nicorandil is a nicotinamide nitrate used as an antian- ginal agent. It has two modes of action. First, by opening adenosine triphosphate–dependent potassium channels, nicorandil increases transmembrane potassium conductance and relaxes peripheral and coronary arteries. Second, with its nitrate moiety, nicorandil increases intracellular concentrations of cGMP, resulting in peripheral vein and coronary artery dilation. Thus, because of its ability to dilate arteries and veins, nicorandil maximizes coronary flow while concomitantly reducing myocardial work through reductions in afterload. For these reasons, nicorandil has been successful in managing angina and hypertension. However, growing evidence suggests that this drug provides additional benefits that reach beyond its original therapeutic indications.

Recently, the Impact of Nicorandil in Angina (IONA) study demonstrated significant improvement in outcomes in patients with angina when comparing a composite end point of morbidity and mortality attributable to coronary heart disease, nonfatal myocardial infarction, and unplanned hospital admission for chest pain.1 The consensus regarding the success of nicorandil in IONA purports an association between cardiac preservation and mitochondrial adenosine triphosphate–dependent potassium (K\textsubscript{ATP}) channel activation.2 In light of what is already known about K\textsubscript{ATP} channels, this is a germane conclusion, specifically, with regard to the pivotal role K\textsubscript{ATP} channels play in cardiac preconditioning and the beneficial actions that are associated with K\textsubscript{ATP} channel activation.

For more than a decade, the connection between K\textsubscript{ATP} channels and cardiac preconditioning has been known. Numerous studies pertaining to ischemic preconditioning, a phenomenon whereby intermittent bouts of transient ischemia render the heart more resistant to future ischemic insults,2 have demonstrated, in some way, the involvement of K\textsubscript{ATP} channels. More specifically, experiments using nicorandil have demonstrated cardioprotection through preconditioning by selectively activating mitochondrial K\textsubscript{ATP} channels.3 Studies using reversible and irreversible ischemic injury models have demonstrated nicorandil could preserve contractile function and reduce infarct size, respectively.4 Taken collectively, these studies demonstrate that nicorandil provides the same cardioprotective benefits through pharmacological means that can be achieved through small bouts of ischemia. Although the connection between cardioprotection and K\textsubscript{ATP} channel activation is known, the molecular basis in which nicorandil achieves this cardioprotective benefit has yet to be discerned. Until now, the major underlying reasons explaining the benefits associated with K\textsubscript{ATP} channel activation have focused on the conservation of adenylate energy charge, protection of mitochondrial function, preservation of mitochondrial integrity, and protecting myocardial cells from apoptosis.5 Only recently has the notion come under investigation that preconditioning could initiate cardiac angiogenesis.6

Angiogenesis initiated by ischemic preconditioning has been shown to trigger a molecular cascade resulting in increased vascular endothelial growth factor (VEGF), a proangiogenic factor, and B-cell lymphoma (Bcl)-2, an anti-apoptotic factor.6 Although it is known that nicorandil increases Bcl-2,7 a connection between K\textsubscript{ATP} channel activators and increased VEGF expression has not been demonstrated. Moreover, the stimulation of capillary and arteriolar growth in the myocardium as a result of nicorandil administration has also been unexplored. In this regard, the work by Xu et al entitled “Nicorandil promotes capillary and arteriolar growth in the failing heart of Dahl salt-sensitive hypertensive rats” demonstrates for the first time that K\textsubscript{ATP} channel activation with nicorandil promotes coronary capillary and arteriolar growth.8 In addition, the Xu study demonstrated that two well-known proangiogenic factors, basic fibroblast growth factor (bFGF) and VEGF,9,10 could be upregulated and associated with nicorandil-mediated vascular growth.8 These findings are interesting for several reasons. First, until now, there were questions regarding whether VEGF actions in angiogenesis were mediated by other angiogenic growth factors. By demonstrating VEGF and bFGF upregulation is associated with nicorandil-mediated vascularization, the Xu study has partially addressed this concern.8 Second, by establishing a connection between nicorandil and proangiogenic factors, this study has demonstrated a potential nonsurgical modality to enhance collateral coronary circulation in patients at high risk for coronary artery disease. Third, pharmacological upregulation of VEGF and bFGF by nicorandil provides an alternative to gene therapy. Finally, knowing that K\textsubscript{ATP} channel activators are associated with angiogenesis, K\textsubscript{ATP} channel blockade may initially provide insight into the molecular basis governing tumor and neoplastic angiogenesis.

By demonstrating that a nonantihypertensive dose of nicorandil preserved hemodynamic function and forestalled pathological cardiac remodeling in hypertensive Dahl salt-
sensitive rats, the Xu study supports the notion that nicorandil is cardioprotective. Moreover, the authors have demonstrated that \( K_{\text{ATP}} \) channel activators could provide a benefit to heart failure patients by increasing vascular growth. To these ends, the Xu study advanced our understanding toward the cardioprotective attributes of nicorandil. However, these findings raise important issues for future studies. Specifically, because nicorandil has two modes of action, it is not clear whether the beneficial actions of nicorandil are indirectly related to increased shear created by this potent vasodilator or by the direct action of nicorandil acting at some point along the molecular cascade associated with preconditioning. This is of particular importance because pathological cardiac remodeling was still inhibited, and angiogenesis still occurred despite the elevated blood pressure in the nicorandil-treated Dahl salt-sensitive rats. Moreover, it would be interesting to see whether other antihypertensive drugs administered concomitantly with nicorandil would improve or exacerbate the reported finding. Equally as important is whether antihypertensive doses of nicorandil would have the same effects on capillary and arteriolar growth in the absence of pressure overload.

As a result of the Xu study, we gained a better understanding of the salutary effects of nicorandil. In doing so, we learned of another potential mechanism whereby \( K_{\text{ATP}} \) channels are cardioprotective and may reduce morbidity and mortality from cardiovascular disease. In addition, we have uncovered yet another pathway that, like multiple diverse signaling pathways, seems to converge on \( K_{\text{ATP}} \) channel activation. With this in mind, we still need to know definitely whether the \( K_{\text{ATP}} \) channel is an initiator, mediator, or end-effector in these various pathways. This is especially important if \( K_{\text{ATP}} \) channel activators are going to be a future therapeutic target for pharmacological preconditioning in patients at risk for heart disease or as a therapy for vascular dysfunction.

References

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