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Coronary microvascular disease

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Over the past three to four decades, the view has evolved that myocardial ischemia in patients with coronary artery disease is caused by atherosclerotic plaques that obstruct flow and may undergo rupture, with subsequent thrombus formation.

However, a large body of evidence challenges this view that attributes myocardial ischemia entirely and exclusively to atherosclerotic obstruction of large epicardial coronary vessels. Altered control of distal coronary tone may aggravate the effects of epicardial obstructions or hinder myocardial perfusion, or both, even in the absence of a proximal obstruction. Abnormalities in coronary vasomotion can contribute to the precipitation and maintenance of ischemia in man. Endothelial dysfunction may impair microvascular adaptation to ischemia, and constrictor responses to reduced intraluminal pressure have been described in isolated microvessels.

A number of experimental and clinical observations support the hypothesis of a more complex pathogenesis of myocardial ischemia. Several investigators, using different techniques, have reported that myocardial perfusion and coronary blood flow reserve remain impaired after ''successful'' coronary recanalization.

The limited impact of revascularization procedures on prognosis and the persistence of angina in a large number of patients after removal of coronary obstructions indirectly support the concept of additional factors contributing to the pathogenesis of coronary syndromes. In the Randomised Intervention Treatment of Angina (RITA)-2 trial, after a median 7 years of follow-up, death or myocardial infarction occurred in 14.5% of patients who had undergone revascularization by percutaneous transluminal coronary angioplasty (PTCA) and in 12.3% of medically treated patients. Furthermore, the prevalence of angina remained increased in both groups, with 70% and 83%, respectively, of patients treated medically or with PTCA receiving at least one antianginal drug at 5 years. In the recent Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, one-third of patients still complained of angina at 1 year of follow-up, in both the medically and the PTCA-treated groups.

Among the additional factors in coronary pathogenesis, microcirculatory dysfunction is emerging as a key mechanism for myocardial ischemia. It manifests as a paradoxical increase in resistance to flow in response to reduced perfusion pressure, and contributes to the precipitation of ischemic attacks both in stable angina and in acute coronary syndromes.

In this issue of *Heart and Metabolism*, the role of the coronary microcirculation in normal and pathologic conditions is described, and strategies to prevent microvascular damage are discussed in detail.

The purpose of this entire issue of *Heart and Metabolism* is to increase awareness that coronary microvascular dysfunction may be a major player in the pathogenesis of ischemic heart disease, and that inclusion of microvascular dysfunction in the clinical assessment of coronary patients may direct treatment and improve the prognosis.

Microvascular control of myocardial perfusion

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Abstract

Myocardial perfusion is closely linked to oxygen demand, which is met by regulation of the resistance to flow in small arteries and arterioles via smooth muscle tone. Adjustment of smooth muscle tone occurs by modulation of the cytosolic calcium concentration, via influx of calcium across the cell membrane through a variety of calcium channels and release of calcium from the sarcoplasmic reticulum by inositol trisphosphate and ryanodine receptors. In addition, the calcium sensitivity of the contractile apparatus is regulated by several signaling cascades that converge on different protein kinases. Among the local mechanisms responsible for coupling perfusion to demand, metabolic mediators are the most potent in decreasing coronary vascular resistance. pH, partial pressure of oxygen, partial pressure of carbon dioxide, and potassium concentration all have profound effects on perfusion, but the identity of the mediator responsible for metabolic dilatation under physiologic conditions remains elusive. Because metabolic mediators reach only the most distal precapillary arterioles in sufficient concentrations, additional mechanisms are required to induce a coordinated dilatory response of the upstream larger resistance vessels. These may include myogenic mechanisms – that is, active contraction of smooth muscle cells in response to increased stretch or, in the case of downstream dilatation, active relaxation in response to decreased luminal pressure. The decrease in resistance as a result of metabolic and myogenic mechanisms in small and midsize arterioles increases flow in the entire upstream system of larger resistance vessels, resulting in endothelium-dependent flow-induced dilatation of this vessel segment.
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Keywords: Myocardial perfusion, microcirculation, metabolic control, myogenic response, flow-induced dilatation

Introduction

Coronary blood flow is closely matched to myocardial oxygen demand. This is achieved by alterations of vascular tone in the coronary vessels that contribute most to overall coronary resistance – that is, small resistance arteries and arterioles of the coronary microcirculation. The mechanisms involved in this regulatory response have elicited increasing interest in cardiologists in recent years, because accumulating evidence suggests that myocardial malperfusion may result, not only from stenoses in the large epicardial blood vessels, but also from inadequate dilatation or obstruction of microvessels. Some excellent reviews have addressed the putative role of coronary microvascular dysfunction in patients [1–3] and the

techniques currently available for its diagnosis [4]. The pathogenetic mechanisms contributing to coronary microvascular dysfunction are not well understood, but may include extravascular components such as extramural compression, structural alterations in the microvessels such as luminal obstruction by microemboli, or functional deficits, including endothelial and smooth muscle cell dysfunction. Research aiming at a better understanding of the pathogenesis of coronary microvascular dysfunction and the development of therapeutic principles is necessarily based on knowledge of the physiological principles governing the microvascular control of myocardial perfusion in healthy individuals. Here, we will briefly review the major mechanisms contributing to the microvascular control of myocardial perfusion.

Regulation of smooth muscle tone

Myocardial perfusion is adapted to metabolic demand by regulation of the diameters of resistance vessel – that is, by regulation of vascular smooth muscle tone in small arteries and in arterioles. Therefore, we now briefly summarize the mechanisms involved in smooth muscle contraction and relaxation. For more detailed analysis, we recommend recent in-depth reviews on this topic [5–7].

Smooth muscle tone depends upon the phosphorylative state of the myosin light chain (MLC), in that phosphorylated MLC (MLC-P) interacts with actin filaments, inducing contraction, whereas dephosphorylated MLC does not, facilitating relaxation (*Figure 1*). The enzymes MLC kinase (MLCK) and MLC phosphatase (MLCP) determine the balance between MLC and MLC-P. Calcium induces contraction by binding to calmodulin*, which then forms a complex with MLCK, thus activating the enzyme and shifting the balance to MLC-P. In addition to cytosolic calcium concentration, the balance between MLC and MLC-P is modulated by phosphorylation of MLCK and MLCP, which alters the calcium sensitivity of the contractile system. Various protein kinases that are activated by G-protein-coupled receptor-dependent signaling pathways* or by signaling molecules that can enter the smooth muscle cell, such as nitric oxide, participate in the regulation of calcium sensitivity and thus of vascular smooth muscle tone.

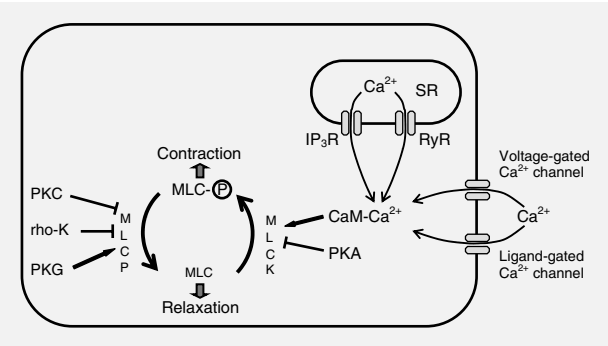

Figure 1. Schematic representation of the basic cellular mechanisms involved in the control of vascular smooth muscle tone. CaM, calmodulin; IP_3R, inositol trisphosphate receptor; MLC, myosin light chain; MLCK, MLC kinase; MLCP, MLC phosphatase; MLC-P, phosphorylated MLC; PKA, protein kinase A*; PKC, protein kinase C*; PKG, protein kinase G*; rho-K, rho-kinase*; RyR, ryanodine receptor*; SR, sarcoplasmic reticulum.*

Calcium enters the cell via a variety of calcium channels, including voltage-operated L-type and T-type calcium channels, which are activated by depolarization of the sarcolemma [6]. In addition, ligand-operated, store-operated, and stretch-sensitive calcium or unspecific cation channels may contribute to calcium entry. A second source of calcium entry is the intracellular calcium store, the sarcoplasmic reticulum. Inositol 1,4,5-trisphosphate (IP_3) is the second messenger of various G-protein-coupled receptors, among them the adrenergic α_1-receptor, which binds to and activates an IP_3-sensitive calcium channel, the IP_3 receptor in the sarcoplasmic reticulum membrane, inducing the release of calcium into the cytosol. Interestingly, at moderately enhanced cytosolic concentrations, calcium seems to enhance the effect of IP_3, forming a positive-feedback loop, which results in calcium-induced release of calcium. A calcium-sensitive calcium channel (the so-called ryanodine receptor) has been shown to be expressed in smooth muscle cells, but its actual contribution to the release of calcium from the sarcoplasmic reticulum remains unclear.

Removal of calcium from the cytosol is achieved by its re-uptake into the sarcoplasmic reticulum by the sarcoplasmic reticulum calcium pump, by calcium transport across the sarcolemma via another pump (Ca^{2+}/H^+-ATPase), which exchanges calcium for protons, and by a sodium–calcium exchanger, which depends upon the electrochemical gradient for the entry of sodium ions.

As mentioned above, cytosolic calcium concentration is not alone in determining smooth muscle tone. Several signaling cascades are involved in modulating the calcium sensitivity of the contractile fibers (*Figure 1*). A multitude of G-protein-coupled receptors convey signals into the cell, resulting in activation of different protein kinases. Protein kinase A (PKA), activated via, among others, β_2-adrenergic receptors, inhibits MLCK, facilitating relaxation. PKG, activated by, for example, natriuretic peptides or nitric oxide, activates MLCP, which also induces relaxation. In contrast, PKC and rho-kinase inhibit MLCP, thus inducing smooth muscle contraction. In addition, these signaling cascades may also modulate the conductivity of sarcolemmal ion channels, facilitating or

inhibiting calcium entry, which contributes to the relaxing or constricting effects, although the quantitative contribution of this mechanism to the total relaxing or constricting effect is unknown.

Metabolic regulation of perfusion

In the coronary circulation, perfusion is particularly well-matched to metabolism, such that coronary venous oxygen tension remains essentially unchanged, even during marked changes in myocardial oxygen demand and consumption. Matching perfusion to metabolic demand is believed to be mediated mainly by locally acting mechanisms, including hypoxia, decreased pH, and increased concentrations of carbon dioxide, potassium, or adenosine, all of which induce vasodilatation of coronary resistance vessels [8–10]. The actual contribution of each of these mechanisms to the metabolic control of myocardial perfusion is, however, still unclear. Hypoxemia and hypercarbia both result in an increase in coronary perfusion, and a combination of the two exerts a synergistic effect, in that a high carbon dioxide concentration potentiates the effect of hypoxia, and vice versa, resulting in a more than additive effect [11]. However, such experiments do not reveal whether altered gas tensions induce vasodilatation directly or via release of a biochemical mediator such as adenosine. In addition, the observed effects explain only part of the increase in flow during increased metabolic demand, suggesting that other factors must be involved [10].

In 1963, two groups of investigators independently suggested adenosine to be the major metabolic dilating factor in the heart [12,13]. Since then, numerous studies have confirmed the potent dilatory effect of adenosine in the coronary circulation, but today it is widely accepted that adenosine becomes important mostly in pathophysiologic conditions such as hypoxia or ischemia, and contributes only little to physiologic metabolic control of flow [14]. Thus other factors must be more important. Among these, the involvement of ATP-sensitive potassium channels (K_{ATP}) in smooth muscle cells has long been favored, although the exact mode of activation remains unclear [8–10,15]. A decreasing ATP concentration in smooth muscle cells is, of course, a major activator of these channels, which then induces hyperpolarization and relaxation of smooth muscle cells. However, because of their much greater oxygen demand, myocardial muscle cells would be hypoxic long before ATP concentrations decrease in smooth muscle cells. Other factors released from cardiac muscle cells would be required to activate these channels, and, indeed, adenosine seems to exert its dilatory effect partly via activation of K_{ATP} channels [10]. At present, experimental data can be interpreted either to support a major role of K_{ATP}* channels in metabolic dilatation [8,15] or to reject it [10].

Numerous other mediators – such as prostaglandins, nitric oxide, or (EDHF) endothelium-derived hyperpolarizing factor* – have been investigated for a possible role in metabolic dilatation, but none of these, either alone or in combination with others, seems sufficient to explain the metabolic coupling of perfusion [10]. An attractive concept is feed-forward β_2-adrenergic-receptor-mediated dilatation of resistance vessels, because the same sympathetic stimulus that increases oxygen demand via β_1-receptors would also induce the increase in perfusion required to meet this oxygen demand. However, while β_2-mediated dilatation of microvessels is readily demonstrated, this mechanism seems to account for only about 25% of the total increase in blood flow during exercise [16]. In conclusion, although several mediators may be involved to a certain degree, the major mechanism responsible for matching coronary perfusion to metabolic demand remains elusive.

Myogenic response

Myogenic activity is an intrinsic property of vascular smooth muscle cells. Thus vascular smooth muscle contracts in response to increased transmural pressure and the resulting increase in circumferential wall tension. Consequently, any distension of the vessel wall is followed, within 20–60 s, by a sustained constriction. The extent of the contraction may result in constriction of the vessel to a final diameter that is considerably smaller than the baseline diameter. Conversely, decreased transmural pressure results in dilatation of the vessel. This mechanism has been observed in most vascular beds of the systemic circulation, and is generally considered to be most pronounced in renal, cerebral, and coronary resistance vessels. Myogenic activity stabilizes organ perfusion during alterations in systemic arterial pressure, and protects the capillaries from excessive changes in transmural pressure and, consequently, fluid filtration.

The mechanisms of myogenic responses seem to include activation of stretch-activated unspecific cation channels, and possibly also of chloride channels in the sarcolemma, inducing influx of calcium and depolarization, which is followed by further influx of calcium via voltage-sensitive calcium channels [17]. This response may be enhanced by calcium-induced release of calcium, and by concomitant activation of membrane-bound phospholipase C and release of IP_3 and diacylglyceride* from the phospholipids of the cell membranes. IP_3 would further increase cytosolic calcium concentration by release from intracellular

stores, and diacylglyceride may increase the sensitivity of the smooth muscle contractile apparatus to calcium by activating PKC [8,17]. The exact mechanisms of the transduction of force into smooth muscle cells – that is, how increased stretch activates ion channels and PKC – remains to be elucidated. As the sarcolemma cannot bear enough force to activate stretch-sensitive ion channels without rupturing, force transduction has been suggested to be achieved via transmembrane adhesion molecules, integrins, which bind to extracellular matrix structures on the outside and to the actin cytoskeleton on the inside of the cell [17]. Negative-feedback mechanisms that protect blood vessels from stretch-induced spasms may involve voltage-activated and calcium-activated potassium channels, which would counter the depolarization of the cell membrane induced by the stretch-activated influx of cations [17].

Flow-induced dilatation

Endothelium-mediated vasodilatation in response to flow can be observed throughout the systemic and pulmonary circulation, in large arteries, in arterioles, muscular venules, and veins. The flow signal is transferred to the endothelial surface via wall shear stress, τ_W, which depends upon the volume flow rate, Q, blood viscosity, η, and vessel radius, r, according to the formula:

$$\tau_W = Q \times \eta \times 4/(r^3 \times \pi)$$

The exact mechanism by which increased wall shear stress is translated to an endothelial response – the mechanotransduction of this signal – has not yet been identified. Putative flow sensors include membrane proteins such as mechanosensitive ion channels, which may be activated directly or via mediation of the glycocalyx* at the endothelial surface [18,19], or membrane-bound G proteins [8,20]. In addition, mechanosensitive kinases may be activated by transmission of the mechanical stimulus to focal adhesion sites on the abluminal membrane by cytoskeletal actin fibers [21].

Among mechanosensitive ion channels, the family of transient receptor potential channels has attracted special interest. At least 18 different such channels have been shown to be expressed in endothelial cells, and several of these are obviously activated by shear stress. Some of these facilitate potassium efflux and hyperpolarization of endothelial cells – and, consequently, calcium entry as a result of the increased electrochemical driving force – whereas others function as shear-stress-sensitive calcium channels [22]. Calcium serves as a second messenger that directly activates endothelial nitric oxide synthase (eNOS) via calmodulin binding, but may also be involved in increased synthesis of prostaglandins (specifically, of prostacyclin), or release of an endothelium-derived hyperpolarizing factor [23]. The identity of this EDHF has not been determined conclusively, but potassium, calcium-activated potassium channels, and cytochrome P-450 metabolites of arachidonic acid are the major candidates [24,25]. The relative contribution of these endothelium-derived dilating mediators to flow-induced dilatation of coronary microvessels is controversial [8], but a prominent role of nitric oxide is unequivocally suggested.

However, increased calcium is not the only mediator of increased eNOS activity [26,27]. Calcium-independent mechanisms, which seem to be responsible for basal eNOS activity during constant shear stress, include, among others, tyrosine phosphorylation* of the enzyme and an increase in expression of protein as a result of increased transcription or mRNA stability.

The actions of the endothelial-dilating mediators on smooth muscle cells follow different pathways. Nitric oxide activates a soluble guanylate cyclase*, resulting in increased cyclic GMP concentration, which desensitizes the smooth muscle cell to calcium by PKG-mediated phosphorylation and activation of MLCP, but may also inhibit the entry of calcium through the sarcolemma. Prostacyclin, by binding to its receptor on the smooth muscle cell surface, activates a G_s protein, which then activates the adenylate cyclase–cyclic AMP–PKA signaling pathway. PKA desensitizes the smooth muscle cell to calcium by phosphorylation and inhibition of MLCK. In addition, a cyclic-AMP-mediated inhibition of calcium entry may contribute to the dilatory effect of prostacyclin. The major effect of the different putative EDHFs is hyperpolarization of the smooth muscle cells and the consequent inhibition of voltage-gated calcium entry channels [8].

Integration of metabolic dilatation with upstream mechanisms of diameter control

Increasing myocardial oxygen demand by pacing [28], as well as perfusion with dipyridamole [29], which increases tissue adenosine concentration, or with adenosine itself [30,31], all induce a similar pattern of vasodilatation across the different segments of the coronary vasculature, in that relative increases in diameter of the resistance vessels are inversely related to resting diameters. In other words, the relative diameter increase is greatest in the smallest precapillary arterioles.

This pattern of vasodilatation would be consistent with the assumption that metabolic mediators released from myocardial muscles would primarily

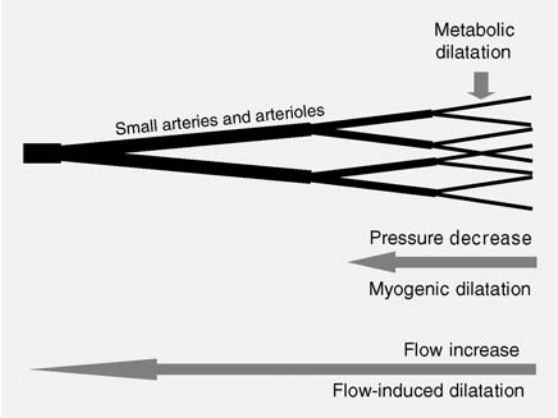

Figure 2. Model for the functional integration of myogenic and endothelium-dependent flow-induced control mechanisms into a coordinated response of the arteriolar vessel tree to increased metabolic demand. After direct dilatation of the most distally located precapillary arterioles in response to metabolic stimuli released from myocardial cells, upstream resistance vessels are indirectly recruited to dilate also. (Modified from Jones et al [9].)

reach these most peripheral arterioles, whereas larger upstream vessels with diameters in the range 50–300 μm remain largely unaffected. However, these upstream vessels contribute substantially to total coronary resistance [32], and full recruitment of the coronary flow reserve requires dilatation of these vessels also. A comprehensive model of how these upstream vessels could be recruited to a coordinated dilatory response of the entire arterial tree to increased metabolic demand was first suggested by Jones et al [9], and is presented in *Figure 2*, with some modifications. Metabolic mediators are released from myocardial cells and induce dilatation of the smallest precapillary arterioles, which also seem to be the most sensitive to these mediators. This in turn induces a decrease in pressure in the next upstream segment of midsize arterioles, inducing myogenic dilatation of these vessels. The resultant decrease in total resistance increases flow, which then induces flow-induced, endothelium-dependent dilatation within the entire upstream segment of larger arterioles and small resistance arteries. This model is supported by the observation, in isolated coronary arterioles, that larger vessels seem to react more sensitively to flow than do smaller vessels [33]; this is, however, in contrast with the findings of a recent in-vivo study in rats, in which acetylcholine, which is considered to activate mechanistic responses in endothelial cells that are similar to those induced by flow, had the strongest dilatory effect in the smallest precapillary arterioles [34]. Differences in species, the experimental model, or the mode of eliciting endothelium-dependent dilatation may account for these conflicting observations. Whether or not midsize arterioles are more sensitive to myogenic stimuli than smaller or larger vessels as proposed by Jones et al [9] is unclear, because of a lack of experimental data. Preliminary data from our laboratory suggest that myogenic responses are maintained in small coronary arterioles, albeit only over a range of low transmural pressures [35], which would be consistent with the pressure profile in these vessels [32]. A similar observation has also been made in isolated skeletal muscle arterioles of hamster cheek pouch [36].

The actual contribution of a distinct mechanism to a vascular reaction depends, not only on the sensitivity of the respective microvascular segment to this mechanism, but also upon the actual exposure of the segment to the respective stimulus. For example, analyses using a comprehensive computer model of the coronary vasculature indicated that small arterioles are effectively shielded from changes in perfusion pressure by the strong myogenic responses of the upstream larger vessels [37]. In addition, flow-induced or myogenic effects on small arterioles may be masked by the potent effects of metabolic stimuli on this vessel segment.

In conclusion, the model of recruitment of upstream vessels to the coordinated response to a metabolic challenge remains valid, independent of the actual distribution of sensitivity to flow-induced dilatation and myogenic responses among different segments of the arteriolar tree.

*See glossary for definition of these terms. ■

REFERENCES

1. Camici PG, Crea F. Coronary microvascular dysfunction. *N Engl J Med*. 2007;356:830–840.
2. Bugiardini R, Bairey Merz CN. Angina with ''normal'' coronary arteries: a changing philosophy. *JAMA*. 2005;293:477–484.
3. Bugiardini R, Badimon L, Collins P, et al. Angina, ''normal'' coronary angiography, and vascular dysfunction: risk assessment strategies. *PLoS Med*. 2007;4:e12.
4. Struijker-Boudier HA, Rosei AE, Bruneval P, et al. Evaluation of the microcirculation in hypertension and cardiovascular disease. *Eur Heart J*. 2007;28:2834–2840.
5. Akata T. Cellular and molecular mechanisms regulating vascular tone. Part 2: regulatory mechanisms modulating Ca2+ mobilization and/or myofilament Ca2+ sensitivity in vascular smooth muscle cells. *J Anesth*. 2007;21:232–242.
6. Akata T. Cellular and molecular mechanisms regulating vascular tone. Part 1: basic mechanisms controlling cytosolic Ca2+ concentration and the Ca2+-dependent regulation of vascular tone. *J Anesth*. 2007;21:220–231.
7. Horowitz A, Menice CB, Laporte R, Morgan KG. Mechanisms of smooth muscle contraction. *Physiol Rev*. 1996;76:967–1003.
8. Komaru T, Kanatsuka H, Shirato K. Coronary microcirculation: physiology and pharmacology. *Pharmacol Ther*. 2000;86: 217–261.
9. Jones CJ, Kuo L, Davis MJ, Chilian WM. Regulation of coronary blood flow: coordination of heterogeneous control mechanisms in vascular microdomains. *Cardiovasc Res*. 1995;29:585–596.
10. Tune JD, Gorman MW, Feigl EO. Matching coronary blood flow to myocardial oxygen consumption. *J Appl Physiol*. 2004;97:404–415.
11. Broten TP, Romson JL, Fullerton DA, Van Winkle DM, Feigl EO. Synergistic action of myocardial oxygen and carbon dioxide in controlling coronary blood flow. *Circ Res*. 1991; 68:531–542.

12. Gerlach E, Deuticke B, Dreisbach RH. Der Nucleotid-Abbau im Herzmuskel bei Sauerstoffmangel und seine mögliche Bedeutung f:ür die Coronardurchblutung. *Naturwissenschaften*. 1963;50:228–229.
13. Berne RM. Cardiac nucleotides in hypoxia: possible role in regulation of coronary blood flow. *Am J Physiol*. 1963;204: 317–322.
14. Tune JD, Richmond KN, Gorman MW, Olsson RA, Feigl EO. Adenosine is not responsible for local metabolic control of coronary blood flow in dogs during exercise. *Am J Physiol Heart Circ Physiol*. 2000;278:H74–H84.
15. Komaru T, Kanatsuka H, Dellsperger K, Takishima T. The role of ATP-sensitive potassium channels in regulating coronary microcirculation. *Biorheology*. 1993;30:371–380.
16. Gorman MW, Tune JD, Richmond KN, Feigl EO. Quantitative analysis of feedforward sympathetic coronary vasodilation in exercising dogs. *J Appl Physiol*. 2000;89:1903–1911.
17. Davis MJ, Hill MA. Signaling mechanisms underlying the vascular myogenic response. *Physiol Rev*. 1999;79:387–423.
18. Nilius B, Droogmans G. Ion channels and their functional role in vascular endothelium. *Physiol Rev*. 2001;81:1415–1459.
19. VanBavel E. Effects of shear stress on endothelial cells: possible relevance for ultrasound applications. *Prog Biophys Mol Biol*. 2007;93:374–383.
20. Gudi SR, Clark CB, Frangos JA. Fluid flow rapidly activates G proteins in human endothelial cells. Involvement of G proteins in mechanochemical signal transduction. *Circ Res*. 1996;79: 834–839.
21. Davies PF. Flow-mediated endothelial mechanotransduction. *Physiol Rev*. 1995;75:519–560.
22. Kwan HY, Huang Y, Yao X. TRP channels in endothelial function and dysfunction. *Biochim Biophys Acta*. 2007; 1772:907–914.
23. de Wit C, Bolz SS, Pohl U. Interaction of endothelial autacoids in microvascular control. *Z Kardiol*. 2000;89 (suppl 9):IX/113–IX/116.
24. Kohler R, Hoyer J. The endothelium-derived hyperpolarizing factor: insights from genetic animal models. *Kidney Int*. 2007;72:145–150.
25. Campbell WB, Falck JR. Arachidonic acid metabolites as endothelium-derived hyperpolarizing factors. *Hypertension*. 2007;49:590–596.
26. Fulton D, Gratton JP, Sessa WC. Post-translational control of endothelial nitric oxide synthase: why isn't calcium/calmodulin enough? *J Pharmacol Exp Ther*. 2001;299:818–824.
27. Boo YC, Jo H. Flow-dependent regulation of endothelial nitric oxide synthase: role of protein kinases. *Am J Physiol Cell Physiol*. 2003;285:C499–C508.
28. Kanatsuka H, Lamping KG, Eastham CL, Dellsperger KC, Marcus ML. Comparison of the effects of increased myocardial oxygen consumption and adenosine on the coronary microvascular resistance. *Circ Res*. 1989;65:1296–1305.
29. Chilian WM, Layne SM, Klausner EC, Eastham CL, Marcus ML. Redistribution of coronary microvascular resistance produced by dipyridamole. *Am J Physiol Heart Circ Physiol*. 1989; 256:H383–H390.
30. Habazettl H, Vollmar B, Christ M, Baier H, Conzen PF, Peter K. Heterogeneous microvascular coronary vasodilation by adenosine and nitroglycerin in dogs. *J Appl Physiol*. 1994; 76:1951–1960.
31. Habazettl H, Conzen PF, Vollmar B, et al. Dilation of coronary microvessels by adenosine induced hypotension. *Int J Microcirc Clin Exp*. 1992;11:51–65.
32. Chilian WM, Eastham CL, Marcus ML. Microvascular distribution of coronary vascular resistance in beating left ventricle. *Am J Physiol Heart Circ Physiol*. 1986;251:H779–H788.
33. Kuo L, Davis MJ, Chilian WM. Longitudinal gradients for endothelium-dependent and -independent vascular responses in the coronary microcirculation. *Circulation*. 1995;92:518–525.
34. Kajiya M, Hirota M, Inai Y, et al. Impaired NO-mediated vasodilation with increased superoxide but robust EDHF function in right ventricular arterial microvessels of pulmonary hypertensive rats. *Am J Physiol Heart Circ Physiol*. 2007; 292:H2737–H2744.
35. Habazettl H, Cornelissen AJM. Combining fluorescence microscopy of isolated hearts with mathematical modeling to study myogenic control of coronary microvessels [abstract]. *J Vasc Res*. 2006;43:37.
36. Davis MJ. Myogenic response gradient in an arteriolar network. *Am J Physiol Heart Circ Physiol*. 1993;264:H2168–H2179.
37. Cornelissen AJ, Dankelman J, VanBavel E, Stassen HG, Spaan JA. Myogenic reactivity and resistance distribution in the coronary arterial tree: a model study. *Am J Physiol Heart Circ Physiol*. 2000;278:H1490–H1499.

Prognostic significance of microvascular dysfunction

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Abstract

Several studies have demonstrated a strong association between coronary vascular endothelial dysfunction and an adverse long-term cardiovascular prognosis. Both conduit arterial and microcirculatory endothelial function are predictive of outcome, independent of the presence of coronary artery disease and its risk factors. Thus assessment of endothelial function or its markers in patients with different cardiovascular disorders may help identify a subgroup of patients at high risk. Whether strategies that improve microvascular function will uniformly improve prognosis needs to be studied prospectively.
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Keywords: Endothelial function, microcirculation, atherosclerosis, coronary arteries

Introduction

The coronary microcirculation, which consists of resistance arterioles, capillaries, and small veins, plays a major part in the delivery of blood and nutrients to the myocardium. In addition to its physiologic role, the coronary microcirculation is affected in a variety of systemic and cardiac disorders [1]. Functional alterations, involving changes in the microvascular vasomotor response, may occur as a result of metabolic and autoregulatory changes and endothelial dysfunction. Alterations in the number and diameter of the coronary microvessels may further trigger structural alterations [1].

Studies of the microvascular responses to drugs and of the impairment of coronary microvessels in cardiovascular diseased conditions provide useful prognostic and therapeutic information [2]. In this article, the prognostic significance of microvascular dysfunction is discussed.

Several studies have demonstrated a strong association between coronary vascular endothelial dysfunction and an adverse long-term cardiovascular prognosis [2–5]. A multivariant analysis describing the association between coronary or peripheral endothelial dysfunction and cardiovascular outcome demonstrated that endothelial dysfunction is strongly and independently associated with cardiovascular events [2]. Both conduit arterial and microcirculatory endothelial function are predictive of outcome, independent of the presence of coronary artery disease and its risk factors [2].

Microcirculation and acute myocardial infarction

According to the vulnerable patient concept [6], myocardial microcirculatory dysfunction may be the consequence of a primary epicardial event or

may contribute to the clinical course of the acute coronary event. Coronary microvascular dysfunction is responsible for the no-reflow phenomenon, which is known to be associated with a worse outcome [7]. In addition to predicting recovery of systolic function, the presence of no-reflow predicts acute complications after acute myocardial infarction (AMI). Patients with the no-reflow phenomenon form the highest-risk subgroup of patients undergoing reperfusion, with increased associated risks of early and sustained congestive heart failure and death [8]. Follow-up studies have documented that the no-reflow phenomenon is associated with malignant arrhythmias, reduced ejection fraction, and an increased risk of cardiac death [8]. Hombach et al [9] have shown that persistent microvascular obstruction has more prognostic importance than ejection fraction in predicting late left ventricular remodeling and survival after AMI.

The fact that coronary blood flow is reduced by 50% in the non-culprit coronary arteries in AMI before and after coronary intervention points to global, rather than regional, myocardial microcirculatory impairment [10]. Inflammation may be a common link between epicardial macrovascular and myocardial microvascular disease. Indeed, Neri Serneri et al [11] demonstrated an acute inflammatory process involving the coronary microvessels, but not the cardiomyocytes, in patients with unstable angina. They emphasized that, in this setting, inflammation of the myocardial microcirculation could not be the consequence of myocardial necrosis or even myocardial ischemia, but rather that of an immunological process, possibly by downstream spread of immunogenic material from ruptured plaques [11]. Intriguingly, widespread activation of neutrophils across the coronary vascular bed has been reported in patients with unstable angina, regardless of the location of the culprit stenosis [12].

Taken together, these observations demonstrate a growing body of multilayered evidence to suggest that the integrity of the coronary microcirculation plays an integral part in the evolution of AMI. In line with the concept of the primary significance of the myocardial microcirculation, pre-existing transient or permanent microcirculatory dysfunction may contribute to the development and prognosis of AMI via reduction in coronary blood flow, leading to an alteration in shear stress and thereby aggravation of endothelial function at the epicardial level, in addition to aggravation of thrombus formation.

Microvascular dysfunction in patients without significant coronary stenoses

Coronary microvascular dysfunction is sufficiently severe to induce myocardial ischemia in at least 20% of patients with chest pain and normal or near-normal angiography [13]. In patients without obstructive coronary artery disease, future cardiovascular events (including acute coronary syndromes) were limited to those with a reduction in endothelium-dependent coronary blood flow [5].

Britten et al [14] confirmed coronary flow reserve, an indicator of the myocardial microcirculation, as an independent predictor of prognosis in patients with angiographically normal or minimally diseased coronary arteries over an average of 6.5 years. They noted a more than 3-fold greater cardiovascular event rate in patients in the lowest tertile of coronary flow reserve compared with the highest (18% compared with 5%, $P = 0.019$), with 36% of all events related to AMI [14]. Similarly, Marks et al [15] followed patients with chest pain/ischemic cardiac disease and normal coronary angiograms over a mean period of 8.5 years and demonstrated a 3-fold greater mortality for those patients with an abnormal coronary flow reserve (20% compared with 7%; $P = 0.016$). Hence, the presence of myocardial microcirculatory dysfunction is a strong predictor of clinical outcome, including future acute coronary events, even in the absence of hemodynamically significant epicardial disease.

Finally, microvascular dysfunction may play a prominent role in the unexpected prevalence of angina after the removal of obstructions in the major coronary branches [16].

Microvascular dysfunction and hypertrophic cardiomyopathy

Patients with hypertrophic cardiomyopathy (HCM) have been shown to have abnormal small coronary resistance vessels. Intramural coronary arteries and subendocardial arterioles have thickened walls and narrowed lumens. The intima layer involving the endothelium is hypertrophied and endothelial cells are structurally abnormal, which provides a morphological substrate for functional impairment of the endothelium [17]. Accordingly, endothelium-dependent vasodilator dysfunction has been demonstrated, using the cold pressor test, in both symptomatic and asymptomatic patients with HCM without a left ventricular outflow tract gradient [17]. In patients with HCM, the degree of microvascular dysfunction is a strong, independent predictor of clinical deterioration and death. Severe microvascular dysfunction is often present in patients with mild or no symptoms, and may precede clinical deterioration by years [18,19].

Coronary microcirculation and heart failure

The myocardial blood flow response to increased demand is a strong independent predictor for

the progression of heart failure [20]. Thus it may be speculated that endothelial dysfunction may lead to repeated episodes of myocardial ischemia and small infarcts that ultimately contribute to the development of heart failure. This hypothesis is supported by the observation that endothelial dysfunction is present both in patients with early asymptomatic heart failure [21] and in those with heart failure that is symptomatic [22].

Coronary microcirculation after heart transplantation

Cardiac allograft vasculopathy continues to limit the long-term success of cardiac transplantation. Recent insights have underscored the fact that innate and adaptive immune responses are involved in the pathogenesis of cardiac allograft vasculopathy [23]. Vascular lesions are the result of cumulative endothelial injuries induced both by alloimmune responses and by non specific insults in the context of impaired repair mechanisms [23]. The prevalence of microvascular endothelial dysfunction increases with increasing time after heart transplantation. Early after transplantation, dysfunction is prominent in 20% of patients; it increases to about 30% during long-term follow-up [24]. As in the epicardial tree, dysfunction of the microvascular system is a variable phenomenon over time [25]. Importantly, there is no association between epicardial and microvascular vasomotor dysfunction after heart transplantation. Thus epicardial and microvascular cardiac allograft vasculopathy are two independent, distinct entities in terms of endothelial dysfunction and morphological involvement, reflecting different pathogenetic mechanisms [23].

In a study using serial intravascular ultrasound and Doppler flow-wire measurements, annual decrements in coronary endothelial function were found to be associated with progressive intimal thickening, whereas abnormal vasomotor response to acetylcholine preceded the development of clinical endpoints [26]. Together, these observations suggest that endothelial dysfunction may represent an early and potentially reversible stage of graft vasculopathy. However, sustained endothelial dysfunction may reflect permanent vascular injury, with or without structural abnormalities.

Importantly, an impaired coronary flow reserve was associated with subsequent reduction in left ventricular ejection fraction during a 2-year follow-up, suggesting that repetitive subendocardial ischemia during myocardial stress resulted in an impairment of left ventricular function after heart transplantation [27]. In addition, Wolford et al [28] demonstrated that an increased variability of coronary vasodilatory reserve correlates with a significantly increased risk of cardiovascular events. ■

REFERENCES

1. Garot P, Teiger E, Dupouy P, Aptecar E, Hittinger L, Dubois-Rande JL. Coronary microcirculation and cardiovascular pathology. *Drugs*. 1999;59:23–31.
2. Lerman A, Zeiher AM. Endothelial function: cardiac events. *Circulation*. 2005;111:363–368.
3. Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation*. 2000;101:1899–1906.
4. Schachinger V, Zeiher AM. Prognostic implications of endothelial dysfunction: does it mean anything? *Coron Artery Dis*. 2001;12:435–443.
5. Suwaidi JA, Hamasaki S, Higano ST, Nishimura RA, Holmes DR Jr, Lerman A. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. *Circulation*. 2000;101:948–954.
6. Lerman A, Holmes DR, Herrmann J, Gersh BJ. Microcirculatory dysfunction in ST-elevation myocardial infarction: cause, consequence, or both? *Eur Heart J*. 2007;28:788–797.
7. Rezkalla SH, Kloner RA. No-reflow phenomenon. *Circulation*. 2002;105:656–662.
8. Ito H. No-reflow phenomenon and prognosis in patients with acute myocardial infarction. *Nat Clin Pract Cardiovasc Med*. 2006;3:499–506.
9. Hombach V, Grebe O, Merkle N, et al. Sequelae of acute myocardial infarction regarding cardiac structure and function and their prognostic significance as assessed by magnetic resonance imaging. *Eur Heart J*. 2005;26:549–557.
10. Gibson CM, Cannon CP, Murphy SA, et al. Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. *Circulation*. 2000;101:125–130.
11. Neri Serneri GG, Boddi M, Modesti PA, et al. Immunomediated and ischemia-independent inflammation of coronary microvessels in unstable angina. *Circ Res*. 2003;92:1359–1366.
12. Buffon A, Biasucci LM, Liuzzo G, D'Onofrio G, Crea F, Maseri A. Widespread coronary inflammation in unstable angina. *N Engl J Med*. 2002;347:5–12.
13. Buchthal SD, den Hollander JA, Merz CN, et al. Abnormal myocardial phosphorus-31 nuclear magnetic resonance spectroscopy in women with chest pain but normal coronary angiograms. *N Engl J Med*. 2000;342:829–835.
14. Britten MB, Zeiher AM, Schachinger V. Microvascular dysfunction in angiographically normal or mildly diseased coronary arteries predicts adverse cardiovascular long-term outcome. *Coron Artery Dis*. 2004;15:259–264.
15. Marks DS, Gudapati S, Prisant LM, et al. Mortality in patients with microvascular disease. *J Clin Hypertens (Greenwich)*. 2004;6:304–309.
16. Marzilli M. Recurrent and resistant angina: is the metabolic approach an appropriate answer? *Coron Artery Dis*. 2004;15 (suppl 1):S23–S27.
17. Ho CY, Seidman CE. A contemporary approach to hypertrophic cardiomyopathy. *Circulation*. 2006;113:e858–e862.
18. Cecchi F, Olivotto I, Gistri R, Lorenzoni R, Chiriatti G, Camici PG. Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy. *N Engl J Med*. 2003;349:1027–1035.
19. Kuhn H, Gietzen F, Leuner C. 'The abrupt no-flow': a no-reflow like phenomenon in hypertrophic cardiomyopathy. *Eur Heart J*. 2002;23:91–93.
20. Neglia D, Michelassi C, Trivieri MG, et al. Prognostic role of myocardial blood flow impairment in idiopathic left ventricular dysfunction. *Circulation*. 2002;105:186–193.
21. Prasad A, Higano ST, Al Suwaidi J, et al. Abnormal coronary microvascular endothelial function in humans with asymptomatic left ventricular dysfunction. *Am Heart J*. 2003;146:549–554.
22. Treasure CB, Vita JA, Cox DA, et al. Endothelium-dependent dilation of the coronary microvasculature is impaired in dilated cardiomyopathy. *Circulation*. 1990;81:772–779.

23. Schmauss D, Weis M. Cardiac allograft vasculopathy: recent developments. *Circulation*. 2008;117:2131–2141.
24. Weis M, Pehlivanli S, von Scheidt W. Heart allograft endothelial cell dysfunction. Cause, course, and consequences. *Z Kardiol*. 2000;89 (suppl 9):IX/58–IX/62.
25. Weis M, Peter-Wolf W, Mazzilli N, et al. Variations of segmental endothelium-dependent and endothelium-independent vasomotor tone after cardiac transplantation (qualitative changes in endothelial function). *Am Heart J*. 1997;134:306–315.
26. Hollenberg SM, Klein LW, Parrillo JE, et al. Coronary endothelial dysfunction after heart transplantation predicts allograft vasculopathy and cardiac death. *Circulation*. 2001;104: 3091–3096.
27. Weis M, Hartmann A, Olbrich HG, Hor G, Zeiher AM. Prognostic significance of coronary flow reserve on left ventricular ejection fraction in cardiac transplant recipients. *Transplantation*. 1998;65:103–108.
28. Wolford TL, Donohue TJ, Bach RG, et al. Heterogeneity of coronary flow reserve in the examination of multiple individual allograft coronary arteries. *Circulation*. 1999;99:626–632.

Non invasive assessment of coronary microvascular dysfunction

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Abstract

Microvascular abnormalities of the coronary circulation are present in several cardiac disorders, are associated with risk factors, and may be present in systemic disease. For the diagnosis and quantification of microvascular dysfunction, non invasive imaging techniques can be used. This paper will highlight the roles of exercise ECG, single photon emission computed tomography, echocardiography, cardiac magnetic resonance imaging, positron emission tomography, and computed tomography.
■ *Heart Metab.* 2008;40:15–19.

Keywords: Microvascular disease, exercise ECG, SPECT, echocardiography, cardiac magnetic resonance imaging, positron emission tomography, computed tomography

Introduction

It has long been recognized that microvascular abnormalities are present in several cardiac disorders. Studies have shown that dysfunction may be present in coronary artery disease, after myocardial infarction, in hypertrophic and dilated cardiomyopathy, in syndrome X, in congenital disease, in non compaction cardiomyopathy, and in systemic disease. Moreover, risk factors such as age, hypertension, diabetes mellitus, hypercholesterolemia, and smoking are all associated with microvascular dysfunction.

Almost all non invasive imaging techniques have been used to identify microvascular dysfunction in a variety of cardiac disorders. In this paper, the use of exercise ECG, single photon emission computed tomography (SPECT), echocardiography, cardiac magnetic resonance (CMR), positron emission tomography (PET), and computed tomography will be discussed.

Exercise ECG

Exercise ECG has mainly been used in patients with syndrome X, which is characterized by anginal complaints, an abnormal exercise ECG, and normal or near-normal coronary arteries at coronary angiography. Typically, these patients show ST-segment depression during exercise testing (for a recent review, see [1]). An example is given in *Figure 1*.

The major advantage of the exercise ECG is that it is inexpensive and readily available. However, quantification of the extent of microvascular dysfunction is not possible.

SPECT

Stress–rest perfusion SPECT imaging with thallium-201 or technetium-99m isonitriles has been used to demonstrate microvascular dysfunction in various cardiac diseases: for example, in patients with syndrome X

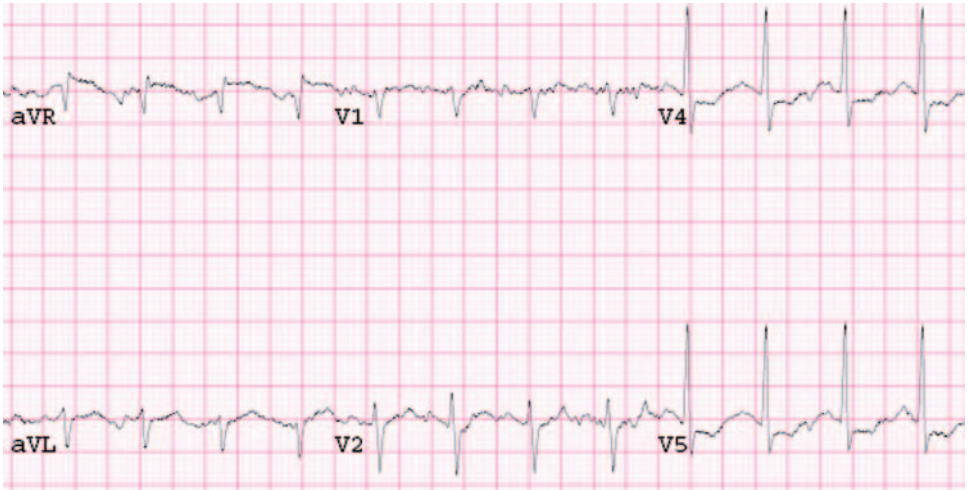

Figure 1. Example of an exercise ECG in a 54-year-old man with anginal complaints. Exercise stress testing showed ST-segment depression in the precordial lateral leads and ST-segment elevation in lead aVR. Angiography revealed normal coronary arteries.

[2], after percutaneous coronary intervention (PCI) [3], in dilated cardiomyopathy [4] and hypertrophic cardiomyopathy [5], and in patients with a metabolic syndrome [6]. All the studies showed reversible perfusion defects in these patients. Interestingly, the perfusion abnormalities have prognostic significance, except in patients with syndrome X, who have a normal prognosis. These differences may be explained by the differences in the underlying disease.

The use of SPECT is limited by the dose of radiation, limiting the number of studies – for example after a therapeutic intervention. More importantly, perfusion imaging is a semi quantitative technique in which perfusion images of different territories are compared. Attempts have been made to quantify the perfusion, but these have not yet been tested in clinical practice [7].

Examples of SPECT images from patients with reversible perfusion defects, despite the presence of normal coronary arteries, are shown in *Figure 2*.

Echocardiography

Using echocardiography, there are three distinct approaches to the detection of microvascular dysfunction.

Stress echocardiography

Similar to exercise ECG and SPECT perfusion imaging, stress echocardiography can be used to detect microvascular dysfunction in patients with syndrome X [8]. In response to stress provoked by dobutamine or adenosine, patients show new regional wall motion abnormalities.

Direct Doppler imaging of the coronary arteries

The Doppler technique directly visualizes the coronary artery, by either transthoracic or transesophageal echocardiography. It enables resting flow and flow after vasodilatation to be obtained, giving the flow reserve of the coronary artery [9]. It has been validated in patients with syndrome X, and in those with dilated and hypertrophic cardiomyopathy. In these groups of patients, a lower flow reserve was found compared with that in control individuals. *Figure 3* shows an example of Doppler-derived images.

Potential problems with this technique include the difficulty of obtaining adequate images, including

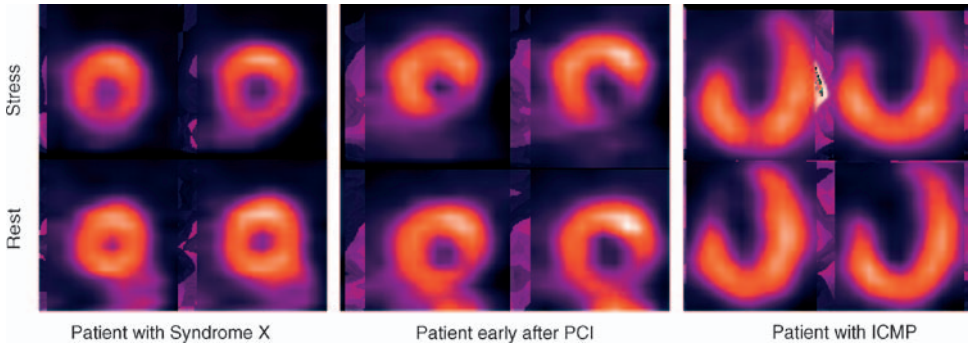

Figure 2. Examples of stress–rest perfusion single photon emission computed tomography in patients with reversible perfusion defects despite the presence of normal coronary arteries, indicating microvascular disease. ICMP, idiopathic dilated cardiomyopathy; PCI, percutaneous coronary intervention.

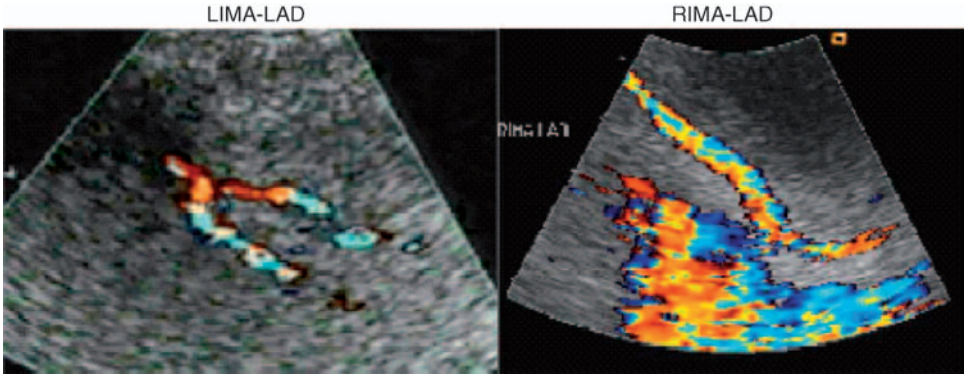

Figure 3. Examples of Doppler-derived images of bypass grafts on the left anterior descending coronary artery (LAD). LIMA, left internal mammary artery; RIMA, right internal mammary artery. (From Voci et al [9], with permission.)

through-plane motion and the angle between the probe and the coronary artery, and the ability to observe only proximal coronary arteries.

Use of contrast agents to visualize perfusion

The third means of identifying microvascular dysfunction uses contrast agents. Microbubbles have been used, in particular, to assess the presence of no-reflow of the infarct area after primary PCI [10]. After intravenous or intracoronary injection, the microbubbles enter the coronary circulation and the myocardium becomes opacified. The opacification of the myocardium is diffuse and uniform in normal individuals (*Figure 4*), whereas, in those with microvascular obstruction, the myocardial area shows no or slow opacification.

An interesting approach is quantification of the wash-in rate of the bubbles as a measure of coronary flow. For this purpose, an interesting intervention is used: at a certain time point, the bubbles are destroyed by a high-energy acoustic wave, and subsequent refilling of the myocardium by the bubbles is followed by echocardiography. From this wash-in rate, the coronary flow can be calculated and – from resting and adenosine-induced hyperemia – the flow reserve [11]. Although initial studies were promising, later studies showed a large variation in data [12], necessitating further refinement of the technique.

Cardiac magnetic resonance imaging

Cardiac magnetic resonance can be used to assess wall motion during stress. However, this approach is cumbersome, and wall motion can be assessed more readily by means of echocardiography. The most widely used application of CMR imaging involves the use of contrast agents. Directly after injection of gadolinium chelates, myocardial perfusion can be measured, in a similar fashion as with echocardiography. *Figure 5* shows an example of lack of opacification of the septal area after the injection of gadolinium benzyloxypropionictetra-acetate (BOPTA) in a patient after infarction.

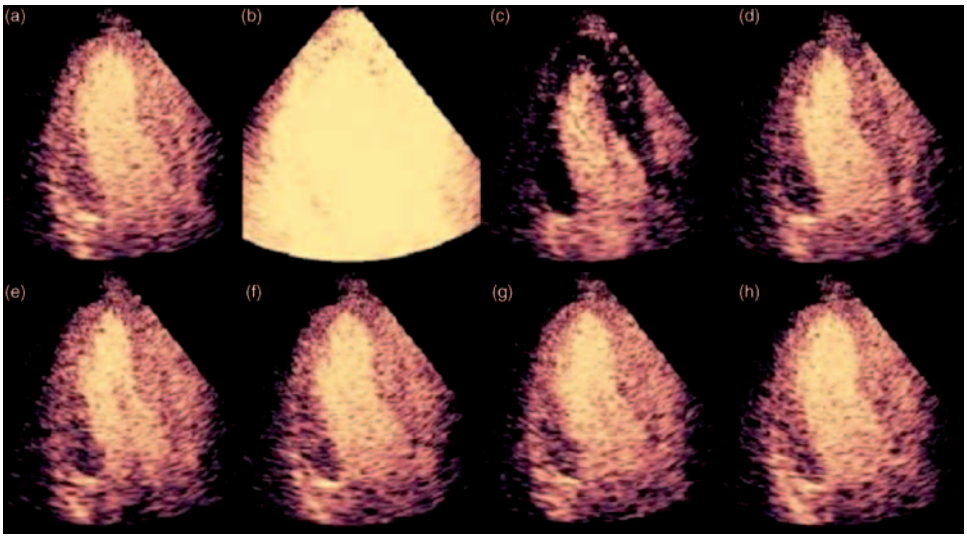

Figure 4. Example of opacification of the myocardium in a normal volunteer, visualized using contrast agents. (From Dijkmans et al [11], with permission.)

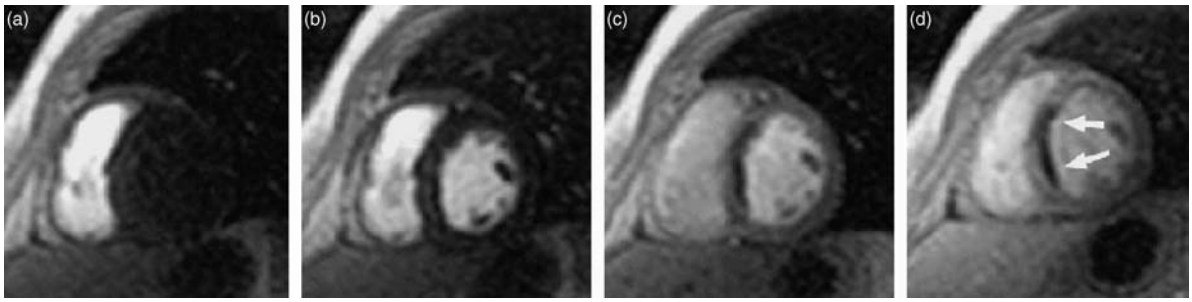

Figure 5. Patient with an anteroseptal infarction with a perfusion defect in the septal area (indicated by arrows) despite reperfusion therapy. (From Schneider et al [13], with permission.)

The time course of distribution of the contrast agent can be quantified by CMR, yielding the coronary flow or perfusion reserve [14]. There are several methodologies available to quantify coronary flow using first-pass perfusion, and the optimal approach remains to be defined. Nevertheless, in patients with syndrome X, a clear reduction in the perfusion reserve has been reported [15].

After injection, gadolinium chelates enter the interstitial space; in areas with microvascular dysfunction, a slow wash-in and wash-out can be observed. This technique is called late enhancement, and is widely used to assess viability and microvascular dysfunction after myocardial infarction [16]. However, late enhancement has also been observed in patients with hypertrophic and dilated cardiomyopathy, and in those with myocarditis. The relationship between microvascular dysfunction and late enhancement, and its clinical significance, thus need further investigation [17].

PET imaging

Flow imaging with PET is considered the gold standard for the assessment of perfusion. Using the flow tracers [^{15}O]H_2O, [^{13}N]ammonia, and rubidium-82, flow can be quantified, and has been widely validated in animal experiments and in humans. It has been extensively studied for use in assessing microvascular dysfunction in coronary artery disease, after myocardial infarction, in hypertrophic and dilated cardiomyopathy, in syndrome X, in congenital and systemic disease, and in non compaction cardiomyopathy (for a review, see [18]). Moreover, the technique has been used in the study of different therapeutic interventions.

An exciting development is the combination of PET and computed tomography in one imaging device. Computed tomography makes it possible to visualize the coronary tree, whereas PET provides perfusion data. An example is given in *Figure 6*.

The major disadvantage of PET is its limited availability, which is related to the cost. In view of the increasingly widespread installation of PET–computed tomography devices nowadays, it is probable that costs will become lower. A second disadvantage of the technique, of course, is that radiation is also involved; however, this is a fraction of that associated with conventional SPECT imaging.

Computed tomography

The technique of computed tomography is the latest development in assessing microvascular dysfunction. As mentioned above, the coronary arteries can be visualized non invasively, and cardiac computed tomography is mainly used for this purpose, to assess the presence of coronary artery disease and calcification. Moreover, with the additional use of iodine contrast agents, myocardial perfusion can also be visualized. As with echocardiography and CMR, the contrast agent can be followed over time after injection, and early and late imaging may show perfusion defects (*Figure 7*).

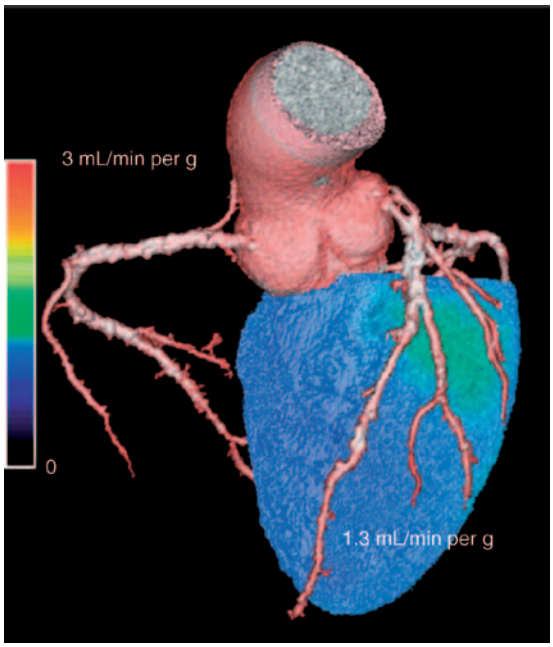

Figure 6. Fusion display of the coronary arteries and flow assessment by [^{15}O]H_2O positron emission tomography, showing a uniform reduction in maximal flow during infusion of adenosine. (From DeKemp et al [18], with permission.)

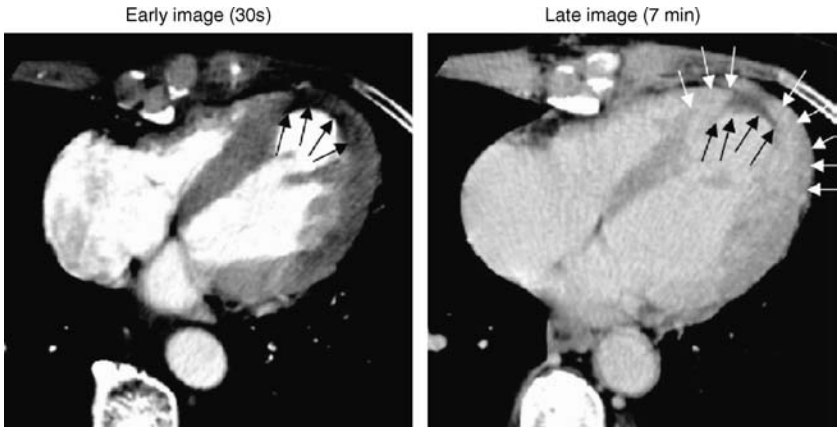

Figure 7. Example of early and late computed tomography imaging. The arrows indicate a region with hypoperfusion. (From Koyama et al [19]. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

Quantification of perfusion imaging is possible with contrast computed tomography, but awaits further validation in larger studies [20]. Computed tomography has excellent spatial resolution, but its role relative to established techniques needs to be assessed. Its major disadvantage is the high dose of radiation that is used, but that may be reduced in future.

Summary

Microvascular dysfunction can be diagnosed with a variety of cardiac imaging tools, from simple techniques such as the exercise ECG to advanced devices such as PET–computed tomography. As microvascular dysfunction is becoming a more and more important target, large validation and therapeutic intervention studies can be expected. ■

REFERENCES

1. Lanza GA. Cardiac syndrome X: a critical overview and future perspectives. *Heart*. 2007;93:159–166.
2. Cavusoglu Y, Entok E, Timuralp B, et al. Regional distribution and extent of perfusion abnormalities, and the lung to heart uptake ratios during exercise thallium-201 SPECT imaging in patients with cardiac syndrome X. *Can J Cardiol*. 2005;21:57–62.
3. Solodky A, Assali AR, Mats I, et al. Prognostic value of myocardial perfusion imaging in symptomatic and asymptomatic patients after percutaneous coronary intervention. *Cardiology*. 2007;107:38–43.
4. Danias PG, Papaioannou GI, Ahlberg AW, et al. Usefulness of electrocardiographic-gated stress technetium-99m sestamibi single-photon emission computed tomography to differentiate ischemic from nonischemic cardiomyopathy. *Am J Cardiol*. 2004;94:14–19.
5. Sorajja P, Chareonthaitawee P, Ommen SR, Miller TD, Hodge DO, Gibbons RJ. Prognostic utility of single-photon emission computed tomography in adult patients with hypertrophic cardiomyopathy. *Am Heart J*. 2006;151:426–435.
6. Shaw LJ, Berman DS, Hendel RC, et al. Cardiovascular disease risk stratification with stress single-photon emission computed tomography technetium-99m tetrofosmin imaging in patients with the metabolic syndrome and diabetes mellitus. *Am J Cardiol*. 2006;97:1538–1544.
7. Storto G, Cirillo P, Vicario ML, et al. Estimation of coronary flow reserve by Tc-99m sestamibi imaging in patients with coronary artery disease: comparison with the results of intracoronary Doppler technique. *J Nucl Cardiol*. 2004;11: 682–688.
8. Fragasso G, Chierchia SL, Lu C, Dabrowski P, Pagnotta P, Rosano GM. Left ventricular dysfunction during dobutamine stress echocardiography in patients with syndrome X and positive myocardial perfusion scintigraphy. *G Ital Cardiol*. 1999;29:383–390.
9. Voci P, Pizzuto F, Romeo F. Coronary flow: a new asset for the echo lab? *Eur Heart J*. 2004;25:1867–1879.
10. Hayat SA, Senior R. Myocardial contrast echocardiography in ST elevation myocardial infarction: ready for prime time? *Eur Heart J*. 2008;29:299–314.
11. Dijkmans PA, Knaapen P, Sieswerda GT, et al. Quantification of myocardial perfusion using intravenous myocardial contrast echocardiography in healthy volunteers: comparison with positron emission tomography. *J Am Soc Echocardiogr*. 2006;19:285–293.
12. Wei K, Jayaweera AR, Firoozan S, Linka A, Skyba DM, Kaul S. Quantification of myocardial blood flow with ultrasound-induced destruction of microbubbles administered as a constant venous infusion. *Circulation*. 1998;97:473–483.
13. Schneider G, Ahlhelm F, Seidel R, et al. Contrast-enhanced cardiovascular magnetic resonance imaging. *Top Magn Reson Imaging*. 2003;14:386–402.
14. Jerosch-Herold M, Seethamraju RT, Swingen CM, Wilke NM, Stillman AE. Analysis of myocardial perfusion MRI. *J Magn Reson Imaging*. 2004;19:758–770.
15. Panting JR, Gatehouse PD, Yang GZ, et al. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *N Engl J Med*. 2002;346:1948–1953.
16. Yan AT, Gibson CM, Larose E, et al. Characterization of microvascular dysfunction after acute myocardial infarction by cardiovascular magnetic resonance first-pass perfusion and late gadolinium enhancement imaging. *J Cardiovasc Magn Reson*. 2006;8:831–837.
17. Vohringer M, Mahrholdt H, Yilmaz A, Sechtem U. Significance of late gadolinium enhancement in cardiovascular magnetic resonance imaging (CMR). *Herz*. 2007;32:129–137.
18. DeKemp RA, Yoshinaga K, Beanlands RS. Will 3-dimensional PET-CT enable the routine quantification of myocardial blood flow? *J Nucl Cardiol*. 2007;14:380–397.
19. Koyama Y, Mochizuki T, Higaki J. Computed tomography assessment of myocardial perfusion, viability, and function. *J Magn Reson Imaging*. 2004;19:800–815.
20. Groves AM, Goh V, Rajasekharan S, *et al*. CT coronary angiography: quantitative assessment of myocardial perfusion using test bolus data – initial experience. *Eur Radiol*. 2008 May 9 [Epub ahead of print].

Improving perfusion at reperfusion

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Abstract

Early reperfusion of the ischemic myocardium has been shown to reduce mortality in acute myocardial infarction. Unfortunately, reperfusion, although necessary to relieve ischemia, may be followed by morphological, functional, and electrical changes that result in additional myocardial damage, known as reperfusion injury. In animal models, several pharmacologic agents and reperfusion strategies have been shown to be effective in preventing reperfusion injury, but most of these measures have failed when transferred to humans. Adenosine is one exception, because it has been shown to limit ischemia-reperfusion damage in several animal models, and has been successfully tested in man. The administration of adenosine as an adjunct to primary percutaneous transluminal coronary angioplasty early in acute myocardial infarction improved myocardial blood flow, prevented the no-reflow phenomenon, reduced the incidence of adverse cardiac events, and improved recovery of ventricular function. More recently, favorable results have been reported with myocardial postconditioning. However, neither of these two therapeutic strategies has been definitively confirmed in man, and their use remains limited to research-oriented laboratories, so that the problem of preventing reperfusion injury and limiting infarct size in the setting of acute myocardial infarction remains largely unsolved.
■ *Heart Metab.* 2008;40:20–22.

Keywords: Reperfusion injury, no-reflow phenomenon, adenosine, postconditioning, infarct size, acute myocardial infarction

Introduction

Evidence-based data for the management of acute myocardial infarction (AMI) have evolved dramatically in the past decade. AMI and unstable angina are now recognized as part of a spectrum of clinical disease collectively identified as acute coronary syndromes, which include unstable angina, non Q-wave myocardial infarction, and Q-wave myocardial infarction [1].

The majority of patients presenting with ST-segment elevation will eventually develop a transmural myocardial infarction. The primary goals of treatment for patients presenting with ST-segment elevation are the reduction of mortality and the prevention of late morbidities. The potential for prevention of cardiac death and reduction of myocardial damage is greatest very early in AMI. Fifty percent of the patients who die of AMI do so before reaching a hospital, the major risk of ventricular tachycardia or ventricular fibrillation occurring during the first 4 h after the onset of symptoms.

Perhaps the most significant advance in treatment of cardiovascular disease in the past decade has been reperfusion therapy for AMI. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI)-1 trial, the first mega-trial to show reduction in mortality associated with fibrinolytic therapy, demonstrated that patients derived the greatest benefit of treatment during the first 3 h, with a maximum reduction in mortality of 47% for patients treated in the first 1 h.

At present, salvage of jeopardized myocardium in acute myocardial infarction appears to be determined mostly by:

- the duration of ischemia
- the stable patency of the infarct-related artery
- a preserved microvascular function.

Time to reperfusion

In animal models, infarct size and left ventricular function are adversely affected, in a non linear fashion, by the duration of coronary occlusion [2]. In dogs, reperfusion after 5–15 min of coronary occlusion leads to virtually complete salvage of myocardium. Significant salvage is still possible even after 3 h of occlusion; however, no improvement of regional function results when perfusion is restored after 3 h of ischemia [3].

Attempts to confirm this association in clinical studies have yielded conflicting results [4–6]. A recent study examining the impact of time on several outcome variables concluded that the beneficial effect of thrombolysis on infarct size and ejection fraction was restricted to treatments given within 2 h of the onset of symptoms [7]. The greatest benefit for mortality was also achieved when thrombolysis was given within 2 h. These observations support the concept that time-dependent myocardial salvage is the explanation for the early survival benefit. Beyond that time, reduction in infarct size was markedly attenuated, and the mortality benefit thus clearly exceeds the impact of therapy on ventricular function and myocardial salvage [8,9].

Restoration of blood flow before the ischemic myocardium becomes fully necrotic is therefore mandatory if infarct size is to be limited in AMI.

Patency of the infarct-related artery

Recanalization of the infarct-related artery is of paramount importance, and intense research continues in order to identify the thrombolytic strategy that achieves the greatest rate of patency [10]. However, even with the ''gold standard'' of accelerated alteplase, aspirin, and heparin, Thrombolysis In Myocardial Infarction (TIMI) 3 patency is obtained only in 50% of patients, with effective reperfusion being obtained in two-thirds of these, and re-occlusion being observed in up to one-third by 3 months [11]. The addition of glycoprotein IIb/IIIa blockers to thrombolytic agents does not seem to improve TIMI 3 patency, or to reduce the frequency of re-occlusion.

Direct coronary angioplasty is superior to fibrinolytic therapy in the restoration of patency of the infarct-related artery. Primary percutaneous coronary intervention assures a greater rate of TIMI 3 flow, and is associated with lower rates of re-occlusion and postinfarction ischemia. However, mortality rates have not declined as expected, and in the vast majority of patients, left ventricular function does not recover, despite a ''successful'' procedure [12].

A convincing explanation for this frustrating observation refers to the time delay between occlusion of the infarct-related artery and its recanalization. In practice, this time interval often exceeds myocardial tolerance to ischemia – that is, the infarct-related artery is re-opened when necrosis of the jeopardized myocardium is already complete.

Unfortunately, early recanalization of the infarct-related artery, which is mandatory to salvage jeopardized myocardium and limit infarct size, may be the cause of further myocardial damage, unless measures are taken to prevent the adverse effects of oxygenated blood returning to tissues previously exposed to ischemia – the so-called ''no-reflow'' phenomenon.

Improving perfusion at reperfusion

Several reports indicate that dysfunctional coronary microcirculation is an important determinant of prognosis for patients with AMI. Lack of myocardial perfusion immediately after successful thrombolysis, as assessed by contrast echocardiography, is a predictor of poor recovery of left ventricular function and is associated with a worse prognosis [13]. In 31 patients with their first myocardial infarction, the coronary flow velocity pattern measured after successful primary stenting was predictive of recovery of regional and global left ventricular function [14].

More recently, it has been reported that the presence of residual flow within the infarct area before reperfusion results in good myocardial salvage and rapid functional recovery from myocardial stunning [15]. Long-term follow-up of patients with AMI treated with aspirin and heparin followed by primary percutaneous transluminal coronary angioplasty (PTCA) has shown that, in patients with evidence of reperfusion before PTCA, outcomes were strikingly better, with less cardiogenic shock, improved procedural results, smaller infarct size, and reduced mortality [16].

Adenosine, an endogenous purine nucleoside, antagonizes many of the biochemical and physiological mechanisms implicated in ischemia-reperfusion injury, and has been shown to limit microvascular damage, and to reduce postischemic ventricular dysfunction. The administration of adenosine in the ischemic territory before vessel re-opening is feasible and safe in the setting of primary percutaneous coronary intervention, and can maximize salvage of jeopardized myocardium by limiting or preventing reperfusion damage [17]. Patients receiving intracoronary adenosine had a more favorable clinical course and a better recovery of left ventricular function at discharge when compared with patients treated with PTCA alone [17,18]. Less impressive results have been obtained when the same agent was given intravenously [19,20].

In animal models, an alternative effective strategy to limit infarct size is ''myocardial preconditioning'':

myocardium previously exposed to a short period of ischemia develops a marked resistance to subsequent coronary occlusion [21]. Preconditioning poses obvious problems to be transferred to clinical practice, given the unpredictability of the acute coronary events, but it could be substituted by a strategy of intermittent reperfusion at the time of primary percutaneous coronary intervention. It has been reported that, in animal models, brief sequences of ischemia-reperfusion applied after the end of the ischemic period (''post-conditioning'') give a myocardial protection comparable to that of classic preconditioning [22–24]. This strategy has recently been tested in man, with encouraging results [25].

Conclusions

Early reperfusion associated with protection from reperfusion injury appears to be the most effective strategy to reduce acute mortality and prevent late morbidity in AMI. To date, intracoronary administration of adenosine and postconditioning appear to be the only two strategies available in man to protect the ischemic myocardium and limit infarct size. Both have been proved to be feasible and safe in the setting of primary percutaneous coronary intervention. However, their clinical application is currently limited to research-oriented laboratories, and their efficacy is in need of conclusive supportive evidence. ■

REFERENCES

1. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 7: the era of reperfusion: section 1: acute coronary syndromes (acute myocardial infarction). *Circulation*. 2000; 102(8 suppl):I172–I203.
2. Reimer KA, Jennings RB. The ''wavefront phenomenon'' of myocardial ischemic cell death, II: transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. *Lab Invest*. 1979;40:633–644.
3. Lavallee M, Cox D, Patrick TA, Vatner SF. Salvage of myocardial function by coronary artery reperfusion 1, 2, and 3 hours after occlusion in conscious dogs. *Circ Res*. 1983;53:235–247.
4. Raitt MH, Maynard C, Wagner G, Cerqueira MD, Selvester RH, Weaver WD. Relation between symptom duration before thrombolytic therapy and final infarct size. *Circulation*. 1996;93:48–53.
5. Newby LK, Rutsch WR, Califf RM, et al., for the GUSTO-I Investigators. Time from symptom onset to treatment and outcomes after thrombolytic therapy. *J Am Coll Cardiol*. 1996;27:1646–1655.
6. Boersma E, Maas AC, Derckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet*. 1996;348:771–775.
7. Chareonthaitawee P, Gibbons RJ, Roberts RS, Christian TF, Burns R, Yusuf S, for the CORE Investigators (Collaborative Organisation for RheothRx Evaluation). The impact of time to thrombolytic treatment on outcome in patients with acute myocardial infarction. *Heart*. 2000;84:142–148.
8. Milavetz JJ, Giebel DW, Christian TF, Schwartz RS, Holmes DR Jr, Gibbons RJ. Time to therapy and salvage in myocardial infarction. *J Am Coll Cardiol*. 1998;31:1246–1251.
9. Brodie BR, Stuckey TD, Wall TC, et al. Importance of time to reperfusion for 30 day and late survival and recovery of left ventricular function after primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol*. 1998;32:1312–1319.
10. Brodie BR, Stuckey TD, Kissling G, Hansen CJ, Weintraub RA, Kelly TA. Importance of infarct-related artery patency for recovery of left ventricular function and late survival after primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol*. 1996;28:319–325.
11. Wilcox R. Patency, perfusion, performance – the desirable triplets of combination thrombolytic therapy. *Eur Heart J*. 2000;21:1495–1497.
12. Natarajan MK, Mehta S, Yusuf S. Management of myocardial infarction: looking beyond efficacy. *J Am Coll Cardiol*. 2000;2: 380–381.
13. Ito H, Tomooka T, Sakai N, et al. lack of myocardial perfusion immediately after successful thrombolysis: a predictor of poor recovery of left ventricular function in acute myocardial infarction. *Circulation*. 1992;85:1699–1705.
14. Wakatsuki T, Nakamura M, Tsunoda T, et al. Coronary flow velocity immediately after primary coronary stenting as a predictor of ventricular wall motion recovery in acute myocardial infarction. *J Am Coll Cardiol*. 2000;35:1835–1841.
15. Lim YJ, Masuyama T, Mishima M, et al. Effect of pre-reperfusion residual flow on recovery from myocardial stunning: a myocardial contrast echocardiography study. *J Am Soc Echocardiogr*. 2000;13:18–25.
16. Brodie BR, Struckey TD, Hansen C, Muncy D. Benefit of coronary reperfusion before intervention on outcomes after primary angioplasty for acute myocardial infarction. *Am J Cardiol*. 2000;85:13–18.
17. Marzilli M, Orsini E, Marraccini P, Testa R. Beneficial effects of intracoronary adenosine as an adjunct to primary angioplasty in acute myocardial infarction. *Circulation*. 2000;101: 2154–2159.
18. Claeys MJ, Bosmans J, et al. Effect of intracoronary adenosine infusion during coronary intervention on myocardial reperfusion injury in patients with acute myocardial infarction. *Am J Cardiol*. 2004;94:9–13.
19. Ross AM, Gibbsons RJ, Stone GW, Kloner RA, Alexander RW. A randomized, double-blinded, placebo-controlled multicenter trial of adenosine as an adjunct to reperfusion in the treatment of AMI. *J Am Coll Cardiol*. 2005;45:1775–1780.
20. Micari A, Belcik TA, Balcells EA, et al. Improvement in microvascular reflow and reduction of infarct size with adenosine in patients undergoing primary coronary stenting. *Am J Cardiol*. 2005;96:1410–1415.
21. Murry CE, Jennings RB, Reimer KA. ''Preconditioning'' with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation*. 1986;5:1124–1136.
22. Zhao ZQ, Corvera JS, Halkos ME, et al. Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. *Am J Physiol Heart Circ Physiol*. 2003;285:H579–H588.
23. Kin H, Zhao HY, Wang N-P, et al. Postconditioning attenuates myocardial ischemia-reperfusion injury by inhibiting events in the early minutes of reperfusion. *Cardiovasc Res*. 2004;62:74–85.
24. Yang XM, Proctor JB, Cui L, Krieg T, Downey JM, Cohen MV. Multiple, brief coronary occlusions during early reperfusion protect rabbit hearts by targeting cell signaling pathways. *J Am Coll Cardiol*. 2004;44:1103–1110.
25. Staat P, Rioufol G, Piot C, et al. Post-conditioning the human heart. *Circulation*. 2005;112:2143–2148.

Reperfusion injury: reduction by Vastarel MR

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Abstract

Ischemia-reperfusion syndrome is defined as myocardial injury caused by the restoration of coronary flow. This phenomenon has a complex pathophysiology and results in a paradoxical reduction of the beneficial effect of myocardial reperfusion. Studies suggest that ischemia-reperfusion injury may account for up to 50% of the final size of a myocardial infarct. Vastarel MR (trimetazidine) is a pharmacological agent that shifts the preference for energy substrate away from fatty acid metabolism and towards glucose metabolism. Furthermore, it reduces intracellular acidosis, and protects against the toxicity induced by oxygen free radicals, which are key participants in ischemia-reperfusion injury. Accordingly, in animal studies a reduction in ischemia-reperfusion injury has been observed in association with the use of trimetazidine. These protective properties of trimetazidine over ischemia-reperfusion have also been suggested in clinical studies.
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Keywords: Acute myocardial infarction, percutaneous coronary intervention, infarct size, ischemia reperfusion, cardiac energy metabolism, oxygen paradox

Introduction

The technique of reperfusion during acute myocardial infarction has led to a dramatic decrease in the morbidity and mortality associated with coronary artery disease in recent decades. Restoration of blood flow within the ''golden hours'' has resulted in a reduction in myocardial infarct size [1]. Although greatly beneficial overall, the abrupt restoration of blood flow in the coronary arteries after occlusion was also, surprisingly, found to be associated with an additional and accelerated myocardial injury beyond that generated by ischemia alone, an observation first reported by Jennings et al [2]. This phenomenon has been called ''ischemia-reperfusion injury'' [3]. The process has a complex pathophysiology leading to cardiomyocyte death that is distinct from that associated with ischemic injury. Because of the deleterious effects of ischemia-reperfusion injury, several treatments aiming to prevent or limit this process have been proposed [2]. Vastarel MR (trimetazidine) is an antianginal drug that acts by switching the energy substrate from fatty acid metabolism to glucose metabolism, thus making possible the increased formation of ATP with a decreased need for oxygen [4]. These properties are of great potential interest to the reduction of ischemia-reperfusion injury.

Pathophysiology of ischemia-reperfusion injury

The pathophysiology of ischemia-reperfusion injury is complex. In this process, the re-oxygenation of ischemic myocardium generates a high degree of myocardial injury as a result of the generation of

potent oxygen-derived free radicals. This phenomenon is known as the ''oxygen paradox''. The oxidative stress also reduces the bioavailability of nitric oxide, which is critical to the improvement of coronary blood flow and inactivation of superoxide radicals.

Reperfusion is also associated with an abrupt increase and overload of intracellular calcium, which cause hypercontracture of cardiomyocytes, leading to cell death.

Activation and accumulation of polymorphonuclear neutrophils occur in the damaged myocardium, and contribute to the ischemia-reperfusion injury. Neutrophils are important for the development of reperfusion injury, releasing oxygen free radicals, proteases, and proinflammatory mediators that further amplify the infiltration of neutrophils into the jeopardized myocardium. Other processes involving platelets and complement also participate in ischemia-reperfusion injury. Acting together, these effects may last hours or months after reperfusion, and participate in sustained cardiomyocyte death [2,5].

The impact of ischemia-reperfusion injury

The exact contribution of ischemia-reperfusion injury to infarct size is difficult to determine. However, on the basis of the observed reduction in infarct size associated with treatments preventing ischemia-reperfusion injury, it is postulated that up to 50% of the final size of the myocardial infarct is linked to the ischemia-reperfusion injury [3]. Reduction of this phenomenon should provide great clinical benefit, and is therefore currently the subject of extensive experimentation.

Mechanism of action of trimetazidine

Trimetazidine is an antianginal drug that has no hemodynamic effect and thus does not affect cardiac myocyte oxygen demand or supply in the same way as other antianginal drugs [6]. The mechanism of action of trimetazidine is related to the inhibition of the enzyme long-chain 3-ketoacyl coenzyme A thiolase, which is critical to the β-oxidation pathway. This inhibition decreases the utilization of free fatty acids as a source of energy for the myocardium, resulting in an increase in glucose oxidation. This metabolic switch acts to improve cardiac energy metabolism by switching ATP production from lipid to glucose oxidation, thus enhancing intramitochondrial coupling and favoring a more efficient mode of ATP production per mole of oxygen. Moreover, trimetazidine reduces intracellular acidosis and protects against the toxicity induced by oxygen free radicals. The drug therefore directly protects myocyte structure and function, and increases cell resistance to hypoxic stress [4,5,7–9].

Trimetazidine in the treatment of ischemia-reperfusion injury

A number of experimental studies have demonstrated that trimetazidine exerts direct anti-ischemic effects, limiting the accumulation of calcium and acidosis, inflammation, and the production of oxygen-derived free radicals after reperfusion [10]. Animal studies have investigated the potential impact of this drug on ischemia-reperfusion injury on the basis of these metabolic properties. They have constantly observed that trimetazidine was able to limit lethal ischemia-reperfusion injury by inhibiting the opening of mitochondrial permeability transition pores, which represents a crucial event in cardiomyocyte death after myocardial ischemia-reperfusion [11–15].

The potential benefit associated with the use of trimetazidine in ischemia-reperfusion injury during percutaneous revascularization in humans has been evaluated in patients with stable coronary artery disease. A study recently published suggested that this metabolic agent could decrease the ischemia-reperfusion injury associated with the procedure. In this prospective randomized study in patients undergoing contemporary percutaneous coronary intervention using direct stenting, we have observed that trimetazidine reduced myocardial ischemia-reperfusion injury as assessed by the release of troponin Ic [16] (*Figure 1*). Importantly, such increases in biomarkers after percutaneous coronary intervention have been associated with long-term outcome [17,18].

Steg et al [19] used a multicenter randomized double-blind study to evaluate intravenous trimetazidine in patients undergoing primary percutaneous

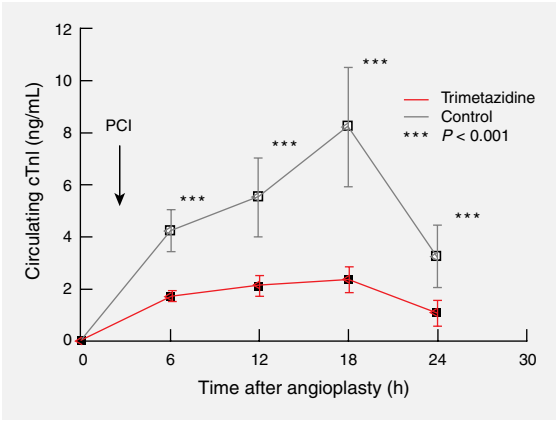

Figure 1. Time course of release of cardiac troponin Ic (cTnI). Values are mean ± SD. $^{***}P < 0.001$.

coronary intervention in the setting of acute myocardial infarction. Although this study was small and underpowered to detect statistical differences in global or regional wall motion or clinical outcome, it was able to detect an earlier and more complete return of the ST-segment toward baseline in patients treated with trimetazidine. ST-segment normalization has been associated with improved coronary reperfusion and outcome. It therefore supports a beneficial effect of the infusion of trimetazidine during reperfusion in acute myocardial infarction, mediated by a reduction in ischemia-reperfusion injury [19].

Conclusion

Ischemia-reperfusion is a complex process that is responsible for a large part of the size of the myocardial infarct after coronary artery occlusion. Trimetazidine exhibits metabolic properties that could be of particular interest in reducing ischemia-reperfusion injury. Accordingly, clinical studies have shown promising findings with this drug in reducing ischemia-reperfusion injury in patients undergoing percutaneous coronary intervention for stable angina pectoris or acute myocardial infarction. ■

REFERENCES

1. Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *JAMA*. 2000;283:2941–2947.
2. Jennings RB, Sommers HM, Smyth GA, Flack HA, Linn H. Myocardial necrosis induced by temporary occlusion of a coronary artery in the dog. *Arch Pathol*. 1960;70:68–78.
3. Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. *N Engl J Med*. 2007;357:1121–1135.
4. Kantor PF, Lucien A, Kozak R, Lopaschuk GD. The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. *Circ Res*. 2000;86:580–588.
5. Moens AL, Claeys MJ, Timmermans JP, Vrints CJ. Myocardial ischemia/reperfusion-injury, a clinical view on a complex pathophysiological process. *Int J Cardiol*. 2005;100:179–190.
6. Pornin M, Harpey C, Allal J, Sellier P, Ourbak P. Lack of effects of trimetazidine on systemic hemodynamics in patients with coronary artery disease: a placebo-controlled study. *Clin Trials Metaanal*. 1994;29:49–56.
7. Mody FV, Singh B, Mohiuddin I, et al. Trimetazidine-induced enhancement of myocardial glucose utilization in normal and ischemic myocardial tissue: an evaluation by positron emission tomography. *Am J Cardiol*. 1998;82:42K–49K.
8. Lopaschuk GD. Treating ischemic heart disease by pharmacologically improving cardiac energy metabolism. *Am J Cardiol*. 1998;82:14K–17K.
9. Weiss JN, Korge P, Honda HM, Ping P. Role of the mitochondrial permability transition in myocardial disease. *Circ Res*. 2003;93:292–301.
10. de Leiris J, Boucher F. Rationale for trimetazidine administration in myocardial ischaemia-reperfusion syndrome. *Eur Heart J*. 1993;14 (suppl G):34–40.
11. Argaud L, Gomez L, Gateau-Roesch O, et al. Trimetazidine inhibits mitochondrial permeability transition pore opening and prevents lethal ischemia-reperfusion injury. *J Mol Cell Cardiol*. 2005;39:893–899.
12. Ruixing Y, Wenwu L, Al-Ghazali R. Trimetazidine inhibits cardiomyocyte apoptosis in a rabbit model of ischemia-reperfusion. *Transl Res*. 2007;149:152–160.
13. Noble MI, Belcher PR, Drake-Holland AJ. Limitation of infarct size by trimetazidine in the rabbit. *Am J Cardiol*. 1995;76: 41B–44B.
14. Kutala VK, Khan M, Mandal R, et al. Attenuation of myocardial ischemia-reperfusion injury by trimetazidine derivatives functionalized with antioxidant properties. *J Pharmacol Exp Ther*. 2006;317:921–928.
15. Pantos C, Bescond-Jacquet A, Tzeis S, et al. Trimetazidine protects isolated rat hearts against ischemia-reperfusion injury in an experimental timing-dependent manner. *Basic Res Cardiol*. 2005;100:154–160.
16. Bonello L, Sbragia P, Amabile N, et al. Protective effect of an acute oral loading dose of trimetazidine on myocardial injury following percutaneous coronary intervention. *Heart*. 2007;93:703–707.
17. Selvanayagam JB, Porto I, Chanon K, et al. Troponin elevation after percutaneous coronary intervention directly represents the extent of irreversible myocardial injury. *Circulation*. 2005;111:1027–1032.
18. Herrmann J, Von Birgelen C, Haude M, et al. Prognostic implication of cardiac troponin T increase following stent implantation. *Heart*. 2002;87:549–553.
19. Steg PG, Grollier G, Gallay P, et al., the LIST Study Group. A randomized double-blind trial of intravenous trimetazidine as adjunctive therapy to primary angioplasty for acute myocardial infarction. *Int J Cardiol*. 2001;77:263–273.

Microvascular obstruction after primary angioplasty: beyond the epicardial artery

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Abstract

Poor tissue perfusion despite removal of the epicardial obstruction remains a problem after primary reperfusion therapies for acute myocardial infarction. It is related to microvascular vessel damage and is associated with poor myocardial recovery and adverse ventricular remodeling. The process is multifactorial and potentially amenable to a variety of treatments that can be administered at the time of reperfusion. Cardiac magnetic resonance has emerged as a safe and highly accurate means of demarking the region of infarction and identifying areas of microvascular obstruction within. This is useful, not only to help determine the patient's prognosis, but also to test the efficacy of treatments to reduce microvascular damage and improve left ventricular recovery.
■ *Heart Metab.* 2008;40:26–29.

Keywords: Microvascular obstruction, primary angioplasty, acute myocardial infarction, poor recovery, cardiac magnetic resonance imaging

Case report

A 65-year-old white man was brought to St Thomas' Hospital with a 4 h history of chest pain and lateral ST-segment elevation on his ECG (*Figure 1*). He had no prior cardiac history. He had several cardiovascular risk factors, including type 2 diabetes for which he was receiving oral hypoglycemic therapy, systemic hypertension treated with amlodipine, previous smoking, and a strong family history of ischemic heart disease. On arrival in the hospital, the patient was pretreated with aspirin 300 mg and clopidogrel 600 mg, and coronary angiography was performed via the right femoral artery, with a 6-French gauge sheath. Heparin 5000 IU was administered intravenously. Angiography revealed a left dominant coronary system with a large occluded circumflex coronary artery. There was minor atheroma in the left anterior descending artery; the right coronary artery was not obstructed.

With the use of an Extra Back-up (EBU) 4 guide, the lesion in the circumflex artery was crossed with a Luge™ angioplasty wire (Boston Scientific®). There was a tight stenosis at the point of occlusion, which was then treated with a 2.5×15 mm Maverick balloon (Boston Scientific®). This resulted in Thrombolysis In Myocardial Infarction [1] (TIMI) grade 2 flow in the distal vessel. A 3.5×20 mm Liberte™ (Boston Scientific®) was deployed across the lesion, with a good angiographic result. Despite this, the flow in the artery remained poor and the patient continued to have chest pain, with persistent elevation of ST-segments. A bolus of the intravenous glycoprotein IIa/IIIb inhibitor, abciximab (ReoPro™, Eli-Lilly®),

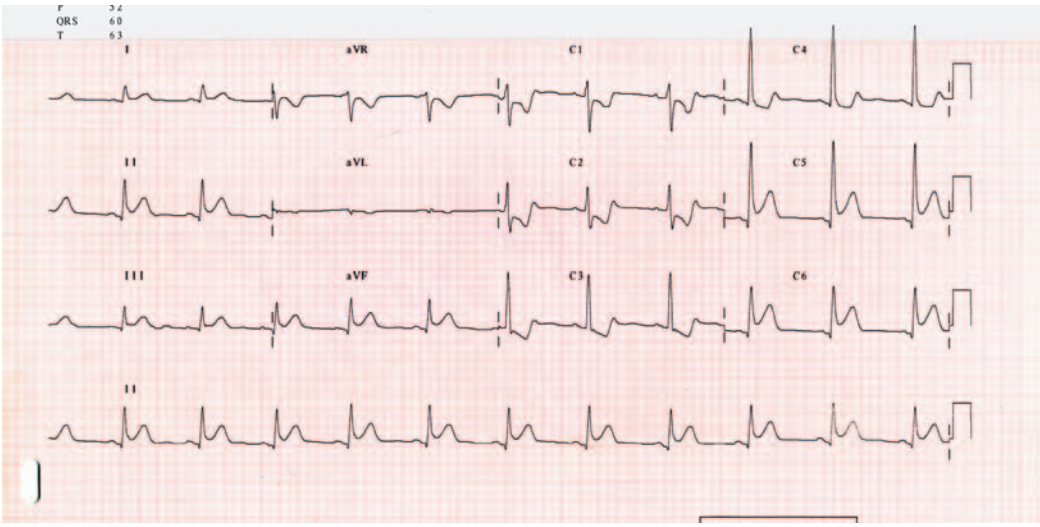

Figure 1. Electrocardiogram showing acute inferolateral myocardial infarction caused by blockage of a dominant circumflex artery, with ST-segment elevation in leads C5, C6, II, III, and aVF, with reciprocal ST-segment depression and T-wave inversion in leads C1–4.

was given and a subsequent infusion commenced. A 1 mg intracoronary injection of isosorbide dinitrate (Isoket™, Schwarz Pharma Limited®) was also administered. Flow remained TIMI 1–2 and the patient continued to suffer chest pain, requiring treatment with intravenous opiates. After 5 min, a further intracoronary bolus of isosorbide dinitrate 1 mg was given, followed by verapamil 20 μg. Eventually, TIMI flow improved to grade 3 and the patient's pain settled. However, myocardial blush grade [2] remained poor, and the ST segments failed to resolve on the surface ECG. The patient remained hemodynamically stable, and was returned to the coronary care unit, where abciximab was continued overnight. The next morning the patient remained well, with no further chest pain. The ECG showed minimal resolution of the ST-segment elevation, with the evolution of significant Q-waves in the lateral leads. The maximum increase in creatinine kinase concentration of 2500 IU/L suggested a moderate/large volume of myocardial infarction.

The patient underwent a contrast-enhanced cardiac magnetic resonance (CMR) study on a Phillips® Intera 1.5 T whole-body system on day 3 after his infarct. First-pass myocardial perfusion was assessed at rest using a novel approach that affords high spatial resolution [3]. Early and late gadolinium-enhanced scans were taken at 2 min and 15 min after intravenous administration of gadolinium-diethylene triamino penta-acetic acid (DTPA) to a total of 0.2 mmol/kg. The perfusion CMR images (*Figure 2a*) revealed a significant area of hypoenhancement, representing microvascular obstruction at the core of the infarct. This corresponds to the dark areas of non uptake on the late gadolinium-enhanced CMR images, in which the dense white areas within the myocardium represent infarcted tissue (*Figure 2*b).

Discussion

Acute myocardial infarction (AMI) and subsequent heart failure constitute a leading cause of death in the UK [4]. Prognosis after AMI is related to the extent of myocardial injury occurring around the time of coronary occlusion [5]. It is known that patients with extensive myocardial infarction are at risk of postinfarction remodeling and heart failure [6]. Early restoration of TIMI 3 blood flow through the infarct-related artery is the main goal of modern treatment [7]. This has led to reduction of infarct size, preservation of left ventricular function, and improved survival [8]. Primary angioplasty is superior to thrombolysis in restoring TIMI 3 flow [9]. Although the restoration of epicardial blood flow does improve the myocardial perfusion of the affected area, the process is not homogenous, and 25–40% of patients have ''no-reflow'', with severely impaired perfusion at tissue level despite restoration of TIMI 3 flow in the infarct-related artery [10].

Treatments to reduce microvascular obstruction

Microvascular obstruction is a multifactorial process, and consequently has several potential therapeutic targets. Duration of ischemia is the most important predictor of microvascular obstruction, and therefore prompt revascularization remains the cornerstone of treatment [11]. The release of vasoactive agents such

Figure 2. (a) Cardiac magnetic resonance (CMR) rest perfusion image after contrast injection, showing a lateral wall myocardial perfusion defect (arrow). (b) Late gadolinium-enhanced CMR scan showing corresponding area of microvascular obstruction (dense black area) within the infarct zone (white area).

as serotonin, thromboxane, and leukotrienes, and their resultant coronary vasoconstrictive effects, have been well described [12], and can be partly ameliorated with intracoronary nitrates and calcium-channel blockers [13]. Other intracoronary agents such as adenosine [14] and nicorandil [15] have also been used to improve endothelial function and reduce neutrophil activation. Plugging of arterioles and capillaries with microthromboembolic debris can be treated with heparin and aggressive antiplatelet therapy, including glycoprotein IIb/IIIa inhibitors, which have been shown to improve the likelihood of TIMI 3 flow in patients undergoing primary percutaneous coronary intervention for AMI [16]. The role of distal protection devices and thrombectomy catheters to reduce embolization of debris at the time of percutaneous coronary intervention remains to be determined. Intra-aortic balloon propulsion has also been used to improve flow after percutaneous coronary intervention and is indicated in cases of refractory ischemia or shock [17]. Another area of interest is the concept of ''postconditioning'', whereby repeated ischemic stimuli applied in the moments after reperfusion may attenuate reperfusion injury by reproducing the powerful, well established protective effect of ischemic preconditioning. This may improve microvascular function and subsequently reduce infarct size. Large multicenter and outcome trials are awaited, but initial results have been promising [18].

Cardiac magnetic resonance imaging and microvascular obstruction

CMR has emerged as a powerful tool in the assessment of ventricular function, perfusion, and viability in AMI. Its high spatial resolution and reproducibility make it an excellent tool for assessing ventricular function over time [19]. With the first-pass administration of gadolinium-DTPA, myocardial perfusion can be assessed, both at rest and with stress, in distinct coronary territories and also transmurally within a single coronary territory. Recent advances permit acquisition of myocardial perfusion data with an in-plane spatial resolution of about 1 mm, which allows more detailed delineation of perfusion defects. Hypoenhanced areas in the first few minutes after the gadolinium injection correlate very closely with regions of microvascular obstruction, documented by the use of radioactive microspheres and histological staining of postmortem specimens with thioflavin [20]. Late CMR imaging 10–20 min after gadolinium injection enables precise localization of myocardial infarction (acutely) and scar (chronically) over the full range of infarct size [21].

The pathophysiology of infarct healing and left ventricular remodeling has been studied in a canine model of AMI using gadolinium-enhanced CMR [22]. Infarct healing seemed to be a continuing process, with early infarct expansion followed by infarct resorption, scar formation, and late wall thinning. Necrotic myocytes, interstitial edema, hemorrhage, and inflammatory cells are resorbed and replaced by collagenous scar tissue. In follow-up studies in humans, there was about a 30% reduction in infarct volume at 5 months after primary reperfusion of AMI, with some recovery of function [23]. Segments containing little microvascular obstruction showed good recovery, with improved wall thickening and function. Segments containing microvascular obstruction became thinned and scarred at 5 months, and showed minimal recovery. The presence of severely delayed microvascular reperfusion is predictive of impaired

left ventricular systolic function, and is a strong predictor of adverse cardiovascular complications, even after control for infarct size [24].

Summary

Microvascular obstruction after acute myocardial infarction remains a major problem, even after prompt revascularization of the epicardial artery with primary percutaneous coronary intervention. It is associated with poor left ventricular recovery and increased adverse events. There are several potential therapeutic interventions to reduce this damage, but their benefit has been difficult to establish because of the limited techniques available to assess microvascular perfusion and subsequent recovery. With CMR, myocardial scar and microvascular obstruction can be delineated with high spatial definition, using first-pass and delayed gadolinium-enhanced imaging. These methods have emerged as potentially useful imaging techniques with which to investigate the efficacy of both current and novel treatment strategies, and can be used to predict left ventricular recovery after AMI. ■

REFERENCES

1. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. TIMI Study Group. *N Engl J Med*. 1985; 312:932–936.
2. Gibson CM, Schomig A. Coronary and myocardial angiography: angiographic assessment of both epicardial and myocardial perfusion. *Circulation*. 2004;109:3096–3105.
3. Plein S, Ryf S, Schwitter J, Radjenovic A, Boesiger P, Kozerke S. Dynamic contrast-enhanced myocardial perfusion MRI accelerated with k-t sense. *Magn Reson Med*. 2007;58:777–785.
4. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet*. 1997;349:1498–1504.
5. Volpi A, De Vita C, Franzosi MG, et al. Determinants of 6-month mortality in survivors of myocardial infarction after thrombolysis. Results of the GISSI-2 data base. The Ad hoc Working Group of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-2 Data Base. *Circulation*. 1993;88:416–429.
6. Pfeffer MA, Pfeffer JM, Lamas GA. Development and prevention of congestive heart failure following myocardial infarction. *Circulation*. 1993;87 (5 suppl):IV120–IV125.
7. Simes RJ, Topol EJ, Holmes DR Jr et al. Link between the angiographic substudy and mortality outcomes in a large randomized trial of myocardial reperfusion. Importance of early and complete infarct artery reperfusion. GUSTO-I Investigators. *Circulation*. 1995;91:1923–1928.
8. Christian TF, Schwartz RS, Gibbons RJ. Determinants of infarct size in reperfusion therapy for acute myocardial infarction. *Circulation*. 1992;86:81–90.
9. The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy Investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. *N Engl J Med*. 1997; 336:1621–1628.
10. Lincoff AM, Topol EJ. Illusion of reperfusion. Does anyone achieve optimal reperfusion during acute myocardial infarction? *Circulation*. 1993;88:1361–1374.
11. Tarantini G, Cacciavillani L, Corbetti F, et al. Duration of ischemia is a major determinant of transmurality and severe microvascular obstruction after primary angioplasty: a study performed with contrast-enhanced magnetic resonance. *J Am Coll Cardiol*. 2005;46:1229–1235.
12. Bush LR, Buja LM, Samowitz W, et al. Recovery of left ventricular segmental function after long-term reperfusion following temporary coronary occlusion in conscious dogs. Comparison of 2- and 4-hour occlusions. *Circ Res*. 1983;53: 248–263.
13. Piana RN, Paik GY, Moscucci M, et al. Incidence and treatment of 'no-reflow' after percutaneous coronary intervention. *Circulation*. 1994;89:2514–2518.
14. Mahaffey KW, Puma JA, Barbagelata NA, et al. Adenosine as an adjunct to thrombolytic therapy for acute myocardial infarction: results of a multicenter, randomized, placebo-controlled trial: the Acute Myocardial Infarction STudy of ADenosine (AMISTAD) trial. *J Am Coll Cardiol*. 1999;34:1711–1720.
15. Ito H, Taniyama Y, Iwakura K, et al. Intravenous nicorandil can preserve microvascular integrity and myocardial viability in patients with reperfused anterior wall myocardial infarction. *J Am Coll Cardiol*. 1999;33:654–660.
16. Montalescot G, Barragan P, Wittenberg O, et al., for the ADMIRAL Investigators. Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med*. 2001;344:1895–1903.
17. Smith SC Jr, Dove JT, Jacobs AK, et al. ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines) – executive summary: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee to Revise the 1993 Guidelines for Percutaneous Transluminal Coronary Angioplasty) endorsed by the Society for Cardiac Angiography and Interventions. *Circulation*. 2001; 103:3019–3041.
18. Thibault H, Piot C, Ovize M. Postconditioning in man. *Heart Fail Rev*. 2007;12:245–248.
19. Grothues F, Smith GC, Moon JC, et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol*. 2002;90:29–34.
20. Judd RM, Lugo-Olivieri CH, Arai M, et al. Physiological basis of myocardial contrast enhancement in fast magnetic resonance images of 2-day-old reperfused canine infarcts. *Circulation*. 1995;92:1902–1910.
21. Kim RJ, Wu E, Rafael A, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med*. 2000;343:1445–1453.
22. Richard V, Murry CE, Reimer KA. Healing of myocardial infarcts in dogs. Effects of late reperfusion. *Circulation*. 1995;92:1891–1901.
23. Baks T, van Geuns RJ, Biagini E, et al. Effects of primary angioplasty for acute myocardial infarction on early and late infarct size and left ventricular wall characteristics. *J Am Coll Cardiol*. 2006;47:40–44.
24. Wu KC, Zerhouni EA, Judd RM, et al. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. *Circulation*. 1998;97:765–772.

Cardiac syndrome X: pathogenesis and management

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Abstract

The term Cardiac Syndrome X (CSX) describes patients presenting with typical exertional chest pain suggestive of myocardial ischemia, a positive exercise stress test result, and angiographically normal epicardial coronary arteries. CSX is more prevalent in women than in men, and the vast majority of women with CSX are peri or post-menopausal. Thus, oestrogen deficiency has been postulated to have a pathogenic role in CSX. Low oestrogen levels are associated with endothelial dysfunction and an impaired function of the natural endogenous opioid system, which results in increased pain perception. CSX patients have a reduced vasodilatory response of the coronary microcirculation that leads to myocardial ischemia in a proportion of patients. The present article reviews the possible pathogenic mechanisms responsible for CSX and briefly summarizes current therapeutic strategies.
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Keywords: Cardiac syndrome X, microvascular angina, endothelial dysfunction, pathogenesis and management

Introduction

The occurrence of typical chest pain and ST-segment changes suggestive of myocardial ischemia (*Figure 1*) in patients who otherwise have completely normal coronary arteriograms is known as ''syndrome X'', as termed by Harvey Kemp in 1973 [1], or ''cardiac syndrome X''(CSX), a name it acquired later in an attempt to differentiate this condition from the metabolic ''syndrome X'', currently known as ''metabolic syndrome''. CSX comprises a heterogeneous group of patients presenting with typical exertional chest pain, a positive exercise stress test, and angiographically normal epicardial coronary arteries, in whom non-cardiac causes of chest pain have been ruled out, along with coronary artery spasm (Prinzmetal's variant angina), left ventricular hypertrophy, valvular heart disease, and cardiomyopathies. This article briefly reviews the pathogenesis of CSX and summarizes current strategies for patient management.

It is estimated that approximately 30% of patients found to have normal coronary arteries on diagnostic angiography have features typical of CSX. The syndrome is more prevalent in women than in men, and the vast majority of women with CSX are peri- or postmenopausal. Postmenopausal women with CSX have abnormal endothelial function, which is improved by the administration of estrogen. Thus estrogen deficiency has been postulated to have a pathogenic role in CSX [2,3]. In addition, and of particular importance, low estrogen states are associated with an impaired function of the endogenous opioid system that controls pain perception. Low estrogen concentrations reduce or suppress the production or release of endorphins and enkephalins,

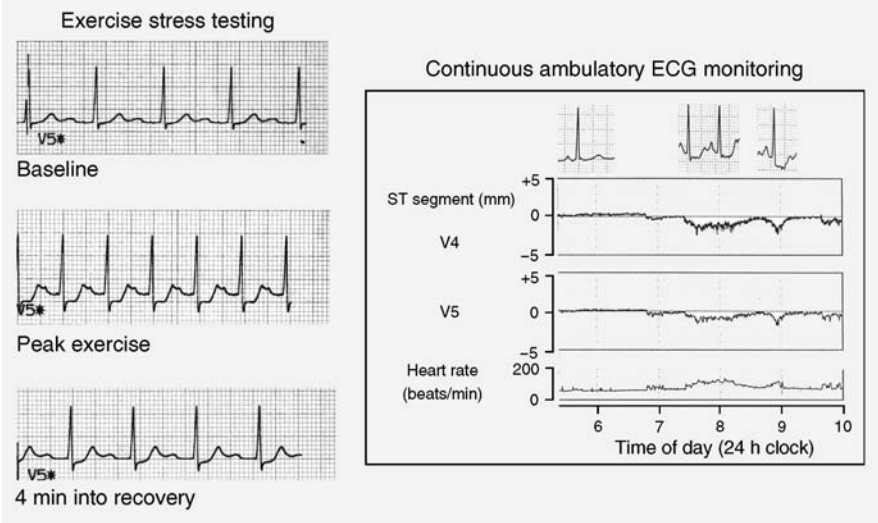

Figure 1. Typical electrocardiographic changes suggestive of myocardial ischemia in a patient with cardiac syndrome X. The tracings show (left) ST-segment depression during exercise stress testing, and (right) 24 h ambulatory monitoring in a patient with typical chest pain despite normal coronary arteriograms.

leading to increased pain perception [4,5], and this may provide a rational explanation for the occurrence of chest pain in women with CSX.

Pathogenesis

Interestingly, 35 years after the initial description of the syndrome, the debate continues as to the mechanisms responsible for CSX. Extracardiac causes, psychological abnormalities, myocardial ischemia, and abnormal pain perception are among the most commonly suggested pathogenic mechanisms.

Myocardial ischemia

The presence of unobstructed coronary arteries, the poor response to the administration of nitrates in 50% of patients and the negative stress echocardiograms in the majority of patients have cast doubts as to the role of myocardial ischemia as a potential cause of CSX [6–8]. However, in patients fulfilling strict selection criteria – typical chest discomfort, ischemic electrocardiographic changes, transient myocardial perfusion abnormalities – myocardial ischemia remains a plausible mechanism. The question also remains as to the mechanisms leading to myocardial ischemia in these patients. Functional coronary microvascular abnormalities leading to a reduced coronary blood flow reserve, often associated with endothelial dysfunction, are likely to be the cause of myocardial ischemia (''microvascular angina'') in patients with CSX.

Indeed, myocardial ischemia has been demonstrated in patients with CSX, using phosphorus-31 nuclear magnetic resonance spectroscopy. Buchthal et al [9] measured high-energy phosphates in the myocardium of women with CSX, before and after stress testing, and found abnormal results compatible with myocardial ischemia in approximately 20% of the patients. Moreover, in an invasive study assessing lipid hydroperoxides and conjugated dienes (two sensitive, independent markers of ischemia-reperfusion oxidative stress) in patients with CSX, before and after pacing-induced tachycardia, Buffon et al [10] found a large cardiac release of these lipid peroxidation products after pacing, consistent with an ischemic origin of CSX. Concordantly, Panting et al [11], using cardiovascular magnetic resonance imaging, demonstrated subendocardial hypoperfusion during the intravenous administration of adenosine in patients with CSX.

Structural and functional coronary microcirculation abnormalities

Whether functional or structural abnormalities in the coronary microvessels are responsible for the findings described above is still under discussion. Structural abnormalities of the coronary microcirculation have been suggested to cause myocardial ischemia in patients with CSX. Endomyocardial biopsy specimens have shown evidence of fibromuscular thickening of vessels less than 100 μm in diameter [12], and both a relative lack of coronary capillaries and narrowing of the capillary lumen as a result of swollen endothelium, have been demonstrated in patients with CSX [13]. Furthermore, morphologic measurements revealed a significant increase in media thickness : lumen diameter ratio in arteries obtained from patients with CSX [14]. Antonios et al [15] reported a significant reduction in skin capillary density in patients

with CSX compared with that in age- and sex-matched controls. These findings appear to indicate that CSX may represent a generalized microcirculatory abnormality, rather than a problem confined just to the coronary microcirculation, but this requires further investigation in ad-hoc studies.

Functional abnormalities of the coronary microvessels have been demonstrated by many investigators over the past three decades [6]. More recently, Masci et al [16] assessed the relation between systemic endothelial dysfunction (abnormal brachial artery flow-mediated dilatation) and myocardial perfusion abnormalities in 41 patients diagnosed with CSX. Patients who had myocardial perfusion defects had significantly lower flow-mediated dilatation values than patients with normal cardiac perfusions scans, indicating a correlation between endothelial dysfunction and abnormalities of myocardial blood flow in CSX. An impaired coronary microvascular vasodilator capacity in patients with CSX was reported by Opherk et al in the 1980s [17]. They showed that patients with CSX had a markedly impaired coronary vasodilator capacity in response to the administration of dipyridamole, a potent vasodilator of coronary arterioles, suggesting that functional abnormalities of the coronary microcirculation could, at least in part, contribute to the pathophysiology of the syndrome by critically impairing myocardial perfusion. Of interest, Kaski et al [18] found that, compared with healthy controls, patients with CSX have greater circulating concentrations of endothelin-1*, a potent constrictor of the coronary microvessels that is produced by the endothelium. Studies from the same group showed a correlation between endothelin concentrations and abnormal coronary microvascular responses in patients with CSX [19]. It is therefore likely that endothelial dysfunction resulting in both increased production of endothelin and reduced bioavailability of nitric oxide is responsible for the abnormal microvascular responses that lead to angina in patients with CSX. Impairment of endothelium-mediated vasodilatation has been demonstrated in patients with this syndrome, and was prevented by the administration of L-arginine (a substrate for nitric oxide production) [20]. Several investigators have also reported the occurrence of endothelial dysfunction, as assessed by different means, affecting both the epicardial coronary arteries and the coronary microvessels in patients with CSX.

The role of inflammation

Inflammation has been investigated as a possible cause for endothelial dysfunction, and both symptoms and ECG changes, in CSX. Increased concentration of circulating C-reactive protein (CRP) – an acute-phase reactant and a marker of chronic inflammation and vascular disease – correlates with vascular abnormalities in patients with CSX, as reported by several authors [21–23]. Teragawa and colleagues [21] showed that the increase in coronary blood flow in response to the administration of acetylcholine – a marker of endothelial function – was attenuated in patients with chest pain and normal coronary arteries who had increased CRP concentrations, compared with patients in whom CRP concentrations were normal. Moreover, Arroyo-Espliguero et al [22] showed that, compared with control individuals, patients with CSX have greater serum concentrations of CRP, increased common carotid artery intima-media thickness, and increased carotid artery stiffness, suggesting a direct relationship between inflammation and vascular abnormalities.

Cosin-Sales et al [23] investigated the relationship among CRP, symptoms, exercise stress test responses, and ST-segment changes during daily life in 137 consecutive patients (mean age 57 years; 33 men) with typical chest pain and normal coronary angiograms. All underwent exercise stress testing, 24 h ambulatory ECG monitoring, and CRP measurements at study entry. CRP concentrations were greater in patients with frequent and prolonged episodes of chest pain and in those with ST-segment depression on exercise testing and Holter monitoring, compared with patients with shorter episodes of chest pain, negative exercise stress testing, and no ST-segment shifts on Holter monitoring. They found a correlation between CRP concentration and number of ischemic episodes during Holter monitoring and with the magnitude of ST-segment depression on exercise testing. CRP was the only independent variable capable of predicting positive findings on Holter monitoring and exercise testing.

Reduced bioavailability of nitric oxide as a result of endothelial dysfunction and enhanced expression of endothelin-1, promoted by inflammatory mechanisms, may be implicated in the impairment of systemic endothelial vasoreactivity leading to microvascular angina in CSX [23].

Abnormal pain perception in cardiac syndrome X

Altered pain perception is likely to be responsible for the occurrence of chest pain in at least a proportion of patients with CSX, as suggested by several clinical observations and recently discussed in a clinical article by Kaski [24]. Shapiro and colleagues [25] demonstrated that patients with CSX developed chest pain during intra-atrial injection of saline – a stimulus which is otherwise painless in other clinical conditions. In a study carried out by Lanza et al [26], global or regional abnormalities, or both, in cardiac meta-iodobenzylguanidine (MIBG) scintigraphy were

observed in a high proportion of patients with CSX, suggesting the presence of an abnormal function of efferent cardiac sympathetic nerve endings and supporting a cardiac origin for chest pain in these patients. Spinal cord stimulation, which is believed to act through enhancement of pain-gate control in the dorsal horn, has been reported to improve anginal symptoms in patients with CSX [27]. As mentioned previously, abnormal responses by the endogenous opioid system have also been implicated in the abnormal pain perception observed in women with CSX [28]. The combined effects of endothelial dysfunction, leading to minor reductions in myocardial blood flow, and increased pain perception may explain the prolonged episodes of typical chest pain observed in subgroups of patients with CSX in whom myocardial ischemia cannot be detected.

Patient management

Despite recurrent chest pain and prolonged episodes of ST-segment depression both on exertion and at rest, prognosis is good in patients with CSX [7,24]. Exceptions to this are patients with left bundle branch block, who may develop dilated cardiomyopathy during long-term follow-up, and patients in whom angina results from the presence of serious conditions affecting the coronary microvessels, such as amyloidosis and myeloma [24]. Quality of life is often poor in patients with CSX, because of the presence of recurrent and prolonged chest pain. Treatment usually requires a combination of pharmacologic agents and lifestyle changes (*Figure 2*) [24]. Successful management usually depends on identifying the prevailing pathogenic mechanism in a given individual, and the therapeutic intervention should be tailored to the needs of the individual patient. Advice on lifestyle changes and aggressive risk factor management are of major importance in almost all patients with CSX [24]. Sublingual nitrates are often effective in patients with documented myocardial ischemia – that is, those with abnormal myocardial perfusion scans.

Analgesic strategies

Treatment with drugs that increase the patient's pain threshold is usually effective in CSX. Both imipramine [29], an antidepressant affecting pain perception, and aminophylline [30,31], an adenosine receptor antagonist, improve chest pain symptoms in patients with CSX. Transcutaneous electrical nerve stimulation and spinal cord stimulation appear to be valuable options for pain control, but larger studies are necessary to define the true role of these treatments in CSX.

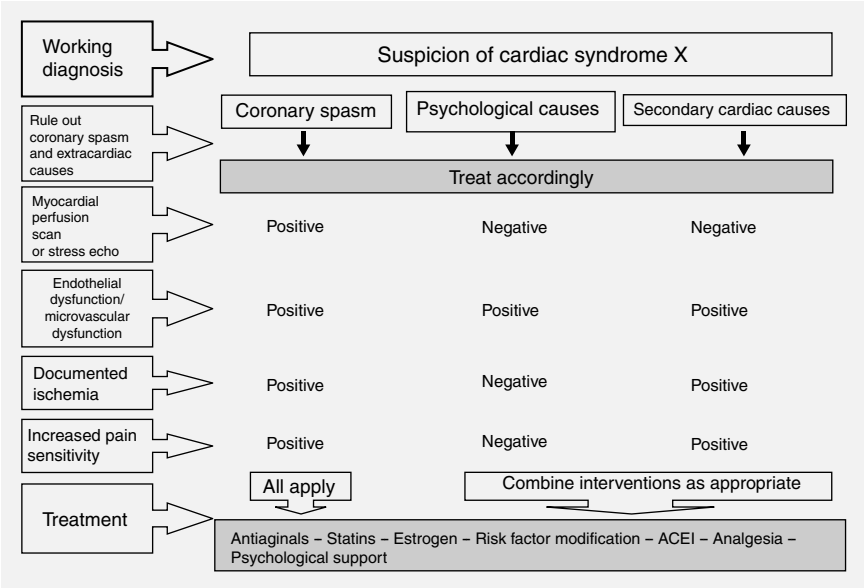

Figure 2. Flow chart showing suggested diagnostic and therapeutic steps in patients with cardiac syndrome X (CSX). Non-cardiac causes of chest pain and coronary artery spasm have to be ruled out. Patients with suspected CSX should undergo objective assessment of myocardial ischemia and endothelial dysfunction, as these conditions determine the therapeutic strategy. Of importance, treatment needs to be tailored to the patient's needs, and largely depends on the prevailing mechanisms responsible for chest pain and the electrocardiographic changes in a given individual. Nitrates, calcium-channel blockers, angiotensin-converting enzyme inhibitors (ACEI), and β-blockers are useful in patients with documented myocardial ischemia and those with microvascular dysfunction. Statins have been shown to improve endothelial function and exercise-induced myocardial ischemia in patients with CSX. Analgesic interventions are useful in individuals with a decreased pain threshold, and estrogen replacement therapy may be effective in postmenopausal women with CSX and endothelial dysfunction. Psychological intervention is effective in several subgroups of patients with CSX, and patients should be assessed accordingly.

Estrogen therapy

Hormone therapy has been shown to improve chest pain and endothelial function in women with CSX [2]. Estrogen treatment antagonizes the effects of endothelin-1 and dilates the coronary vessels, in addition to modulating pain perception at a central level [2,3,5]. It has been recommended that hormone replacement therapy should not be given for the prevention of chronic conditions [32], and these recommendations apply also to CSX. Short-term estrogen treatment, however, may be useful in specific patients with CSX in whom a direct relationship has been established between estrogen deficiency and symptoms [24].

Cognitive behavioral intervention

Various psychological treatments have been shown to be beneficial in patients with CSX [33]. Cognitive behavioral therapy has been used successfully in the management of patients with CSX with non ischemic chest pain [34].

Exercise

Physical exercise improves pain threshold and endothelial function and delays the onset of exertional pain in patients with typical chest pain and normal coronary arteriograms [35].

Antianginal agents

Commonly used antianginal agents include sublingual nitrates for the relief or prevention of angina, calcium-channel blockers and – in certain patients – β-blockers and nicorandil. Angiotensin-converting enzyme inhibitors and statins have been reported to improve exercise-induced angina in patients with CSX [24,36,37].

Conclusions

Cardiac syndrome X encompasses heterogeneous patient subgroups in whom the common denominator is typical chest pain and ECG changes despite angiographically normal coronary arteries. Controversy still surrounds the pathogenesis of CSX, which is likely to differ in different subgroups of patients. Increased sensitivity to pain and myocardial ischemia as a result of microvascular dysfunction (''microvascular angina'') [38] are two of the most likely pathogenic mechanisms, albeit ischemia is documented in a small proportion of patients. Identification of pathogenic mechanisms is important if rational management is to be provided. A multidisciplinary approach – involving cardiologists, general physicians, pain units, and psychologists, together with phone ''hot'' lines or internet ''clinics'' – is usually effective, and reduces unnecessary hospital admissions and expensive investigations. Lifestyle changes are of paramount importance to improve endothelial function. Pharmacologic interventions should be directed towards the relief of angina and myocardial ischemia. Prognosis is generally good in patients with CSX.

*See glossary for definition of these terms. ■

REFERENCES

1. Kemp HG. Left ventricular function in patients with anginal syndrome and normal coronary arteriograms. *Am J Cardiol*. 1973;32:376–1376.
2. Kaski JC. Cardiac syndrome X in women: the role of oestrogen deficiency. *Heart*. 2006;92 (suppl 3):5–9.
3. Roqué M, Heras M, Roig E, et al. Short-term effects of transdermal estrogen replacement therapy on coronary vascular reactivity in postmenopausal women with angina pectoris and normal results on coronary angiograms. *J Am Coll Cardiol*. 1998;31:139–143.
4. Kennedy SE, Zubieta JK. Neuroreceptor imaging of stress and mood disorders. *CNS Spectr*. 2004;9:292–301.
5. Zubieta JK, Smith YR, Bueller JA, et al. Regional mu opioid receptor regulation of sensory and affective dimensions of pain. *Science*. 2001;293:311–315.
6. Kaski JC. Cardiac syndrome X and microvascular angina. In: *Chest Pain With Normal Coronary Angiograms: Pathogenesis, Diagnosis and Management*. Edited by Kaski . London: Kluwer Academy Publishers; 1999. pp. 1–12.
7. Kaski JC, Rosano GM, Collins P, Nihoyannopoulos P, Maseri A, Poole-Wilson PA. Cardiac syndrome X: clinical characteristics and left ventricular function. Long-term follow-up study. *J Am Coll Cardiol*. 1995;25:807–814.
8. Nihoyannopoulos P, Kaski JC, Crake T, Maseri A. Absence of myocardial dysfunction during stress in patients with syndrome X. *J Am Coll Cardiol*. 1991;18:1463–1470.
9. Buchthal SD, den Hollander JA, Merz CN, et al. Abnormal myocardial phosphorus-31 nuclear magnetic resonance spectroscopy in women with chest pain but normal coronary angiograms. *N Engl J Med*. 2000;342:829–835.
10. Buffon A, Rigattieri S, Santini SA, et al. Myocardial ischemia-reperfusion damage after pacing-induced tachycardia in patients with cardiac syndrome X. *Am J Physiol Heart Circ Physiol*. 2000;279:H2627–H2633.
11. Pantin JR, Gatehouse PD, Yang G-Z, et al. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *N Engl J Med*. 2002;346:1948–1953.
12. Mosseri M, Yarom R, Gotsman MS, Hasin Y. Histologic evidence for small-vessel coronary artery disease in patients with angina pectoris and patent large coronary arteries. *Circulation*. 1986;74:964–972.
13. Mosseri M, Schaper J, Admon D, et al. Coronary capillaries in patients with congestive cardiomyopathy or angina pectoris with patent main coronary arteries – ultrastructural morphometry of endomyocardial biopsy samples. *Circulation*. 1991;84:203–210.
14. Bund SJ, Tweddel A, Hutton I, Heagerty AM. Small artery structural alterations of patients with microvascular angina (CSX). *Clin Sci*. 1996;91:739–743.
15. Antonios TF, Kaski JC, Hasan KM, Brown SJ, Singer DR. Rarefaction of skin capillaries in patients with anginal chest pain and normal coronary arteriograms. *Eur Heart J*. 2001;22:1144–1148.
16. Masci PG, Laclaustra M, Lara JG, Kaski JC. Brachial artery flow-mediated dilation and myocardial perfusion in patients with cardiac syndrome X. *Am J Cardiol*. 2005;95:1478–1480.
17. Opherk D, Zebe H, Wiehe E, et al. Reduced coronary dilatory capacity and ultrastructural changes of the myocardium in patients with angina pectoris but normal coronary arteriograms. *Circulation*. 1981;63:817–825.

18. Kaski JC, Elliott PM, Salomone O, et al. Concentration of circulating plasma endothelin in patients with angina and normal coronary angiograms. *Br Heart J*. 1995;74:620–624.
19. Cox ID, Botker HE, Bagger JP, Sonne HS, Kristensen BO, Kaski JC. Elevated endothelin concentrations are associated with reduced coronary vasomotor responses in patients with chest pain and normal coronary arteriograms. *J Am Coll Cardiol*. 1999;34:455–460.
20. Egashira K, Hirooka Y, Kuga T, Mohri M, Takeshita A. Effects of L-arginine supplementation on endothelium-dependent coronary vasodilatation in patients with angina pectoris and normal coronary arteriograms. *Circulation*. 1996;94:130–134.
21. Teragawa H, Fukuda Y, Matsuda K. Relation between C reactive protein concentrations and coronary microvascular endothelial function. *Heart*. 2004;90:750–754.
22. Arroyo-Espliguero R, Mollichelli N, Avanzas P, et al. Chronic inflammation and increased arterial stiffness in patients with cardiac syndrome X. *Eur Heart J*. 2003;24:2006–2011.
23. Cosin Sales J, Pizzi C, Brown S, Kaski JC. C-reactive protein, clinical presentation and ischemic activity in patients with chest pain and normal coronary angiograms. *J Am Coll Cardiol*. 2003;41:1468–1474.
24. Kaski JC. Pathophysiology and management of patients with chest pain and normal coronary arteriograms (cardiac syndrome X). *Circulation*. 2004;109:568–572.
25. Shapiro LM, Crake T, Poole-Wilson PA. Is altered cardiac sensation responsible for chest pain in patients with normal coronary arteries? Clinical observations during cardiac catheterization. *BMJ*. 1988;296:170–171.
26. Lanza GA, Giordano A, Pristipino C, et al. Abnormal cardiac adrenergic nerve function in patients with syndrome X detected by metaiodobenzylguanidine myocardial scintigraphy. *Circulation*. 1997;96:821–826.
27. Lanza GA, Sestito A, Sgueglia GA, et al. Effect of spinal cord stimulation on spontaneous and stress-induced angina and ''ischemia-like'' ST-segment depression in patients with cardiac syndrome X. *Eur Heart J*. 2005;26:983–989.
28. Fedele F, Agati L, Pugliese M, et al. Role of the central endogenous opiate system in patients with CSX. *Am Heart J*. 1998;136:1003–1009.
29. Cannon RO III, Quyyumi AA, Mincemoyer R, et al. Imipramine in patients with chest pain despite normal coronary angiograms. *N Engl J Med*. 1994;330:1411–1417.
30. Elliott PM, Krzyzowska-Dickinson K, Calvino R, Hann C, Kaski JC. Effect of oral aminophylline in patients with angina and normal coronary arteriograms (cardiac syndrome X). *Heart*. 1997;77:523–526.
31. Yoshio H, Shimizu M, Kita Y, et al. Effects of short-term aminophylline administration on cardiac functional reserve in patients with syndrome X. *J Am Coll Cardiol*. 1995;25: 1547–1551.
32. Paoletti R, Wenger NK. Review of the international position on women's health and menopause: a comprehensive approach. *Circulation*. 2003;107:1336–1339.
33. Potts SG, Bass C. Chest pain with normal coronary arteries: psychological aspects. In: Kaski JC, ed. *Chest Pain With Normal Coronary Arteries: Pathogenesis, Diagnosis and Management*. Boston, MA: Kluwer Academic Publishers; 1999. pp. 13–32.
34. Mayou RA, Bryant BM, Sanders D, Bass C, Klimes I, Forfar C. A controlled trial of cognitive behavioural therapy for non-cardiac chest pain. *Psychol Med*. 1997;27:1021–1031.
35. Eriksson BE, Tyni-Lenne R, Svedenhag J, et al. Physical training in syndrome X: physical training counteracts deconditioning and pain in syndrome X. *J Am Coll Cardiol*. 2000;36:1619–1625.
36. Kaski JC, Valenzuela Garcia LF. Therapeutic options for the management of patients with cardiac syndrome X. *Eur Heart J*. 2001;22:283–293.
37. Braunwald E, Antman E, Beasley J, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST segment elevation myocardial infarction – executive summary and recommendations. A report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients With Unstable Angina). *Circulation*. 2000; 102:1193–1209.
38. Cannon RO III, Epstein SE. ''Microvascular angina'' as a cause of chest pain with angiographically normal coronary arteries. *Am J Cardiol*. 1988;61:1338–1343.

Featured research

Abstracts and commentaries

Comparison of coronary flow reserve and fractional flow reserve in patients with versus without diabetes mellitus and having elective percutaneous coronary intervention and abciximab therapy (from the PREDICT Trial)

Kini AS, Kim MC, Moreno PR, Krishnan P, Ivan OC, Sharma SK. *Am J Cardiol*. 2008;101:796–800.

Patients with diabetes mellitus have poor long-term outcome after percutaneous coronary intervention (PCI), partly because of microvascular disease and distal embolization. Microvascular obstruction can be assessed by measuring coronary flow reserve (CFR). The Prediction of CK-MB Release During Successful Stenting Correlating with Indicators of Microvascular Obstruction (PREDICT) trial compared the CFR in patients with and without diabetes mellitus during PCI. Patients undergoing elective PCI were prospectively enrolled according to diabetic ($n = 36$) and non diabetic ($n = 36$) status. All patients received a drug-eluting stent with abciximab and were followed for 30 days for major adverse cardiac events. CFR and fractional flow reserve (FFR) before and after stenting were measured before and after administration of an intracoronary bolus of adenosine. Procedural success, concentrations of the MB enzyme of creatine kinase (CK-MB) and troponin I, increases in high-sensitive C-reactive protein, vascular complications, and major adverse cardiac events were not different between the groups. Before stenting, FFR was 0.77 ± 0.03 in patients with diabetes mellitus and 0.76 ± 0.02 in those without it ($P = 0.69$); after stenting it was 0.97 ± 0.03 and 0.99 ± 0.01 ($P = 0.26$), respectively. CFR before stenting was 1.36 ± 0.31 in patients with diabetes mellitus and 1.49 ± 0.25 in patients without it ($P = 0.064$); however, after stenting CFR was significantly lower in patients with diabetes mellitus than in those who were not diabetic (1.89 ± 0.30 compared with 2.44 ± 0.67; $P < 0.001$, respectively). CFR after stenting only moderately correlated with CK-MB and high-sensitive C-reactive protein after PCI, but did not correlate with 30-day major adverse cardiac events. It was concluded that patients with diabetes mellitus have significantly lower CFR after stenting, despite equivalent FFR and myonecrosis, compared with patients without diabetes mellitus, indicating greater microvascular obstruction after PCI despite treatment with abciximab.

Commentary

Diabetic patients with ischemic heart disease have a worse prognosis than those who are not diabetic, regardless of the type of treatment (medical, PCI, or bypass surgery). Several factors have been proposed to explain this poor outcome, including microvascular dysfunction. In this study by Kini et al, FFR and CFR were measured in diabetic and non diabetic patients undergoing PCI. FFR expresses the resistance to flow across the epicardial stenosis, and CFR expresses the vasodilating capability of the coronary microcirculation. Coronary stenting abolished the epicardial obstruction and normalized FFR in both groups. Conversely, CFR remained significantly lower in individuals with diabetes than in those who were not diabetic, suggesting a persistent microvascular dysfunction, despite equivalent FFR, similar amount of myocardial damage, and abciximab administration. The authors attribute the lower CFR after stenting that was observed in diabetic patients to greater microvascular obstruction secondary to distal embolization of atherosclerotic or thrombotic material, or to exaggeration of the microvascular disease itself, or a combination of both.

The observation that CFR tended to be lower in individuals with diabetes, even before stenting, is consistent with the hypothesis that a diffuse microvascular dysfunction pre-exists in these patients, but does not exclude the possibility of a worsening associated with the PCI procedure. This point could be clarified by the measurement of CFR in the non target

reference vessel. Unfortunately, this measurement was performed only at the end of the study, and the data are not reported in detail.

In conclusion, the findings of this study support the concept that the worse prognosis of ischemic heart disease in patients with diabetes relates to the presence of a severe microvascular dysfunction, which precedes the revascularization procedure, prevents recovery of CFR after stenting, and is diffuse to non target vessels.

Mario Marzilli

Sodium-hydrogen exchange inhibition by cariporide to reduce the risk of ischemic cardiac events in patients undergoing coronary artery bypass grafting: results of the EXPEDITION study

Mentzer RM Jr, Bartels C, Bolli R, et al, for the EXPEDITION Study Investigators. *Ann Thorac Surg*. 2008;85:1261–1270.

The EXPEDITION study addressed the efficacy and safety of inhibiting the sodium-hydrogen exchanger isoform-1 (NHE-1) by cariporide in the prevention of death or myocardial infarction in patients undergoing coronary artery bypass graft surgery. The premise was that inhibition of NHE-1 limits the intracellular accumulation of sodium and thereby limits Na^+–Ca^+-exchanger-mediated calcium overload to reduce infarct size. High-risk coronary artery bypass graft (CABG) surgery patients ($n = 5761$) were randomly allocated to receive either intravenous cariporide (180 mg in a 1 h preoperative loading dose, then 40 mg/h over 24 h and 20 mg/h over the subsequent 24 h) or placebo. The primary composite endpoint of death or myocardial infarction was assessed at 5 days, and patients were followed for as long as 6 months. At 5 days, the incidence of death or myocardial infarction was reduced from 20.3% in the placebo group to 16.6% in the treatment group ($P = 0.0002$). Paradoxically, myocardial infarction alone declined from 18.9% in the placebo group to 14.4% in the treatment group ($P = 0.000005$), whereas mortality alone increased from 1.5% in the placebo group to 2.2% with cariporide ($P = 0.02$). The increase in mortality was associated with an increase in cerebrovascular events. Unlike the salutary effects that were maintained at 6 months, the difference in mortality at 6 months was not significant. The EXPEDITION study is the first phase-3 myocardial protection trial in which the primary endpoint was achieved and proof of concept demonstrated. As a result of the increased mortality associated with an increase in cerebrovascular events, it is unlikely that cariporide will be used clinically. The findings suggest that NHE-1 inhibition holds promise for a new class of drugs that could significantly reduce myocardial injury associated with ischemia-reperfusion injury.

Commentary

The NHE-1 isoform is a cell membrane protein expressed in various organs and cells, including the heart and cardiac myocytes. As its name suggests, it exchanges hydrogen ions for sodium ions. During ischemia, the protons accumulating within cardiac myocytes are exchanged for external sodium. The intracellular sodium ions then accumulate as a result of the coincident decrease in high-energy phosphate charge, preventing active extrusion through the sodium pump (Na^+–K^+-ATPase). The accumulation of intracellular sodium, in turn, causes the accumulation of intracellular calcium, through reduced calcium efflux and increased influx through the Na^+–Ca^+ exchanger. The accumulation of intracellular calcium is very damaging, contributing to hypercontracture, mitochondrial calcium overload, and myocyte death. A wealth of preclinical studies have investigated these events during ischaemia and demonstrated without doubt that NHE-1 inhibition reduces infarction. The maximum cardioprotective effect is seen in animal studies when the NHE-1 inhibitor is present throughout ischemia and when definite reperfusion occurs. These two key criteria were absent in some of the groups of patients investigated in previous large-scale clinical studies of NHE-1 inhibition – a deficiency that probably contributed to their negative findings (reviewed in [1]).

Cariporide is a selective and potent inhibitor of NHE-1, previously investigated in a dose-ranging phase 2/3 study, GUARDIAN, that recruited patients who had evolving myocardial infarction, or were undergoing high-risk percutaneous coronary intervention or CABG surgery [2]. It was only in this last group, fulfilling the key criteria of cariporide being present throughout ischemia and definite reperfusion, that possible protection was seen. This ''signal'' provided the basis for the EXPEDITION study [3].

As can be seen, EXPEDITION was a positive study in that the incidence of the primary composite endpoint was significantly lower in the cariporide group than in the placebo group. Although all components of a primary endpoint contribute equally to the accrual of events, they obviously are not biologically equivalent. This was the problem in EXPEDITION.

The rationale behind EXPEDITION was that cariporide, given 2 h before CABG surgery and continued for 2 days, would reduce perioperative myocardial infarction to such an extent that this would be

reflected in all-cause mortality. Although cariporide was associated with a marked and highly significant reduction in the incidence – and the severity – of myocardial infarction, it increased mortality! The incidence of myocardial infarction, assessed 5 days after surgery, was reduced from 18.9% to 14.4%, a relative risk reduction of 24% that was statistically highly significant ($P = 0.000005$). At the same time point, mortality increased from 1.5% to 2.2% – an escalation in relative risk of 53.5% that was statistically significant ($P = 0.028$). The determination of cause-specific mortality was not mandated in the trial protocol. However, it seems likely that the excess deaths in the cariporide group were related to cerebrovascular events. Focal persistent neurological deficits occurred in 4.5% of the cariporide group, compared with 2.5% of the placebo group, an approximate 80% increase in relative risk that was statistically highly significant ($P = 0.0001$). There were similarly statistically significant increases in postoperative confusional states without focal neurological deficits. The increase in mortality together with these non fatal, but serious, adverse events more than offset the benefit of cariporide on non fatal myocardial infarction and, even though the investigational agent met its primary efficacy endpoint, it is not being developed further by its manufacturer, Sanofi-Aventis. I consider this to be a reasonable decision, given the clinical importance of death and disabling cerebrovascular accident over non fatal myocardial infarction.

Despite the unpredicted effects of cariporide in increasing mortality, confusional states, and cerebrovascular events, there are aspects of the trial that offer encouragement. First, to my knowledge, this is the first large phase-3 trial that demonstrates unequivocally that it is possible to increase myocardial resistance to ischemia and thereby reduce infarction. Moreover, this increased resistance is manifest with a definition of myocardial infarction that did not involve minor increases in troponin, but a 10-fold increase in CK-MB above the upper limit of normal or the postoperative appearance of new Q-waves using a conservative objective ECG scoring system. Secondly, it leaves the door open for further studies. At present it is not known whether the excess mortality and adverse cerebrovascular effects are the result of NHE-1 inhibition or an off-target action specific to the cariporide molecule. Although there is no doubt that the cloud of the EXPEDITION study will cast a shadow over the concept of cardioprotection, it is important not to ignore its very silver lining.

REFERENCES

1. Avkiran M, Marber MS. Na(+)/H(+) exchange inhibitors for cardioprotective therapy: progress, problems and prospects. *J Am Coll Cardiol*. 2002;39:747–753.
2. Theroux P, Chaitman BR, Danchin N, et al. Inhibition of the sodium-hydrogen exchanger with cariporide to prevent myocardial infarction in high-risk ischemic situations: main results of the GUARDIAN trial. *Circulation*. 2000;102:3032–3038.
3. Mentzer RM Jr, Bartels C, Bolli R, et al., for the EXPEDITION Study Investigators. Sodium-hydrogen exchange inhibition by cariporide to reduce the risk of ischemic cardiac events in patients undergoing coronary artery bypass grafting: results of the EXPEDITION study. *Ann Thorac Surg*. 2008;85:1261–1270.

Michael Marber

Glossary

Gary D. Lopaschuk

Calmodulin

Calmodulin is a calcium-binding protein expressed in all eukaryotic cells. Calmodulin binds to and regulates many different protein targets. Calmodulin often acts as a calcium sensor, and can modulate the activity of proteins in response to changes in cellular calcium. Binding of calcium to calmodulin alters the proteins conformation, allowing calmodulin to interact with a number of other proteins. In the heart, calcium binding to calmodulin can facilitate excitation contraction coupling by facilitating the interaction of calmodulin with a number of proteins involved in excitation contraction coupling.

EDHF; Endothelium-derived hyperpolarizing factor

EDHF is secreted by endothelial cells, which leads to nitric oxide- and prostacyclin-independent vasodilation. EDHF relaxes vascular smooth muscle cells. If both NO and prostacyclin production are inhibited, arterioles still continue to dilate if they are stimulated by agents such as acetylcholine or bradykinin. This observed increase in blood vessel dilation is dependent on potassium channel activity and endothelium-dependent hyperpolarization of the smooth muscle cells.

Endothelin-1

Endothelin-1 is a small peptide produced in the endothelium of blood vessels that can cause vasoconstriction. Normally the action of endothelin-1 is kept in balance with other vasoregulatory pathways, but can contribute to high blood pressure (hypertension) and heart disease is the peptide is over-expressed.

Glycocalyx

Glycocalyx is an extracellular polymeric network of polysaccharides that project from cellular surfaces, such as those of bacteria. In bacteria the glycocalyx protects the bacterium or allows the bacterium to attach itself to inert surfaces.

G_s protein

Guanine nucleotide-binding proteins, or G proteins, are a family of proteins involved in second messenger cascades. G proteins belong to the larger group of enzymes called GTPases. G proteins are inactive if guanosine diphosphate (GDP) is bound to the protein and active ifguanosine triphosphate (GTP) is bound. The stimulatory G protein (G_s) links a number of receptors to intracellular action. A good example is how G_s links the ß-adrenergic receptor to adenylate cyclase.

IP_3R: inositol trisphosphate receptor

Inositol trisphosphate (IP3) is released from a cell membrane phospholipid called phosphatidylinositol 4,5-bisphosphate (PIP_2), via the action of phospholipase C. IP_3 binds to and activates an IP3 receptor (IP_3R), which can be found on the membrane of the sarcoplasmic reticulum. The IP_3R functions as a sensor for IP3, resulting in the release of calcium from the sarcoplasmic reticulum. The IP_3R can be phosphorylated and regulated by kinases, such protein kinase C, Ca2+ calmodulin-dependent protein kinase, and protein kinase A.

K_{ATP}

K_{ATP} is a potassium channel that is inhibited by ATP. As a result, K_{ATP} is a metabolically regulated potassium channel. For instance, K_{ATP} is one of the potassium channels responsible for pancreatic ß-cell insulin release.

Phospholipase C and release of IP_3 and diacylglycerol

Phospholipase C (PLC) plays an important role in signal transduction processes. Phospholipase C participate in phosphatidylinositol bisphosphate (PIP_2) metabolism and lipid signaling pathways in a calcium-dependent manner. PLC hydrolyzes PIP_2 into two important second messenger molecules, IP_3 and

diacylglycerol. These two second messentges have many important downstream functions, which include: ion channel modification, neurotransmission, endocrine functions, vesicular trafficking, cell proliferation, cell differentiation, cell apoptosis, and cytoskeleton remodeling.

PKA; protein kinase A

Protein kinase A, sometimes called cAMP-dependent protein kinase, is activated by increases in cellular cAMP. Protein kinase A can then phosphorylate and modify the activity of a number of intracellular proteins, including those involved in muscle contraction.

PKC; protein kinase C

Protein kinase C (PKC) is a family of kinases initially identified as requiring diacylglycerol, calcium, or phospholipids for activation. The conventional PKCs require calcium, diacylglycerol, and phosphatidylcholine for activation. Novel PKCs require diacylglycerol, but do not require calcium for activation. The conventional and novel PKCs are activated through the same signal transduction pathway as phospholipase C. Some atypical PKCs have also been identified that require neither calcium or diacylglycerol for activity. The PKCs have numerous cellular targets.

PKG; protein kinase G

Protein Kinase G (PKG), sometimes referred to as cGMP-dependent protein kinase is activated by cGMP. Protein kinase G phosphorylates a number of biologically important targets, some of which are involved in the regulation of smooth muscle relaxation. Nitric oxide (NO) acts via PKG stimulation.

Protein kinases activated by G-protein receptor dependent signalling pathways

A number of different protein kinases can be activated by G protein-coupled receptors. A large number of cell membrane receptors (one example being ß-receptors) are coupled to G-proteins to mediate their intracellular events. The G-proteins in turn are linked to a number of down-stream kinases which initiate various signaling pathways. An example of a downstream kinase is protein kinase A. In the ß-adrenergic signaling pathway the stimulation of the ß-receptor stimulates a Gs protein, which results in a stimulation of adenylate cyclase resulting in an increase in cAMP, and an activation of protein kinase A. Protein kinase A phosphorylates and modifies the activity of a number of intracellular proteins, including those involved in muscle contraction. This is but one example of numerous G protein receptor-dependent signalling pathways.

Rho-K; rho-kinase

Rho-kinase (Rho-K) is a serine/threonine kinase that is activated by GTP-bound RhoA. Rho-K is involved in the regulation of number of cellular activities which include smooth muscle contraction, cell morphology, formation of stress fibers and focal adhesions. Rho-K regulates smooth muscle contraction by phosphorylating the regulatory subunit of myosin light chain.

RyR: ryanodine receptor

Ryanodine receptors are intracellular calcium channels present in excitable cells, such as muscle and neurons. In sarcoplasmic reticulum of muscle cells, the ryanodine receptor a major source of calcium release that initiates muscle contraction.

Soluble guanylate cyclase

Nitric oxide (NO) is important for many physiological functions including vascular smooth muscle relaxation, neuronal signal transduction and inhibition of platelet aggregation. The primary receptor for NO is soluble guanylate cyclase (sGC), which catalyzes the conversion of GTP to the second messenger molecule cyclic GMP (cGMP). cGMP can then activate PKG to initiate smooth muscle relaxation.

Tyrosine phosphorylation

Protein kinases act by primarily phosphorylating two types of amino acids. One type are serine/threonine kinases, the other are tyrosine kinases. Tyrosine phosphorylation is involved in many cellular processes. A well known tyrosine kinase is the insulin receptor, which results in a tyrosine phosphorylation of the insulin receptor substrate to initiate the insulin-signaling pathway.