Myocardial perfusion and coronary microcirculation: From pathophysiology to clinical application

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The clinical use of radioisotopes in the evaluation of patients with ischemic heart disease is largely based on noninvasive methodology suitable for visualizing myocardial perfusion. Although contrast echocardiography and magnetic resonance imaging have been proposed recently for the same purpose, at present most of the noninvasive tests for assessing myocardial perfusion reside in nuclear cardiology. The most popular radioactive flow tracers are characterized by a rapid myocardial extraction followed by either a sequestration (for technetium 99m–labeled agents) or a very slow washout (for thallium 201). These features make the tracer uptake proportional to blood flow in each myocardial region, but the quantitation of absolute flow is not possible with these techniques. Despite this limitation, myocardial perfusion can be imaged and underperfusion can be detected as a relative uptake defect compared with the better perfused myocardium. As "significant" coronary stenosis regionally impairs flow reserve, myocardial perfusion imaging has become a common tool for the diagnosis of coronary artery disease and coronary angiography the gold standard for defining its sensitivity and specificity.

This review will not discuss the diagnostic accuracy of myocardial perfusion scintigraphy in detecting coronary stenosis, but rather the significance of perfusion imaging in the light of recent research documenting the presence of coronary microvascular alterations in various heart diseases and will focus on possible pathophysiologic mechanisms.

MYOCARDIAL BLOOD FLOW REGULATION: MORE PLAYERS FOR AN INTEGRATED TUNING

Because of the aerobic nature of myocardial metabolism and the high baseline oxygen extraction, a close linear relationship exists between myocardial oxygen consumption and flow. This relationship has been recognized for many years, and thus far, myocardial metabolism has been considered the most powerful determinant of coronary vasomotor tone. Because of its tissue origin, the metabolic signal is thought to affect the most distal portion of the coronary arterial tree only. This is in agreement with the high sensitivity of vessels smaller than 200 μm in diameter to adenosine, one of the most powerful putative metabolic mediators.[1] Thus the isolated vasodilation of these arterioles has been thought to be responsible for the physiologic large excursion in coronary flow to up to 5 to 6 times resting values. Such an increase in flow has no effect on distal vascular pressure provided that no appreciable resistance is present in the upstream vascular segments. This crucial assumption has been challenged by Chilian et al,[2,3] who documented a pressure drop of roughly 30% in small upstream arteries under baseline conditions as well as under maximal vasodilation induced by dipyridamole. Theoretically, the presence of such a resistance not accessible to metabolic control has two major implications. First, metabolic vasodilators could not decrease the global coronary resistance below the value of the more proximal vasculature—ie, about 30% of baseline in contrast to the 20% to 17% corresponding to the 5 to 6 times increase in flow. Second, because of Hagen Poiseuille's Law, any change in flow through proximal segments with a "fixed" resistance would call for reciprocal changes in intravascular pressure including the capillaries. This phenomenon would profoundly affect microvessel patency distribution and exchange of water and solutes between intravascular and extravascular space because of changes in Starling forces.[4]

These considerations suggest that the distal metabolic signal needs to be spread to more proximal segments of the coronary vascular tree in order to maintain the capillary pressure constant. In agreement with this hypothesis, several sets of data indicate that different mechanisms operate in different microvascular segments and that their interaction can provide integrated control of both blood flow and pressure in the coronary microcirculation.[5] The pathways of signaling within the microvascular network still remain largely unknown; however, the endothelial control of flow velocity seems to play an important role. Along this line, the increased shear stress, due to distal vasodilation and augmented

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flow, induces the release of nitric oxide, which vasodilates the more proximal vascular segments. This mechanism amplifies the resistance response to changes in metabolic demand and represents a feedback pathway, which allows blood flow changes without affecting capillary pressure.[5]

ENDOTHELIAL DYSFUNCTION AND MYOCARDIAL PERFUSION IMAGING

To the best of our knowledge, an altered microcirculatory sensitivity to metabolic vasodilators has never been described in human heart disease. Conversely, a specific alteration of coronary endothelial function has been found in patients with different diseases such as atherosclerosis,[6] dilated cardiomyopathy,[7] and arterial hypertension.[8] However, the relevance of endothelial dysfunction to physiologic flow control has not been directly documented. Accordingly, coronary artery stenosis is still considered the only factor able to affect coronary blood flow regulation in a relevant fashion during daily life.

Nevertheless, previous considerations suggest that the endothelium is an important factor in the integrated response of flow, even to agents affecting vasomotor tone, through direct action on smooth muscle cells. In fact, the lack of the endothelial contribution might limit the effect of endothelium independent agents on flow. Several studies have actually documented abnormal flow responses to dipyridamole or atrial pacing in the myocardium supplied by angiographically normal coronary arteries in patients with dilated cardiomyopathy[9] or arterial hypertension[10] and even in patients with remote stenosis (ie, on other coronary arteries).[11]

Thus far, the link between reduced vasodilator response and endothelial dysfunction has not been tested directly. However, the coincidence of both abnormalities in populations with various heart diseases suggests their possible association in the same patient and thus a potential pathophysiologic link between the two. With regard to myocardial perfusion imaging, the reduction in maximal flow capacity due to microvascular alterations causes a reduction in perfusion differences between territories perfused by angiographically normal and stenotic vessels during vasodilator stress,[11] thus explaining the relative decrease in sensitivity of myocardial perfusion scintigraphy in the detection of single-vessel coronary artery disease.[12] On the other hand, microvascular dysfunction might produce regional flow abnormalities per se, thus hampering the postulated cause-effect relationship between epicardial stenosis and perfusion defect. In agreement with this concept, Zeiher et al[13] demonstrated that coronary microvascular endothelial dysfunction was associated with a high incidence of reversible perfusion defects at stress myocardial perfusion imaging despite the absence of coronary stenosis. According to the traditional criteria, the abnormal scan results of these patients are considered to be "false positive." In contrast, this feature might represent an actual stenosis-independent abnormality in blood flow distribution rather than the effect of technical artifacts such as attenuation or partial-volume effect.

This concept seems of great relevance, as monitoring of microvascular function can also be used for assessing therapy efficacy. Gould[14] demonstrated that aggressive cholesterol lowering is able to reduce reversible perfusion defects induced by dipyridamole. Guethlin et al[15] showed that statin therapy improves myocardial blood flow response to adenosine independently of stenosis severity in the related vessel. The most striking feature of these findings is that the interventions thought to improve endothelial function actually improved the flow response to endothelial independent stimuli, underlining the relevance of the endothelium in the integrated tuning of vasomotor tone.

VASOMOTOR CONTROL DOWNSTREAM FROM A SEVERE STENOSIS

The myocardium supplied by a severely stenotic coronary artery can become ischemic under conditions of increased flow demand. This phenomenon is generally attributed to the additional resistance of epicardial obstruction limiting the increase in flow, despite maximal distal vasodilation. In contrast to this view, we clinically documented a progressive decrease in flow (ie, an increase in coronary resistance during atrial pacing), up to angina and ST-segment depression, in the territory supplied by a severely stenotic coronary artery. Intracoronary adenosine infusion, during pacing and ischemia, markedly decreased coronary resistance and in some cases abolished the electrocardiographic signs of ischemia without affecting systemic hemodynamics.[16] This finding suggests either an altered sensitivity of vascular tone to the metabolic signal or the presence of other factors affecting the metabolic control of coronary flow. In a second study, in which coronary blood flow response to cardiac pacing was monitored together with distal coronary pressure, the progressive decrease in flow during tachycardia was contrasted with a constant coronary pressure. Although this phenomenon was not affected by pretreatment with alpha-blockade, it fully disappeared after angioplasty.[17] These data led us to hypothesize that the coronary microvascular response to excessively low perfusion pressure could be a heterogeneous constriction, maintaining the driving pressure adequate for some vascular units while eliminating

others. This hypothesis could explain the documented heterogeneity of flow distribution during hypoperfusion, as well as the heterogeneous distribution of metabolic fingerprints of ischemia in tiny microareas of both inner and outer myocardial layers.[18]

To test this hypothesis and, in particular, to assess the relationship between coronary driving pressure and microvascular recruitment and derecruitment, in addition to measuring both the flow entering a myocardial territory and the distal coronary pressure, it would be necessary to assess the amount of tissue perfused. In an attempt to accomplish this difficult task, we measured blood flow entering the stenotic coronary vessel by the Doppler catheter while simultaneously measuring myocardial blood flow per unit of perfused tissue by the washout curve of xenon 133.[19] As the protocol was performed before and after coronary angioplasty, all parameters were respectively evaluated at low and high driving pressure. The study documented that the myocardial volume accessible to xenon markedly increased after angioplasty, being positively and linearly correlated with the increase in coronary driving pressure.[19]

These studies together point toward interactions between pressure and flow control in the microcirculation downstream from a severe stenosis. Modulation of vasomotor tone might be the result of the intrinsic control mechanisms of coronary circulation finalized not only to satisfy metabolic needs, but also to maintain driving pressure in a range of values high enough to perfuse vessels with relatively high opening pressure but low enough to prevent capillary damage. Pressure control might be as powerful as metabolic control and act in the same or in the opposite direction.

The additional resistance imposed by the epicardial obstruction represents an "amplifier" of the inverse relationship existing between flow and microvascular pressure. Under these conditions, the microcirculatory network might react to the excessively low perfusion pressure with a heterogeneous vasoconstriction, able to maintain pressure even by the exclusion of some vascular units.

These data have relevant implications with regard to the pathophysiology of dysfunctioning viable myocardium subtended by a severely stenotic coronary artery. Thus far, whether regional dysfunction is the result of chronic hypoperfusion (myocardial hibernation)[20] or of repetitive ischemic episodes (myocardial stunning)[21] is still being debated. Controversy mainly arises from conflicting results on myocardial blood flow, which has been found to be reduced in some studies but normal in others.

Differences in the methods used for the assessment of myocardial blood flow could provide an explanation for such a difference. Most studies using diffusible tracers such as inert gas washout reported normal flow values, whereas studies using deposit tracers, such as microspheres or technetium-labeled agents, reported a relatively high prevalence of resting perfusion defects in dysfunctioning segments. The same discrepancy holds even when the quantitation of flow is provided by positron emission tomography (PET). In fact, baseline myocardial blood flow was found to be normal in studies using O-15–labeled water but reduced in most studies using N-13 ammonia.

The effect of revascularization on resting blood flow is also intriguing. Measurements obtained through use of deposit tracers as well as intracoronary Doppler velocimetry[17] have consistently documented the increase in flow at different time intervals after revascularization, whereas data obtained by diffusible tracers have not.

This puzzling conflict can be solved by considering the kinetics of the different tracers. Water is freely diffusible between plasma and tissue, whereas ammonia is trapped in myocardial cells. Accordingly, flow is estimated by the analysis of washout rate with water and by the analysis of uptake with ammonia. Although these features are of limited relevance when flow is homogeneously distributed within the interrogated myocardial segment, they result in marked differences when flow is heterogeneous. Under these conditions, the amount of both ammonia and water reaching the myocardium is proportional to flow, being higher in high-flow areas and lower in hypoperfused areas. However, whereas measured ammonia uptake in a region of interest will reflect the mean flow in that region, the washout of water will mainly refer to the highly radioactive (perfused) regions (Figure 1).[22] As a result, water tends to overestimate flow with respect to ammonia.

Regional myocardial dysfunction often originates from the mixture of scarred and viable tissue, a condition paralleled by heterogeneous perfusion. Under these conditions, ammonia will provide mean flow in the nonperfused scar and in the normally perfused myocardium, whereas water will only (or mostly) trace flow to the residual perfused myocardium.[23] The concept of a histologic heterogeneity within dysfunctional myocardium is confirmed by much of the literature. However, the same differences between the two families of flow tracers will arise from histologic heterogeneity, as well as from flow heterogeneity in a histologically homogeneous myocardium. However, histologic heterogeneity does not fit with the flow improvement after revascularization, as scar tissue should not participate to perfusion. On the contrary, the finding of a pressure-mediated increase in perfused volume that we have documented after percutaneous transluminal coronary angioplasty[19] strongly supports the hypothesis of vascular derecruitment in dysfunctioning myocardium.

Should this hypothesis be confirmed, it would account for the discrepancy between the results obtained by

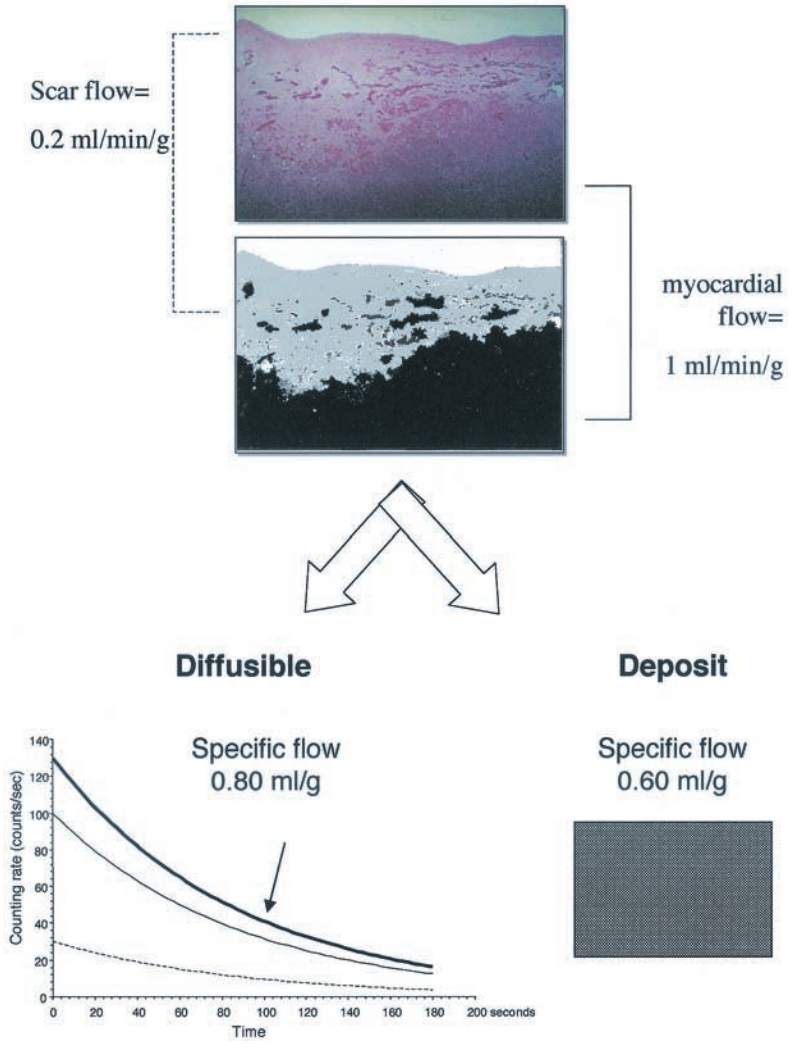

Figure 1. Heterogeneity of tissue and flow values obtained with diffusible or deposit tracers. Myocardial dysfunction often occurs in infarcted segments, characterized by a mixture of scar and viable tissue *(top panel).* Within the interrogated myocardial region, these tissues display different flows, as shown in the *middle panel* with underperfused scar (*gray area*, flow = 0.2 mL/min/g) and viable tissue (*black area*, flow = 1 mL/min/g). Under these conditions, deposit tracer provides the mean flow value between the two tissues *(right)*. By contrast, diffusible tracer washout will mostly reflect the highest flow, as a larger amount of tracer will be delivered to and washed out from the normoperfused area.

deposit versus diffusible tracers. The increase in the number of perfused vascular units after revascularization would lead to an increased flow within the territory, without necessarily affecting the flow in the single perfused vascular units and thus the washout rate of diffusible tracers.

CORONARY MICROCIRCULATION IN DILATED CARDIOMYOPATHY

It is commonly believed that primary cardiomyopathies are diseases of myocardial muscle with a relevant genetic component. Their phenotypical pattern is mainly characterized by structural and functional abnormalities of the myocytes leading to hypertrophy and/or progressive dilatation of heart chambers and heart failure. In this context, observed perfusion abnormalities in the absence of coronary artery disease are thought to be secondary to the structural and functional changes in the myocardium.[24]

In the presence of either severe myocardial hypertrophy or severe ventricular dysfunction, many extravascular factors—such as increased but not adequately vascularized myocardial mass and/or increase in ventric-

ular filling pressure in hypertrophic cardiomyopathy[25] or increase in wall stress in dilated cardiomyopathy[26]—may affect myocardial perfusion. Moreover, a reduction in myocardial contractility may also cause a decrease in energy demand with matched downregulation of resting myocardial blood flow.[27]

More recent studies have hypothesized that, in addition to extravascular factors, structural and functional abnormalities may primarily involve the coronary microcirculation in these populations. It has been demonstrated that in hypertrophic cardiomyopathy, a reduction in coronary vasodilating capacity is not regionally correlated with hypertrophy.[28] In explanted hearts from patients with dilated cardiomyopathy, resting myocardial blood flow is severely depressed, but no relationship exists between the extent of reduced myocardial perfusion and the extent of myocardial fibrosis that involves no more than 20% of the myocardium.[29] Finally, regionality of perfusion abnormalities can hardly be explained by hemodynamic alterations, which should affect the different regions of the left ventricle equally.

In hypertrophic cardiomyopathy, as in hypertrophy secondary to hypertension, structural abnormalities of the small coronary vessels involving hypertrophy of the tunica media have been demonstrated[30] and are thought to be responsible for an intrinsic impairment of coronary microcirculatory vasodilatory capacity. In dilated cardiomyopathy, similar arteriolar structural changes could not be demonstrated. However, in the past few years, other evidence of functional alterations of the coronary microcirculation has been collected. Clinical studies have documented endothelial dysfunction of both coronary[7] and systemic microcirculation.[31,32] Endothelial dysfunction is able to strongly limit the coronary vasodilatory response to stress, creating the basis for ischemic functional and metabolic alterations. It is not clear, however, whether perfusion abnormalities occur in patients with dilated cardiomyopathy once heart failure is already established or at an earlier stage, possibly being responsible for progressive myocardial deterioration. Thus it is of particular interest to study patients in the early stage of the disease when ventricular dysfunction is associated with neither the hemodynamic nor the neurohumoral alterations typical of overt heart failure.[33] In many of these patients, abnormal values of myocardial blood flow have been found at rest and in response to increased cardiac work or after pharmacologic vasodilation, strongly suggesting coronary microvascular dysfunction.[9] With regard to the prognostic significance of such abnormalities, we have recently observed that the severity of coronary vasodilation impairment predicts deterioration of ventricular dysfunction and progression to overt heart failure (Figure 2).[34] The "microvascular ischemic hypothesis" as a potential cause of progressive

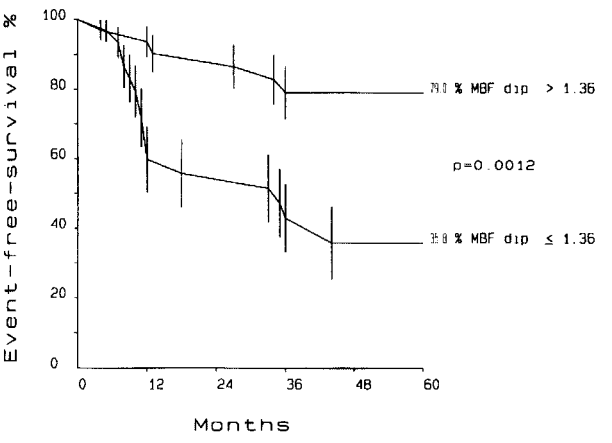

Figure 2. Kaplan-Meier event-free (cardiac death and development or progression of heart failure) survival curves obtained in 67 patients with idiopathic left ventricular dysfunction stratified according to the mean value of maximal myocardial blood flow *(MBF)* during dipyridamole *(dip)*. Patients showing dipyridamole MBF of 1.36 mL/min/g (median value in the whole population) at enrollment had a more severe prognosis, with a 35.8% event-free survival rate at 5 years. (Redrawn with permission from Neglia D et al. Circulation 2002;105:186–93).

ventricular dysfunction in dilated cardiomyopathy has been supported by recent studies showing that in these patients, in regions of dysfunctioning myocardium, depressed coronary vasodilation coexists with both increased glucose uptake[35] and reduced aerobic metabolism.[36] Actually, this particular "flow-metabolism mismatch pattern" associated with contractile dysfunction is considered the distinctive metabolic and functional marker of ischemia (Figure 3).

CORONARY MICROCIRCULATION IN ARTERIAL HYPERTENSION

In patients with arterial hypertension, reduced coronary vasodilating capability has been documented even in the absence of coronary stenosis.[37] To investigate the potential mechanisms responsible for reduced coronary flow reserve, its relationship with increased arterial blood pressure and structural myocardial and vascular changes has been studied.

In animal studies, increase in ventricular afterload is followed by hypertrophy of the myocytes, interstitial fibrosis, and vascular growth (generally inadequate for the increase in tissue mass).[38] The functional consequences of this process include left ventricular diastolic dysfunction, reduced coronary flow reserve, and subendocardial ischemia during stress.[39]

In patients with hypertension the reduction in coronary reserve has generally been attributed to myocardial hypertrophy.[40] However, in contrast to this finding, a

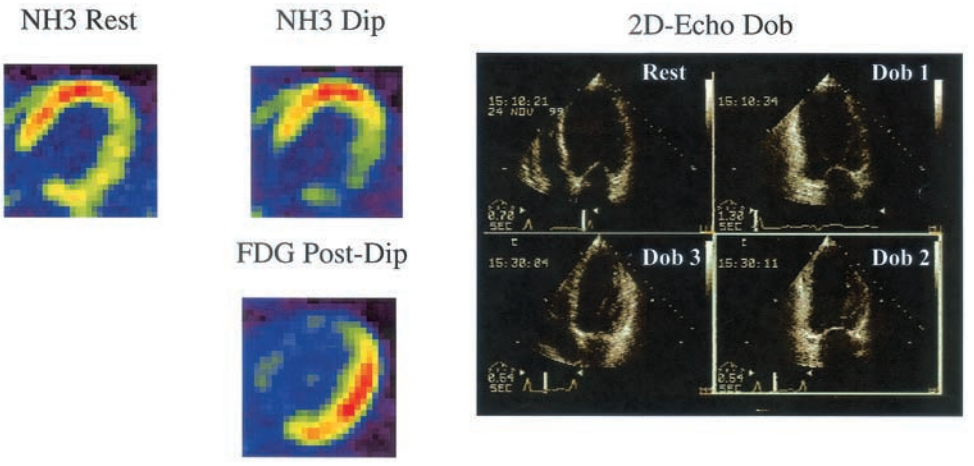

Figure 3. *Left,* Left ventricular myocardial transaxial slices obtained in a single patient with idiopathic left ventricular dysfunction by PET after injection of N-13 ammonia *(NH3)*, as flow tracer, at rest and after intravenous dipyridamole *(NH3 Dip)* and after injection of F-18 fluorodeoxyglucose, as glucose uptake tracer, 30 minutes after dipyridamole *(FDG Post-Dip)*. A regional perfusion defect involving the posterolateral wall of the left ventricle is evident at rest, which becomes more severe during dipyridamole. The same region shows increased glucose uptake (flow-metabolism mismatch pattern). *Right,* End-systolic 2-dimensional echocardiographic frames from the same patient, obtained in 4-chamber apical view at rest and during increasing doses of dobutamine (*Rest,* resting conditions; *Dob 1,* 5 μg/min; *Dob 2,* 10 μg/min; *Dob 3,* 20 μg/min). The posterolateral wall is akinetic at rest while showing preserved contractility at dobutamine testing.

reduction in coronary reserve has been documented even in hypertensive patients not affected by myocardial hypertrophy.[41] More recently, in a large population of patients with arterial hypertension and a variable degree of myocardial hypertrophy, no relationship could be demonstrated between myocardial mass and the extent of perfusion impairment.[42] Furthermore, regionality of perfusion abnormality in the presence of global and equally distributed ventricular hypertrophy stands against a cause-effect relationship between the two. Similarly, regionality hardly seems compatible with a leading role of hemodynamic factors in the pathogenesis of perfusion defects.

These observations suggest microvascular remodeling independent of myocardial hypertrophy, likely related to the hypertrophy of the tunica media of small resistance vessels.[43–45] On one hand, microvascular remodeling would protect the distal portion of the coronary arterial tree from excessive perfusion pressure; on the other hand, it would reduce microvascular cross section. However, functional abnormalities could also contribute to the impairment of myocardial perfusion. For example, impairment of the endothelium-dependent coronary vasodilation has been documented in patients with arterial hypertension.[8,46,47]

It is conceivable that the uncoordinated, abnormal myocardial, interstitial, and microvascular growth, together with the partial loss of intrinsic control of vascular tone, may act synergistically to cause repetitive episodes of ischemia regardless of the presence of coronary epicardial stenosis. Repetitive ischemia might cause myocardial functional deterioration, leading to ventricular dysfunction and heart failure over time. According to the above observations, the target of medical treatment has been modified in recent years to include not only the need for lowering blood pressure levels but also for inhibiting myocardial and vascular growth and restoring endothelial function.[10,32]

QUANTITATIVE REGIONAL MYOCARDIAL BLOOD FLOW IN SEVERE AORTIC VALVE STENOSIS

The prevalence of angina pectoris has been reported to vary from 50% to 70% of patients with severe aortic valve stenosis. However, only half of patients or fewer reporting angina show coronary lesions at angiography. As compared with arterial hypertension, aortic valve stenosis leads to the mechanical uncoupling of the aorta from the left ventricle with a relative reduction in coronary perfusing (aortic) pressure. In this instance, myocardial ischemia is thought to be the result of an excess in myocardial oxygen demand combined with the reduction in coronary blood supply, which is in turn attributed to inadequate perfusion pressure, microvascular structural changes, and/or increased extravascular compression.

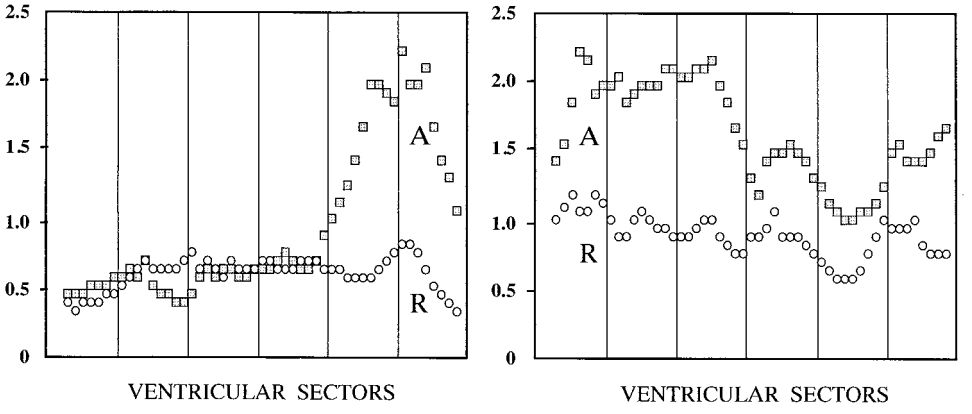

Figure 4. Flow profiles of one transverse section of the left ventricle obtained by PET and N-13 ammonia in 2 patients with severe aortic valve stenosis and normal coronary arteries, at rest *(R)* and after intravenous adenosine *(A)*. Flow profile encompasses 6 segments of the left ventricular wall (intervals between vertical lines in each panel), starting from the posterior septum *(left)* up to the posterior wall. Each profile is outlined by single flow values of adjacent radiants. Mean flow at rest *(circles)* is below normal values in the patient on the left but within normal values in the patient on the right. Following adenosine *(squares)*, a marked heterogeneity of perfusion and coronary flow reserve (the area between the two profiles) becomes evident in both patients. The pattern of adenosine flow profiles goes in an opposite direction in the 2 patients.

Few reports on myocardial perfusion in patients with aortic valve stenosis have been published. Scintigraphic studies have been focused on the role of myocardial scintigraphy in predicting the presence of coronary artery disease.[48–52] A more direct approach to investigate microcirculatory alterations was attempted by Strauer[53] and Tauchert and Hilger,[54] who measured flow per gram in the left ventricle at rest and after dipyridamole, using argon clearance, and found a marked reduction in coronary reserve. Marcus et al[55] measured coronary reserve during heart surgery using a Doppler probe positioned on the left anterior descending coronary artery. They found that reactive hyperemia was strikingly impaired. Finally, coronary flow was also measured by coronary sinus thermodilution; no correlation was found between angina and coronary reserve, whereas a significant correlation was found with "inadequate" left ventricular hypertrophy.[56,57]

Each of the methods used in the above studies has some limitations, which prevent a more exhaustive description of microcirculatory abnormalities. In fact, in order to answer the questions of whether microcirculatory derangement is a diffuse or rather a regional phenomenon and whether flow abnormalities are related to hypertrophy and its geometry, the quantitation of flow per gram of myocardium at rest and after maximal vasodilation, as well as its regional distribution, is required.

To obtain such information, we quantitatively assessed regional myocardial blood flow by use of PET in 14 consecutive patients with severe predominant aortic stenosis, left ventricular ejection fraction of less than 0.45, and normal coronary arteries at angiography. The mean aortic valve area was 0.8 ± 0.2 cm^2 and maximal transvalvular pressure gradient 87 ± 16 mm Hg. Six patients reported angina pectoris. N-13 ammonia was used as a flow tracer. Of the 7 cross-sectional planes, the 3 planes that best encompassed the left ventricle were used to generate flow profile curves. Mean basal flow in the entire population was not different from that reported in the normal population. Conversely, mean flow during adenosine was markedly reduced. When a cutoff of less than 15% for variation coefficient was used as an index of flow heterogeneity, 4 patients showed highly heterogeneous basal perfusion. During adenosine, heterogeneity became apparent in 7 of 14 patients. The pattern of heterogeneity was not uniform among patients. Figure 4 shows examples of a single slice in 2 patients with perfusion heterogeneity. Comparing the basal and adenosine flow profiles, these were parallel in 7 patients (regardless of profile pattern) and divergent in the remaining 7. Neither flow nor heterogeneity was correlated with ventricular hypertrophy and its distribution as detected by transesophageal echocardiography.

Thus, even in the clinical model of aortic valve stenosis, abnormalities in perfusion are frequently ob-

served. These do not necessarily reflect the presence of coronary stenosis and are the expression of microvascular alterations. Perfusion defects are not directly related to myocardial hypertrophy, and their regionality makes it difficult to attribute the pathogenesis to hemodynamic factors.

CONCLUSIONS

In the past 2 decades, enough evidence has been produced by different centers and by means of different methodologies to demonstrate the existence of coronary microvascular abnormalities in various cardiovascular diseases. Unfortunately, because of the technical difficulties in exploring coronary microcirculation, studies currently available on this subject are limited to relatively small groups of patients, preventing a definitive conclusion on the clinical relevance of peculiar microvascular alterations in each disease in terms of prevalence, incidence, and prognosis. Despite this limitation, available information strongly calls for caution in the binary attribution of perfusion abnormalities to coronary stenosis or, by exclusion, to technical artifacts. In this respect, it is now clear that perfusion defects secondary to microcirculatory dysfunction are frequent and indistinguishable from the defects commonly observed in ischemic heart disease, relative to regionality, extension, and severity.

With regard to the physiopathology of microvascular disorders, it should be considered that the models of coronary pathology in "healthy" animals, developed in the last half century, are largely inadequate for the reproduction of human pathology, in light of new acquisitions in the field of vascular and molecular biology. It appears evident that the classical model of coronary circulation suffers from oversimplification and that the regional increase in microvascular resistance observed in patients cannot simply be attributed to extrinsic factors such as hemodynamics or ventricular hypertrophy. Understanding the nature and significance of functional and structural intrinsic factors as they relate to human coronary pathology requires a greater research effort, primarily in clinical models.

References

1. 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;65:1296-305.
2. Chilian WM, Eastham CL, Marcus ML. Microvascular distribution of coronary vascular resistance in beating left ventricle. Am J Physiol 1986;251(4 Pt 2):H779-H788.
3. Chilian WM, Layne SM, Klausner EC, Eastham CL, Marcus ML. Redistribution of coronary microvascular resistance produced by dipyridamole. Am J Physiol 1989;256(2 Pt 2): H383-H390.
4. Landis EM, Pappenheimer JR. Exchange of substances through capillary walls. In: Hamilton WF, Dow P, editors. Handbook of physiology. Volume II, section 2. Circulation. Chapter 29. Bethesda: American Physiological Society; 1927. p. 961–1034.
5. Kuo L, Chilian WM, Davis MJ. Interaction of pressure- and flow-induced responses in porcine coronary resistance vessels. Am J Physiol 1991;261:H1706-H1715.
6. Chilian WM, Dellsperger KC, Layne SM, Eastham CL, Armstrong MA, Marcus ML, et al. Effect of atherosclerosis on the coronary microcirculation. Am J Physiol 1990;258: H529-H539.
7. Treasure CB, Vita JA, Cox DA, Fish RD, Gordon JB, Mudge GH, et al. Endothelium-dependent dilation of the coronary microvasculature is impaired in dilated cardiomyopathy. Circulation 1990;81:772-9.
8. Panza JA, Quyyumi AA, Brush JE, Epstein SE. Abnormal endothelium-dependent relaxation in patients with essential hypertension. N Engl J Med 1990;323:22-7.
9. Neglia D, Parodi O, Gallopin M, Sambuceti G, Giorgetti A, Pratali L, et al. Myocardial blood flow response to pacing tachycardia and to dipyridamole infusion in patients with dilated cardiomyopathy without overt heart failure. A quantitative assessment by positron emission tomography. Circulation 1995; 92:796-804.
10. Parodi O, Neglia D, Palombo C, Sambuceti G, Giorgetti A, Marabotti C, et al. Comparative effects of enalapril and verapamil on myocardial blood flow in systemic hypertension. Circulation 1997;96:864-73.
11. Sambuceti G, Marzullo P, Giorgetti A, Neglia D, Marzilli M, Salvadori P, et al. Global alteration in perfusion response to increasing oxygen consumption in patients with single vessel coronary artery disease. Circulation 1994;90:1696-705.
12. Beller GA, Zaret BL. Contributions of nuclear cardiology to diagnosis and prognosis of patients with coronary artery disease. Circulation 2000;101:1465-78.
13. Zeiher AM, Krause T, Schachinger V, Minners J, Moser E. Impaired endothelium-dependent vasodilation of coronary resistance vessels is associated with exercise-induced myocardial ischemia. Circulation 1995;91:2345-52.
14. Gould KL. Myocardial perfusion after cholesterol lowering. J Atheroscler Thromb 1996;3:59-61.
15. Guethlin M, Kasel AM, Coppenrath K, Ziegler S, Delius W, Schwaiger M. Delayed response of myocardial flow reserve to lipid-lowering therapy with fluvastatin. Circulation 1999;99: 475-81.
16. Sambuceti G, Marzilli M, Marraccini P, Schneider-Eicke J, Gliozheni E, Parodi O, et al. Coronary vasoconstriction during myocardial ischemia induced by rises in metabolic demand in patients with coronary artery disease. Circulation 1997;95:2652-9.
17. Sambuceti G, Marzilli M, Fedele S, Marini C, L'Abbate A. Paradoxical increase in microvascular resistance during tachycardia downstream from a severe stenosis in patients with coronary artery disease: reversal by angioplasty. Circulation 2001;103:2352-60.
18. Miyazaki K, Hori S, Inoue S, Adachi T, Bessho M, Kuwahira I, et al. Characterization of energy metabolism and blood flow distribution in myocardial ischemia in hemorrhagic shock. Am J Physiol 1997;273:H600-H607.
19. Sambuceti G, Marzilli M, Mari A, Marini C, Marzullo P, Testa R, et al. Clinical evidence for myocardial derecruitment downstream from severe stenosis: pressure-flow control interaction. Am J Physiol Heart Circ Physiol 2000;279:H2641-H2648.

20. Rahimtoola SH. Chronic myocardial hibernation. Circulation 1994;89:1907-8.
21. Camici PG, Dutka DP. Repetitive stunning, hibernation, and heart failure: contribution of PET to establishing a link. Am J Physiol 2001;280:H929-H936.
22. Klocke FJ. Coronary blood flow in man. Prog Cardiovasc Dis 1976;19:117-66.
23. Yamamoto Y, de Silva R, Rhodes CG, Araujo LI, Iida H, Rechavia E, et al. A new strategy for the assessment of viable myocardium and regional myocardial blood flow using ^{15}O-water and dynamic positron emission tomography. Circulation 1992;86:167-78.
24. Yamaguchi S, Tsuiki K, Hayasaka M, Yasui S. Segmental wall motion abnormalities in dilated cardiomyopathy: hemodynamic characteristics and comparison with thallium-201 myocardial scintigraphy. Am Heart J 1987;113:1123-8.
25. Cannon RO, Rosing DR, Maron BJ, Leon MB, Bonow RO, Watson RM, et al. Myocardial ischemia in patients with hypertrophic cardiomyopathy: contribution of inadequate vasodilator reserve and elevated left ventricular filling pressures. Circulation 1985;71:234-43.
26. Inoue T, Sakai Y, Morooka S, Hayashi T, Takaianagi K, Yamanaka T, et al. Coronary flow reserve in patients with dilated cardiomyopathy. Am Heart J 1993;125:93-8.
27. Weiss MB, Ellis K, Sciacca RR, Johnson LL, Schmidt DH, Cannon PJ. Myocardial blood flow in congestive and hypertrophic cardiomyopathy: relationship to peak wall stress and mean velocity of circumferential fiber shortening. Circulation 1976;54:484-93.
28. Camici P, Chiriatti G, Lorenzoni R, Bellina RC, Gistri R, Italiani G, et al. Coronary vasodilation is impaired in both hypertrophied and non hypertrophied myocardium of patients with hypertrophic cardiomyopathy: a study with nitrogen-13 ammonia and positron tomography. J Am Coll Cardiol 1991;17: 879-86.
29. Parodi O, De Maria R, Oltrona L, Testa R, Sambuceti G, Roghi A, et al. Myocardial blood flow distribution in patients with ischemic heart disease or dilated cardiomyopathy undergoing heart transplantation. Circulation 1993;88:509-22.
30. Maron BJ, Wolfson JK, Epstein SE, Roberts WC. Intramural ("small vessel") coronary artery disease in hypertrophic cardiomyopathy. J Am Coll Cardiol 1986;8:545-57.
31. Drexler H, Hayoz D, Munzel T, Hornig B, Just H, Brunner HR, et al. Endothelial function in chronic heart failure. Am J Cardiol 1992;69:1596-601.
32. Drexler H. Endothelium as a therapeutic target in heart failure. Circulation 1998;98:2652-5.
33. Neglia D, Levorato D, Berti S, Marzilli M, Pelosi G, Marcassa C, et al. Diagnosi e caratterizzazione funzionale di iniziale danno miocardico in pazienti con aritmie cardiache. Cardiologia 1987;32:713-9.
34. Neglia D, Michelassi C, Trivieri MG, Sambuceti G, Giorgetti A, Pratali L, et al. Prognostic role of myocardial blood flow impairment in idiopathic left ventricular dysfunction. Circulation 2002;105:186-93.
35. Neglia D, Marini Ce, Toschi E, Sorace O, Salvadori P, Sambuceti G, et al. Regional myocardial flow-metabolism relationship in patients with idiopathic dilated cardiomyopathy [abstract]. J Am Coll Cardiol 2001;37:187.
36. van den Heuvel AF, van Veldhuisen DJ, van der Wall EE, Blanksma PK, Siebalink HM, Vaalburg WM, et al. Regional myocardial blood flow reserve impairment and metabolic changes suggesting myocardial ischemia in patients with idiopathic dilated cardiomyopathy. J Am Coll Cardiol 2000;35:19-28.
37. Opherk D, Mall G, Zebe H, Schwartz F, Weheie E, Manthey J, et al. Reduction of coronary reserve: a mechanism for angina pectoris in patients with arterial hypertension and normal coronary arteries. Circulation 1984;69:1-7.
38. Marcus ML, Mueller TM, Eastham CL. Effects of short- and long-term ventricular hypertrophy on coronary circulation. Am J Physiol 1981;241:H358-H362.
39. Hittingher L, Mirsky I, Shen YT, Patrick TA, Bishop SP, Vatner SF. Hemodynamic mechanism responsible for reduced subendocardial coronary reserve in dogs with severe left ventricular hypertrophy. Circulation 1995;92:978-86.
40. Marcus ML, Koyoanagi S, Harrison DG, Doty DB, Hiratzka LF, Eastham CL. Abnormalities in the coronary circulation that occur as a consequence of cardiac hypertrophy. Am J Med 1983;75:62-6.
41. Brush JE, Cannon RO, Shenke WH, Bonow RO, Leon MB, Maron BJ, et al. Angina due to microvasculature disease in hypertensive patients without left ventricular hypertrophy. N Engl J Med 1988;319:1302-7.
42. Gimelli A, Schneider Eicke J, Neglia D, Sambuceti G, Giorgetti A, Bigalli G, et al. Homogeneously reduced versus regionally impaired myocardial blood flow in hypertensive patients: two different patterns of myocardial perfusion associated with degree of hypertrophy. J Am Coll Cardiol 1998;31:366-73.
43. Brilla GC, Janicki JS, Weber KT. Impaired diastolic function and coronary reserve in genetic hypertension: role of interstitial fibrosis and medial thickening of intramyocardial coronary arteries. Circ Res 1991;69:107-15.
44. Gibbons GH, Dzau VJ. The emerging concept of vascular remodeling. N Engl J Med 1994;330:1431-8.
45. Schwartzkopff B, Motz W, Frenzel H, Voght M, Knauer S, Strauer BE. Structural and functional alterations of the intramyocardial coronary arterioles in patients with arterial hypertension. Circulation 1993;88:993-1003.
46. Treasure CB, Klein JL, Vita JA, Manoukia SV, Renwick G H, Selwyn AP, et al. Hypertension and left ventricular hypertrophy are associated with impaired endothelium mediated relaxation in human coronary resistance vessels. Circulation 1993;87:86-93.
47. Antony I, Lerebours G, Nitemberg A. Loss of flow-dependent coronary artery dilatation in patients with hypertension. Circulation 1995;91:1624-8.
48. Bailey IK, Come PC, Kelly DT, Burow RD, Griffith LS, Strauss HW, et al. Thallium-201 myocardial perfusion imaging in aortic valve stenosis. Am J Cardiol 1977;40:889-98.
49. Pfisterer M, Muller-Brand J, Brundler H, Cueni T. Prevalence and significance of reversible radionuclide ischemic perfusion defects in symptomatic aortic valve disease patients with or without concomitant coronary disease. Am Heart J 1982;103:92-6.
50. Kupari M, Vitanen KS, Turto H, Viitasalo M, Manttari M, Lindroos M, et al. Exclusion of coronary artery disease by exercise thallium-201 tomography in patients with aortic valve stenosis. Am J Cardiol 1992;70:635-40.
51. Huikuri HV, Korhonen UR, Ikaheimo MJ, Heikkila J, Takkunen JT. Detection of coronary artery disease by thallium imaging using a combined intravenous dipyridamole and isometric handgrip test in patients with aortic valve stenosis. Am J Cardiol 1987;59:336-40.
52. Samuels B, Kiat H, Friedman JD, Berman DS. Adenosine pharmacologic stress myocardial perfusion tomographic imaging in patients with significant aortic stenosis. J Am Coll Cardiol 1995;25: 99-106.
53. Strauer BE. Ventricular function and coronary hemodynamics in hypertensive heart disease. Am J Cardiol 1979;44:999-1006.

54. Tauchert M, Hilger HH. Application of the coronary reserve concept to the study of myocardial perfusion. In: Shaper W, ed. The pathophysiology of myocardial perfusion. Amsterdam: Elsevier\North Holland Biomedical Press; 1979. p. 141-67.
55. Marcus ML, Doty DB, Hiratzka LF, Wright CB, Eastham CL. Decreased coronary reserve. A mechanism for angina pectoris in patients with aortic stenosis and normal coronary arteries. N Engl J Med 1982;307:1362-7.
56. Eberli FR, Ritter M, Schwitter J, Bortone A, Schneider J, Hess OM, et al. Coronary reserve in patients with aortic valve disease before and after successful aortic valve replacement. Eur Heart J 1991;12:127-38.
57. Julius BK, Spillmann M, Vassalli G, Villari B, Eberli FR, Hess OM. Angina pectoris in patients with aortic stenosis and normal coronary arteries: mechanisms and pathophysiological concepts. Circulation 1997;95:892-8.