Metabolic flow regulation in human coronary artery disease

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Citation for published version (APA):
Chapter 1

Coronary physiology

Published in part in:
CHAPTER 1

1. Introduction

In the past decades, experimental work in animals has given insight in static and
dynamic aspects of coronary blood flow control. In anesthetized open-chested dogs
and goats, coronary blood flow responses following changes in heart rate and
perfusion pressure have extensively been studied under different conditions.
However, in humans, there is little information about the control of coronary blood
flow, while there is no information at all about the dynamics of this control system.
Therefore, it is not known whether extrapolation of animal data to the human
situation is justified. In the present thesis, static and dynamic aspects of human
coronary flow control are described. These clinical observations were obtained in
patients with coronary artery disease, scheduled for coronary artery bypass grafting.
The methodology is based on concepts from the field of medical physics and
pharmacology and in the first two chapters these concepts will be addressed.

2. The coronary circulation

As applies to every other organ, the heart is dependent on the blood flowing through
its vessels, the coronary circulation. The inlet of the coronary circulation is situated
just above the aortic valve structure in the sinuses of Valsalva, where the right and
left coronary artery branch from the aorta. These major coronary arteries and their
principal branches course across the epicardial surface of the heart and serve as
conduit vessels, which normally offer little resistance to coronary blood flow. The
conduit vessels in turn give rise to smaller vessels which penetrate the heart muscle
approximately at right angles. Within the myocardium, there is a further division of
these branches into extensive networks of small arteries and arterioles (diameters of
30-300 μm), frequently designated as resistance vessels. Finally, the resistance vessels
branch in order to supply the dense capillary network of the heart with blood. It is at
this capillary level where oxygen and substrates are exchanged between blood and
muscle cells.

As in any vascular bed, blood flow in the coronary bed depends on the driving
pressure and the resistance offered by this bed. The coronary resistance is distributed
heterogeneously along the total coronary vasculature. By measuring pressures at
different segments of the coronary circulation, the relative contribution of each
segment to the overall coronary vascular resistance has been determined. Thus, it
was found that approximately 20% of coronary vascular resistance was located in
vessels > 200 μm in diameter [1], which indicates that under normal conditions with
intact vascular tone the majority of coronary vascular resistance is located in
coronary arterioles < 200 μm in diameter. However, the proportional contribution of
coronary vessels > 200 μm in diameter to total coronary vascular resistance can be
greatly magnified under conditions of pharmacological arteriolar vasodilation, e.g.
with papaverine [2] or dipyridamole [3].

Coronary vascular resistance is controlled by several mechanisms. In line with the
heterogeneous distribution of coronary vascular resistance, it has been shown that
the sensitivity of coronary vessels of different size varies for the various mechanisms
The present line of thought is that metabolic control of coronary blood flow resides in the smallest vessels (< 150 \mu m in diameter), whereas neurohumoral and flow-dependent mechanisms are located more upstream in the larger coronary vessels, > 200 \mu m in diameter [7]. Although all coronary microvessels thus contribute to autoregulatory control of coronary blood flow, the predominant level of regulation is supposed to be located in arterioles < 150 \mu m in diameter.

3. Characteristics of coronary flow control

The physiology of steady-state coronary flow regulation has been characterized by two phenomena, i.e. metabolic coronary flow regulation and autoregulation. The former is the matching of coronary blood flow to changes in myocardial oxygen demand and the latter is the relative compensation of changes in perfusion pressure by changes in coronary resistance. Figure 1.1 shows the interaction of both phenomena. In the lower panel, autoregulation curves are shown at three different levels of oxygen consumption. In the upper panel, metabolic regulation is shown at two levels of perfusion pressure. Both panels show that the overall effect of coronary blood flow regulation leads to the phenomenon that steady state coronary blood flow is determined by a linear combination of coronary perfusion pressure and myocardial oxygen consumption. In this relation, the variation related to myocardial oxygen consumption was demonstrated to be the most important determinant of coronary flow under physiological conditions.

3.1 Metabolic coronary flow regulation

Coronary blood flow is closely coupled to oxygen consumption in normal hearts. The oxygen consumption of the heart is not constant but depends on the work done by the myocardium, which is, among others, influenced by heart rate, contractility, left ventricular wall tension and basal metabolism [8]. The tight relation between coronary flow and myocardial oxygen consumption is not surprising since the myocardium depends almost completely on aerobic metabolism. This indicates that at every cardiac work load, the supply of oxygen should be sufficient to match the cardiac oxygen requirements in order to maintain normal cardiac function. Under normal conditions the myocardium extracts 70 % of all the oxygen from the blood flowing through its arteries, permitting little additional oxygen extraction. Since oxygen stores in the heart are limited, increases in the oxygen demand of the heart, must be matched by increases in oxygen supply. Since myocardial oxygen extraction is near-maximal, the most important way the heart can increase oxygen supply is by increasing myocardial blood flow through coronary vasodilation. Vasodilation of coronary resistance arteries (diameters between 30 and 300 \mu m) is controlled by a regulatory process, which controls the balance between the supply and demand of oxygen. This regulation mechanism is called metabolic coronary flow control, although sometimes it is referred to as functional hyperemia or active hyperemia. Figure 1.1 typically shows the relation between coronary blood flow and myocardial oxygen consumption, as it has been found in numerous studies in both animal and humans.
3.2 Autoregulation

When sudden alterations in coronary perfusion pressure occur, the resulting changes in coronary blood flow are only transient, with flow almost returning to the previous steady state level. Thus, in response to a sudden increase in perfusion pressure, coronary flow initially increases (passive), but is then directed towards its control value by vasoconstriction. A decrease in perfusion pressure in turn induces a vasodilatory response through a decrease in vascular resistance. This phenomenon is termed 'autoregulation'. In other words, coronary autoregulation refers to the
intrinsinc ability of the heart to maintain blood flow relatively constant over a wide range of perfusion pressures, when myocardial oxygen demand is constant.

Demonstration of autoregulation in the coronary vasculature is only feasible when coronary perfusion pressure can be altered, without changing the aortic or left ventricular pressure. A concomitant alteration in aortic or left ventricular pressure will affect myocardial oxygen consumption and will influence the position of the autoregulation curve. At different levels of myocardial oxygen consumption, the autoregulation curves are shifted parallel to the initial autoregulation curve. Thus, under controlled experimental conditions in which perfusion pressure is altered without changing the principal determinants of myocardial oxygen consumption, coronary autoregulation can be demonstrated. Figure 1.1 shows that autoregulation is present at coronary perfusion pressures as low as 50 mmHg and as high as 140 mmHg. In this autoregulatory range, coronary blood flow is relatively constant. When coronary perfusion pressure falls below the lower autoregulatory breakpoint, coronary flow will decrease. Conversely, when coronary perfusion pressure exceeds the higher autoregulatory breakpoint, coronary flow will increase.

4. Mechanisms of coronary flow control

4.1 Metabolic control by the oxygen model

Autoregulation and metabolic coronary flow regulation do not necessarily involve two different control systems. In the contrary, both phenomena can be explained by one regulation process. This regulation process has been simplified to a model in which tissue oxygen tension (or any other mediator) is coupled to coronary vascular resistance as a regulating principle [9]. In this model, steady state coronary blood flow is determined by coronary perfusion pressure and coronary vascular resistance (figure 1.2).

Metabolic coronary flow regulation is then simulated by this model in the following way: if myocardial oxygen consumption is increased, because of an increase in heart rate, tissue oxygen tension will decrease. This in turn results in a decrease in coronary resistance, which leads to an increase in oxygen supply through an increase in coronary blood flow. The steady state result is a relatively constant myocardial tissue oxygen tension and the matching of myocardial oxygen supply to oxygen demand, i.e. metabolic coronary flow regulation.

Autoregulation in turn can also be explained by this model: when coronary perfusion pressure is increased at a constant level of myocardial oxygen consumption, tissue oxygen tension will increase because of the proportional change in coronary oxygen supply. According to the model, the increase in tissue oxygen tension will lead to an increase in coronary vascular resistance, to such an extent that tissue oxygen tension is kept constant. Due to the increase in coronary vascular resistance, coronary blood flow almost returns to its previous level, despite the increased coronary perfusion pressure. In summary, this model predicts that coronary blood flow (CBF) is linearly related to both myocardial oxygen
Figure 1.2: Schematic representation of the oxygen control model representing the metabolic control of coronary flow by tissue oxygen tension. $F_1$ = oxygen consumption by the myocardial cells. $F_2$ = oxygen extraction from the blood. $R$ = coronary vascular resistance. $P_a$ = coronary arterial pressure, $CBF$ = coronary blood flow, $PO_2$ = tissue oxygen tension. (Redrawn from Vergroesen et al. [10]).

Consumption ($MVO_2$) and perfusion pressure ($P_v$), according to the following equation:

$$CBF = aMVO_2 + bP_v + c$$

The predictions of this model were confirmed by Vergroesen et al. [10], who fitted the linear equation to the experimental data of dogs and goats and demonstrated a close correlation between the model data and the experimental data. This supported the idea that changes in tissue levels of metabolic substrates or metabolites following alterations in metabolism or perfusion pressure, may (in)directly modulate coronary vasomotor tone. However, the mechanism linking metabolic activity to coronary vascular resistance, has yet to be clarified, although a large number of studies have identified several mediators that may contribute to coronary flow control. The exact role of these mediators, including adenosine, nitric oxide, prostaglandins, oxygen and carbon dioxide is reviewed in chapter 2, and will not be discussed here.

4.2 The myogenic response

Studies on isolated vessels have demonstrated that the contractile state of the smooth muscle cells in the vessel wall may be affected by the transmural pressure [11]. Theoretically, this may contribute to the control of coronary blood flow in vivo since an elevation of the pressure induces a constriction by an increase in vascular
smooth muscle tone, and a pressure reduction causes dilation through relaxation of the smooth muscle cells. This effect of pressure alteration on the vascular smooth muscle tone is called the myogenic response.

Vessel wall tension has been suggested as the controlled variable in this myogenic response. Wall tension (T) is defined as the product of wall stress (σ), defined by the Laplace law¹, and wall thickness (h).

\[ T = \sigma h = P r \]

According to this hypothesis, a pressure elevation, which increases wall tension would activate the myogenic response and initiate a myogenic constriction, bringing back wall tension to its previous level [12]. But in order to maintain wall tension constant in the light of an increase in pressure, it is necessary for the vessel to constrict below its control diameter. Indeed, this was confirmed in cannulated blood vessels, in which a reduction of steady-state diameter in response to an increase in pressure was observed [12,13].

At present, many uncertainties exist about the transduction mechanisms potentially involved in the myogenic response [14]. Several potential mechanisms have been proposed. Opening of stretch dependent cation channels may produce membrane depolarization [15], which may activate voltage operated calcium channels, leading to an influx of calcium and vasoconstriction [16]. In addition, calcium release from intracellular stores and sensitization of the contractile machinery to calcium, possibly via activation of protein kinase C, may occur [17,18]. Finally, stimulation of α-adrenoceptors has been shown to potentiate the myogenic response, which may be explained by activation of the same transduction pathways. In general, it is accepted that the myogenic response is a phenomenon in which mechanical stimuli act directly on the vascular smooth muscle cell to elicit contraction.

The magnitude of the myogenic response depends on the species and the tissue from which the vessels are isolated [19]. Especially, arteries from the cerebral, renal, coronary and skeletal muscle vasculature display a high level of myogenic reactivity. The sensitivity to perturbations in pressure also depends on the size of the vessel: the smaller the vessels the greater the responsiveness to pressure [20]. Since arterioles are the main determinants of vascular resistance, a myogenic regulatory mechanism in these vessels may play a role in the autoregulation of coronary blood flow. Under passive conditions, an elevation in pressure will increase vessel radius (r) and, according to Poiseuille’s law², this will augment flow (Q). However, under active conditions (myogenic control), the vessel radius will reduce in response to an increase in pressure, bringing back flow to its previous level, despite the higher perfusion pressure. Thus, in the autoregulatory pressure range, the decrease in

¹ \( \sigma = (P \cdot r) / h \), where P is transmural pressure, r is vessel radius and h is wall thickness.

² \( Q = \frac{\pi \cdot \Delta P \cdot r^4}{8 \cdot \eta \cdot l} \), where \( \Delta P \) is the pressure gradient, r is vessel radius, \( \eta \) is viscosity of the blood plasma and l is the length of the vessel.
steady-state vessel diameter with pressure elevations may contribute to the maintenance of coronary blood flow during autoregulation.

A number of investigators raised objections against the myogenic hypothesis. One of the major objections is the positive feedback mechanism implicitly involved in this hypothesis. Perfusion pressure induced-vasoconstriction will lead to a further increase in perfusion pressure. Thus, without an effective brake mechanism, the initial pressure change would result in overcompensation, which has never been observed. Another objection concerns the rate of the myogenic response. In isolated vessels, it takes minutes to complete the myogenic response. However, in vivo, the autoregulatory responses to alterations in pressure are swift and never last longer than one minute (see section 5). Furthermore, the myogenic response is an isolated response of coronary vessels, whereas for autoregulation coronary blood flow has to be tuned to metabolism. Thus, although myogenic tone may potentially facilitate autoregulation, it cannot be the pivotal control mechanism. This supports the idea that another mechanism such as metabolic control likely contributes to, and probably dominates, coronary autoregulation.

4.3 Flow-induced vasodilation

Increases in flow may by itself induce a vasodilatory response. By modulating the flow rate in perfused isolated microvessels studied at constant intraluminal pressure, it was demonstrated that vascular conductance increased with increasing flow rates [21-23]. Furthermore, this response was demonstrated to be dependent on the presence of intact vascular endothelium [22]. This indicates that hydrodynamically-induced shear forces may result in endothelium-dependent relaxation of vascular smooth muscle cells, which leads to vasodilation.

Although flow-induced vasodilation has been observed in coronary resistance arteries, it is far more important in the larger coronary vessels [4]. Therefore, it has been suggested that this phenomenon may act as an amplification of error signals produced by substances or tissue metabolites that only influence the arterioles. The flow increase induced by dilation of these smallest vessels (e.g. in response to a metabolic stimulus) may then induce flow-induced dilation of vessels located more upstream. This would provide the coronary circulation with a mechanism capable of coordinating the dilation along the vascular tree, resulting in an adaptation of the overall vascular conductance to the new flow load [24].

This is supported by a recent report by Stepp et al. [25]. Using an in vivo canine model, they demonstrated that shear stress was effectively regulated in small coronary arteries, i.e. it remained constant with increases in flow, since the flow-induced vasodilation normalized shear stress to its initial values. However, in downstream arterioles shear stress increased proportional to flow, indicating that other factors were primarily responsible for coronary arteriolar tone in vivo, despite the demonstrated ability of these vessels to regulate shear stress in vitro [25].

It has been shown that the vasodilation in response to increases in wall shear stress is mediated by endothelial release of nitric oxide [25]. At the moment it is still unclear how a mechanical force as shear stress may induce biochemical events as the production and release of nitric oxide. There is evidence, however, that shear stress
increases intracellular free calcium by several mechanisms, which activates the calcium/calmodulin-dependent enzyme nitric oxide synthase, thus leading to increased nitric oxide synthesis and vasodilation [5].

4.4 Integration of mechanisms for flow control
Many different regulatory factors may thus influence coronary vascular resistance. To gain insight in the complex interplay between these various factors, a heterogeneous system for metabolic, myogenic and flow-mediated control of coronary blood flow has been proposed (figure 1.3). In this system, an increase in myocardial oxygen consumption and the subsequent change in tissue levels of metabolites initially leads to an adjustment in vessel tone preferentially in the smallest arterioles. Metabolic vasodilation of these arterioles results in a change in pressure and flow more upstream, which in turn might act as signals triggering vasodilatory responses in the larger arterioles and small coronary arteries, via myogenic and flow-dependent mechanisms. The presence of negative feedback loops are elemental in this system. The upstream vasodilation allows for transmission of pressure to the downstream segments, which attenuates further myogenic or autoregulatory vasodilation. Also, the overall decrease in coronary vascular resistance, and thus the increase in flow, would induce washout of vasoactive metabolites, which attenuates further
metabolite-induced vasodilation. Such a well regulated system in which a heterogeneously distributed series of regulatory mechanisms interact in a coordinated manner would thus allow for adequate control of coronary blood flow, and ultimately oxygen delivery, under a variety of physiological conditions.

Another example of the complex interplay between the various flow regulatory mechanisms is the coronary flow response following the release of a coronary artery occlusion, i.e. reactive hyperemia. Obviously, several flow regulatory mechanisms are involved in this hyperemic flow response. First, there is a role for metabolic coronary flow regulation, because the heart is deprived of oxygen and substrates during the occlusion. Tissue levels of potential mediators of coronary flow will accumulate and will influence coronary vasomotor tone. After the release of the occlusion, the vasodilated vascular bed gives rise to the initial reactive hyperemic peak flow. Directly following the release of the occlusion there is a sudden change in perfusion pressure that may trigger an autoregulatory or myogenic vasoconstrictive response. Theoretically, this vasoconstrictive response reduces the peak flow and shortens the duration of the reactive hyperemia. In addition, shear stress will also be elevated during the reactive hyperemia, which will stimulate the endothelial release of nitric oxide. The enhanced release of nitric oxide in turn may attenuate the pressure-induced vasoconstriction following the release of the occlusion. This theory is in fact supported by experiments in isolated rabbit hearts showing a much stronger and faster increase in coronary vascular resistance following rapid pressure elevations after inhibition of nitric oxide [26]. This example illustrates that the integrated control of coronary flow is dependent on the normal functioning of all segments, whereas in the presence of diseased segments, e.g. coronary artery disease or endothelial dysfunction, the proper adjustments may occur only partially or not at all.

5. Dynamics of coronary flow control

The transients in coronary flow are the result of the flow regulating mechanisms of which the steady relations have been described in section 3. However, a potential control mechanism should not only explain the steady state pressure flow relation, but should also provide a sufficient explanation for the observed transients in coronary flow that occur in response to different interventions, including changes in heart rate and coronary perfusion pressure.

5.1 Dynamic response to a change in heart rate

In 1977, the dynamic behavior of the coronary arterial system to a change in heart rate was described by Belloni and Sparks [27], who studied the response of coronary resistance and venous oxygen content to a change in heart rate in the isolated heart preparation. They used constant flow perfusion and measured the change in mean coronary pressure as index of coronary resistance, corrected for the delay in the measurement of venous oxygen content. The half time of the coronary resistance response to a change in heart rate was approximately 10 seconds [27]. In addition, they found that coronary sinus oxygen content changes preceded the adjusted time
Figure 1.4: Response of the coronary resistance to a change in oxygen consumption according to the oxygen model of coronary flow control. Dotted lines are normalized responses at two levels of pressure perfusion. The solid line shows the response at two levels of flow perfusion. (Redrawn from Dankelman et al. [28]).

course of vascular resistance, which supports the hypothesis that coronary vascular resistance is regulated in part by factors closely linked to oxidative metabolism.

Dankelman et al. [28,29] extensively tested the dynamic characteristics of the model described earlier, to find out whether this model could accurately predict the dynamic change in coronary vascular resistance following a sudden change in heart rate and perfusion. To be able to compare the rate of change of the coronary responses to different interventions, Dankelman et al. used an index of coronary vascular resistance, which was calculated as the beat-averaged ratio of coronary arterial pressure and coronary flow [28]. During steady state, this coronary resistance index is identical to coronary vascular resistance. However, during fast dynamic changes in pressure or flow, the ratio does not reflect coronary vascular resistance, since slow changes may be related to coronary capacitance in stead of resistance [30]. The model predictions were that the coronary adjustments in response to a sudden increase in heart rate would be slower with constant flow perfusion compared to constant pressure perfusion as is shown in figure 1.4. Furthermore, the model predicted that during constant flow perfusion, the rate of this response would be independent of the flow level, whereas during constant pressure perfusion, the rate would be pressure-dependent [28].

The difference in the response rate for both perfusion conditions is explained by the feedback which is present at constant pressure perfusion (flow can vary), but which is absent at constant flow perfusion (flow is constant). Thus the feedback signal, responsible for the change of flow perfusion, is faster when flow is allowed to vary freely. With constant flow perfusion the flow is fixed, the feedback loop is opened and as a result the feedback limited. Under this perfusion condition the model is linear which means that the rate of the response does not depend on the coronary
flow level. However, during constant pressure perfusion, the model is non-linear because coronary flow is dependent on coronary perfusion pressure and coronary vascular resistance [28].

These model predictions were in good agreement with experimental results obtained in open chest goats, with cannulated left main coronary arteries, which could be perfused at constant pressure or constant flow (figure 1.5) [28]. As predicted by the model, the coronary response to a heart rate step was faster during constant pressure perfusion, compared to constant flow perfusion. Moreover, at constant pressure perfusion, the response was dependent on the pressure level, being faster at low perfusion pressure.

However, the experimental results differed from those predicted by the theory in that the changes described above were preceded by a brief change in the resistance index in the opposite direction, i.e. up with an increase in heart rate and down with a decrease in heart rate. This initial reversed response was postulated to result from a mechanical effect due to greater compression of the coronary microvasculature with more frequent contractions and from the induced changes in vascular volume [28]. In the absence of coronary flow regulation, which was achieved by maximal vasodilation with adenosine, a sudden change in heart rate still produced the initial change in the pressure-flow ratio, but not the subsequent adaptation over 13-25 seconds, confirming that the former effect was attributable to a passive mechanical mechanism.
5.2 Dynamic response to a change in perfusion

Dankelmann et al. [29] also verified the model predictions regarding the dynamic changes of the coronary resistance index in response to sudden changes in perfusion pressure or coronary flow. Whereas the model prediction for the dynamic autoregulatory response following an increase in pressure or flow was in line with the experimental results, there was a remarkable difference between the model and the experiments regarding the response to a decrease in pressure or flow at constant pressure perfusion and constant flow perfusion, respectively. The reduction in perfusion pressure in the experiments resulted in a flow response which was much faster than the response predicted by the model. Especially, at constant pressure perfusion, the response to a decrease in pressure was different from the response to an increase in pressure. Following the decrease in pressure, there was a sharp rise in the index of coronary resistance resulting in an overshoot, which was not observed in response to the increase in pressure. Although less pronounced, this directional sensitivity was also present at constant flow perfusion. Dankelmann et al. [29] concluded that the model lacked an element that could explain the directional sensitivity of the autoregulatory coronary response.

So far, no simple explanatory mechanism for the increased response rate following a decrease in perfusion has been described, although a facilitating mechanism of nonmetabolic nature is indicated. An attractive explanation may be related to the effect of cardio-cardiac reflexes, mediated by coronary and ventricular mechanoreceptors [31]. Upon stimulation, the main effect of these mechanoreceptors is a reduction in sympathetic and an increase in vagal tone, with vasodilation being the net effect in vascular beds [31]. An increase in coronary perfusion pressure may stimulate coronary arterial baroreceptors, resulting in reflex vasodilation. Such vasodilation, in the face of simultaneous autoregulatory vasoconstriction, slows down the speed of the response to an increase in coronary perfusion pressure [32]. Furthermore, it was shown that the reflex vasoconstriction which occurs when the stimulus to coronary baroreceptors is removed, i.e. following a pressure-step down, develops more slowly [33]. The concomitant autoregulatory vasodilation is thus relatively unopposed and occurs faster, which may explain the directional sensitivity observed in the coronary response rate to changes in perfusion pressure.

5.3 Coronary response rates: the $t_{50}$ values

The response rates of the coronary vascular tree to changes in heart rate and perfusion were quantified by a $t_{50}$ value, which was defined as the time in seconds after the intervention (i.e. HR step or change in perfusion) at which the change in coronary vascular resistance index had reached half of its total final change. For the goat, figure 1.6 summarizes these $t_{50}$ values for the vasodilating responses to either an increase in heart rate or a decrease in perfusion, and for the vasoconstricting responses to a decrease in heart rate or an increase in perfusion, for both pressure and flow controlled perfusion [28,29]. The rate of the vasoconstricting responses were similar as one would expect under conditions in which a single control loop determines coronary flow. However, as discussed before, the rate of the vasodilatory
response to a decrease in perfusion was much faster than the vasodilation in response to an increase in heart rate.

Later, the same protocols were repeated in anesthetized dogs, instrumented similarly [34]. Again the model predictions were confirmed in that the coronary responses to changes in heart rate or perfusion were faster with constant pressure perfusion, as compared with constant flow perfusion. It was also confirmed that the coronary response rate was dependent on the level of pressure during constant pressure perfusion, whereas it did not depend on the level of flow during constant flow perfusion. However, the $t_{50}$ values of the coronary responses for the dog were about two times smaller than for the goat [34]. This indicates that the dynamic coronary responses were faster in the dog than in the goat, whereas the steady state control of coronary flow was not different. No explanation for this large and specific discrepancy in dynamic behavior of flow control between the two species has yet been identified.
6. Extravascular resistance

So far, some aspects of the steady state and dynamic behavior of coronary flow control have been addressed. However, an additional factor which complicates the understanding of coronary flow control, is related to the beating of the heart. Systolic ventricular wall tension compresses the intramyocardial blood vessels every time the heart contracts. Therefore, most of the antegrade coronary arterial blood flow occurs during diastole, whereas during systole flow is reduced or even reversed into retrograde flow. Although the arterial systolic flow reduction is mainly due to capacitive effects, coronary vascular resistance is increased as well, as a result of the reduction in vascular volume. The increased coronary resistance during systole is often referred to as extravascular resistance and may be attributed to a number of extravascular systolic compressive forces.

One of the compressive forces is generated by the left ventricular systolic intracavitary pressure, which is transmitted fully to the subendocardium, but decreases to atmospheric pressure at the epicardial surface. Thus, during systole, extravascular pressure is assumed to be a function of left ventricular pressure and depth within the myocardium.

Another compressive force, perhaps even more important, is caused by the direct interaction between the contraction of the myocyte and myocardial microvessels. Thus, according to this concept, the systolic extravascular resistance is the result of the compression and bending of small arterioles coursing through the ventricular wall as the heart contracts. This may also explain the systolic impediment of flow in the empty beating heart, which is not developing left ventricular pressure. The incomplete understanding of the interaction between cardiac contraction and coronary blood flow has lead to the development of several models, which give insight in the controversy not yet resolved (for review see Spaan [35]), but that are beyond the scope of this thesis.

7. Effect of coronary artery disease

In the presence of coronary artery disease static and dynamic aspects of coronary flow control are also involved. In patients with coronary stenoses, autoregulation of the coronary circulation compensates for the drop in perfusion pressure distal of a stenosis by decreasing the arteriolar coronary resistance to maintain coronary flow at normal levels. This compensation mechanism works as long as the coronary flow does not reach the maximal obtainable flow at the pressure level distal to the stenosis [36].

In figure 1.7 the influence of a stenosis on the coronary flow control system is depicted by a dashed curved line and illustrates the maximal change in flow that can be induced either pharmcologically or physiologically. This figure illustrates that the resistance of a coronary stenosis depends on the level of coronary blood flow. The pressure drop across a coronary stenosis is larger at higher coronary flows because of
the fluid mechanical laws of Poiseuille\(^1\) and Bernoulli\(^2\), describing the frictional or viscous energy losses and the dynamic losses due to convective acceleration, respectively. This implies that the degree of flow-limitation by a coronary stenosis may only become apparent at high rates of myocardial oxygen consumption, while at normal activity coronary flow control may still compensate for the post-stenotic pressure-drop.

Similarly, the ability of autoregulation to compensate for the effect of a proximal epicardial obstruction may be compromised by a reduction in aortic pressure. This reduction in pressure in turn can lower distal perfusion pressure below the lower autoregulatory breakpoint, thereby lowering myocardial perfusion and intensifying myocardial ischemia. The consequent increase in left ventricular filling pressure will decrease the perfusion gradient even further. Since left ventricular hypertrophy narrows the range of autoregulation, especially in the subendocardium, this mechanism also explains why patients with severe hypertrophy may suffer from subendocardial ischemia, even in the absence of coronary stenosis. The detrimental effects of distal coronary perfusion pressures lower than the autoregulatory breakpoint can be counteracted by the insertion of an intra-aortic balloon pump. The beneficial effect of this procedure is based on the balloon pump-induced increase in diastolic perfusion pressure, which restores coronary perfusion pressure distal of the stenosis so that autoregulation is reestablished and myocardial ischemia lessened [8].

The transstenotic pressure drop is inversely proportional to the fourth power of the minimum luminal diameter. As a result, seemingly small changes in diameter are amplified to large changes in stenosis resistance, causing substantial hemodynamic effects [37]. This may especially occur in the presence of severe eccentric stenoses, in which the atherosclerotic plaque involves only a portion of the arterial wall, while the remaining arc of the wall is relatively normal and often compliant. Changes in vascular tone or distending pressure may then alter luminal caliber and thereby stenosis severity [38]. Importantly, a decrease in distending pressure may thus occur following an increase in blood flow, e.g., due to a metabolic or pharmacological stimulus, which increases the pressure drop over the stenosis. This in turn may lead to passive collapse of pliable segments, increasing the degree of the stenosis even further [39]. Passive collapse of pliable stenosis may also occur when aortic pressure is lowered.

The coronary autoregulatory capacity is capable of compensating for the reduced distal pressures until the constriction reaches 85% of the diameter. Until this point, resting coronary flow is not altered [40]. However, maximal coronary flow begins to

\[ \Delta P = \left( 8 \cdot \mu \cdot 1 \cdot Q \right) / \left( \pi \cdot r^4 \right), \] where \( \Delta P \) is the pressure gradient due to viscous energy loss, \( \mu \) is viscosity, 1 is the length of the vessel, \( Q \) is the flow through the vessel and \( r \) is the radius.

\[ P + \frac{1}{2} \rho \cdot v^2 = \text{constant}, \] where \( \rho \) is the fluid density and \( v \) the local velocity. Because of the conservation of energy at the prestenotic segment and at the stenotic site, this yields \( \Delta P = \frac{1}{2} \cdot \rho \cdot Q^2 \cdot (\Delta \% A^2 / A_0^2) \), where \( \Delta P \) is the pressure gradient due to convective acceleration, \( Q \) is the flow, \( \Delta \% A^2 \) is the percentage decrease in square area between the prestenotic segment and the stenotic region, and \( A_0^2 \) is the square area of the stenotic region. Note that the pressure drop due to convective acceleration is proportional to the square of the flow, whereas the viscous pressure loss is proportional to flow.
Figure 1.7: Influence of a coronary stenosis on the coronary flow regulation characteristics. Shown are three different autoregulation curves at three levels of MVO2. In healthy subjects the measured flow (at a perfusion pressure of 100 mmHg) would change from A to B respectively C at increasing levels of MVO2. In the presence of a coronary stenosis (dashed curved line) the flow will be only slightly affected due to the autoregulation, as long as the maximal pressure-flow relation is not reached. The flow will change from a to b respectively c in these circumstances. The stenosis induced drop in pressure will increase at higher coronary flow levels, due to the hydrodynamic law of Bernoulli and the occurrence of turbulence at higher flows.

Decline when stenosis diameter exceeds 30 to 45%. However, assessment of the percentage narrowing of coronary artery lumen is associated with major limitations, because it does not account for its absolute diameter, length, or eccentricity. This probably explains the poor correlation between the percentage narrowing and the physiological significance of a stenosis, especially for lesions of moderate severity [41].

The aforementioned observations demonstrate the important influence of mechanical aspects of coronary stenoses on the adequacy of coronary perfusion, not to mention the effect of coronary artery disease on the control of coronary blood flow itself.
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