Impaired Hypoxic Coronary Vasodilation and ATP-Sensitive Potassium Channel Function
A Manifestation of Diabetic Microangiopathy in Humans?

Neal L. Weintraub

Hypoxic coronary vasodilation contributes to the maintenance of oxygen supply to the working heart during increased metabolic demand. Mechanisms of hypoxic coronary dilation have been studied extensively and differ considerably depending upon the species and experimental model. In isolated coronary vessels, several mechanisms have been implicated either alone or in combination, including release of vasodilatory factors (ie, nitric oxide, prostaglandins, and adenosine), activation of ATP-sensitive potassium (KATP) channels and Ca\(^{2+}\)-activated K\(^{+}\) channels, and inhibition of voltage-gated Ca\(^{2+}\) channels. To date, however, relatively few studies have been conducted in human blood vessels. Furthermore, whereas most prior studies have examined hypoxic dilation in conduit coronary arteries, coronary microvessels (<150 μm in diameter) are considered to be the principal regulators of coronary blood flow in response to metabolic stress. Thus, despite extensive studies conducted over the past several decades, surprisingly little is known about mechanisms of hypoxic coronary microvascular dilation in humans, and how it might be altered in disease states.

In this issue of Circulation Research, Miura and colleagues provide evidence that hypoxic dilation of human coronary microvessels is mediated primarily by activation of KATP channels in vascular smooth muscle cells (SMCs), independent of the endothelium. Moreover, they report that both hypoxic dilation and vasodilation induced by the KATP opener aprikalim are attenuated in microvessels from patients with diabetes mellitus, suggesting impaired KATP function. These findings provide new insight into mechanisms of coronary vasoregulation in humans, and they suggest that impaired microvascular KATP channel function might contribute to increased cardiovascular morbidity and mortality in patients with diabetes.

KATP channels are distributed in a variety of tissues, including cardiomyocytes, SMCs, skeletal muscle, and pancreatic β-cells. These octameric channels are composed of four inwardly rectifying potassium channel subunits (Kir) and four regulatory sulfonylurea receptor subunits (SUR). Channel complexes composed of less than 8 subunits are retained in the endoplasmic reticulum and thus cannot be targeted to the cell membrane. Two different KIR (KIR6.1 and KIR6.2) and SUR (SUR1 and SUR2) gene products have been identified to make up KATP channels. Splice variants of SUR2 (SUR2A and SUR2B) further add to the structural diversity of KATP channels. The molecular structure of KATP channels varies depending upon the species and tissue and is an important determinant of channel function, including sensitivity to ATP, nucleotide diphosphates, and potassium channel openers (KCO). Channel activity may also be regulated by posttranslational modification (ie, glycosylation, phosphorylation, and inositol phosphate metabolism). A characteristic feature of KATP channels is inhibition by sulfonylurea compounds such as glibenclamide.

Recently, Farouque et al demonstrated that intracoronary infusion of glibenclamide reduced resting coronary blood flow in humans, suggesting that KATP channels contribute to basal regulation of the coronary circulation. In coronary arterioles from the right atrial appendages of humans (the same vessels used in the present study), nicorandil, a nonselective KCO compound, was demonstrated to induce vasodilation that was unaffected by methylene blue but markedly attenuated by glibenclamide, consistent with activation of KATP channels. The study by Miura et al confirms and extends these findings by demonstrating that dilation to aprikalim, a selective KCO, is markedly attenuated by glibenclamide, but unaffected by removal of the endothelium or by inhibitors of nitric oxide synthase or cyclooxygenase. These findings confirm that KATP channels are functionally expressed in human coronary microvessels and indicate that aprikalim acts directly on these channels to produce microvascular dilation.

The authors also provide evidence that Kir6.1 and SUR2B are expressed in human coronary microvessels. Deletion of Kir6.1 in mice was recently shown to induce coronary vasospasm and to block vasodilatory responses to KCO in vivo and in vitro, implying that this subunit is a constituent of coronary vascular SMC KATP channels. Also, deletion of SUR2 resulted in increased blood pressure in mice. Among the SUR2 variants, SUR2B is thought to be the most prevalent in vascular SMCs. Interestingly, coexpression of Kir6.1 and SUR2B formed a channel that was not sensitive to inhibition by ATP, although the channel was robustly activated by nucleotide diphosphates and KCO, and it was inhibited by glibenclamide. Thus, the channel is perhaps
better classified as a nucleotide diphosphate-dependent K\(^+\) channel, rather than a K\(_{ATP}\) channel. It remains to be determined whether the K\(^+\) channels described in this study in human coronary microvessels exhibit the same functional characteristics as Kir6.1/SUR2B.

Diabetes in humans is associated with a substantial increase in risk of development of cardiovascular disease.\(^{16,17}\) Moreover, diabetics that suffer myocardial infarction have increased morbidity and mortality as compared with nondiabetics.\(^{18,19}\) Many factors likely contribute to the increased cardiovascular risk and adverse outcomes associated with diabetes, including concurrent dyslipidemia and hypertension, altered myocardial metabolism, etc.\(^{20}\) The use of older sulfonylurea drugs such as glibenclamide has also been associated with adverse cardiovascular outcomes in some studies,\(^{21,22}\) perhaps due to inhibition of mitochondrial K\(_{ATP}\) channels that mediate ischemic preconditioning in the myocardium.\(^{23}\)

In the present study, impairment of vascular K\(_{ATP}\) channel function was observed in coronary microvessels from patients with diabetes. The findings are consistent with recent reports showing impaired relaxation responses to KCO in human saphenous veins and corporeal tissue strips from diabetic patients.\(^{24,25}\) In the study by Miura et al,\(^{7}\) K\(_{ATP}\) dysfunction in human coronary microvessels cannot be ascribed to sulfonylurea drugs, because impaired dilation to aprikalim was observed in microvessels from type I as well as type II diabetics (patients with type I diabetes are not treated with sulfonylurea drugs). Also, because the inhibitory effects of glibenclamide were reversible, rinsing the microvessels should have removed the drug even if it were taken before surgery. Endothelial dysfunction is commonly observed in diabetics, and impaired KCO-dependent dilation of cerebral arteries from diabetic rats was attributed to endothelial dysfunction.\(^{26}\) In the present study, dilation to aprikalim was unaffected by removal of the endothelium, and endothelium-dependent responses to bradykinin were similar in microvessels from diabetics versus nondiabetics. Consequently, the impaired dilatory responses observed in diabetic microvessels were not due to endothelial dysfunction. Finally, hypertension and hyperlipidemia are present in many diabetics and have been associated with impaired K\(_{ATP}\) channel-dependent relaxation;\(^{27}\) however, data analysis suggests that these conditions did not account for the findings of the present study. The presence of coronary artery disease was likewise not correlated with microvascular K\(_{ATP}\) channel dysfunction. Thus, taken together, these findings suggest that impaired coronary microvascular K\(_{ATP}\) function is intrinsic to diabetes in humans. A number of issues remain to be resolved; for example, the patients in this study were predominately elderly, and most had atherosclerosis severe enough to warrant bypass surgery. Therefore, it is possible that microvascular K\(_{ATP}\) dysfunction is specific to this subset of patients with diabetes. Also, the relationship between microvascular K\(_{ATP}\) function and metabolic control can not be ascertained from available data. Finally, the potential modulating influence of medications such as insulin, insulin-sensitizing agents, and inhibitors of the renin-angiotensin system on microvascular K\(_{ATP}\) function in these patients is unknown.

What might account for impaired coronary microvascular K\(_{ATP}\) function in diabetes? The cellular and metabolic abnormalities linked to diabetic microvascular disease in the kidneys, eyes, and peripheral nerves are likely suspects (Figure). Elevated blood glucose per se, which is strongly associated with diabetic microvascular disease, could be the major instigator. Admission blood glucose and hemoglobin A\(_1c\) were identified to be independent predictors of mortality in diabetics with acute myocardial infarction, and improved metabolic control after infarction was associated with reduced long-term mortality. Elevated glucose was demonstrated to acutely impair voltage-gated K\(^+\) channel function in rat coronary arteries through generation of reactive oxygen species. Whether acute hyperglycemia also impairs coronary microvascular K\(_{ATP}\) channel function, and the mechanisms by which this might occur, remain to be determined.

What are the potential clinical implications of coronary microvascular K\(_{ATP}\) channel dysfunction in diabetes? Assuming that responses in atrial microvessels can be extrapolated to coronary resistance vessels in general, the findings by Miura et al\(^{7}\) suggest that K\(_{ATP}\) channel dysfunction could contribute significantly to myocardial ischemia in patients with diabetes. Interestingly, some patients with diabetes suffer from microvascular angina (chest pain due to myocardial ischemia in the absence of obstructive epicardial coronary artery disease). Although this disorder has been associated with endothelial dysfunction and insulin resistance, perhaps microvascular K\(_{ATP}\) channel dysfunction is a contributing factor. In addition, impaired metabolic coronary arteriolar vasodilation due to K\(_{ATP}\) channel dysfunction could potentially increase the extent of myonecrosis and contribute to worsened prognosis in diabetic patients who suffer myocardial infarction. Finally, if K\(_{ATP}\) channel dysfunction affects resistance vessels in general, it could contribute to systemic hypertension. Potential consequences of microvascular K\(_{ATP}\) channel dysfunction in diabetes are summarized in the Figure.

In summary, the study by Miura and colleagues establishes a role for K\(_{ATP}\) channels in mediating hypoxic coronary microvascular dilation in humans, and it suggests that dys-
function of K_{ATP} channels represents a manifestation of diabetic microangiopathy that could help to explain the increased incidence of cardiovascular disease in diabetic patients.

References


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