Ranolazine Injection Into Coronary or Femoral Arteries Exerts Marked, Transient Regional Vasodilation Without Systemic Hypotension in an Intact Porcine Model

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Background—We examined whether intracoronary or intrafemoral administration of ranolazine produces local vasodilation.

Methods and Results—Effects of intra-arterial ranolazine on coronary and femoral artery vasodilation and systemic hemodynamic function were studied in anesthetized pigs (n=27). Ranolazine, nitroglycerin, or saline (control) was injected into the left anterior descending (LAD) coronary artery or femoral artery (2-mL bolus in 10 seconds). Pretreatment with prazosin (300 μg/kg IV) allowed determination of α1-adrenergic receptor involvement (n=8). Rapid intracoronary administration of ranolazine (0.048 mg/kg) to achieve high local concentrations resulted in 91±11% increase in LAD coronary artery flow and 39±7% reduction in coronary vascular resistance (both, P<0.0001). This effect lasted 2–3 minutes without change in heart rate or rate-pressure product. Mean arterial pressure decreased marginally (by 2±1 mm Hg, P=0.01). Maximum systemic plasma concentration (0.93±0.29 μmol/L) remained in subtherapeutic range. Pretreatment with prazosin abolished these effects. Intracoronary nitroglycerin (100 μg) increased LAD coronary artery flow by 112±25% (P=0.02), but the effect lasted <2 minutes; mean arterial pressure decreased by 4±1 mm Hg (P=0.01). Intrafemoral injection of ranolazine (0.24 mg/kg, ie, one-tenth of the systemic bolus) resulted in a 70±19% increase in femoral artery flow (P=0.05) and 26±5% reduction in femoral artery resistance (P=0.004). At 2 minutes after the injection, the femoral flow remained 16±9% above the baseline and dilatory effects occurred without tolerance to repeated injections.

Conclusions—Intracoronary or intrafemoral ranolazine bolus exerts a marked, 2- to 3-minute dilatory effect that is comparable to nitroglycerin in magnitude but more persistent, attributable primarily to α1-adrenergic blockade. (Circ Cardiovasc Interv. 2011;4:481-487.)

Key Words: vasodilation ▪ vasospasm ▪ percutaneous coronary intervention ▪ sodium ▪ potassium ▪ percutaneous peripheral intervention

Ranolazine is an antianginal agent1-4 that has also shown promise in the treatment of atrial fibrillation and in decreasing the incidence of ventricular tachyarrhythmias5-8. In the therapeutic plasma concentration range (2–8 μmol/L), the effects of ranolazine are largely due to inhibition of late sodium current (late INa) and the rapid component of delayed rectified potassium current (IKr) with potencies (IC50 values) of 6 and 12 μmol/L, respectively.1,2 At supratherapeutic plasma concentrations (eg, ≥50 μmol/L), ranolazine also inhibits certain other ion channels and transporters such as late calcium current, sodium-calcium exchanger, and slow component of delayed rectified potassium current.1,2,4

Evidence from studies in rats indicates that ranolazine binds to α1-adrenergic receptors,5 but the hemodynamic significance of this effect is unclear. To our knowledge, the possibility has not been examined whether achieving high local concentrations of ranolazine by intra-arterial administration may promote coronary or femoral vasodilation through an effect on vascular α1-adrenergic receptors. Such an action could be of value in reversing percutaneous coronary intervention (PCI)-induced vasospasm, particularly as ranolazine also exerts anti-ischemic and antifibrillatory actions.1-4,8,10,11

The current investigation explored the possibility that α1-adrenergic receptor–blocking actions of ranolazine could be used in intra-arterial injections to produce local dilation in left anterior descending (LAD) coronary artery or in femoral artery without affecting systemic hemodynamic function.
WHAT IS KNOWN

- Intravenous administration of ranolazine, a novel antianginal agent, can result in a small, short-lived coronary vasodilation in conscious dogs, which is potentially attributable to an α-blocking effect of high concentrations of the drug.

WHAT THE STUDY ADDS

- Our study demonstrates that direct intra-arterial administration of a subsystemic ranolazine dose into the coronary or femoral arteries in an intact porcine model results in a sizeable vasodilation without changes in heart rate or systemic blood pressure.

- The unique vasodilatory effect of intravascular ranolazine occurs without tolerance to repeated injection.

- The possibility that intravascular ranolazine could be useful in reversing vasoconstriction encountered during percutaneous intervention deserves exploration.

Methods

Experimental Preparation

This study conformed to the “Position of the American Heart Association on Research Animal Use,” as well as to the Declaration of Helsinki. The protocol was approved by our institutional animal use committee. Data were gathered in male Yorkshire pigs (n=27) weighing 31.3±2.0 kg (mean±SD). The animals were preanesthetized with telazol (4.7 mg/kg IM) and then anesthetized with either α-chloralose (n=25) or isoflurane (1.5–2.0% by inhalation, n=2). The right femoral artery and vein were cannulated with 8F introducer sheaths, using the Seldinger technique. For intracoronary studies (n=20), a thoracotomy was performed and a Doppler volumetric flow probe (Transonic, Inc, Ithaca NY) was positioned around the origin of the LAD coronary artery. A second flow probe was positioned around the right femoral artery. Arterial blood pressure was continuously monitored from a femoral sheath, and a gauge to monitor aortic arch pressure was connected to the left carotid artery sheath. Intravenous fluids along with investigational drugs were administered into the LAD coronary artery, right femoral artery, or a femoral vein. Intracoronary injections were performed with a 27-gauge needle under direct visualization into the vessel exposed by cutaneous incision (n=8). The injections were administered downstream of the probe position, minimizing the effect of the volume injected in the flow measurement. The left femoral vein was cannulated and an electrode catheter was advanced into the right atrium under fluoroscopic guidance for atrial pacing. ECGs were obtained through a Prucka Cardiolab workstation (GE Medical Systems, Milwaukee, WI).

Drugs

Either ranolazine, nitroglycerin, or saline (control) was injected into the LAD coronary or femoral artery (2 mL bolus in 10 seconds). The ranolazine dose of 0.048 mg/kg (ie, one-fiftieth of the intravenous bolus of 2.4 mg/kg given in our previous series) was used for LAD coronary artery injections (n=20). The dose of 0.24 mg/kg (ie, one-tenth of the intravenous bolus) was used for intrafemoral injections (n=8) because this dose maximally dilated the femoral bed without resulting in systemic hypotension. Nitroglycerin 100 μg, a dose used in clinical practice to alleviate a coronary spasm, was injected into LAD coronary artery (n=8) and nitroglycerin 200 μg was used in the femoral artery (n=8). The time interval between injections was either 5 minutes or the time required for hemodynamic parameters to return to the baseline levels, whichever was longer. Data were analyzed only after intravascular injections in which inserting the needle per se did not disturb flow. Pretreatment with prazosin (300 μg/kg IV), which blocks 90% of α1-adrenoceptor activity, allowed determination of the effect of intra-arterial ranolazine after near-complete α1-adrenoergic receptor blockade (n=8).

The effects of ranolazine on the pressor response to the α1-agonist phenylephrine (5 μg/kg IV) were studied in 6 animals. To preclude a role of L-type calcium channel blockade, diltiazem (0.02 mg/kg IV, across 10–12 minutes) was first administered, and the response to phenylephrine was tested. Thereafter, ranolazine (2.4 mg/kg IV bolus) was then administered and the pressor response to phenylephrine was tested after 2–4 minutes. During phenylephrine administration, heart rate was maintained constant by right atrial pacing at 130 bpm.

Determination of Ranolazine Plasma Concentrations

After intravenous or intrafemoral ranolazine bolus administration, blood samples were collected in sodium heparin tubes at 1, 2, 3, 4, 5, and 10 minutes in 6 animals. The samples were centrifuged and frozen at −80°C until drug level determinations were performed at Gilead Palo Alto, Inc, using a high-performance liquid chromatography–tandem mass spectrometric assay. Quantification of ranolazine was achieved by an internal standard method (deuterated d3 analog of ranolazine, CVT-3023). The quantification limit was 50 ng/mL, using 0.1 mL of plasma. The dynamic range of quantification was 50 to 10 000 ng/mL.

Measured and Calculated Parameters

Heart rate and blood pressure in the right femoral artery and aortic arch were continuously recorded. Rate-pressure product, an index of cardiac metabolic demand, was calculated as heart rate×systolic pressure in the aortic arch. Blood flow in the LAD coronary artery and in the femoral artery was recorded continuously. Arterial resistance for the LAD coronary artery was calculated as mean aortic arch pressure divided by LAD coronary artery flow and for the femoral artery as mean arterial pressure in the femoral artery divided by femoral flow.

Statistical Analysis

All data are expressed as mean±SEM. The analyses were performed on absolute measurements. The overall influence of injection of drugs was assessed with repeated-measures of ANOVA (RANOVA, Figures 1 through 4). For intravenous injection of ranolazine, RANOVA was used in the measurements at baseline and at 1 to 10 minutes after initiation of ranolazine. In the case of intra-arterial injections, RANOVA was applied to all the 6 points in time (baseline, 30 seconds, and each minute from 1–5). If RANOVA was statistically significant, a paired, 2-tailed Student t test with Bonferroni multiple testing correction was used to compare measurements at baseline and at each point in time (Figures 1–4). Figures 2 through 5 are based on percent changes to facilitate visual comparisons. The pressor response to phenylephrine with and without diltiazem and ranolazine was tested using ANOVA with Bonferroni correction for multiple testing (Figure 6). Statistical significance was assumed at P<0.05.

Results

Hemodynamic Changes After Intravenous Ranolazine Administration

Intravenous injection of ranolazine (2.4 mg/kg IV, bolus followed by 0.135 mg/kg per minute) resulted in a transient although significant increase in coronary blood flow and decrease in coronary vascular resistance (Figure 1). Concurrently, there was a brief period of hypotension and a reduction in heart rate.
Hemodynamic Changes After Intracoronary Ranolazine Injection

Rapid administration of ranolazine into the LAD coronary artery of 0.048 mg/kg (one-fiftieth of the systemic bolus of 2.4 mg/kg) to achieve high local concentrations resulted in a 91±11% increase in LAD coronary artery flow and a 39±7% reduction in coronary vascular resistance (peak effects, both, P<0.001, Figure 2, upper panel). At 2 minutes after the injection, the LAD coronary artery flow remained 40±8% (P=0.002) above baseline. Neither heart rate (baseline 128±6 versus 129±6 bpm at peak effect, P=0.15) nor cardiac work metabolic demand as assessed by rate-pressure product (11 077±822 versus 10 893±826 mm Hg×bpm, P=0.20) was altered by intracoronary ranolazine injection, whereas mean arterial pressure minimally decreased (83±5 versus 81±5 mm Hg, P=0.01). Injection of one-twentieth of the systemic bolus (n=4) caused a 90±44% maximum increase in LAD coronary artery flow. Administration of one one-hundredth of the systemic bolus (n=3) exerted only 20% maximum increase in LAD coronary artery flow. Maximum systemic plasma levels with one-fiftieth of the systemic bolus were 0.93±0.29 μmol/L (mean±SD), remaining in the subtherapeutic range.1

Figure 1. Hemodynamic responses to intravenous ranolazine injection. Time courses of coronary artery flow, coronary vascular resistance (intracoronary mean pressure×coronary flow), rate-pressure product (intracoronary systolic pressure×heart rate), heart rate, and mean arterial pressure (n=7) after ranolazine administration (2.4 mg/kg IV bolus, followed by 0.135 mg/kg per minute infusion). The probability values are from repeated ANOVA, using the measurements at baseline and at 1–10 minutes after initiation of ranolazine. Asterisk indicates significant changes from baseline.
In comparison, intracoronary nitroglycerin (100 μg) increased LAD coronary artery flow by 112/25% (peak effect, P=0.02) and reduced coronary vascular resistance by 37/8% (peak effect, P=0.01) without change in heart rate (P=0.42) or rate-pressure product. Intracoronary ranolazine and nitroglycerin exerted significant LAD coronary vasodilation, as evidenced by an increase in LAD coronary artery flow and decrease in coronary vascular resistance. With both agents, LAD coronary artery vasodilation occurred in the absence of changes in cardiac metabolic demand, as evidenced by a relatively unchanging rate-pressure product. No sustained vasodilatory changes occurred after intracoronary saline administration. Asterisk indicates significant changes from baseline.

Intracoronary Ranolazene Injection

After α₁-Adrenergic Blockade

Prazosin (300 μg/kg IV) decreased systolic (from 95±5 to 83±2 mm Hg, P=0.04) and mean (from 79±5 to 65±1 mm Hg, P=0.03) blood pressure and tended to decrease diastolic pressure (from 65±6 to 50±2 mm Hg, P=0.06). Thereafter, intracoronary injection of ranolazine (0.048 mg/kg, ie, one-fiftieth of the systemic dose) neither increased LAD coronary artery flow (41±13%, P=0.11) nor decreased LAD coronary artery resistance (23±7%, P=0.09, n=8, Figure 3) significantly. The maximum increase in LAD flow, as well as the duration of the effect of ranolazine, was decreased compared with that observed in the absence of prazosin.

Hemodynamic Changes After Intrafemoral Artery Injection of Ranolazene

Intrafemoral artery injection of ranolazine (0.24 mg/kg, ie, one-tenth of the systemic bolus) resulted in 70±19% increase in femoral artery flow (P=0.05) and 26±5% reduction in femoral artery resistance (P=0.004) (Figure 4). At 2 minutes after injection, femoral artery blood flow (P=0.05) and femoral vascular resistance (P=0.004) significantly decreased compared with baseline.

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Figure 2. Comparative coronary artery vasodilatory response to intracoronary ranolazine and nitroglycerin administration. Influence of intracoronary ranolazine 0.048 mg/kg (solid lines, upper panel), intracoronary nitroglycerin 100 μg (dashed lines, upper panel), and intracoronary saline (lower panel) injection on left anterior descending (LAD) coronary artery flow, coronary vascular resistance, and rate-pressure product. Intracoronary ranolazine and nitroglycerin exerted significant LAD coronary vasodilation, as evidenced by an increase in LAD coronary artery flow and decrease in coronary vascular resistance. With both agents, LAD coronary artery vasodilation occurred in the absence of changes in cardiac metabolic demand, as evidenced by a relatively unchanging rate-pressure product. No sustained vasodilatory changes occurred after intracoronary saline administration. Asterisk indicates significant changes from baseline.

Figure 3. Attenuation of intracoronary ranolazine-induced coronary artery vasodilation by prazosin. Effects of α₁-receptor blockade with prazosin (300 μg/kg IV) on the vasodilatory response to intracoronary injection of ranolazine 0.048 mg/kg (n=8). Blockade of α₁-receptors markedly attenuated the effects of ranolazine on left anterior descending coronary artery flow and vascular resistance. None of the changes were significant with comparison to baseline.

Figure 4. Comparative femoral artery vasodilatory response to intrafemoral ranolazine or nitroglycerin injection. Effects of intrafemoral ranolazine 0.24 mg/kg (solid lines) and intrafemoral nitroglycerin 200 μg (dashed lines) on femoral artery blood flow, femoral vascular resistance, and rate-pressure product are shown. Intrafemoral ranolazine and nitroglycerin exerted significant vasodilation, as evidenced by an increase in femoral artery blood flow and decrease in femoral vascular resistance. Asterisk indicates significant changes from baseline.
after the injection, femoral flow remained 16±9% above the baseline. Heart rate marginally increased (baseline 125±9 vs 127±10 bpm at peak effect, \( P=0.05 \)), whereas mean arterial pressure (93±5 vs 91±5 mm Hg, \( P=0.13 \)) and rate-pressure product (13 463±1113 vs 13 512±1124 mm Hg×bpm, \( P=0.64 \)) remained at preinjection levels. Femoral artery flow was not significantly altered by intravenous (5.9±4.9%, \( P=0.25 \)) or intracoronary injection of ranolazine (0.7±2.6%, \( P=0.80 \)).

Intrafemoral artery injection of nitroglycerin (200 μg) resulted in 46±9% increase in femoral artery flow (\( P=0.008 \)) and 21±7% reduction in femoral artery resistance (\( P=0.11 \)) (Figure 4). At 2 minutes after the injection, the femoral flow remained 1±4% above the baseline.

Repetitive injection of ranolazine at one-tenth of the systemic bolus into the femoral artery resulted without tolerance in significant increases in flow by 72–74% and decreases in vascular resistance by 23–28% with each of 3 sequential injections (Figure 5).

Effects of Intravenous Ranolazine Injection on the Pressor Response to Phenylephrine

Three test boluses of phenylephrine (5 μg/kg IV) were administered. First, the drug was given alone. Second, diltiazem was infused to rule out a role for L-type channels. The third injection followed ranolazine administration. Although diltiazem attenuated the pressor response, the effect of ranolazine was significantly more marked, implicating an important effect of ranolazine in inhibiting \( \alpha_1 \)-adrenergic stimulation (Figure 6).

Discussion

To our knowledge, the present study is the first to demonstrate that intracoronary or intrafemoral administration of ranolazine induces local vasodilation. The dilation appears to result from a direct effect on the coronary vasculature due to \( \alpha_1 \)-adrenergic antagonism and not to changes in cardiac metabolic demand, as rate-pressure product was not altered. The increase in coronary artery flow was comparable to that elicited by intra-arterial injection of nitroglycerin, the gold standard to alleviate intervention-induced vasospasm. However, the vasodilatory effects of ranolazine were more persistent than those of nitroglycerin. Neither agent caused in an appreciable change in systemic blood pressure. Femoral artery dilation by ranolazine was achieved without drug tolerance.

Previous Studies

Ranolazine administration has been shown to result in an anti-ischemic effect through novel mechanisms of action that decrease anginal frequency and improve exercise capacity in patients with chronic stable angina. The basis for alleviation of myocardial ischemia appears to be inhibition of the late phase of the inward sodium current, which is augmented during myocardial ischemia and heart failure, with consequent attenuation of intracellular calcium overload. This effect in turn improves ventricular diastolic compliance, thereby reducing compressive forces on the coronary arteries and increasing late diastolic coronary artery flow. Clinical studies have demonstrated that the improvement in coronary hemodynamic function occurs in the absence of changes in heart rate and arterial blood pressure. The anti-ischemic effects of ranolazine may also account in part for its antiarrhythmic effects in patients with acute coronary syndrome. However, it is also well documented that ranolazine has direct antiarrhythmic effects on the myocardium as shown in vitro studies and in intact large animal investigations, in which the agent was shown to reduce ischemia-induced T-wave alternans and to increase the ventricular fibrillation threshold during fixed-flow coronary artery stenosis. However, little is known about the effect of ranolazine on coronary or femoral artery hemodynamic function. Ma et al reported that a 4-week regimen of large oral doses of ranolazine in patients with intermittent claudication increased pain-free walking time.
Recently, Zhao et al. demonstrated in conscious canines that intravenous ranolazine exerts a transient, dose-dependent increase in coronary blood flow and decrease in vascular resistance that lasted <1 minute. There is a corresponding increase in heart rate, left ventricular contractility, and a decrease in mean arterial pressure. Autonomic blockade with hexamethonium enhanced hypotension and abolished the increase in heart rate. Antiadrenergic effects of ranolazine in response to the α-agonist phenylephrine and the β-agonist isoproterenol were demonstrable only at higher ranolazine plasma concentrations >10 μmol/L and concurrent autonomic blockade.

Present Study

Our results concur with the finding by Zhao et al. that intravenous injection of ranolazine results in a transient coronary vasodilation with concurrent, brief hypotension. Rather than reflex sinus tachycardia, we observed bradycardia. The basis for this finding is unclear. One possibility is that autonomic reflexes are more powerful in the conscious canine than in the anesthetized porcine. In addition, the more sustained bolus over 1–2 minutes as compared with 30 seconds may have caused a sufficiently persistent peak in ranolazine that could have inhibited I_{Ca,L} slowing the sinoatrial node. Such an effect could be akin to the pattern observed in response to calcium channel blockers, which can cause hypotension with concurrent reduction in heart rate due to direct effects of the agent in suppressing sinus node activity.

In the present investigation, we explored a new approach to increasing coronary and femoral artery flow and vasodilation by direct intra-arterial delivery of ranolazine to achieve high local concentrations in these vascular beds. The rationale was that the increased local concentrations of ranolazine beyond the traditional therapeutic levels would have the potential to recruit other potential vasodilatory mechanisms, particularly α₁-adrenergic receptor blockade. Intracoronary administration of ranolazine (0.048 mg/kg, ie, one-fiftieth of the traditional therapeutic levels) could have inhibited I_{Ca,L} slowing the sinoatrial node. Such an effect could be akin to the pattern observed in response to calcium channel blockers, which can cause hypotension with concurrent reduction in heart rate due to direct effects of the agent in suppressing sinus node activity.16

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The precise site of action of ranolazine is unknown. Relaxation may have occurred in both the large epicardial vessels as well as the small resistance vessels. α₁-Adrenergic–blocking agents such as prazosin are known to affect both large and small vessels. However, because the small vessels have a much greater effect on vascular resistance than on epicardial vessels, it is likely that this site of action was primarily involved in the increase in flow and decrease in vascular resistance for both coronary and femoral arteries (Figure 2; upper panel, 4). However, a concurrent effect of ranolazine on large vessel diameter remains a possibility, although not tested in the present study.

By comparison, nitroglycerin exerts its primary effect on epicardial vessels, although it is not without influence on downstream arteries.17–19 Vessels in the range of 200–300 μm are highly responsive to nitroglycerin and those in the range of 100–200 μm demonstrated an intermediate response to the drug, while those in the range of <100 μm responded minimally. Thus, segments of the vascular tree that contribute to coronary vascular resistance (100–300 μm) were likely to have been influenced by nitroglycerin, leading to an increase in coronary artery blood flow and decrease in coronary vascular resistance.

Mechanisms of Ranolazine

In light of evidence from studies conducted in rats and rabbits indicating that ranolazine binds to α₁-adrenergic receptors20 and influences ischemia-induced upregulation of these receptors,9 there has been interest in examining whether the drug may exert an effect on vasomotor responsiveness. Ranolazine has been shown in rabbits to blunt the pressor effects of the α₁-agonist methoxamine in a dose-dependent manner.20 The present observation that intravenous administration of ranolazine markedly reduced the pressor response to the selective α₁-agonist phenylephrine is also consistent with an antiadrenergic action (Figure 6). However, unlike the α₁-adrenergic blocker prazosin, ranolazine did not produce a rightward shift of the dose-response curve of the pressor effects of phenylephrine.20 Because of the differing responses to the 2 different α₁-agonists, it was suggested that the effects of ranolazine in inhibiting α₁-mediated vasoconstriction may in part be functional, as compared with the potent and selective α₁-antagonist prazosin.20 After prazosin administration, the vasodilatory response to ranolazine was no longer statistically significant (Figure 3). This observation does not entirely preclude a potential effect of ranolazine in counteracting vasoconstriction through an effect on calcium influx, as this agent has been shown at high concentrations to inhibit late I_{Ca,L} current in cardiac myocytes.1 The possibility that ranolazine influences this current in vascular smooth muscle deserves exploration, as disturbances in intracellular calcium handling have been implicated in vasospastic disease.17,21 We are unaware of any information that suggests that peak sodium or potassium channel inhibition may contribute the vasodilatory effect of ranolazine.

Limitations

The question arises as to whether α-chloralose anesthesia may have influenced vasoreactivity, which could potentially limit extrapolation of the results to conscious humans. We selected α-chloralose for our investigations because extensive evidence from several laboratories, including our own, demonstrated that this agent has minimum disruptive effects on vascular smooth muscle reactivity. Cox in particular provided systematic evidence comparing vasoreactivity in chronically instrumented dogs during both the awake state and after α-chloralose anesthesia.22 He demonstrated that after 15 minutes of anesthesia, hemodynamic variables were equivalent to the preanesthesia state. He also demonstrated that...
responses to adrenergic agents including norepinephrine and isoproterenol were only slightly affected by α-chloralose. Also, he found no direct action on vascular smooth muscle responsiveness. These findings are consistent with our previous investigations of coronary-reactive phenomena in conscious canines and those under α-chloralose anesthesia. An important question for future investigations is clarification of the relative effects of ranolazine on epicardial and small coronary resistance vessels.

Conclusions and Implications

Intracorony or intrafemoral ranolazine bolus injection exerts a transient α1-adrenergically mediated primary dilation effect that is comparable to nitroglycerin in magnitude but is more persistent and does not exhibit tolerance (Figure 5). The significant inhibition of α1-adrenergic receptors by ranolazine delivered locally could potentially counteract high levels of adrenergic tone, such as may occur in clinical conditions that predispose to inappropriate vasoconstriction. Ranolazine has previously been shown to confer anti-ischemic and antifibrillatory actions, and the effects reported in this article suggest that the drug could be useful in reversing vasoconstriction encountered during percutaneous intervention.

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Disclosures

Dr Belardinelli is employed by Gilead Palo Alto, Inc, all other authors declare no conflict of interest.

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