Unveiling the Mechanism of Coronary Metabolic Vasodilation
Voltage-Gated Potassium Channels and Hydrogen Peroxide

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Most organs are able to modulate both blood flow and oxygen extraction to meet oxygen demand during increases in metabolism. However, the heart extracts oxygen near maximally (60%–80%) at rest and, therefore, relies almost exclusively on changes in perfusion to meet this demand. This requires moment-to-moment changes in arteriolar (resistance artery) tone to match changes in oxygen demand with flow. It is generally thought that a metabolic dilator substance released from the myocardium serves as the signal for vasodilation. However, despite several decades of investigation, the chemical mediator of cardiac metabolic dilation remains elusive.

Recently, Chilian laboratory has proposed hydrogen peroxide (H$_2$O$_2$) as the link between cardiac metabolism and coronary dilation. Although H$_2$O$_2$ had been studied extensively as an endothelium-derived vasodilator, its role in metabolic dilation had not been well-defined. H$_2$O$_2$ has several characteristics that support a role in metabolic dilation. It is a product of cardiac metabolism, is produced in large quantities proportional to mitochondrial respiration, is cell membrane permeable, and has a sufficiently long half-life to serve as an intercellular signaling molecule. H$_2$O$_2$ elicits a dose-dependent dilation in coronary arterioles.

On the basis of these characteristics, H$_2$O$_2$ has been studied as a mediator of metabolic dilation. Chilian laboratory used a bioassay where effluent from freshly isolated cardiomyocytes was dripped onto rat coronary arterioles. The resulting dilation was shown to be catalase-sensitive and related to the metabolic rate of the cultured myocytes. A variation of that preparation was used by Shimokawa laboratory, where pressurized coronary arterioles from a rabbit were placed on a canine beating heart. Pacing the dog heart induced a catalase-inhibitable dilation in the overlying rabbit arteriole, suggesting a role for H$_2$O$_2$ in metabolic dilation. Similar support for a role for H$_2$O$_2$ was observed in an in vivo dog model, where pacing-induced epicardial coronary arteriolar dilation was observed during increases in metabolism.

Over the past 5 years, a role for H$_2$O$_2$ in metabolic dilation has emerged, but the mechanism by which H$_2$O$_2$ elicits this dilation remains unclear. Numerous candidate pathways exist, including activation of Kca channels, Katp channels, endothelial nitric oxide synthase, Akt, and protein kinase G. Paradoxically, in some cases, H$_2$O$_2$ can inhibit these same pathways. H$_2$O$_2$ can also mediate mitochondrial Katp-induced dilation by stimulating calcium sparks on vascular smooth muscle cell membranes.

Rogers et al expanded on these mechanisms by which H$_2$O$_2$ can elicit dilation by demonstrating a role for Kv channels. Saiioh et al in the same laboratory extended that observation to metabolic dilation in the heart. Using the same bioassay described above, cardiomyocyte effluent elicited a 4-aminopyridine-sensitive vasodilation suggesting a role for Kv channels. Unfortunately, >70 genes encoding for voltage-gated K+ channels have been identified in the human genome. Most of these channels are blocked by 4-aminopyridine, many of which are expressed in vascular smooth muscle cell. Furthermore, 4-aminopyridine is not specific, blocking Katp channels as well.

In this article, Ohanyan et al provide compelling evidence of a critical role for a specific Kv channel mediating myocardial metabolic dilation. They show blunted metabolic dilation in a mouse with global absence of the redox-sensitive Kv1.5 channel. Return of function was observed when Kv1.5 was conditionally restored only to vascular smooth muscle in knockout animals using a doxycycline switch-on approach.

Two key elements of this article deserve special emphasis. This is the first study to use genetic techniques to determine the role of an ion channel in metabolic dilation. This provides long-needed confirmation of previous studies that relied almost exclusively on pharmacological modulation of channel activity, and sets a new bar for future investigation of vascular physiological studies using rodent models. Second, the authors use the innovative technique of contrast echocardiography to measure myocardial perfusion in the intact mouse heart, validating these measurements with the gold standard, microspheres. This echo technique allows for serial measurements of myocardial perfusion over time in anesthetized rodents, merging the ability to assess complex physiology over time (previously available only in larger animal species) with access to a large cadre of genetically modified animals. This creates a powerful platform for investigating physiological responses at a molecular level.

This study focuses on physiology in healthy strains of mice. A role for reduced Kv channel function in diabetes...
null animals. This fits with the well-described role of Kv channels in controlling resting membrane potential and resting, steady-state vascular tone.

In summary, Ohanyan et al. provide compelling evidence that Kv1.5 α-subunit in smooth muscle is involved in controlling metabolic coronary flow during increased cardiac work. Absence of this subunit decouples myocardial blood flow from oxygen consumption, resulting in tissue hypoxia and eventual failure to maintain blood pressure. Reintroduction of the Kv1.5 subunit in smooth muscle rescues the abnormal phenotype, eliminating the imbalance in tissue oxygenation during increased metabolic demand. This study is the first to address coronary metabolic control of blood flow in vivo using a genetic approach, and sets the stage to explore the intricate mechanism(s) of metabolic dilation not possible using traditional methods, with important implications for human cardiovascular disease.

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References


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