Left Ventricular Support Systems for High-Risk PCI:
How Can We Improve Outcomes for Rare Procedures?

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High-risk percutaneous coronary interventions (PCI) are becoming more prevalent as the ability to perform complex coronary interventions continues to improve. Patients for whom high-risk interventions are considered generally have severe diffuse coronary artery disease, a single last patent conduit, or significant left main disease with large territories of myocardial ischemia. In addition, these patients also typically have reduced left ventricular function (ejection fraction less than 25% to 35%) with comorbidities that make them high risk for standard coronary artery bypass grafting. Thus, PCI is increasingly used as a viable alternative for coronary revascularization, but it too is associated with a high degree of morbidity and mortality.

Coronary ischemia can transiently worsen during PCI through repeated balloon inflations, stent manipulations, and contrast injections that result in a negative inotropic effect.\(^1\) In patients with left ventricular dysfunction and large territories of ischemia who have little reserve, this can lead to reductions in blood pressure that make it hard to complete the revascularization. Hemodynamic support during the conduct of the PCI, such as that provided by intra-aortic balloon pump (IABP) counterpulsation or Impella\(^\text{TM}\), may therefore maintain perfusion pressure throughout the procedure to reduce the risk associated with these complex interventions.

Kahn and colleagues reported the first use of intra-aortic balloon pumps to support high-risk PCI in 1990 among 28 patients with severe LV dysfunction undergoing PCI for 3-vessel or left main coronary artery disease.\(^2\) This study established that IABP support in this setting was safe and allowed the PCI to be completed without untoward risk. IABP use for this indication has continued to grow since that time and now is one of the more common reasons for IABP use in the cardiac catheterization laboratory, reflective of the growing number of high-risk PCIs being performed by interventional cardiologists.\(^3\)
In an analysis by Brennan and colleagues from the National Cardiovascular Data Registry (NCDR) evaluating the use of PCI as a revascularization strategy for unprotected left main coronary artery (ULMCA) stenosis in the United States, they demonstrated that this was being performed in almost 5% of patients with unprotected left main coronary artery stenosis, accounting for almost 6,000 PCIs during the interval studied (2004-2008). Furthermore, the proportion of patients with ULMCA stenosis treated with PCI was increasing during that time. Among the patients included in the NCDR registry, 95% of those who had unprotected left main coronary artery stenting survived to hospital discharge. However, by 30 months, greater than 40% of these patients had died, indicating the high-risk nature of these interventions and the need for long-term follow-up.

The Balloon Pump-Assisted Coronary Intervention Study (BCIS-1) was the first randomized controlled study to assess the efficacy of elective intra-aortic balloon pump use in patients undergoing elective high-risk PCI. In this study, over 300 patients with severe left ventricular systolic dysfunction and extensive coronary disease were randomized to IABP or no IABP before elective high-risk PCI. In general, these patients were older, with severe left ventricular dysfunction (mean LVEF of 24%), and more than half had class III or IV heart failure symptoms. The primary end point for this study was major adverse cardiac and cardiovascular events (MACCE) defined as death, acute myocardial infarction, cerebrovascular event, or further revascularization prior to hospital discharge, capped at 28 days.

In the BCIS-1 study, MACCE at hospital discharge was 15.2% in the elective IABP group versus 16.0% in the control arm and was not statistically significantly different (OR=0.94, 95% CI=0.51-1.76; p=0.85). Prophylactic IABP use was associated with more minor bleeding (15.9% vs. 7.3%, OR=2.39, 95% CI=1.07-5.61, p=0.02) and vascular access site complications.
(3.3% vs 0%, p=0.06). However, procedural complications were significantly more common in
the no IABP group (10.7% versus 1.3%; OR=0.11; p<0.001), driven mostly by episodes of
prolonged procedural hypotension in the control group. It is also important to note that in this
study there was significant cross-over from no IABP to placement of an IABP, which occurred in
18 of the 151 patients (12%) assigned to the control arm, usually because of profound
hypotension. In the initial publication, the secondary endpoint of all-cause mortality at six
months was reported. This showed a trend toward improved six-month all-cause mortality in the
IABP group at 4.6% versus 7.4% in the control group (OR=0.61, (95% CI=0.24-1.62), p=0.32).
The Kaplan-Meier cumulative mortality estimates for the two arms in the study showed that this
trend is not evident until at least 2 months after the PCI, and at 6 months, the K-M mortality
curves still appear to be diverging.

In this issue of Circulation, we now learn of the five-year mortality outcomes of the
BCIS-1 trial. Strikingly, it shows a significant reduction in all-cause mortality among those
randomized to prophylactic IABP with a relative reduction in mortality of 34% (7.9% vs. 12.1%;
HR=0.66, (95% CI=0.44-0.98), p=0.039). The Kaplan-Meier curves for survival not only
demonstrate a significant difference at 5 years, but that the Kaplan-Meier curves appear to be
continuing to diverge even at five years.

The use of a central national database to determine vital status led to the remarkable
achievement of 100% long-term follow-up. Because of the nature of the data collected, the
cause of death for these patients is unknown, and our ability to understand the mechanisms
behind the improved survival 5 years after IABP use is hindered. The authors conclude that the
effect on mortality may be due to reductions in procedural ischemia and myocardial infarction or
from more aggressive revascularization in the setting of prophylactic IABP use in high-risk PCI.
The results of BCIS-1 parallel those seen in the recently published PROTECT II study, which randomized patients undergoing elective high-risk PCI to either hemodynamic support with the Impella 2.5™ device or IABP. While the primary endpoint in PROTECT II of 30-day major adverse events was not different between the two groups, the 90 day per protocol analysis demonstrated improved outcomes with the Impella™ device over IABP (RR=0.79, (95% CI=0.64-0.97), p=0.023). Examination of the Kaplan-Meier event rates demonstrates that with longer follow-up there appears to be a growing difference in the event rates that seems to be still diverging at the end of follow-up (90 days). Again, the reasons for the improved outcomes with more hemodynamic support over less support that becomes increasingly apparent with longer-term follow-up are not entirely clear. Reductions in myocardial ischemia and necrosis, as well as more aggressive revascularization with improved hemodynamic support are possible contributing factors. The authors of PROTECT II suggest that 30 day follow-up was insufficient in this study to fully demonstrate the differences between the groups and that out-of-hospital events that occur beyond 30 days have important safety and cost implications and should be captured in future studies like this.

What are the implications for interventional cardiologists that are about to perform a high-risk PCI in a patient with severe left ventricular function and left main disease that the “Heart Team” has suggested should be best managed with PCI because of the co-morbidity? On the surface, the primary endpoints of both BICIS-1 and PROTECT-II were neutral, suggesting that these devices did not offer any additional benefit when examined at 30 days. In fact, both devices offer very good hemodynamic support, with the advantage to the Impella™ device that allows higher cardiac output and greater support at a price of larger cannulas and the potential for more vascular access issues. However, both studies suggest a possible later effect. The later
outcomes data with IABP (at 5 years) and Impella\textsuperscript{TM} (at 90 days) suggest that when more complete revascularization is desirable, these devices will offer the potential to improve outcomes with high-risk PCI.

The question that remains is how can we better ascertain the long-term outcomes with relatively rare high-risk procedures like this? The US Food and Drug Administration has suggested that longer-term safety data is desirable for approved medical devices. In September of 2012, the US FDA released its vision for post-market surveillance for medical devices.\textsuperscript{8} While the primary objective of these post-market surveillance systems is to assess for long-term safety, these systems can and should be utilized to also assess efficacy. It has already been demonstrated that automated safety surveillance of clinical registries for approved cardiovascular devices can provide early warnings regarding the safety of approved cardiovascular devices in clinical practice.\textsuperscript{9} It is our belief that similar to what was carried out in the BICIS-1 study, long-term follow up using a death index, would allow safety information such as mortality to be collected prospectively without holding up an approval process. This would be of particular value for high-risk intervention where long-term mortality data are not usually available.

We need to acknowledge that revascularization with PCI is an iterative science where gradual changes to procedures such as the use of left ventricular support devices in high-risk PCI can offer new avenues for us to treat the most complex patients. While the use of prophylactic IABP or Impella\textsuperscript{TM} can improve outcomes compared to a more stand-by approach, we must recognize that newer support devices may be on the horizon. We need to approach them with a more mature process for data-collection so that we can truly understand major outcomes, such as mortality, without holding up the process of moving the science of improving patient outcomes forward. The data from BCIS-1 and PROTECT-II that demonstrate more robust differences in
the treatment arms with longer follow-up should be a call to investigators that future studies of hemodynamic support devices must include long-term follow-up.

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