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CLINICAL RESEARCH

A Prospective Feasibility Trial Investigating the Use of the Impella 2.5 System in Patients Undergoing High-Risk Percutaneous Coronary Intervention (The PROTECT I Trial)

Initial U.S. Experience

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Objectives We sought to evaluate the safety and feasibility of the Impella 2.5 system (Abiomed Inc., Danvers, Massachusetts) in patients undergoing high-risk percutaneous coronary intervention (PCI).

Background The Impella 2.5 is a miniaturized percutaneous cardiac assist device, which provides up to 2.5 l/min forward flow from the left ventricle into the systemic circulation.

Methods In a prospective, multicenter study, 20 patients underwent high-risk PCI with minimally invasive circulatory support employing the Impella 2.5 system. All patients had poor left ventricular function (ejection fraction ≤35%) and underwent PCI on an unprotected left main coronary artery or last patent coronary conduit. Patients with recent ST-segment elevation myocardial infarction or cardiogenic shock were excluded. The primary safety end point was the incidence of major adverse cardiac events at 30 days. The primary efficacy end point was freedom from hemodynamic compromise during PCI (defined as a decrease in mean arterial pressure below 60 mm Hg for >10 min).

Results The Impella 2.5 device was implanted successfully in all patients. The mean duration of circulatory support was 1.7 ± 0.6 h (range: 0.4 to 2.5 h). Mean pump flow during PCI was 2.2 ± 0.3 l/min. At 30 days, the incidence of major adverse cardiac events was 20% (2 patients had a periprocedural myocardial infarction; 2 patients died at days 12 and 14). There was no evidence of aortic valve injury, cardiac perforation, or limb ischemia. Two patients (10%) developed mild, transient hemolysis without clinical sequelae. None of the patients developed hemodynamic compromise during PCI.

Conclusions The Impella 2.5 system is safe, easy to implant, and provides excellent hemodynamic support during high-risk PCI. (The PROTECT I Trial; NCT00534859) (J Am Coll Cardiol Intv 2009;2:91–6) © 2009 by the American College of Cardiology Foundation

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In patients with poor left ventricular (LV) function undergoing high-risk percutaneous coronary intervention (PCI), even brief episodes of myocardial ischemia may result in hypotension and decreased cardiac output leading to a vicious cycle of coronary hypoperfusion, heart failure, and hemodynamic collapse. Accordingly, prophylactic stabilization is often employed in these high-risk patients to prevent hemodynamic instability and adverse periprocedural outcomes. The Impella 2.5 system (Abiomed Inc., Danvers, Massachusetts) is a novel, minimally invasive LV assist device, which is placed retrogradely across the aortic valve via the femoral artery using conventional catheterization techniques (1). Using a miniaturized rotary pump, blood is drawn from the LV cavity and expelled into the ascending aorta, providing up to 2.5 l/min forward flow at its maximum rotation of 51,000 rpm. Initial clinical studies have demonstrated that the Impella device effectively unloads the LV, improves coronary perfusion, and augments cardiac output (2,3). The PROTECT I (A Prospective Feasibility Trial Investigating the Use of the IMPELLA RECOVER LP 2.5 System in Patients Undergoing High Risk PCI) trial was designed to evaluate the safety and feasibility of the Impella 2.5 system in patients undergoing high-risk PCI.

Abbreviations and Acronyms

EF = ejection fraction

INR = international normalized ratio

LV = left ventricle/ventricular

PCI = percutaneous coronary intervention

Methods

Study population. The PROTECT I trial enrolled 20 patients undergoing high-risk, nonemergent PCI at 7 centers between July 2006 and April 17, 2007 (investigational device exemption: G050017). Eligible patients had a LV ejection fraction (EF) ≤35% and were required to undergo PCI on either an unprotected left main coronary artery or the last patent coronary conduit. Exclusion criteria were: age <40 or >80 years, ST-segment elevation myocardial infarction within 7 days; pre-procedure cardiac arrest within 24 h of enrollment requiring cardiopulmonary resuscitation; cardiogenic shock (defined as cardiac index <2.2 l/min/m^2 and pulmonary capillary wedge pressure >15 mm Hg); LV mural thrombus; presence of a mechanical aortic valve or a heart constrictive device; aortic stenosis (valve area ≤1.5 cm^2); moderate or severe aortic regurgitation (≥2+ by echocardiography); severe peripheral vascular disease that would preclude placement of the Impella 2.5 device; chronic renal dysfunction (serum creatinine ≥3.5 mg/dl); history of liver dysfunction with elevation of the liver enzymes and bilirubin ≥3 times the upper limit of normal or international normalized ratio (INR) ≥2.0; severe pulmonary disease (FEV1 ≤1.0); uncorrectable abnormal coagulation parameters (defined as platelet count ≤75,000 or INR ≥2.0 or fibrinogen ≤1.5 g/l); subjects with sustained or nonsustained ventricular tachycardia; active systemic infection; stroke or transient ischemic attack within 3 months; allergy or intolerance to aspirin, clopidogrel, heparin, or contrast media; patients with heparin-induced thrombocytopenia; or participation in another investigational drug or device trial. The study was approved by the institutional review board at each center. Written informed consent was obtained from each patient before enrollment.

Impella system. The Impella 2.5 device is a miniaturized 12-F rotary blood pump that is placed across the aortic valve (Fig. 1). The device aspirates blood from the LV cavity, which is then expelled into the ascending aorta. Under clinical conditions, the pump provides up to 2.5 l/min at its maximal rotation speed of 51,000 rpm. The device is inserted percutaneously through a 13-F femoral sheath and is mounted on a 9-F pigtail catheter, allowing it to be easily placed across the aortic valve, and left in place for up to 5 days. The Impella 2.5 catheter is connected distally to a portable mobile console that displays invasive pressure with the actual revolutions per minute of the pump, thus guiding the correct positioning and functioning of the device.

Impella procedure. After insertion of a 13-F femoral arterial sheath, the Impella 2.5 system was advanced retrogradely across the aortic valve using a monorail technique and positioned in the mid-LV cavity. All patients were anticoagulated with unfractionated heparin before pump insertion to achieve an activated clotting time >250 s. The pump requires an activated clotting time of 160 to 180 s during operation. Circulatory support was initiated before PCI with a target flow of 2.5 l/min. PCI was then performed using conventional equipment and techniques. Glycoprotein receptor inhibitors were administered at the operator's discretion. The timing of device explanation was left to the discretion of the physician. For patients who were hemodynamically stable during PCI, weaning was commenced in the cardiac catheterization laboratory by decreasing the pump performance level in 2 steps in intervals of 2 to 10 min. Once the performance level was reduced to performance level P2 (range: P1 to P9; P9 = maximum flow) for 10 min without hemodynamic instability, the Impella pump was pulled back into the aorta and explanted. In patients in whom weaning was unable to be achieved in the catheterization laboratory, the Impella 2.5 could remain implanted for up to 5 days. Manual compression was used to achieve hemostasis.

Study procedures. Transthoracic echocardiography was performed before and after pump implantation, at pump removal, and 30 days after the procedure. Studies were analyzed at the Duke University Core Echocardiographic Laboratory. Hemodynamic measurements were recorded before support and every 30 min until the device was removed. Serial blood sampling was obtained before, during, and after Impella support for cardiac enzymes, hemo-

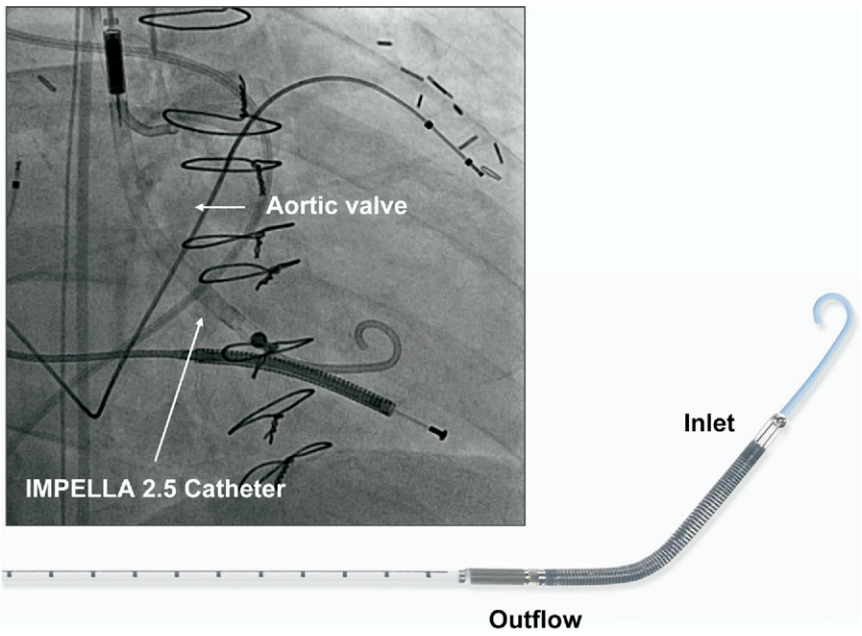

Figure 1. Photograph of the Impella 2.5 Catheter

Photograph of the Impella 2.5 catheter positioned across the aortic valve.

lysis, biochemistry, blood gases, and hematology. Neurological assessment was performed before PCI and daily until hospital discharge.

Data management and analysis. Study data, collected prospectively by research coordinators, were verified against source documentation by trial monitors. An independent committee adjudicated all adverse clinical events. All investigators had access to study data.

Study end points and definitions. The primary safety end point was the incidence of major adverse cardiac events defined as death, myocardial infarction, target vessel revascularization, urgent coronary artery bypass surgery, or stroke at 30 days. Secondary safety end points included aortic valve injury, aortic insufficiency, cardiac tamponade, cardiogenic shock, device malfunction, hemolysis, hepatic failure, insertion site infection, limb ischemia, perforation, renal failure, respiratory failure, sepsis, thrombocytopenia, thrombotic (noncentral nervous system) complication, transfusion, vascular injury, ventricular fibrillation, and ventricular tachycardia. The primary efficacy end point was freedom from hemodynamic compromise during PCI, defined as a decrease in the mean arterial pressure below 60 mm Hg for more than 10 min or the requirement for additional pressor support. Secondary efficacy end points were freedom from procedural-related events (ventricular fibrillation, tachycardia requiring electrical cardioversion), and angiographic success was defined as residual stenosis <30% after stent implantation or <50% after balloon angioplasty alone. Myocardial infarction was defined as an increase of the creatine kinase-myocardial band >3 times the upper limit of normal.

Results

Clinical data. A total of 20 patients were enrolled at 7 sites in 2 countries (6 in the U.S., 1 in the Netherlands). All patients had poor LV function (mean EF: 26 ± 6%, range: 15% to 35%) and multiple comorbidities including prior myocardial infarction (60%) and congestive heart failure (85%) (Table 1). All patients underwent PCI on a vessel supplying a large proportion of the myocardium (n = 14 unprotected left main coronary artery; n = 6 on a last remaining conduit) (Table 2). The mean number of lesions treated was 2.4 ± 0.9.

Procedural data. The Impella device was implanted successfully in all patients. The mean duration of circulatory support was 1.7 ± 0.6 h (range: 0.4 to 2.5 h). Mean pump flow was 2.2 ± 0.3 l/min during PCI, and 1.2 ± 0.4 l/min during pump weaning. All patients had the Impella 2.5 device removed uneventfully in the cardiac catheterization laboratory after PCI. There were no cases of device malfunction. The mean arterial pressure and heart rate were stable during pump support. Compared with baseline parameters, a small decrease in systolic, diastolic, and mean arterial pressure was observed after the device was removed (Table 3). Mean procedure time was 3.3 ± 0.9 h.

Table 1. Clinical Characteristics (N = 20)

Age, yrs	60 ± 12
Male	17 (85%)
BMI, kg/m^2	27.5 ± 4.4
Diabetes mellitus	9 (45%)
Hypertension	10 (50%)
Hyperlipidemia	15 (75%)
Congestive heart failure	17 (85%)
Class IV	7 (35%)
Class III	5 (25%)
Current smoker	8 (40%)
Previous MI	12 (60%)
Previous PCI	9 (45%)
Previous CABG	8 (40%)
COPD	7 (35%)
Renal failure	9 (45%)
Pacemaker/ICD	7 (35%)

BMI = body mass index; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; ICD = implantable cardioverter-defibrillator; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Primary safety end point. At 30 days, the primary safety end point had occurred in 4 (20%) patients (Table 2). Two patients had enzymatic evidence of a periprocedural myocardial infarction without clinical sequelae (1 occurred in a patient undergoing rotational atherectomy and stenting of the left main, left anterior descending, and circumflex arteries; the other patient had a large dissection of the left main coronary artery with transient subtotal occlusion during PCI). No patients had a stroke, target vessel revascularization, or coronary artery bypass graft surgery. There were 2 deaths: 12 and 14 days after PCI and device removal. Neither death was related to the investigational device. One patient, who had a history of severe cardiomyopathy, died suddenly while in a cardiac rehabilitation center (day 14). The other patient developed acute-on-chronic renal failure and progressive heart failure after PCI, culminating in cardiac arrest on day 12.

Secondary safety end points. Two patients had laboratory evidence of mild hemolysis. In 1 patient, hemolysis was observed during pump use (peak plasma-free hemoglobin 75.8 mg/dl 1 h after insertion). The plasma-free hemoglobin had returned to normal 24 h after the device was removed. In the other patient, the plasma-free hemoglobin was normal at device removal, but the level was elevated 14 h after removal (67.8 mg/dl). Neither patient required treatment or had any clinical sequelae. Two patients required blood transfusion (1 patient had baseline anemia; the other patient had hematuria secondary to bladder cancer). Eight patients developed a hematoma at the Impella femoral access site (diameter: <4 cm in 2 patients, 4 to 8 cm in

Table 2. Procedural and Outcome Data

Patient #	Age, yrs	Sex	EF	Target Vessel	Lesions Treated (n)	Duration of Support (h)	Pump Flow During PCI (l/min)	Angiographic Success	MACE at 30 Days	Secondary End Points
1	64	F	25	ULM	3	1.5	2.2	Y	MI	—
2	80	M	35	LPC	3	2.4	2.3	Y	—	—
3	80	M	20	ULM	2	2.1	2.0	Y	—	—
4	73	M	26	LPC	3	2.5	2.1	Y	Death (day 14)	—
5	69	M	28	LPC	1	0.7	2.1	Y	—	—
6	64	M	20	ULM	1	0.7	2.1	Y	—	—
7	81	M	18	ULM	2	1.8	2.0	Y	—	—
8	46	F	30	ULM	2	2.3	2.3	Y	—	—
9	36	M	32	ULM	3	1.9	2.3	Y	—	—
10	77	M	29	ULM	4	1.1	2.4	Y	—	Hemolysis
11	66	M	30	LPC	2	0.4	2.4	Y	—	—
12	59	F	32	ULM	3	1.3	2.5	Y	—	Transfusion
13	67	M	27	LPC	2	2.1	1.9	Y	MI	—
14	47	M	24	LPC	3	2.1	2.2	Y	—	VT
15	68	M	15	LPC	2	2.0	2.4	Y	—	—
16	77	M	35	ULM	4	2.1	2.4	Y	—	—
17	70	M	30	ULM	1	2.3	2.6	Y	Death (day 12)	Hemolysis, renal failure, transfusion, VT
18	57	M	34	ULM	3	1.7	2.3	Y	—	—
19	63	M	16	ULM	3	1.6	2.1	Y	—	—
20	79	M	24	ULM	3	1.5	1.5	Y	—	—

— = not applicable; EF = ejection fraction; LPC = last patent conduit; MACE = major adverse cardiac events; MI = myocardial infarction; PCI = percutaneous coronary intervention; Pt = patient; ULM = unprotected left main; VT = ventricular tachycardia; other abbreviations as in Table 1.

Table 3. Hemodynamics With the Impella 2.5 System

	Before Support	On Support	After Support	p Value*
Systolic BP, mm Hg	123.5 ± 23.6	125.3 ± 23.0	110.3 ± 18.1	0.001
Diastolic BP, mm Hg	65.7 ± 11.5	71.8 ± 12.6	59.8 ± 10.3	0.03
Mean arterial pressure, mm Hg	84.5 ± 14.3	89.0 ± 14.8	76.0 ± 11.9	0.004
Heart rate, beats/min	68.1 ± 9.0	70.0 ± 8.5	72.6 ± 8.9	0.1

*Comparing before and after support values.
BP = blood pressure.

3 patients, and unknown in 3 patients). None of the patients required invasive treatment of the hematoma. One patient developed acute-on-chronic renal failure. Two patients had ventricular tachycardia secondary to their underlying cardiac disease (1 patient on day 26 after the procedure; 1 patient on day 14 just prior to death). There were no cases of cardiac perforation, vascular injury, or limb ischemia. No patients developed evidence of neurologic dysfunction during or after Impella support.

Efficacy end points. The primary efficacy end point, freedom from hemodynamic compromise, was observed in all patients (100%). There were no cases of ventricular fibrillation or ventricular tachycardia requiring cardioversion during PCI. Angiographic success was achieved in all patients.

Echocardiographic findings. There was no echocardiographic evidence of injury to the aortic or mitral valves, or LV during or after device use. One patient developed moderate aortic regurgitation during pump support, but this resolved after the device was removed. At 30 days, a follow-up echocardiogram was performed on 16 patients, none of whom had moderate or severe aortic regurgitation. An improvement in EF was observed at 30 days (pre-PCI: EF = 26 ± 6% vs. 30 days post-PCI: EF = 34 ± 11%, p = 0.003).

Discussion

In the present study, we found that use of the Impella 2.5 system was safe and feasible during high-risk PCI in patients with profound LV dysfunction and multiple comorbidities. The Impella 2.5 device was easy to implant, performed well, and was associated with a low rate of adverse events.

Hemodynamic effects of the Impella pump. By continuously aspirating blood from the LV cavity, the Impella pump has been shown to have a direct effect on LV unloading, coronary flow, and overall cardiac output (2,3). Pressure-volume loop recordings demonstrate a reduction in LV end-diastolic pressure and end-diastolic volume during pump activation, which theoretically decreases LV wall tension and myocardial oxygen demand. The Impella pump also has a favorable effect on coronary flow hemodynamics in humans (3). With increasing levels of Impella support, an increase in mean distal coronary pressure (85 ± 11 mm Hg to 94 ± 11 mm Hg, p = 0.001), hyperemic flow velocity (61 ±24 cm/s to 72 ± 27 cm/s, p = 0.001), and coronary flow reserve (1.88 ± 0.52 to 2.34 ± 0.63, p < 0.001) has been observed. Additionally, a significant decrease in the coronary microvascular resistance was seen that was perhaps related to collateral recruitment and the decrease in intramyocardial pressure.

Previous experience with Impella pump. Since its introduction in Europe in 2004, the Impella 2.5 technology has been used in a wide range of clinical settings including, but not limited to, high-risk PCI, cardiogenic shock, acute myocardial infarction, postcardiotomy syndrome, and myocarditis (4–6). Henriques et al. (7) reported use of the Impella 2.5 device in 19 patients during high-risk PCI (63% patients had EF <25%). The Impella system was placed successfully in all patients, and there were no device-related deaths or other serious adverse events. One patient developed a groin hematoma requiring transfusion.

Safety of the Impella device. Because the Impella 2.5 device requires placement across the aortic valve, there are potential risks of injury to the valve or of inducing aortic regurgitation by tenting open the valve leaflets. Detailed echocardiographic evaluation was therefore performed as part of this pilot trial. The Core Laboratory analysis showed no evidence of injury to the valve or significant change in the degree of aortic insufficiency, which is consistent with observations from other clinical studies (7). Nor did we observe any cases of ventricular arrhythmia related to the Impella catheter positioned in the LV cavity. Another potential concern with the Impella system is a risk of hemolysis that may be induced by the high shear stress of the axial pump on red blood cells. In the present study, we observed a small increase in plasma-free hemoglobin in 1 patient during pump use; however, the rise was mild, transient, and did not require treatment. Mild hemolysis has also been observed in other clinical studies but is usually transient and not clinically significant. An early increase may be observed within the first 6 h of support, with a rapid decrease thereafter even if patients are supported for several days. Additionally, the Impella device requires insertion of a

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13-F sheath in the femoral artery, which may be associated with an increased risk of access site bleeding or ischemia. Indeed, we observed hematoma in 8 of the 20 patients enrolled in our study. Although none of these patients required transfusion or vascular repair, we believe alternative strategies, including use of advanced closure techniques, need to be studied in the future to address this issue.

Study limitations. Although we planned to measure cardiac output and right heart hemodynamics at various stages of the PCI procedure, including during balloon occlusion, these data were not available for all patients. Given the brittle nature of the patients, operators employed very short balloon inflations to minimize ischemia, thus precluding adequate time to perform Fick or thermodilution measurements of cardiac output. For the echocardiographic analysis, 4 patients did not have a 30-day follow-up echocardiogram performed, so we cannot completely exclude any late adverse effects of the Impella device on the aortic valve, although this seems unlikely given that there was no evidence of injury on the immediate post-PCI studies.

Conclusions

This study demonstrated that the Impella 2.5 system is safe, easy to use, and provides effective hemodynamic support during high-risk PCI. Based on these data, a pivotal randomized clinical trial is planned to compare the efficacy of prophylactic circulatory support during high-risk PCI with the Impella 2.5 device versus conventional intra-aortic balloon pump counterpulsation.

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Key Words: percutaneous coronary intervention ■ high risk ■ circulatory support.

APPENDIX

For a list of PROTECT I Trial clinical sites and principal investigators, please see the online version of this article.