



# Do we need to lower coronary resistances?

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## **Abstract**

The coronary blood flow (CBF) and thus coronary resistances are controlled by several factors including intramyocardial resistances related to systolic compression. Because left ventricular systole exerts a striking effect on left CBF, it is obvious that CBF will be reduced by factors such as tachycardia, or enhancement of left ventricular contractile force. Coronary resistances are under metabolic, endothelial, myogenic, and neurohumoral control. The vegetative nervous system has both vasoconstriction ( $\alpha$ -adrenergic and parasympathetic cholinergic) and vasodilatation ( $\beta$ -adrenergic) effects. Actually, under vasodilatation conditions, the major part of the coronary resistance is located at the capillary level. Therefore, the low myocardial capillary density observed in experimental models of hypertension and in patients is a major component of increased coronary resistance. Exercise training is associated with adaptations in the coronary microvasculature, including increased arteriolar densities and/or diameters and increased capillary density providing a morphometric basis for the observed decrease in coronary resistance in exercise-trained animals and patients. Several antihypertensive drugs have shown evidence of beneficial effects on myocardial microvascular densities and thus on coronary resistances. A combination of perindopril and indapamide has been tested in several experimental models and in hypertensive patients. Microvascular remodeling and resulting decreased coronary resistance were clearly evidenced in animals and in patients treated with a combination of perindopril/indapamide.

**Keywords:** Coronary reserve; coronary flow; capillary density; hemorheology; myocardial perfusion; pharmacology; vasodilatation.

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## **Main determinants of coronary resistance**

### **The blood**

Vascular resistance depends on blood viscosity. Hematocrit is the main determinant of viscosity [1]. In hypertension, hematocrit can be elevated; however, reports on this subject are not consistent: an increase in blood viscosity in hypertension could precede or follow blood pressure changes [2]. Viscosity may also be elevated by decreased cell deformability, as in long-term hyperglycemia, resulting in the formation of advanced glycation end products and thus stiffer red cells, or an increased tendency for cell aggregation. Leukocytes could also significantly contribute to blood viscosity; leukocytes provide approximately 20% of resistance to blood flow in skeletal muscle [3].



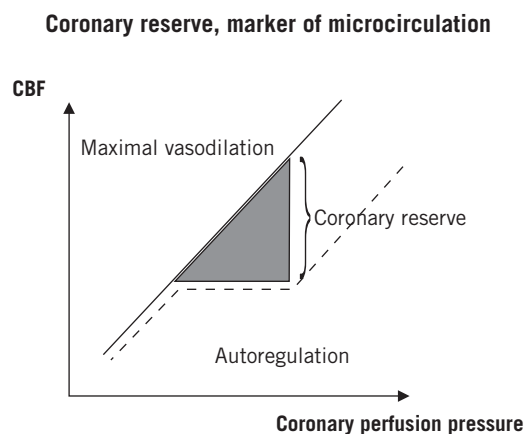


## NEW THERAPEUTIC APPROACHES - BERNARD I. LÉVY

### Perfusion pressure

Under maximal vasodilatation of the coronary bed, a direct relationship was observed between the coronary blood flow (CBF) and the effective perfusion pressure, or driving pressure (aortic pressure minus intraventricular pressure) (Figure 1). In control coronary bed, autoregulation, ie, a relative constancy of flow in the face of imposed changes in perfusion pressure, was observed. Autoregulation is most prominent (the CBF curve is nearly horizontal) at pressures between 40 and 160 mm Hg. At low pressures, maximal vasodilatation occurs, and with further reduction in pressure, blood flow falls off linearly with pressure, whereas at high pressures, the contractile force of the vascular smooth muscle is overcome by the intravascular pressure; the vessel become stretched to the limits of its elasticity and blood flow increases linearly with increments in pressure. Resting myocardial blood flow is linearly related to cardiac work. Therefore, when comparing different patients in the clinical setting it is important to correct resting myocardial blood flow for the main determinants of external cardiac workload, ie, as blood pressure and heart rate (rate-pressure product).

Three different mechanisms account for the autoregulation of CBF: tissue pressure, myogenic factors and metabolic factors. Tissue, ie, intramyocardial pressure, deserves more explanation because it is responsible for extravascular resistance. The heart is unique because it supplies the force necessary for its own blood supply, but it can also modify its blood supply by compression of the coronary vessels that course through the myocardium. Because left ventricular systole exerts a striking effect on left CBF, it is obvious that



**Fig. 1** Relationship between CBF and perfusion pressure under control and maximal coronary vasodilatation conditions. In the absence of large coronary stenosis, the maximal CBF reflects the conductance of the microcirculatory bed. CBF = coronary blood flow.

CBF will be reduced by factors such as tachycardia, in which the ratio of systole to cycle is increased (more time in systole), or enhancement of left ventricular contractile force, as with cardiac sympathetic stimulation or increased outflow resistance (greater vascular compression). Bradycardia or decreased left ventricular force or both will elicit an increase in CBF. In an arteriosclerotic coronary artery with a significant lumen stenosis, the coronary perfusion pressure distal to the flow-limiting stenosis could be critically low and below the autoregulatory range.

### Metabolic coronary vasoregulation

Any increase in cardiac contractile function and thus in metabolic activity causes dilation in arteriolar diameter. This dilation is largest in the smallest arterioles, and is thought to be mediated by the release of local metabolites; ie, interstitial concentration of adenosine, enhanced tissue osmolarity and tissue acidosis.

Under physiological conditions, perfusion is tightly matched to metabolic demand. This is achieved by modulating coronary vascular resistance through adjustment of vascular tone. This process is under metabolic, endothelial, myogenic, and neurohumoral control. In the presence of a pathological increase in vascular resistance, such as that resulting from a stenosis of an epicardial artery, regulatory mechanisms may become progressively exhausted and blood supply may fall short relative to demand, promptly resulting in myocardial ischemia as myocardial oxygen extraction can only slightly increase in ischemic conditions.

### Neurohumoral control of CBF

Coronary resistance vessel tone results from the addition of multiple vasodilator and vasoconstrictor influences, including neurohormones and endothelial and myocardial factors. Cardiac sympathetic nerve stimulation or epinephrine or norepinephrine produces coronary vasodilatation, often preceded by vasoconstriction. In the presence of a  $\beta$ -blocker, only vasoconstriction is observed, whereas, in the presence of a  $\alpha$ -blocker, only vasodilatation is observed. When both  $\alpha$  and  $\beta$ -blockers are administered, intracoronary epinephrine or norepinephrine is without effect on CBF.

Investigation of the effect of the vagus nerves on the coronary vessels provided divergent results attributable to the associated chronotropic and inotropic effects on the myocardium. In controlled experimental conditions (fibrillation, pacing...) vagus nerve stimulation produced



## NEW THERAPEUTIC APPROACHES - BERNARD I. LÉVY

a small to moderate increase in CBF, mimicked by the intracoronary injection of acetylcholine.

Drug-induced venodilatation (eg, by nitrovasodilators) will improve myocardial perfusion. Actually, the direct vasodilator effect of nitro derivatives on coronary resistance is rather small and the main effect on CBF is obtained by reducing left ventricular wall stress via preload reduction.

### How to increase CBF and myocardial perfusion

Traditionally, the identification and treatment of augmented coronary resistance have focused on obstructive atherosclerosis of the epicardial arteries. However, over the past two decades it has become increasingly apparent that augmented vascular resistance may also reside in the coronary microcirculation in a number of clinical conditions [4]. The general assumption among cardiologists is that myocardial ischemia occurs only in the presence of obstructive coronary artery disease. This is based on the misconception that abnormal coronary flow reserve is associated only with coronary stenosis and results from the increased resistance offered by the stenosis. When the normal coronary vasculature is maximally dilated, the capillaries (which do not have smooth muscle and hence do not vasodilate) are the bottleneck to hyperemic flow [5, 6]. Therefore, although the capillaries provide only a quarter of the total microvascular resistance (MVR) at rest, they offer three-quarters of the total MVR during hyperemia. Even in the presence of an epicardial luminal diameter stenosis of 85–90%, the attenuation of the hyperemic response, in abnormal or pathological conditions, is due mainly to the capillaries and not the stenosis itself.

At rest, the total MVR decreases in the presence of a non critical stenosis (depending on the degree of stenosis) because of autoregulation, ie, vasodilatation of pre capillary arterioles, with no change in capillary resistance. During hyperemia, the coronary artery pressure distal to the stenosis decreases, leading to capillary de-recruitment to maintain a constant capillary hydrostatic pressure [7]. Therefore, unlike the normal coronary circulation in which total MVR decreases during hyperemia, in the presence of a stenosis, it increases. In this situation, because arteriolar and venular resistances are already minimal, the increase in MVR is due to increased capillary resistance caused by de-recruitment, making it the predominant component of the total MVR.

Exercise training is the most physiological and probably the more efficient way to improve the coronary cir-

ulation network [8]. Exercise is associated with adaptations in the coronary microvasculature including increased arteriolar densities and/or diameters, providing a morphometric basis for the observed increase in peak CBF rates in exercise-trained animals. The formation of new capillaries maintains capillary density at a level corresponding to the degree of exercise-induced physiological myocardial hypertrophy. Maintenance of  $\alpha$  and  $\beta$ -adrenergic tone in the presence of lower circulating catecholamine levels appears to be due to increased receptor responsiveness to adrenergic stimulation. Training augments endothelium-dependent vasodilatation throughout the coronary microcirculation. This enhanced responsiveness appears to result principally from an increased expression of nitric oxide (NO) synthase. Finally, physical conditioning decreases extravascular compressive forces at rest and at comparable levels of exercise, mainly because of a decrease in heart rate. The coronary collateral system embodies a dynamic network of interarterial vessels that can undergo both long and short-term adjustments that can modulate blood flow to the dependent myocardium. Long-term adjustments, including recruitment and growth of collateral vessels in response to arterial occlusion, are time dependent and determine the maximum blood flow rates available to the collateral-dependent vascular bed during exercise. Rapid short-term adjustments result from active vasomotor activity of the collateral vessels. Mature coronary collateral vessels are responsive to vasodilators such as atrial natriuretic peptide, and to vasoconstrictors such as vasopressin, angiotensin II, and the platelet products serotonin and thromboxane A<sub>2</sub>. During exercise,  $\beta$ -adrenergic activity and endothelium-derived NO and prostanoids exert vasodilator influences on coronary collateral vessels. Importantly, alterations in collateral vasomotor tone, eg, by exogenous vasopressin, inhibition of endogenous NO or prostanoid production, or increasing local adenosine production, can modify collateral conductance, thereby influencing the blood supply to the dependent myocardium. In addition, vasomotor activity in the resistance vessels of the collateral perfused vascular bed can influence the volume and distribution of blood flow within the collateral zone. Finally, there is evidence that vasomotor control of resistance vessels in the normally perfused regions of collateralized hearts is altered, indicating that the vascular adaptations in hearts with a flow-limiting coronary obstruction occur at a global as well as a regional level. Exercise training does not stimulate growth of coronary collateral vessels in the

## NEW THERAPEUTIC APPROACHES - BERNARD I. LÉVY

normal heart. However, if exercise produces ischemia, which would be absent or minimal under resting conditions, there is evidence that collateral growth can be enhanced. In addition to ischemia, the pressure gradient between vascular beds, which is a determinant of the flow rate and therefore the shear stress on the collateral vessel endothelium, may also be important in stimulating growth of collateral vessels.

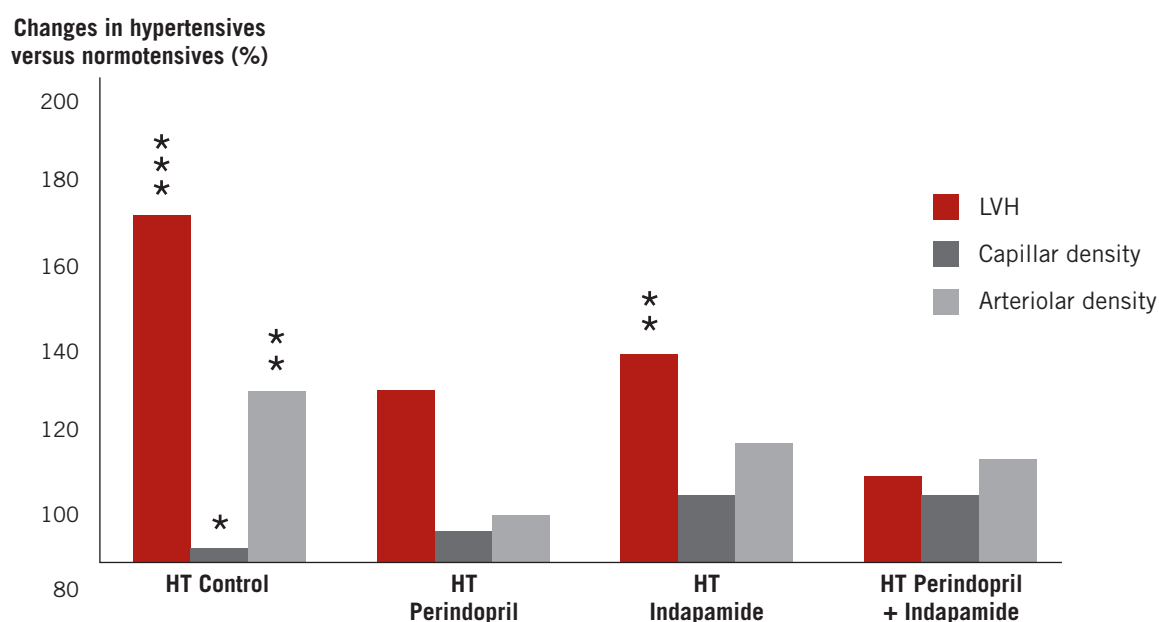
### Pharmacological interventions

We do not have many data showing evidence of the effects of drugs, especially antihypertensive drugs, on the CBF and resistance. Most of the data were obtained in animals or patients treated with an angiotensin converting enzyme (ACE) inhibitor and/or a diuretic (Figure 2). Rakusan and co-workers [9] evaluated the effect of treatment with the ACE inhibitor, perindopril, the diuretic indapamide, and a combination of the two on microvascular structure in hearts from stroke-prone spontaneously hypertensive rats. Young adult male spontaneously hypertensive rats treated with indapamide, perindopril, or both were compared with untreated animals after 8 weeks of treatment. Only perindopril alone or in combination with indapamide significantly decreased blood pressure and cardiac mass. Treatment also significantly increased capillary and cardiomyocyte densities; arteriolar density tended to decrease with treatments. Treatment with indapamide alone at this

dosage did not significantly influence most responses, but in combination with perindopril it strengthened the effect of perindopril. In the same way, we showed evidence of the effects of perindopril alone or in combination with indapamide in a Goldblatt model of renovascular hypertensive [10]. Coronary microvessel densities (arterioles and capillaries) were evaluated in sections of the left ventricular inner myocardium. After 4 weeks of hypertension, cardiac hypertrophy (+59%,  $P < 0.001$ ) was associated with a significant increase in myocardial arteriolar density (+27%,  $P < 0.01$ ), and a decrease in capillary density (+112%,  $P < 0.05$ ).

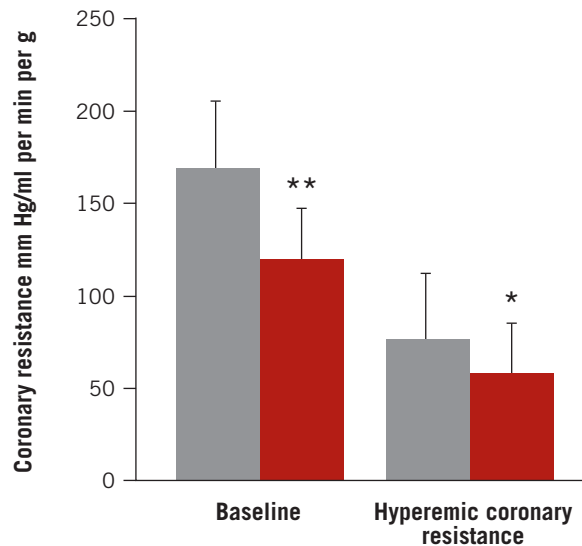
Treatment with perindopril alone prevented the increase in arterial pressure, heart weight, and arteriolar density, but did not significantly affect the coronary capillary density. Treatment with indapamide alone preserved normal capillary myocardial density, but did not significantly lower the blood pressure and only slightly reduced left ventricular hypertrophy. The combination of the drugs perindopril and indapamide resulted in normal level of arterial pressure and complete normalization of cardiac hypertrophy and arteriolar and capillary myocardial densities.

Mourad and co-workers [11] used positron emission tomography in a small group of young, uncomplicated hypertensive patients, and reported that the coronary reserve was decreased in all the hypertensive subjects at baseline compared with normotensive sub-



**Fig. 2** Changes in LVH, capillary density and arteriolar density in the left myocardial wall are expressed as percentage changes versus the normotensive control group. In the untreated hypertensive group there was a marked cardiac hypertrophy, and significant abnormalities in capillary and arteriolar densities. The combination of perindopril and indapamide normalized all three parameters: LVH and capillary and arteriolar densities. \* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ . HT = hypertension; LVH = left ventricular hypertrophy.

## NEW THERAPEUTIC APPROACHES - BERNARD I. LÉVY



**Fig. 3** Baseline and hyperemic coronary resistance at initiation (month 0, grey) and after 6 months of treatment (month 6, red).  $P^* < 0.05$  and  $P^{**} < 0.01$  month 0 versus month 6. Adapted from Neglia et al [12].

jects. After 6 months of therapy with a perindopril/indapamide combination, the coronary reserve was significantly improved and reversed to normal values.

More recently, Neglia et al [12] used a positron emission tomography protocol for measuring myocardial blood flow at rest and after maximal vasodilatation induced by intravenous dipyridamole (0.56 mg/kg) in 20 hypertensive patients with left ventricular hypertrophy. Blood pressure, left ventricular mass index and myocardial blood flow were measured at baseline and after 6 months of treatment with perindopril plus indapamide. Treatment decreased blood pressure ( $161 \pm 10/96 \pm 5$  to  $136 \pm 12/81 \pm 6$  mm Hg,  $P < 0.0001$ ) and left ventricular mass index ( $93 \pm 16$  to  $85 \pm 17$  g/m<sup>2</sup>,  $P < 0.01$ ) while increasing baseline ( $0.69 \pm 0.13$  to  $0.88 \pm 0.36$  ml/min per gram,  $P < 0.05$ ) and maximal myocardial blood flow ( $1.42 \pm 0.32$  to  $1.94 \pm 0.99$  ml/min per gram,  $P < 0.05$ ) (Figure 3).

Maximum myocardial blood flow and minimal coronary resistance improved significantly after treatment, but these changes were not correlated with a reduction in blood pressure or left ventricular mass. These findings suggest that the favorable effects of perindopril/indapamide on coronary flow are more related to reverse remodeling of coronary arterioles and an increase in capillary density than to changes in hemodynamic parameters or cardiomyocyte mass.

Improvements in endothelial function might have contributed to the increase in resting and maximal myocardial blood flow through a better regulation of rest-

ing coronary tone and a more appropriate response to changes in shear stress. Overall, the authors found a significant inverse relationship between hyperemic coronary flow and arteriolar medial area. Indapamide alone, however, led to a similar reduction in medial area, but had no effect on coronary flow, supporting the hypothesis that perindopril may increase myocardial blood flow not only by promoting reverse remodeling of the coronary microvessels, but also by improving endothelial function.

### Conclusions

In conclusion the clinical and animal data demonstrate consistently that treatment with perindopril/indapamide is associated with improved myocardial perfusion. Animal data demonstrate that the improvement in coronary flow is associated with reverse remodeling of intramural coronary arterioles and with increased myocardial capillary density. •

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