An Artery Has Many Masters

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During the last 25 years, a large number of stimuli have been reported to alter the tone of the coronary arteries. Arterial caliber is now known to be affected by the distending pressure, by factors external to the artery (e.g., neural stimulation and humoral substances in the blood perfusing the arterial wall), by the substances produced by the arterial endothelium, and by metabolically mediated changes in microvascular tone.\(^1\)-\(^3\) In addition, many stimuli selectively affect one part of the vasculature (e.g., large epicardial vessels) differently from other portions of the arterial tree (e.g., the microvasculature).\(^4\)\(^,\)\(^5\)

Despite the large body of information accumulated about the potential effects of specific molecules and stimuli on coronary function, a wide breach exists between the knowledge of what a stimulus can do in highly specified experimental conditions and what it actually does in humans. Compounds that exert profound effects on arterial tone when administered in supraphysiologic doses may have minimal effects when studied at physiologic concentrations. Neural reflexes present in animal models are not always operative in humans.\(^6\) Furthermore, diseases not present in experimental preparations appear to alter the normal response to many stimuli, making difficult the extrapolation of experimental data obtained in normal animals to patients with atherosclerosis or other pathologic abnormalities.\(^7\)\(-\)\(^16\) Hence, the coronary artery is capable of responding to many masters— but to which masters is it compelled to respond to and under what in vivo conditions can the response be modified?

In this issue of Circulation, Nabel et al\(^17\) described an important observation in search of a mechanism. They examined the effects of rapid atrial pacing on the caliber of the epicardial coronary arteries and coronary blood flow. In normal arteries, they found the expected: pacing resulted in an increase in coronary blood flow and dilation of the epicardial vessel. Presumably, the initial increase in blood flow was caused by metabolically mediated microvascular dilation. Relaxation of the large upstream coronary artery followed as a result of endothelial-dependent large vessel dilation. In nonstenotic atherosclerotic vessels, pacing failed to elicit large vessel dilation, presumably related to loss of endothelial-mediated flow-dependent vasodilation. Surprisingly, however, pacing also failed to cause an increase in coronary blood flow. More surprisingly, in severely stenotic vessels, both large vessel caliber and coronary blood flow fell during pacing. Their findings contrast with previous reports showing that coronary blood flow usually increases with atrial pacing in patients with atherosclerosis.\(^18\) What could account for their observations of coronary vasoconstriction in the face of increased metabolic demands?

**Passive Arterial Collapse**

One explanation put forth by Nabel and colleagues is that tachycardia caused metabolically mediated microvascular dilation that secondarily caused an increase in stenosis resistance. The concept of passive vascular collapse was first suggested by Schwartz et al\(^19\) and Gould and Kelley.\(^20\) In animal models with a severe stenosis in a normal vessel, they showed that vasodilators can cause a transient reduction of coronary blood flow. Two potential mechanisms were proposed. Schwartz et al postulated that vasodilator stimuli, by eliciting small vessel dilation, caused "depressurization" of the arterial segment distal to the severe stenosis. The fall in distal arterial pressure resulted in collapse of the arterial lumen at the site of the stenosis and in the distal vessel, increasing stenosis resistance. There is evidence, however, that this mechanism does not frequently occur in humans. Atherosclerotic vessels are much less compliant than the normal arteries of animals. Logan\(^21\) studied the effects of distal arterial pressure on stenosis resistance in an in vitro hydraulic model that used segments of atherosclerotic human coronary arteries. Only eccentric stenoses (in which part of the stenotic arterial circumference was relatively compliant) exhibited passive collapse; concentric lesions did not. It is unlikely that all of the patients studied by Nabel et al had eccentric lesions.

Gould and Kelley\(^20\) showed in dogs that the vasodilator papaverine caused dilation of the arterial segment immediately distal to a severe stenosis.
induced by external vascular compression. They postulated that an increase in the stenosis exit angle caused more outflow turbulence, consequently increasing stenosis resistance (calculated from hydraulic formulas) and reducing blood flow. In humans, however, vasodilator administration only rarely elicits a fall in blood flow in atherosclerotic arteries with severe stenoses. We have observed fall in blood flow after intracoronary papaverine in only two of more than 100 patients with a severe coronary stenosis (minimum lesion cross-sectional area, less than 1 mm²) and have never found it in arteries with a minimum lesion area of greater than 1.00 mm². Moreover, this mechanism is unlikely to have been operative in the patients studied by Nabel et al, because the distal arterial segment fell in caliber and presumably the exit angle became less severe, reducing turbulent losses.

Hence, passive arterial collapse may not be common in atherosclerotic vessels, perhaps in part related to the noncompliant nature of such vessels. It seems unlikely that five of five atherosclerotic vessels with a minimum lesion area of greater than 1.00 mm² studied by Nabel et al would exhibit passive collapse with a submaximal vasodilator stimulus (pacing). Moreover, passive collapse could not account for the failure of coronary blood flow to rise in nonstenotic vessels or the observed 50% fall in the area of the arterial segment proximal to the stenosis. The primary explanation for the findings of Nabel et al probably resides elsewhere.

**Sympathetic Vasoconstriction**

Another, more plausible explanation for vasoconstriction observed during atrial pacing is that increases in heart rate induced ischemia that, in turn, caused sympathetic vasoconstriction. The patients with severe stenoses (group 3) all developed angina during pacing. Because ischemia is often associated with activation of the sympathetic nervous system, the patients with a severe stenosis probably developed an increase in cardiac sympathetic tone.

The normal response to sympathetic stimulation is relative vasoconstriction. In the absence of increased metabolic workloads, large and small vessel coronary caliber decreases. If sympathetic stimulation is associated with increased myocardial work (e.g., during exercise), increased coronary sympathetic tone blunts the magnitude of metabolically mediated vasodilation. Thus, in normal animals, the coronary response to exercise and ischemia (with reflex increases in heart rate and arterial blood pressure) is one of competition between metabolically mediated dilation and an increase in sympathetic tone that partially checks the metabolic dilation. Of importance, however, sympathetic stimulation can override metabolically induced vasodilation even in the presence of a stenosis severe enough to induce ischemia at rest.

Atherosclerosis is generally believed to augment the vasoconstrictor response to sympathetic stimulation. Maneuvers that activate the sympathetic nervous system, such as sustained handgrip exercise, cause constriction of large atherosclerotic coronary vessels and can cause a severe reduction in the minimal lumen area of stenotic lesions. The degree of constriction caused by sustained handgrip exercise is similar to that observed by Nabel et al in the patients with severe stenoses who underwent atrial pacing. Consequently, the large vessel constriction and a fall in blood flow observed during pacing by Nabel et al are consistent with ischemia-induced reflex sympathetic constriction in patients with atherosclerosis. It is unclear whether the sympathetic stimulus was solely neural or whether increases in circulating norepinephrine levels also played a role. A repetition of these studies in the presence of various receptor antagonists (e.g., β-adrenoceptor antagonists) would more precisely elucidate the mechanism of pacing-induced coronary vasoconstriction, particularly in patients with severe stenoses in epicardial vessels.

**Diffuse Atherosclerosis**

Neither passive collapse nor sympathetic vasoconstriction can explain the failure of blood flow to increase during atrial pacing in patients with minimal atherosclerosis (i.e., luminal irregularities but no significant focal lesion). Why would blood flow to the myocardium remain unchanged despite a marked increase in oxygen demand that is usually a powerful metabolic stimulus for vasodilation? Inability of a diffusely diseased vessel to conduct hyperemic blood flow was almost surely not operative. Unless severely diffusely narrowed, the large coronary vessels provide only minimal resistance to blood flow, even at maximal flow rates. Studies from our laboratory, for example, have shown that moderate diffuse atherosclerosis (i.e., 50% reduction in lumen area, similar to that reported by Nabel et al) does not impair papaverine-induced hyperemia. The mechanism that prevented (or failed to cause) an increase in coronary blood flow in response to increased metabolic demand is not clear but must reside, in part, from abnormalities at the microvascular level.

**Microvascular Dysfunction**

Microvascular disease can impair the normal microvascular vasodilator response to increased metabolic oxygen requirements. Rapid atrial pacing fails to evoke a normal rise in coronary blood flow, a compensatory increase in myocardial oxygen extraction can be measured, and coronary flow reserve (measured with a vasodilator) is reduced. There are many causes of microvascular dysfunction. Some, such as myocardial infarction or prolonged ischemia, indirectly result from atherosclerosis. Other causes frequently coexist with atherosclerosis (e.g., hypertension and hypertrophy), whereas still other causes are unrelated to large vessel coronary disease (e.g., cardiomyopathies and collagen vascular diseases). Of importance, nearly all of the
with "minimal atherosclerosis" studied by et al had hypertension, and many had electrographic evidence of ischemia at rest or during cise. Consequently, it is highly likely that these patients may have had some form of microvascular vasodilator insufficiency in addition to early large vessel atherosclerosis and that the microvascular disease may have prevented blood flow from rising normally during atrial pacing.

This interpretation of their findings is consistent with prior studies in patients with atherosclerotic coronary disease that demonstrated an increase in myocardial blood flow during atrial pacing16 (in contrast to that found by Nabel et al) and evidence that the microvasculature of atherosclerotic arteries dilates normally in response to pharmacologic vasodilators that have a nonendothelial dependent mechanism of action (e.g., papaverine and dipyridamole).22,23,30 Measurements of coronary flow reserve in the patients studied by Nabel et al might have determined whether microvascular vasodilator dysfunction caused coronary blood flow not to rise normally during atrial pacing.

Endothelial Dysfunction

Nabel et al suggested that the endothelial dysfunction associated with atherosclerosis might also have impaired the vasodilator response to atrial pacing. Defective endothelial regulation of atherosclerotic arteries is well established.7,9,16 The vasomotor response of large, atherosclerotic coronary vessels to a host of humoral agents acting through endothelial-dependent mechanisms is known to be absent or paradoxical.7-9,16 Despite the potential role of atherosclerosis-induced endothelial dysfunction in causing the large vessel constriction, changes in epicardial arterial caliber observed by Nabel et al paralleled changes in blood flow, indicating that endothelial-dependent mechanisms may have been operating appropriately. It is possible, however, that the responses to sympathetic stimuli could have been amplified (or unmasked) by endothelial dysfunction.

The importance of the endothelium in modulating microvascular tone is uncertain. It does not seem possible, however, that endothelial dysfunction in the epicardial coronary arteries could totally prevent microvascular dilatation during pacing, particularly because the microvasculature can regulate tone on a beat-to-beat basis in response to changes in arterial pressure or metabolic demand.39 To prevent metabolically related hyperemia would require the upstream endothelium to "know" that metabolic demand was increased before blood flow velocity increased. Moreover, we have recently demonstrated that blood flow rises substantially during atrial pacing in transplanted human coronary arteries, a model in which endothelial dysfunction in large arteries is common.40

The microvascular endothelium has been shown to modulate microvascular tone.5,41,42 The endothelium might potentially play a more important role in the regulation of the small vessels than in large vessels because the ratio of endothelial cell surface area to vascular lumen area is several orders of magnitude greater in the microvasculature than in the epicardial arteries. It has yet to be shown, however, that atherosclerosis itself alters microvascular endothelial function without an intermediate event (e.g., prolonged episodes of ischemia and infarction). A repetition of the studies by Nabel et al in other intact models with endothelial dysfunction might determine whether endothelial dysfunction alters the linkage of metabolic oxygen demand to microvascular tone.

Conclusion

The "paradoxical vasoconstriction" during atrial pacing observed by Nabel et al might be explained by enhanced sympathetic vasoconstriction due to pacing-induced ischemia, microvascular disease associated with (but not necessarily caused by) atherosclerosis, large vessel endothelial dysfunction, and perhaps passive arterial collapse. Because a heterogeneous group of patients was studied, the contributions of each mechanism may have varied between patients. Of importance, however, the study underscores the number of mechanisms ("masters") by which vascular smooth muscle tone can be altered, the many ways that atherosclerosis can alter coronary physiology, and the importance of carefully selecting patients for physiologic studies of the coronary circulation.

Many of the factors that influence vascular smooth muscle tone must share a common final mechanism. The route (and gates) to that final effector mechanism(s), however, are unclear and appear to vary with the stimulus and location of the arterial segment. The extension of basic research to studies in the catheterization laboratory should more clearly define in humans the mechanisms and hierarchical structure of vascular control and the modulating effects of disease. We are fortunate that many tools have already been developed to measure indirectly coronary arterial tone at the large and small vessel level in humans and that these tools are available to most research catheterization laboratories. Further studies should more precisely define the mechanism of the observations presented by Nabel et al and elucidate which of the many masters the artery is following.

References

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