Editorial Comment

Hypertension, Hypertrophy, and the Coronary Circulation

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The effects of hypertension and hypertrophy on the coronary circulation are subjects of increasing investigative interest.1-3 Animal studies have shown that the major conduit arteries are enlarged in pressure-overloaded, hypertrophied ventricles, but this increase falls short of paralleling the extent of hypertrophy.4 This enlargement is accompanied by an increase in the extracellular component of the medial wall.5 A decrease in capillary density and resultant increase in diffusion distance has been noted in many forms of hypertrophy, especially in the subendocardium.5,6 Such findings are not seen in experimental hypertrophy occurring in utero or in response to thyrotoxicosis.3,7 Physiological studies in animals have demonstrated that although total flow may be elevated, flow per gram of the myocardium in the hypertrophied ventricle is generally normal at rest.8 However, relative subendocardial hypoperfusion may occur when severe hypertrophy (greater than 75% increase in mass) is present. Even before the onset of this severe stage of hypertrophy, transmural distribution of flow in response to stress may be abnormal in the presence of more moderate hypertrophy and can be manifested by a less-than-expected increase in subendocardial blood flow. This is especially the case if aortic diastolic pressures are not proportionally increased.9,10 Coronary reserve is usually lower and minimum vascular resistance is usually higher even when measured per gram of tissue. This suggests that vascular growth has not kept pace with the hypertrophic process, although increases in systolic compressive forces and alterations of vasomotor tone of the resistive vessels may also play a role. In some models of prolonged hypertension and hypertrophy, these abnormalities dissipate over time, presumably because angiogenesis has ensued.11 In occlusion models, previous studies12-14 have demonstrated that acute mortality, the rate of progression of myocardial necrosis, and the ultimate infarct size are increased for any given area at risk in animals with hypertension and left ventricular hypertrophy compared with normal subjects. However, these differences are not solely due to hypertrophy because they can be abolished by acute lowering of the hypertension during the occlusion. Last, in the presence of hypertension and hypertrophy, autoregulation is impaired in the subendocardium.15

Few studies, however, have been undertaken to directly demonstrate that these underlying pathophysiological mechanisms are operant in humans. Despite this, there are ample observations suggesting a direct parallel between these laboratory findings and the cardiac manifestations of patients with hypertension or hypertrophy, or both. For example, the mechanism of angina in patients with significant aortic stenosis, some forms of congenital heart disease, cardiomyopathy, and hypertension with normal coronary angiograms has been related to impaired vasodilator reserve in the hypertrophic ventricle. Hypertension is also an established risk factor for myocardial infarction and its complications (heart failure, rupture, sudden death, and arrhythmias).16

Of even more overriding concern are the disappointing results of attempts to lower coronary heart disease mortality in various long-term and large-scale clinical trials of antihypertensive therapy. Although the overall mortality rate associated with hypertension has been reduced by effective therapy, this has been due almost entirely to a decrease in morbidity associated with cerebrovascular illness. Coronary mortality has not been affected.17 Several cogent hypotheses related directly to abnormalities of coronary flow have been proposed to partially explain these results.18,19 They are proposed in the context of the differences in the determinants of oxygen demand in the brain and heart and the resultant implications for autoregulation of blood flow. In contrast to the cerebral circulation, aortic pressure is a determinant of both the supply (coronary perfusion pressure) and demand (mechanical work) factors affecting coronary flow. In addition, oxygen extraction in the brain can be increased, whereas extraction is nearly maximal at rest in the coronary circulation. Elevated aortic pressure is also a potent stimulus for cardiac hypertrophy, an adaptive response to chronically increased afterload. Last, the

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subendocardium is exquisitely prone to ischemia, has impaired vasodilator reserve, and, even in normal circumstances, demonstrates impairment of autoregulation at higher pressures than do the remaining layers. Thus, hypertension increases demand on a hemodynamic basis, and in the long term, the induction of hypertrophy further aggravates the demand. This, in turn, is partially met by maintenance of an adequate perfusion pressure that is especially critical for maintenance of subendocardial flow. Any attempt to arrest and reverse this complex interplay then presents several real problems of potential clinical importance.

The study by Polese and colleagues in this issue of Circulation focuses on one of these problems, namely that in the face of a less-steep relation between maximal coronary flow and pressure (i.e., decreased maximal coronary conductance or increased minimal coronary resistance) and a higher autoregulated level of total flow in hypertrophic ventricles, one would predict that during lowering of perfusion pressures, maximal vasodilation and eventual exhaustion of autoregulation should occur at a higher-than-normal perfusion pressure. Any further lowering below this elevated and critical level of perfusion pressure could induce actual ischemia. Indeed, this clinical study shows that patients subjected to short-term, steady-state pressure lowering do have a reduction in coronary blood flow and increased oxygen extraction at a higher pressure than do control subjects. Most importantly, these findings occurred only in those hypertensive patients who also demonstrated echocardiographic evidence of hypertrophy.

Limitations of the study are few and do not detract from the overall message of the report. One limitation is the use of the term “autoregulation” in the face of a potential coronary dilator and in the absence of independent control of coronary perfusion pressure and aortic pressure. “Autoregulation” is strictly defined as the ability of the heart to maintain its blood flow relatively constant following changes in perfusion pressure when myocardial oxygen demands are constant.

Therefore, because aortic pressure is a major determinant of myocardial oxygen demand, any change in coronary vascular resistance resulting from alterations in aortic pressure will necessarily include both autoregulatory and metabolic components and cannot be attributed to autoregulation alone. To study autoregulation, coronary perfusion pressure must be controlled independently of aortic pressure, or adjustments must be made for metabolic effects. Even when perfusion pressure is independently regulated, a change in coronary artery pressure and flow may, in itself, alter myocardial contractility and oxygen consumption. Thus, examining such issues in the intact circulation of patients undergoing catheterization is very difficult. Second, because aortic pressure is a prime determinant of oxygen consumption, in the absence of other effects such as tachycardia, a progressive fall would have been expected in coronary flow with each lowering of aortic pressure in these patients. The demonstrated plateau in flows may, therefore, be an artifact of the insensitivity of the coronary sinus flow measurement method to small changes in flow. This may have been compounded by an increment in oxygen consumption that possibly may be due to tachycardia or increased contractility due to sympathetic activation that may not have been adequately accounted for by the tension-time index. The plateau in flow measurements should, therefore, not be interpreted as demonstrating autoregulation in the strict sense. Similarly, the increase in coronary flow at low perfusion pressures in normal subjects may be in keeping with coronary vasodilation in conjunction with increased myocardial oxygen consumption, again due to tachycardia or enhanced contractility related to sympathetic activation.

Accordingly, although the demonstrated flow phenomena are of interest, the most convincing and important data reside in the clear-cut increase in oxygen extraction in the patients with both hypertension and hypertrophy at perfusion pressures that were well tolerated in the other patients. Because the measurements made with the coronary sinus sampling method could easily have underestimated an even more profound degree or earlier onset of increased oxygen extraction in the subendocardial layers, the demonstration of such differences in oxygen extraction in these patients should be considered all the more impressive.

Definitional and technological issues aside, the report has its greatest value in the provocative questions that it raises: When considering antihypertensive therapy, should therapy be stratified based on the presence or absence of increased mass? In fact, existing data from clinical trials of antihypertensive therapy could be reanalyzed to address this question. Can we improve on available methods of measuring absolute coronary flow, perfusion, and myocardial mass so that the adverse consequences of pressure lowering can be assessed more easily and accurately? Should the point at which flow can no longer be “autoregulated” be determined specifically in selected patients and used as a goal of initial therapy until some demonstrable regression of hypertrophy has occurred or until this perfusion pressure can be shown to have been lowered? When treatment is prescribed in patients with increased mass, should special precautions be taken during therapy to look for potential exacerbation of ischemia, especially during sleep, using Holter monitoring and ST segment analyses, or are invasive studies as performed by Polese et al required? Is our zeal for 24-hour blood pressure control with long-acting medications justified, or is it potentially dangerous in the subset of patients with hypertrophy, particularly in light of the striking nocturnal hypotension that may occur in some patients? Should initial therapy in selected patients be with only those agents known to induce regression of hypertrophy, a reduction in the determinants of myocardial oxygen demand and the po-
tential to maintain a degree of vasodilatation and coronary hyperemia? Last, can such stratified and stepwise therapy impart an improvement in coronary death rates without sacrificing the substantive and definite amelioration in cerebrovascular death rates that general antihypertensive therapy already provides? These are only some of the questions that the work of Polese and coworkers motivates us to address in clinical studies.

References
4. Stack RS, Rembert JC, Schirmer B, Greenfield JC: Relation of left ventricular mass to geometry of the proximal coronary arteries in the dog. Am J Cardiol 1983;51:1728–1731
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