EDITORIAL COMMENT

Dobutamine and the Coronary Vasomotion Paradox*

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Dobutamine, a structural relative of dopamine, acts directly on alpha- and beta-adrenergic receptors without the release of norepinephrine or activation of dopaminergic receptors. For clinical use, dobutamine is a racemic mixture of a levo-isomer acting as a potent alpha-1 agonist and a dextro-isomer counterbalancing this effect as an alpha-1 antagonist. Both isomers are complete beta-receptor agonists with the dextro-isomer 10-fold more potent than the levo-isomer (1). Intravenous dobutamine is widely used to determine the significance of coronary atherosclerotic disease (2) and to support the myocardium during heart failure (3). Depending on dose, dobutamine has been demonstrated to evoke myocardial ischemia and identify myocardial hibernation and viability (4,5).

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Dobutamine’s major mechanisms, increasing inotropy and chronotropy, are produced principally but not exclusively through the activation of the adrenergic receptor system, which stimulates myocardial oxygen demand (6). In the setting of limited coronary blood flow, the heightened adrenergic response tips the balance of the myocardial oxygen supply and demand equation toward ischemia. While increasing contractility, dobutamine also decreases microvascular resistance (7), simultaneously activating additional vascular receptors, depending on the presence or absence of a normally functioning endothelium (8). In experimental animals, dobutamine produces vasodilation through a net balance between an endothelial flow-mediated vasodilation in response to increased metabolic demand and the direct stimulation of vascular and cardiac beta-1 and beta-2 adrenergic receptors. These vasodilatory forces are counteracted by the vasoconstrictive effects of dobutamine–stimulated alpha-1 adrenergic receptors within the vessel wall (9).

This potential multiplicity of vascular mechanisms has given rise to a question about dobutamine and paradoxical coronary vasomotor responses. For example, why does dobutamine-induced stress testing produce more false negatives than direct hemodynamic assessment of coronary stenoses (10)? Additionally, physical exercise induces coronary vasodilation in normal arteries but paradoxically vasoconstricts diseased coronary arteries with endothelial dysfunction (11). Does dobutamine vasodilate atherosclerotic epicardial coronary arteries?

In this issue of the Journal, Barbato et al. (12) elegantly addressed the question of dobutamine and coronary vasomotion in humans and which receptor mechanisms might be involved. The ambitious well-designed protocol studied six groups of patients with quantitative coronary angiography during escalating infusions of dobutamine. Intravenous dobutamine, in doses from 10 to 40 μg/kg/min, was given to 19 normal patients (group 1), 23 patients with mild atherosclerotic artery disease (group 3), and 12 patients with severely stenotic arteries (group 4). Saline infusions were used in 8 control patients (group 2). Dobutamine infusions were preceded by the alpha-blocker phenolamine (12 μg/kg) in 12 patients (group 5) or the nitric oxide substrate l-arginine (150 μg/min) in 11 patients (group 6) followed by the dobutamine infusions as performed in groups 1, 3, and 4. Patients in groups 5 and 6 both had severely diseased arteries.

The investigators found that, for identical increases in the heart rate–pressure product, dobutamine induced coronary vasodilation of 19% in normals, 8% in mildly atherosclerotic arteries, and produced no vasomotion in the severely stenotic arteries (−3%). This failure to vasodilate was partially improved to 10% by l-arginine and fully restored to 19% by phenolamine in the severely diseased coronary artery patients. These findings indicated that a combination of endothelial dysfunction and enhanced alpha-adrenergic tone contributed to the failure of dobutamine to induce atherosclerotic coronary arteries to dilate. Of importance, unlike reports of exercise coronary vasomotion, a paradoxical vasoconstriction during dobutamine infusion did not occur.

The study cited (12) should be viewed as a paradigm in the examination of coronary physiologic responses to pharmacologic challenge. The investigators should be congratulated for adherence to a rigorous protocol, which notably included agents to dissect and test postulated mechanisms of vascular receptor activity in both normal and diseased coronary arteries. These responses are of interest because dobutamine directly stimulates alpha-1, beta-1, and beta-2 adrenergic receptors within the vessel wall (13) with beta-adrenergic vasorelaxation being partly mediated by nitric oxide activation—that is, normal endothelial function of both conductance and resistance circuits (14). Some investigators believe that endothelial function plays a relatively minor role in enhancing vasodilation through a flow-mediated mechanism, whereas beta-receptor activation is a more powerful epicardial coronary vasodilator (15).
beta-1 and beta-2 adrenergic receptors on the coronary vasculature are distributed in a heterogeneous fashion, beta-1 receptors appear crucial to epicardial coronary vasoconstriction, whereas beta-2 receptors are more important to the smaller resistance arteriolar function. Activation of these receptors also increases contractility and oxygen consumption, potentiating the release of vasodilatory substances, acting independently of endothelial function. In this setting, adenosine appears to be one of the prototypical stimulatory agents affecting both epicardial arteries and, to a greater degree, the microvasculature (16).

In theory, beta-adrenergic blockade could paradoxically cause myocardial ischemia through unopposed alpha-adrenergic vasoconstriction in coronary disease patients when subjected to mixed adrenergic stimuli (17,18). In contrast to normal artery responses, exercise-induced vasoconstriction is attributed to the atherosclerotic dysregulation of endothelium, accentuated in the presence of hypercholesterolemia, hypertension, and smoking. Further demonstrations of this mechanism are gleaned from studies of cold pressor testing, mental stress, and atrial pacing, which similarly produce alpha-mediated vasoconstrictor responses in patients along a gradient of increasingly severe endothelial dysfunction.

In the Barbato et al. study (12), dobutamine had minimal (~3% change in luminal diameter) vasoconstrictive effects seen only at the lowest dose in the severely stenotic artery patient groups. The absence of vasoconstriction or dilation during dobutamine in these patient groups was not due to vessel stiffness as all arteries diluted with exposure to intracoronary isosorbide dinitrate. Apparently, some vascular smooth muscle remains functional even in some highly diseased vessels, suggesting vasomotor responses persist and may be in part due to alpha-1 and beta-adrenergic receptor interaction.

As with all complex protocols, the inherent limitations are worth reviewing. Concomitant medical therapy may attenuate coronary vasomotor responses to any pharmacologic or physiologic challenges. For example, angiotensin-converting enzyme inhibitors and statins, which may improve endothelial function, could potentiate a vasodilatory response. No medication differences were observed among the six patient groups. Also, some investigators note that diurnal variations of vasomotor responses may be a substantial confounding influence in a study such as this (19). Finally, the methodology of using quantitative coronary angiography has inherent limitations in detecting small differences in vessel dimensions, especially lumen diameter for calculation of cross-sectional area, and may be influenced by the timing, imaging technique, and method of injection. Over a large patient series, these differences would be minimal and not likely to lead to a systematic error.

The action of dobutamine on the coronary artery is ultimately the net result of the interplay of alpha- and beta-adrenergic receptors (Table 1) and endothelial function. In a dose-dependent manner, dobutamine vasodilates normal and mildly atherosclerotic arteries, whereas in severely diseased arteries, paradoxical alpha-adrenergic vasoconstriction is not observed to any significant degree. Barbato et al. (12) advance our understanding and interpretation of dobutamine stress testing and its relationship to coronary blood flow in patients with coronary artery disease.

### REFERENCES


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