Metabolic flow regulation in human coronary artery disease
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Chapter 3

A critical appraisal of the RPP as index of MVO$_2$ for the study of metabolic coronary flow regulation

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CHAPTER 3

Abstract

Background. For the assessment of metabolic coronary vasodilation, changes in systolic rate pressure product (RPP) are frequently used to estimate the pacing- or exercise induced changes in myocardial oxygen consumption (MVO₂). The present study was designed to test whether this is justified in patients with coronary artery disease.

Methods. To study the relation between RPP and changes in MVO₂ under different conditions, we used data from 21 patients who participated in two previous studies investigating the effect of nitroglycerin (NTG) and anesthesia on metabolic coronary flow regulation. At control, during administration of NTG 1 µg/kg/min (n = 11), and during anesthesia (n = 10), coronary sinus blood flow, MVO₂ and RPP were measured at sinus rhythm and during atrial pacing (30 beats/minute above sinus rate) and the relation between the percentage increase in RPP (Δ%RPP) and MVO₂ (Δ%MVO₂) was analyzed, using standard linear regression analysis.

Results. Although a significant relation between Δ%MVO₂ and Δ%RPP was found at control and during anesthesia, prediction intervals were very wide and only 40 % and 60 % of the variation in Δ%MVO₂, respectively, could be explained by the variation in Δ%RPP. During administration of NTG 1 µg/kg/min no significant relation was found between Δ%MVO₂ and Δ%RPP.

Conclusion. For the study of metabolic coronary flow regulation, pacing induced changes in MVO₂ cannot be predicted accurately from changes in RPP.
1. Introduction

Metabolic coronary flow regulation can be characterized by the linear dependency of coronary blood flow on myocardial oxygen consumption (MVO₂) [1,2].

To study this regulation process in patients with and without coronary artery disease (CAD), a growing number of investigators is using the coronary flow-velocity Doppler catheter in combination with quantitative coronary angiography [3-8]. Only in a limited number of studies a coronary sinus catheter is introduced to draw blood for the measurement of coronary sinus oxygen content [3]. Direct calculation of changes in MVO₂ is therefore frequently omitted and in stead, several hemodynamic parameters, such as systolic rate pressure product (RPP) are used to estimate the metabolically induced changes in MVO₂. However, it remains questionable whether this is justified. To date, the studies describing the relation between absolute values of MVO₂ and RPP in humans have yielded conflicting results, which may be related to methodological pitfalls or to the different interventions and conditions that were studied [10-24]. Although the majority of these studies reported a significant correlation between absolute values of MVO₂ and RPP, the accuracy to predict changes in MVO₂ from changes in RPP has never been established.

Since there is evidence that of all hemodynamic parameters RPP correlates best with MVO₂ [12,14], the present study was designed to evaluate the accuracy and usefulness of the change in RPP as a predictor of the change in MVO₂ for the study of metabolic coronary vasodilation. Therefore, we studied changes in MVO₂ and RPP, induced by atrial pacing, in patients undergoing coronary artery surgery.

2. Materials and methods

2.1 Patients

Data from 21 patients with stable CAD, who participated in two previous studies investigating the effect of nitroglycerin (NTG) and anesthesia on metabolic coronary flow regulation [25,26], were used to study the relation between pacing induced changes in MVO₂ and RPP. All patients were scheduled for elective coronary artery surgery and gave written informed consent to participate in these studies, which were approved by the local ethical committee.

2.2 Instrumentation

All patients received a 20-gauge radial artery catheter, a thermodilution pulmonary artery catheter (Baxter Health Care Corporation, Irvine, CA) and a coronary sinus thermodilution catheter (Wilton-Webster Laboratories, Altadena, CA) as described previously [25]. Coronary sinus blood flow (CSBF) was measured with the thermodilution technique, using normal saline at room temperature at a rate of 45 ml/min as indicator [27].

2.3 Protocol

In all 21 participating patients, series of measurements were performed during sinus rhythm, during pacing (at a pacing rate of 30 beats per minute above sinus rate) and
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after discontinuation of pacing. After these control measurements, infusion of NTG at a rate of 1 µg/kg/min was started in 11 consecutive patients and additional series of measurements were performed at sinus rhythm, during pacing at the same pacing rate as during control pacing, and after the cessation of pacing. In the 10 remaining patients, these series of measurements were repeated 15 minutes after the induction of general anesthesia (fentanyl 100 µg/kg and pancuronium bromide 8 mg), endotracheal intubation and the start of mechanical ventilation (F₁O₂ = 0.5).

2.4 Measurements
Each series of measurements included the recording of coronary sinus blood flow (CSBF), arterial blood pressure (ABP), pulmonary artery pressure (PAP), right atrial pressure (RAP), and ECG lead II for at least 30 seconds of steady state, the measurement of pulmonary capillary wedge pressure and cardiac output (in triplicate) and the simultaneous drawing of blood samples from the coronary sinus and radial artery, for determination of plasma hemoglobin concentration, oxygen partial pressure (ABL III, Radiometer, Copenhagen, Denmark), hemoglobin oxygen saturation (OSM-II hemoxymeter, Radiometer, Copenhagen, Denmark) and lactate concentrations [28].

2.5 Data analysis
All recordings were digitized on line by a custom made A/D converter at a sampling rate of 80 Hz and stored on disk of a personal computer for off line analysis. Using a signal analysis program (Matlab v. 4.2c, MathWorks Inc., Natick, MA), mean values of CSBF, ABP, PAP and RAP were calculated for each series of measurements, by averaging the recording over a period of 30 seconds. Oxygen content was calculated according to the standard formula. MVO₂ was calculated as the product of mean CSBF and the arterio-venous oxygen content difference, RPP was calculated as the product of systolic blood pressure (SBP) and HR, whereas myocardial lactate extraction (MLE) was determined as the quotient of the arterio-venous lactate concentration difference and the arterial lactate concentration.

2.6 Statistical analysis
Values obtained during sinus rhythm and values obtained during pacing were compared using two way paired standard t tests (i.e. the comparison of control vs. NTG, and control vs. anesthesia). Results are presented as mean ± SD. A value of p < 0.05 was considered significant.

To study the relation between the percentage increase in RPP (Δ%RPP) and the percentage increase in MVO₂ (Δ%MVO₂) induced by pacing, linear regression analysis was used (Statistical Package for Social Sciences, version 6.1), yielding equations for the regression lines obtained at control, during administration of NTG 1 µg/kg/min and during anesthesia. The slopes of these regression lines are reported with their 95 % confidence intervals and are compared using analysis of variance for differences between regression slopes [29]. The accuracy of the prediction of Δ%MVO₂ from Δ%RPP, was assessed by calculating the 95 % prediction intervals which are depicted in the accompanying scatterplots.
3. Results

Table 3.1 shows systemic and coronary hemodynamic variables and the coronary arterio-venous oxygen content differences from which values of RPP and MVO₂ were derived. Values obtained at sinus rhythm and during pacing are reported for the three conditions studied: control, during administration of NTG 1 µg/kg/min and during anesthesia. In each condition, the values obtained at sinus rhythm after cessation of pacing, were similar to the values obtained at sinus rhythm before pacing. Therefore, post-pacing values are not included in table 3.1.

During the study period in which patients were awake, none of the patients experienced episodes of angina. MLE did not change in response to pacing and remained positive in all our patients during all measurements series, both at control, during administration of NTG and during anesthesia. Furthermore, we did not observe electrocardiographical signs of myocardial ischemia. This implies that the possible confounding effects of myocardial ischemia did not play a role in the present study.

To investigate whether individual changes in RPP can be used to predict the pacing induced changes in MVO₂, we analyzed the relation between Δ%RPP and Δ%MVO₂. At control (figure 3.1, upper panel), the regression analysis resulted in a regression line with a slope of 0.87 (95% CI: 0.35-1.39, p = 0.002). The R² value was 0.40, which indicates that despite the statistically significant slope, the majority of the variability in Δ%MVO₂ could not be explained by the variation in Δ%RPP.

During administration of NTG 1 µg/kg/min (figure 3.1, middle panel), the slope of the regression line was −0.27 (95% CI: -1.33-0.77, p = 0.56, R² = 0.04). Thus, after the start of the infusion of NTG, there no longer was a significant relation between Δ%RPP and Δ%MVO₂. In addition, analysis of variance revealed that the slope of the regression line obtained during infusion of NTG was significantly different from the regression line obtained at control.

During general anesthesia (figure 3.1, lower panel), the regression line was characterized by a slope of 0.78 (95% CI: 0.26-1.31, p = 0.009). The R² value (0.60) indicated that 60% of the variability in Δ%MVO₂ could be attributed to the variation in Δ%RPP. Thus, only at control and during anesthesia, but not during administration of NTG, a significant relation between Δ%RPP and Δ%MVO₂ was found. The wide confidence intervals of the regression coefficients (i.e. slope of regression lines) however indicate that there is considerable doubt about the strength of the estimated relationship.

Figure 3.1 also shows the 95% prediction intervals for the prediction of Δ%MVO₂ for any given individual Δ%RPP. Both at control and during anesthesia, these prediction intervals were very wide, which indicates that for a given Δ%RPP there is a substantial uncertainty about the accuracy of the prediction of Δ%MVO₂. At control for example, a 50% increase in RPP resulted in a prediction interval of −7% to 76%.

There is thus a 95% probability of an individual’s Δ%MVO₂ being within this interval, given the 50% increase in RPP. These wide prediction intervals imply that it
### Table 3.1:
Systemic and coronary hemodynamics at sinus rhythm and during pacing

<table>
<thead>
<tr>
<th></th>
<th>Control (n=21)</th>
<th>NTG 1 μg/kg/min (n=11)</th>
<th>Anesthesia (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SR Pacing</td>
<td>SR Pacing</td>
</tr>
<tr>
<td>HR (1/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>63 (9)</td>
<td>91 (8)*</td>
<td>68 (9)</td>
</tr>
<tr>
<td>NTG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacing</td>
<td>91 (8)*</td>
<td></td>
<td>143 (19)*</td>
</tr>
<tr>
<td>Anesthesia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacing</td>
<td>96 (9)*</td>
<td></td>
<td>148 (19)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>147 (25)</td>
<td>153 (29)</td>
<td>143 (19)*</td>
</tr>
<tr>
<td>Pacing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>71 (10)</td>
<td>79 (12)*</td>
<td>71 (10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>99 (14)</td>
<td>107 (17)*</td>
<td>95 (12)*</td>
</tr>
<tr>
<td>Pacing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAP (mmHg)</td>
<td>21 (6)</td>
<td>25 (8)*</td>
<td>18 (6)*</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>7 (3)</td>
<td>5 (4)*</td>
<td>5 (3)*</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>11 (5)</td>
<td>10 (5)</td>
<td>7 (3)*</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>2.7 (0.6)</td>
<td>3.5 (0.6)*</td>
<td>3.0 (0.6)</td>
</tr>
<tr>
<td>SVR (dynes.s/cm⁵)</td>
<td>1347 (342)</td>
<td>1180 (243)*</td>
<td>1276 (318)</td>
</tr>
<tr>
<td>CSBF (ml/min)</td>
<td>121 (44)</td>
<td>171 (77)*</td>
<td>108 (33)</td>
</tr>
<tr>
<td>MVO₂ (mlO₂/min)</td>
<td>15.3 (6.8)</td>
<td>21.4 (11.0)*</td>
<td>13.0 (3.3)*</td>
</tr>
<tr>
<td>RPP (mmHg/min)</td>
<td>9256 (2253)</td>
<td>14008 (2843)*</td>
<td>9729 (1550)</td>
</tr>
<tr>
<td>AVOX (ml O₂/dl)</td>
<td>12.6 (1.9)</td>
<td>12.4 (1.8)</td>
<td>12.4 (1.8)</td>
</tr>
</tbody>
</table>

Values are mean (SD). Values of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), mean pulmonary artery pressure (PAP), mean right atrial pressure (RAP), pulmonary capillary wedge pressure (PCWP), cardiac index (CI), systemic vascular resistance (SVR), coronary sinus blood flow (CSBF), myocardial oxygen consumption (MVO₂), systolic rate pressure product (RPP) and coronary arterio-venous oxygen content difference (AVOX) are shown at sinus rhythm (SR) and during pacing, for each condition: at control, during infusion of NTG 1 mcg/kg/min and during general anesthesia.

* p < 0.05 versus value at sinus rhythm. † p < 0.05 versus corresponding control value.
is practically impossible to predict relative changes in MVO$_2$ from relative changes in RPP.

4. Discussion

For the assessment of metabolic coronary flow regulation, information about the metabolically induced changes in MVO$_2$ is a prerequisite. Frequently, the RPP is used as an index of MVO$_2$ [5-9], based on the assumption that changes in MVO$_2$ are directly reflected by changes in RPP. However, the results from the present study do not support this assumption.

Table 3.2 summarizes most of the clinical studies describing the relation between RPP and MVO$_2$. The majority of these studies originates from the field of cardiology, since Robinson et al. [30] showed that the onset of angina in response to various types of exercise, was consistently related to a fixed, critical level of RPP. Many investigators also studied the relationship between RPP and MVO$_2$ in the perioperative period, since it would provide the anesthesiologist with a potentially useful and readily available predictor of myocardial ischemia [16-23]. In patients undergoing coronary artery surgery, Wilkinson et al. [16] found a significant correlation ($r = 0.78$) between the two parameters and concluded that the hemodynamic changes which occurred during anesthesia did not decrease the sensitivity of RPP as an index of MVO$_2$. However, the clinical usefulness of this alleged relationship was disputed by others [22,31,32]. Moffitt et al. [22] could not confirm Wilkinson’s findings in a similar, though larger study, pointing out possible methodological pitfalls in the statistical analysis of the relation between RPP and MVO$_2$.

Since in most studies shown in table 3.2, a repeated measures design was employed, several observations were obtained in each subject under different conditions. But, when multiple data points from individual subjects are included in a single regression analysis, the assumption of independent error terms (i.e. the error for each observation is independent of the error terms of other observations) is probably violated [29]. The pooling of non-independent data may thus have resulted in inadvertently positive correlations.

Table 3.2 illustrates that high correlations between MVO$_2$ and RPP ($r$ values: 0.77-0.92) were only found in those studies in which more than two data points from each patient were included in the analysis [10-16,23,24]. In contrast, low correlations ($r$ values: 0.09-0.28) were found in those studies in which only single data points from each subject were used to analyze the correlation of MVO$_2$ to RPP [17,22]. This supports the conclusion that correlations obtained from pooled data of multiple observations from individual subjects should be interpreted with caution and stresses the importance of using independent observations for regression analysis, which implies that only single data points per individual should be used [33].

4.1 Relation between pacing induced $\Delta$%RPP and $\Delta$%MVO$_2$

To avoid pooling of non-independent data points in the present study, we analyzed the relation between relative changes in RPP and MVO$_2$ using only single data points per subject for the regression analysis. The regression of $\Delta$%MVO$_2$ to $\Delta$%RPP was
statistically significant at control and during anesthesia. However, whether this relation is clinically important is quite a different matter, because both at control and during anesthesia, only 40 and 60% of the variation in \(\Delta\%\text{MVO}_2\), respectively, could be explained by the variation in \(\Delta\%\text{RPP}\) (figure 3.1). In addition, the 95% prediction intervals showed that for a given value of \(\Delta\%\text{RPP}\) there is a substantial uncertainty about the accuracy of the prediction of \(\Delta\%\text{MVO}_2\). To justify the use of the change in RPP for the prediction of the change in \(\text{MVO}_2\), a much tighter prediction interval is needed.

It is interesting that during administration of NTG the relationship between \(\Delta\%\text{MVO}_2\) and \(\Delta\%\text{RPP}\) disappeared (figure 3.1, middle panel), which suggests that the magnitude of the pacing-induced increase in \(\text{MVO}_2\) during NTG was influenced by other factors than the change in RPP. One possible factor may be found in the study by Bernstein et al. [34] who demonstrated that blockade of nitric oxide synthesis with L-nitro-arginine resulted in an augmented increase in \(\text{MVO}_2\) for comparable increases in triple product. They concluded that nitric oxide directly impaired myocardial metabolism, possibly by inhibiting the mitochondrial respiration [35], leading to reduction in \(\text{MVO}_2\) for comparable levels of cardiac work. Our previous finding that administration of NTG as a nitric oxide donor attenuates the pacing induced increase in \(\text{MVO}_2\) [26], supports the notion that nitric oxide may impair myocardial metabolism directly [36,37]. This may explain why NTG and L-nitro-arginine may alter the magnitude of the metabolically induced change in \(\text{MVO}_2\), while this change is not being reflected in the RPP. Thus, it is important to measure \(\text{MVO}_2\) invasively, which can be illustrated by the following examples. Based on the observation that RPP and coronary flow responses to pacing were similar before and after inhibition of nitric oxide, Canty et al. [38] and Egashira et al. [5] concluded that nitric oxide had no effect on metabolic coronary vasodilation. However, they did not measure \(\text{MVO}_2\). If the pacing induced change in \(\text{MVO}_2\) was greater after inhibition of nitric oxide, as reported by Bernstein et al. [34], a greater change in coronary blood flow should have occurred. The fact that the associated increase in flow remained unchanged after inhibition of nitric oxide, suggests that, in contrast to their conclusion, metabolic coronary vasodilation may have been impaired.

4.2 Limitations.

Because of the absence of a Gold Standard technique for the measurement of coronary blood flow, human studies addressing \(\text{MVO}_2\) are always subjected to inaccuracies related to the method of coronary flow measurement [39]. In the present study, the coronary venous thermodilution technique was chosen, because this technique measures the volume of coronary flow, allows sampling of coronary venous blood, and can be repeated several times so that each patient can serve as his/her own control. However, there are a number of limitations to its use, that are primarily related to the existence of cardiac venous intercommunications, resulting in drainage of left anterior descending blood through routes other than the coronary sinus [40]. As a result, absolute values of CSBF, and thus \(\text{MVO}_2\), may be underestimated, which makes it difficult to compare absolute values of CSBF between several patients. In addition, since the larger the underestimation of CSBF the
Figure 3.1: Relation between pacing induced changes in rate pressure product (RPP) and myocardial oxygen consumption (MVO2) at control (n = 21) (upper panel), during administration of nitroglycerin (NTG) 1 mcg/kg/min (n = 11) (middle panel), and during general anesthesia (n = 10) (lower panel). Pacing induced changes are expressed as % change from values during sinus rhythm. The solid lines represent the regression lines with their 95 % confidence intervals (dotted lines). Dashed lines delineate the 95% prediction intervals.
### Table 3.2:
Clinical studies reporting on the relation between RPP and MVO<br>

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>CAD</th>
<th>n</th>
<th>Data</th>
<th>Conditions</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holmberg[11]</td>
<td>1971</td>
<td>no</td>
<td>10</td>
<td>2-4</td>
<td>control and 1-3 stages of exercise</td>
<td>0.98</td>
</tr>
<tr>
<td>Holmberg[12]</td>
<td>1971</td>
<td>no</td>
<td>14</td>
<td>3</td>
<td>control, pacing, and pacing + exercise</td>
<td>0.92</td>
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<tr>
<td>Kitamura[13]</td>
<td>1972</td>
<td>no</td>
<td>10</td>
<td>2-3</td>
<td>2-3 stages of upright exercise</td>
<td>0.90</td>
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<td>Jorgensen[14]</td>
<td>1973</td>
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<td>9</td>
<td>2</td>
<td>2 stages of upright exercise with propranolol</td>
<td>0.85</td>
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<tr>
<td>Nelson[15]</td>
<td>1974</td>
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<td>10</td>
<td>3</td>
<td>upright exercise, static exercise, and combined</td>
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<tr>
<td>Gobel[16]</td>
<td>1977</td>
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<td>27</td>
<td>2</td>
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<tr>
<td>Wilkinson[17]</td>
<td>1978</td>
<td>yes</td>
<td>16</td>
<td>2</td>
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<tr>
<td>Sonntag[18]</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>2</td>
<td>low and high dose halothane anesthesia</td>
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<tr>
<td>Reiz[19]</td>
<td>1981</td>
<td>yes</td>
<td>8</td>
<td>2</td>
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<td>Reiz[20]</td>
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<td>2</td>
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<td>Sonntag[21]</td>
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<td>9</td>
<td>4</td>
<td>4 stages during anesthesia</td>
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<tr>
<td>Reiz[22]</td>
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<td>yes</td>
<td>10</td>
<td>2</td>
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<tr>
<td>Moffitt[23]</td>
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<td>1</td>
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<td>Høeft[24]</td>
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<td>Kodama[25]</td>
<td>1993</td>
<td>yes</td>
<td>11</td>
<td>5-6</td>
<td>5-6 stages of supine exercise</td>
<td>0.81</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease. n indicates number of subjects included in the correlation analysis. Data refers to the number of data points from each subject that was used for the statistical analysis. The r-value denotes the correlation coefficient.
smaller the increase in CSBF, absolute (pacing induced) flow responses may become dependent on initial flow values. In the present study, these possible confounding effects were minimized by using each patient as his own control and by focusing on the relative in stead of absolute, changes in CSBF and MVO₂. Furthermore, recalculation of data (using single observations per individual) from studies in which different methods of coronary flow measurement were employed [11],[10,15] revealed that prediction intervals were similar to the ones found in the present study. This suggests that the accuracy of the relationship between Δ%RPP and Δ%MVO₂ was not substantially affected by the technique of coronary flow measurement.

4.3 Implications
The present study demonstrated that pacing induced changes in MVO₂ cannot be predicted accurately from changes in RPP. Therefore, studies reporting on metabolic coronary vasodilation using changes in RPP as index of changes in MVO₂, should be interpreted with caution. Direct measurement of the changes in MVO₂ is recommended.

5. References

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