increased COHb levels, and only few reports correlate carboxyhemoglobinemia in cases with ongoing hemolytic anemia.[13] COHb levels > 2% were recently described as a reliable diagnostic marker of hemolysis among patients requiring ICU care with better diagnostic accuracy than LDH and unconjugated bilirubin and described good correlation between the level of COHb with severity of hemolysis.[14] Furthermore, COHb has been found to correlate with hemolysis and lower hospital survival among patients supported with ECMO, suggesting that elevated COHb among ECMO patients should trigger diagnostic and therapeutic interventions.[15]

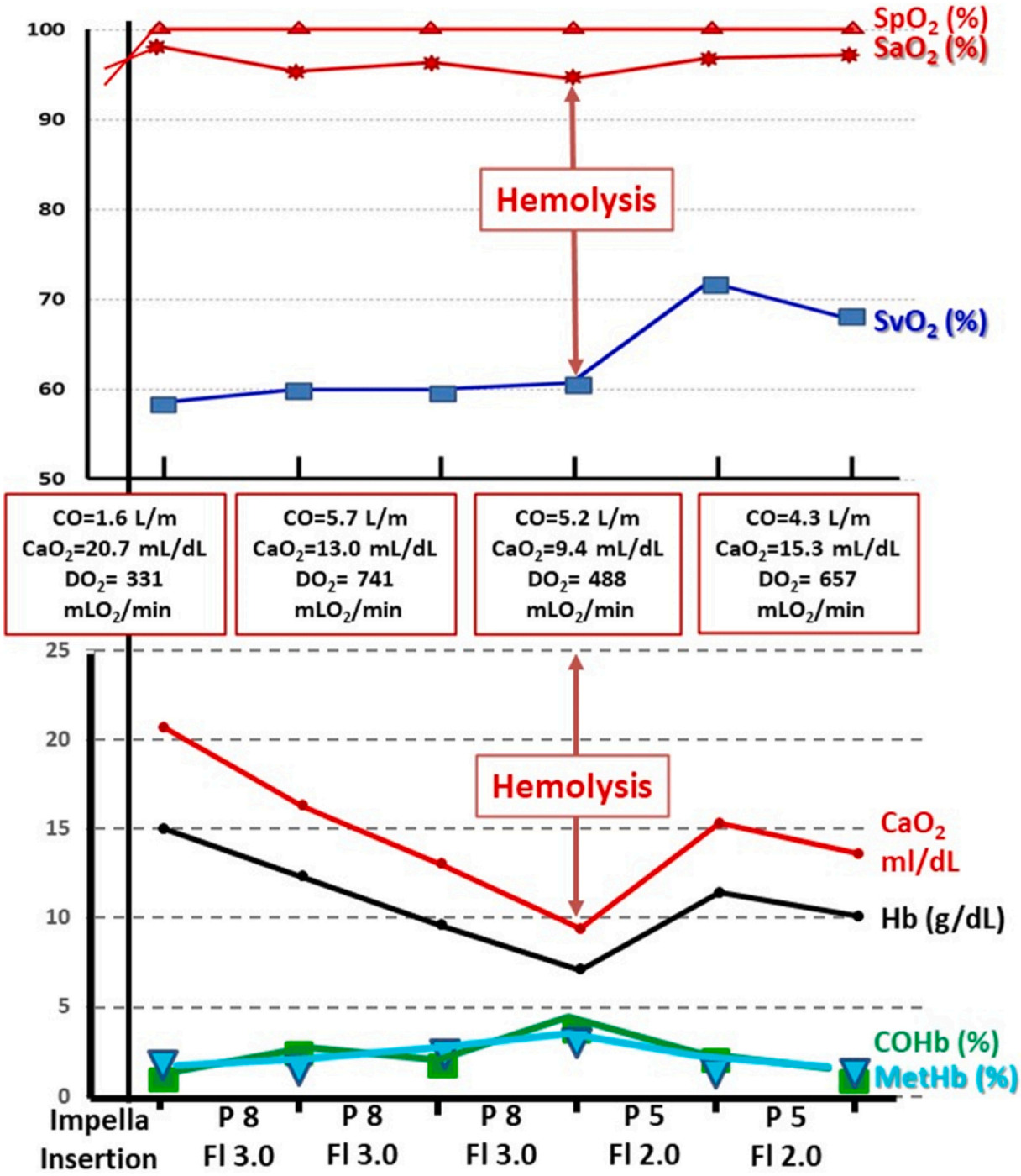

Figure 2 Case 2. Hemodynamic and gas exchange before and after Impella insertion. SpO_2, oxygen saturation measured by pulse oximetry (%); SaO_2, oxyhemoglobin measured by arterial blood gases (ABG) (%); SvO_2, mixed venous oxygen saturation (%); CO, cardiac output (liter/m); CaO_2, arterial oxygen content (ml/dL); DO_2, systemic oxygen delivery (ml O_2/min); Hb, hemoglobin (g/dl); COHb, carboxyhemoglobin (%); MetHb, methemoglobin (%). Early hemolytic anemia following insertion of Impella device was disclosed by raising COHb and MetHb levels, prompting reduction in power level on Impella device, rapidly resolving hemolysis. Figure shows elevation of COHb and MetHb levels following Impella insertion consistent with hemolysis (confirmed by standard laboratory testing). Adjustment lowering the device's power output was followed by return of COHb and MetHb down to normal values indicating resolution of hemolytic episode. The secondary effects of hemolysis including drop in Hb, SaO_2, CaO_2, and DO_2 are also shown, as well as their recovery after resolution of hemolysis.

MetHb levels can be elevated due to a variety of genetic congenital defects or more commonly by exposure to a variety of different drugs, such as antimalarial agents, dapsone, sulfonamides, and local anesthetics. Methemoglobinemia can also occur in susceptible individuals such as those with glucose-6-phosphate dehydrogenase deficiency.[16] Methemoglobinemia has not been widely recognized as marker of active hemolysis, although a recent case report described an infant with severe intravascular hemolysis, methemoglobinemia, and renal failure related to complications of a left

ventricular assist device,[17] just as the patients in this case report.

The reported cases demonstrate that carboxyhemoglobinemia and methemoglobinemia may be readily available markers of active hemolysis among patients supported with MCSD, and the trend of theses variables can provide immediate feedback for diagnostic and therapeutic interventions to manage hemolysis. It is also important to recognize that hemolysis-induced elevation of COHb and MetHb will not only reduce the proportion of hemoglobin available for carrying oxygen causing decreased oxyhemoglobin levels measured by SaO_2 but will also contribute to a left shift in the oxygen dissociation curve, increasing the affinity of adjacent hemoglobin molecules for oxygen therefore rendering the RBCs less able to release oxygen to tissues.[18] Additionally, the decline in oxyhemoglobin levels measured by SaO_2 in ABG will not be accurately displayed by a standard pulse oximeter which is not designed to capture the effect of dyshemoglobinemias. A standard pulse oximeter display of SpO_2 measuring tissue light transmission at 2 wavelengths best represents the summation of SaO_2 plus COHb plus MetHb and is therefore an unreliable marker of hypoxemia among patients with active hemolysis.[18,19]

Furthermore, it is important to recognize that active hemolysis producing a decline in the main components of oxygen content, Hb, and SaO_2 causes a reduction in CaO_2, which makes oxygen delivery to tissues suboptimal despite acceptable CO, and all these phenomena combine to produce worsening lactic acidosis. If achieving improved CO with MCSD comes at the expense of severe hemolysis that causes a drastic reduction in CaO_2, the expected benefit in tissue perfusion may be negated, as a significant reduction in CaO_2 will outweigh the benefit of the increased CO, and therefore the patient may fare better with reduced support or no support at all if that is what is required to avoid hemolysis.

Continuous monitoring of COHb and MetHB is currently available using newer pulse oximeter platforms utilizing multiple wavelengths, with the capability to measure COHb and MetHb concentrations noninvasively,[14,18,19] which may provide more efficient ways to monitor active hemolysis among these patients. Simultaneous monitoring of Hb, COHb, and MetHb can also differentiate hemolysis from hemorrhaging, as patients with hemolysis will have drop in Hb, with increasing levels of COHb and MetHb, while those patients showing drop in Hb with normal COHb and MetHb levels are more likely to be actively bleeding.

Conclusions

Traditional laboratory monitoring of hemolysis in critically ill patients supported with cardiac devices takes longer than using available ABG results and may delay immediate necessary changes to therapy. Alternatively, progressive increases in levels of COHb and MetHb with reduced SaO_2 in ABGs are readily available, yet under-recognized markers of clinically significant hemolysis. Likewise, the effectiveness of therapeutic adjustments to avoid hemolysis can be objectively and promptly observed by following the trend in COHb and MetHb levels. Further prospective studies are needed to better demonstrate the diagnostic and prognostic value of these variables among critically ill patients, obtained either by sequential ABGs or using newer models of multiwavelength pulse oximetry for noninvasive monitoring of these variables.

Disclosure statement

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