Myocardial Hypoxia in Dilated Cardiomyopathy: Is it Just a Matter of Supply and Demand?

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Eighty years ago Tennant and Wiggers1 made the seminal observation that coronary artery occlusion lead to systolic left ventricular (LV) dysfunction laying the foundation for the current well-accepted physiological paradigm of tight coupling between myocardial blood flow (MBF) and systolic function. The link between MBF and function is oxygen, which serves as the final electron acceptor in oxidative phosphorylation, the primary process for generating cellular ATP. Consequently, myocardial health and thus normal LV function is dependent on a balance between oxygen supply and demand. In contrast to other vascular beds, the resting myocardial extraction of oxygen is high, ≈75% of the arterial oxygen content. Thus, the ability of the myocardium to further increase oxygen extraction is limited. As a consequence, the demands for increased myocardial oxygen are met via increases in oxygen delivery, which is determined by MBF and arterial oxygen content. The major determinants of the myocardial oxygen demand or consumption are heart rate, wall stress, and LV contractility with wall stress being directly related to systolic blood pressure and LV diameter and inversely related to wall thickness. Thus, under normal conditions where oxygen supply and demand are balanced, oxygen extraction will not change, whereas during ischemia where oxygen supply is inadequate to meet demand, oxygen extraction will increase, albeit modestly.

The LV dysfunction of idiopathic dilated cardiomyopathy (DCM) is characterized by abnormalities in resting MBF, vasodilator function as evidenced by impaired MBF reserve (peak MBF/rest MBF in response to vasodilator stress) and impaired energetics.2–4 On the basis of the aforementioned discussion on the tight linkage of MBF and LV function, it would be reasonable to surmise that in DCM myocardial oxygenation must be inadequate resulting in tissue hypoxia. Indeed, the induction hypoxia-inducible factor 1α, which functions as a master regulator of oxygen homeostasis by controlling both the delivery and the utilization of oxygen, by hypoxia, further supports this notion.5 However, studies examining the level of tissue oxygenation have provided conflicting results. For example, coronary sinus blood content is reduced in patients with DCM consistent with ischemia and is a marker of poor prognosis.6 Yet, studies where positron emission tomography was used to measure myocardial oxygen consumption, a putative index of oxygenation, demonstrated either similar or reduced levels at rest in patients with DCM when compared with controls.7–10 Determining whether myocardial oxygenation is reduced or preserved in patients with DCM is of relevance as this information would help direct whether therapeutic strategies should target increasing MBF and thus oxygen delivery or focus on more downstream processes reflecting altered metabolism, impaired energy transduction, or increased fibrosis.

In this issue of Circulation: Heart Failure, Dass et al11 describe an elegant study designed to address this conundrum. In 14 patients with well-characterized DCM and 12 age- and sex-matched controls, magnetic resonance imaging was performed to measure the MBF and myocardial oxygenation responses to vasodilator stress induced with adenosine. In addition, magnetic resonance imaging measurements of LV mass, volume and ejection, and phosphorous-31 magnetic resonance spectroscopy measurements myocardial energetics (PCr/ATP ratio) were performed at rest and after oxygen supplementation. Measurements of MBF in response to vasodilator stress or the myocardial perfusion index (MPRI) were determined from the ratio of the slope of the myocardial signal intensity curve post contrast obtained at stress divided by the slope of the curve obtained at rest. Myocardial oxygenation was based on the blood oxygen level dependent (BOLD) effect on magnetic resonance imaging. This techniques exploit the fundamental difference in the paramagnetic properties of deoxyhemoglobin and oxyhemoglobin. Deoxyhemoglobin is paramagnetic, whereas oxyhemoglobin is diamagnetic. As a consequence, deoxyhemoglobin causes local dephasing of water protons and hence signal reduction on T2- or T2*-weighted imaging, whereas oxyhemoglobin does not. Thus, conditions that either increase deoxyhemoglobin in the venous blood or increase the venous blood volume will lead to signal loss, whereas conditions that decrease deoxyhemoglobin content or blood volume will lead to signal gain. Implicit in this measurement is that only changes in blood oxygen content in response to an intervention (eg, change from rest to stress) can be detected as opposed to absolute levels for a given state (eg, rest or stress). In the normal heart, the induction of stress by exercise or dobutamine should lead to a balanced increase in oxygen supply and demand with no change in oxygen extraction or deoxyhemoglobin levels and as a consequence to no change in BOLD signal. In contrast, with vasodilator stress, MBF blood flow or oxygen supply exceeds oxygen demand leading to reduced myocardial oxygen extraction, decreased deoxyhemoglobin...
levels, and an increased BOLD signal. In the case of the stress-induced ischemia, oxygen supply does not meet demand resulting in increased myocardial oxygen extraction, increased deoxyhemoglobin levels, and decreased BOLD signal.

Consistent with the known impairment in myocardial vasodilator capacity with DCM, the authors observed that MPRI was reduced by ≈19% in patients when compared with controls. However, changes in oxygenation were equivalent between the groups. Of note, both groups exhibited a similar response in the rate-pressure product, suggesting equivalent increases in oxygen demand. As anticipated, PCR/ATP levels at rest were lower in the patients with DCM than in the controls consistent with impaired energetics. However, supplemental oxygen in the patients had no effect on either PCR/ATP levels or LV function. On the basis of these results, the authors concluded that myocardial oxygenation is not impaired in patients with DCM and thus as a corollary, it seems that myocardial hypoxia does not contribute to the impaired energetics and LV dysfunction in these patients.

So what can the readers make of these results? First, given that the patients with DCM had normal hemoglobin levels and were stable New York Heart Association class II–III (and thus not likely to be hypoxemic), it is not surprising that supplemental oxygen failed to improve myocardial energetics and LV function. Consequently, these results neither confirm nor repudiate the presence of tissue hypoxia. The presence of changes in oxygenation between patients with DCM and controls despite impaired vasodilator capacity in the patients with DCM is harder to explain. When reviewing Figure 2, one cannot help but be struck by the marked variability in the oxygenation responses in both patients with DCM and normal controls, particularly when compared the MPRI measurements. The MR method used to measure oxygenation is sensitive to heart rate variability, so increased arrhythmias during adenosine might have contributed to the variability. In addition, the pulse sequence to measure BOLD signals is also sensitive to $B_0$ and $B_1$ inhomogeneity. However, it should be noted that using similar methods with similar amounts of measurement variability, these investigators have demonstrated reduced levels of myocardial oxygenation commensurate with reduced levels in MPRI in patients with diabetes mellitus and aortic stenosis. So why does the dissociation between oxygenation and MPRI occur in patients with DCM? A potential explanation is the likely greater heterogeneity in cause and disease presentation in the patients with DCM compared with the diabetic and aortic stenosis cohorts. The definition of DCM was made based on echocardiographic measurements of LV size and function and the absence of flow-limiting lesions on coronary angiography. Thus, the presence of other causes for DCM such familial-genetic, autoimmune, postviral, or alcohol-induced that might show variable oxygenation patterns is unknown. Moreover, prevalence of comorbidities that can impair vasodilator function and oxygenation, such as hypertension and diabetes mellitus, is unclear. As mentioned previously, augmentation in the oxygenation signal is inversely related to blood volume. In ischemic myocardium subjected to vasodilator stress, significant capillary derecruitment can occur that will lead to decrease in myocardial blood volume. Thus, in patients with DCM, if adenosine induces significant ischemia because of microvascular disease, myocardial oxygenation will be uncoupled from blood flow.

Ultimately how does one reconcile this study and put it into context with the current literature? Perhaps I way is to view the question from the perspective of whether the level of myocardial oxygenation is adequate to meet the oxygen demands of the myocardium under the conditions studied. At rest, the LV myocardial oxygen demand in DCM typically exceed those of normal hearts because of a higher rate-pressure product and the increased LV cavity size and thinner myocardial wall that results in increased LV wall stress. Consequently, similar levels of oxygenation between patients with DCM and controls would imply ischemia, and thus hypoxia, would be more likely in patients with DCM. Indeed, the magnitude coronary sinus blood deoxygenation as biomarker of poor prognosis would support this notion. Moreover, this disparity in oxygen supply and demand should become more pronounced with forms of stress where increase in oxygen demand drives the increase in MBF, and thus oxygen delivery, such as with exercise, pacing, or adrenergic stimulation, as opposed to vasodilator stress where increases in MBF are uncoupled to myocardial oxygen demand. Indeed, in response to 20 µg/kg per minute of dobutamine, patients with DCM exhibit a blunted response in oxygen consumption (measured with positron emission tomography) compared with controls. Moreover, in these same patients, there was evidence of accelerated glucose metabolism relative to MBF, and thus oxygen delivery, such as with exercise, pacing, or adrenergic stimulation. So as we continue to study the relationship between MBF, oxygenation, and LV function in CV health and disease, it may be useful to keep as a reference the law of supply and demand.

Disclosures

None.

References


**Key Words:** Editorials ■ arrhythmias, cardiac ■ cardiomyopathy, dilated ■ hypoxia-inducible factor 1 ■ oxygen consumption ■ positron emission tomography
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