Metabolic flow regulation in human coronary artery disease
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Citation for published version (APA):
Chapter 7

Calcium channel blockade with felodipine does not affect metabolic coronary vasodilation in patients with coronary artery disease

Submitted
Abstract

Objective. The effect of calcium channel blockers may affect the feedback mechanism between myocardial metabolic activity and coronary blood flow. To test this hypothesis we studied the effect of calcium channel blockade on metabolic coronary flow regulation.

Methods. In ten patients with stable coronary artery disease, we measured coronary sinus blood flow and myocardial oxygen supply and consumption (MVO$_2$) both at sinus rhythm and during atrial pacing (30 beats/min above sinus rate), at control and during infusion of felodipine, a vasoselective dihydropyridine. For the evaluation of metabolic coronary flow regulation, changes in myocardial oxygen supply were related to pacing-induced changes in MVO$_2$, using standard regression analysis.

Results. The myocardial oxygen supply/consumption ratio at control (i.e. the slope of the regression line characterizing normal metabolic flow regulation) was 1.58 (95% CI, 1.38 - 1.80). Following infusion of felodipine, systemic and coronary vascular resistance during sinus rhythm decreased by 20 ± 11 % and 23 ± 15 %, respectively, while coronary venous oxygen saturation increased from 36 ± 6 % at control to 42 ± 7 % (p = 0.047) during infusion of felodipine. Pacing during infusion of felodipine resulted in similar increases in MVO$_2$ compared to control. The myocardial oxygen supply/consumption ratio, characterizing metabolic flow regulation during felodipine, was 1.52 (95% CI, 1.26 - 1.78) and thus not different from control.

Conclusions. Metabolic coronary flow regulation was not affected by administration of a calcium channel blocker, although the setpoint of this regulation mechanism might have been offset by the initial drug-induced coronary vasodilation which persisted during pacing.
1. Introduction

Calcium channel blockers are widely used for the management of angina pectoris and hypertension. In addition to their well established blocking-effects on the voltage gated L-type calcium channels, it has recently become clear that calcium channel blockers may have a beneficial effect on endothelial dysfunction, because they reverse the impairment in endothelium-dependent, nitric oxide mediated vasodilation in animals [1,2] and patients with risk factors for coronary artery disease [3,4].

Hypothetically, both the effect of calcium channel blockers on the relaxation of coronary resistance and conduit vessels, and the effect of these agents on nitric oxide availability, may affect the feedback mechanism between myocardial metabolic activity and coronary blood flow. This process, known as metabolic coronary flow regulation is characterized by the linear relationship between myocardial oxygen supply and consumption and is mainly active at the level of the coronary resistance vessels.

Surprisingly little is known about the effect of calcium channel blockers on metabolic coronary flow regulation. Frielingsdorf et al. [5] and Kaufmann et al. [6] reported that intracoronary administration of calcium channel blockers normalized the reduced epicardial coronary vasodilation in response to exercise in patients with hypertension and hypercholesterolemia, respectively. However, in those studies, only epicardial vasomotor responses were measured by biplane quantitative coronary angiography, a technique not allowing for the assessment of coronary resistance vessel responses, responsible for metabolic flow regulation. In addition, myocardial oxygen consumption cannot be measured directly which is necessary to quantify the metabolic challenge used to induce metabolic coronary vasodilation.

A different approach to analyze metabolic coronary vasomotor responses was recently applied by Kal et al. [7], who measured coronary venous blood flow and myocardial oxygen consumption (MVO2) to calculate the ratio of pacing induced changes in myocardial oxygen supply and MVO2 in patients with CAD. This technique was used in the present study, which was designed to assess the effect of intravenous administration of the vasoselective calcium channel blocker felodipine on metabolic coronary flow responses in patients with multivessel CAD.

2. Methods

2.1 Patients

The study group consisted of 10 patients with stable CAD, without clinical or echocardiographic evidence of congenital, valvular or hypertrophic heart disease. All patients gave written informed consent to participate in this study which was approved by the local ethical committee. The patients were scheduled for elective coronary artery surgery and were enrolled in the study when left ventricular and coronary angiography revealed a left ventricular end diastolic pressure lower than 18 mmHg, a left ventricular ejection fraction higher than 45% and the absence of a left main coronary artery stenosis. Patients with atrioventricular conduction defects or unstable angina were excluded from the study. Calcium channel blockers and long
acting nitrates were discontinued at least 36 hours before surgery, whereas only β
adrenoceptor blockers were given until the morning of surgery. Premedication
consisted of lorazepam 2-3 mg orally, which was given two hours before start of the
study.

2.2 Instrumentation
On arrival in the operating room, ECG leads were connected and lead II, III and V5
were continuously monitored (HP Merlin System, Hewlett-Packard, Böblingen,
Germany). A wide bore peripheral venous catheter and a 20-gauge radial artery
catheter were inserted under local anaesthesia. A thermodilution pulmonary artery
catheter (Baxter Health Care Corporation, Irvine, California, USA) and a coronary
sinus thermodilution catheter (Wilton-Webster Laboratories, Altadena, California,
USA) were introduced via the left subclavian vein. The coronary sinus catheter was
advanced into the coronary sinus using image intensification fluoroscopy and
injection of contrast medium, so that the external thermistor lay 1.5-2 cm from the
ostium and that there was no major sidebranching vein in the vicinity. The coronary
sinus catheter was connected to a Wheatstone bridge (Wilton-Webster Laboratories,
Altadena, California, USA). Coronary sinus thermodilution signals were recorded
with a multi-channel amplifier/recorder system. Catheter calibration factors provided
by the manufacturer were used. The absence of right atrial admixture in coronary
sinus blood was checked by injection of cold saline in the right atrium, while
coronary sinus temperature curves were recorded simultaneously [8]. Under
fluoroscopy, atrial pacing (via coronary sinus catheter) was used during 10-30
seconds to ascertain the stability of the position of the tip of the coronary sinus
catheter in relation to the surrounding anatomical structures and fluoroscopic
landmarks. If the stability of the catheter could not be guaranteed, the experiment
was discontinued. For the measurement of coronary sinus blood flow (CSBF)
normal saline at room temperature was used as indicator and infused into the
coronary sinus at a rate of 45 ml/min via a Mark IV infusion pump (Medrad
Technology for people, Pittsburgh, Pennsylvania, USA) [9].

2.3 Measurements
After adequate instrumentation and a resting period of 20 minutes, two series of
measurements were performed in each patient. Each series included both an increase
in HR (HR step up, induced by pacing) and a decrease in HR (HR step down,
induced by the discontinuation of pacing). The first series of measurements was
performed to obtain baseline values (control), whereas the second series of
measurements was performed during infusion of felodipine.

Each series of measurements was started during sinus rhythm with the
determination of capillary wedge pressure (PCWP) and the simultaneous sampling of
blood from the radial artery and coronary sinus. In addition, thermodilution CO was
obtained in triplicate, using normal saline at room temperature as injectate. The three
CO values were averaged. Subsequently, continuous recording (digitized on-line at a
sampling rate of 80 Hz) of CSBF, arterial blood pressure (ABP), right atrial pressure
(RAP), pulmonary artery pressure (PAP) and electrocardiographic lead II was started.
Following ten seconds of steady state recording, yielding values at sinus rhythm, HR was increased by 30 beats/minute above sinus rate by pacing via the coronary sinus catheter (HR step up). Ten seconds after a new steady state had been reached (usually well within 50 seconds following the HR step), yielding values during pacing, recording was stopped. The total duration of the recordings was about 70 seconds. Subsequently, CO and PCWP were measured during pacing and blood sampling was repeated. Then, during recording of CBF, ABP, PAP, RAP and ECG, pacing was stopped (HR step down) and recording continued until a new steady state had been recorded, again yielding values at sinus rhythm. A final series of PCWP and CO measurements and blood sampling completed this series of measurements.

Following the completion of this first series of control measurements, the effect of the calcium channel blocker felodipine (AstraZeneca, Mölndal, Sweden) on pacing induced changes in coronary blood flow was studied. Felodipine was dissolved in ethanol 10% and polyethylene glycol (20%) by the manufacturer. Patients received an intravenous infusion of felodipine at a rate of 30 μg/min for the first five minutes, followed by an infusion at a rate of 5 μg/min. For the measurement of plasma concentrations of felodipine, arterial blood samples were taken before, five and 20 minutes after the start of the felodipine infusion. Measurements during felodipine infusion were started immediately following the five minutes bolus infusion.

2.4 Laboratory analysis and calculations
Arterial and coronary sinus blood samples were analyzed to determine plasma hemoglobin concentration, oxygen partial pressure (pO₂) (ABL III, Radiometer, Copenhagen, Denmark), and hemoglobin oxygen saturation (SO₂) (OSM-II hemoxymeter, Radiometer, Copenhagen, Denmark). Felodipine plasma concentrations were measured by automated capillary gas chromatography with electron capture detection [10].

Coronary vascular resistance (CVR) was calculated as (ABP-RAP)/CBF. Myocardial oxygen content was calculated as $1.39 \cdot Hb \cdot SO_2 + 2.24 \cdot 0.00136 \cdot pO_2$. MVO₂ was calculated as CBF - arterio-coronary sinus oxygen content difference. Myocardial oxygen supply was calculated as CBF - arterio oxygen content.

2.5 Data analysis
Using a signal analysis program (Matlab v 3.5), The MathWorks Inc., Natick, Massachusetts, USA), ABP, PAP, RAP and CBF were averaged over periods of eight seconds of steady state, before and after HR steps up and down. Therefore two values were obtained during pacing, one after the HR step up, and one before the HR step down. Since these values during pacing were not significantly different, reflecting both the same steady state situation, they were averaged.

The steady state aspects of metabolic flow regulation were analyzed by means of the oxygen supply-demand diagram, showing myocardial oxygen supply as a linear function of MVO₂ (demand), for a given perfusion pressure [11,12]. As reported previously, we modified this diagram by plotting the changes in oxygen supply against the changes in MVO₂ that were induced by cardiac pacing, to correct for the
influence of the variation in coronary perfusion pressure and heart weight [7]. The changes in oxygen supply are related to the changes in MVO$_2$ by standard regression analysis without intercept, since in response to pacing, a change in myocardial oxygen supply cannot occur without a change in MVO$_2$. This yields the equation: $\Delta O_2$ supply = ratio $\cdot \Delta$MVO$_2$. The slope of the obtained line is the reference supply-demand ratio, defining normal metabolic coronary flow regulation. [13]

In the present study, the reference supply-demand ratio was used to evaluate the effect of felodipine on coronary metabolic regulation. This ratio obtained at control, was therefore compared with the supply-demand ratio, obtained from pacing induced changes in oxygen supply and MVO$_2$ during infusion of felodipine (defining metabolic regulation during felodipine). Upward deflection of the regression line, i.e. an increase in the supply-demand ratio, then implies increased metabolic vasodilation, whereas downward deflection means decreased metabolic vasodilation.

2.6 Statistical analysis
Data obtained at control and during felodipine were compared using two-way analysis of variance for repeated measurements. Paired standard t-tests were used to compare values at sinus rhythm to values obtained during pacing. A value of $p < 0.05$ was considered significant. Results are reported as mean (SD) or as percentage change (SD) where applicable.

Changes in myocardial oxygen supply were related to changes in MVO$_2$ using standard regression analysis. To compare the slopes of the regression lines obtained at control and during felodipine, we used analysis of variance for differences between regression slopes [14]. The slopes of the obtained regression lines, i.e. the myocardial oxygen supply/consumption ratios, are reported with their 95% confidence intervals (95% CI).

3. Results
3.1 Characteristics of the patients
Patients’ characteristics and clinical findings are shown in table 7.1. The study group consisted of seven male and three female patients, comparable with respect to age, weight and height. Seven patients had three-vessel CAD, whereas three patients had two-vessel disease. All but three patients were using triple therapy for angina, consisting of long-acting nitrates, beta-adrenergic blocking agents and calcium channel blockers. All patients discontinued the use of nitrates and calcium channel blockers at least 36 hours before surgery. None of the patients was taking felodipine orally.

3.2 Normal metabolic coronary flow regulation: the reference supply/demand ratio
Pacing the heart at an average of 32 ± 1 beats/min above sinus rate at control resulted in a significant increase in MVO$_2$ from 14.0 ± 4.1 ml O$_2$/min during sinus rhythm to 20.5 ± 5.9 ml O$_2$/min during pacing (figure 7.1). This increase was
Table 7.1: 
Patient characteristics and clinical data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
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</thead>
<tbody>
<tr>
<td>Age (yr)</td>
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<td>(10)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77</td>
<td>(6 )</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
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<td></td>
</tr>
<tr>
<td>Treated hypertension</td>
<td>6/10</td>
<td></td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>10</td>
<td>(5 )</td>
</tr>
<tr>
<td>Extent of coronary artery disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two vessels</td>
<td>3/10</td>
<td></td>
</tr>
<tr>
<td>Three vessels</td>
<td>7/10</td>
<td></td>
</tr>
<tr>
<td>Preoperative medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrates</td>
<td>9/10</td>
<td></td>
</tr>
<tr>
<td>Ca antagonist</td>
<td>9/10</td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>9/10</td>
<td></td>
</tr>
<tr>
<td>Triple therapy</td>
<td>7/10</td>
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</tr>
</tbody>
</table>

Data are expressed as n or mean (SD). LVEDP, left ventricular end-diastolic pressure.

completely matched by an increase in CSBF from $138 \pm 38$ ml/min to $200 \pm 53$ ml/min (through a $25 \pm 13 \%$ reduction in CVR), because myocardial oxygen extraction percentage remained unchanged ($61 \pm 7 \%$ and $62 \pm 4 \%$, respectively). After cessation of pacing, values of MVO$_2$ and CSBF returned to prepacing values in all patients (figure 7.1).

Individual changes in myocardial oxygen supply, related to pacing-induced changes in MVO$_2$, are shown in figure 7.2 (top). Metabolic coronary flow regulation is illustrated by the linear relation between the changes in oxygen supply and consumption. The slope of the calculated regression line (the supply/demand ratio), which is used as reference ratio quantifying normal metabolic flow regulation at control, was 1.58 (95% CI, 1.38-1.80).

3.3 Felodipine plasma levels

Felodipine was not detected in the plasma of blood samples drawn before the start of the felodipine infusion. Following five minutes bolus infusion of felodipine 30 μg/min, the mean plasma level of felodipine was $13 \pm 4$ nmol/l. After 20 minutes of felodipine infusion (five minutes bolus infusion and 15 minutes continuous infusion at a rate of 5 μg/min) the mean plasma level of felodipine was $4 \pm 1$ nmol/l.

3.4 Systemic and coronary dynamic effects of felodipine

The effect of felodipine on baseline values of hemodynamic variables at sinus rhythm and during pacing are shown in table 7.2. In response to felodipine, there was a reflex increase in sinus rate from $62 \pm 6$ beats/min at control to $70 \pm 8$ beats/min during felodipine, which was associated with a concomitant decrease in
Figure 7.1: Values of coronary sinus blood flow (CSBF), myocardial oxygen consumption (MVO₂) and myocardial oxygen extraction (MO₂E) are shown at sinus rhythm, during pacing and again at sinus rhythm after cessation of pacing, both at control and during infusion of felodipine. Note that values after cessation of pacing always returned to pre-pacing values. Values are shown as mean (SEM). *p < 0.05 versus corresponding value at control.
Figure 7.2: Effect of felodipine on metabolic coronary flow regulation. Shown is the effect of small pacing-induced changes in heart rate (30 beats/min above sinus rate) on myocardial oxygen supply ($O_2$ supply) and myocardial oxygen consumption (MVO$_2$) at control (top) and during administration of felodipine (bottom). Top: the dashed line, characterizing metabolic coronary flow regulation at control, is the result of regression analysis to the data ($\triangle O_2$ supply = 1.58 (95% CI: 1.38 - 1.80) $\cdot$ MVO$_2$) and was used as reference in the bottom panel. Bottom: the regression line calculated from the data during infusion of felodipine ($\triangle O_2$ supply = 1.52 (95% CI: 1.26 - 1.78) $\cdot$ MVO$_2$) was not significantly different from the reference line at control, suggesting that metabolic coronary flow regulation was not changed during infusion of felodipine.
arterial blood pressure. In addition, felodipine decreased left ventricular afterload, which is reflected by a significant decrease in SVR. Felodipine, had little effect on cardiac preload, because PCWP did not change significantly.

Following infusion of felodipine, CSBF increased from 143 ± 38 ml/min to 170 ± 47 ml/min (p = 0.030). This change in CSBF was associated with a decrease in CVR of 23 ± 15 %. The concomitant increase in MVO₂ was not significant: 14.9 ± 3.8 ml O₂/min at control and 16.3 ± 5.9 ml O₂/min during infusion of felodipine (p = 0.37). Thus, the felodipine-induced increase in CSBF appeared to be larger than was expected on the basis of the concomitant change in MVO₂, which suggests a true coronary vasodilatory action of felodipine. Our finding that coronary venous oxygen saturation increased significantly from 36 ± 6 % at control to 42 ± 7 % (p = 0.047) during infusion of felodipine, supports this suggestion.

3.5 Felodipine and metabolic coronary flow regulation
The pacing-induced increase in heart rate during infusion of felodipine, was comparable to the pacing-induced change in heart rate at control. However, to correct for the felodipine-induced increase in sinus rate, pacing rate was increased to 100 ± 8 beats/min during infusion of felodipine, compared to the pacing rate of 94 ± 6 beats/min at control.

Felodipine did not change the increase in MVO₂ that was induced by pacing. The accompanying increase in CSBF was 46 ± 14 ml/min, which was not different (p = 0.23) from the pacing-induced increase in CSBF at control, being 62 ± 33 ml/min. Thus, in addition to the aforementioned felodipine-induced decrease in CVR of 23 ± 15 %, CVR decreased further by 16 ± 11 % in response to pacing (figure 7.3). This resulted in a CVR which was significantly lower than the CVR during pacing in the control condition.

The individual changes in myocardial oxygen supply related to the pacing-induced changes in MVO₂ during infusion of felodipine, are shown in figure 7.2 (bottom). Thus, during felodipine, metabolic coronary flow regulation was characterized by a supply/demand ratio of 1.52 (95 % CI, 1.26 -1.78), which was not significantly different from the supply/demand ratio at control. This suggests that infusion of felodipine did not affect metabolic coronary flow regulation.

4. Discussion
This study in awake patients with CAD showed that intravenous administration of the calcium channel blocker felodipine resulted in both peripheral and coronary vasodilation. However, felodipine did not change the ratio of pacing-induced changes in myocardial oxygen supply and MVO₂. At control, this supply/demand ratio reflects normal metabolic coronary flow regulation [13]. Thus, metabolic coronary flow regulation was not affected by felodipine.

For the present study felodipine was chosen as a pharmacological tool to study the effect of calcium channel blockade on metabolic coronary flow regulation. This agent is a second-degree dihydropyridine with a high degree of vasoselectivity, indicating that felodipine inhibits vascular smooth muscle tissue at concentrations
Table 7.2:
Systemic hemodynamics at sinus rhythm and during pacing

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Felodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR (beats/min)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SR</td>
<td>62 (6)</td>
<td>70 (8)*</td>
</tr>
<tr>
<td>Pacing</td>
<td>94 (6)</td>
<td>100 (8)*</td>
</tr>
<tr>
<td>SR</td>
<td>61 (6)</td>
<td>70 (8)*</td>
</tr>
<tr>
<td><strong>SBP (mmHg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SR</td>
<td>147 (22)</td>
<td>137 (19)*</td>
</tr>
<tr>
<td>Pacing</td>
<td>155 (27)</td>
<td>146 (22)*</td>
</tr>
<tr>
<td>SR</td>
<td>149 (24)</td>
<td>137 (18)*</td>
</tr>
<tr>
<td><strong>MAP (mmHg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SR</td>
<td>100 (13)</td>
<td>93 (11)*</td>
</tr>
<tr>
<td>Pacing</td>
<td>108 (18)</td>
<td>102 (14)**</td>
</tr>
<tr>
<td>SR</td>
<td>98 (15)</td>
<td>92 (11)*</td>
</tr>
<tr>
<td><strong>DBP (mmHg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SR</td>
<td>69 (8)</td>
<td>66 (7)**</td>
</tr>
<tr>
<td>Pacing</td>
<td>80 (11)</td>
<td>75 (9)**</td>
</tr>
<tr>
<td>SR</td>
<td>71 (7)</td>
<td>69 (8)**</td>
</tr>
<tr>
<td><strong>PAP (mmHg)</strong></td>
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<tr>
<td>SR</td>
<td>25 (7)</td>
<td>28 (8)*</td>
</tr>
<tr>
<td>Pacing</td>
<td>26 (8)</td>
<td>30 (11)**</td>
</tr>
<tr>
<td>SR</td>
<td>23 (6)</td>
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<tr>
<td><strong>RAP (mmHg)</strong></td>
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<tr>
<td>SR</td>
<td>8 (4)</td>
<td>9 (5)**</td>
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<tr>
<td>Pacing</td>
<td>5 (4)</td>
<td>7 (6)**</td>
</tr>
<tr>
<td>SR</td>
<td>7 (4)</td>
<td>9 (6)**</td>
</tr>
<tr>
<td><strong>PCWP (mmHg)</strong></td>
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</tr>
<tr>
<td>SR</td>
<td>10 (3)</td>
<td>11 (3)**</td>
</tr>
<tr>
<td>Pacing</td>
<td>9 (4)</td>
<td>11 (5)**</td>
</tr>
<tr>
<td>SR</td>
<td>9 (4)</td>
<td>12 (4)**</td>
</tr>
<tr>
<td><strong>CI (L/min/m²)</strong></td>
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<tr>
<td>SR</td>
<td>2.8 (0.3)</td>
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</tr>
<tr>
<td>SR</td>
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<td>3.4 (0.7)*</td>
</tr>
<tr>
<td><strong>SVR (dynes/cm²)</strong></td>
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<tr>
<td>SR</td>
<td>1399 (264)</td>
<td>1094 (146)*</td>
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<tr>
<td>Pacing</td>
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<tr>
<td>SR</td>
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<td>1124 (230)*</td>
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<tr>
<td><strong>RPP (mmHg/min)</strong></td>
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<tr>
<td>SR</td>
<td>9169 (1953)</td>
<td>9628 (2074)**</td>
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<tr>
<td>Pacing</td>
<td>14569 (2822)</td>
<td>14645 (2574)**</td>
</tr>
<tr>
<td>SR</td>
<td>9121 (1829)</td>
<td>9616 (1830)**</td>
</tr>
</tbody>
</table>

Values at sinus rhythm of heart rate (HR), mean systolic arterial blood pressure (SBP), mean arterial blood pressure (MAP), diastolic arterial blood pressure (DBP), pulmonary artery pressure (PAP), right atrial pressure (RAP), pulmonary capillary wedge pressure (PCWP), cardiac index (CI), systemic vascular resistance (SVR) and rate-pressure product (RPP) are reported at control and during infusion of felodipine.

Values are expressed as mean (SD).* p < 0.05 versus corresponding control value; **, not significant.
that are free of significant negative inotropic activity [15,16]. This is of particular importance since the direct negative inotropic effects of calcium channel blockade would complicate the interpretation of drug actions upon metabolic coronary vasodilation. Although other calcium channel blockers including nicardipine, amlodipine or isradipine are also available, they are associated with more reflex tachycardia, a lower degree of vasoselectivity, and a longer duration of action, respectively [15].

The measured plasma levels of felodipine were within the therapeutic range for the chronic treatment of patients with hypertension (2-20 nmol/l) and in accordance with the felodipine plasma concentrations found by Emanuelsson et al. [17] following a continuous infusion rate of 10-25 μg/min. Although the mean plasma level decreased following twenty minutes of felodipine infusion compared with the plasma level directly following the five minutes bolus infusion, stable hemodynamic conditions existed; systemic and coronary hemodynamics at sinus rhythm after pacing were not significantly different from values before pacing (table 7.2, figure 7.1). Thus, in the present study, stable hemodynamic conditions existed during infusion of felodipine, during which the process of metabolic vasodilation could be studied.

4.1 Metabolic coronary flow regulation
Although the precise mechanisms responsible for metabolic coronary flow regulation remain largely unknown, it has recently become clear that the coronary endothelium may play an important role. In patients with endothelial dysfunction (e.g. patients with hypercholesterolemia, hypertension and/or CAD), metabolic coronary vasodilation has been shown to be reduced [18-23], which has partly been explained by the diminished release of endothelium derived relaxant factors, including nitric oxide. Other studies demonstrated that after blockade of endogenous nitric oxide synthesis with L-arginine analogues, metabolic coronary vasodilation was attenuated in both dogs [24] and humans [22,25,26], suggesting that nitric oxide was a possible mediator in the metabolic control of coronary flow. However, others could not confirm these findings [27]. Furthermore, nitric oxide donor substances have recently been shown to increase metabolic coronary vasodilation in patients with CAD [7], which indicates that excess nitric oxide may restore the effect of the reduced endogenous nitric oxide activity in these patients [28].

4.2 Calcium channel blockers and endothelial dysfunction
In rabbits [1,2] and patients with hypertension [3] or hypercholesterolemia [4], calcium channel blockers have been reported to reverse the impairment in endothelium dependent, nitric oxide mediated vasodilation. Since vascular resistance remained unchanged in these studies, this effect was probably not due to the calcium channel blocking effects of these agents. However, it was suggested that this beneficial effect was caused by a specific improvement of impaired nitric oxide availability due to a reduction in superoxide generation (resulting in reduced catabolism of nitric oxide) [4,29]. The finding that lipid peroxidation in vitro is reduced and that cultured endothelial cells and isolated rat hearts are protected
Felodipine and metabolic coronary vasodilation

**Figure 7.3:** Effect of pacing on coronary vascular resistance (CVR) at control (●) and during infusion of felodipine (○). Shown is the percentage change in CVR compared to the CVR at sinus rhythm (SR) in the control condition. Values are shown as mean (SEM). Note that following the felodipine-induced decrease in CVR, a further decrease in CVR in response to pacing was observed, indicating that metabolic coronary flow regulation was still active during infusion of felodipine. Note also that the combined effect of pacing and felodipine infusion on CVR was larger than the effect of pacing alone. However, this was not due to increased metabolic vasodilation during infusion of felodipine (figure 7.2), rather than felodipine-induced vasodilation which persisted during pacing. Thus, felodipine altered the setpoint for the process of metabolic coronary flow regulation.

Against free-radical-induced injury in the presence of a calcium channel blocker, supports this idea [30-32]. In agreement, Kitikaze et al. [33] demonstrated in dogs that nifedipine acutely increased the release of nitric oxide metabolites in coronary venous blood. Furthermore, the chemical structure of dihydropyridine calcium-antagonists is consistent with antioxidant properties, since these drugs possess aromatic resonance rings, a feature common to most classic chain-breaking antioxidants. Thus, it is conceivable that, besides their direct vasodilatory effect on vascular smooth muscle, calcium channel blockers may have an effect on nitric oxide availability.

### 4.3 Calcium channel blockers and metabolic coronary vasodilation

Although the acute effects of calcium channel blockers, including felodipine, on coronary blood flow and MVO$_2$ have been studied extensively in conditions of pacing induced ischemia [17,34-37], little is known about the effect of these agents...
on metabolic flow regulation itself. Regarding metabolic flow regulation, interpretation of the aforementioned studies [17,34-37] is difficult because during myocardial ischemia, other than metabolic coronary flow regulating mechanisms may prevail. Furthermore, most studies failed to report the magnitude of pacing or exercise induced changes in $\text{MVO}_2$, which is a prerequisite for quantification of metabolic vasodilation.

Using biplane quantitative coronary angiography, but without measuring coronary blood flow or $\text{MVO}_2$, Kaufmann et al. [6] and Frielingsdorf et al. [5] studied the effect of calcium channel blockers on the response of normal and stenotic epicardial arteries to physiological exercise in hypertensive and hypercholesterolemic patients with CAD. They concluded that the impaired epicardial vasodilation in response to exercise in these patients was reversed by administration of nicardipine or diltiazem. This was most likely due to drug-induced direct relaxation of smooth muscle in the epicardial vasculature, which persisted during exercise, but an effect of the calcium channel blockers on endothelial function and nitric oxide availability could not be excluded. In line with the findings by Kaufmann et al. [6] and Frielingsdorf et al. [5], but using coronary venous blood flow responses, we found that the reduction in CVR during pacing and felodipine infusion was more pronounced, compared to the reduction in CVR during pacing in the control situation (figure 7.3). This extends their conclusions based on measurements in the epicardial vasculature to the coronary flow regulating microcirculation. However, these findings do not necessarily imply that felodipine improved or normalized impaired metabolic coronary flow responses. In the present study, despite the felodipine-induced decrease in CVR, we observed a further decrease in CVR in response to pacing, which suggests that metabolic coronary flow regulation was still active during infusion of felodipine. Comparing metabolic coronary vasodilation during infusion of felodipine to control, we found that felodipine did not change the ratio of pacing-induced changes in myocardial oxygen supply and consumption (figure 7.2). Therefore, we conclude that with the techniques used in the present study, metabolic coronary flow regulation was not affected by administration of a calcium channel blocker, although the setpoint of this regulation mechanism may have been offset by the initial felodipine induced coronary vasodilation.

5. References


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CHAPTER 7


