Cardiac hemodynamics in PCI: effects of ischemia, reperfusion and mechanical support
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Citation for published version (APA):
Remmelink, M. (2009). Cardiac hemodynamics in PCI: effects of ischemia, reperfusion and mechanical support

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Effects of left ventricular unloading by Impella Recover LP2.5 on coronary hemodynamics

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*Catheter Cardiovasc Interv* 2007;70:532-537
Abstract

Objectives. Patients with compromised left ventricular (LV) function undergoing high-risk percutaneous coronary intervention (PCI) may benefit from LV unloading. Limited information is available on the effects of LV unloading on coronary hemodynamics. We studied the effects of LV unloading by the Impella on coronary hemodynamics by simultaneously measuring intracoronary pressure and flow and the derived parameters fractional flow reserve (FFR), coronary flow velocity reserve (CFVR), and coronary microvascular resistance (MR).

Methods. Eleven patients (mean LV ejection fraction of 35±11%) underwent PCI during LV support by the LV unloading device (Impella Recover® LP2.5). Intracoronary measurements were performed in a non-stenotic coronary artery after the PCI, before and after adenosine-induced hyperemia at 4 different support levels (0 to 2.5 L/min).

Results. Aortic and coronary pressure increased with increasing support levels, whereas FFR remained unchanged. Baseline flow velocity remained unchanged, while hyperemic flow velocity and CFVR increased significantly with increasing support levels (61±24 to 72±27 cm/s, p=0.001 and 1.88±0.52 to 2.34±0.63, p<0.001 respectively). The difference between baseline MR and hyperemic MR significantly increased with increasing support levels (1.28±1.32 to 1.89±1.43 mm Hg·cm⁻¹·s, p=0.005).

Conclusions. Unloading of the LV by the Impella increased aortic and intracoronary pressure, hyperemic flow velocity and CFVR, and decreased microvascular resistance. The Impella-induced increase in coronary flow, probably results from both an increased perfusion pressure and a decreased LV volume-related intramyocardial resistance.
Introduction

High-risk percutaneous coronary intervention (PCI) may be facilitated by the use of left ventricle (LV) support devices. A novel device is the Impella Recover® LP2.5 (Impella), which directly unloads the LV and generates an increase in total cardiac output, by continuously aspirating blood from the LV cavity and expelling it into the ascending aorta. Recently, we reported its clinical safety and feasibility in high-risk PCI patients. However, little is known about the effects of LV unloading on coronary hemodynamics. We hypothesized that the enhanced Impella-driven blood flow over the aortic valve would increase coronary perfusion pressure, as well as that the Impella-induced unloading of the LV would decrease coronary blood flow resistance. Combined pressure and flow measurements in PCI have been shown to be useful to evaluate coronary hemodynamics including assessment of microvascular resistance. Therefore, we studied, for the first time, the effects of LV unloading by the Impella on coronary hemodynamics by simultaneously measuring intracoronary pressure and flow, and their derived parameters fractional flow reserve, coronary flow velocity reserve, and coronary microvascular resistance.

Methods

Patients

The study population consisted of 11 consecutive patients (7 males, mean age 67±9 years) with stable angina, who underwent an elective high-risk PCI with circulatory support by the Impella. Patients were included if the planned PCI was considered high-risk on the basis of a poor LV function combined with left main coronary artery, last remaining vessel or equivalent PCI procedure. All patients had a decreased LV function (ejection fraction 35±11%), as determined by echocardiography or nuclear scintigraphy. Exclusion criteria were severe valvular disease and left ventricular thrombus, as assessed by echocardiography before the procedure. The study complied with the Declaration of Helsinki and was approved by the institutional research and ethics committee. All subjects gave written informed consent.

Cardiac Catheterization and Cardiac Support

All patients were pretreated with aspirin (100 mg), clopidogrel (300 mg) and received a bolus of heparin (5000 IU IV) before the PCI. The Impella Recover® LP2.5 (Impella Cardiotechnik, Aachen, Germany), a pigtail catheter-based microaxial flow device (catheter: 4 mm, 12 Fr outer diameter), was inserted retrogradely into the LV across the aortic valve via the femoral artery through a 13 Fr sheath. The Impella continuously aspirates blood from the cannula’s inlet in the apex of the LV cavity and expels it into
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the ascending aorta just above the aortic valve /near the coronary ostia. It has 9 support
levels, producing a flow up to 2.5 L/min (50,000 rpm). The differential pressure sensor at
the tip of the cannula allows proper positioning of the pump and continuously registers
the intracavitory and aortic blood pressure to derive pump flow and control its rotational
speed, which is displayed on the mobile driving console. After insertion of the Impella,
PCI was performed following routine procedures. Additional heparin was given every 60
minutes.

Hemodynamic Measurements

Hemodynamic measurements were performed in an angiographic non-stenotic vessel
(left anterior descending or circumflex artery) after completion of the PCI procedure, and
administration of intracoronary nitroglycerin (0.1 mg). In case of a last remaining vessel,
measurements were performed in the stented vessel (n=3). Intracoronary pressure and
flow signals were simultaneously recorded using the 0.014 inch diameter WaveWire® and
FloWire® (Volcano Corporation, Rancho Cordova, CA, USA). Heart rate was monitored
and aortic pressure was measured via the 6F guiding catheter. At four different support
levels of the Impella (ranging from 0 L/min at level 1 to 2.5 L/min at level 9), pressure
and flow measurements were performed at baseline and during maximal hyperemia.
Hyperemia was induced by an intracoronary bolus of adenosine (30 to 40 µg). From the
pressure and flow signals at hyperemia, both pressure-derived myocardial fractional flow
reserve (FFR= mean distal coronary pressure/ mean aortic pressure) and Doppler-derived
coronary flow velocity reserve (CFVR= coronary flow velocity at maximum hyperemia/
coronary flow velocity at rest) were assessed.5, 7-11

Data Analysis

Mean aortic pressure (Pa), mean distal coronary pressure (Pd), instantaneous flow velocity
and the ECG were digitally recorded on a personal computer after 12-bit analog-to-
digital conversion at 120 Hz for off line analysis. Per-beat averages of the recorded Pd, Pd
and instantaneous flow velocity were calculated (StudentLab Pro 3.6.2, Biopac Systems).
Baseline average peak flow velocity (APV) was defined as the average of 8 consecutive
per-beat velocity averages. Hyperemic APV was defined as the highest average of 3
consecutive per-beat velocity averages after adenosine administration. By using distal
pressure and flow velocity during hyperemic conditions, the hyperemic microvascular
resistance (MR) index can be calculated as MR= Pd/APV.8, 9, 12 The variable arteriolar
resistance index, which represents autoregulatory function, was expressed as baseline
MR minus hyperemic MR.13, 14

Statistical Analysis

Data are expressed as mean ± SD or n (%). Hemodynamic measurements at different
support levels of the Impella were compared with the situation of no support and with
the previous support level using the within subjects variance component of ANOVA with repeated measures, followed by linear contrast analysis. SPSS release 12.0.2 statistical software package for windows (SPSS Inc. 2003, Chicago, Illinois) was used for analyses. A p-value of less than 0.05 was considered statistically significant.

Results

Patient Characteristics

The baseline characteristics of the 11 patients are shown in Table 1. All patients had moderate to severe anginal complaints, 2 patients had Canadian Cardiovascular Society

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n = 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, &gt;65 y</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Male</td>
<td>7 (64)</td>
</tr>
<tr>
<td>Coronary risk factors</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (36)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>7 (64)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>7 (64)</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>5 (45)</td>
</tr>
<tr>
<td>Prior MI</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
</tr>
<tr>
<td>ß-blockers</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>7 (64)</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>2 (18)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>10 (91)</td>
</tr>
<tr>
<td>Statins</td>
<td>9 (82)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Target lesion</td>
<td></td>
</tr>
<tr>
<td>LM</td>
<td>1 (7)</td>
</tr>
<tr>
<td>LAD</td>
<td>8 (57)</td>
</tr>
<tr>
<td>LCx</td>
<td>5 (36)</td>
</tr>
<tr>
<td>Physiologic parameters</td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>70 ± 14</td>
</tr>
<tr>
<td>Mean systolic blood pressure (mm Hg)</td>
<td>125 ± 25</td>
</tr>
<tr>
<td>Mean diastolic blood pressure (mm Hg)</td>
<td>65 ± 15</td>
</tr>
<tr>
<td>Left Ventricular Ejection Fraction</td>
<td>35 ± 11</td>
</tr>
</tbody>
</table>

Values are n (%) or mean ± SD. CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; LM, left main coronary artery; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery.
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Classification class II, 7 patients class III, and 2 patients class IV. The 14 target lesions were located in the left main coronary artery (n=1), left anterior descending coronary artery (n=8), and the left circumflex coronary artery (n=5).

Hemodynamic Data
In Table 2 the hemodynamic data during baseline and hyperemic conditions are listed for different support levels of the Impella. The $P_a$ and $P_d$ increased significantly at baseline and during hyperemia, predominantly during the increase up to support level 6. Increases in these mean pressures resulted from increased systolic and diastolic pressures. FFR did not change indicating that hemodynamic measurements were not influenced by a coronary stenosis and were solely induced by the Impella support. Heart rate did not change (data not shown). Baseline APV did not increase, whereas the hyperemic APV increased significantly with increasing support levels, which resulted in the enhanced CFVR. In accordance to the pressure measurements both diastolic as well as systolic flow velocity increased. The baseline MR did not change significantly, whereas the hyperemic MR showed a non significant decrease with increasing support levels. The variable arteriolar resistance (baseline MR minus hyperemic MR) significantly increased with increasing support levels. The $P_{d}$, coronary flow velocity and MR changes are illustrated in Figure 1.

Table 2. Hemodynamic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Impella' support level</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Baseline $P_a$</td>
<td>85 ± 11</td>
<td>93 ± 13</td>
</tr>
<tr>
<td>Baseline $P_d$</td>
<td>85 ± 11</td>
<td>92 ± 13</td>
</tr>
<tr>
<td>Hyperemic $P_a$</td>
<td>85 ± 12</td>
<td>91 ± 15</td>
</tr>
<tr>
<td>Hyperemic $P_d$</td>
<td>81 ± 12</td>
<td>86 ± 16</td>
</tr>
<tr>
<td>FFR</td>
<td>0.97 ± 0.03</td>
<td>0.96 ± 0.04</td>
</tr>
<tr>
<td>Baseline APV</td>
<td>33 ± 11</td>
<td>34 ± 12</td>
</tr>
<tr>
<td>Hyperemic APV</td>
<td>61 ± 24</td>
<td>67 ± 26</td>
</tr>
<tr>
<td>CFVR</td>
<td>1.88 ± 0.52</td>
<td>2.10 ± 0.62</td>
</tr>
<tr>
<td>Baseline MR</td>
<td>2.99 ± 1.79</td>
<td>3.23 ± 1.96</td>
</tr>
<tr>
<td>Hyperemic MR</td>
<td>1.71 ± 0.93</td>
<td>1.64 ± 0.82</td>
</tr>
<tr>
<td>$\Delta MR$</td>
<td>1.28 ± 1.32</td>
<td>1.58 ± 1.52</td>
</tr>
</tbody>
</table>

Values are mean ± SD. Pa, mean aortic pressure (mm Hg); Pd, mean distal coronary pressure (mm Hg); FFR, fractional flow reserve; CFVR, coronary flow velocity reserve; APV, average peak flow velocity (cm/s); MR, coronary microvascular resistance index (mm Hg·cm$^{-1}$·s$^{-1}$); $\Delta$MR, variable arteriolar resistance index (mm Hg·cm$^{-1}$·s$^{-1}$).
In this study, we demonstrated positive effects of direct LV unloading on coronary hemodynamics in patients with decreased LV function. Increasing the support level of the Impella resulted in an increase in aortic and coronary perfusion pressure, both in resting conditions and during hyperemia. Furthermore, an increase in hyperemic coronary flow velocity and CFVR, as well as a decrease in microvascular resistance during hyperemia, was induced by increasing Impella support levels.

The Effect of Impella on Coronary Hemodynamics

Positive effects on aortic pressure may be expected because of the mechanism of the Impella, i.e. it expels blood from the LV into the aorta, thereby producing an increase in cardiac output. Our findings are supported by other studies, where the Impella increased aortic pressure and decreased LV end-diastolic pressure in an animal model, and in a case report of a patient in postcardiotomy heart failure. Moreover, by our intracoronary measurements we found a concomitant increase in coronary pressure.

Figure 1. Effects of different Impella support levels during baseline and hyperemia on distal coronary pressure (A), coronary flow velocity (B), and coronary microvascular resistance (MR) (C). Data are shown as mean ± SD, *P=0.001, †P=0.02, ‡P=0.005 (variable arteriolar resistance).

Discussion

In this study, we demonstrated positive effects of direct LV unloading on coronary hemodynamics in patients with decreased LV function. Increasing the support level of the Impella resulted in an increase in aortic and coronary perfusion pressure, both in resting conditions and during hyperemia. Furthermore, an increase in hyperemic coronary flow velocity and CFVR, as well as a decrease in microvascular resistance during hyperemia, was induced by increasing Impella support levels.
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The positive effects of the Impella on hyperemic flow velocity and CFVR were clearly shown in our study. These findings indicate that the high velocity ejection of blood from the Impella outflow tract adjacent to the coronary ostia certainly does not negatively influence coronary hemodynamics. It is noteworthy that we observed a baseline flow velocity that was approximately twice as high as usual in coronary arteries. Even so, in these patients the CFVR of 2.34±0.63 at maximal Impella support indicate quite a remaining flow reserve. This relatively high baseline flow velocity is probably due to autoregulation in patients with a decreased LV function, to meet the higher myocardial oxygen demand.

From the combined simultaneously measured intracoronary pressure and flow velocity, we calculated coronary microvascular resistance, which decreased during hyperemia. We found a significantly increased variable arteriolar resistance (baseline MR minus hyperemic MR), with increasing support levels.

The changes in coronary perfusion pressure, flow velocity and variable arteriolar resistance correlated with the degree of Impella support. The decrease in resistance may be secondary to two distinct mechanisms: 1) The Impella generates a continuous and enhanced flow over the aortic valve, which increases total cardiac output. This results in an increased aortic and coronary perfusion pressure. The latter may decrease coronary microvascular resistance by passively recruiting collapsed collateral arterioles, thus reducing resistance to flow. This is in line with a study where coronary microvascular resistance was assessed after restoration of coronary pressure by PCI. 2) The Impella reduces volume from the LV, reducing intramyocardial pressure, thereby reducing compression of the microvasculature, enlarging its lumen diameter, thus reducing resistance to flow. In line with this theory it was shown that LV elastance and LV volume, rather than LV pressure, influenced coronary blood flow. Most likely a combination of both of the above mechanisms is responsible for the observed reduction in microvascular resistance.

We found no Impella support related change in heart rate. If anything, a decrease in heart rate at increasing support levels would be expected, since the Impella enhances cardiac output. However, most patients were treated with beta-blockers and underwent the PCI under stable conditions.

Comparison of LV Support Devices

Currently there are a few types of continuous non-pulsatile axial flow devices clinically available apart from the percutaneous implanted Impella. These surgically implanted devices (e.g. HeartMate II, Jarvik 2000 and MicroMed DeBakey VAD) directly unload the LV (up to 6-10 L/min depending on the device) via implantation into the apex, bypassing the aortic valve with the outflow graft anastomosed to the ascending or descending aorta. There is however very limited data on coronary perfusion; in 1 study patient an increased coronary blood flow was measured with the Jarvik 2000 anostomosed to the ascending aorta. The intra-aortic balloon counterpulsation (IABP)
has been shown to reduce cardiac work by reducing afterload and to enhance coronary perfusion by increasing diastolic aortic pressure.\textsuperscript{2, 26–31} In animals, the Impella showed more effective LV unloading than the IABP, while the effects on coronary flow were similar.\textsuperscript{2} In line with the above data, our data show that in humans with reduced LV function the Impella causes an increase in aortic and coronary pressure and an Impella support-related decrease in coronary microvascular resistance.

Limitations
There are a few limitations of our study with respect to the interpretation of the data. We did not measure myocardial oxygen consumption and lactate metabolism to determine whether the Impella support decreases myocardial metabolic demand. Central venous pressure was not measured to assess possible collateral flow, and no direct intracavitary hemodynamics of the LV was obtained. Furthermore, our measurements were performed during short duration of Impella support and immediately after the PCI procedure. Whether long periods of Impella support and long term effects of PCI will influence the data is unknown. Lastly, these results may only reflect changes in poor LV patients, who are however the patients that may benefit from LV support.

Clinical Implications
The present study is the first to show the effects of directly unloading the LV on coronary circulation by the LV assist device Impella in angioplasty. Whether PCI patients will benefit from the above mentioned positive hemodynamic effects of the Impella remains to be determined, however, we have shown that no adverse effects on coronary hemodynamics occur.

Conclusions
Unloading of the LV by the left ventricular support device Impella caused an increase in aortic and intracoronary perfusion pressure, hyperemic flow velocity and CFVR, and a decrease in microvascular resistance. We conclude that the Impella-induced increase in coronary flow probably results from both an increased perfusion pressure and a decreased LV volume-related intramyocardial resistance.

Acknowledgments
The authors acknowledge our nursing staff of the cardiac catheterization laboratory for their skilled assistance (head, M.G.H. Meesterman, RN).
References


