Myocardial blood volume and coronary resistance during and after coronary angioplasty

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Indermühle A, Vogel R, Meier P, Zbinden R, Seiler C. Myocardial blood volume and coronary resistance during and after coronary angioplasty. Am J Physiol Heart Circ Physiol 300: H1119–H1124, 2011. First published January 7, 2011; doi:10.1152/ajpheart.01022.2010.—Animal experiments have shown that the coronary circulation is pressure distensible, i.e., myocardial blood volume (MBV) increases with perfusion pressure. In humans, however, corresponding measurements are lacking so far. We sought to quantify parameters reflecting coronary distensibility such as MBV and coronary resistance (CR) during and after coronary angioplasty. Thirty patients with stable coronary artery disease underwent simultaneous coronary perfusion pressure assessment and myocardial contrast echocardiography (MCE) of 37 coronary arteries and their territories during and after angioplasty. MCE yielded MBV and myocardial blood flow (MBF; in ml·min⁻¹·g⁻¹). Complete data sets were obtained in 32 coronary arteries and their territories from 26 patients. During angioplasty, perfusion pressure, i.e., coronary occlusive pressure, and MBV varied between 9 and 57 mmHg (26.9 ± 11.9 mmHg) and between 1.2 and 14.5 ml/100 g (6.7 ± 3.7 ml/100 g), respectively. After successful angioplasty, perfusion pressure and MBV increased significantly (P < 0.001 for both) and varied between 64 and 118 mmHg (93.5 ± 12.8 mmHg) and between 3.7 and 17.3 ml/100 g (9.8 ± 3.4 ml/100 g), respectively. Mean MBF increased from 31 ± 20 ml·min⁻¹·g⁻¹ during coronary occlusion, reflecting collateral flow, to 121 ± 33 ml·min⁻¹·g⁻¹ (P < 0.01), whereas mean CR, i.e., the ratio of perfusion pressure and MBF, decreased by 20% (P < 0.001). In conclusion, the human coronary circulation is pressure distensible. MCE allows for the quantification of CR and MBV in humans.

Coronary circulation; distensibility; myocardial blood flow; contrast echocardiography

Accordingly, the impact of coronary distensibility and the associated changes in MBV and CR on coronary hemodynamics in clinical practice are still unknown. In contrast, the clinical importance of resistance changes in other vascular beds, such as systemic arterial resistance or pulmonary resistance, is well appreciated. Establishing the means to study CR and MBV in a clinical setting is the first step to fill this gap in knowledge.

Recently, we demonstrated that myocardial contrast echocardiography (MCE) can be used to derive MBV (in ml/100 g), i.e., MBV per tissue mass, and MBF (in ml·min⁻¹·100 g⁻¹), defined as MBV times its exchange rate (β; in 1/min) (19). MCE is a bedside technique that can be performed in the catheterization laboratory and, therefore, allows for the quantification of MBV and MBF in patients during coronary angioplasty. The objective of this study was to investigate whether MCE can be used to assess parameters of coronary distensibility for clinical purposes.

METHODS

Study Population and Measurement Setup

Thirty patients with stable coronary artery disease eligible for percutaneous coronary intervention (PCI) of one or more lesions were enrolled. Patients maintained their routine medication and were not screened for echocardiographic image quality. Coronary angioplasty was chosen as the measurement setup to investigate the influence of a significant perfusion pressure drop on the downstream myocardial microcirculation.

All invasive and MCE measurements were performed in the catheterization laboratory during one session with the patient being conscious and placed in the supine position on the catheterization laboratory table. During coronary angioplasty, distal perfusion pressure, i.e., coronary occlusive pressure (Pocci), and MCE images of the corresponding myocardial territory were obtained simultaneously at the end of a 1-min balloon occlusion to guarantee stationary conditions (14, 15). After successful completion of the intervention and the cessation of reactive hyperemia, i.e., 20 min, mean aortic pressure (Pao) was measured, and MCE imaging of the same territory was repeated.

This study protocol was approved by the Ethics Committee of the Canton of Bern, Switzerland. All participants gave written informed consent to participate in the study.

Cardiac Catheterization and Pressure Measurements

A coronary angiogram was performed via the right femoral approach using 5-Fr diagnostic catheters after the oral administration of 0.8 mg isosorbide dinitrate.

Indication for ad hoc PCI was based on the visual estimate of the stenosis percent diameter reduction (≥50%). During balloon occlusion, mean Pocci was measured distal to the inflated balloon using a 0.014-in. guide wire equipped with a pressure sensor at the tip (PressureWire, RADI Medical, Uppsala, Sweden).
After successful PCI, perfusion pressure, i.e., $P_{\text{aer}}$, was measured through a 6-Fr guiding catheter. The coronary artery stenosis severity was quantitatively assessed offline as the percent diameter reduction of the vessel (Philips DA, Best, The Netherlands).

**MCE**

**Data acquisition.** Ultrasound contrast agent (UCA) was administered via the right cubital vein using a parallel infusion of Optison (3 ml) at a rate of 10–30 ml/h (Per fusor, B. Braun Melsungen, Melsungen, Germany) and physiological saline solution at a rate of 400 ml/h (Volumed μ-V-P2001, Arcomed, Regensdorf, Switzerland). The UCA infusion pump was manually agitated to guarantee UCA homogenization.

When myocardial enhancement reached steady state, transthoracic imaging was performed with an Acuson Sequoia C256 ultrasound scanner (Siemens Medical Solutions, Mountain View, CA) equipped with a 3V2c transducer and Coherent Contrast Imaging. Settings were as follows: mechanical index for microsphere detection, 0.08; mechanical index for microsphere destruction, 1.3; and dynamic range, 60 dB. The image plane was aligned to the myocardial territory of the coronary artery undergoing angioplasty. Gain was adjusted for optimal visualization of the myocardium and held constant throughout image acquisition. Destruction-refill sequences were generated using the manual bubble destruction feature of the scanner and recorded digitally for offline image analysis. The clip length was set to 200 frames with a triggering interval of 75 ms. Before manual bubble destruction, two cardiac cycles were captured for the calculation of MBV.

**Data analysis.** The data analysis has been previously described in detail (19). Briefly, image visualization and quantification were done with DataPro 2.11 (Noesis, Courtaboeuf, France). Logarithmic signal compression was removed, and linearized signal intensity data were expressed in arbitrary units. Quantitative perfusion analysis was performed using only end-systolic frames of the perfusion sequence. Regions of interest within the myocardium (entire wall thickness) and periphery (entire vessel) were manually set. Myocardial signal intensity data were corrected for noncontrast signals arising from the tissue by subtracting the signal intensity of the first frame after manual bubble destruction. Myocardial plateau signal intensity ($A_{\text{LV}}$) was calculated by averaging myocardial signal intensity data from frames before manual bubble destruction:

$$y(t) = A \times (1 - e^{-\beta t})$$  \hspace{1cm} (1)

Averaged LV signal intensity data of all but the frames during and the first one after manual bubble destruction yielded $A_{\text{LV}}$. In analogy to our previous work (19), MBV (in ml/100 g) was calculated as follows:

$$\text{MBV} = \frac{A_{\text{LV}} \times \rho_T \times 100}{\rho_T \times 100} = \frac{\text{rBV}}{\beta} \times 100$$  \hspace{1cm} (2)

where $\rho_T$ is tissue density ($\rho_T = 1.05$ g/ml) and rBV is relative blood volume.

MBF (in ml·min$^{-1}$·100 g$^{-1}$) was calculated as the product of $\beta$ and MBV as follows:

$$\text{MBF} = \frac{\beta \times \text{rBV}}{\rho_T} \times 100 = \beta \times \text{MBV}$$  \hspace{1cm} (3)

CR (in mmHg·min·100 g·ml$^{-1}$) during angioplasty, i.e., the resistance of the vascular pathway downstream the occlusion, and after angioplasty was calculated as follows:

$$\text{CR}_{\text{occl}} = \frac{P_{\text{occl}}}{\text{MBF}_{\text{occl}}} \quad \text{and} \quad \text{CR}_n = \frac{P_{\text{ao}}}{\text{MBF}_n}$$  \hspace{1cm} (4)

where the subscripts “occl” (occlusive) and “n” (normal) refer to measurements during and after angioplasty, respectively. The comparison of CRs of the vascular pathway downstream the occlusion during angioplasty and the entire coronary pathway after angioplasty is justified, since the resistance of a normal epicardial segment can be neglected.

**Statistical Methods**

Demographic and clinical data are expressed as means ± SD. Paired, two-sided t-tests were used for the comparison of pressure and MCE data during and after angioplasty. Correlations were calculated using linear and nonlinear regression analysis, and the accuracy of the prediction was measured by the SE of the estimate (SEE). $P$ values of <0.05 were considered to indicate statistical significance.

**RESULTS**

**Feasibility of Pressure and Perfusion Measurements**

Invasive pressure data were obtained in all 30 patients and 37 coronary lesions. Perfusion analysis failed in five territories (1 lateral and 4 inferior territories) of four patients due to poor echo image quality. All statistical analysis was based on the remaining 32 coronary arteries/territories with complete pressure and perfusion data sets measured in 26 patients.

**Patient Characteristics**

Patient characteristics and angiographic data are shown in Table 1. The medical history of the 26 patients revealed stable angina in 21 cases. LV ejection fraction ranged between 30% and 100% (70% to 90% in 8 cases). PCI was performed in 32 coronary arteries; their percent diameter reduction ranged between 30% and 100%, including 6 nonsignificant stenoses.

**MBV**

Figure 1 shows individual MBV and perfusion pressure data during (filled circles) and after (open circles) angioplasty. Mean MBV was 6.7 ± 3.7 ml/100 g (1.2–14.5 ml/100 g) during angioplasty and 9.8 ± 3.4 ml/100 g (3.7–17.3 ml/100 g).

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total no. of patients (men/women)</th>
<th>Age, yr</th>
<th>Body mass index, kg/m²</th>
<th>Heart rate, beats/min</th>
<th>Left ventricular ejection fraction, %</th>
<th>Stenosis severity, %diameter stenosis</th>
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<tr>
<td></td>
<td>26 (21/5)</td>
<td>64 ± 14</td>
<td>29 ± 4</td>
<td>73 ± 13</td>
<td>60 ± 11</td>
<td>73 ± 22</td>
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<td>Distribution of stenoses severity, no. of stenoses</td>
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<td>&lt;50%</td>
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<tr>
<td>≥50% to &lt;70%</td>
<td>8†</td>
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<tr>
<td>≥70% to &lt;90%</td>
<td>8†</td>
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<tr>
<td>≥90%</td>
<td>10†</td>
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<td>Family history</td>
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</table>

Values are means ± SD unless otherwise indicated.
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after angioplasty ($P < 0.001$). After angioplasty, MBV increased in 25 cases (Fig. 1, solid lines) and decreased in 7 cases (Fig. 1, dashed lines).

The mean percent increase of MBV was 48% for an average pressure rise of 66.6 mmHg. Linear and nonlinear regression analysis did not reveal any significant relationships either between MBV and perfusion pressure during or after angioplasty or between individual differences of MBV and perfusion pressure during and after angioplasty. However, a significant linear relationship ($y = 0.83x - 0.15, r^2 = 0.18, SE = 0.25, P = 0.04$) was found between relative pressure changes ($[P_{occl} - P_{no}]$) and relative MBV changes ($[MBV_n - MBV_{occl}] / MBV_n$) when the seven cases with decreasing MBV after angioplasty were neglected.

**Perfusion Pressure and MBF**

Pressure and perfusion measurements during and after angioplasty are shown in Table 2. During angioplasty, perfusion pressure, i.e., $P_{occl}$, and MBF$_{occl}$ were $26.9 \pm 11.9$ mmHg and $31 \pm 20$ ml-min$^{-1}$-100 g$^{-1}$, respectively (Fig. 2, filled circles). After successful angioplasty, perfusion pressure, i.e., mean $P_{no}$, and MBF$_n$ increased to $93.5 \pm 12.8$ mmHg and $121 \pm 33$ ml-min$^{-1}$-100 g$^{-1}$, respectively (Fig. 2, open circles). Regression analysis of pressure and flow data during angioplasty followed an exponential relationship $(y = -74.4 + 75.9e^{0.0118x}, r^2 = 0.64, SE = 12.10, P < 0.001)$; however, no correlation was found after angioplasty. Mean percent increases of perfusion pressure and MBF were 113% and 122%, respectively ($P < 0.001$ for both).

**CR**

Figure 3 shows CR data calculated from MBF and perfusion pressure measurements. Mean CR was $1.04 \pm 0.43$ mmHg-min$^{-1}$-100 g$^{-1}$ (0.36–2.32 mmHg-min$^{-1}$-100 g$^{-1}$) during angioplasty, i.e., the resistance of the vascular pathway downstream of the occlusion, and $0.84 \pm 0.28$ mmHg-min$^{-1}$-100 g$^{-1}$ (0.41–1.47 mmHg-min$^{-1}$-100 g$^{-1}$) after angioplasty. Compared with the occluded state, CR after angioplasty decreased in 23 cases and increased in 9 cases. Mean CR decreased by 20% for an average increase in perfusion pressure by 66.6 mmHg ($P < 0.001$).

**DISCUSSION**

For the first time, MBV and CR were obtained in patients during and after coronary angioplasty using simultaneous pres-

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**Table 2. Pressure and perfusion data**

<table>
<thead>
<tr>
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<th>Means ± SD</th>
<th>Range</th>
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<tr>
<td>$P_{occl}$, mmHg</td>
<td>$26.9 \pm 11.9$</td>
<td>9.0–57.3</td>
</tr>
<tr>
<td>$P_{no}$, mmHg</td>
<td>$93.5 \pm 12.8^*$</td>
<td>64.0–117.5</td>
</tr>
<tr>
<td>MBV$_{occl}$, ml/100 g</td>
<td>$6.7 \pm 3.7$</td>
<td>1.2–14.5</td>
</tr>
<tr>
<td>MBV$_n$, ml/100 g</td>
<td>$9.8 \pm 3.4^*$</td>
<td>3.7–17.3</td>
</tr>
<tr>
<td>$\beta_{exch}$, l/min</td>
<td>$5.7 \pm 4.0$</td>
<td>0.5–22.4</td>
</tr>
<tr>
<td>$\beta_n$, l/min</td>
<td>$13.7 \pm 6.4^*$</td>
<td>5.9–38.8</td>
</tr>
<tr>
<td>MBF$_{occl}$, ml-min$^{-1}$-100 g$^{-1}$</td>
<td>$31 \pm 20$</td>
<td>6–88</td>
</tr>
<tr>
<td>MBF$_n$, ml-min$^{-1}$-100 g$^{-1}$</td>
<td>$121 \pm 33^*$</td>
<td>68–177</td>
</tr>
<tr>
<td>CR$_{occl}$, mmHg-min$^{-1}$-100 g$^{-1}$</td>
<td>$1.04 \pm 0.43$</td>
<td>0.36–2.32</td>
</tr>
<tr>
<td>CR$_n$, mmHg-min$^{-1}$-100 g$^{-1}$</td>
<td>$0.84 \pm 0.28^*$</td>
<td>0.4–1.47</td>
</tr>
</tbody>
</table>

Subscripts “occl” (occlusive) and “n” (normal) indicate values measured during and after angioplasty, respectively; $P_{occl}$, mean coronary occlusive pressure; $P_{no}$, mean aortic pressure; MBV, myocardial blood volume; $\beta$, exchange frequency; MBF, myocardial blood flow; CR, coronary resistance. *$P < 0.001$ vs. the respective value during angioplasty.

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Fig. 1. Individual pressure ($P$ in mmHg) and myocardial blood volume (MBV; in ml/100 g) data during (●) and after (○) angioplasty, respectively. MBV increased in 25 cases (solid lines) and decreased in 7 cases (dashed lines).

Fig. 2. Individual pressure (in mmHg) and myocardial blood flow (MBF; in ml-min$^{-1}$-100 g$^{-1}$) data during (●) and after (○) angioplasty. The long-dashed and short-dashed lines indicate means ± SD of MBF after angioplasty. During angioplasty, perfusion pressure and MBF followed an exponential relationship (solid curved line; the dashed-dotted curved lines indicate the confidence band). SEE, SE of the estimate.

Fig. 3. Boxplot showing coronary resistance (CR) data during (occlusive (occl)) and after (normal (n)) angioplasty. ●, Values below and above the 10th and 90th percentile, respectively. The dotted lines represent the mean.
MBVs During and After Coronary Angioplasty

We found mean MBVs of 6.7 ± 3.7 and 9.8 ± 3.4 ml/100 g at a perfusion pressure of 26.9 mmHg during angioplasty and 93.5 mmHg after angioplasty, respectively (Fig. 1). Our findings are in accord with experimental data from animal studies: in the isolated myocardial septum of dogs, MBVs were 7.5 and 12.1 ml/100 g at perfusion pressures of 20 and 90 mmHg, respectively, using digital subtraction angiography (8). Morgenstern et al. (13) found MBV values of 11.0 and 17.8 ml/100 g at perfusion pressures of 70 and 170 mmHg, respectively, using a dye dilution technique. This positive correlation between MBV and perfusion pressure is most likely due to the passive, pressure-dependant distensibility of capillaries.

This notion is corroborated by Bosman et al. (2), who found a direct relation between perfusion pressure and capillary diameters: in rabbit skeletal muscle, capillary diameter decreased by 6% after a decrease of perfusion pressure by 66 mmHg. Capillary diameter changes can be related to MBV changes according to the following reasoning. As stated above, capillary blood volume is the major constituent of MBV. The contrast signal reflecting MBV is determined by the UCA concentration, ultrasound beam elevation, and total capillary cross-sectional area. Assuming that these three parameters remain constant during and after PCI, the percent average decrease of the capillary diameter (d) of our study population can be estimated as follows:

\[ \% \frac{d_n - d_{occl}}{d_n} = 100 \times \frac{\sqrt{MBV_n} - \sqrt{MBV_{occl}}}{\sqrt{MBV_n}} = 17.4\% \]  

for an average perfusion pressure drop of 67 mmHg. Of course, the comparability with rabbit skeletal muscle is limited, moreover since our data may be confounded by autoregulation and the different measurement techniques we used.

Pressure-Perfusion Relationship, CR, and Autoregulation

To the best of our knowledge, the human pressure-perfusion relationship has not been investigated so far. This is most probably due to the challenging setup. We found an exponential relationship between perfusion pressure and MBF during balloon occlusion, where coronary autoregulation is expected to be exhausted. In this state, the curve reflects the relationship between perfusion pressure and MBF derived from coronary collaterals. The shape of the fitting curve implies that CR increases with decreasing perfusion pressure, as predicted by Spaan et al. (17). This behavior can only be explained by a pressure-distensible vasculature. Our exponential fitting curve intercepts the pressure axis at −1.5 mmHg, resulting in a negative zero-flow pressure. Conversely, in dog hearts, Messina et al. (11) found a positive zero-flow pressure that even exceeded coronary sinus pressure. We extrapolated zero-flow pressure from the fitting curve of our pressure-perfusion data during angioplasty, which may be problematic due the following issues: 1) our data showed a large scatter as we obtained measurements from a patient collective with variable anatomy rather than from a single patient and 2) the quantification algorithm is more prone to systematic errors for lower MBF values, as indicated by the larger variation in this range.

After coronary angioplasty, no correlation was found between perfusion pressure and MBF (Fig. 2). This may be explained by the wide interindividually variation of normal perfusion pressure and MBF, which has been found in previous studies (3, 19) using positron emission tomography and MCE. Moreover, the return of coronary autoregulation after coronary angioplasty counterbalances pressure-induced changes of MBF. These facts explain the lack of a relationship between CR and perfusion pressure after angioplasty.

We compared CRs of the vascular pathway downstream of the occlusion during angioplasty and the entire coronary
pathway after angioplasty. This approach is valid, since the vascular resistance of a normal epicardial segment can be neglected. Mean CR downstream of the occlusion was $1.04 \pm 0.43 \text{ mmHg} \cdot \text{min} \cdot 100 \text{ g} \cdot \text{ml}^{-1}$ and decreased to $0.84 \pm 0.28 \text{ mmHg} \cdot \text{min} \cdot 100 \text{ g} \cdot \text{ml}^{-1}$ after angioplasty or by 20%. This decrease of mean CR with increasing perfusion pressure is most likely due to the pressure-distensible nature of the coronary circulation, which is supported by the concomitant increase in MBV. The return of coronary autoregulation after coronary angioplasty may have reduced the pressure-induced decrease of CR due to increased arteriolar resistance after the normalization of perfusion pressure. This notion is corroborated by data from isolated dog hearts without coronary autoregulation, where CR increased by 66% after an increase in perfusion pressure from 20 to 80 mmHg (6).

**Clinical Implications**

The influence of coronary artery stenosis on CR has been vigorously debated (17). The controversy is mainly due to the fact that CR could not be measured so far. Resistance indexes have been proposed using coronary blood flow velocity and mean transit time as estimates of coronary blood flow (for territorial resistance) and MBE (for regional resistance), respectively (1, 16). In this regard, measurement of CR using simultaneous invasive pressure and MCE-derived perfusion measurements may be useful to resolve this issue.

We have shown that MBV as well as changes of this parameter can be measured by quantitative contrast echocardiography (7). Since this parameter may vary with diseases such as ischemic heart disease, hypertensive heart disease, cardiomyopathies, or microvascular diseases, MBV measurements can be expected to provide further clinical benefits that remain to be determined by future clinical studies. Most of our patients had one or more risk factors of microvascular disease. Our study population was too small to analyze its impact on MBV or CR, and, in fact, the presence of microvascular disease may explain some of the interindividual scatter of our data. However, one would assume that the presence of microvascular disease would rather decrease pressure-induced changes in coronary distensibility due to the increased resistance of diseased arterioles, which reduce capillary perfusion pressure. Using our quantitative approach by MCE, studies aimed at the determination of the impact of coronary distensibility on clinical decision making can now be performed.

**Limitations**

Our results may have been affected by distal embolization during PCI, which leads to microvascular obstruction. In seven cases, MBV decreased after angioplasty despite a significant rise in perfusion pressure. This notion is supported by the fact that cardiac biomarkers were elevated after angioplasty in five of these cases. Consequently, we may have rather underestimated pressure-induced effects on MBV.

Although we took every precaution to locate the same myocardial territory during and after angioplasty, we cannot exclude that mismatched tomographic planes may have affected our results.

**Conclusions**

The present clinical study demonstrates, for the first time, that the human coronary circulation is pressure distensible, as predicted by animal experiments.

MCE provides the means for the quantification of MBV, CR, and, subsequently, coronary distensibility. The impact of the pressure-distensible nature of the coronary circulation on clinical decision making, e.g., the calculation of hemodynamic indexes such as the coronary flow reserve and fractional flow reserve, can now be examined.

**GRANTS**

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

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