Introduction

The heart, because of its continuous beating, requires large amounts of oxygen and metabolic substrates, which can be obtained only by increasing blood flow availability. As most of the coronary vascular resistance resides in arterial microvessels [1], coronary arterioles and small arteries are responsible for this matching and for determining the flow conductance by changing their tone from moment to moment. Coronary flow conductance is determined by several controllers: factors intrinsic to the vascular wall (myogenic control and flow-induced diameter changes), local metabolic factors, and neurohumoral factors. Direct observations of coronary microvessels in vivo and in vitro have clearly shown that each factor regulating the coronary flow acts on specific sites at the microvascular level, and that the responses of the microvessels are heterogeneous according to spatial distribution.

Spatial and temporal heterogeneity of pressure and resistance along the coronary microvasculature

The distribution of resistance in the coronary circulation is reflected by the profile of microvascular pressures (Figure 1). Resistance of any segment is directly proportional to the magnitude of the pressure drop across that segment. A significant proportion of resistance that resides in
small arteries is partly due to active mechanisms, and may, therefore, be modulated by vasodilators and constrictors. Coronary microvascular resistance also appears to vary across the wall of the left ventricle. Indeed, at each level of perfusion pressure, arteriolar pressures in the endocardium are lower than those in the epicardium; while endocardial venular pressures are higher than those in epicardial venules. This suggests that transmural arterioles, which course through the ventricular wall and are upstream from the endocardial microcirculation, contribute significantly to the total endocardial resistance, as suggested by the lower pressures in the endocardial versus epicardial arterioles. Moreover, microvascular resistance in the subendocardium is significantly lower than that in the subepicardium, because the arteriolar–venular pressure difference is much smaller. Because the coronary vasculature courses through the myocardium, the dynamics of coronary flow are strongly affected by cyclical mechanical forces during contraction and relaxation in each cardiac cycle. Mechanical forces impact on coronary blood flow distribution via direct effects on the calibre of the resistance vessels (compression), and via indirect influences on vasomotor tone. This produces the characteristic pattern of phasic coronary blood arterial and venous flows, while affecting the distribution of myocardial perfusion across the ventricular wall [2]. Accordingly, myocardial inflow is prevalent during diastole and flow is hindered during systole. Subendocardial coronary arterioles demonstrate a large systolic retrograde flow and a 10–20% decrease in diameter from diastole to systole. In contrast, less phasic changes in diameter and flow occur in the subepicardial arterioles. The unequal transmural effects of myocardial contraction on the distribution of coronary flow are related to the non uniform development of forces within the myocardial wall. Accordingly, systolic intramyocardial pressure is largest in the subendocardial layer and then linearly decreases towards the superficial layer; systolic myocardial deformation is also largest in the deeper one third of the transmural wall. Interestingly, despite higher mechanical stress in the endocardium, mean coronary flow is greater than in the epicardium (endocardial–epicardial flow ratio). Most studies indicate endocardial–epicardial flow ratio greater than 1 (from 1.05 to about 1.4), which indicates that coronary regulatory mechanisms can overcome extravascular mechanical forces under physiological conditions [3]. Two different mechanisms are known to operate: myogenic control, which senses vascular perpendicular stress (stretch) due to intraluminal pressure, and shear stress-induced vasodilatation, which senses the friction along the vascular long axis between bloodstream and vascular endothelium. These mechanisms concomitantly operate in response to momentary changes in pressure and flow, respectively, and regulate appropriate active tone of vascular smooth muscle in the local vasculature. Myogenic control operates to adjust vascular tone in response to intraluminal pressure (ie, contraction occurs when intraluminal pressure increases, and dilation occurs when pressure decreases). Active myogenic response is evident in both subendocardial and subepicardial arterioles. However, subepicardial arterioles when compared to subendocardial arterioles exhibit greater vasodilator responses at low pressures and augmented constriction at higher pressures. This mechanism has several purposes: autoregulatory adjustments in tone, regulation of pressure in exchange vessels, protection of the vessels from excessive dilation during acute increases in pressure, prevention of vascular collapse during decreases in pressure (hypoperfusion), and facilitation of vascular network responses to metabolism. The myogenic response is reported to be prominent in coronary microvessels that are 50–80 μm in diameter. Although the reason for this size-dependent heterogeneity is still unclear, it may facilitate longitudinal communication by acting as a relay from the metabolic regulation in peripheral smaller microvessels (mainly <50 μm) to the flow-induced vasodilatation in proximal larger microvessels (mainly 80–150 μm).

**Fig. 1** A scheme for the distribution of coronary resistance along the vascular bed. The percentage value represents the proportion of total resistance contained by the specific segment. The most important factors are neurohumoral factors and shear stress in coronary arteries, metabolic factors in arterioles, and neurohumoral factors in coronary veins. Modified from Toyota, 2001.
Effect of coronary stenosis on coronary blood flow regulation and distribution

The impact of coronary stenosis on coronary blood flow regulation was extensively investigated by Gould and colleagues [4] in normal open-chest, anesthetized dogs. The authors found that progressive reduction of the coronary lumen has no effect on resting blood flow until the vessel is almost totally occluded [5]. Only when lumen reduction exceeds 80–85% of the original diameter, further reductions are associated with significant drops in flow. Moreover, maximal blood flow begins to decrease only when the vessel diameter reduction exceed 75% of the original dimension and declines progressively thereafter (Figure 2). The maintenance of the baseline levels of both autoregulated and maximal coronary blood flow, despite a progressive reduction in vessel diameter, has been attributed to a parallel reduction of microvascular resistance, compensating the resistance produced by the stenosis. According to this hypothesis, ischemia would develop when microvascular vasodilatation capability is fully exhausted, and this is expected to occur for stenosis severity exceeding 75% in diameter reduction. However, the effects of coronary stenosis on perfusion pressure and myocardial blood flow are not so linear and predictable; several factors intervene to contradict this highly simplistic theory. As mentioned above, a spatial and temporal gradient exists in the distribution of the coronary blood flow within the left ventricular wall. Any coronary stenosis severe enough to generate some resistance to flow will results in a trans-stenotic pressure gradient. Because the proximal pressure is always equal to the aortic pressure, the presence of a pressure gradient implies a post-stenotic pressure drop (due to Ohm’s law). This pressure drop is linearly related to the severity of the stenosis and to the volume of flow. That is to say, the more severe the stenosis and the greater the flow, the lower will be the post-stenotic pressure, which ultimately is the effective coronary perfusion pressure. Therefore, a coronary stenosis severe enough will automatically result in subendocardial underperfusion and possibly ischemia [6].

There is ample evidence that coronary stenosis triggers microvascular changes in post-stenotic myocardium. Animal studies suggest that vascular remodelling occurs in coronary resistance vessels downstream of a severe coronary stenosis, resulting in elevated “minimal” microvascular resistance. More recently, both structural and functional abnormalities have been reported by Sorop et al [7]. Arterioles extracted from post-stenotic myocardium showed reduced myogenic responsiveness and increased sensitivity to endothelin-1. These microcirculatory abnormalities may interfere with coronary blood flow regulation, independently from the effects of the stenosis. Gould et al [4] postulated that minimum microvascular resistance is independent of epicardial stenosis severity and that microvascular vasodilatation capability is preserved downstream of a coronary stenosis. Using combined measurements of myocardial perfusion pressure and coronary blood flow, Marzilli and coworkers [8] estimated total (trans-stenotic plus microvascular) and distal (microvascular) resistances to flow in the culprit vessel of patients with stable and unstable coronary syndromes. Measurements were performed at control conditions, at maximal vasodilatation, during pacing-induced myocardial ischemia, before and after stenosis removal by coronary angioplasty and stenting. As expected from the studies of Gould et al [4], increases in heart rate would be associated with progressive microvascular dilation and a decrease in coronary resistances. By contrast, the authors found an increase in coronary resistances during pacing, both at the level of the stenosis and at the microcirculatory level, reaching its maximum at the appearance of ischemia [9, 10]. Contrary to predictions from animal models, coronary resistances distal to a severe coronary stenosis augment during increases in myocardial oxygen consumption, contributing to the development of ischemia and angina. Similar results were observed in patients with unstable angina. Here again, myocardial ischemia was associated with a marked and dynamic increase in the resistances to flow at both the stenosis level and at the trans-stenotic level. Moreover, maximal blood flow was unaffected by vessel constriction until coronary stenosis reached 80–85% of the vessel diameter, while maximal coronary blood flow started to decrease for stenosis more severe than 50%. Adapted from Gould, 1974.

![Fig. 2 Effect of lumen reduction (coronary stenosis) on resting and maximal blood flow in normal, anesthetized, open-chest dogs. Resting blood flow was unaffected by vessel constriction until coronary stenosis reached 80–85% of the vessel diameter, while maximal coronary blood flow started to decrease for stenosis more severe than 50%. Adapted from Gould, 1974.](image-url)
microcirculatory level, confirming the prominent role of microcirculatory vasmotor tone in the precipitation of myocardial ischemia in men [8]. Several mechanisms, either passive or active, might explain this paradoxical increase in stenotic and microvascular resistance during increases in myocardial oxygen consumption. Above other things, it is possible that this behavior expresses the activation of intrinsic control mechanisms of the coronary circulation aiming at the maintenance of the driving pressure in a range of values high enough to perfuse vessels with high opening pressures and low enough to prevent capillary damage. Such an active control in some pathological conditions could override the metabolic control and exclude some vascular units, in order to maintain an adequate pressure to the perfused area [11, 12]. The reversal of pacing-induced ST-segment depression by intracoronary adenosine administration strongly supports this hypothesis. Such a phenomenon seems to be triggered, at least in part, by the lower coronary pressure downstream of the stenosis. However, parts of previous results may be explained by altered responses to vasoactive substances, downstream of a coronary stenosis. Along with this go the observations that serotonin, which exerts a powerful vasodilatation effect in normal coronary vessels, elicits vasostriction in post-stenotic vascular networks [13, 14]. Moreover, endothelial dysfunction associated with coronary atherosclerosis changes the vascular response to acetylcholine from vasodilatation to vasoconstriction in post-stenotic vascular networks [13, 14]. In addition, platelets, activated by exposure to damaged endothelium, may produce vasoactive substances that contribute to elevated microvascular resistance. Experimental studies have documented that a severe coronary stenosis, by reducing effective coronary perfusion pressure, reduces the volume of perfused myocardium. Indeed, stenosis removal by angioplasty and stenting increases distal coronary pressure and perfused volume [16, 17]. The increases in driving pressure and in perfused volume appear linearly related. These findings suggest that, in the presence of a severe stenosis, observed resting blood flow is distributed only to a portion of the vascular units and is consistent with the hypothesis that a chronic underperfusion is present in myocardial regions exposed to a reduced driving pressure because coronary microvasculature reacts to a reduction of perfusion pressure by an active constriction.

Conclusions
The presence of a tight coronary stenosis is associated with functional and structural changes in the dependent microcirculation that markedly modify microvascular behavior both under control conditions and during physical or pharmacological stimuli. Contrary to predictions from animal models, an increase in myocardial oxygen demands is associated with active vasoconstriction in the coronary microcirculation downstream of a severe stenosis that contributes to precipitation of ischemia. This paradoxical behavior is promptly reverted by stenosis removal. However, minimal microvascular resistances may remain markedly elevated after stenosis removal and persistently impair coronary blood flow reserve.

REFERENCES