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Clinical Perspectives

Coronary stenosis vasoconstriction: impact on myocardial ischaemia

Introduction

Coronary vasomotor tone has been recognized to play a crucial role in determinating the ischaemic threshold and the occurrence of spontaneous as well as exercise-induced myocardial ischaemia. The traditional concept of the 'rigid tube' has been changed during the past 15 years and the coronary arteries are considered today to represent a 'dynamic tube'. Changes in coronary artery dimensions are caused through the contraction and relaxation of the smooth musculature within the vessel wall. Vasoactive substances released from the endothelium play a crucial role in the regulation of vessel size and coronary vasomotor tone. The endothelium is the largest and most active paracrine organ in the body, producing potent vasoactive, procoagulant, fibrinolytic, and anticoagulant substances. Thus, a diseased coronary endothelium may have a dramatic effect on the function of the vessels and may cause or contribute to the occurrence of myocardial ischaemia under high demand situations, such as physical exercise or mental stress. An important variable in this regulation is coronary blood flow.

Pathophysiologic determinants of coronary vasomotion

Regional coronary blood flow is dependent on several factors such as perfusion pressure, metabolic demands, coronary resistance and vasomotor tone[1]. Coronary vasomotor tone is the result of vasoconstricting and vasodilating stimuli originating from the autonomic nervous system, hormones and vessel (wall-derived) vasoactive substances. Several studies have shown the presence of both α- and β-adrenergic receptors in animal and human coronary arteries. An increase in α-adrenergic tone has been associated with the occurrence of coronary artery vasoconstriction, whereas α-adrenergic blockade has been shown to reduce attacks of variant angina and to abolish coronary vasoconstriction. However, an increase in β-adrenergic tone has been associated with coronary artery vasodilation[2].

Coronary vasomotion is an important determinant of myocardial perfusion, not only in normals but also in patients with angina pectoris[3]. Disturbances in vasomotion are closely linked to the development of atherosclerosis and play an integral part in the pathophysiology of myocardial ischaemia[4]. In patients with angina pectoris, there is a circadian variation in ischaemic events, being most frequent in the morning hours[5]. This is due to the enhanced release of epinephrine and norepinephrine[6], which results in an increase in heart rate and blood pressure as well as enhanced platelet aggregability[7]. Accordingly, vascular resistance has been shown to be increased and ischaemic threshold to be reduced in the morning hours[8]. This enhanced release of catecholamines leads to coronary vasoconstriction and transient reductions in coronary blood flow with a spontaneous decrease in anginal threshold, a condition referred to as 'mixed angina'[9].

Role of the endothelium

The endothelium modulates coronary vasomotion by the uptake, storage, and metabolism of numerous substances[10–12], such as serotonin, norepinephrine, bradykinin, acetylcholine etc. (Fig. 1). Paracrine-released substances (autacoids) such as the endothelium-derived relaxing factor (EDRF), prostacyclin (PGI_2), platelet activating factor, and endothelin are synthesized and released from the endothelium for vascular control and haemodynamic homeostasis. Nitric oxide has been recognized to be EDRF, although some of the pharmacological actions of EDRF cannot be explained by nitric oxide solely. Nitric oxide is continuously synthesized and released, both without stimulation (basal nitric oxide release) and with stimulation (stimulated release) elicited by local and circulating agonists (such as

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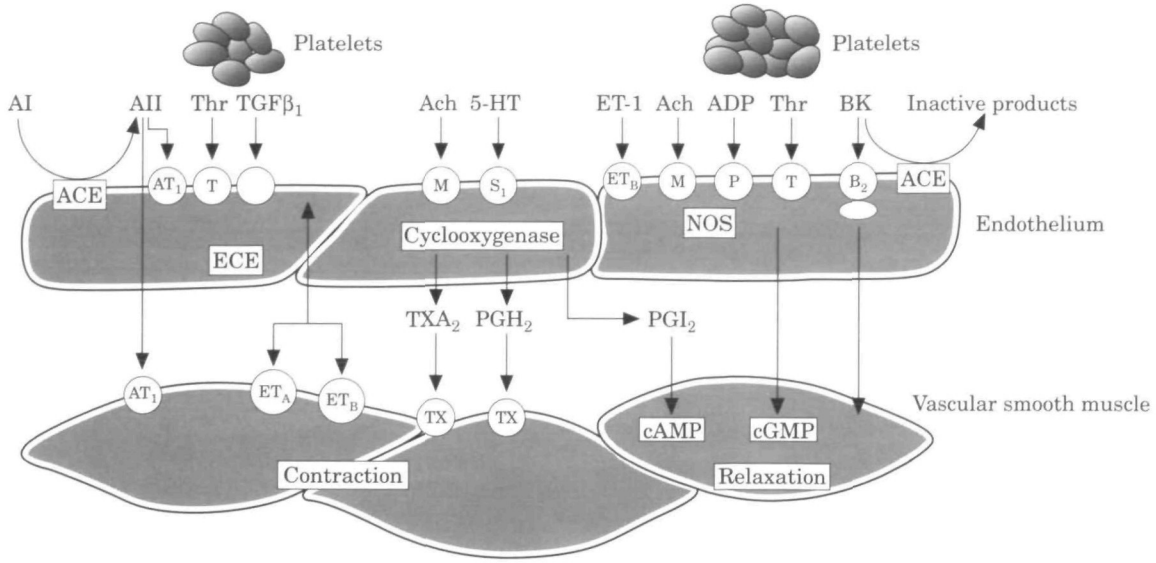

Figure 1 **Determinants of coronary vasomotor tone. In an intact endothelium, various stimulatory compounds elicit NO-mediated dilation or vasoconstriction. ACE=angiotensin converting enzyme; Ach=acetylcholine; ADP=adenosine diphosphate; Bk=bradykinin; cAMP/cGMP=cyclic adenosine/guanidine monophosphate; ECE=endothelin converting enzyme; EDHF=endothelial derived hyperpolarizing factor; ET-1=endothelin-1; 5HT=5-hydroxytryptamine (serotonin); L-arg=L-arginine; NO=nitric oxide; PGH_2=prostaglandin H_2; PGI_2=prostacyclin I_2; TGFβ=tranforming growth factor β_1; Thr=thrombin; TXA_2=thrombozane A_2. Circles represent receptors (AT=angiotensinergic; B=bradykininergic; M=muscarinergic; P=purinergic; T=thrombin receptor). (Reproduced with permission from Lüscher TF and Noll G. The endothelium in coronary vascular control. In: Heart disease — Update 3. Philadelphia: W. B. Saunders Company, 1995: 2).**

bradykinin, serotonin, norepinephrine) or, most importantly by viscous drug-induced shear stress from the perfusing blood (resulting in flow-dependent dilation). The pulsatile stretching of the endothelium adds to this mechanically stimulated nitric oxide release[13]. Furthermore, all vasoactive compounds and drugs modulate endothelial nitric oxide synthesis and release in either a receptor-dependent or in a flow-dependent (=shear stress-mediated) manner[14]. Under physiological conditions, the continuous dilator action of endothelial autacoids compensates for the continuous constrictor effect of norepinephrine released from the nerve endings[15]. In patients with impaired endothelial function flow-dependent, nitric oxide-mediated dilator responses are diminished[16] and at the same time the myogenic constrictor responses are enhanced resulting in an enhanced autoregulatory response[17].

Previous studies on coronary vasomotor tone in humans used conventional coronary angiography for measuring changes in response to various pharmacological stimuli[18–20]. Recently, Schächinger and Zeiher[4] combined angiographic measurements and intracoronary ultrasound for calculation of vasomotor tone. They used the ratio of a change in circumference divided by the total vasomotor range as a measure of vasomotor tone. However, pressure as an important determinant of vascular tone was neglected in this model[4].

Vasomotion in coronary artery disease

Normal vessels

A number of pharmacological agents such as serotonin, norepinephrine, vasopressin, papaverine, but mainly acetylcholine have been used to study the vasomotor response of coronary arteries[21–24]. In clinical studies, intracoronary acetylcholine has been shown to constrict coronary arteries in the presence of atherosclerotic lesions, whereas it dilates normal coronary arteries[25]. Constriction during static but dilation during dynamic exercise has been reported previously[3]. A heterogeneous response of angiographically smooth vessels has been described. Undetected atherosclerosis in angiographically normal vessels of patients with coronary artery disease may account for insufficient vasodilator response due to endothelial dysfunction. Progressive impairment of endothelial function has been reported with different stages of coronary atherosclerosis in patients with angiographically smooth coronary arteries[16]. Thus, a functional disorder of the 'normal' coronary

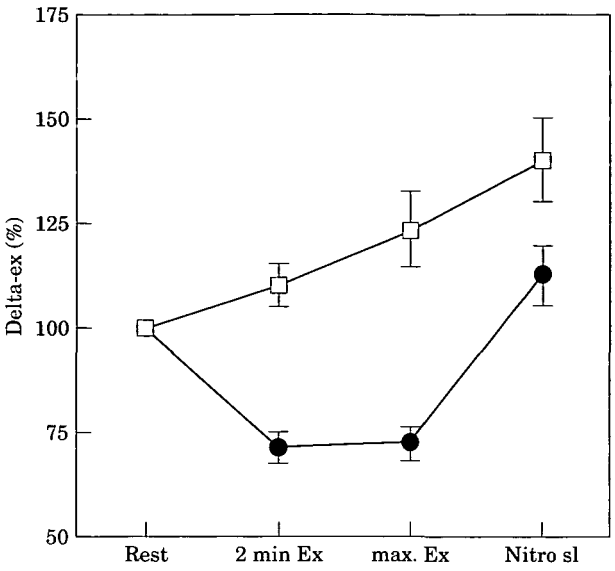

Figure 2 **Normal vessels (open squares) show exercise-induced dilation which is further enhanced after sublingual nitroglycerin (Nitro sl). In contrast, stenoses show exercise-induced vasoconstriction, which is reversed after sublingual nitroglycerin. delta-Ex, percent change of cross-sectional area.**

arteries may account for the abnormal response of various physiological and pharmacological stimuli in patients with coronary artery disease.

Stenosis

The observation that stenotic arteries can change its diameter depends on the fact that approximately 70% of all stenotic lesions are eccentric and have a normal musculo-elastic wall segment within the stenosis[3,26,27]. Intracoronary acetylcholine induces vasoconstriction of stenotic coronary arteries. In contrast to the normal coronary arteries, constriction of stenotic vessels has been reported during static[28] and dynamic exercise[3,29,30] (Fig. 2). The mechanism of coronary stenosis narrowing during exercise or after intracoronary acetylcholine is not clear but might be explained by either:

(1) endothelial dysfunction with insufficient production of EDRF
(2) an increase in circulating catecholamines during exercise[31–33]
(3) platelet aggregation with release of the vasoconstricting compounds serotonin and thromboxane A_2
(4) a passive collapse of the free vessel wall when coronary flow velocity increases during exercise (Bernoulli mechanism)[34] and/or
(5) a reduction of coronary blood flow increase during exercise due to tachycardia with a decrease in diastolic perfusion time[30].

Cardiovascular risk factors and coronary vasomotion

Hypercholesterolaemia

There has been increasing interest in the literature on the functional impact of hypercholesterolaemia on coronary vascular function[6,35,36]. Impairment of endothelium-dependent vasodilation in angiographically normal coronary arteries has been reported in the presence of hypercholesterolaemia[16,37,38]. This has been attributed to a dysfunction of the endothelium via an attenuation of EDRF release by oxidised low-density lipoproteins (LDL)[39,40] and/or stimulation of endothelin-mRNA as well as the release of endothelin[41]. Lerman and co-workers[42] showed that hypercholesterolaemia elevates plasma endothelin concentration and enhances coronary artery tissue endothelin immunoreactivity, which is thought to be responsible for abnormal endothelial function. These changes play an important role in the development of early atherosclerotic lesions, which is characterized by functional alterations of the endothelial cell before morphological changes are detectable. Hypercholesterolaemia impairs exercise-induced coronary vasodilation in angiographically normal coronary arteries: as total serum cholesterol increases exercise-induced dilation is diminished. In humans, an inverse correlation between total or LDL cholesterol and exercise-induced vasodilation in angiographically normal coronary arteries has been reported by Seiler *et al.*[43] (Fig. 3). An increase in serum cholesterol above 200 mg . 100 ml^{-1} reduces exercise-induced vasodilation to 12%, whereas in the presence of a normal serum cholesterol vasodilation amounts to 20%. When serum cholesterol is increased above 250 mg . 100 ml^{-1} coronary vasomotion is abolished (+4% vasodilation during exercise, P=ns). However, no influence of serum cholesterol was observed in stenotic vessels. Similar observations have been made in children with familiar hyperlipidaemia[44] and in porcine coronary arteries with diet-induced hypercholesterolaemia[45].

The effect of hypercholesterolaemia on human vascular function has been evaluated by Creager *et al.* in the forearm of patients with normal and those with elevated serum cholesterol. The forearm vessels were chosen for investigation since they almost never show atherosclerotic changes[46]. There was a diminished flow increase to methacholine in

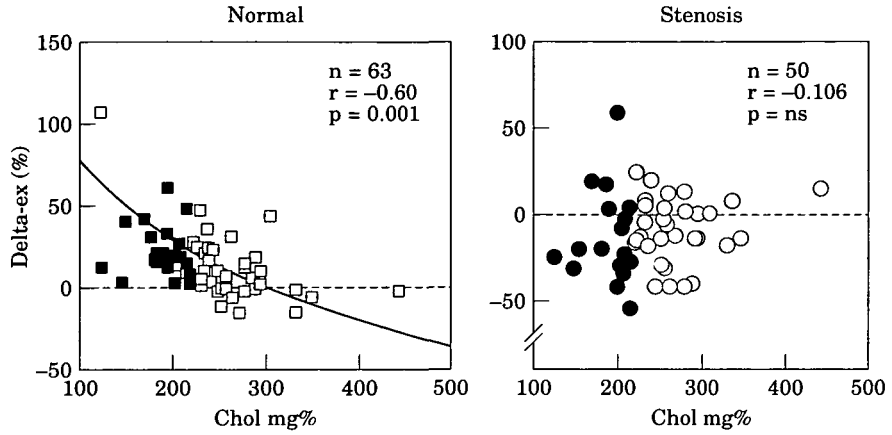

Figure 3 **An inverse correlation is found between total serum cholesterol and exercise-induced vasomotion of angiographically normal but not of stenotic coronary artery segments. Chol=total serum cholesterol; delta-Ex=percent change of cross-sectional luminal area. Solid symbols=normal serum cholesterol; open symbols=elevated serum cholesterol.**

hypercholesterolaemic patients compared to normal subjects. They concluded that hypercholesterolaemia in the absence of atherosclerosis is associated with abnormal function of the vascular endothelium. Thus, abnormal coronary vasomotion in patients with hypercholesterolaemia[43,47] may not necessarily be associated with overt atherosclerosis. Thus, two-different mechanisms of hypercholesterolaemia in the pathophysiology of coronary artery disease must be postulated: (1) a direct (toxic?) effect of oxidized LDL-cholesterol on the endothelium (functional disorder) and (2) a chronic effect inducing structural changes of the vessel wall.

Hypertension

High blood pressure has a direct effect on the arteries which is characterized by structural changes of the vessel wall such as media hypertrophy, increase in endothelial cell volume, microvascular rarefication, and augmentation of the extracellular matrix[48–51]. These changes may lead to impaired endothelium-dependent relaxation[52,53]. In hypertensive patients with angiographically documented coronary artery disease, Frielingsdorf *et al.* found a markedly blunted vasodilatory response of non-stenotic vessels compared with normotensive control subjects[54] (Fig. 4). Furthermore, reduced coronary vasodilation of normal coronary arteries was found in response to exercise, whereas endothelium-independent vasodilation to nitroglycerin was maintained in hypertensive patients. This suggests a preserved function of the vascular smooth musculature but a primary defect of the 'normal' epicardial coronary arteries in hypertensive patients with coronary artery disease. Alterations of endothelial function are probably a consequence rather than a cause of high blood pressure, and hence the degree of endothelial dysfunction and its mechanism change with increasing severity and duration of hypertension. In animal models with antihypertensive treatment, reductions of blood pressure are able to reverse endothelial dysfunction[55,56], although the exact mechanism is not fully understood.

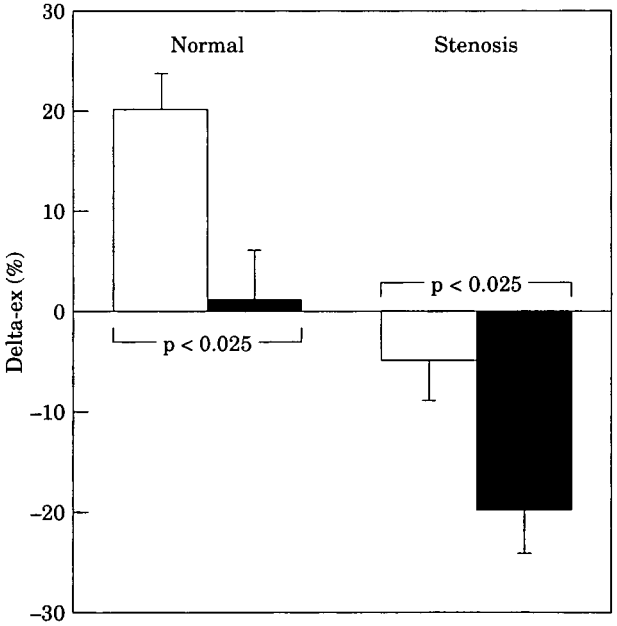

Figure 4 **Luminal area change during exercise of normal and stenotic coronary arteries in hypertensive patients (■) and normotensive control subjects (□) with coronary artery disease. Values are mean ± SEM.**

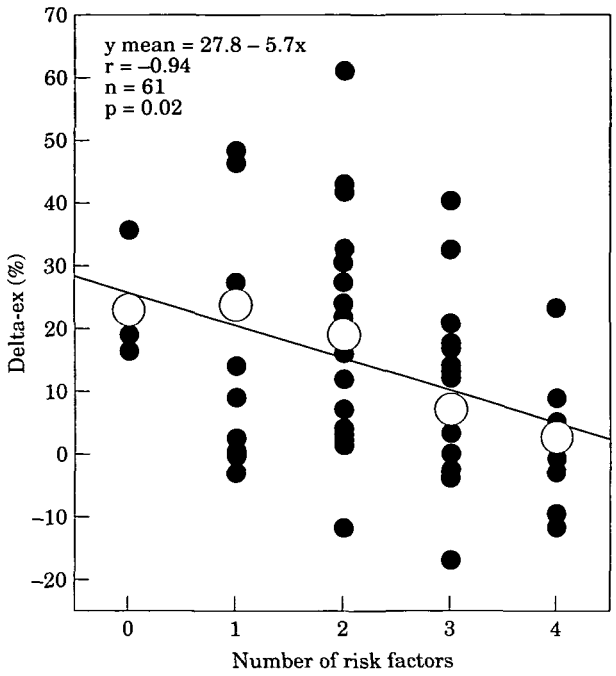

Figure 5 **There is a significant, inverse correlation between the number of cardiovascular risk factors (horizontal axis) and mean exercise-induced percent change in coronary luminal area (delta-ex, %; vertical axis). ○=mean delta-ex (%).**

Other coronary risk factors

Although hypercholesterolaemia and hypertension have been identified as major risk factors for endothelial dysfunction, several additional coronary risk factors are known to be responsible for impaired coronary vasomotion. Long-term cigarette smoking has been found to be associated with impaired endothelium-dependent coronary vasodilation regardless of the presence or absence of coronary atherosclerotic lesions[57]. A significant inverse correlation has been reported between the mean exercise-induced vasomotor response and the number of coronary risk factors[43], such as hypercholesterolaemia, hypertension, family history, obesity and smoking, indicating that the accumulation of different risk factors show an additive (adverse) effect (Fig. 5)

Vascular remodelling

The basis for the development of atherosclerosis is damage to the arterial endothelium with accumulation of lipids, adhesion of monocytes, and platelet aggregation. Release of various growth factors leads to the migration and proliferation of smooth muscle cells[58]. An accelerated form of this process can be induced by a denuding, deep endothelial injury as it often occurs during percutaneous transluminal coronary angioplasty, in patients undergoing coronary bypass grafting, or by an immune injury such as in patients undergoing heart transplantation[59].

A direct relationship between left ventricular muscle mass and coronary dimensions has been reported in experimental animals and clinical studies[60–66]. As a regulatory mechanism for this increase in vessel dimensions, blood flow velocity has been postulated. An increase in mean flow velocity has been associated with a change in shear stress, which has been shown to be a mediator for the release of EDRF, i.e. nitric oxide. In low and moderate grades of left ventricular hypertrophy, an appropriate increase in coronary artery size was reported, whereas in severe left ventricular hypertrophy an inappropriate growth of the coronary arteries with a reduction in cross-sectional vessel area per 100 g muscle mass was described in primary[67] as well as in secondary[67,68] left ventricular hypertrophy. In severe hypertrophy the coronary arteries seem to be too small for the increase in left ventricular muscle mass as a result of inadequate growth of the coronary arteries. Furthermore, impaired vasodilator capacity of the epicardial coronary arteries in patients with secondary left ventricular hypertrophy has been reported previously[69]. This has been attributed to an increase in resting flow. Although the size of the coronary arteries is not a limiting factor for myocardial perfusion, functional adaptation via the release of EDRF seems to be inadequate in severe hypertrophy. Insufficient growth of the coronary arteries has been observed in severe left ventricular hypertrophy[70] and, thus, may explain the occurrence of myocardial ischaemia under high demand situations such as exercise. The exact control mechanism of the coronary growth is not completely understood, but may involve several factors, such as structural (vascular remodelling) and functional (endothelial dysfunction) changes[67].

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