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 ($H_2O_2$) as the link between cardiac metabolism and coronary dilation. Although $H_2O_2$ had been studied extensively as an endothelium-derived vasodilator, its role in metabolic dilation had not been well-defined. $H_2O_2$ 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. $H_2O_2$ elicits a dose-dependent dilation in coronary arterioles.

On the basis of these characteristics, $H_2O_2$ 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 $H_2O_2$ in metabolic dilation. Similar support for a role for $H_2O_2$ 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 $H_2O_2$ in metabolic dilation has emerged, but the mechanism by which $H_2O_2$ elicits this dilation remains unclear. Numerous candidate pathways exist, including activation of $Kca$ channels, $Kap$ channels, endothelial nitric oxide synthase, Akt, and protein kinase G. Paradoxically, in some cases, $H_2O_2$ can inhibit these same pathways. $H_2O_2$ can also mediate mitochondrial $Kap$-induced dilation by stimulating calcium sparks on vascular smooth muscle cell membranes.

Rogers et al expanded on these mechanisms by which $H_2O_2$ can elicit dilation by demonstrating a role for $Kv$ channels. Saitoh 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 $Kap$ 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...
mellitus has been suggested by Li et al, where high glucose or diabetes mellitus can reduce dilation to Kv channel activation by raising levels of reactive oxygen species. Because reactive oxygen species are implicated in impaired vasodilation in a variety of cardiovascular diseases, the role of Kv channels in vascular pathophysiology could be profound.

Uncoupling vasodilation from myocardial metabolism by eliminating Kv1.5 was associated with myocardial hypoxia and reduced pressure generation during increased cardiac work. This has implications for other situations characterized by impaired coronary microvascular dilation. Microvascular disease has been linked with a host of cardiomyopathic conditions, including diabetes mellitus, hypertension, Takatsubo cardiomyopathy, and more recently heart failure with preserved ejection fraction. The no-reflow phenomenon observed after coronary reperfusion after percutaneous coronary intervention is a microvascular disease consisting of reduced vasomotor responsiveness and anatomic obstruction. The role of dysfunctional Kv1.5 channels in these conditions is supported by reduced vascular expression of Kv1.5 in patients with hypertension.

The focus on Kv1.5 is laudable but as the authors suggest, it is likely that cardiac metabolic dilation is mediated by redundant mechanisms so that blocking one will not be sufficient to eliminate dilation. Indeed, after removal of Kv1.5, a residual dilation was observed to both H2O2 and metabolic stimulation. Tune et al showed the combined, but not individual, importance of KATP, nitric oxide synthase, and adenosine in mediating exercise-induced coronary dilation in a dog model. The extent to which other putative metabolic dilators play a role in this study was not tested. The situation may be more complex because Kv channels exist as functional heterotetrameric units. Elimination of Kv1.5 in this study was associated with upregulation of Kv1.2 and Kv1.3. Kv1.5 may also play a role in metabolic dilation. Thus, compensatory dilation may occur through other mediators or via H2O2 acting on ion channel complexes of different compositions.

It is interesting to speculate that metabolic dilation comprises a multistep process, one responsible for initiation and another for maintenance of dilation. This concept has been proposed for metabolic dilation in skeletal muscle, where blood flow can be regulated within a second of the onset of contraction (similar responsiveness has been described in the coronary circulation). Although numerous compounds have been proposed as the metabolic dilator in skeletal muscle, including lactate, oxygen, ATP, nitric oxide, hydrogen, or potassium ions, none dilates vessels rapidly enough (<1 s) to mimic metabolic dilation, nor has blocking of any of them eliminated metabolic dilation. Multiple mediators with different dilator mechanisms probably participate in skeletal muscle metabolic dilation, supporting the importance of both redundancy and diversity in the responsible mediators, which may play a key role at different time points in the process (initiation versus steady-state dilation). In this context, perhaps Kv play a greater role in maintenance of metabolic dilation with some other mechanism responsible for initiation of the dilation, since failure to maintain arterial pressure was observed only after 30 to 45 s after norepinephrine in the Kv1.5 null animals. This fits with the well-described role of Kv channels in controlling resting membrane potential and resting, state-wide 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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None.

References


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