Integrated control of coronary microvascular tone: in series mechanisms for a differential regulation of flow and capillary pressure

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Abstract

Myocardial signals modulate vasomotor tone of most distal segments of the coronary microcirculation to fit oxygen availability to the largely variable oxygen demand. This flexibility implies an adaptation of coronary resistance in vascular segments upstream from the action of metabolic signals to maintain a stable capillary pressure despite the variable flow rate. This task is accomplished by different mechanisms cooperating in series to modulate the pressure drop along the vascular tree and encompasses both endothelium and myogenic control of vascular tone. Altogether, these factors configure a true intrinsic control system whose role is control of intravascular pressure and whose alterations can contribute to atherosclerosis progression.

Keywords: Atherosclerosis; coronary blood flow; coronary microcirculation; endothelium; 1-25-dihydroxy-vitamin D; parathyroid hormone.

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Introduction

Under physiological conditions, perfusion is tightly matched to metabolic demand. This is achieved by modulating coronary vascular resistance through adjustments of vascular tone [1].

Administration of drugs such as adenosine or ATP causes a marked increase in flow documenting a vasoconstrictor tone under baseline conditions. This process primarily involves the smooth muscle cells of the small coronary arteries and arterioles (50–200 µm in diameter) [2] whose structure, characterized by two or three circular and concentric layers of smooth cells, is suited to modulate coronary resistance. From a structural point of view, the different factors regulating vasomotor tone act on specific sites permitting the identification of three distinct "microdomains": small arterioles (50–80 µm), most sensitive to metabolic mediators; intermediate

arterioles (150 µm) mainly controlled by myogenic mechanisms and large arterioles (>150 µm) in which flow-induced dilation predominates [3].

From a functional point of view, local control of the vasomotor tone in coronary microcirculation can be divided into two major components: the intrinsic mechanisms, dedicated to maintain intravascular and mostly capillary pressure, and the extrinsic factors, adapting flow rates to the needs of supplied myocardial tissue.

Intrinsic control mechanisms

Autoregulation and myogenic reflex

Changes in transmural pressure, i.e. the difference between intravascular and extravascular pressure, modulate the contractile status of vascular smooth muscle cells: an increase in transmural pressure due to an increase in venous pressure or to dilation of arterioles causes a contraction of the latter; on the contrary, a reduction in transmural pressure leads to a relaxation of the precapillary vessels. This phenomenon is called "myogenic reflex" and is responsible for coronary autoregulation [4]. This term is most often used to describe the ability of the vascular bed to maintain a constant flow rate despite changes in driving pressure [5]. However, it also occurs in isolated vessels indicating its nature in the pressure control mechanism.

In this way, myogenic constriction would protect downstream vessels from sudden increases in arterial pressure from whatever causes. It is especially prominent in encapsulated organs such as the brain, heart and kidney, where rapid changes in volume, and/or the development of edema would have disastrous consequences. However, it is also extremely relevant in those microcirculatory areas in which resistance is most tightly controlled [6].

In a study from Jones and Berne [7] in dog skeletal muscle, blood flow remained constant despite sudden variations in driving pressure from 60 to 120 mm Hg. Similarly, Kuo et al [8] showed in pig coronary arterioles that progressive increases of transmural pressure caused progressive reduction in vessel diameter. To date, how vessel distension leads to vasoconstriction remains not fully elucidated, although most authors propose a direct depolarization of smooth muscle cell membranes caused by the activation of stretch-sensitive cation channels resulting in an inward cation current [9]. In fact, stretch-activated channels have been found in freshly isolated and cultured smooth muscle cells [10], and in isolated small arteries [11]. The type of ion channels depends on the vascular bed studied. However, the involvement of the largely expressed calcium-activated K channels seems to play a relevant role in this process, as confirmed by the experimental observation that blockage of calcium-activated K channels with a specific inhibitor, iberiotoxin, enhanced myogenic tone in rat cerebral arteries [12].

Myogenic reflex and autoregulation can thus be considered as the mechanism adapting the coronary arteriolar resistance in order to avoid changes in aortic pressure (caused by whatever stressor) impairing the Frank–Starling forces governing the exchange of fluids, gases, nutrients and ions between capillaries and tissue.

Endothelium-mediated regulation

Among the large number of variables affecting pressure distribution at a local level, flow demand plays a relevant role. Obviously, signals released by tissue only act on most distal arterioles, while they cannot affect vasomotor tone in the upstream arterial tree. This issue has been scarcely considered up to late 1980s when Chilian and coworkers [2] documented that vascular segments proximal to adenosine-responsive arteries actually account for 30–35% of total coronary resistance at baseline. This finding has an enormous relevance because it indicates that a pressure gradient is needed to move blood through these proximal vessels. Moreover, according to the Poiseuille law, it also indicates that every increase in flow would be necessarily paralleled by corresponding changes in pressure drop that would impair Frank–Starling forces.

This deleterious effect is prevented by the presence of a countercurrent propagation of vasodilating signals to vascular segments located upstream of the site of metabolic flow regulation. A large number of studies indicate that this servomechanism is at least partly regulated by the endothelium that senses flow velocity as an index of pressure gradient. In fact, changes in shear stress trigger a complex signaling process that results in the release of factor(s) that cross the basement membrane and act on the underlying smooth muscle to induce vasodilatation. The resulting vasodilatation is termed flow-mediated dilatation [5]. It occurs ubiquitously throughout the circulation, is endothelium dependent and is particularly prominent in arteriolar vessels [13]. Some of the most clear-cut evidence about the role of endothelium in this setting comes from the experience of Kuo et al [8]. These au-

thors used a circuit permitting the modulation of flow velocity and direction without modifying average pressure. The circuit included two arterioles (one with endothelium and one denuded) placed in series. Increasing flow dilated the normal arteriole, while it did not affect the diameter of the denuded one. The signal underlying this important adaptation was related to nitric oxide (NO).

The paramount relevance of this gas in modulating cell function and vessel tone can be thus partly attributed to its capability to modulate the vascular tone across the different segments in order to allow changes in flow in the absence of variations in capillary pressure. In this way, the endothelium can be considered an organ able to sense the pressure drop by measuring flow velocity along the pertinent vascular segment. This regulation implies the presence of mechanosensitive elements in endothelial cells that can reflect both the glycocalyx composition [14], or dedicated ion channels such as the transient receptor potential vanniloid channel 4 subtype cation channel, which has been implicated in multiple vascular beds [15].

Regardless of the molecular mechanisms, this relevant physiologic role implies that disorders affecting endothelial function represent the basis for the development of atherosclerotic lesions on major coronary arteries. However, they also largely contribute to the precipitation of ischemia limiting maximal flow capacity as well as to the microcirculatory adaptation to the hydraulic effect of epicardial obstruction. Neglecting this variable limits our comprehension of the mechanisms underlying the progression and complication of coronary atherosclerosis and ischemic heart disease.

Extrinsic control mechanisms

Metabolic regulation

Because the high oxygen extraction that characterizes coronary circulation, there is a closer relationship between myocardial metabolism and coronary blood flow compared to other organs. This implies the presence of powerful mechanisms adapting coronary blood flow to the rapidly changing myocardial oxygen consumption. This mechanism has been first documented by studying the reactive hyperemia occurring soon after a short-lasting ischemia. This reaction is characterized by a transient flow increase that reflects the local release of vasodilator metabolites. In agreement with the concepts described above about the role of endothelium in adapting the diameter of the whole involved vascular area, the magnitude of peak dilation is greater in small microvessels while the dilation of larger arterioles is more prolonged.

Several factors have been described as putative mediators of this coupling between metabolism and vasomotor tone. Adenosine is one of the key mediators of metabolic blood flow regulation. It diffuses from myocytes into interstitial fluid, where it exerts powerful arteriolar dilator effects through the stimulation of A2 adenosine receptors on smooth muscle cells. Adenosine production increases in the case of an imbalance in the supply or demand ratio of myocardial oxygen, with the rise in interstitial concentration of adenosine paralleling the increase in coronary blood flow [16]. However, the evidence that a virtual removal of adenosine, obtained by the saturation of cardiac interstitium with adenosine deaminase, does not produce any substantial change in metabolic regulation of coronary blood flow indicates that adenosine is probably not the only signal involved in the match of flow and metabolism [17].

Myocardial tissue oxygen tension would seem to play a role in this context as it represents the ideal signal for the activity of myocardium metabolism. A decrease of arterial PO_2 is probably the most powerful stimulus for coronary vasodilatation. A pathological decrease of the PO_2 in the coronary system may affect the function of ion channels of smooth muscle and endothelial cells, and thereby cause coronary vasodilatation. Voltage gated calcium channels in coronary smooth muscle respond to a decreased PO_2 with a fall in the ion current with a consequent decrease of cytosolic calcium concentration and thus smooth muscle relaxation. In addition to a fall in vascular smooth muscle Ca^{2+} currents, opening of coronary smooth muscle ATP-sensitive potassium channels in response to hypoxia has been reported [18].

Interstitial carbon dioxide tension appears to be involved in the microcirculatory blood–tissue oxygen exchange due to the close spatial relationship between arterioles and venules in the coronary microcirculation: PCO_2 gradients determine small drops in arteriolar pH, a reduction of hemoglobin affinity for oxygen and an increased oxygen availability [19]. This phenomenon already occurs under baseline conditions due to a countercurrent mechanism caused by the proximity of arterioles and venules. Increased tension of carbon dioxide increases proton concentrations that directly facilitate coronary vasodilatation [20].

Autonomic nervous control

The coronary circulation receives sympathetic nervous fibers exerting their action via a release of noradrenaline acting on different adrenergic receptors. These receptors are classified as pre and postsynaptic, according to their site, and on the basis of their affinity of specific antagonists in $\alpha 1$, $\alpha 2$, $\beta 1$ and $\beta 2$. Vascular smooth muscle cells express $\alpha 1$ and $\beta 2$ postsynaptic receptors whose activation leads to vasoconstriction and vasodilatation, respectively. The resting α-adrenergic tone in arterial microvessels is minimal and although both $\alpha 1$ and $\alpha 2$-receptors exist functionally, vasomotion by stimulation of α-receptors is masked by autoregulatory control, by NO release, and by endogenous adenosine in normal conditions [20]. Accordingly, the complex receptor asset of the different catecholamine receptors results in complex responses, because alpha-mediated vasoconstriction is at least partly masked by alpha-induced NO release. Similarly, beta vasodilatation is largely overcome by the effect of beta stimulation on cardiomyocyte oxygen consumption.

Regulation of coronary microvascular function under disease conditions

In the western world, cardiovascular diseases are the most relevant cause of mortality and morbidity. The largest part of these disorders comes from atherosclerosis that, in the coronary tree, is usually identified by the presence of focal obstructions in the major coronary arteries. The hydraulic impact of epicardial stenoses on myocardial blood flow regulation has been intensively studied, and current models imply that resting blood flow is usually preserved while an orderly relationship exists between the degree of lumen obstruction and the severity of reduction in maximal flow capacity [21]. When translated into clinical practice, this model justifies the frequent use of epicardial stenosis severity as a major determinant in therapeutic choice. However, the complex physiology of coronary tone regulation and the interference of the atherosclerotic process on these pathways can markedly contribute to aggravate or reduce the hydraulic relevance of coronary plaques even in chronic disease forms. As a matter of fact, a number of studies have documented that the atherosclerosis process can impair the regulation of coronary microvascular resistance long before the development of epicardial plaques. Moreover, recent imaging approaches have shown that the total atherosclerotic burden in each single coronary branch closely predicts the degree of microvascular dysfunction in the pertinent microcirculatory bed.

From a pathophysiological point of view, this evidence indicates that coronary blood regulation can be influenced by a number of signals that must be considered to predict the effectiveness of pharmacologic interventions aimed at improving ischemia tolerance in atherosclerotic patients. Different mechanisms can obviously act in different clinical conditions, complicating the identification of possible therapeutic targets. In this way, one of the most complex scenarios is represented by chronic kidney disease, which represents one of the most severe risk conditions for cardiovascular events. Although this association has been most often attributed to the impact of kidney disease on the renin–angiotensin–aldosterone system, more recently parathyroid hormone (PTH) and active 1-25-dihydroxy-vitamin D (1,25D) have been discovered to exert important vasoactive effects on coronary microcirculation.

The interest in PTH vascular action came from the evidence that messenger RNA encoding for PTH/PTH-related peptide receptors is actually expressed in the large majority of mammalian tissues [22] and, in particular, in vascular endothelial and smooth muscle cells. The former modulate NO synthase activity and thus NO production via their effect on transmembrane calcium influx [23]. The latter, instead, promote the expression of proinflammatory chemokine monocyte chemoattractant protein 1, eventually resulting in macrophage infiltration and arteriolar wall thickening [24, 25]. This latter effect seems of particular relevance because patients with primary hyperparathyroidism display a reduction in coronary flow reserve that is predicted by the estimated duration of endocrine disorder [26].

Similar considerations apply to 1,25D. Vitamin D is produced by conversion of its precursor in the skin exposed to ultraviolet B. This substance is then hydroxylated to 25-hydroxy-vitamin D in the liver and is further modified to 1,25D by an enzyme mainly present in the kidney (1-alpha-hydroxylase). The interest in this hormone in coronary circulation arose from epidemiological evidence reporting an increased cardiovascular risk under conditions of reduced exposure to ultraviolet B radiation such as in winter months [27] or in regions far from the equator [28]. Although this link has been most often attributed to an anti-atherogenic effect of 1,25D, recent evidence indicates a coronary regulatory function of 1,25D. From a structural point of view,

Koleganova and coworkers [29] recently reported that the reduction in coronary capillary density in mice exposed to subtotal nephrectomy is at least partly prevented by treatment with 1,25D. From a functional point of view, several studies have documented that 1,25D regulates the activity of Ca^{2+}-dependent NO synthase through specific receptors in endothelial cells [30] facilitating the NO response to the increased shear stress caused by vasodilatation. The relevance of these series of phenomena has recently been documented by Capitanio et al [31], who showed a tight direct correlation between circulating levels of 1,25D and coronary vasodilator response to the increased interstitial concentration of adenosine caused by dipyridamole infusion.

Conclusions

The task of coronary microcirculation is the coupling between myocardial oxygen demand and oxygen supply from the arterial blood. This task implies a fine regulation of coronary resistance in order to warrant that adequate flow is provided maintaining capillary pressure stable within a very narrow range. This goal is accomplished by the presence of different mechanisms in series regulating the tone along the arterial tree. Therefore, the ultimate effect of vasodilating signals on coronary blood flow is only partly related to their direct action on target microvessels. Rather it also depends from the coronary adaptation of upstream and downstream segments whose vasomotor tone is independent from the signal itself. A deeper comprehension of these distinct pathways might help in a more specific therapeutic targeting in order to realize the best therapy for each individual patient. •

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