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EDITORIAL COMMENT

Ranolazine and the Myocardial Demand–Supply Balance*

Francis J. Klocke, MD
Chicago, Illinois

The emergence of ranolazine as an effective antianginal agent (1,2) has prompted recurring interest in identifying mechanisms by which this agent can favorably affect the imbalance between myocardial oxygen demand and supply underlying anginal episodes.

POSSIBLE INFLUENCES ON MYOCARDIAL OXYGEN DEMAND

Early studies of ranolazine centered on reductions in myocardial oxygen demand produced by partial inhibition of fatty acid oxidation, particularly as free fatty acid levels increase locally during ischemic episodes. More recent studies report that this mechanism is unlikely to be operative at the plasma levels of ranolazine associated with beneficial clinical effect. A reduction in myocardial oxygen demand has also been questioned, because ranolazine only minimally decreases resting and peak values of systolic pressure and heart rate during exercise.

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Despite the established value of the pressure-rate product as an index of global left ventricular (LV) oxygen consumption, it might not fully reflect other factors known to influence myocardial metabolic requirements (e.g., contractile state and muscle shortening). The global index could conceivably also fail to reflect ranolazine-induced reductions in locally increased fatty acid oxidation during ischemia.

POSSIBLE INFLUENCES ON MYOCARDIAL OXYGEN SUPPLY

As recently reviewed by Hale et al. (3), studies establishing that ranolazine inhibits the late sodium current (I_{Na}) in cardiac cells have led to proposals that it improves myocardial perfusion by attenuating diastolic contractile dysfunction caused by calcium overload. Several laboratories have reported reductions in myocardial necrosis and LV dysfunction in isolated hearts and occlusion-reperfusion animal models. However, quantitative measurements of myocardial flow have been performed infrequently. In a rabbit model of reperfused infarction in which ranolazine reduced infarct size, it did not have a significant effect on full-thickness regional flow measured with radioactive microspheres (4).

PILOT SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY PERFUSION STUDY IN ANGINA PATIENTS

In this issue of *iJACC*, Venkataraman et al. (5) report that short-term ranolazine therapy improved some measures of myocardial perfusion in a small group of coronary patients with stable angina or an anginal equivalent and reversible perfusion defects during treadmill exercise testing. With automated analysis of sestamibi single-photon emission computed tomography images and a 17-segment LV model, the addition of ranolazine to conventional antianginal therapy improved summed stress and summed difference scores systematically in the full 20-patient cohort. With automated analysis of polar maps, statistically significant improvement was also achieved in 14 patients in whom the extent and severity of ischemia was judged to be reduced on side-by-side visual analysis.

The authors carefully point out that this is a small nonrandomized single center study that does not

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From the Feinberg Cardiovascular Research Institute and the Division of Cardiology, Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois.

include a placebo control and shows considerable interindividual variability in degree of improvement. The findings are based on measurements of relative rather than absolute perfusion, with patterns of perfusion in patients evaluated against a normal database.

FACTORS INFLUENCING FLOW DISTAL TO CORONARY STENOSES

Microvascular vasodilator reserve and extravascular compressive forces play pivotal roles in regulating myocardial flow distal to a coronary artery stenosis. Although, ranolazine-induced reductions in diastolic dysfunction are receiving increasing attention, its effects on microvascular resistance vessels remain undefined.

Extravascular compressive forces. Extravascular compressive forces have complex effects on impedance to flow, involving important capacitive and inertial as well as resistive factors (6). The magnitude of these effects varies transmurally in diastole as well as systole, reflecting the corresponding differences between intraventricular and intrapericardial pressures. Systolic compression of intramyocardial vessels limits coronary inflow and displaces a significant fraction of intravascular blood volume (primarily antegradely but to some degree retrogradely as well). Because of the large transmural gradient in systolic compressive forces, these effects restrict flow particularly in the subendocardium. The speed with which intramyocardial vessels compressed during systole refill during early diastole depends on the speed of myocardial relaxation. Perhaps more importantly, elevations in intraventricular pressure (and therefore wall tension) can restrict flow throughout diastole, again particularly in the subendocardium. In the setting of a flow-limiting stenosis, the shorter diastolic durations associated with increasing heart rates can be another limiting factor.

It has long been appreciated that compressive effects limiting subendocardial perfusion are amplified as preload increases (7,8). These effects assume increasing importance during exercise, particularly in the presence of a coronary stenosis (9). Thus, the possibility that ranolazine increases myocardial perfusion by mitigating adverse effects of augmented diastolic compressive forces clearly merits further study. Quantitative measurements of ranolazine's effects on transmural flows in reversibly (rather than irreversibly) injured myocardium could be helpful in evaluating this possibility.

Emerging complexities of microvascular vasodilator reserve. The primary locus of coronary vasodilator reserve has traditionally been thought of as a homogeneous array of resistance vessels that become maximally dilated when myocardium becomes ischemic and whose caliber is influenced primarily by metabolic factors. As recently reviewed by Duncker and Bache (10), several complexities relevant to antianginal agents have now been identified.

First, factors affecting microvessel caliber vary importantly with vessel size. Metabolic vasodilation originates primarily in arterioles <100 μm in diameter. Conversely, 100- to 400-μm arterioles are influenced primarily by endothelial production of vasodilating agents such as nitric oxide. The 100- to 400-μm vessels constitute a substantial fraction of coronary resistance under basal conditions and an even higher fraction in ischemic areas when <100-μm vessels are dilated by local metabolic factors. The terms "endothelium-dependent" and "endothelium-independent" vasodilation are now used to characterize the differing responses of these "larger" and "smaller" arterioles. Increases in flow during exercise involve both. As flow increases in response to metabolic vasodilation in smaller arterioles, concomitant increases in shear stress on the endothelial surface of larger arterioles stimulate increased production of nitric oxide and other vasodilators. When endothelium is dysfunctional, the amount of potential vasodilation in larger arterioles is reduced, causing reductions in both subendocardial and full-thickness flow reserve. Interestingly, Deshmukh et al. (11) have recently reported that ranolazine can improve endothelial function in peripheral arterial beds in patients with stable coronary disease.

Second, the inner layers of myocardium are also supplied by specialized intramural penetrating arteries. These vessels vary in diameter from 100 to 500 μm and traverse the LV wall to the subendocardium without in-wall branching. Intra-arterial pressure decreases along their length. They too are more responsive to endothelium-dependent than metabolic stimuli. Variations in their tone can directly affect subendocardial flow. Nitroglycerin-induced relief of angina often involves their vasodilation.

Third, in the presence of a flow-limiting stenosis, clinical as well as experimental studies indicate that coronary resistance vessels are not always dilated maximally in regions that become ischemic. This reflects, at least in part, the limited sensitivity of larger arterioles to metabolic factors. In addition, residual vasoconstrictor responses to alpha-adrenoceptor activity,

platelet products, and neurohormonal factors such as angiotensin II and endothelin have been reported in both large and small arterioles. Hale et al. (3) have noted that ranolazine has binding affinity for alpha1- and beta1-adrenergic receptors and serotonin 5-HT1A and 5-HT2 receptors, but the significance of these observations (if any) is unknown.

Fourth, microvascular vessel caliber also depends importantly on local intravascular distending pressure. As reflected by curvilinear pressure-flow relationships in coronary beds that are maximally vasodilated, resistance vessel diameters decrease alinearly and increasingly rapidly as intravascular pressure falls below 60 mm Hg (12,13).

CONCLUSIONS

As emphasized by Venkataraman et al. (5), their current study must be considered hypothesis-generating rather than definitive. At the same time, it seems to be the first such study in humans, and the participants represent an important subset of coronary patients. Thus, the study heightens interest in possible effects of ranolazine on factors adversely affecting coronary flow during ischemia. If beneficial effects on extravascular compressive forces and/or microvascular vasodilator reserve do occur clinically, their magnitude no doubt varies among angina patients and might influence individual responses. Studies providing further understanding of ranolazine's effects on pre-load and augmented diastolic compressive forces are needed. Possible effects of ranolazine on larger and smaller coronary resistance vessels, and persistent vasoconstrictor influences during ischemia, also merit consideration.

Reprint requests and correspondence: Dr. Francis J. Klocke, 950 North Michigan Avenue, Apartment 5102, Chicago, Illinois 60611-7532. *E-mail: f-klocke@northwestern.edu.*

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