

EDITORIAL COMMENT

Ranolazine and Its Anti-Ischemic Effects

Revisiting an Old Mechanistic Paradigm Anew?*

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Seventy-five years ago, Tennant and Wiggers (1) first described the pathophysiologic effects of coronary occlusion on myocardial contraction and were the first to document the sequence of ischemia-mediated perturbations of both regional and global systolic and diastolic function during acute myocardial ischemia. In these seminal observations, the authors were the first to describe segmental diastolic dysfunction followed closely by systolic aneurysmal bulging as the earliest manifestations of acute myocardial ischemia.

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Since that time, our scientific understanding of the consequences of myocardial ischemia has been viewed through the pathophysiologic lens of supply versus demand and how the sequence of changes induced by coronary occlusion (or increasing stenosis) might lead to objective findings of ischemia, hemodynamic and electrocardiographic abnormalities, and symptoms of angina. This sequence has often been referred to as the “ischemia cascade” (2,3), wherein the very first abnormalities that occur are acute alterations in regional lusitropic properties, followed by segmental systolic dysfunction and acute alterations in left ventricular (LV) mechanical performance, after which electrocardiographic repolarization changes are noted to occur (often 20 to 30 s after coronary occlusion). Clinically, anginal symptoms are the last to occur in this temporal cascade.

As a result, the mechanistic principle that ischemia and angina are a fundamental consequence of a myocardial oxygen supply-demand imbalance is a remarkably simple construct to understand and has provided the pathophysiologic basis of our scientific understanding as to why phar-

macologic therapies that ameliorate the supply-demand mismatch improve both angina and ischemia (4,5). Conventional anti-anginal therapies, including beta-blockers, calcium-channel blockers (CCBs), and nitrates reduce myocardial oxygen demand by reducing the hemodynamic determinants of heart rate (HR), systolic blood pressure (SBP), myocardial contractility, and wall tension (6–16). As such, these pharmacologic interventions exert their therapeutic benefits *systemically* by reducing the rate-pressure product (RPP) both at rest and during exercise, as compared with placebo, which results in an attenuation of ischemia throughout the entire duration of exercise (from submaximal to maximal). In essence, drugs like the beta-blockers (6–11) and CCBs (especially HR-lowering agents like verapamil and diltiazem) (13–16) favorably alter hemodynamic parameters and permit patients with ischemic heart disease to exercise longer (and to a higher external workload), even though the peak RPP reductions achieved with active therapy might be the same as that achieved with placebo. Thus, a fundamental premise of such therapies that reduce global myocardial oxygen demand is that patients remain below the physiologic or hemodynamic threshold at which ischemia and angina develop (4,5).

In this issue of the *Journal*, Stone et al. (17) marshal critically new scientific information that provides important insight into the mechanism of action of ranolazine in patients with chronic angina and stable ischemic heart disease. In their exceedingly detailed and comprehensive assessment of the effects of graded exercise on HR, SBP, RPP, and ischemic ST-segment depression (during submaximal and maximal exercise) among 175 patients from the MARISA (Monotherapy Assessment of Ranolazine In Stable Angina) trial who were randomized to ranolazine (500, 1,000, or 1,500 mg twice daily) versus placebo, the authors used a novel statistical approach (a mixed model repeated measures analysis of variance) where the changes in RPP and ST-segment depression could be compared within each of the respective exercise stages, taking into account the treatment received (ranolazine vs. placebo), treatment sequence (differential ranolazine dosing), cross-over period, the exercise stage, and the interaction of treatment with exercise stage. Consequently, this careful explanatory analysis provided the authors an opportunity to accurately assess the dose-dependent effects of ranolazine on the change in ST-segment depression from pre-exercise (summed over 11 electrocardiographic leads) through each stage of submaximal to maximal exercise and controlled for RPP across the exercise duration spectrum (17).

The novel and important findings are that: 1) ranolazine 500 to 1,000 mg twice daily had negligible effects on resting HR and SBP, unlike beta-blockers and HR-lowering CCBs, which fundamentally alter systemic hemodynamic status; 2) at submaximal exercise (3 to 9 min), ranolazine 500 mg twice daily had negligible effects on RPP, whereas 1,000 mg twice daily reduced RPP by 3.8% at 3 min and by

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7.2% at 9 min of exercise; 3) at maximal exercise (12 min), ranolazine 500 mg twice daily did not alter RPP, whereas 1,000 mg twice daily reduced RPP by only 8%; 4) at submaximal exercise (3 to 9 min), the reduction in ST-segment depression from pre-exercise ranged from 15% to 20% with ranolazine 500 mg twice daily and from 30% to 35% with ranolazine 1,000 mg, whereas at peak exercise (12 min), the amount of ischemic ST-segment depression compared with placebo (and controlled for RPP) was reduced by 22% with ranolazine 500 mg twice daily and by 35% with 1,000 mg twice daily; and thus 5), compared with placebo, ranolazine produced a dose-dependent reduction in ST-segment depression that became more marked as exercise-induced ischemia became more severe, indicating that the *magnitude of ischemia reduction was out of proportion to the minor reductions observed in HR or RPP*.

What are the therapeutic implications of these findings and what does this tell us about mechanism of action of ranolazine? First, ranolazine seems to be unique therapeutically in that the objective evidence of ischemia reduction and angina relief is not mediated by the traditional reductions in hemodynamic status and a decrease in myocardial oxygen demand. Second, anti-ischemic effects of ranolazine appeared only after a substantial amount of external cardiac work was achieved and ischemic ST-segment depressed had occurred (17). This suggests that the therapeutic benefits of ranolazine might be more *regional* (i.e., in ischemic myocardial segments) rather than *global* (i.e., involving the entire myocardium). Third, the clear improvements in angina and myocardial ischemia observed in the present MARISA trial analysis are further reinforced by similar findings from both the CARISA (Combination Assessment of Ranolazine in Stable Angina) (18) and MERLIN (Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndromes) trials (19)—both of which showed that exercise-induced ischemia and angina frequency were reduced by ranolazine, whereas the MERLIN trial showed further that the clinical end point of recurrent ischemia was reduced significantly by ranolazine. In particular, among the 55% of MERLIN trial patients who exhibited a history of chronic angina before their qualifying acute coronary syndrome event at the time of randomization, ranolazine significantly reduced the composite trial primary end point of cardiac death, myocardial infarction, and recurrent ischemia (20).

Ischemia is associated with disruption in cellular sodium and calcium homeostasis. In ischemic cardiomyocytes, there is an enhancement of late inward sodium current, which leads to an excessive or pathologic leak of increased cytosolic sodium ion concentration, due to incomplete closure or inactivation of the sodium channel (21–24). This, in turn, is followed by an increase in intracellular calcium through the sodium–calcium exchanger, resulting in intracellular calcium overload. Intracellular calcium overload causes arrhythmias and correlates well with increases in diastolic tension. These regional lusitropic changes result in in-

creased myocardial segmental stiffness—the earliest manifestations that precede regional ischemic contractile impairment (21,22). This leads to increases in myocardial oxygen consumption of ischemic cells and further reductions in regional myocardial blood flow to ischemic segments, thereby exacerbating the imbalance between oxygen supply and demand. Thus, ischemia begets ischemia (Fig. 1 in Shryock and Belardinelli [25]).

Experimentally, ranolazine has been shown to selectively inhibit late inward sodium current, which in turn disrupts the vicious cycle of ischemia and consequently reduces the myocardial oxygen supply-demand imbalance (26–28). Ranolazine, by decreasing intracellular sodium-dependent calcium overload, improves diastolic function, which has been demonstrated clinically in patients with ischemic heart failure as well as in patients with ischemic heart disease who have shown improved LV regional diastolic function (29,30). The increase in regional peak filling rate after ranolazine administration might be attributed to the improvement of regional relaxation in ischemic segments (31). Thus, an agent that reduces LV diastolic dysfunction would likely interrupt the earliest phase of the “ischemic cascade” (2,3); and ranolazine, as a positive lusitropic drug, would decrease myocardial oxygen consumption and improve angina (29–31).

The authors hypothesize that the progressive magnitude of ischemia reduction with ranolazine, which is out of proportion to the minimal reductions in HR or RPP, “is likely due to an improvement (or preservation) in regional coronary blood flow in areas of myocardial ischemia” (17). Although a recent scintigraphic imaging study does support the observation that ranolazine might improve myocardial perfusion in zones of myocardial ischemia during treadmill exercise without alterations in HR or RPP at rest or during peak exercise, these data were derived from an open-label, nonrandomized cohort of 27 patients and must be considered hypothesis-generating (32). Additionally, Stone et al. (17) did not perform any direct measurements of myocardial blood flow in the MARISA trial to support this potentially important mechanism, and although plausible, this must continue to be regarded as speculative.

In summary, ranolazine is an effective anti-anginal and anti-ischemic agent that does not exert its therapeutic effects through global hemodynamic alterations or significant reductions in HR or RPP (17–19). As such, we might need to advance a different mechanistic paradigm (or revisit an old one) (1), that ranolazine acts as a positive lusitropic agent that improves regional LV diastolic dysfunction and segmental ischemia through inhibition of exaggerated late inward sodium current and a restoration of normal cellular sodium and calcium homeostasis (21,22,25,29–31). By interrupting the “ischemic cascade,” which begins with regional diastolic dysfunction, ranolazine reduces myocardial oxygen consumption of ischemic cells or segments and thereby reduces exercise-induced ST-segment depression and angina. Future studies will be needed to further eluci-

date the precise mechanism of action and whether ranolazine likewise favorably alters regional myocardial perfusion.

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