Hypoxia-Induced Adaptation to Mitral Regurgitation

A Role for $K_{ATP}$ Channel Up-Regulation?*

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Mitral regurgitation (MR) is a common cardiac problem that increases dramatically with age. The consequences of MR are left ventricular volume overload, cardiac hypertrophy, and the eventual development of left ventricular dilation and dysfunction. Compensated or decompensated MR can result in a number of molecular changes in the myocardium that may be either adaptive or maladaptive. Tissue hypoxia is one of the manifestations that can occur in MR. This presence of hypoxia can have significant consequences on organ function, one of which is related to marked changes in cardiac energy metabolism.

From a metabolic perspective, hypertrophy secondary to volume overload can decrease the contribution of overall mitochondrial oxidative metabolism to cardiac adenosine triphosphate (ATP) production while increasing the contribution of glycolysis to ATP production (1–3). Part of this switch to glycolysis probably occurs secondary to an up-regulation of hypoxia-inducible factor–1-alpha (HIF-1α), a transcription factor that is up-regulated in hypoxic tissue. In addition to metabolic genes, results from the study of Raeis-Dauvé et al. (4) in this issue of the Journal suggest that HIF-1α can alter the expression, at the messenger ribonucleic acid (mRNA) level, of Kir6.2, a subunit of the $K_{ATP}$ channel.

$K_{ATP}$ channels were originally described as a cardiac sarcolemmal outward $K^+$ conductance, which is subject to inhibition by the application of intracellular ATP but not adenosine monophosphate (5). The sensitivity of these $K^+$ channels to high-energy phosphates (e.g., ATP) positions the channel as a potentially important regulator of not only cellular electrical excitability but also energy substrate metabolism. Since the original description, the molecular characteristics of the $K_{ATP}$ channel have been delineated in some detail. The channels are heterotetramers composed of a tetrameric arrangements Kir6.x subunits, which form the central channel pore and contain the inhibitory ATP binding site, surrounded by a tetramer of regulatory sulfonylurea receptor subunits, which possess intrinsic ATPase activity (6,7).

$K_{ATP}$ channels form macromolecular complexes with a number of metabolically relevant enzymes, including adenylate kinase and creatine kinase, as well as the glycolytic enzymes, glyceraldehyde phosphate dehydrogenase, triose phosphate isomerase, pyruvate kinase, and lactate dehydrogenase (8–11). Interestingly, the glycolytic enzyme phosphoglycerate kinase, which generates glycolytically derived ATP, binds to the cardiac sarcolemmal membrane (12,13). Pyruvate kinase and phosphoglycerate kinase are the ATP-generating enzymes of glycolysis, and their close proximity to the $K_{ATP}$ channel may produce localized microdomains of elevated cytosolic ATP concentration above the cytosolic mean concentration. Although the regulation of $K_{ATP}$ channel activity by ATP and adenosine diphosphate is complex, the channel is suggested to be preferentially regulated by glycolytically derived ATP (14). Interestingly, almost every glycolytic enzyme is under the transcriptional control of HIF-1α (15). The up-regulation of HIF-1α observed in patients with mild to moderate MR may thus be a part of an early adaptive response that contributes to the metabolic phenotype of increased glycolysis in the setting of cardiac hypertrophy. Such an increase in glycolytic enzymes may also be required to ensure proper regulation of the cardiac $K_{ATP}$ channel, which has decreased responsiveness to ATP in the presence of cardiac hypertrophy (15). Such effects may allow the heart to adapt to the mild to moderate pathology described by Raeis-Dauvé et al. (4). However, it remains to be determined whether the increased expression of Kir6.2 observed in the study by Raeis-Dauvé et al. (4) results in the generation of competent $K_{ATP}$ channels, especially as the expression of regulatory sulfonylurea receptor 2A isoform (the major sulfonylurea receptor isoform in ventricular muscle) (16) was not assessed.

Although it is not possible to ascertain the functional significance of increased Kir6.2 and HIF-1α expression in the study by Raeis-Dauvé et al. (4), previous studies do suggest that increased Kir6.2 expression may contribute to limiting cardiac pathology. Increased cardiac hemodynamic load in response to transverse aortic constriction predisposes to the development of cardiac hypertrophy and heart failure. Previous reports implicate both the pore-forming Kir6.2 subunit and the regulatory sulfonylurea receptor 2A subunit of $K_{ATP}$ channels as contributing to limiting cardiac pathology. Specifically, genetic deletion of Kir6.2 leads to increased mortality as well as an increased severity of heart

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failure after transverse aortic constriction (17), while mutations in \( ABCC9 \) (the gene encoding the regulatory sulfonylurea 2A subunit) predispose to the development of dilated cardiomyopathy (18). Increased sarcolemmal \( K_{\text{ATP}} \) channel activity is proposed to limit cardiac pathology at least in part by decreasing cardiac myocyte excitability and thereby attenuating cardiac myocyte \( Ca^{2+} \) overload. Furthermore, a proteomics approach has identified Kir6.2 deficiency as remodeling the cardiac proteome such that there is increased risk for susceptibility to cardiomyopathy in response to hemodynamic stress, with the majority of proteins affected being related to cardiac energy substrate metabolism (19–21). These previous findings may support the proposal that up-regulation of Kir6.2 is part of the adaptive response of the myocardium to pathophysiological stress states, including pressure overload cardiac hypertrophy. This may suggest that the alterations in Kir6.2 expression observed in the study by Raeis-Dauvé et al. (4) accompany an early adaptive metabolic response of the myocardium to increased hemodynamic load secondary to MR, whereby the left ventricle can progress to eccentric hypertrophy to manage increased stroke volume (i.e., forward stroke volume and regurgitated volume).

Although further studies are necessary, the work of Raeis-Dauvé et al. (4) does raise the intriguing possibility that targeting \( K_{\text{ATP}} \) channels could be an approach to delaying surgical therapy for MR. It also raises the possibility that measuring the venous partial pressure of oxygen may predict hypoxia and the possible up-regulation of a subunit of the \( K_{\text{ATP}} \) channel in MR.

The study by Raeis-Dauvé et al. (4) demonstrates several interesting associative correlations in patients with mild to moderate MR. Specifically, the study defines: 1) an inverse correlation between the expression of left-heart Kir6.2 protein and the venous partial pressure of oxygen; 2) a positive correlation between Kir6.2 mRNA and HIF-1\( \alpha \) mRNA; and 3) associations between left ventricular HIF-1\( \alpha \) and Kir6.2 mRNA with cardiac hemodynamic parameters, including systolic aortic pressure and left ventricular size, as well as systolic and diastolic aortic pressures, respectively. The study, interestingly, also identifies dissociation between the expression of Kir6.2 protein and Kir6.2 mRNA.

As is often necessary when working with clinical biopsies, the study was limited to samples of diseased myocardium and therefore lacks an ideal control group. Although this is a small observational study and can thus be subject to “chance bias,” the reported findings are nonetheless interesting. However, the correlative nature of the study makes it difficult to establish cause-effect as well as cause- consequence relationships and therefore requires further investigation to tailor potential therapies for this cardiac pathology. As a corollary, additional study will also be required to define the physiological and functional significance of increased Kir6.2 protein expression in experimental models of MR. Interestingly, several previous studies have demonstrated that Kir6.2 expression is part of the adaptive response of the myocardium to pathophysiologial stress states, including pressure overload cardiac hypertrophy. As is often necessary when working with clinical biopsies, the study was limited to samples of diseased myocardium and therefore lacks an ideal control group. Although this is a small observational study and can thus be subject to “chance bias,” the reported findings are nonetheless interesting. However, the correlative nature of the study makes it difficult to establish cause-effect as well as cause-consequence relationships and therefore requires further investigation to tailor potential therapies for this cardiac pathology. As a corollary, additional study will also be required to define the physiological and functional significance of increased Kir6.2 protein expression in experimental models of MR. Interestingly, several previous studies have demonstrated that Kir6.2 expression is part of the adaptive response of the myocardium to pathophysiologial stress states, including pressure overload cardiac hypertrophy. As is often necessary when working with clinical biopsies, the study was limited to samples of diseased myocardium and therefore lacks an ideal control group. Although this is a small observational study and can thus be subject to “chance bias,” the reported findings are nonetheless interesting. However, the correlative nature of the study makes it difficult to establish cause-effect as well as cause- consequence relationships and therefore requires further investigation to tailor potential therapies for this cardiac pathology. As a corollary, additional study will also be required to define the physiological and functional significance of increased Kir6.2 protein expression in experimental models of MR. Interestingly, several previous studies have demonstrated that Kir6.2 expression is part of the adaptive response of the myocardium to pathophysiologial stress states, including pressure overload cardiac hypertrophy.

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