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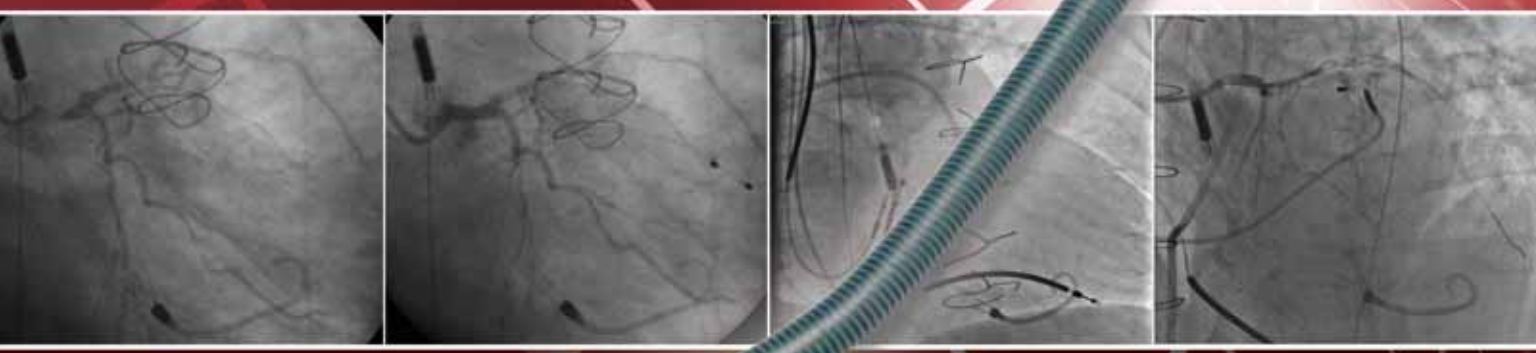
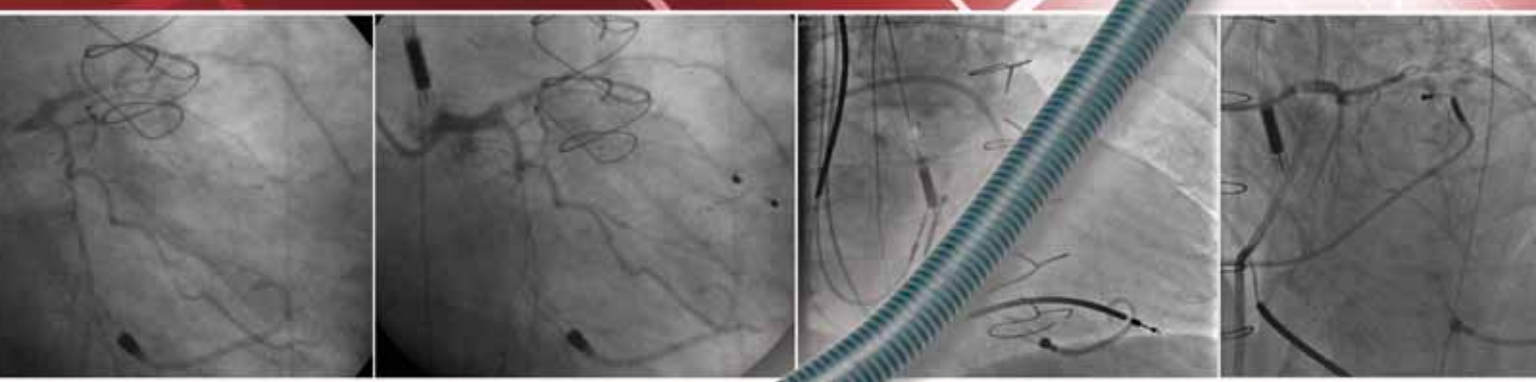
Principles of Hemodynamics



The New Science of Cardiac Support in the Cath Lab

Principles of Hemodynamics



The Impella 2.5 Percutaneous Cardiac Support System is intended for partial circulatory support using an extracorporeal bypass control unit for periods up to 6 hours. It is also intended to be used to provide partial circulatory support (for periods up to 6 hours) during procedures not requiring cardiopulmonary bypass. The Impella 2.5 Percutaneous Cardiac Support System also provides pressure measurements, which are useful in determining intravascular pressure.

The Impella 5.0 catheters are intended for circulatory support using an extracorporeal bypass control unit, for periods up to 6 hours. They are also intended to be used to provide circulatory support (for periods up to 6 hours) during procedures not requiring cardiopulmonary bypass. The Impella 5.0 catheters also provide pressure measurements, which are useful in determining intravascular pressure.

Principles of Impella Cardiac Support

The evolution of cardiac support technology toward the ideal assist device.

BY DAVID M. WEBER, PHD; DANIEL H. RAESS, MD, FACC, FACS;
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The ideal cardiac assist device for the catheterization laboratory provides effective support for both elective high-risk patients, as well as acute or emergent patients, and has a safety and ease-of-use profile appropriate to each procedure setting. For elective high-risk percutaneous coronary interventions (HR PCI), the clinical goals of the ideal device are (1) to maintain stable systemic hemodynamics while avoiding disruptions in cardiac output, clinical challenges to end-organ function, and neurological instabilities that disrupt patient compliance; (2) to provide more time for complex PCI by raising the patient's ischemic threshold to minimize myocardial cell damage from balloon inflation or coronary dissection; and (3) to provide a prophylactic safety and ease-of-use profile—minimizing complications such as bleeding (arising from large sheaths and the need for full anticoagulation) or embolization to end organs (such as stroke or limb ischemia). In short, it provides a low-risk, simple-to-use "safety net" that ensures its success, improves its outcome, and extends the PCI procedure to a broader range of patients who would otherwise be denied revascularization due to excessive risk either in surgery or the catheterization lab.

In the emergent setting of acute myocardial infarction (AMI), the roles of the ideal assist device to augment systemic hemodynamics and improve the myocardial ischemic environment are also of prime importance. However, unlike the prophylactic role they play in HR PCI for AMI patient care, assist devices are needed to provide prompt therapeutic benefit with the shortest delay possible because clinical outcome in AMI, with or without hemodynamic compromise, is strongly correlated with time to therapy.[1] In AMI, the "time is muscle" paradigm remains, and in the case of hemodynamic shock, there is also a strong relationship between duration of shock and clinical outcome.[1] The clinical goals of the ideal assist device for the AMI patient are (1) to restore and stabilize systemic hemodynamics to reverse the decline of end-organ perfusion, reduce the risk of end-organ failure and break the deadly cycle of cardiogenic shock; to (2) minimize residual infarct size by reducing the level of myocardial ischemia, halting further cell damage, maximizing residual cardiac function and reducing the overall risk of cardiogenic mortality; and (3) to provide an ease-of-use and safety profile consistent with the critical treatment time scenarios and the risk-benefit considerations of emergency care.

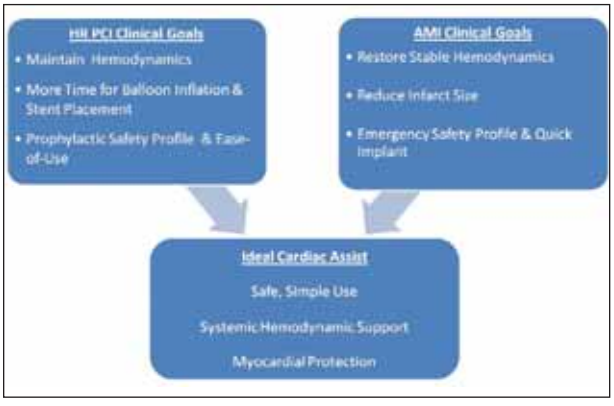

Figure 1. Clinical goals of the ideal cardiac assist device in the catheterization lab.

The ideal assist device, therefore, spans the needs of both elective and emergent patient settings, provides systemic hemodynamic support and myocardial protection, and is safe and simple to use (Figure 1).

We discuss herein a brief history of cardiac assist technologies in the catheterization lab that have struggled to achieve these goals, and we introduce Impella technology (Abiomed, Inc., Danvers, MA), which is the first cardiac assist technology designed to attain this comprehensive ideal.

THE EVOLUTION OF CARDIAC SUPPORT IN THE CATHETERIZATION LAB

Evolving from Gibbon's[2] pioneering roller pump-oxy-

genator work in the 1950s, cardiac assist in the catheterization lab (Figure 2) had its origins in the form of extracorporeal membrane oxygenators (ECMO), which were used to support children in respiratory failure. However, because the catheterization lab was predominately a diagnostic venue at this time, there was limited need in this environment for a therapeutic technology.

With the clinical introduction of an intra-aortic balloon pump (IABP) by Kantrowitz in 1968,[3] cardiologists diagnosing and treating patients with acute coronary syndromes began applying IABP therapy in the catheterization lab but usually in concert with the surgeons, largely due to the need for a graft on the femoral artery to prevent limb ischemia. Although gradually accepted, there was little clinical evidence of improved survival or function during shock secondary to AMI.[4,5] Specifically, studies comparing the safety and effectiveness of the IABP to nonassisted care in patients with AMI reported no improvement in mortality or composite major adverse cardiac and cerebrovascular events (MACCE), yet there was a significant increase in the incidence of stroke and bleeding.

Widespread application of IABP followed the introduction of truly percutaneous systems that employed 8.5- to 9-F sheaths (circa 1975). At the close of the 1970s and with the birth of PCI in the early 1980s, the IABP offered cardiologists a truly percutaneous system that could be employed during an intervention or whenever circulatory support was needed. Although deployment of an IABP is relatively simple and does not require a surgeon for implantation or removal, a steady and reliable electrocardiogram (ECG) and/or pressure signal (to ensure its proper deflation right before the onset of the systolic period) is required due to its placement in the descending aorta. When supporting patients undergoing high-risk PCI or compromised by AMI (which is usually diagnosed by changes in the ECG), the difficulty of maintaining a steady and reliable ECG timing signal adds complexity to IABP use. The safety and effectiveness of an IABP depends on predictable rhythms and is affected when timing signals are compromised.[6,7] The IABP movement (inflation/deflation) can also interfere with the movement and guidance of the therapeutic catheter and compromise the quality of the intervention.

Although IABP use has been found to augment coronary perfusion,[8] overall myocardial ischemic improvements are limited by the fact that it provides little or no reduction in native ventricular work and myocardial oxygen demand.[9,10] Furthermore, it should be recognized that the IABP is not an active forward-flow pump; it is a volume displacement device. Therefore, any improvements in forward flow (ie, cardiac output) in the presence of IABP support are accomplished by the native heart itself and have been demonstrated in failing hearts to be only modest improvements of approximately 0.2 L/min.[11] For this reason, it is typical to combine IABP support with the administration of multiple doses of inotropic drugs that induce higher output from the failing native heart to maintain adequate systemic circulation. This pharmacologic induction increases ventricular work and myocardial oxygen demand, further challenging the myocardial ischemic balance and feeding a downward cycle of increased ischemia, heart failure, and ultimately cardiogenic shock. In a study of more than 3,000 patients with postoperative cardiogenic shock, Samuels et al[1] demonstrated a linear relationship between in-hospital mortality and the level of inotropic support. They reported a 21% mortality rate for patients on a high dose of a single inotrope, 42% for a high dose of two inotropes, and 80% for a high dose of three inotropes. Therefore, although the IABP gained widespread use in the catheterization lab based on its relative ease of insertion, its lack of hemodynamic impact leading to a reliance on inotropic drug support limited its ability to meet the ideals described previously.

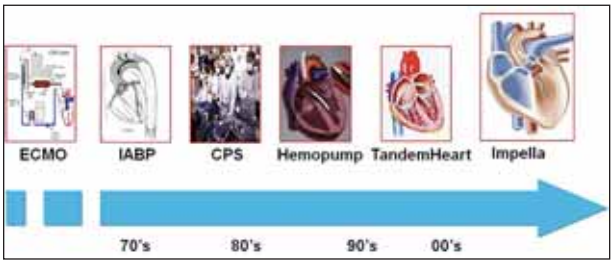

Figure 2. Evolution of cardiac assist in the catheterization lab.

Cardiopulmonary support (CPS) systems were introduced in the 1970s,[12] filling a void between what the IABP could provide in the catheterization lab and what full cardiopulmonary bypass provided in the surgical suite. Essentially, CPS systems were an iteration of ECMO that was mobile, supported percutaneous implantation, and was limited to short durations of use. CPS systems consisted of a mobile pump (either roller type or centrifugal) on a moveable cart containing an oxygenator, a portable oxygen supply, a small heat exchanger, a mobile power supply, and all the needed cannula for rapid percutaneous cannulation. These devices employed a femoral cannulation strategy that drew femoral venous blood into the pump and deposited the newly oxygenated blood volume into the femoral artery. Although this support strategy was more effective at augmenting systemic hemodynamics than the IABP, it had little or no effect on the myocardial ischemic balance, providing no support of coronary perfusion or reduction of ventricular work. Another disadvantage was its safety profile. Even in circuits using heparin-coated tubing, complications remained high and included renal failure requiring dialysis (47%), bacteremia or mediastinitis (23%),

stroke (10%), leg ischemia (70%), oxygenator failure (43%), and pump change (13%).[13] Although CPS allowed longer inflations in the percutaneous transluminal coronary angioplasty era, the vascular complications and the need for frequent transfusion limited widespread use.[14] From the perspective of ease-of-use, some form of vascular repair was typically needed upon completion of the procedure (due to the relatively large cannula size), and use of the CPS system required a perfusionist to be in constant attendance in the catheterization lab and in all other departments. Therefore, despite the fact that this technology was the first to provide a moderate level of hemodynamic support in the catheterization lab, it also fell short of the ideal in a number of ways.

The Hemopump (Medtronic, Inc, Minneapolis, MN), introduced in the late 1980s,[15] was an application of an Archimedes screw, or axial pump, with the motor residing outside the body. The axial pump head was positioned in the left ventricle, and the external motor transferred energy to the pump head through a high-speed, rotating shaft running inside an arterial steering catheter. The Hemopump was attractive to cardiologists because it was implanted via femoral artery access in a nearly percutaneous fashion (although, similar to the early days of the IABP, it was usually in concert with a surgeon due to the need for a graft on the femoral artery to prevent limb ischemia), and it was the first active forward-flow pump that did not require an extracorporeal transit of the blood. Furthermore, the clinical goal of high-risk PCI support was evolving beyond just providing systemic circulatory support during the procedure to an increased emphasis on protecting the heart muscle from the ischemic insult of the PCI procedure itself. The Hemopump, with its direct left ventricular access, theoretically provided a high level of myocardial ischemic protection due to the efficient unloading of left ventricular work (reducing myocardial oxygen demand), while its outflow, which was at or near the aortic root, held promise of also augmenting coronary flow (increasing myocardial oxygen supply). Despite its conceptual advantages over the currently available systems and the coincidence with many of the ideal goals of cardiac assist in the catheterization lab, the Hemopump never reached significant application and fell into disuse in the catheterization lab and market due to design flaws (mostly related to the long high-speed rotating drive shaft) that limited its reliability in clinical practice.

More than a decade after the introduction of the Hemopump, the TandemHeart (Cardiac Assist, Inc., Pittsburgh, PA) received United States clearance in 2003 as an evolution of the CPS portable assist system. In this iteration of percutaneous cardiac support, the oxygenator was removed in favor of a cannulation method that facilitated

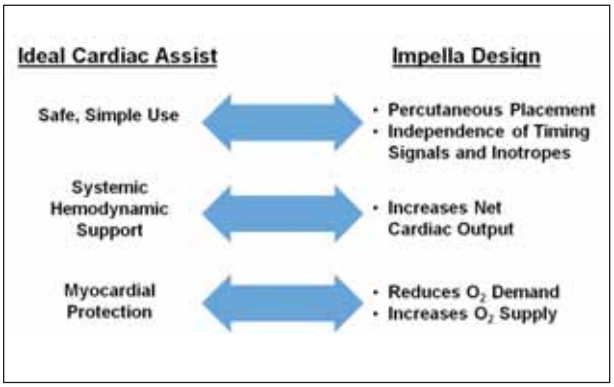

Figure 3. Principles of Impella support in relation to the clinical goals of the ideal cardiac assist device.

pumping blood oxygenated by the patient's own lungs. The cannulation strategy drew blood from the left atrium (via femoral vein access and transseptal puncture) and returned blood to the femoral artery in a retrograde fashion. Therefore, similar to CPS or ECMO systems, this assist strategy, while providing moderate systemic hemodynamic support, offered little myocardial ischemic protection because its femoral artery outflow provided no support to the coronary circulation, and its atrial cannulation limited left-heart unloading (ventricular work reduction). Furthermore, due to the significant fraction of blood that remained in the left ventricle, sustained left heart ejection was necessary to avoid left ventricular distension. Other limitations were that the large 21-F cannula size led to frequent peripheral vascular compromise, there was a residual potential for a left-right shunt due to the transseptal approach,[16] and atrial cannulation, which has a higher risk of wall suction disruptions compared to a direct ventricular approach, limited forward flow through the pump circuit. Although introduced as a 2.5-L/min device and later modified as a 5-L/min device, Kar et al reported clinical pump flow rates of 2 to 3 L/min in a five-patient high-risk PCI group,[17] and Thiele et al[18] reported flow rates ranging from 2.4 to 3.9 L/min depending on the outflow cannula used (either single 15–17 F or dual 12 F). Trials comparing the IABP to the TandemHeart for cardiogenic shock showed no difference in clinical outcome, but patients with the TandemHeart had many more complications, such as bleeding, transfusions, and limb ischemia sometimes requiring device extraction.[18,19] Finally, the complexity of the cannulation, the transseptal technique, and the need for full anticoagulation limited its use to the most experienced staff and was associated with long implantation times.

Development of cardiac assist in the catheterization lab has, therefore, progressed through a number of iterations during the last 50 years. With each generation, the technol-

ogy has struggled with the challenges of becoming either easy to implant, safer for the patient, and/or more effective in providing circulatory support and myocardial protection.

The Impella technology is the latest generation of cardiac assist and represents a significant step in the history of technology development described previously. Its design facilitates a support strategy that represents the ideal of cardiac assist—safe and simple use consistent with both elective and emergent clinical environments, while supporting systemic hemodynamics and protecting the myocardium from ischemic damage (Figure 3).[8,10,11,20-24] Impella's safety and simplicity is provided by its percutaneous placement combined with an independence from both physiologic timing signals and the consistent need for supplemental inotropic drug support.[8,19-23,25-32] Its hemodynamic support results from the design feature that provides active forward flow[21,33] that increases net cardiac output,[8,11,20-23] and its ability to address the needs for myocardial protection stems from simultaneously unloading work from the ventricle (decreasing myocardial oxygen demand)[10,11,20-22] and augmenting coronary flow (increasing oxygen supply).[10,24]

We provide a brief description of the Impella technology, review its experience with regard to clinical usability and patient safety, discuss its fundamental principles of action, and review the scientific and clinical investigations that have demonstrated these principles.

DEVICE DESCRIPTION

The Impella 2.5 is a catheter-mounted microaxial flow pump capable of pumping up to 2.5 L/min of blood from the left ventricle, across the aortic valve, and into the aortic root. The cannula portion of the device, which sits across the aortic valve, is contiguous to the integrated motor that comprises the largest-diameter section of the catheter (12 F) (Figure 4.). The small diameter of the cannula is designed to allow easy coaptation of the aortic valve leaflets around it,

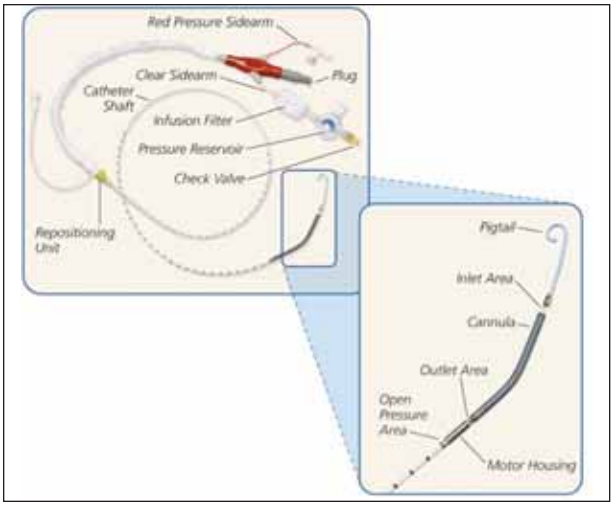

Figure 4. The Impella 2.5 catheter.

resulting in the lack of aortic valve insufficiency. A repositioning device allows removal of the introducer sheath after placement, leaving the modest 9-F catheter at the arterial access site.

The Impella catheter is powered and controlled by the Impella console (Figure 5), which is also used for the entire family of Impella devices, both existing and in development. An infusion pump controls a purge system designed to keep blood from entering the motor compartment by creating a pressure barrier against the blood that the device is exposed to. Future controllers will incorporate the purge function into the console itself. Unlike the IABP, the device control does not require synchronization with ventricular activity. There is no need for timing of the device cycle and no need for ECG or pressure triggering. ECG signal deterioration typically seen in sick patients, such as those with atrial tachycardia, S-T segment changes, fibrillation, or intractable arrhythmia, does not compromise device function and efficacy, as it frequently can with the IABP.[6,7]

Impella 2.5 has been available for general use in the

TABLE 1. SAFETY AND EASE-OF-USE CHARACTERISTICS OF CARDIAC ASSIST DEVICES

	ECMO/CPS	TandemHeart	IABP	Impella 2.5
Vascular surgery required	Yes	Yes	No	No
Vascular access points	Multiple	Multiple	Single	Single
Catheter/cannula size	20–28 F	17–21 F	7–8 F	9 F
Cardiac wall puncture	No	Yes	No	No
Inotropic drug dependency	No	No	Yes	No
Physiologic timing	No	No	Yes	No

United States since June 2008 and is available in more than 40 countries, including Europe and Canada. The Impella 5-L/min devices (Impella 5.0 and Left Direct [LD]) have been cleared for general use in the United States since April 2009. The entire family of Impella products has been CE Mark approved and approved by Health Canada. The Impella 2.5 duration of support specified under the CE Mark is 5 days. In parallel to its general-use clearance in the United States (which is for partial circulatory up to 6 hours), the Impella 2.5 is also the subject of a number of ongoing clinical trials (involving up to 5 days of support).

DEVICE INSERTION

Impella 2.5 is inserted using a modified monorail technique under direct fluoroscopic control. Impella uses both a pressure lumen adjacent to the motor, as well as motor current monitoring to give positioning verification to the operator. The device is placed using fluoroscopic control to avoid kinking the catheter and compromising the purge lumen. Transesophageal echocardiography is used as an adjunct only and is useful to confirm device position. After arterial access is achieved, the 13-F peel-away sheath is positioned. A coronary guiding catheter (typically JR-4) and, subsequently, an 0.018-inch guidewire are placed across the aortic valve into the left ventricle. Once the guidewire is across the aortic valve, the guiding catheter is removed, and the Impella catheter is threaded onto the wire. Several guidewires have been certified by Abiomed for use with the Impella system (see Abiomed Impella Instructions for Use and Technical Bulletin 9 for details). With the device positioned in the ventricle (Figure 6), the wire is removed, and the performance level on the Impella console is started at its minimum setting (just enough to counteract physiologic forces and stabilize the device position).

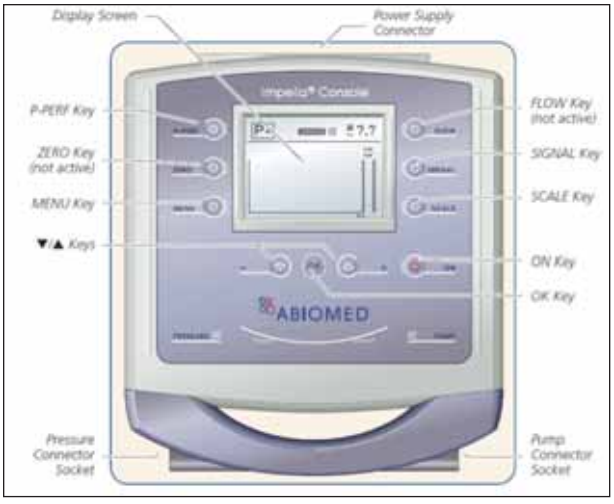

Figure 5. The Impella console.

Once positioned across the aortic valve, the console can be used to confirm that the device placement is proper and stable. At this point, the device performance is typically adjusted to a higher level.

SAFETY AND USE PROFILE

The safety and ease-of-use of Impella technology is founded on three principles. The first is its size. Impella's 12-F pump head and 9-F catheter enable percutaneous placement with a single vascular access point, requiring no cardiac wall puncture and imparting no damage to the aortic valve.[8,20,21,26,33] In short, its size and implantation methods are designed to

TABLE 2. REPORTED ADVERSE EVENT RATES FOR IMPELLA 2.5 HR PCI AND AMI STUDIES

Study	Device	N	Aortic Regurgitation	Valve/ Trauma	Limb Ischemia	Device-Related Bleeding	Intrasupport Modality
HR PCI							
Burzotta et al (2008)[21]	2.5	10	0%	0%	0%	0%	0%
Dixon et al (2009)[33]	2.5	20	0%	0%	0%	0%	0%
Henriques et al (2006)[20]	2.5	19	0%	0%	0%	6%	0%
AMI							
Seyfarth et al (2008)[8]	2.5	13	0%	0%	8%	0%	23%[a]
Sjauw et al (2008)[26]	2.5	10	0%	0%	0%	0%[b]	0%

[a]*Cardiogenic shock patients.*
[b]*After implementing adjusted heparin protocol.*

facilitate reduced complications relative to its predecessor technologies. Second, Impella is an active flow pump that, unlike the IABP, provides hemodynamic support without the need for inotropic drug support and its associated mortality risks.[1] Third, Impella provides support independent of the need for ECG or pressure waveform synchronization, limiting the overall complexity of the set-up and support maintenance. Table 1 summarizes these safety and ease-of-use advantages relative to competing technologies.

Impella implantation time compared to the IABP has been reported by Seyfarth.[8] Figure 7 summarizes these results. In this cardiogenic shock patient population, IABP implantation times range from 6 to 22 minutes, with a mean of 14 minutes. Impella implantation times were reported to range from 14 to 31 minutes, with a mean of 22 minutes, with no statistical difference between the mean implantation times ($P = .4$). It is also noteworthy that this investigation represented early experience with Impella implantation.

Several studies have reported an extremely low incidence of failure to implant or achieve support, as well as a very low incidence of complications, including groin issues, hemolysis, or any evidence of acute or chronic complications relating to the aortic valve or aortic insufficiency.[20-33] Table 2 summarizes reported adverse event rates for Impella 2.5 in five key studies spanning both HR PCI and AMI patients.

FUNDAMENTAL PRINCIPLES OF ACTION

In addition to the safety and ease-of-use aspects described previously, Impella is designed to address the other two ideals of cardiac assist—hemodynamic support and myocardial protection.

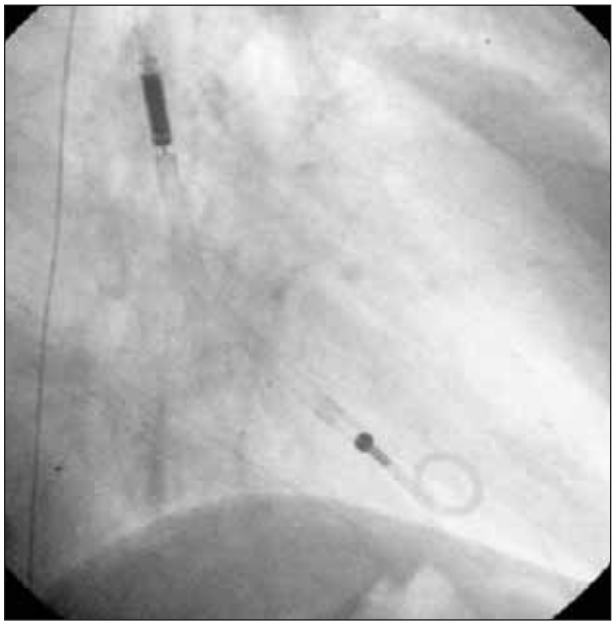

Figure 6. Placement of the Impella 2.5.

The innate ability of Impella to simultaneously provide systemic hemodynamic support and myocardial protection is based on its fundamental principles of support. In short, Impella is designed to replicate the natural function of the heart—moving blood from the ventricle, through the aortic valve, and into the aortic root. For the heart, this flow

TABLE 3. SUMMARY OF IMPELLA STUDIES DEMONSTRATING SYSTEMIC HEMODYNAMIC SUPPORT AND MYOCARDIAL PROTECTION

Impella Study	Systemic Hemodynamic Support	Myocardial Protection	
		Increased O_2 Supply (Coronary Flow)	Decreased O_2 Demand (LV Unloading)
Burzotta et al (2008)[21]	✓		
Sauren et al (2007)[10]		✓	✓
Valgimigli et al (2005)[25]	✓		✓
Meyns et al (2003)[24]	✓		✓
Meyns et al (2003)[27]			✓
Remmelink et al (2007)[38]	✓	✓	
Reesink et al (2004)[11]	✓		✓
Dixon et al (2009)[33]	✓		
Seyfarth et al (2008)[8]	✓		

TABLE 4. REPORTED CORONARY FLOW AUGMENTATION IN ACUTE ANIMAL MODEL

	Baseline	IABP	Impella
Coronary flow (mL/min)	47 ± 24	53 ± 26[a]	69 ± 34[a]

[a]P < .05 versus baseline.

path is essential to accomplishing its native function because blood flow is conveyed from the aortic root to the systemic circulation through the ascending aorta, and to the myocardial circulation through the coronary ostia. Because Impella's flow path mimics this natural direction of forward flow, it too conveys blood flow to the systemic and coronary circulation.

With the outflow of the Impella device in the aortic root, it provides both an active flow and systemic pressure (AOP) contribution leading to increased cardiac power output (Figure 8). Furthermore, with the inflow of the device drawing blood directly from the ventricle, it reduces ventricular end-diastolic volume and pressure (EDV, EDP).[25] Reducing EDV and EDP leads to a reduction of mechanical work and myocardial wall tension, both of which reduce myocardial oxygen demand.[34-37] Additionally, the increased AOP combined with reduced wall tension leads to increased coronary flow, which increases myocardial oxygen supply. In total, Impella favorably alters the balance of myocardial oxygen demand and supply, improving the muscle's ability to survive ischemic challenges.[10,11]

Impella technology is, therefore, the first clinically viable cardiac assist technology to provide this natural forward flow from the ventricle, through the aortic valve, and into the aortic root, simultaneously supporting systemic hemodynamics and protecting the myocardium from ischemic damage (by increasing myocardial oxygen supply and decreasing myocardial oxygen demand).[8,10,11,20-24] These principles, combined with its established safety profile[8,20-23,25-32] and ease-of-use, comprise a comprehensive approach to all of the ideals described earlier (Figure 3). We will now discuss these principles in more detail and review the scientific and clinical investigations through which they have been demonstrated (Table 3).

SYSTEMIC HEMODYNAMIC SUPPORT

The hemodynamic support provided by Impella stems from both a flow and pressure augmentation that leads to improved cardiac power output. Beginning with the flow contribution, Impella is an active forward flow pump that is designed to provide up to 2.5 L/min (Impella 2.5) or up to 5 L/min (Impella 5.0 and Impella LD) of flow support. The forward flow achieved clinically is dependent on the pump support level setting ("P" level) and the pressure gradient

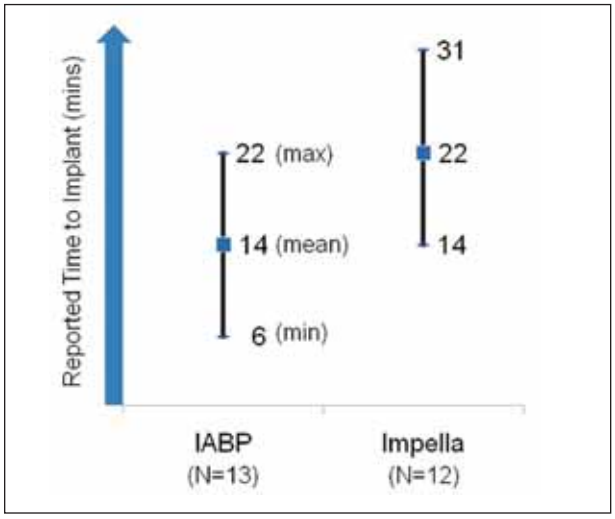

Figure 7. Reported Impella implantation times compared to IABP (*P* = .4) in AMI cardiogenic shock patient population.

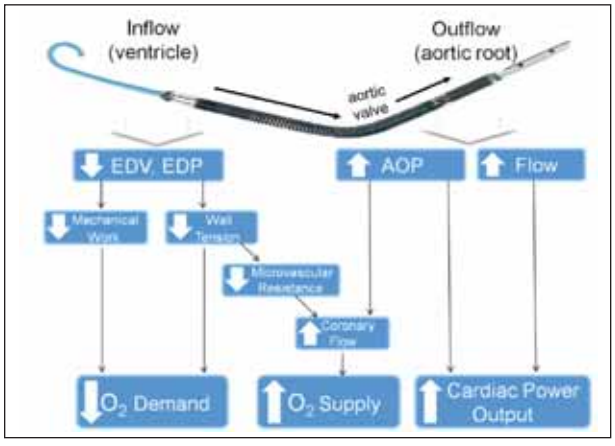

Figure 8. Schematic of the hemodynamic design principles of Impella.

between the aorta and ventricle that the pump experiences. Higher P level settings or lower pressure gradients result in higher flow augmentation. The relationship between P level setting, pressure, and flow through the Impella 2.5 pump is illustrated in Figure 9.

This active forward flow was measured and reported by Reesink et al[11] and Meyns et al[24] in acute animal models, and by Burzotta et al,[21] Valgimigli et al,[25] and Dixon et al[33] in humans. Valgimigli also reported a total net cardiac output increase associated with Impella 2.5 support of 23%. It is important to clarify, however, that this cardiac output increase was the net effect of (1) a native or true cardiac output reduction (the result of ventricular unloading discussed below) and (2) the forward flow contribution of the Impella pump leading to a systemic observed cardiac output increase (Figure 10).

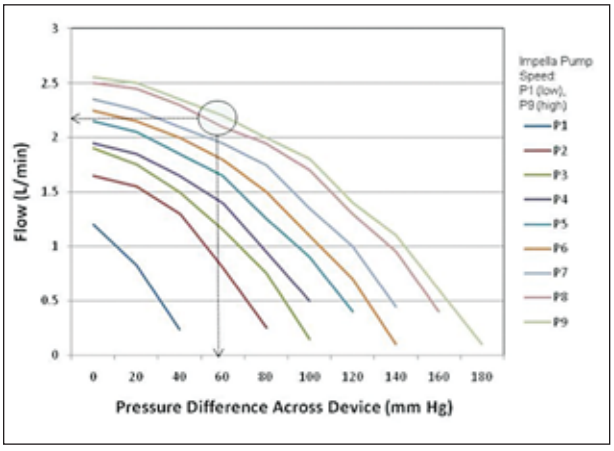

Figure 9. Impella 2.5 flow-pressure relationship. Active forward flow through the device depends on the pressure difference across the device (the difference between left ventricular and aortic pressure) and the pump support level (*P* value).

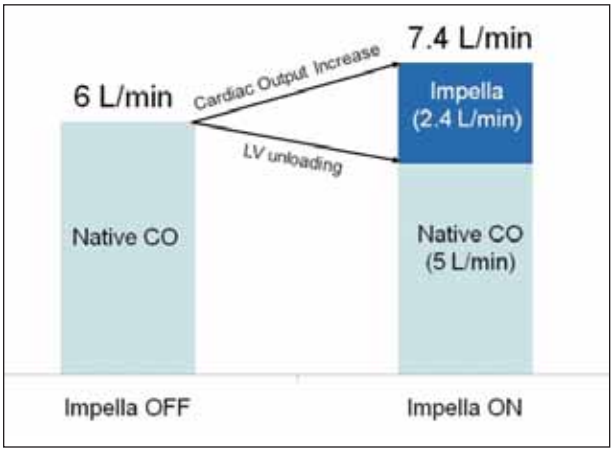

Figure 10. Case report of an Impella-supported high-risk PCI patient. Total system cardiac output increase with Impella is the net effect of (1) a native or true cardiac output reduction (the result of ventricular unloading), and (2) the forward-flow contribution of the Impella pump leading to a systemic observed cardiac output increase.

Furthermore, when properly placed, the outflow of the Impella device resides in the aortic root just above the valve plane (Figure 11A) and provides a sustained augmentation of the diastolic aortic pressure in correlation to the level of Impella support. This systemic pressure augmentation was demonstrated by Remmelink et al,[38] who reported a correlation between Impella 2.5 support level and mean AOP (Figure 11B).

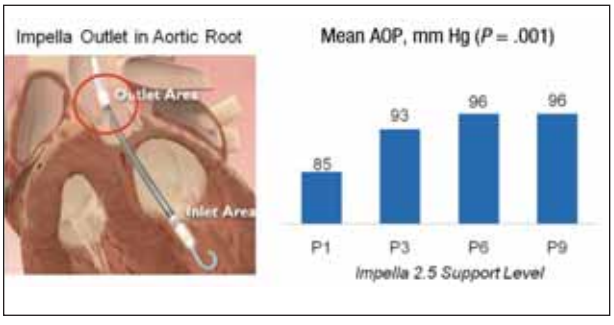

Figure 11. Outflow of Impella in the aortic root augments aortic pressure. Mean AOP is demonstrated to correlate with increasing Impella support level (*P* = .001).

MYOCARDIAL PROTECTION

Augmenting Coronary Flow: Increasing O_2 Supply

Flow through any particular coronary artery is dependent on both the pressure gradient across the coronary artery and the vascular resistance. If we assume the venous (distal) pressure and the resistance of the primary artery are fixed, the flow through the coronary artery will be proportional to the ratio of the aortic pressure and the resistance of the microvasculature into which the coronary artery flows (Figure 12).

In addition to the augmentation of the aortic pressure demonstrated by Remmelink, the Impella-induced reduction of the left ventricular volume and pressure reduces myocardial wall tension and microvascular resistance. The maximum ventricular wall tension (T) occurs at end diastole and can be estimated using the Law of LaPlace as:

$$T \propto \frac{(EDP \times EDV)}{w} \propto Microvascular\ Resistance$$

in which EDP is the end-diastolic pressure, EDV is the end-diastolic volume, and w is the ventricular wall thickness. As Impella draws blood directly from the ventricle, the EDP and EDV are reduced, thereby reducing the maximum wall tension and microvascular resistance. This effect was also demonstrated by Remmelink in patients undergoing increasing levels of Impella support (Figure 13).

It follows that the combination of the increase in AOP and the reduction of microvascular resistance with increasing Impella support levels would lead to a subsequent augmentation of the coronary flow, and this effect has been well demonstrated by a variety of investigators.[10,38] Hunziker, using results from a sophisticated hemodynamic simulator model, predicted an increase in diastolic aortic pressure and coronary flow with Impella 2.5 support (personal communication, October 2008). This model was used to compare the predicted pressure and subsequent coronary flow augmentation of the Impella compared to the IABP (Figure 14). The simulation results demonstrated coronary flow augmentation (blue line) from both devices but a more sustained augmentation with Impella throughout the diastolic period (black

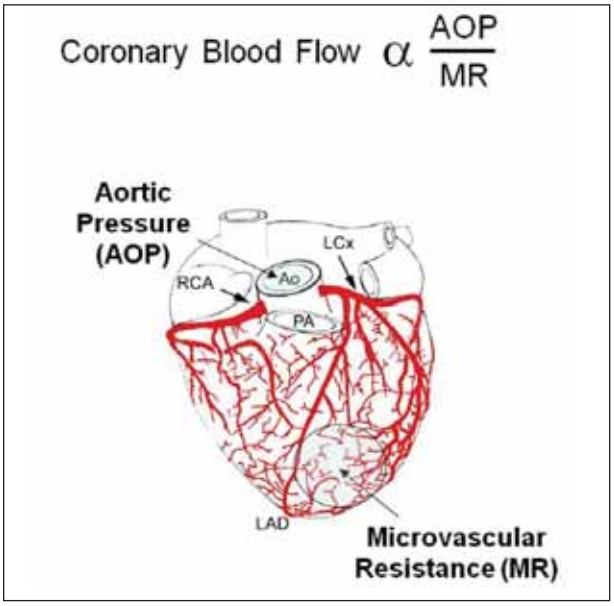

Figure 12. Coronary blood flow is proportional to the ratio of the AOP and the MR.

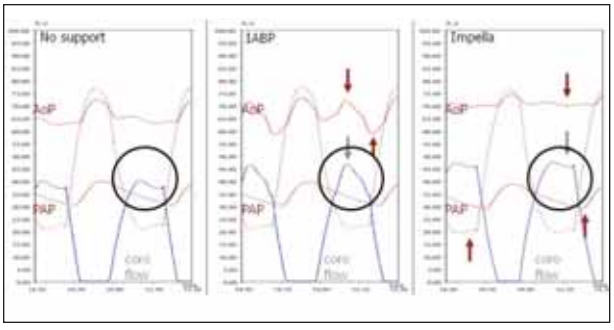

Figure 14. Hemodynamic simulator-predicted coronary flow enhancement (blue line) with Impella (right) compared to baseline (left) and IABP (center). (Reprinted with permission from Hunziker et al. 2006.)

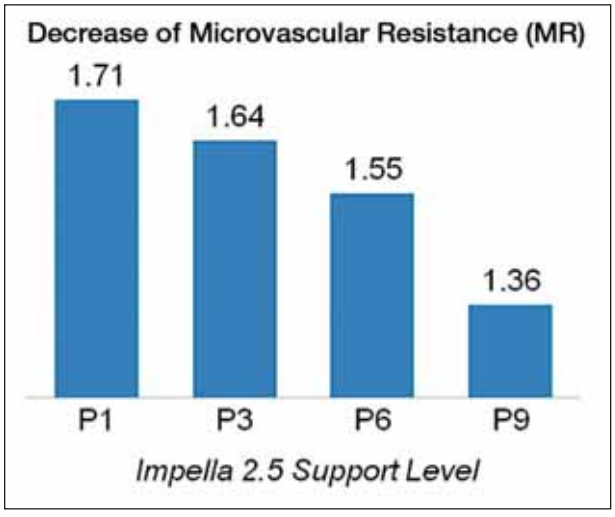

Figure 13. Microvascular resistance (mm HG - cm/sec) is demonstrated to decrease with increasing Impella support level (*P* = .005).

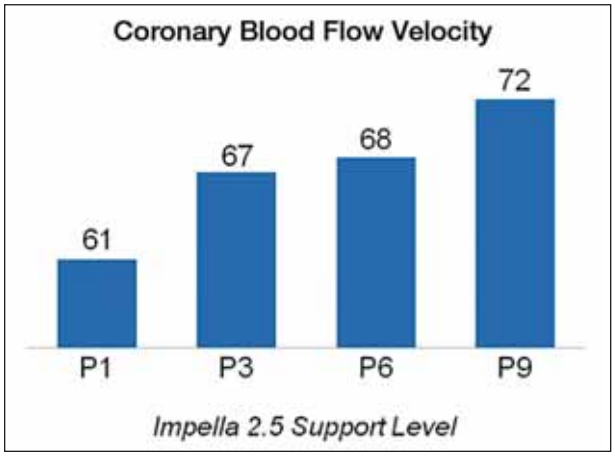

Figure 15. Coronary flow velocity (cm/sec) is demonstrated to correlate with increasing Impella 2.5 support level (*P* = .001).

circles). This is attributed to the constant flow of the Impella, which sustains an elevated diastolic pressure. Due to the required deflation of the IABP in late diastole, it provides only a transient pressure increase early in diastole but reverses this augmentation just before systole, lowering the end-diastolic pressure. IABP deflation in late diastole has been postulated to result in late diastolic flow reversal over and above that seen with physiologic normal pulsatile flow. This has been thought to create a coronary or possibly cerebral steal phenomenon, robbing the heart and brain circulation of much-needed blood flow. This effect has been observed in animal models, and Sjauw's meta-analysis of IABP literature[5] showed evidence of more central nervous system complications in patients treated with IABP therapy.

Hunziker's predictions were validated in animals by Sauren,[10] who reported a maximum 47% increase in coronary flow with Impella (Impella 5.0 operated at 3.8 L/min) compared to a 13% increase with IABP (Table 4).

Finally, Remmelink[38] demonstrated this coronary flow augmentation in Impella patients, reporting a significant correlation between the level of Impella 2.5 support and the hyperemic coronary flow velocity (Figure 15).

Additionally, Aqel et al[39] used Technetium-99m sestamibi myocardial perfusion imaging to demonstrate the effects of Impella support on the microcirculation (Figure 16). In this case study of a patient with triple-vessel disease, prophylactic Impella support was used during PCI of the primary left anterior descending artery stenosis. Secondary stenoses remained untreated. Technetium-99m sestamibi

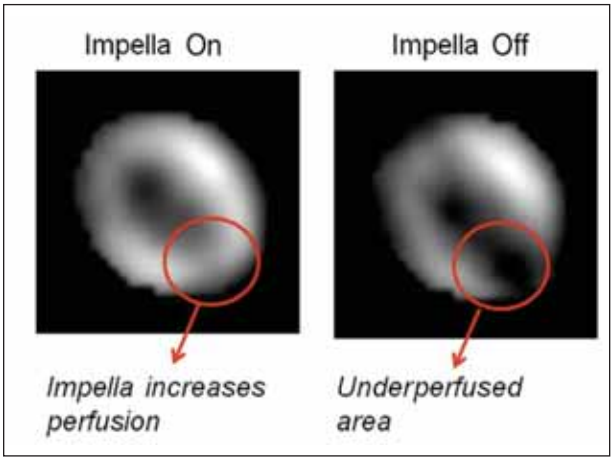

Figure 16. Improvement in myocardial perfusion with Impella support (Technetium-99m sestamibi imaging) (Reprinted with permission from Aqel RA, et al. J Nucl Cardiol. 2009).[39]

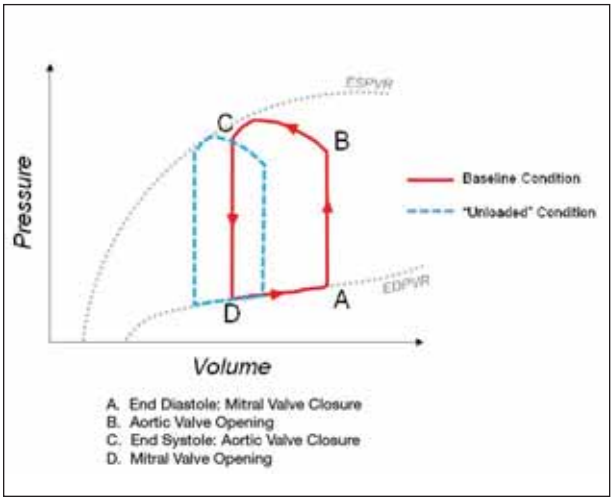

Figure 17. Pressure-volume (PV) loop of the cardiac cycle in baseline and unloaded conditions.

perfusion imaging was performed after revascularization while remaining on Impella support (Figure 16A), and then again after removal of the Impella device (Figure 16B). Comparison of these images illuminates an area of focal hypoperfusion after removal of the Impella that had remained adequately perfused while on Impella support. One explanation of this is that Impella support augmented the blood flow through the collateral pathways supplying this area of the myocardium. This explanation is consistent with the observations of the Remmelink study that reported increased intracoronary pressure and decreased microvascular resistance while on Impella support, both of which will result in increased collateral circulation.

Ventricular Unloading: Decreasing O_2 Demand

Ventricular unloading is often characterized by the PV loop (Figure 17). The PV loop depicts the dynamics of the ventricular pressure and volume during one complete cardiac cycle. At point A, the heart begins its contraction, and pressure builds up rapidly prior to any change in volume. At point B, the aortic valve opens, and a volume of blood is ejected into the ascending aorta. Beyond point B, the pressure continues to build to its maximum until, at point C, the aortic valve closes, and the pressure falls rapidly to point D, where the mitral valve opens, and the chamber begins filling with a new volume of blood for the next heart cycle.

The PV loop is bounded below by the end-diastolic pressure-volume relationship curve and on top by the end-systolic pressure-volume relationship curve. Because one expression of mechanical work is the product of pressure and volume, the area circumscribed by the PV loop is equal to the mechanical work (sometimes called the "external" work) of the heart during each cycle.

There are a variety of ways to affect the PV loop depending on what type of treatment or assist device is applied (Figure 18). Inotropic drugs, for example, have the effect of shifting the end-systolic pressure-volume relationship up, thereby increasing the peak pressure and stroke volume. This increases the area of the PV loop and increases the overall work of the muscle. An IABP has the effect of reducing the pressure at which the aortic valve opens (point B on the PV loop), also known as the *afterload*, but that often comes with an increased overall stroke volume. This offsets the pressure reduction, leaving little or no change in the overall area of the PV loop. Note also that due to their limited improvement in cardiac output, IABPs are most often used in conjunction with inotropic drugs, offsetting any IABP-induced reduction in afterload with the significant increase in mechanical work caused by the inotropes. Active unloading devices, such as traditional ventricular-assist devices and Impella, pull blood from the ventricle, which reduces the overall filling volume and pressure. According to the Frank-Starling curve,[40] this reduction in filling volume and pressure leads to a reduction in stroke volume (if the heart fills less, it expands less and reduces its subsequent stroke output). In terms of the PV loop, this is expressed as a reduction in its overall area, corresponding to a reduction in its mechanical work, and is one aspect of unloading.

The ultimate goal of unloading with an assist device is to reduce the inherent oxygen demand of the myocardium. Reducing oxygen demand places the muscle in a more protective state in the event of an ischemic insult (eg, AMI, PCI, coronary dissection). The amount of mechanical or kinetic work the muscle produces is one component that determines its oxygen demand but, as discussed by a number of

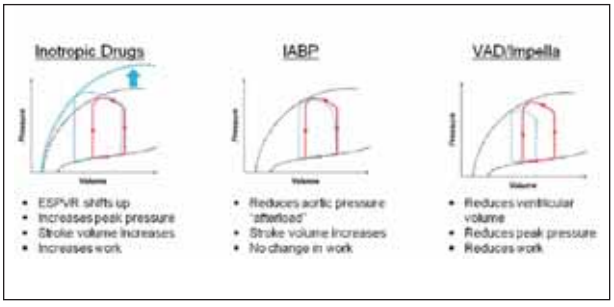

Figure 18. PV loop changes with treatment.

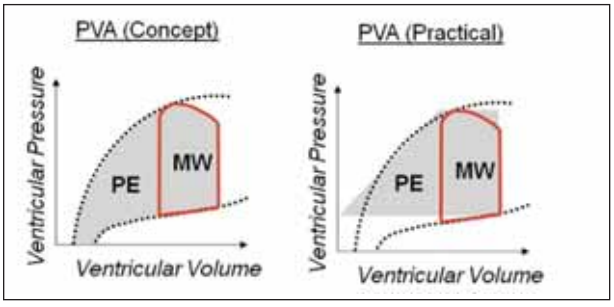

Figure 19. Pressure-volume area (PVA) represents the sum of the myocardial mechanical work (MW) and potential energy (PE). The PVA has been shown to correlate with myocardial oxygen consumption.

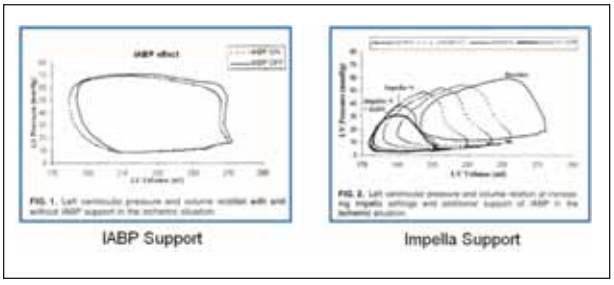

Figure 20. PV loop in vivo. Comparison of Impella and IABP. (Adapted with permission from Sauren LD et al. Artif Organs. 2007).[10]

authors,[10,34,41] an additional determiner of myocardial oxygen demand is the amount of potential energy in the myocardium. The myocardial potential energy is related to the amount of wall tension that is present in the muscle, which has been shown to be highly correlated with myocardial oxygen demand.[34-37] As discussed previously, maximum wall tension is related to the EDP and EDV through the Law of LaPlace, and reductions in these parameters lead to reduced microvascular resistance and increased myocardial perfusion. It is important to note that in addition to this perfusion effect (increasing myocardial oxygen supply), Impella-induced reductions in EDP, EDV, and wall tension (T) lead to reduced myocardial oxygen demand:

$$T \propto \frac{EDP \times EDV}{w} \propto Myocardial\ Oxygen\ Demand.$$

The EDP and EDV, which comprise point A on the PV loop (Figure 17), are significant determiners of the myocardial oxygen balance because, through their relationship to wall tension, they impact both sides of the demand-supply equation.

Myocardial oxygen demand has, therefore, two components: mechanical work and potential energy (wall tension). One analogy is the difference between flexing the arm at the elbow and holding the arm steady but extended from the body for a sustained period of time. In the flexing experiment, the bicep is producing mechanical energy (work), which drives muscular oxygen demand. In the static experiment, the deltoid muscle (among others) is flexed (under tension) and storing potential energy, which also drives oxygen demand even though no kinetic work is being done. In the case of the heart, the more the myocardium stretches during the heart cycle, the more tension it stores within, and the more oxygen it requires to achieve these volumes. Therefore, the total oxygen demand of the myocardium is proportional to the sum of the MW and the stored PE.

Bringing the discussion back to the PV loop, the MW is simply the area inside the loop, and the PE can be characterized by the area to the left of the loop bounded by the end-systolic pressure-volume relationship and end-systolic pressure-volume relationship (Figure 19A). Conceptually, the sum of the MW and PE is known as the *pressure volume area* (PVA) and is proportional to the total myocardial oxygen demand. In order to practically estimate the sum of these areas, Sauren and others have employed a simple expression of the PVA as a method of characterizing the total oxygen demand based on simple hemodynamic points on the PV loop:

$$PVA = MW + PE$$

with

$$MW = (ESV - EDV) \times (Ppeak - EDP)$$

and

$$PE = 0.5 \times ESV \times (Ppeak - EDP),$$

in which ESV is the end-systolic volume and P_{peak} is the maximum pressure. A depiction of this practical estimate of the PVA in the context of the PV loop is shown in Figure 19B.

In summary, ventricular unloading is ultimately about

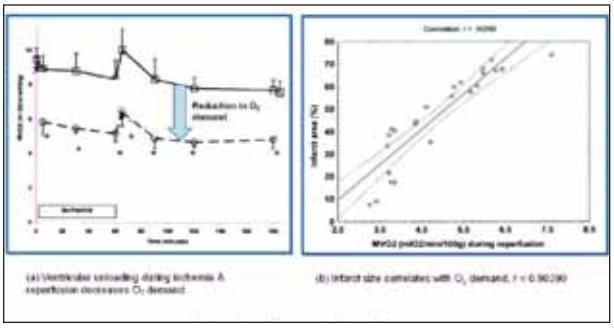

Figure 21. Impact of unloading on O_2 demand and infarct size. Ventricular unloading during ischemia and reperfusion decreases O_2 demand (A). Infarct size correlates with O_2 demand (r = 0.90290) (B). *Animals supported with Impella 5.0 device. (Adapted with permission from Meyns et al. J Am Coll Cardiol. 2003.)[27]

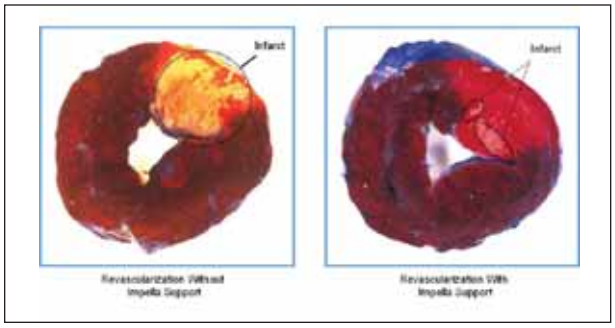

Figure 22. Impella 5.0 device. Reduction of infarct size with Impella. Revascularization without Impella support (A). Revascularization with Impella support (B). (Adapted with permission from Meyns et al. J Am Coll Cardiol. 2003.)[27]

reducing myocardial oxygen demand. It is possible to characterize the oxygen demand of the myocardium in terms of hemodynamic variables, and the PV loop provides a convenient expression of hemodynamics. In particular, the position of the PV loop in the pressure-volume space, as well as the area circumscribed by it, correlates well with myocardial oxygen demand, and the unloading impact of a cardiac assist device is expressed in the PV loop by a leftward shift in its position and an overall reduction in its area.

This effect (leftward shift in its position and overall reduction in its area) was demonstrated (Figure 20) by Sauren et al[10] in an acute animal model that compared the hemodynamic impact of Impella (Impella 5.0) and an IABP. They reported a significant reduction from baseline (ie, no support) in both ventricular work and end-diastolic pressure-volume with Impella. Changes in these same parameters with the IABP were not found to be significant. Note that in the Impella 5.0 data in Figure 20 (right panel), an Impella support level of "5" is approximately equivalent to the maximum support level of the Impella 2.5 device. Valgimigli et al[25] also observed similar Impella-induced changes in the PV loop in a single-patient experience report. It is important to note that although some investigators have also reported on the combined hemodynamic impact of the simultaneous use of the Impella and the IABP, this practice is not recommended due to uncertainties in device interactions that have yet to be characterized.

Going beyond the expression of unloading in the PV loop, Meyns et al[27] further demonstrated a reduction in myocardial oxygen demand in an Impella-supported acute animal model (Figure 21A), and that the reduction in oxygen demand correlates with a reduction in eventual infarct size (Figures 21B and 22).

Improving Oxygen Demand-Supply Ratio

From the perspective of the myocardium, the net desired impact of the Impella cardiac assist device is, therefore, to decrease myocardial oxygen demand (unload) and to augment oxygen supply through an increase in coronary flow. Reesink et al[11] investigated this combined effect in an acute animal model. Considering only the kinetic work component of oxygen demand, they characterized the demand-supply balance as the ratio of the mechanical work to the coronary flow (MW/QCOR) and demonstrated a 36% improvement with Impella compared to an 18% improvement with the IABP. These results also illustrated a dependence of this difference on the baseline (presupport), or native cardiac output, with the Impella benefit more pronounced at lower native cardiac output (Figure 23). Sauren et al[10] also investigated the net change in this oxygen demand-supply ratio, this time, however, taking into account the potential energy component. Characterizing the ratio using the pressure-volume area and the coronary flow (PVA/QCOR), they reported a 69% improvement with Impella compared to a 15% improvement with IABP alone. It is important to note that both of these studies employed an Impella 5.0 device operating at 3.8 and 4.2 L/min, respectively.

CLINICAL EXPERIENCE

The first clinical activity in the United States with Impella 2.5 was in the context of the PROTECT I clinical trial. PROTECT I (20 patients) established the safety and feasibility of Impella 2.5 for a high-risk PCI patient population and was completed in 2007.[33] Before PROTECT I, there was already extensive use of Impella in Europe.

In addition to use in the context of clinical trials in the United States, Impella 2.5 was granted Food and Drug Administration clearance under 510(k) in June 2008 for up to 6 hours of partial circulatory support. Since this clearance, more than 300 institutions have adopted the Impella

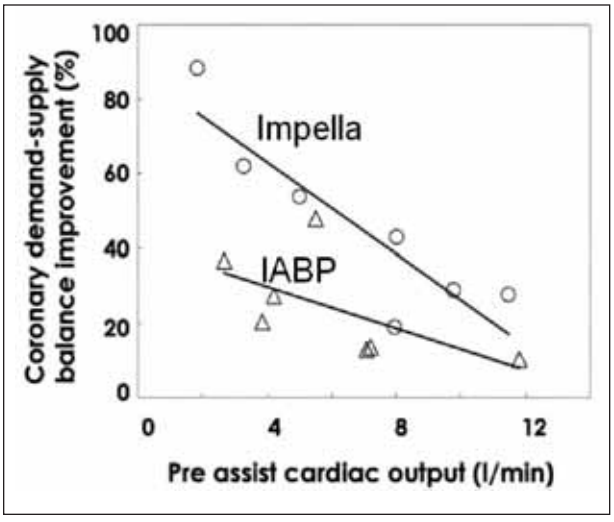

Figure 23. Impella 5.0 Device. Improvement (%) in myocardial oxygen demand-supply balance verses baseline cardiac output. Comparison of Impella assist and IABP. (Reprinted with permission from Reesink et al. Chest. 2004.)[11]

2.5, and it has been used to support more than 1,000 patients. Thus far, physicians have decided to treat the high-risk PCI population (64% of Impella general use), followed by hemodynamically unstable AMI patients (16% of Impella general use). Other patient groups that physicians have decided (on a case-by-case basis) could potentially benefit from the Impella include cardiomyopathy with acute decompensation, postcardiotomy shock, off-pump coronary artery bypass graft surgery, transplant rejection, and support for high-risk electrophysiology (EP) ablation procedures.[42]

Outside of the catheterization lab, the surgical experience with Impella has predominantly been in Europe and Canada, and has mostly involved the Impella 5.0 and LD (5-L devices). The Impella 5.0 devices were granted 510(k) clearance in the United States in April 2009. Before this clearance, North American surgeons had been using the Impella 2.5 device in greater numbers than their European counterparts. These applications have also been encouraging and are similar to the Canadian experience recently reported by Cheung.[43] As with all devices, partial circulatory support (< 5.0 L/min) must be escalated to full-support and/or biventricular devices should the clinical situation warrant. Guidelines for monitoring adequacy of circulatory support include freedom from large-dose inotropic administration, maintenance of normal acid-base status (lactate levels), evidence of continued systemic end-organ function, and overall survival.

With the success of the PROTECT I trial in the United States, two pivotal trials have been initiated and are ongoing in parallel with Impella general use under the 510(k) clearance. PROTECT II and RECOVER II are randomized studies comparing Impella 2.5 to IABP in high-risk PCI and in AMI with hemodynamic compromise, respectively. Note that favorable reimbursement exists for hospitals using Impella, and both clinical trials receive reimbursement as class II-B trials. An additional study in Europe is evaluating Impella in post-MI patients compared to IABP treatment (IMPRESS in STEMI).

CONCLUSION

Impella 2.5 is now available for widespread general use outside of the ongoing clinical trials and is being applied by treating physicians with growing frequency in high-risk PCI, AMI, and other patient groups. It is the first catheter-based therapy of its kind available to cardiologists and has been well established in the literature to be hemodynamically superior to the IABP. Within the landscape of circulatory support, it is the only available device designed to safely and effectively support the natural transport of blood from the ventricle through the aortic valve to the aortic root, simultaneously improving systemic cardiac output, augmenting coronary flow (increasing myocardial oxygen supply), and unloading ventricular work (reducing myocardial oxygen consumption). Along with an established safety profile of low adverse events and independence from the detrimental effects of supplemental inotropic drugs, as well as an ease-of-use profile appropriate for both elective and emergent patient settings, Impella addresses the ideal criteria for circulatory support in the catheterization lab. In the high-risk PCI study (PROTECT II), Impella support is expected to demonstrate the ability to provide stable hemodynamics during significant ischemic challenges, allow more time for balloon inflation and stent placement, and extend PCI therapy to patients who would otherwise be denied revascularization due to excessive surgical risk relative to existing treatment modes. In the AMI patient population, RECOVER II is expected to demonstrate the ability to restore stable hemodynamics, reduce infarct size to improve residual cardiac function, and reduce overall mortality from cardiogenic shock relative to existing treatment modes. In short, these randomized clinical trials are designed to demonstrate how the established hemodynamic superiority of Impella over the IABP translates to favorable outcomes in high-risk PCI and AMI patient populations. ■

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A Case of Percutaneous Coronary Intervention for Acute Myocardial Infarction

Infarction cardiogenic shock supported by the Impella device.

BY ARTHUR GRANT, MD, FACC, FAHA, FSCAI, AND ZEHRA JAFFREY, MD

Patients presenting in cardiogenic shock have poor in-hospital outcomes despite emergent revascularization, inotropic support, and intra-aortic balloon pump implantation.[1] We report the case of a patient with acute myocardial infarction who presented in cardiogenic shock and underwent emergent left main (LM) percutaneous coronary intervention (PCI) supported by the Impella 2.5 left ventricular assist device (Abiomed, Danvers, MA).

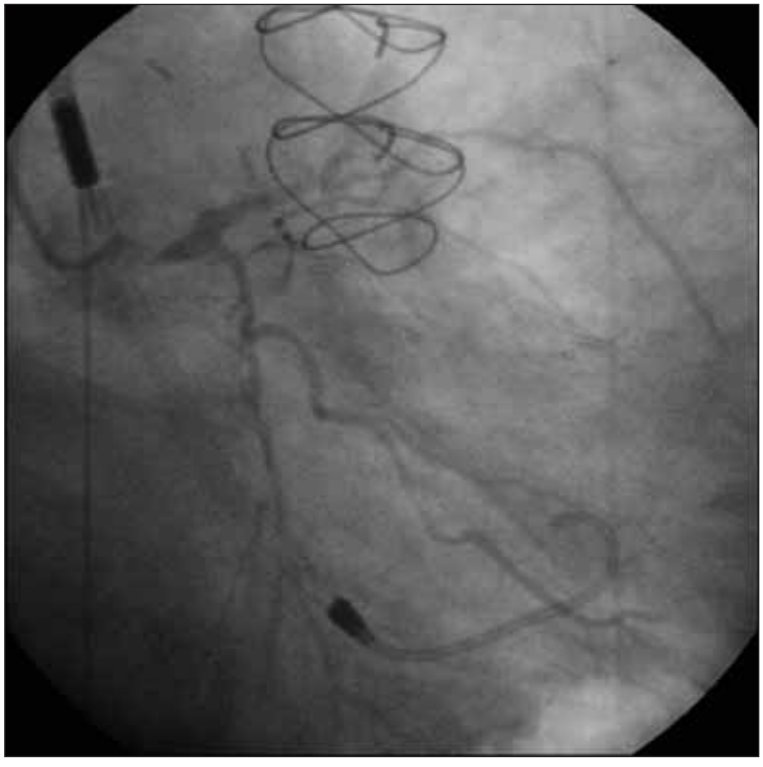

Figure 1. Subtotal occlusion of the left main.

CASE REPORT

A 71-year-old man with a history of three-vessel coronary artery bypass surgery was transferred to Ochsner Medical Center for high-risk PCI. He had a medical history of multiple vascular procedures (abdominal aortic aneurysm repair and carotid endarterectomy). He initially presented to an outside facility with non-ST segment elevation myocardial infarction. Cardiac catheterization revealed a patent left internal mammary artery graft to a small distal left anterior descending artery, a patent saphenous vein graft to the posterior descending artery, an occluded saphenous vein graft to an obtuse marginal branch, and a subtotal occlusion of the LM leading to an unrevascularized left circumflex (LCX) system (Figure 1). He was initially stable after arrival to our center on intravenous nitroglycerine and enoxaparin. However, within minutes, he reported chest pain, developed cardiogenic shock, and was taken to the cardiac catheterization laboratory for an emergent PCI.

The Impella 2.5 circulatory support device was inserted via the left common femoral artery using a 14-F sheath (Figure 2). A diagnostic coronary catheter was used to place the 0.018-inch wire across the aortic valve into the left ventricle. After removing the catheter, the Impella 2.5 was loaded onto the 0.018 wire and placed in the left ventricle using monorail technique. Angiography was used to confirm appropriate positioning of the Impella 2.5 catheter with the inlet area resting in the left ventricle and the outlet area located above the aortic valve.

A 6-F JL 5 guide was inserted into the ostial LM, and a 0.014-inch wire was inserted into the LCX. A 2.5-mm X

20-mm balloon was inserted into the LM and was inflated. At this point, the patient became asystolic. The hemodynamic monitor showed the loss of a biphasic arterial waveform. Despite this, the Impella device continued to provide cardiac output, and the patient's mean blood pressure remained above 50 mm Hg. Because the patient remained awake and responsive, cardiopulmonary resuscitation was not initiated. A 5-F pacing wire was then inserted into the right ventricle and pacing was initiated. At this point, the hemodynamic monitor showed return of a biphasic arterial waveform. A 2.5-mm X 15-mm stent was inserted into the ostial LCX and a 4-mm X 15-mm stent was inserted into the proximal LM. At the end of the procedure, the patient had TIMI 3 flow in the LM and LCX system (Figure 3).

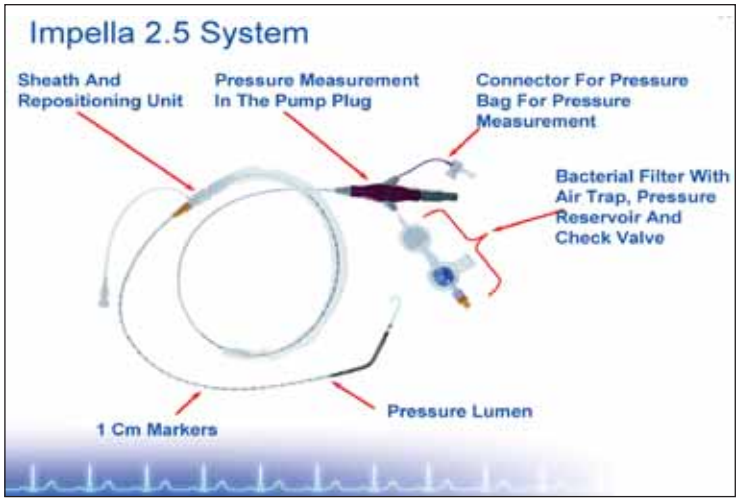

Figure 2. Components of the Impella 2.5 system.

The Impella device remained in place for an additional 4 days to provide augmented coronary and end-organ perfusion after the procedure. The patient showed early signs of significant improvement hemodynamically and was weaned off all inotropic and vasopressor support within the first 24 hours. On day 5 of Impella support, the device was successfully removed without complication. The patient was discharged to home in good condition 9 days after admission.

DISCUSSION

The Impella 2.5 provided support both to successfully conduct PCI in the setting of an acute coronary syndrome and to resolve cardiogenic shock in the postinterventional period. The device maintained an adequate cardiac output during a period of asystole, allowing the patient to maintain adequate blood pressure and remain responsive through a short period of hemodynamic instability.

Similar data in the literature confirm the role of the Impella in high-risk patients who are to undergo angioplasty.[2,3] A recently reported randomized trial also confirmed the safety and feasibility of the Impella device as compared to an intra-aortic balloon pump in patients presenting in cardiogenic shock.[4] ■

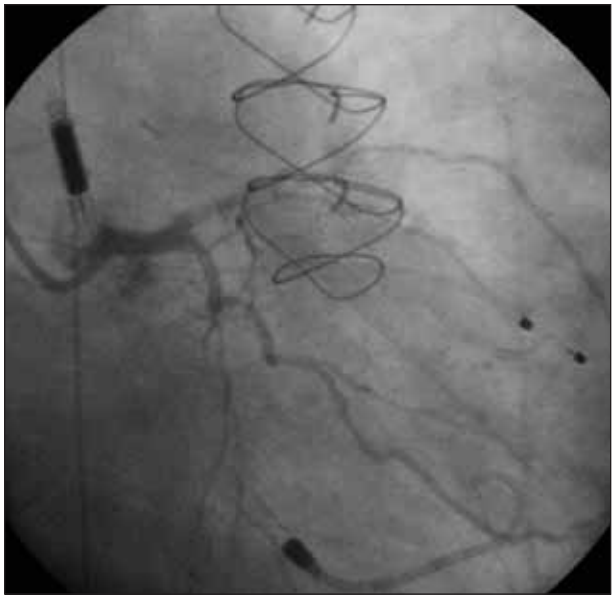

Figure 3. Postprocedure left coronary angiogram.

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Invited Commentary

BY DANIEL H. RAESS, MD, FACC, FACS

ABIOMED MEDICAL DIRECTOR

Since the FDA clearance of the Impella 2.5 (Abiomed, Danvers, Mass.) in June 2008, more than 1,000 patients have been treated with the Impella 2.5, with more than 300 hospitals employing the technology.[1] Simultaneously, the PROTECT II clinical trial, a randomized clinical trial comparing the intra-aortic balloon pump (IABP) to Impella 2.5 in high-risk percutaneous coronary intervention (PCI), continues to actively enroll patients. Furthermore, 2009 brought the publication of encouraging data from PROTECT I,[2] the safety trial for Impella 2.5, as well as IDE approval of the acute myocardial infarction trial (RECOVER II), a randomized trial comparing Impella 2.5 with the IABP in patients who are experiencing hemodynamic compromise during acute myocardial infarction. While PROTECT II and RECOVER II address the superiority of Impella with respect to clinical outcomes, the hemodynamic superiority of Impella 2.5 has already been demonstrated by a number of investigators.[2-4] Seyfarth,[3] for example, compared the hemodynamic impact of Impella 2.5 and IABP in STEMI patients. This study (ISAR-SHOCK) was a prospective randomized clinical trial of 26 patients to evaluate the safety and efficacy of the Impella 2.5 versus the IABP for treatment of cardiogenic shock caused by myocardial infarction. The primary endpoint of the study was the change (from baseline at 30 minutes after the initiation of support) in observed cardiac index. The study met its primary endpoint demonstrating a significant (P = .02) difference in the cardiac index improvement with Impella versus IABP. Although the study was not powered to demonstrate mortality differences (an estimated 635 patients are needed to show a mortality difference at accepted MAE rates), Impella was found to be safe, effective, and free of complications. Furthermore, the left ventricular ejection fraction was significantly improved in Impella patients at both 4 days and 120 days compared to IABP patients. The finding of sustained improvement in left ventricular ejection fraction has also been documented in other studies.[2,4] As only the second Impella 2.5 case at this institution, it was apparent that Impella made a significant difference in a high-risk PCI procedure during an acute coronary syndrome in a patient experiencing cardiogenic shock. This particular case showed that the support was adequate to allow this patient to be conscious and comfortable while a pacing wire was placed and pacing was initiated. In the past, circulatory support has not been available in the cath lab without having our cardiac surgery colleagues or a vascular surgery team available. This may indeed be the most important aspect of the Impella technology; the potential to extend the interventional procedure. Early experience is encouraging for patients supported with Impella during PCI for STEMI.[3]

This case is illustrative of the fact that successful use of the Impella catheter beyond the high-risk PCI case is not limited to centers that have extensive Impella case experience.

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A Pressure Wire Study on the Effect of Impella 2.5 Support

How this device benefits coronary hemodynamics during high-risk angioplasty.

BY SALMAN A. ARAIN, MD, FACC, AND LAWRENCE O'MEALLIE, MD, FACC

The Impella 2.5 (Abiomed, Inc., Danvers, MA) is a percutaneously placed axial flow pump that is capable of delivering 2.5 L/min from the left ventricle (LV) to the ascending aorta. Previous studies have shown that left ventricular unloading by the device improves coronary flow in nonstenotic arteries, but the effects of unloading within a diseased coronary artery are unknown. This study is designed to determine the impact of Impella 2.5 mediated augmentation of cardiac output on coronary flow reserve (CFR) and fractional flow reserve (FFR) during percutaneous coronary intervention (PCI).

CASE REPORT

A 51-year-old man with advanced ischemic cardiomyopathy (LV ejection fraction approximately 15% with chronic systolic heart failure) was referred to the Tulane Heart and Vascular Institute for cardiac transplant evaluation. Coronary angiography showed angiographically nonobstructive disease in the left anterior descending (LAD), severe stenoses within the major diagonal branches, occlusion of a major obtuse marginal branch, and multifocal disease within the right coronary artery (Figure 1). Pressure wire evaluation of the LAD demonstrated the presence of hemodynamically significant disease within the proximal segment, (FFR 0.75, ischemic by definition) (Figure 2). A subsequent viability study showed the presence of viable myocardium in the anterior, anterior-lateral, and posterior segments.

The patient was deemed not suitable to be a candidate for surgical coronary revascularization because of poor graft targets and multiple comorbidities (chronic congestive heart failure (CHF), moderate mitral regurgitation, pulmonary hypertension, and renal insufficiency). During a subsequent admission for acute-on-chronic CHF, the patient was scheduled to undergo multivessel PCI utilizing the Impella 2.5 for intraoperative hemodynamic support.

PROCEDURE DETAILS

Access for the planned PCI was achieved via the right common femoral artery (CFA) using a standard 8-F sheath. A second 8-F sheath was introduced into the left CFA in preparation for the insertion of the Impella 2.5 device. After

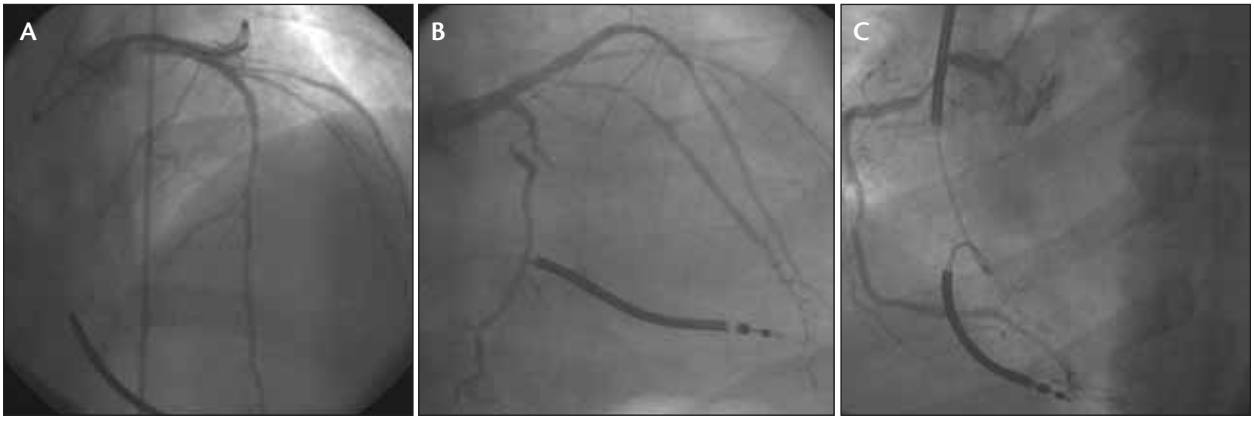

Figure 1. Selective coronary angiography showed nonobstructive LAD disease, severe major diagonal branch stenosis, and occlusion of the obtuse marginal artery. Right coronary artery disease is diffuse.

diagnostic coronary angiography, a coronary pressure wire was inserted and positioned within the mid-LAD. Mean coronary artery (Pd) and mean aortic pressures (Pa) were recorded at baseline and after induction of hyperemia using intravenous adenosine. FFR was calculated from these measurements: FFR = Pd/Pa at maximal hyperemia. CFR was calculated using coronary thermodilution curves recorded at baseline and during hyperemia.

The Impella 2.5 device was inserted via the left CFA using a technique that has previously been described by Raess et al.[1] Briefly, the 8-F sheath was exchanged for a 13-F sheath to accommodate the largest diameter of the device at the motor (12 F). The device catheter (with a smaller diameter of 9 F) was advanced across the aortic valve over an 0.018-inch wire using the monorail technique. The distal tip of the device was positioned in the mid-left ventricle under fluoroscopic guidance. Excessive catheter length was removed, and the catheter was secured at the groin to prevent forward migration.

After confirmation that the Impella catheter was correctly positioned across the aortic valve, mid-LAD FFR and CFR values were recorded at three different levels of support: P3, P6, and P8/P9. The mid-LAD lesion was then treated by placing a drug-eluting stent (DES), utilizing the pressure wire as a guidewire, and the FFR and CFR measurements were repeated at the maximum support level (P8/P9). The first and second diagonal branches and the right coronary artery were then revascularized by DES placement. Impella support was continued for an additional 14 hours after the procedure while the patient was monitored in the coronary care unit. Eventually, the patient was weaned off the Impella catheter over a short period of time and the device was removed. Hemostasis was achieved by manual compression at the groin.

RESULTS

The FFR and CFR values within the LAD for different levels of support are shown in Table 1 (Figure 3). The baseline FFR of 0.76 did not change during augmentation of the cardiac output. Conversely, the CFR improved significantly from a value of 1.6 (abnormal) at baseline to 2.4 (normal) at P6 and was lower at peak augmentation (P8/P9). After LAD revascularization, the FFR increased to 0.85, which is above the ischemic threshold, and the CFR improved to 2.5, which is within the normal range.

DISCUSSION

The Impella 2.5 is a unique device that enables interventional cardiologists to promptly and conveniently implement mechanical circulatory support in the cardiac catheterization lab. The compact design of the catheter allows percutaneous insertion in the lab, thereby eliminating

Figure 2. FFR data demonstrated by hemodynamic significance of an LAD lesion.

the need for major cardiac or vascular surgery in patients who may be too unstable to undergo such surgery. Previous studies have shown that the LV unloading by Impella improves the coronary microcirculatory hemodynamics in nonstenotic arteries. Remmelink's[2] observations in patients undergoing PCI, and Sauren's[3] findings from animal studies, reveal that augmentation of coronary flow occurs at the subendocardial level due to the combination of a direct increase in coronary blood flow and decreased microvascular resistance. Our findings suggest that a similar favorable effect may be seen in stenotic arteries even before revascularization has been achieved. The long-term clinical sequelae of this phenomenon could have profound implications for treating patients with ischemic heart disease, particularly in regards to the selection of periprocedural therapy that would have the most favorable effect on the coronary microcirculation. For example, a recent meta-analysis of intra-aortic balloon counterpulsation (IABP) use during primary PCI for ST-elevation myocardial infarction showed that in randomized controlled studies, IABP therapy had no effect on 30-day survival or the recovery of LV function.[4] Our patient had an ejection fraction of 25% (+10 points) during follow-up at 4 weeks, and he reported a marked improvement in his exertional capacity and CHF symptoms. Similar improvements in EF were reported[5-7] after Impella supported PCI. Ongoing randomized clinical trials comparing the effectiveness of Impella 2.5 and IABP in both high-risk PCI and STEMI patients (Protect II and Recover II) will help to further characterize the effectiveness of this unique percutaneous therapy.

We used a pressure wire in our patient because of the advantages it offers over angiography or intravascular ultrasound in the evaluation of diffusely diseased arteries. When FFR is derived via pressure wire, it allows the functional

TABLE 1. FFR AND CCR DURING IMPELLA SUPPORT					
	Baseline	**P3**	**P6**	**P8/9**	**After PCI**
Pd (mean, mm Hg)	46	47	53	43	58
Pa (mean, mm Hg)	62	62	70	58	68
FFR	0.74	0.76	0.76	0.75	0.85
CFR	1.6	2	2.4	1.9	2.5
Support (L/min)	-	1.3	1.8	2.4	2.4

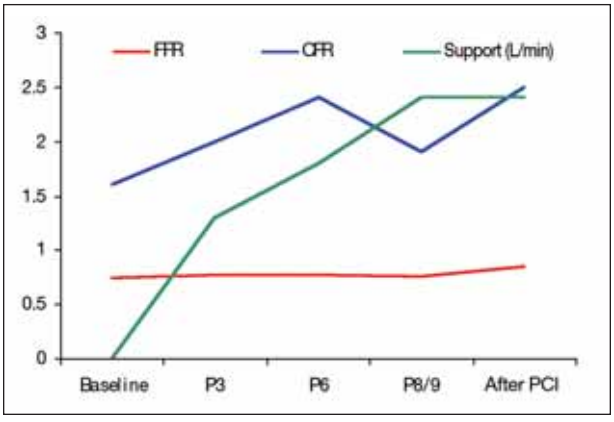

Figure 3. Graph depicting FFR and CCR during Impella support.

assessment of multisegmental atherosclerosis with a very high spatial resolution independent of ventricular loading conditions (such as heart rate, pressure, and contractility). When CFR is derived by pressure wire, it employs the principle of thermodilution to evaluate microcirculatory hemodynamics, and has been validated against CFR that is derived via Doppler (flow) wire. In analysis of our FFR and CFR data, it appears that there was a significant increase in the CFR during the early phases of augmentation, followed by a decline at the maximum support level (P8/P9). This may have been due to the reduction in systemic pressure that was observed after administration of an additional sedative at this point in the procedure. The -12 mm Hg difference in mean aortic pressure between P6 and P8/P9 supports the notion that a decrease in resting blood pressure results in a lower-than-expected CFR reading. It is also possible that not enough time was allowed between measurements at P6 and P8/P9, and that some adenosine receptors were still occupied, resulting in a "partial hyperemic" starting state for the final measurement.

On the other hand, the FFR value remained stable at all levels of augmentation, confirming that this parameter is indeed lesion specific and is not affected by the cardiac output or the changing state of distal circulation (provided maximal hyperemia is achieved). The observation that CFR improved while FFR remained unchanged strongly argues that any improvement in vascular bed reactivity is a direct effect of the Impella device. Also, it is interesting to note that PCI of the LAD resulted in an FFR value that was above the ischemic threshold but yielded a CFR reading that was similar to that achieved by Impella support in the absence of revascularization. To the best of our knowledge, this is the first report of the effects of LV unloading by a cardiac assist device such as the Impella 2.5 on the hemodynamics within a stenotic artery before and immediately after PCI. Additional studies in a larger cohort of patients are warranted to confirm these findings, but the potential for salvage of myocardium before and during Impella-supported PCI is obvious and encouraging. ■

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