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Pharmacologic Considerations in the Management of Patients Receiving Left Ventricular Percutaneous Mechanical Circulatory Support

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Abstract

Percutaneous mechanical circulatory support (MCS) devices, including the intra-aortic balloon pump, Impella, and TandemHeart, are often used for hemodynamic support in the setting of refractory cardiogenic shock. The thrombotic and bleeding complications associated with these devices is well recognized, and the Impella and TandemHeart devices have unique anticoagulation considerations that may influence patient outcomes. Both devices typically require use of a heparinized purge solution in combination with intravenous unfractionated heparin, thereby providing multiple sources of heparin exposure. Each device also has specific monitoring requirements and goal ranges. The purpose of this review is to provide an overview

of percutaneous MCS devices commonly used in the acute management of left ventricular failure, with an emphasis on pharmacologic considerations. We review recent evidence and guidelines and provide recommendations for appropriate use of anticoagulation during device support. Approaches to managing heparinized purge solutions, monitoring, and the utility of non-heparin anticoagulants are also provided, as high-quality evidence in the literature is limited.

Introduction

Cardiogenic shock is a syndrome characterized by myocardial dysfunction leading to systemic tissue hypoperfusion.[1] Typically, a myocardial insult (e.g., ischemic event) leads to reduced cardiac output (cardiac index [CI] < 1.8 L/min/m^2), fall in blood pressure (BP) (systolic BP < 90 mm Hg), and subsequent hypoperfusion of vital organs.[1,2] Myocardial hypoperfusion results in further ischemia and worsening of cardiac output.[2] Similarly, decreases in tissue perfusion promote compensatory neurohormonal activation, resulting in vasoconstriction frequently accompanied by elevations in systemic vascular resistance (SVR) and progressive myocardial dysfunction.[2] Residual end-systolic volume resulting from a reduction in stroke volume can lead to increases in left ventricular (LV) end-diastolic pressure and pulmonary capillary wedge pressure (PCWP), resulting in pulmonary congestion. Although event rates have declined in recent years, in-hospital mortality for patients with cardiogenic shock remains high, ranging from 29–47%.[3]

Treatment of cardiogenic shock often requires one or more of the following interventions: treatment of precipitating causes (e.g., coronary revascularization), optimization of volume status (e.g., diuretics, renal replacement therapy), intravenous (IV) vasopressors to maintain adequate

BP, and IV inotropes to increase cardiac output. For cardiogenic shock refractory to pharmacologic interventions, intra-aortic balloon pump (IABP) counterpulsation and extracorporeal membrane oxygenation (ECMO) have represented the mainstays of therapy. The recent development of percutaneous ventricular assist devices (pVADs) has considerably expanded the therapeutic modalities available for this critically ill population. Guidelines highlight the use of these nondurable devices as a reasonable strategy for achieving clinical recovery, or until a decision can be made regarding definitive therapies, such as durable mechanical circulatory support (MCS) or cardiac transplantation (a class IIa recommendation, level of evidence B).[4] With increased use, there is increasing concern about the complexities of overall management and potential complications, such as the well-documented risks of thrombosis and bleeding. The purpose of this review is to describe the devices and the important anticoagulation considerations for nondurable percutaneous MCS used for the acute management of LV failure. Readers are referred elsewhere for a discussion of the pharmacokinetic and pharmacodynamic aberrations conferred by ECMO, as they are beyond the scope of this review.

Intra-Aortic Balloon Pump

The most common percutaneous circulatory support device used in practice is the IABP, which consists of a double-lumen catheter with a polyethylene balloon attached at the distal end and an exterior pump console that controls inflation and deflation.[1] The IABP is inserted percutaneously via the femoral artery, and the balloon is advanced into the descending thoracic aorta (Figure 1A).[5] The balloon inflates with helium gas at the onset of diastole and deflates at the onset of systole, a mechanism most often triggered by continuous electrocardiogram input.[1]

The hemodynamic effects of an IABP include increased diastolic BP, decreased preload and afterload, decreased myocardial oxygen consumption, increased coronary artery perfusion, and a modest improvement in cardiac output.[1,6] For these reasons and the speed with which it can be inserted, an IABP is often used to stabilize hemodynamics in emergent situations such as ST-segment–elevation myocardial infarction with cardiogenic shock. Although the benefits of an IABP in this setting remains controversial, its use remains common, and it often serves as the standard against which newer MCS devices are compared.[7]

Percutaneous Left Ventricular Assist Devices

Impella

The left-sided Impella devices (2.5, 5.0, CP, LD; Abiomed, Inc., Danvers, MA) are extracorporeal microaxial continuous-flow pumps that provide LV support. Although many aspects of the right-sided Impella (Impella RP) are similar to models used for LV support, the focus of this review will be the latter. The Impella catheters used for left-sided support are most often inserted into the arterial system percutaneously via either a femoral or axillary approach (2.5, 5.0, CP) whereas the LD catheter requires surgical placement directly into the ascending aorta (Figure 1A).[8] The microaxial pump motor, which runs at up to 51,000 revolutions per minute (Impella 2.5), extracts blood from the left ventricle through the inlet cage into the cannula portion of the pump, and ejects it into the ascending aorta just above the aortic valve.[6,8,9] The main hemodynamic benefits of the Impella devices result from direct unloading of the left ventricle, thereby reducing LV wall tension and PCWP, resulting in reduced myocardial oxygen demand.[1,9,11] Increases in mean arterial pressure, diastolic pressure, and cardiac output augment coronary flow and systemic perfusion.[2,9,10] Maximum flow rates (cardiac output) generated by

the devices are 2.5 L/minute for the Impella 2.5 catheter, 3.5 L/minute for the CP catheter, and 5.3 L/minute for the 5.0 and LD catheters.[8,9]

Owing to its potential benefits, Impella devices are indicated for temporary (≤ 6 hours) MCS during high-risk percutaneous coronary intervention (PCI) (2.5 and CP models) and short-term use (≤ 6 days) to treat cardiogenic shock due to LV dysfunction refractory to standard therapy immediately following myocardial infarction (MI) or open heart surgery (2.5, 5.0, CP, and LD models). These indications are based on the major clinical trials conducted to date (Table 1). Of note the Impella devices have been compared to the IABP in three major trials and have shown improvements in hemodynamics but not mortality or other long-term clinical outcomes.[11-13] One meta-analysis of patients with acute MI complicated by cardiogenic shock also demonstrated no significant difference in outcomes between IABP or Impella (30-day all-cause mortality, relative risk 0.99, p=0.95).[14] Similarly there were no significant differences in 6-month all-cause mortality or left ventricular ejection fraction. This meta-analysis could have been limited by the use of two different Impella devices (CP and 2.5), the lack of a control arm, and potentially heterogeneous patient populations in the included trials, as the definition of cardiogenic shock varied.

TandemHeart

The TandemHeart device (CardiacAssist, Inc., Pittsburgh, PA) is an extracorporeal centrifugal continuous-flow pump capable of providing up to 4.5 L/minute of assisted cardiac output and can be used for both left- and right-sided mechanical support.[15,16] A cannula is inserted into the femoral vein and introduced into the left atrium by means of a trans-septal puncture. Blood is then channeled into the pump, and a femoral artery cannula returns blood to

the systemic arterial circulation. Unlike Impella, this unique cannulation approach enables TandemHeart to be used in patients with aortic regurgitation, aortic valve prostheses, aortic stenosis, or LV mural thrombus. In addition, during TandemHeart support, both the left ventricle and the device contribute flow to the aorta simultaneously, thereby working in tandem. The redirection of blood from the left atrium reduces LV preload, LV workload, filling pressures, wall stress, and myocardial oxygen demand. Increases in arterial BP and cardiac output support systemic perfusion. Depending on device speed, LV contraction can virtually cease, and perfusion becomes pump dependent, as evidenced by a loss of pulse pressure. Ventricular tachycardia or fibrillation usually (but not always) renders the TandemHeart ineffective due to loss of right ventricular (RV) function. Since the TandemHeart can produce full cardiac support, it is indicated for short-term (< 6 hours) use in the management of cardiogenic shock refractory to IABP counterpulsation and/or high-dose vasopressor support, although longer durations have been used clinically.[17] As with Impella devices, the TandemHeart confers greater hemodynamic improvements versus IABP but does not impact morbidity and mortality (Table 1).[18,19]

Pharmacologic Considerations

The multidisciplinary team caring for patients with a percutaneous support device must be vigilant in monitoring for the development of adverse events (Table 2). As with durable MCS, the most challenging aspect of care in patients receiving temporary support is balancing the competing risks of thrombosis and bleeding, which is made more complicated by the release of heparinized purge solutions by the Impella and TandemHeart devices. Clinical considerations related to anticoagulation will therefore be the focus of the following section.

IABP

Several components of percutaneous MCS devices interface with the systemic circulation, serving as a nidus for platelet activation and initiation of the coagulation cascade. Systemic anticoagulation is therefore used to mitigate the risk of device malfunction or systemic embolization due to thrombus formation. Debate exists regarding the need to systemically anticoagulate patients receiving IABP support, and evidence for its use in this setting remains limited.[20] Nonetheless, systemic anticoagulation is commonly used in this population, particularly when balloon support is provided every other (e.g., 1:2) or every third (e.g., 1:3) cardiac cycle, a less physiologic configuration than 1:1 support. Some experts contend that the decision regarding anticoagulation should be made in light of concomitant indications (e.g., atrial fibrillation) and contraindications (e.g., bleeding) rather than as a routine intervention for the IABP itself.[20]

Impella

A unique aspect of the Impella system is the release of a dextrose-based purge solution from the motor housing, which flows countercurrent to the discharge of blood from the outlet area (Figure 2). The resulting pressure barrier prevents the entry of blood into the motor housing, thus reducing the risk of thrombosis-related complications. Purge flow is automatically regulated by the Impella controller (Figure 1B) to maintain a purge pressure of between 300 and 1100 mm Hg, which typically corresponds to flow rates of between 2 and 30 mL/hour.[8] In older device configurations, dextrose 20% in water (D20W) was recommended as the default purge solution. In specific situations, however, dextrose concentrations of between 5% and 40% can be used based on the viscosity required to maintain goal purge pressure. For example, if the controller

alarms "purge pressure high" (i.e., > 1100 mm Hg) and no kinks are found within the purge system, the manufacturer recommends to decrease the concentration of dextrose in the purge solution.[8]

In September 2015, Abiomed issued updated guidance recognizing dextrose 5% in water (D5W) as the default purge solution.[21] According to the manufacturer, the rationale for this change was the widespread availability of D5W and that purge cassettes containing D5W may be used for 5 days or longer, whereas cassettes containing higher viscosity solutions were often replaced every 24 hours.[21] Although the impact of this change in the default dextrose concentration remains unclear, the manufacturer estimates that 30-40% faster purge flow rates are expected with administration of the less viscous D5W solution compared to D20W.[21]

During device insertion, administration of IV heparin to target an activated clotting time (ACT) ≥ 250 seconds is required (≥ 200 seconds if patients are also receiving a glycoprotein IIb/IIIa inhibitor) to further reduce the risk of thrombus formation.[8] The manufacturer also recommends adding heparin to the dextrose purge solution as soon as possible.[8] The default heparin concentration is 50 units/mL, although concentrations of between 5 and 50 units/mL are recognized in the product manual.[8,21] Regardless of the concentration selected, an ACT of 160-180 seconds is recommended for the duration of Impella support.[8] Despite systemic exposure to heparin in the purge solution, the amount of drug released by the Impella system is not intended to provide therapeutic anticoagulation, and patients may require the addition of a systemic IV heparin infusion to achieve goal ACT. However, given typical purge flow rates, patients may be exposed to up to 1500 units/hour or more of heparin using a default concentration of 50 units/mL. Now that default dextrose concentrations have been reduced to 5%, greater heparin exposure is likely. Some patients may experience supratherapeutic anticoagulation from

systemic exposure of heparin from the purge solution alone.[21] Since purge flow is automatically controlled by the device, the rate of systemic heparin must be adjusted. Changes of between 2 and 11 times per day have been documented.[22] In addition, the concentration of heparin in the purge and/or systemic solutions may need to be decreased.

Anticoagulation practices within each of the major Impella trials varied widely, and in some cases were not well described. In the ISAR-SHOCK trial, all patients received IV heparin titrated to an activated partial thromboplastin time (aPTT) of 60-80 seconds, and a heparin-free purge solution was used.[11] Significantly more Impella-treated patients experienced hemolysis within the first day of treatment, and one Impella-treated patient had acute limb ischemia requiring surgical intervention. In the PROTECT II study, anticoagulation with IV heparin or bivalirudin was titrated to an ACT > 250 seconds, but details regarding the purge solution and bleeding events were not provided.[12] Finally, the IMPRESS in Severe Shock trial evaluated the Impella CP versus IABP support in patients with cardiogenic shock.[13] However, the approach to anticoagulation management was not described. Three device-related bleeding events occurred in the Impella group (one retroperitoneal requiring surgery and two bleeds at the puncture site) compared to one puncture-site bleed in the IABP group. Hemolysis prompted device removal in two Impella-treated patients. One ischemic stroke was also observed in each group.

TandemHeart

TandemHeart has an external controller that controls the flow rate of a purge solution to prevent thrombus formation in the centrifugal pump housing. The manufacturer of TandemHeart recommends using a heparinized purge solution to target a goal aPTT of 65-80 seconds or a goal ACT of 180-220 seconds for the duration of device support.[15] The base fluid must be saline, as

dextrose-containing products may damage the TandemHeart motor and lead to catastrophic device failure.[15] The default concentration for the purge solution is 90 units/mL.[15] Unlike Impella devices, the TandemHeart purge solution is released at a fixed rate of 10 mL/hour.[15] Although some patients may achieve supratherapeutic aPTTs or ACTs on the standard concentration of heparin in the purge solution, others may require supplemental IV heparin to maintain therapeutic anticoagulation.[15]

In one single-center trial by Thiele et al., patients randomized to TandemHeart received heparin via the purge solution whereas IABP-treated patients received IV heparin.[18] An ACT of 180-200 seconds was targeted in both groups. Device-related complications were more common in the TandemHeart group; significantly more blood products were required versus those in the IABP group, and 7 patients developed limb ischemia versus none in the IABP group (p=0.009). In another study by Burkhoff et al., patients in the TandemHeart group were anticoagulated to a target ACT $\geq$ 400 seconds during trans-septal puncture and 180-200 seconds during circulatory support.[19] No details were provided regarding the anticoagulation strategy for IABP-treated patients. Complication rates were similar between the two groups; one patient in the TandemHeart group experienced device failure, and another required device explantation due to cannula thrombosis.

Approaches to Managing Bleeding Risk

In a meta-analysis of 12 studies evaluating percutaneous MCS support in the setting of high-risk PCI, major bleeding rates were 7.1% and 3.6% for patients treated with the Impella and TandemHeart devices, respectively.[23] Access-site bleeding is the most common source of

hemorrhage with percutaneous MCS devices.[24-26] With the Impella device, in particular, an incidence as high as 28.6% has been reported.[27] Despite these risks, neither device manufacturer provides specific guidance for managing systemic anticoagulation in patients receiving percutaneous MCS support. However, navigating this challenging clinical scenario has been the subject of several retrospective studies and case series.

Given the variability in purge flow conferred by the Impella device, lower heparin concentrations may be considered in certain patients, such as those with low body weight or those in whom anticoagulation parameters are supratherapeutic with default concentrations. In one case series, a heparin concentration of 25 units/mL (12,500 units of heparin in 500 mL of D20W) was used to minimize the risk of overdosing low–body weight patients.[22] The protocol consisted of IV heparin titrated to a goal aPTT of 55-75 seconds. Initial IV dosing was adjusted for the amount of heparin delivered via the purge solution to yield a total dose of 12 units/kg/hour (maximum 1000 units/hr). For example, if a 70-kg patient received 400 units/hour of heparin via the purge solution, the initial systemic rate would be decreased to 440 units/hour to account for both routes of heparin exposure (i.e., a combined total heparin exposure of 840 units/hr, or 12 units/kg/hr x 70 kg). Subsequently, the infusion rate of IV heparin was adjusted every hour by subtracting the units/hour delivered via the purge from the 12-unit/kg/hour rate. Nurses adjusted the IV heparin rate every 6 hours if the aPTT was not within goal range. All four patients survived to hospital discharge, and no thrombotic events or major bleeding episodes occurred during Impella support.

Another group of authors published a strategy for balancing IV heparin with the TandemHeart purge solution.[28] In this retrospective analysis, 15 patients who received heparin according to an institutional protocol (adaptation shown in Table 3) were compared to 10

patients in a non-protocol group. Overall, 60% of patients in both groups received IV heparin in addition to the heparinized purge solution. Therapeutic aPTT values were more common in the protocol group (46% vs 35% in the non-protocol group, p=0.049), whereas supratherapeutic aPTT values were more common in the non-protocol group (39% vs 22%, p<0.001). No significant differences in clinical outcomes were detected.

A retrospective review described the outcomes of an anti–factor Xa (anti-Xa)-based anticoagulation strategy in CentriMag (Thoratec, Pleasanton, CA)/TandemHeart and Impella cohorts.[29] In contrast with the preceding studies, which used only aPTT guidance, this study evaluated anticoagulation practices with both aPTT and anti-Xa concentrations. At the time of the study, the anti-Xa goal range was 0.2-0.4 units/mL, which correlated to an aPTT range of 55-75 seconds. In the CentriMag/TandemHeart group, five patients had anti-Xa monitoring versus 12 patients with aPTT monitoring. The time-in-therapeutic range was 68.9% with anti-Xa monitoring versus 43.2% with aPTT monitoring, respectively. Bleeding and thrombotic outcomes were numerically higher in the aPTT-monitored group compared to the anti-Xa group. Among the 8 Impella-treated patients, time-in-therapeutic range was 71.9% with anti-Xa monitoring versus 52.9% with aPTT monitoring. No thrombotic events occurred in the Impella group, but three patients experienced a combined total of seven major bleeding events (6 gastrointestinal bleeds, 1 bleed at the cannulation site). In the 24 hours preceding these bleeds, the median anti-Xa value was 0.280 units/mL (0.050–1.380 units/mL). Using these results, the investigators revised their institutional heparin protocols (adaptation shown in Table 4), reinforcing the importance of individualized therapeutic targets in response to high intrapatient and interpatient variability. The most notable change was the use of revised anti-Xa goal ranges for Impella support (0.15-0.25 or 0.20-0.30 units/mL) and for CentriMag/TandemHeart devices

(0.2-0.3 or 0.3-0.4 units/mL). Usual initial intravenous heparin infusions were 10-12 units/kg/hour with each type of pVAD. For the Impella device, the default heparinized purge solution concentration was 12.5 units/mL with either D10W or D5W.

Alternative Anticoagulants in Heparin-Intolerant Patients

Another challenging scenario in patients receiving percutaneous MCS is the management of heparin-induced thrombocytopenia (HIT). The incidence of HIT in this population is relatively high (10% to > 25%), although the proportion of patients who develop thromboembolic complications remains low.[30,31] Identifying HIT during percutaneous MCS is further complicated by other common etiologies for both thrombocytopenia and thrombosis (e.g., presence of a foreign device, alterations in physiologic blood flow, critical illness, and concomitant medications). Nonetheless, the potentially deleterious consequences associated with HIT often necessitate use of alternative anticoagulants (e.g., argatroban, bivalirudin) until HIT is ruled out or after its presence has been confirmed.

For the Impella device, clinicians are urged by the manufacturer to use an anticoagulant-free purge solution and an alternative IV anticoagulant, although neither argatroban nor bivalirudin is specifically recommended.[8] The rationale for an anticoagulant-free purge solution in the setting of HIT is unclear, particularly given recommendations by the manufacturer to use a heparinized purge solution under normal circumstances. A single case report described the use of argatroban in the purge solution (0.1 mg per mL of D5W) for 6 days in a patient with suspected HIT.[32] Intravenous administration was not initiated due to the presence of supratherapeutic aPTT values, and therapeutic anticoagulation was achieved by the purge solution alone. Although the patient was eventually deemed negative for HIT, argatroban was continued for the management

of device-related hemolysis. Based on their experience, the authors recommended considering a lower argatroban concentration in the purge solution (0.05 mg/mL).

For the TandemHeart device, isolated case reports for both argatroban and bivalirudin have been published.[33,34] In one case report, argatroban was used in the purge solution (7 mcg/mL of normal saline) and as the IV anticoagulant (target aPTT of 2.5 times normal) for 9 days in a patient with advanced heart failure and HIT requiring TandemHeart support as a bridge to transplantation.[33] A second case report described the use of bivalirudin in a patient with advanced heart failure (but without HIT) requiring TandemHeart support for balloon aortic valvuloplasty.[34] In contrast with the prior case, bivalirudin was used as the IV anticoagulant (target ACT of $\geq$ 250 seconds), and the purge solution consisted of only normal saline. In both cases, alternative anticoagulation was successfully maintained for the duration of MCS, and no thrombotic or hemorrhagic complications were observed.

Hemolysis and Other Hematologic Complications

Hematologic complications (Table 2) in the setting of percutaneous MCS may also result from physical damage to blood components. Hemolysis due to mechanical erythrocyte shearing as well as inappropriate device preparation and placement has been described in both studies and case reports.[35,36] Elevated lactate dehydrogenase (LDH), total bilirubin, plasma free hemoglobin, and serum potassium concentrations as well as low haptoglobin concentrations may indicate the presence of hemolysis. Although the reported incidence of hemolysis varies widely, the risk appears to be greater with Impella devices, which may be a consequence of the microaxial mechanism used to generate blood flow. Hemolysis was observed in only 7.5% of 120 patients included in the EUROSHOCK registry, whereas a single-center case series of 118 patients found

a cumulative incidence rate of 62.5%.[27,37] Although pharmacologic strategies exist for the management of hemolysis in patients receiving durable MCS (often the result of pump thrombosis), none have been proposed for percutaneous devices. Severe cases of hemolysis may necessitate device removal. In addition to the effects of percutaneous MCS on red blood cells, thrombocytopenia is common across all three devices, as platelets can be damaged by the balloon or pump as well as exposure to heparin.[27,38]

Best Practice Recommendations

Product Availability

The complicated equipoise between systemic IV heparin and heparinized purge solutions requires expert management to reduce the potential for medication error and patient harm. To minimize the risk of medication errors due to incorrect admixture and administration techniques, standard concentrations of systemic anticoagulants should be used.[39] Commercial availability of premixed products meeting these specifications permits storage in automated dispensing cabinets or satellite pharmacies in cardiac catheterization laboratories and operating rooms. In certain situations, alternative concentrations of heparinized purge solutions may be needed to manage patients receiving pVAD support.

Anticoagulation Monitoring

The development and standardization of dosing nomograms to achieve target anticoagulation parameters (aPTT, ACT, or anti-Xa) is imperative for optimizing patient safety with heparin. The ACT is a point-of-care test that allows for rapid assessment and adjustment of

IV heparin, but it may not be feasible outside of procedural areas (e.g., catheterization laboratory, surgical suite). aPTT is more accessible, but goal aPTT ranges are institution specific. In addition, aPTT is influenced by several other clinical variables and may underestimate the degree of anticoagulation provided during MCS support.[40,41] Thus, anti-Xa concentrations have been proposed as an alternative method for monitoring anticoagulation, as better correlations with heparin activity are often observed.[40,42,43] The reported reference range for anti-Xa is 0.3–0.7 units/mL, but alternative goal ranges have been previously described during pVAD use (0.15-0.30 units/mL for Impella and 0.2-0.4 units/mL for TandemHeart).[29,44]

Regardless of the institution-specific monitoring strategy, anticoagulation parameters should be monitored frequently to mitigate risks of thrombosis and bleeding. Subtherapeutic or supratherapeutic values should prompt adjustment of systemic anticoagulation and/or heparinized purge solution concentrations. Adjustments to initial and subsequent infusion rates to account for the heparinized purge solution may also be considered.

Complete blood counts should also be monitored at least daily. Changes in hemoglobin level and hematocrit may reflect internal bleeding or red blood cell destruction, and monitoring platelet trends may be important for distinguishing device-related thrombocytopenia from HIT. Frequent monitoring of hemolysis laboratories (e.g., LDH, total bilirubin, plasma free hemoglobin levels) should also be considered in order to minimize end-organ injury, particularly with the Impella device.

Given the limited data in this setting, no firm recommendations can be made for patients with HIT who require percutaneous MCS. Although manufacturers recommend against the use of alternative anticoagulants in the purge solution, this practice is inconsistent with the recommendation to use a heparinized purge solution in patients without HIT.[8] Given the increased thromboembolic risk conferred by the presence of HIT, use of an alternative anticoagulant in the purge solution may be considered. The decision to use argatroban or bivalirudin for either the purge solution or IV anticoagulation will likely be institution specific, although advantages may exist for either medication in an individual patient. For example, argatroban may be more optimal in patients with severe kidney impairment, whereas bivalirudin may be more advantageous in patients with severe hepatic impairment.

Conclusion

Percutaneous MCS devices, including the IABP, Impella, and TandemHeart, are often used to support patients with refractory cardiogenic shock. Although the devices may improve hemodynamics, they are associated with a number of adverse effects. In addition, the manufacturers of Impella and TandemHeart recommend heparinized purge solutions during device support but do not provide specific recommendations for dose adjustments and/or changes to the default heparin concentration in response to subtherapeutic or supratherapeutic anticoagulation parameters. Similarly, the manufacturers do not provide specific recommendations for how best to manage patients with heparin-induced thrombocytopenia. Although several case reports with various anticoagulation management strategies have been published, there is no consensus. Until guidelines or larger prospective studies are available, a

strategy that optimizes effectiveness and patient safety may need to be developed at each institution.

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Table 1. Trials Comparing Percutaneous Mechanical Circulatory Support Devices

Study	Inclusion Criteria	Exclusion Criteria	Treatment Groups	Primary Outcome
[11]Seyfarth M, et al.	AMI within previous 48 hours and cardiogenic shock	Age < 18 years, resuscitation > 30 minutes, HOCM, LV thrombus, severe valvular disease or mechanical heart valve, ventricular septal defect or wall rupture, > second-degree acute MR or AR, RV failure or need for RV assist device, sepsis, known cerebral disease, PE, allergy to heparin, known coagulopathy, bleeding requiring surgery, pregnancy	Impella 2.5 (n=13) vs IABP (n=13)	Change in CI from baseline to 30 minutes in Impella group vs IABP group: 0.49 vs 0.11 L/min/m^2 (p=0.02)
[12]O'Neill WW, et al.†	Need for hemodynamic	Recent AMI with persistent	Impella 2.5	Occurrence of major

	support during PCI on an unprotected left main or last patent coronary vessel with LVEF ≤ 35%, or 3-vessel disease and LVEF ≤ 30%	elevation of cardiac enzyme levels, pre-procedure cardiac arrest, cardiogenic shock, LV thrombus, coagulopathy, CVA/TIA within previous month, intolerance to heparin or various antiplatelet agents, mechanical aortic valve, AS, moderate to severe AI, or severe PVD that precluded passage of the device	(n=225) vs IABP (n = 223)	adverse events‡ at 30 days in Impella group vs IABP group: 35.1% vs 40.1% (p=0.277)
[13]Ouweneel, D, et al.	Mechanically ventilated patients with AMI complicated by cardiogenic shock, with	Severe aorto-iliac arterial disease impeding placement of IABP or Impella, known severe aortic valvular	Impella CP (n=24) vs IABP (n=24)	Mortality at 30 days in IABP group vs Impella group: 50% vs 46% (p=0.92)

	planned revascularization of the infarcted artery using PCI	disease, life expectancy < 1 year, CABG within the previous week		
[18]Thiele H, et al.	AMI complicated by cardiogenic shock, with planned revascularization of the infarcted artery using PCI	Age > 75 years, mechanical complications of AMI, duration of shock > 12 hours, right heart failure, sepsis, significant AR, severe cerebral damage, resuscitation > 30 minutes, severe PVD and terminal disease	TandemHeart (n=21) vs IABP (n=20)	Cardiac power index at 2 hours in TandemHeart group vs IABP group: 0.37 vs 0.28 W/m^2 (p=0.004)
[19]Burkhoff D, et al.[†]	Onset of cardiogenic shock within previous 24 hours	Age < 18 years, isolated RV failure, coagulopathy, sepsis, severe PVD, CVA within	TandemHeart (n=19) vs IABP (n=14)	Reversal of hemodynamic profile of cardiogenic shock[‖] in TandemHeart group vs

	previous 6 months, ≥ 2+ AR, ventricular septal rupture	IABP group: 37% vs 14% ($p<0.05$ for change in CI and PCWP)

AI = aortic insufficiency; AMI = acute myocardial infarction; AR = aortic regurgitation; AS = aortic stenosis; CABG = coronary artery bypass grafting; cardiac index; CI = cardiac index; CVA = cerebrovascular accident; DBP = diastolic blood pressure; HOCM = hypertrophic obstructive cardiomyopathy; IABP = intra-aortic balloon pump; LV = left ventricular; LVEF = left ventricular ejection fraction; MAP = mean arterial pressure; MR = mitral regurgitation; PCI = percutaneous coronary intervention; PCWP = pulmonary capillary wedge pressure; PE = pulmonary embolism; PVD = pulmonary vascular disease; RV = right ventricular; TIA = transient ischemic attack.

[†]Study was discontinued prematurely due to futility.

[‡]Major adverse events included a composite of the following: all-cause death, Q-wave or non–Q-wave myocardial infarction, stroke, or transient ischemic attack, any repeat revascularization procedure (PCI or coronary artery bypass grafting), need for a cardiac or a vascular operation (including a vascular operation for limb ischemia), acute renal insufficiency, severe intraprocedural hypotension requiring therapy, cardiopulmonary resuscitation or ventricular tachycardia requiring cardioversion, aortic insufficiency, and angiographic failure of PCI.

[‖]Composite of the following 4 criteria being met: (1) the patient did not die during support or within 24 hours of device removal, (2) cardiac index was ≥ 2.2 L/kg/min, (3) PCWP was ≤ 24 mm Hg, and (4) MAP was ≥ 70 mm Hg, with all hemodynamic parameters reflecting the average values during support.

Table 2. Adverse Events Reported with Percutaneous Mechanical Circulatory Support Devices[8,24,27,38]

Organ System	IABP	Impella	TandemHeart
Cardiac	Aortic insufficiency	Aortic insufficiency, aortic valve injury, atrial fibrillation, cardiac tamponade, myocardial infarction, perforation, severe hypotension, ventricular arrhythmias, acute RV failure	Cardiac tamponade, septal defects, worsening of right ventricular failure, atrial fibrillation, ventricular arrhythmias, acute RV failure
Hematologic	Access-site bleeding, thrombocytopenia	Access-site bleeding, hemolysis, thrombocytopenia	Access-site bleeding, hemolysis, thrombocytopenia
Neurologic	Stroke	Transient ischemic attack, stroke	Stroke
Renal	None reported	Acute kidney dysfunction, kidney failure	Acute kidney dysfunction
Vascular	Aortic aneurysm, aortic dissection, infection at the	Infection at the site of insertion, limb ischemia, thrombotic event (non-CNS),	Limb ischemia, thromboembolism, vascular injury requiring repair,

	site of insertion, limb ischemia, aortic dissection	vascular injury requiring surgery	wound infection
Other	Compartment syndrome	Death, device malfunction, hepatic failure, sepsis	Air embolism, atrial-septal defect, compartment syndrome, dislodgement of the cannula, femoral arteriovenous fistula, lymphocele

IABP = intra-aortic balloon pump; CNS = central nervous system; RV = right ventricular.

Table 3. Example of a Heparin Protocol for the TandemHeart Device

aPTT (seconds)	Instructions
< 55	Continue current purge (heparin 45,000 units/500 mL saline) at 10 mL/hour, and initiate intravenous heparin at 2 units/kg/hour
55 – 75	Therapeutic (no changes)
76 – 90	Switch purge to heparin 25,000 units/500 mL saline at 10 mL/hour, and initiate intravenous heparin at 2 units/kg/hour
91 – 110	Switch purge to heparin 25,000 units/500 mL saline at 10 mL/hour; do not start intravenous heparin
> 110	Switch purge to saline (no heparin) at 10 mL/hour

aPTT = activated partial thromboplastin time.

Adapted from reference 28.

Table 4. Example of a Heparin Protocol for the Impella Device Using Anti–Factor Xa Concentration

Low Anti–Factor Xa Range (0.15-0.25 IU/mL)	Current IV Heparin Change	High Anti–Factor Xa Range (0.20-0.30 IU/mL)	Current IV Heparin Change
< 0.10	Increase by 2 units/kg/hr	< 0.15	Increase by 2 units/kg/hr
0.10-0.14	Increase by 1 unit/kg/hr	0.15-0.19	Increase by 1 unit/kg/hr
0.15-0.25	No change	0.20-0.30	No change
0.26-0.35	Decrease by 1 unit/kg/hr	0.31-0.40	Decrease by 1 unit/kg/hr
0.36-0.45	Decrease by 2 units/kg/hr	0.41-0.50	Decrease by 2 units/kg/hr
> 0.45	Withhold heparin and call attending physician or PharmD	> 0.50	Withhold heparin and call attending physician or PharmD

Adapted from reference 29.