Novel insights into the complexity of ischaemic heart disease derived from combined coronary pressure and flow velocity measurements
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Chapter 13

Intracoronary hemodynamic effects of pressure-controlled intermittent coronary sinus occlusion (PICS0): results from the first-in-man prepare PICS0 study


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Abstract

Background
Myocardial reperfusion is frequently suboptimal after ST-segment elevation myocardial infarction (STEMI) treated by primary percutaneous coronary intervention (PCI). Using a balloon-tipped catheter positioned in the coronary sinus (CS), pressure-controlled intermittent coronary sinus occlusion (PICSO) results in an intermittent obstruction of coronary venous outflow of the left anterior descending artery (LAD), and may improve myocardial perfusion by augmenting redistribution of blood to the border zone of ischemic myocardium. We sought to document the intracoronary hemodynamic effects of PICSO during PCI.

Methods
We included 15 patients with stable angina scheduled for PCI of the LAD. Balloon occlusion of the LAD was performed twice, once with and once without PICSO and lasting maximally 3 minutes each, to document the effect of PICSO on CS pressure and LAD wedge pressure.

Results
Catheter delivery was successful in all patients. The study protocol could not be conducted in 5 patients due to initial calibration difficulties (n=3), a pressure wire problem (n=1), and a vagal response at the start of the procedure (n=1). In the remaining 10 patients, CS occlusion caused a marked increase in mean CS pressure (4.1±7.3 mmHg vs. 22.0±12.6 mmHg; P<0.001) and CS pulse pressure (4.3±0.8 mmHg vs. 36.1±6.3 mmHg; P<0.001). Concomitantly, mean distal LAD wedge pressure and wedge pulse pressure increased (32.4±12.2 mmHg vs. 35.5±12.6 mmHg; P<0.001 and 39.1±27.2 mmHg vs. 45.9±26.0 mmHg; P<0.001, respectively). At 30 day follow-up, no device-related events occurred.

Conclusions
PICSO safely augments CS pressure, thereby increasing LAD coronary wedge pressure. These findings support further evaluation of PICSO in the setting of STEMI.
INTRODUCTION

Contemporary reperfusion therapy in the setting of ST-segment elevation myocardial infarction (STEMI) aims at early restoration of blood flow in the culprit coronary artery by means of primary percutaneous coronary intervention (PCI).\textsuperscript{1} Despite a high success-rate in restoration of epicardial blood flow by primary PCI, perfusion at the myocardial level is frequently hampered although optimal epicardial reperfusion is achieved.\textsuperscript{2-5} Impaired myocardial reperfusion is considered a consequence of multiple factors,\textsuperscript{6,7} and is suboptimal in approximately 40\% of patients after primary PCI for STEMI. It is associated with higher mortality, larger infarct size and reduced left ventricular function at follow up,\textsuperscript{2-4,8} and reversal of this phenomenon was shown to be associated with a favourable effect on left ventricular remodelling, even without apparent improvement in regional contractile function.\textsuperscript{9,10} Myocardial reperfusion, as well as its improvement during follow-up, is therefore an important determinant of clinical outcome after primary PCI for STEMI,\textsuperscript{11,12} and its optimization is considered a target to improve clinical outcomes.

Pressure-controlled intermittent coronary sinus occlusion (PICS\textsuperscript{O\textregistered}) is a novel concept, which aims to improve perfusion at the microvascular level. The PICS\textsuperscript{O\textregistered} Impulse System (Miracor Medical Systems GmbH, Vienna, Austria) consists of the PICS\textsuperscript{O\textregistered} Impulse catheter (Figure 1), which is delivered into the coronary sinus (CS) over-the-wire, and is controlled by the PICS\textsuperscript{O\textregistered} Impulse console. Using the balloon-tipped Impulse catheter, the CS is intermittently occluded based on the pressure plateau reached in the CS.

Figure 1 | PICS\textsuperscript{O\textregistered} Impulse catheter. A low-profile dedicated balloon on the distal end of a flexible hypotube catheter, which inflates and deflates automatically based on proprietary measurements of the coronary sinus pressure and the patient’s ECG signal. The catheter contains a fluid-filled line through which the coronary sinus pressure is continuously measured.
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The mechanism of PICSO in STEMI is based on the following three concepts. First, PICSO results in improvement of myocardial perfusion by redistribution of blood from the venous outflow tract of the left anterior descending (LAD) coronary artery to the border zone of the ischemic anterior wall myocardium.\textsuperscript{13,14} Second, the periodic increase in pressure resulting from PICSO is transferred onto the venous endothelium, which may improve long term outcome due to the release of vascular growth factors.\textsuperscript{15-17} Third, the intermittent release of pressure is expected to facilitate washout of deleterious agents from the microcirculation.\textsuperscript{18} In contrast to other retroperfusion techniques,\textsuperscript{19-22} the retroperfusion by PICSO is passive of nature. Moreover, the technique claims that not only redistribution of venous flow, and the facilitation of microvascular washout, but also activation of the venous vasculature is an important denominator of its beneficial effects.\textsuperscript{16,23} A meta-analysis of 7 animal studies evaluating the effect of PICSO on infarct size showed a significant reduction in infarct size in the treatment group compared with the placebo group (mean infarct size 48.7\%, and 78.8\% respectively, weighted mean difference -29.3\%; 95\% confidence interval -40.9\% to -11.7\%; P<0001).\textsuperscript{24}

The essential mechanism of action of PICSO is based upon an intermittent increase of pressure in the CS to a plateau pressure that is transmitted to the microcirculation of the LAD. In the presence of LAD occlusion, and in the absence of microvascular obstruction, this pressure increase will be transmitted to the distal coronary artery, augmenting distal coronary wedge pressure.\textsuperscript{14,25} To document this key intracoronary hemodynamic change induced by PICSO, this first-in-man study evaluated the direct effect of balloon occlusion of the coronary sinus on intracoronary pressure parameters distal to an LAD occlusion during elective PCI.

**METHODS**

**Study oversight**

The Prepare PICSO study was a non-randomized single center study to evaluate the direct effect of balloon occlusion of the coronary sinus on intracoronary hemodynamic parameters in presence of LAD occlusion during elective PCI. The study was funded by a research grant from Miracor Medical Systems. The protocol was designed by Investigators from the Academic Medical Center, Amsterdam, The Netherlands, in collaboration with the Sponsor. Data management was coordinated by the Academic Medical Center, and all data were independently monitored by MedPass (Paris, France). Statistical analyses were performed by the Investigators. The study was approved by the institutional ethics review board of the Academic Medical Center, Amsterdam.
Patient population
A total of 15 consecutive patients of at least 18 years of age with stable coronary artery disease, scheduled for elective PCI of the LAD were prospectively selected. We excluded patients with severely impaired left ventricular function (left ventricular ejection fraction <35%), significant valvular abnormalities, severe anemia at screening (hemoglobin <10g/dL or <6.2 mmol/L), severe renal function impairment (estimated glomerular filtration rate <30mL/min/1.73m²), acute myocardial infarction within 72 hours, history of coronary artery bypass graft surgery, history of stroke or transient ischemic attack within 6 months prior to screening, or the presence of pacemaker- or other electrodes in the CS. Furthermore, we excluded patients with cardiac arrhythmias or conduction disorders on routine electrocardiography.

Study procedures
After successful left coronary artery catheterization, the anatomy of the CS was visualized by fluoroscopic evaluation of the venous return phase of a standard coronary angiogram. Subsequently, the PICSO Impulse catheter was introduced into the ostium of the CS, using the right femoral venous route and a 9 French (inner diameter) steerable sheath (Channel Steerable Sheath, C.R. Bard Inc., New Jersey, USA). Wiring of the CS was then performed, followed by over-the-wire delivery of the catheter. After secure positioning of the Impulse catheter was achieved, the guide wire was removed and the steerable sheath was retracted into the right atrium for support (Figure 2 A/B). A 0.014” pressure sensor equipped guide wire (ComboWire®, Volcano Corp., San Diego, USA) was then introduced into the LAD, over which a standard PCI balloon was introduced.

Figure 2 | Coronary sinus catheterization. A) Positioning of the PICSO Impulse catheter. The guiding sheath is in the right atrium for support. B) PICSO Impulse catheter balloon inflated during low pressure balloon occlusion of the LAD.
Patients underwent two low pressure LAD balloon occlusions, lasting a maximum of 3 minutes each or until the occurrence of subjective severe angina. Complete occlusion of the LAD was verified by angiography. LAD occlusion was performed once with PICSO and once without PICSO. PICSO in concert with the LAD inflation/deflation cycle was continued until a total of 10 minutes of PICSO treatment was provided (Figure 3). CS pressure was measured continuously through the PICSO Impulse catheter, and intra-coronary pressure was measured continuously with the sensor-equipped guide wire. All hemodynamic information was recorded simultaneously on the PICSO Impulse console. A 12-lead surface ECG was monitored continuously and recorded every minute during LAD occlusion for evaluation of the ST-segment deviation score. After completion of the study procedure, PCI of the target lesion was completed according to standard of care.

Initially, PICSO was provided during the second LAD occlusion. After documentation of a clear difference in ST-segment deviation between the LAD occlusion with, and the LAD occlusion without PICSO in the first six patients, the order was reversed in the final 4 patients (Figure 3) to discriminate the effect of PICSO from the effect of sequential coronary artery balloon occlusions on ST-segment deviation (and to correct for any effect of post-conditioning).

Follow up for adverse events was performed prior to hospital discharge and at 30 days after the procedure by means of a telephone survey.

**Figure 3** | Study protocol timings. Patients underwent two left anterior descending coronary artery (LAD) occlusions; one with and one without PICSO. After relief of the LAD occlusion, the concomitantly initiated PICSO-treatment was continued until 10 minutes of PICSO was provided in total. In patient 1 to 6, LAD occlusion was performed without PICSO first, followed by the LAD occlusion with PICSO (top panel). This order was reversed in the subsequent patients (bottom panel).

**Data analysis**

Changes in distal LAD wedge pressure were evaluated during LAD occlusion both with and without PICSO after adjustment for the baseline wedge pressure. Furthermore, to appropriately address the pulsatile nature of the technique, we evaluated the direct effect of balloon occlusion of the coronary sinus on LAD wedge pressure by comparing the
coronary sinus occlusion phase (inflated PICSO Impulse balloon) with the non-occlusion phase (deflated PICSO Impulse balloon) during the LAD occlusion with PICSO. We evaluated both differences in mean pressure, as well as pulse pressure, defined as the increase in pressure from diastole to systole per heartbeat. All analyses were performed based on per beat averages of the hemodynamic data, which were extracted using Acknowledge software for Windows version 4.1 (Biopac Systems, Inc, Goleta, USA).

Data are presented as mean (± standard deviation), frequency (percentage) or median (25th – 75th percentile). Standard crossover analysis was performed for the ECG deviation score, which was defined as the sum of ST-segment deviation on a standard 12-lead surface ECG, to evaluate the presence of a period effect or treatment-period interaction. A paired student t-test was used to test for differences between groups. Correlation between parameters was tested using Pearson’s correlation coefficient. A two-sided alpha level of 0.05 was considered statistically significant.

RESULTS

Patients and procedural characteristics
A total of 15 patients (mean age: 62±7 years) with stable angina pectoris were included in the study. CS catheterization and delivery of the PICSO Impulse catheter was successful in all patients. Median duration from insertion of the steerable sheath until successful delivery of the PICSO Impulse catheter into the CS was 12 minutes (IQR: 9-18 minutes).

Initial console calibration difficulties occurred in the first 3 patients, precluding conduction of the study protocol. Additionally, the study protocol was not completed in 2 patients, one because of a vagal response at the start of the procedure, and another in whom the pressure sensor guide wire could not be positioned in the distal LAD. These 5 patients were excluded from hemodynamic analysis. Therefore, the study population consisted of 10 patients. Baseline characteristics of all patients are shown in Table 1. Optimal positioning of the PICSO Impulse catheter, enabling adequate elevation of the coronary sinus pressure, was achieved in all 10 study patients.

Hemodynamic impact of PICSO
Figure 4 shows a typical recording of aortic pressure, distal LAD wedge pressure and CS pressure during a low pressure balloon occlusion of the LAD without (Figure 4A) and with PICSO (Figure 4B). Concomitant intermittent occlusion of the CS resulted in an intermittent obstruction of venous outflow, which increased the CS pressure. As highlighted in Figure 5, this pressure increase in the coronary venous system due to PICSO correlated with a simultaneous increase in distal LAD wedge pressure.
Initial wedge pressures were not significantly different between the two LAD occlusions (31±14 mmHg without PICSO versus 29±13 mmHg with PICSO; P=0.34). The difference in mean LAD wedge pressure compared to the baseline wedge pressure was higher during LAD occlusion with PICSO than without PICSO (2±4 mmHg without PICSO versus 5±4 mmHg with PICSO; P<0.001).

Subsequently, we compared the occlusion phase of PICSO (inflated balloon) with the non-occlusion phase (deflated balloon) to evaluate the pulsatile nature of PICSO. Table 2 shows the absolute values of CS pressure and distal LAD wedge pressure during LAD occlusion with PICSO than without PICSO (2±4 mmHg without PICSO versus 5±4 mmHg with PICSO; P<0.001).

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<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>All patients (n=15)</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Age, yrs</td>
<td>62±7</td>
</tr>
<tr>
<td>Male sex</td>
<td>10 (67)</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>5 (33)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (73)</td>
</tr>
<tr>
<td>Positive family history</td>
<td>8 (53)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>7 (47)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>5 (33)</td>
</tr>
<tr>
<td>Prior coronary intervention</td>
<td>1 (7)</td>
</tr>
<tr>
<td><strong>Medication</strong></td>
<td></td>
</tr>
<tr>
<td>B-Blockers</td>
<td>12 (80)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>4 (27)</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Lipid-lowering drugs</td>
<td>13 (87)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>14 (93)</td>
</tr>
</tbody>
</table>

Data presented as mean±SD or n(%)

Notably, the increase in mean and pulse pressure in the CS was enhanced in those patients with a high initial coronary wedge pressure; high coronary wedge pressures correlated with a high increase in CS pressure during CS occlusion (r 0.806; p=0.005). Furthermore, the mean CS pressure, averaged over 2 PICSO cycles, increased significantly
after LAD balloon deflation (22.3±5.6 mmHg with LAD occluded versus 26.9±6.8 mmHg with LAD not occluded; P=0.003).

![Hemodynamic measurements during a low pressure balloon occlusion in the left anterior descending artery (LAD). A) LAD occlusion without PICSO. B) LAD occlusion with PICSO. Of note: the coronary sinus pressure plateau is higher when the LAD occlusion has ended.](image)

**Figure 4**

*Myocardial ischemia: ST-segment deviation score*

No period effect or treatment-period interaction in ST-segment deviation was found (p=0.34 and p=0.35 respectively). When PICSO was performed during the first LAD oc-
clusion, ST-segment deviation was similar to the second LAD occlusion without PICSO (Table 3). When the order was reversed, and PICSO was provided during the second LAD occlusion, ST-segment deviation was numerically lower during the LAD occlusion with PICSO, but the difference did not reach statistical significance. Overall, electrocardiographic measures of ischemia during LAD occlusion with PICSO were numerically lower when compared to the LAD occlusion without PICSO, but did not reach statistical significance (13±6 mm versus 11±6 mm; P=0.26).

Table 2 | Hemodynamic effects of coronary sinus occlusion during LAD occlusion

<table>
<thead>
<tr>
<th>Hemodynamic Effects</th>
<th>Patent</th>
<th>Occluded</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary Sinus</td>
<td>5±5</td>
<td>22±5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAD wedge</td>
<td>32±13</td>
<td>35±13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse Pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary Sinus</td>
<td>4±1</td>
<td>36±6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAD Wedge</td>
<td>39±27</td>
<td>46±26</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data presented as mean±standard deviation.

Table 3 | ST-segment deviation scores

<table>
<thead>
<tr>
<th>ST-segment deviation scores</th>
<th>LAD occlusion</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First</td>
<td>Second</td>
</tr>
<tr>
<td>PICSO during first occlusion (mm)</td>
<td>10±6</td>
<td>10±6</td>
</tr>
<tr>
<td>PICSO during second occlusion (mm)</td>
<td>15±6</td>
<td>11±6</td>
</tr>
</tbody>
</table>

Data presented as mean±standard deviation.

Follow-up

No coronary sinus perforation, dissection or thrombosis occurred. Two adverse events occurred during 30-day follow-up. A periprocedural myocardial infarction developed in 1 patient from compromise of a small diagonal sidebranch after LAD stent implantation performed after PICSO. The second patient required repeat revascularization of a non-target vessel because of residual angina. No other adverse events were observed during the follow-up period.

DISCUSSION

In this first-in-man study, we have demonstrated that the PICSO catheter can be introduced into the coronary sinus, and PICSO treatment can be provided without the occur-
Intracoronary hemodynamic effects of PICSO

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rence of device-specific adverse events during an elective PCI procedure. PICSO resulted in an immediate increase in CS mean and pulse pressure, which resulted in an increase in distal LAD wedge pressure and wedge pulse pressure. These effects on intracoronary hemodynamics support a potential benefit of PICSO in STEMI, and are concordant with previous findings.\textsuperscript{13-15,18,24} These results therefore justify further evaluation of this novel technique in patients with acute LAD occlusion and STEMI.

Hemodynamic effect of PICSO

In this study, we have documented that PICSO results in an increase in pressure in the LAD venous outflow tract, resulting in a significant, although modest, increase in coronary wedge pressure. When the CS is occluded in the presence of an LAD occlusion, the pressure build up in the venous outflow tract depends on the inflow of blood through either venous connections proximal to the point of occlusion in the coronary sinus, or collateral connections on the arterial side. The correlation between high baseline wedge pressure and LAD wedge pressure results in a simultaneous increase in distal LAD pressure.

Figure 5 | Coronary sinus and LAD wedge pressure measurements. Elevation of coronary sinus pressure results in a simultaneous increase in distal LAD pressure.

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\textsuperscript{13-15,18,24} These results therefore justify further evaluation of this novel technique in patients with acute LAD occlusion and STEMI.
pressure and the increase in CS pressure suggests an inflow-dependency of the rise in CS pressure. The significant increase in mean CS pressure observed after opening of the LAD also supports the inflow-dependency of CS pressure during PICSO (Figure 3). PICSO was capable of intermittently increasing coronary sinus pressure to a plateau pressure, the level of which is dependent on the magnitude of inflow, and resulted in an increase in LAD wedge pressure, suggesting redistribution of blood from the venous outflow tract into the microcirculation of the culprit coronary artery, although blood flow was not measured directly. These findings are consistent with the anticipated protective mechanism of PICSO in STEMI, which relies on this redistribution\textsuperscript{14} in order to reduce infarct extension, and facilitate washout of harmful agents via the periodic obstruction of venous outflow with subsequent release of pressure.\textsuperscript{18} The periodic increase in pressure transferred onto the venous endothelium may also improve long-term outcomes due to stimulating release of vascular growth factors.\textsuperscript{15-17}

**Myocardial ischemia**

One of the anticipated effects of PICSO is protection from myocardial ischemia. It is important to note that myocardial ischemia is expected to be attenuated during sequential coronary occlusions, as performed in this study.\textsuperscript{26} Thus, in cases in which PICSO was established during the second LAD occlusion, PICSO would be expected to result in a more pronounced reduction of ST-segment deviation, but the effect of PICSO cannot be differentiated from an attenuation effect. Conversely, when PICSO was established during the first LAD occlusion, the reduction in ST-segment deviation from PICSO compared to the second (non-PICSO aided) LAD occlusion would be expected to be diminished.

In the present study, when PICSO was performed during the first LAD occlusion, no difference between ST-segment deviation scores was found, which suggests that PICSO may have provided protection from myocardial ischemia. This finding is supported by the fact that in those patients where the first LAD occlusion was performed without PICSO, ST-segment deviation was 50% higher compared with the patients where the first LAD occlusion was performed with PICSO (Table 3). Furthermore, when PICSO was performed during the second LAD occlusion, ST-segment deviation was numerically lower than with the first LAD occlusion without PICSO, although an attenuation effect cannot be excluded in this case. Overall, no statistically significant differences in ST-segment deviation scores between the LAD occlusion with and without PICSO was found in this small study population, and thus larger studies with a randomized balloon inflation crossover design are required to determine the extent to which PICSO modulates ischemia.

**Limitations**

This study was performed to evaluate the immediate hemodynamic effects of PICSO in a stable patient population. The small study population limits further evaluation. The
findings on myocardial ischemia are illustrative and qualitative in nature, but the study lacks statistical power to draw more definite conclusions. However, the hemodynamic effect demonstrates the underlying mechanism for protection from myocardial ischemia, as well as an increased washout effect, and a periodic pressure increase in the venous system, which in our judgement justifies further evaluation of this novel technique in the setting of STEMI.

CONCLUSIONS

The results from this first-in-man study show that introduction of the PICSO Impulse catheter can be performed in a timely manner using the femoral venous route, and that PICSO can be performed without the occurrence of adverse events during elective PCI. PICSO intermittently increases CS pressure, translating into an increase in distal coronary wedge pressure. These findings support the hypothesized mechanism of PICSO, and are concordant with the results from previous experimental studies. These results therefore provide the basis for further research to determine the potential protective benefits of PICSO in patients with STEMI undergoing primary PCI, as well as its effect on long-term clinical outcomes.
REFERENCES


