

# Impact of myocardial function on perfusion

Giacinta Guarini

Cardiovascular Medicine Division, Cardio Thoracic and Vascular Department, University of Pisa, Pisa, Italy

Correspondence: Dr Giacinta Guarini, Cardiovascular Medicine Division, Cardio Thoracic and Vascular Department, University of Pisa, Via Paradisa, 2, 56100 Pisa, Italy  
Tel: +393494544161, email: giacinta\_guarini@yahoo.it

## Abstract

The coronary tree has to ensure adequate blood flow to the needs of the working myocardium, which is a direct expression of the metabolic activity of all other organs and systems. Indeed, a variety of mechanisms all together orchestrate myocardial perfusion in order to match the central and peripheral requests. In the next article the regulation of coronary blood flow will be investigated, focusing particularly on the role played by the coronary microcirculation and the metabolic dilation.

**Keywords:** Coronary autoregulation; coronary metabolic dilation; coronary microcirculation; myocardial function; myocardial perfusion.

■ Heart Metab; 2013;59:34–37

## Introduction

The coronary circulation is organized as a vascular tree. Moving from the epicardium through the endocardium, vessels of different size and composition are hierarchically organized to constitute a network of “microdomains”, in which each unit is specialized and regulated predominantly by different stimuli. Mechano-energetic interaction between coronary vessels and myocardium is tightly coupled because of the high oxygen consumption and flow rate of the myocardium. Such interaction is not uniformly distributed transmurally: the mechanical effect of cardiac contraction on the myocardial vessels is greater in deeper myocardial layers than in the superficial myocardial layers, as it is the greater metabolic demand of the deeper myocardium. Several vasomotor control mechanisms contribute to the regulation of myocardial perfusion [1]. The complex interplay of these mechanisms must be finely regulated to guarantee, beat by beat, a perfect match between oxygen and nutrient delivery to cardiac and peripheral requests. Continuous regulation of pressure and blood flow in the coronary circulation must allow sufficient oxygen and nutrient availability to the metabolic demands of the myocardium. That is, blood flow must be able to change consistently with changes in metabolic demand. Moreover, capillary pressure must be regulated and maintained in a relatively constant range, despite changes in perfusion pressure, to prevent damage or collapse of the exchanging vessels. The coronary microcirculation is organized in microdomains, which are characterized by longitudinal gradients for pressure, flow and metabolism; their responsiveness

to different stimuli is integrated into a complex system that allows matching coronary blood flow to myocardial metabolic demands:

1. Small arterioles (<30  $\mu\text{m}$ ), which are the most sensitive to metabolic stimuli. They dilate during increased metabolic demand, lowering microvascular resistance and favoring myocardial perfusion.
2. Arterioles (30–60  $\mu\text{m}$ ), which are the most sensitive to myogenic dilatation. They modulate their tone and size according to changes in pressure, decreasing vascular resistance when needed.
3. Large arterioles (120–150  $\mu\text{m}$ ), which exhibit predominantly flow-mediated dilatation (FMD). They dilate as a consequence of increased flow, further reducing network resistance.

The majority of coronary vascular resistance is located at the coronary microcirculatory level, that is, in vessels less than 150–200  $\mu\text{m}$  in diameter; therefore, understanding the regulatory mechanisms that exercise control of the tone of these vessels is paramount to our understanding of the control of myocardial perfusion both in normal and in pathological condition [2, 3]. Increased metabolic demand, changes in pressure and flow elicit a different response in a specific microdomain of the coronary bed; the final effect is to modulate microvascular resistance in order to adjust myocardial blood flow.

### Metabolic control

Coronary blood flow is tightly coupled to myocardial oxygen consumption, a process termed “coronary metabolic dilation”. Despite the pivotal role played by the metabolic dilation in regulating coronary blood flow, it is incompletely understood how cardiac myocytes communicate a change in metabolic activity to the coronary vasculature [4]. In the traditional view, regulation of flow is thought to be a negative feedback pathway, in which an imbalance between oxygen supply (delivered via flow) and oxygen demands results in the release of a metabolic dilator. For several years, a prominent role in the metabolic regulation of coronary blood flow was attributed to adenosine, a purine nucleotide produced by cardiac myocytes and released in the extracellular space, with a very short half-life, which is rapidly taken up by circulating red blood cells, preventing systemic effects. In this sense, the adenosine hypothesis was a negative feedback scheme. According to this hypothesis, when oxygen demands exceed oxygen supply, cardiac myocytes would release adenosine through the hydrolysis of ATP and subse-

quent dephosphorylation of ADP and AMP [5]. Recent studies have, however, proposed an alternative hypothesis (feed-forward theory) with a specific role for reactive oxygen species (ROS) and particularly for hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) [6] in the regulation of coronary vascular tone. The negative feedback hypothesis for metabolic regulation of coronary blood flow implies that after blood flow is increased to match oxygen supply with demand, there is no error signal to sustain the dilation. On the other hand, the  $\text{H}_2\text{O}_2$  hypothesis is centered on a different scheme, one in which the metabolic dilator is produced in direct proportion to the metabolic demand of the working myocardium. That is,  $\text{H}_2\text{O}_2$  would act in a feed-forward manner. Moreover,  $\text{H}_2\text{O}_2$  has all the requirements of a metabolic dilator, being vasoactive [7, 8], has a short half-life (it is metabolized rapidly by catalase), it reacts rapidly with free thiol groups, and is freely permeable. Furthermore, the presence of catalase in the bloodstream limits its vasoactive effects to the producing organ system; this prevents any spill-over of the dilator to non metabolically active organ systems.

Despite several unresolved issues, general consensus is that metabolically active cardiac myocytes produce vasomotor substances, such as adenosine [9, 10], nitric oxide (NO) [11], prostacyclin [12], bradykinin [13], ROS [14] and  $\text{H}_2\text{O}_2$  [15, 16] to promote vasodilatation and sustain myocardial oxygen consumption. Although an increase in metabolic activity undoubtedly produces an increase in vasoactive metabolites at all levels of the coronary vasculature, metabolic control mechanisms appear to play a prominent role in small coronary arterioles. When the effect of short coronary occlusions was studied in canine epicardial microvessels, only vessels less than 100  $\mu\text{m}$  in diameter dilated during the period of occlusion, whereas both large and small microvessels dilated during the reactive hyperemia [17].

### Pressure-induced dilation: myogenic control

One of the main purposes of the control mechanisms operating in the coronary circulation is to prevent edema, microvascular damage and collapse by maintaining capillary hydrostatic pressure relatively constant despite large changes in coronary perfusion pressure. The importance of these mechanisms becomes obvious when we consider that even minor changes of perfusion pressure at the capillary level result in major shifts in the amount of fluid that is exchanged between

the intravascular and extravascular space. Indeed, reductions in perfusion pressure produce significant dilation of coronary arterioles smaller than 100–150  $\mu\text{m}$  in diameter [18]; there is an inverse relationship between vessel diameter and myogenic responsiveness. Similar to other species, the human coronary microcirculation exhibits a myogenic response; this autoregulatory mechanism is preserved in individuals with coronary atherosclerosis [19, 20]. The current concepts as to how vascular smooth muscle cells respond to increases in pressure include membrane depolarization via modulation of ion channels, molecular signaling cascades, and generation of ROS.

One of the best supported hypotheses is that stretch-activated cation channels on smooth muscle cells carry an inward current resulting in cell membrane depolarization during myogenic vasoconstriction [21]. Recent studies have identified specific channels of the transient receptor potential family on cerebral arteries of rats involved in stretch-mediated myogenic response [22, 23]. Several endogenous mediators have also been proposed to be involved in the myogenic constriction through regulation of calcium-activated potassium ( $K_{Ca}$ ) channel activity, among them NO [24], protein kinase C [25], mitogen-activated protein kinase signal transduction cascades [26, 27] and ROS [20]. For instance, it should be mentioned that a specific mediator may be involved in the myogenic response in a vascular bed but not in another, that more than a mediator may be involved [28], and that species variability may also exist.

#### **Flow-induced dilation: shear stress**

Similar to pressure-activated control, changes in coronary blood flow velocity, and thus in vascular shear stress, also elicit immediate reactions of the coronary smooth muscle tone. It has been suggested that FMD provides continuity in the dilator response throughout a vascular bed, allowing communication between resistance arterioles and epicardial coronary arteries. The metabolic response is more prominent at the arteriolar level, where it induces vasodilatation and a fall in vascular resistance with the aim of increasing tissue perfusion. However, this increase in flow elicits FMD in the upstream conduit vessel, thus facilitating the proper delivery of blood. Indeed, it has been documented that FMD is predominant in epicardial coronary arteries, where it causes dilatation when flow velocity increases

and constriction when it tends to decrease, in order to keep a stable blood flow velocity and shear stress.

In most vessels from different species and vascular bed NO has been documented to be involved in FMD [29–31]. Human coronary arterioles from individuals without coronary artery disease or other risk factors dilate to shear stress. This response is blocked by  $N^{\omega}$ -nitro-L-arginine methylester, which is a potent inhibitor of NO synthase; conversely indomethacin, an inhibitor of cyclooxygenase, has no impact on FMD. These data suggest that in humans with no coronary artery disease, FMD is predominantly mediated by NO [32]. On the contrary, in patients with coronary atherosclerosis, FMD is still an endothelium-dependent mechanism, but is inhibited by blocking  $K_{Ca}$  channels suggesting a critical role for endothelium-derived hyperpolarizing factor (EDHF). Moreover, in this subset of patients EDHF seems to compensate for NO loss. Similarly, dilation to bradykinin is also mediated by EDHF, and relatively independent from NO [33]. In older people, EDHF is the predominant dilator to maintain the same amount of dilation as bradykinin [34]. Coronary artery disease, hypertension, diabetes and hypercholesterolemia are conditions associated with excess of ROS. As a result, NO bioavailability is reduced and NO-mediated vasodilatation is impaired. In this context EDHF plays a more prominent role in agonist-induced vasodilatation. Therefore, in conditions of enhanced oxidative stress when NO levels are reduced, EDHF can compensate for loss of NO-mediated vasodilatation. Despite the fact that compensatory mediators and mechanisms are engaged in pathological conditions to maintain homeostasis, an alteration of one of these control mechanisms can exert a profound effect on the others, even when the signaling pathways of the latter are preserved. For instance, although atherosclerosis does not affect adenosine-mediated vasodilatation, it markedly affects the endothelial response to an increase in shear stress, and thus reduces NO-mediated regulation of vasomotor tone.

#### **Conclusions**

The coronary circulation is governed by different stimuli, all of which have the final effect of modulating myocardial perfusion in order to match metabolic demand. In doing so, continuous adjustment of vascular tone is needed in response to fluctuations in perfusion pressure and shear stress. •

## REFERENCES

- Duncker DJ, Bache RJ (2008) Regulation of coronary blood flow during exercise. *Physiol Rev* 88:1009-1086
- Chilian WM, Eastham CL, Marcus ML (1986) Microvascular distribution of coronary vascular resistance in beating left ventricle. *Am J Physiol* 251(4 Pt 2):H779-788
- Jones CJ, Kuo L, Davis MJ, et al (1995) Regulation of coronary blood flow: coordination of heterogeneous control mechanisms in vascular microdomains. *Cardiovasc Res* 29:585-596
- Deussen A, Ohanyan V, Jannasch A, et al (2012) Mechanisms of metabolic coronary flow regulation. *J Mol Cell Cardiol* 52:794-801
- Tune JD, Gorman MW, Feigl EO (2004) Matching coronary blood flow to myocardial oxygen consumption. *J Appl Physiol* 97:404-415
- Saitoh S, Kiyooka T, Rocic P, et al (2007) Redox-dependent coronary metabolic dilation. *Am J Physiol Heart Circ Physiol* 293:H3720-3725
- Yada T, Shimokawa H, Hiramoto O, et al (2003) Hydrogen peroxide, an endogenous endothelium-derived hyperpolarizing factor, plays an important role in coronary autoregulation in vivo. *Circulation* 107:1040-1045
- Koller A, Bagi Z (2004) Nitric oxide and H<sub>2</sub>O<sub>2</sub> contribute to reactive dilation of isolated coronary arterioles. *Am J Physiol Heart Circ Physiol* 287:H2461-2467
- Headrick J, Willis RJ (1988) Contribution of adenosine to changes in coronary flow in metabolically stimulated rat heart. *Can J Physiol Pharmacol* 66:171-173
- Duncker DJ, van Zon NS, Pavsek TJ, et al (1995) Endogenous adenosine mediates coronary vasodilation during exercise after K(ATP)+ channel blockade. *J Clin Invest* 95:285-295
- Ishibashi Y, Duncker DJ, Zhang J, et al (1998) ATP-sensitive K<sup>+</sup> channels, adenosine, and nitric oxide-mediated mechanisms account for coronary vasodilation during exercise. *Circ Res* 82:346-359
- Lavallee M, Takamura M, Parent R, et al (2001) Crosstalk between endothelin and nitric oxide in the control of vascular tone. *Heart Fail Rev* 6:265-276
- Hecker M, Fleming I, Busse R (1995) Kinin-mediated activation of endothelial NO formation: possible role during myocardial ischemia. *Agents Actions Suppl* 45:119-127
- Sato A, Sakuma I, Gutterman DD (2003) Mechanism of dilation to reactive oxygen species in human coronary arterioles. *Am J Physiol Heart Circ Physiol* 285:H2345-2354
- Rogers PA, Dick GM, Knudson JD, et al (2006) H<sub>2</sub>O<sub>2</sub>-induced redox-sensitive coronary vasodilation is mediated by 4-aminopyridine-sensitive K<sup>+</sup> channels. *Am J Physiol Heart Circ Physiol* 291:H2473-2482
- Kokusho Y, Komaru T, Takeda S, et al (2007) Hydrogen peroxide derived from beating heart mediates coronary microvascular dilation during tachycardia. *Arterioscler Thromb Vasc Biol* 27:1057-1063
- Kanatsuka H, Sekiguchi N, Sato K, et al (1992) Microvascular sites and mechanisms responsible for reactive hyperemia in the coronary circulation of the beating canine heart. *Circ Res* 71:912-922
- Chilian WM, Layne SM (1990) Coronary microvascular responses to reductions in perfusion pressure. Evidence for persistent arteriolar vasomotor tone during coronary hypoperfusion. *Circ Res* 66:1227-1238
- Miller FJ, Jr, Dellsperger KC, Gutterman DD (1997) Myogenic constriction of human coronary arterioles. *Am J Physiol* 273(1 Pt 2):H257-264
- Nowicki PT, Flavahan S, Hassanain H, et al (2001). Redox signaling of the arteriolar myogenic response. *Circ Res* 89:114-116
- Meininger GA, Davis MJ (1992) Cellular mechanisms involved in the vascular myogenic response. *Am J Physiol* 263(3 Pt 2):H647-659
- Folgering JH, Sharif-Naeini R, Dedman A, et al (2008) Molecular basis of the mammalian pressure-sensitive ion channels: focus on vascular mechanotransduction. *Prog Biophys Mol Biol* 97:180-195
- Earley S, Waldron BJ, Brayden JE (2004) Critical role for transient receptor potential channel TRPM4 in myogenic constriction of cerebral arteries. *Circ Res* 95:922-929
- Roman RJ (2002) P-450 metabolites of arachidonic acid in the control of cardiovascular function. *Physiol Rev* 82:131-185
- Sligh DF, Welsh DG, Brayden JE (2002) Diacylglycerol and protein kinase C activate cation channels involved in myogenic tone. *Am J Physiol Heart Circ Physiol* 283:H2196-2201
- Khan TA, Bianchi C, Ruel M, et al (2003) Mitogen-activated protein kinase inhibition and cardioplegia-cardiopulmonary bypass reduce coronary myogenic tone. *Circulation* 108 (Suppl 1):II348-353
- Wang SY, Friedman M, Franklin A, et al (1995) Myogenic reactivity of coronary resistance arteries after cardiopulmonary bypass and hyperkalemic cardioplegia. *Circulation* 92:1590-1596
- Recchia FA, Senzaki H, Saeki A, et al (1996) Pulse pressure-related changes in coronary flow in vivo are modulated by nitric oxide and adenosine. *Circ Res* 79:849-856
- Ueeda M, Silvia SK, Olsson RA (1992) Nitric oxide modulates coronary autoregulation in the guinea pig. *Circ Res* 70:1296-1303
- Kuo L, Chilian WM, Davis MJ (1991) Interaction of pressure- and flow-induced responses in porcine coronary resistance vessels. *Am J Physiol* 261(6 Pt 2):H1706-1715
- Joannides R, Haefeli WE, Linder L, et al (1995) Nitric oxide is responsible for flow-dependent dilatation of human peripheral conduit arteries in vivo. *Circulation* 91:1314-1319
- Miura H, Wachtel RE, Liu Y, et al (2001) Flow-induced dilation of human coronary arterioles: important role of Ca(2+)-activated K(+) channels. *Circulation* 103:1992-1998
- Miura H, Liu Y, Gutterman DD (1999) Human coronary arteriolar dilation to bradykinin depends on membrane hyperpolarization: contribution of nitric oxide and Ca2+-activated K+ channels. *Circulation* 99:3132-3138
- Sato A, Miura H, Liu Y, et al (2002) Effect of gender on endothelium-dependent dilation to bradykinin in human adipose microvessels. *Am J Physiol Heart Circ Physiol* 283:H845-852