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

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Chapter 8

General discussion
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1. Introduction

Although the regulation of myocardial blood flow and its close relationship with myocardial oxygen consumption have been studied for many years, it is still not adequately understood. However, it is becoming increasingly clear that regulation and modulation of coronary blood flow is the result of heterogeneous control mechanisms, including metabolic control, flow-mediated vasodilation, and myogenic responses, as discussed in chapter 1. However, the relative importance of each mechanism varies between different segments of the coronary (micro)circulation. Whereas flow mediated mechanisms are predominantly present in small coronary arteries, mechanisms mediating autoregulation and metabolic regulation are located more downstream in arterioles < 150 μm in diameter, that constitute the major fraction of total coronary vascular resistance. The metabolic control of coronary blood flow in these vessels is thought to be the most important regulatory mechanism in the coronary circulation.

Several approaches to study metabolic coronary flow regulation in humans have been described. First, it should be noted that in light of the heterogeneous distribution of the control mechanisms, quantitative coronary angiography is not suited to study metabolic coronary flow control. Studies using this technique [1] only look at epicardial vasomotor responses, rather than metabolic coronary flow responses. Although these epicardial responses are initially induced by a metabolic stimulus, they are eventually the result of different control mechanisms.

Alternatively, ultrasonic Doppler techniques have been used to assess the metabolically induced changes in coronary flow velocity [2]. However, the principal drawback of this technique is the fact that velocity rather than flow is measured. For the correct interpretation of results, it is crucial to have precise knowledge of the magnitude and direction of any change in the cross sectional area of the coronary vessel in response to a metabolic stimulus. Otherwise, statements regarding changes in absolute flow and metabolic coronary flow control are not valid. This has prompted some authors to combine quantitative coronary angiography and Doppler flow-velocity measurements to obtain a more reliable estimate of coronary blood flow in order to draw conclusions on metabolic coronary flow responses [3]. However, this combined technique still precludes correction for differences in the magnitude of metabolically-induced changes in myocardial oxygen consumption, unless a coronary sinus catheter is also introduced for the sampling of coronary venous blood. Unfortunately, this has frequently been omitted, which renders the change in myocardial oxygen consumption an important confounding factor of metabolic coronary flow regulatory responses.

Another approach is applied in the present thesis. Using the continuous thermodilution technique, described by Ganz et al. [4] in 1971, absolute coronary sinus blood flow (in contrast to velocity) could be measured and metabolic coronary flow responses could be evaluated. In addition, this technique has the advantage that coronary venous blood samples can be drawn for the determination of myocardial oxygen consumption in order to correct coronary flow responses for the metabolically-induced changes in myocardial oxygen consumption. Using this 'old'
technique as a new approach to study metabolic coronary flow regulation, the effects of exogenous nitric oxide, calcium-entry blockade and anesthesia with high dose fentanyl/pancuronium bromide on metabolic coronary flow responses were studied. Based on the results of the studies presented in this thesis and the available literature discussed in chapters 1 and 2, several observations regarding metabolic coronary flow regulation can be made.

1.1 Change in myocardial oxygen consumption
The mechanisms involved in metabolic coronary flow regulation lead to a change in coronary blood flow that is proportional to the induced change in myocardial oxygen consumption. In other words, coronary blood flow is linearly related to myocardial oxygen consumption. Therefore, it is important to be informed about the magnitude of the induced change in myocardial oxygen consumption. In chapter 3 it is demonstrated that changes in other parameters, including the rate pressure product, cannot be used as surrogate for the adequate assessment of the change in myocardial oxygen consumption. An additional finding in that study was that the relationship between the percentage increase in myocardial oxygen consumption and rate pressure product completely disappeared during administration of the nitric oxide donor substance nitroglycerin, which was explained by the fact that nitric oxide might have influenced the change in myocardial metabolism directly, without having an effect on the change in rate pressure product.

We compared the results described in chapter 3, with previous studies [5-7], in which individual data points, obtained with different methods of coronary flow measurement, were reported. The recalculated regression lines from those studies, together with the regression lines from the study described in chapter 3, are shown in figure 8.1. This figure once again illustrates that changes in myocardial oxygen consumption cannot be predicted accurately from the changes in rate pressure product. In addition it is shown that, compared to pacing, exercise resulted in a more pronounced increase in myocardial oxygen consumption for comparable increases in rate pressure product. A likely explanation may be that endogenous catecholamines, released during exercise but not during pacing, contributed to the increase in myocardial oxygen consumption through an effect on myocardial metabolic and contractile state, while this is not being reflected in the rate pressure product. Finally, this figure suggests that for comparable increases in rate pressure product, myocardial oxygen consumption increases more in patients with coronary artery disease than in patients without coronary artery disease. Knowing that in patients with coronary artery disease nitric oxide availability is reduced [8], this observation is in line with the finding that in the absence of nitric oxide an augmented increase in myocardial oxygen consumption for comparable increases in triple product was observed [9]. Theoretically, this may further support the hypothesis that nitric oxide may impair myocardial metabolism directly [10,11]

In conclusion, for the study of metabolic flow regulation, it is recommended to measure myocardial oxygen consumption directly. In addition, it may be clear that studies regarding metabolic flow regulation, that do not measure myocardial oxygen consumption directly, should be interpreted with caution.
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Figure 8.1: Shown are the recalculated regression lines from different studies in patients with (solid lines) and without (dashed lines) coronary artery disease (CAD). The regression lines characterise the relation between the percentage increase in rate pressure product (RPP), either induced by pacing (thin lines) or exercise (bold lines), and the percentage increase in myocardial oxygen consumption (MVO₂). Pacing and exercise induced changes are expressed as % change from values during sinus rhythm and resting conditions, respectively.

1.2 Heterogeneous distribution of coronary vascular resistance
As stated above, coronary vascular resistance is heterogeneously distributed along the coronary vascular tree, with the majority of resistance localized in the coronary resistance vessels < 150 μm in diameter, that are most sensitive to changes in perfusion pressure and metabolism. We believe that the importance of pharmacological or pathophysiological changes in the distribution of this resistance is underestimated, since this mechanism might theoretically explain many of the observed changes in metabolic coronary vasodilation. For example, the observation in chapter 5 that nitroglycerin increased metabolic coronary vasodilation in patients with coronary artery disease was explained by the fact that administration of nitroglycerin shifted the predominant site of resistance in the direction of the smaller microvessels, responsible for metabolic flow control. A metabolic stimulus will then result in relatively more pronounced vasodilation, compared with the situation in which coronary vascular resistance is distributed in the larger coronary vessels, less sensitive to changes in metabolism. On the other hand, following inhibition of nitric oxide synthesis, it was shown that small coronary arteries constricted, whereas arterioles dilated [12], suggesting that the increase in coronary vascular resistance, observed following L-arginine analogues, is the result of a more pronounced vasoconstriction of small coronary arteries, moving the predominant site of
resistance away from the metabolically active arterioles. Thus, under these conditions, it may not be surprising that the coronary vasodilatory response to a metabolic stimulus has been shown to be mitigated [3,13,14].

The distribution of the coronary vascular resistance in the presence of nitric oxide and under conditions in which nitric oxide availability is reduced (e.g. during administration of NOS inhibitors, or in the presence of endothelial dysfunction) is schematically shown in figure 8.2 [15]. This figure shows that metabolic control of arteries increases from proximal to distal vessels, whereas nitric oxide effects decrease in the same order [16], partly because the inhibitory effect of nitric oxide on myogenic and sympathetic constriction is functionally more important in the vascular section with larger arterioles. Based on the distribution of the relative significance of these regulation mechanisms, Pohl and de Wit [15] hypothesized that inhibition of nitric oxide should not only result in a reduction in basal flow, but also in an inadequate adaptation of blood flow to altered demands. The finding that metabolic flow adaptation is attenuated in patients with endothelial dysfunction [3,13] and the finding that excess nitric oxide may restore metabolic vasodilation to a certain extent (chapter 5) supports this idea.

The absence of an effect of felodipine on metabolic coronary flow control can also be explained on the basis of the heterogeneous distribution of coronary vascular resistance. From the data presented in chapter 7, it is clear that intravenous

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**Figure 8.2:** Relative significance of metabolites (Meta), nitric oxide (NO), and myogenic constriction (Myo) in large and small arterioles. Although under control conditions these influences are balanced (see balance between constriction (C) and dilation (D), a reduction of NO has functional consequences predominantly in large arterioles. (Redrawn from Pohl and de Wit [15])
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administration of felodipine resulted in vasodilation of coronary resistance vessels. From experimental studies it is known that larger epicardial arteries also dilate in response to calcium channel blockers [17,18], which may be either due to a direct effect on the smooth muscle cells or to a flow-dependent vasodilatory mechanism. In response to felodipine, the degree of coronary vasodilation may thus have been distributed evenly along the total coronary vascular tree. Despite the substantial felodipine-induced decrease in coronary vascular resistance, the predominant site of resistance probably remained unchanged, as was the flow response to the subsequently induced metabolic stimulus. This suggests that metabolic coronary vasodilation itself was not influenced by calcium channel blockade, even though the setpoint of this regulation process was changed to a higher level of coronary blood flow.

The different effects of nitroglycerin and felodipine on metabolic coronary flow regulation may thus be explained by their different action on the distribution of coronary vascular resistance. However, it is not known what is more beneficial for the patient with coronary artery disease: improved metabolic vasodilation as observed with nitroglycerin, or unaffected metabolic vasodilation at a different setpoint as observed with felodipine. Their completely different effects on coronary vascular resistance and myocardial oxygen consumption are summarized in figure 8.3. Both the observation that nitroglycerin induced a larger decrease in coronary vascular resistance in relation to the pacing-induced increase in myocardial oxygen consumption, as well as clinical experience suggest that nitroglycerin is beneficial for the patient with coronary artery disease. However, this may also be related to other effects of nitroglycerin, including its aforementioned direct effect on myocardial metabolism.

1.3 Coronary vasodilator agents and metabolic vasodilation
Knowledge of metabolic coronary flow regulation should be used when evaluating the potential coronary vasodilator action of various agents. As discussed before, most investigators interpret changes in vessel diameter measured angiographically as changes in myocardial oxygen supply [1,19]. Implicitly, they assume that aortic pressure, myocardial oxygen consumption and distal coronary vessel tone remain unchanged. To improve the interpretation of these measurements, coronary blood flow velocity is measured as well. This yields a measure of flow, if diameter and flow velocity are measured at the same location [13]. If aortic pressure is known, resistance can also be calculated [3]. Changes in myocardial oxygen consumption are usually not monitored in these studies. To obtain this variable, both arterial and coronary sinus oxygen content should be measured.

It has been suggested to monitor only coronary sinus oxygen content to judge the vasoactivity of drugs [20]. Coronary venous oxygen content should increase with direct vasodilators. This is true, but from venous oxygen content alone one cannot judge the stress impact (=degree of change in myocardial oxygen consumption) of the vasoactive drug. In chapter 4 the use of the myocardial oxygen supply/demand ratio was explained as reference for coronary vasodilatory drug effects. Using the myocardial oxygen supply/demand ratio, it was shown that many vasoactive drugs
do not exert a direct coronary vasodilatory effect, when administered intravenously in physiologic doses. However, only when administered intracoronary, these drugs may produce direct coronary vasodilation, but under these conditions drug concentrations are often unnaturally high. This makes extrapolation of data obtained under those conditions to the effects of the same drugs when taken orally very difficult.

A disadvantage of the use of the slope of the myocardial supply/demand ratio as measure for drug induced vasoactivity is the fact that the same measurement of coronary blood flow is used for the calculation of myocardial oxygen supply and
demand. Errors in the coronary blood flow measurement and natural variations among patients add to the fit of the regression line. The correlation coefficients obtained are artificially high and should be used with caution. The most ideal situation would be to measure oxygen consumption by a method independent of coronary blood flow. In practice this cannot be done yet. As a second best alternative, the oxygen extraction ratio being a flow independent measure, can be used for the test of statistical significance. Any significant change in oxygen supply/demand ratio in a group of patients in reaction to any treatment, should yield a significant change in oxygen extraction ratio as well (see chapters 5 to 7).

In chapter 4, we introduced the coronary vasodilation potency as an additional measure to describe vasoactivity. To quantify the average vasodilating potency of vasoactive drugs, the mean difference between the measured coronary oxygen supply and predicted oxygen supply, based on the physiological oxygen supply/demand relation in humans, was calculated. The advantage of this measure is that it takes the normal physiological variation in oxygen supply into account, while testing drugs for coronary vasoactivity. It was shown that the coronary vasodilating action of several intravenously administered drugs, was mainly attributable to metabolically induced changes in myocardial oxygen supply. Metabolic coronary flow regulation, being the most predominant flow regulatory mechanism, thus frequently overrules any vasodilatory drug action.

1.4 Dynamics of coronary flow regulation
Although a large number of studies has been done to unravel the mechanisms involved in the control of coronary flow, very few investigators looked at the rate of coronary flow control. However, several observations indicate that the dynamics of coronary flow regulation may provide additional information about the mechanisms responsible for the control of coronary flow.

In 1994, Dankelman et al. [21] showed in anesthetized goats that the rate of coronary flow regulation in response to a change in heart rate could specifically be decelerated by glibenclamide. Furthermore, as discussed in chapter 1, it was shown that the rate of regulation was dependent on the mode of coronary perfusion. Constant flow perfusion resulted in slower responses compared to constant pressure perfusion, while during constant pressure perfusion, but not during constant flow perfusion, the response rate was also dependent on the level of coronary perfusion pressure, being faster at lower pressures [22,23]. Moreover, the dynamics of coronary flow regulation appeared to be species dependent, because the coronary response rate appeared to be faster in the anesthetized dog, compared to the anesthetized goat [22,23]. That the importance of the dynamics of coronary flow regulation is easily overlooked, is also illustrated by the fact that regulation mechanisms are sometimes presumed to be involved in coronary flow control, while their time constants do not match with the observed coronary responses (chapter 1). Thus, these independent observations demonstrate that the response time of the coronary system is a specific aspect of coronary flow control, which should not be neglected.

In this thesis, for the first time, the dynamics of metabolic coronary flow regulation in humans have been described. In chapter 6 it was shown that in awake
patients with coronary artery disease, the rate of coronary flow regulation in response to a change in heart rate could be characterized by a t₅₀-value of ± 5 seconds. Furthermore, it was shown that rate of regulation, but not the change in coronary vascular resistance, was mitigated by high dose fentanyl/pancuronium bromide-anesthesia to a t₅₀-value of ± 10 seconds.

We hypothesized that pancuronium bromide might have been responsible for the reduced coronary response rate, since it may hypothetically attenuate parasympathetically mediated vasodilation due to its muscarinic receptor blocking effects. In this respect, there has been one earlier observation in goats showing that the type of general anesthesia may influence the rate of coronary flow regulation [23]. The coronary response to a pressure-step down (during constant pressure perfusion) was significantly slower in goats anesthetized with atropine-sulphate and ketamine-hydrochloride (5.3 seconds), compared to a group of goats anesthetized with fentanyl and pancuronium bromide (4.4 seconds) [23]. Since muscarinic receptor blockade is more pronounced with atropine compared to pancuronium bromide, it may indeed be that muscarinic receptor blockade has been involved in the deceleration of the coronary response in the study described in chapter 6 too.

An alternative explanation might involve the cardio-cardiac reflexes, that were already mentioned in chapter 1 (section 5.2). It is conceivable that ventricular mechanoreceptors, responsible for these reflexes, increase their rate of firing with an increase in heart rate, since they are stimulated more often per minute. Since the main effect of these receptors is a reduction in sympathetic tone and an increase in vagal tone, reflex coronary vasodilation is expected to occur [24,25]. This reflex vasodilation probably speeds up the concomitant metabolic vasodilation, that also occurs in response to the increase in heart rate. This idea is supported by the observation that surgical denervation of the heart slowed down the speed of the coronary response to an increase in heart rate in dogs [26]. Similarly, general anesthesia may impair these cardio-cardiac reflexes, which would at least partly explain the observed slower coronary response rate following an increase in heart rate under general anesthesia.

It should be noted that at present we do not know whether a fast coronary response rate is more beneficial than a slow response rate, or whether patients with coronary artery disease have a different coronary response rate than patients with normal coronary arteries. These questions still remain to be elucidated in future research. Although at the present time the clinical relevance of measurement of the rate of coronary flow control still remains uncertain, it is important that parameters describing the dynamics of human coronary flow regulation have now become available, so that they can be used for the modeling of the coronary control system in order to broaden our overall knowledge of the mechanisms responsible for the process of coronary flow control.

2. Implications
The above considerations concerning metabolic coronary flow regulation may have some direct implications. First, it has become clear that measuring the change in myocardial oxygen consumption is a prerequisite for the adequate interpretation of
metabolic flow regulation and/or the assessment of the degree of metabolic vasodilation. Second, the heterogeneous distribution of the coronary vascular resistance should be taken into account when coronary blood flow regulating processes are studied, since many of the observed coronary (metabolic) responses can be explained on the basis of redistribution of coronary vascular resistance. Third, the conclusions that nitroglycerin, in addition to its unloading properties, specifically attenuates heart rate-induced increases in myocardial oxygen consumption and furthermore increases the associated metabolic coronary vasodilation, support the liberal use of this agent in patients with coronary artery disease, both in the stable awake situation and during the stressful peri-operative period. Finally, we have stressed the importance of quantifying the degree of metabolic vasodilation when evaluating the true vasodilator potency of putative coronary vasodilator agents.

3. Future perspectives

In this thesis, it has been shown that metabolic coronary flow regulation is an intriguing, but extremely complex aspect of coronary flow control. This complexity is related to a number of factors, including the number of different mediators that are involved and the phenomenon that these mediators may substitute each other under different physiological and pathophysiological conditions. The fact that metabolic flow regulation is mainly governed by the smallest coronary resistance vessels that are difficult to study directly, further complicates the search for the mechanisms involved in this regulation process. New technologies developed for the imaging of the (human) microcirculation, such as orthogonal polarization spectral imaging [27], might in this respect prove to be helpful. Thus, these complicating factors will probably be overcome and in the future the mechanisms involved in metabolic flow regulation will undoubtedly further be clarified.

In future studies, the mediator nitric oxide will probably play an important role, especially now it has become clear that 1. endothelial dysfunction is linked to a pathological imbalance between the production of nitric oxide and superoxide, which is partly regulated by tetrahydrobiopterine, a cofactor of nitric oxide synthase [28], 2. many exogenous agents, including ascorbic acid and calcium channel blockers, improve nitric oxide availability by reducing the amount of circulating radicals, through an anti-oxidant effect [29], 3. nitric oxide has an effect on larger coronary arteries rather than coronary resistance vessels, and 4. nitric oxide has an inhibitory effect on myocardial cell-metabolism [9]. However, these studies involving nitric oxide may not clarify the mechanisms behind the initial metabolically induced change in diameter of coronary resistance vessels, since other mechanisms are probably responsible for this initial response of metabolic control of coronary blood flow.
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