Squeezing tubes: a case of remodeling and regulation: Coronary reserve in hypertensive heart disease

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1. Introduction

Essential hypertension is a main risk factor for left ventricular hypertrophy (LVH), ischemic heart disease and hypertensive cardiomyopathy [1]. In addition to the increased prevalence of atherosclerotic stenoses in epicardial arteries, hypertensive subjects with no relevant coronary artery disease or LVH have impaired coronary vasodilator reserve [2,3] that has been reported to correlate with scintigraphic evidence of myocardial ischemia [4].

Impaired coronary reserve could be an important factor for inadequate delivery of oxygen and substrate to myocytes, precipitating myocardial ischemia and contributing to deterioration of myocardial function [2–4]. The potential mechanisms of impaired coronary reserve include abnormal processes of contraction and relaxation of a structurally remodeled myocardium, increased extravascular compressive forces, rheologic factors, metabolic factors as well as functional and structural alterations of the intramyocardial coronary arteries and arterioles (Fig. 1). The purpose of the present review is to discuss the pathophysiologic mechanisms that may be involved in reduced vasodilator capacity in human hypertensive heart disease and to report about therapeutic interventions.

2. Physiological conditions of coronary circulation

In the coronary venous blood, oxygen content is about 5 ml/100 ml, which corresponds to about 25–30% saturation and a $p_{O_2}$ of 18–25 mm Hg. Thus, given significant oxygen extraction, any relevant additional oxygenation can only be made available by a proportional increase in coronary blood flow. The normal heart can increase its blood flow by a factor of 4 to 5 [2–5]. Coronary autoregulation enables the heart to keep coronary flow unchanged over a wide range of perfusion pressures (from ~50 to 120 mm Hg) (review [5,6]). This is reflected by a pressure–flow relationship with a central portion running parallel to the pressure axis that is followed by a steep increase in flow at higher perfusion pressures (Fig. 2). If, however, coronary vessels are maximally dilated then such autoregulation is lost and a steep, almost linear pressure–flow relationship results for a wide range of perfusion pressure. On the side of low inflow pressures (<40 mm Hg), pressure–flow curves in the maximally dilated state may become curvilinear due to discharge of vascular capacitance [6], and here the intercept with the pressure axis defines ‘back pressure’, reflecting the combined effects of extravascular myocardial compression and intraventricular pressure [5,6]. Coronary autoregulation is affected by metabolic, myogenic, vascular, adrenergic and neural factors as well as tissue pressure [2,6–9]. Regional differences in pressure and flow exist within the myocardium, where pressure is higher in the subendocardium than in the subepicardium, which is associated with an increased metabolic demand and a greater coronary blood flow (endo/epi ratio 1.1–1.4); but during vasodilatation (metabolic/tachycardic/pharmacological) the endo/epi ratio may be dramatically inverted with a relative under-perfusion of the subendocardium [10].

The coronary flow reserve is defined as the maximal coronary flow [5] above its resting level at a given perfusion pressure when coronary vasculature is maximally dilated. Small differences in perfusion pressure can produce big differences in coronary flow reserve, thus comparisons at different basal conditions of pressure are difficult to make. Minimal coronary resistance is represented by the inverse of the slope of the maximally dilated pressure–flow curve, thus minimal coronary resistance can be used to describe the state of ‘maximal coronary dilation’ [2,5]. In particular, minimal coronary resistance correlates with the cross-sectional area of intramyocardial resistance vessels, reflecting the structural component of coronary vasodilator capacity [7].

A reduced coronary reserve has been reported in hypertensive patients with and without LVH even in the...
absence of coronary stenosis, in response to increased metabolic demand (atrial pacing [11] and to pharmacological stimulation testing non-endothelial (e.g. papaverine [4,12], less specifically dipyridamole [2,11]) or endothelial vasodilator capacity (e.g. acetylcholine [13]).

2.1. Metabolic, myocardial and extravascular compressive factors, limiting coronary reserve in hypertension

Increased myocardial oxygen consumption, caused by an increase in LV-wall stress, tachycardia or other metabolic stimulation (e.g. hyperthyroidism) leads to a limitation of coronary reserve by increased diastolic coronary flow at basal conditions and thus to an upward shift of the coronary autoregulatory curve [2,14]. In normal hearts, coronary flow reserve was found to be unaltered within a mean blood pressure range from 95 to 130 mm Hg, further increase in blood pressure led to an exhaustion of coronary reserve [14]. With increasing age but independent of gender, baseline myocardial blood flow is augmented with an age-related increase in cardiac work, while minimal coronary resistance is in the normal range [15]. An augmented autoregulatory coronary flow curve due to increased metabolic demand is also found in the dilated ventricle as LV wall stress is increased according to the law of Laplace [2]. Furthermore, systolic impedance to coronary flow has been reported to correlate with contraction and contractility rather than with the level of systolic wall stress [16], contributing to impaired coronary reserve. LVH should not be considered per se to be associated with a reduced coronary reserve, as athletic training showed a normal coronary reserve in the presence of normal diastolic and systolic function (review [17]).

Coronary perfusion takes place mainly during diastole, thus left ventricular end diastolic pressure effects coronary blood flow particularly to the subendocardium and represents the main determinant of extravascular compressive forces and increased back pressure. Acutely or chronically increased preload, e.g. volume overload in the context of fluid retention either by endocrine, cardiac and/or renal causes, leads to increased end diastolic wall stress and consequently to a critical impairment of coronary blood flow, especially in the subendocardium of dilated ventricles. Impaired relaxation and an even more reduced distensibility of the ventricle either by concentric ventricular remodeling and/or increased wall stiffness (e.g. interstitial remodeling by collagen accumulation=fibrosis) may contribute to elevated filling pressures [2,18]. This rightward shift of the end diastolic pressure–flow curve may be considered to place the myocardium in a potentially dangerous condition in the event of a critical reduction of perfusion pressure.

2.2. Architecture of the intramyocardial coronary vessels in hypertensive heart disease

Epicardial coronary arteries are mainly conduit arteries, whose diameters are in the range of 0.5 to 4 mm and represent only 5–10% of the total coronary length. In-
draining into venules and later venules. The capillary and venous system contribute together about 20% of coronary resistance [7,8].

In hypertensive heart disease pressure overload means a burden to the ventricle as well as to the coronary vasculature that has several potential consequences for the coronary circulation: (1) resistance vessels, capillaries, perivascular interstitium and myocytes are liable to suffer damage by hyperperfusion and insolation of plasma proteins, (2) arterial vascular walls are under increased shear and wall stress, (3) hypertrophy of myocytes leads to an increased distance between parallel orientated arterioles and capillaries (relative rarefaction). A diminished lumen size, by wall thickening of arterioles is a potential mechanism to normalize increased pressure in the capillary bed. Thickening of the walls of resistance vessels can be due to an increase in the number (hyperplasia) or the diameter of smooth muscle cells (hypertrophy) in the media, both increasing the cross sectional area of the media (hypertrophic remodeling) or merely by a reorganisation of smooth muscles without increased wall area (eutrophic remodeling) (review [19]). Furthermore, it has to be kept in mind that every increase in media/lumen ratio is associated with an impaired vasodilator capacity for geometrical reasons and leads to a more pronounced lumen reduction at a comparable circumferential contraction of smooth muscle cells.

An increased media/lumen ratio of intramural resistance vessels has been reported in experimental [10,20] as well as clinical studies [21] of hypertension that was found to be associated with an impaired coronary reserve. To assess the structural component of coronary reserve, non-endothelial dependent vasodilation has to be tested. Papaverine quickly relaxes vascular smooth muscle cells for a short period. Its use is limited to intracoronary administration and may induce higher coronary blood flows than under adenosine or after dipyridamole. It should be considered that in experimental studies mainly vasodilation of small arteries and clinically some toxic effects have been reported. Dipyridamole inhibits adenosine uptake and metabolism in erythrocytes. Adenosine dilates arterioles by binding to purinergic receptors and causing vasodilation by activating adenylate cyclase. Adenosine and dipyridamole cause more dilation of smaller (20–40 μm) than larger arterioles (80–150 μm) and have a greater influence on subendocardial than subepicardial arterioles [8]. Administration can be carried out intravenously, but it has to be kept in mind that in some patients with hypertensive LVH, high dose dipyridamole (i.v.) or adenosine may cause a further reduction in coronary resistance [15,17]. An additional endothelial component, following the increased blood flow after arteriolar vasodilation, induced by adenosine, has been found experimentally in small arteries (reviews [8,9,22]), but in a clinical study, the inhibition of nitric oxide (NO) synthesis by intracoronary L-NMMA did not attenuate maximal coronary blood flow [23].

Fig. 2. With intact autoregulation (A) and in the presence of maximal vasodilatation (D) there is nearly constant flow in a wide range of perfusion pressure. The differences between the curves indicate coronary flow reserve (R) for a given perfusion pressure. Minimal coronary resistance is obtained from the inverse of the slope of the maximally dilated pressure–flow curve. The intercept with the pressure axis defines back pressure. In hypertensive heart disease the slope of maximally dilated curve is reduced, indicating an impaired vasodilator reserve due to increased minimal coronary resistance. Vascular and myocardial factors reduce the slope of maximally dilated curve, while extravascular compressive force additionally influence back pressure and shift in the curve to the right. Metabolic factors increase resting flow and lead to an upward shift of the auto-regulated curve, that also reduces coronary reserve (adapted from [5,6]).
Growing evidence suggests that structural remodeling of the vasculature is caused by the interrelationship between mechanical stretch (vascular wall stress), shear stress, hormonal stimulation, metabolic factors and growth factors that are independently regulated from cardiomyocytic hypertrophy [18–20,24]. In particular, the renin–angiotensin system seems to be involved [18,20]. Besides the involvement of resistance vessels, hypertensive perfusion was reported to decrease capillary density and to increase heterogeneity of distribution of capillaries (review [7]). As intramural resistance vessels contribute more to the arterial venous pressure drop than capillaries, increased media/lumen ratio of intramural arterioles has to be considered the most relevant structural vascular mechanism contributing to an impaired coronary flow reserve.

2.3. Endothelial function in the coronary microcirculation

Endothelial cells produce and release both vasodilator and vasoconstrictor factors (review [25]). The major factor modulating vasodilatation is NO produced from L-arginine by NO synthase [23,26]. NO is continuously released from endothelial cells and basal release into coronary circulation can be increased severalfold by various stimuli, such as acetylcholine, bradykinin, substance P, histamine, serotonin and most importantly by flow (shear stress). NO is the main regulator of coronary tone, predominantly of conduit arteries, and smaller intramyocardial arteries.

To assess endothelial function, acetylcholine is administered directly into the coronary artery, which leads to a dose-dependent increase in coronary blood flow, mediated by the endothelium via NO and associated with an almost homogeneous vasodilatation along the whole length of intramyocardial vessels (review [8]). In patients with hypertension an impaired increase in coronary blood flow or even a paradoxical vasoconstriction have been reported, indicating endothelial dysfunction that may even precede impaired non-endothelial vasodilator capacity [25]. Furthermore, endothelial dysfunction of the coronary microcirculation could be a precursor of epicardial coronary artery disease. The potential pathophysiological mechanisms of a dysfunctional endothelium include inadequate NO formation in response to flow and shear stress. Apart from a reduced synthesis [26], the bioavailability of NO may be limited because of an exaggerated breakdown of NO, e.g. by oxygen derived radicals. In addition the sensitivity of vascular smooth muscle to NO might be reduced or vasoconstrictor substances such as endothelin and endothelium derived hyperpolarizing factor may over-ride the basal endothelium derived NO release [19,25,26].

Furthermore, the interdependence of structural alterations and endothelial dysfunction is unclear. In the presence of remodelled intramyocardial resistance vessels even an overproduction of vasodilator substances could be still insufficient in relation to wall thickness or an imbalance of vasodilators in comparison to increased vasoconstrictors (e.g. endothelin) could be causative for the impaired vasodilator reserve.

2.4. Antihypertensive therapy and coronary microcirculation in man

Cardioreparation in terms of improvement of coronary circulation is an important clinical aim to reduce the ischemic burden of the hypertensive myocardium and thus the potential consequences of ventricular remodeling and failure [2,18]. Clinical studies have demonstrated the effectiveness of long-term antihypertensive treatment on regression of LV mass, but very few reports evaluated the effects of antihypertensive drugs on myocardial perfusion.

Lowering of abnormally augmented systolic wall stress and consequently a reduction in metabolic demand shifts the autoregulatory curve down, resulting in an augmented coronary reserve. Furthermore, reduction of filling pressures and extravascular compressive forces improves diastolic subendocardial blood flow. Nevertheless, acute antihypertensive treatment may differ in respect to coronary blood flow. Calcium antagonists of the dihydropyridine type increase coronary blood flow [27] while minimal coronary resistance is lowered. Beta blockers mainly act by a reduction in metabolic demand, while minimal coronary resistance is not reduced. The acute effect of the diuretic furosemide was followed by a significant reduction in coronary sinus blood flow and an increase in coronary resistance that was interpreted by the activation of the renin–angiotensin system and its potential coronary vasoconstriction ability, correspondingly the application of the ACE-inhibitor captopril restored coronary blood flow and resistance to pretreatment values [28].

Especially long-term antihypertensive treatment should aim to improve coronary reserve by cardioreparative effects on the myocardium as well as on the coronary microcirculation. It was found that under therapy in hypertensive patients without left ventricular hypertrophy, coronary reserve was nearly normal, while it was significantly impaired in untreated patients without LVH and even more in untreated but also in treated patients with LVH [12]. After 6 months of treatment with verapamil, but not with enalapril, independent from changes in perfusion pressure and left ventricular hypertrophy, there was an increase in maximal coronary blood flow during pacing and under dipyridamole [11], while enalapril reduced the inhomogeneity of regional flow distribution. In a long-term study of 12 months with enalapril, left ventricular mass was significantly reduced and coronary reserve significantly improved caused by a lower minimal coronary resistance [29]. Similar findings were reported after the dihydropyridine calcium channel blocker isradipine [30]. Cardioreparation rather than acute effects of antihypertensive medication can be assumed and anti proliferative effects on smooth muscle cells of the resistance vessels as
well as regression of collagenous fibers in the vascular wall and the perivascular region have been discussed as both for ACE-inhibitors [18,20] and as for calcium channel blockers [11,30]. Nevertheless, time dependence of cardio-reparative effects is still unclear. Furthermore, it is difficult to differentiate between the influences of therapy on the myocardial factor (myocyte hypertrophy, myocardial fibrosis) as well as on vascular factors (media hypertrophy, eutrophic remodeling, vascular collagen, endothelial function).

Further investigations are necessary to understand the mechanisms of squeezing vascular tubes in hypertensive heart disease: remodeling of vessel wall and myocardial tissue and/or endothelial dysregulation as well as the effects of therapy need to be defined.

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References