EDITORIAL COMMENT

Noninvasive Measurements of Myocardial Oxygen Consumption—Can We Do Better?*

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Normal cardiac performance reflects the interdependence between myocardial mechanical function, myocardial oxygen consumption (MVO₂), and blood flow. Indeed, physiologic processes directly associated with systolic function (e.g., wall stress, shortening, heart rate, contractility) are major determinants of MVO₂. Conversely, when myocardial blood flow is interrupted, there is rapid cessation of MVO₂ and systolic function. The linkage between myocardial blood flow and mechanical function provided by MVO₂ reflects primarily the oxidation of substrates for myocardial energy production. Consequently, because of the central role of MVO₂ in cardiac physiology, the noninvasive quantification of MVO₂ is crucially important in both cardiovascular investigation and clinical cardiology.

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Currently, positron emission tomography (PET) using ¹¹C-acetate is the most accurate and commonly used method of measuring MVO₂ noninvasively. Once taken up by the heart, acetate, a two-carbon chain free fatty acid, is rapidly converted to acetyl–coenzyme A (CoA). The primary metabolic fate of acetyl-CoA is metabolism through the tricarboxylic acid cycle. Because of the tight coupling of the tricarboxylic acid cycle and oxidative phosphorylation, the myocardial turnover of ¹¹C-acetate reflects overall flux in the tricarboxylic acid cycle and, thus, overall oxidative metabolism or MVO₂. When bi-exponential curve fitting is used to measure the myocardial kinetics of the tracer, the rate constant k₁, which describes the myocardial clearance of ¹¹C activity (in the form of ¹¹CO₂), correlates closely and directly with MVO₂ over a wide range of conditions (1–3). Because of the relative simplicity of curve fitting, it is the most commonly used method to measure the myocardial kinetics of ¹¹C-acetate. Indeed, the method has been simplified further to measure the clearance from the linear portion of the myocardial time–activity curve (kmono) (3).

The study reported by Stolen et al. (4) in this issue of the Journal is a prime example of how measurements of MVO₂, when combined with measurements of myocardial blood flow and mechanical function, can provide unique insights into the benefits of a specific cardiac therapy. In brief, the authors assessed the impact of exercise training on MVO₂ in both the right and left ventricles (RV and LV), as well as myocardial blood flow and mechanical function in the LV, in patients with nonischemic dilated cardiomyopathy (DCM) and mild heart failure (HF). MVO₂ was measured by PET with ¹¹C-acetate using the k mono method. Myocardial blood flow was also measured by PET using ¹⁵O-water. Various parameters of LV volume and systolic function, as well as LV external work, were measured by echocardiography. Measurements were performed before and after five months of participation in an exercise training program and compared with a comparable group of patients with DCM who did not participate in the exercise program. This study makes several key observations regarding exercise training in patients with DCM and mild HF:

1. It confirms the beneficial effects of exercise training on exercise capacity, exercise duration, and quality of life.
2. It provides further evidence that exercise training improves LV systolic function (ejection fraction and stroke volume) without an increase in external work (primarily because of a decrease in heart rate).
3. It provides new evidence that LV MVO₂ decreases in response to training, which, when coupled with a lack of change in external work, results in an improvement in LV efficiency.
4. It provides intriguing evidence that exercise training has salutary effects on RV oxidative metabolism.

Taken in sum, these findings demonstrate that the salutary effects of exercise training on exercise capacity and quality of life in patients with DCM are due not only to peripheral adaptations, such as improved peripheral endothelial function and increased oxidative capacity in skeletal muscle, but also to an improvement in LV energetics, function, and efficiency. Although measurements of RV external work were not obtained, the decline in MVO₂ suggests that RV energy transduction would be improved as well.

Given that the role of MVO₂ measurements by PET ¹¹C-acetate is central in these results and that the decline in MVO₂ after exercise training was modest (~10%), certain questions arise. First, are there effects that might confound the measurements of the myocardial kinetics of ¹¹C-acetate using the k mono method and thus reduce or obscure the accuracy of the MVO₂ measurements? If so, are there approaches that could reduce the impact of these effects and, as a consequence, improve the accuracy of the measurements? Finally, are there other approaches on the horizon that may make it easier to obtain or more accurately measure MVO₂ or that may provide additional information leading to a more comprehensive understanding of myocardial energetics and efficiency?

*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

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Exponential curve fitting of myocardial $^{11}$C-acetate is susceptible to several factors. The curve fitting is sensitive to the shape of the time–activity curve in the blood. Said another way, the accuracy of the estimates of $\text{MVO}_2$ will be affected by the rate of delivery of tracer to the heart during the imaging interval (5,6). With respect to the RV, the shape of the blood curve reflects the type of tracer injection (intravenous bolus or infusion) and recirculation of $^{11}$C-acetate. In the case of the LV, the shape of the blood curve primarily reflects the cardiac output and tracer recirculation. The slower the initial delivery of $^{11}$C-acetate to the myocardium and/or the more recirculation there is, the slower the clearance rates and thus the lower the estimates of $\text{MVO}_2$. It should be noted that the sensitivity of exponential curve fitting to this effect is more pronounced when mono-exponential fitting, as opposed to bi-exponential fitting, is used (6). The impact of this effect in the current study was probably small, considering that the patients had class I/II HF and an average LV ejection fraction of 33%. Moreover, the decline in rest myocardial blood flow with exercise training provides further evidence that the decline in $\text{MVO}_2$ after exercise training was physiologically significant. A second potential disadvantage is that curve fitting may be sensitive to spillover activity from either the blood or the lungs. If significant, this would lead to an underestimation of the myocardial clearance of tracer and, again, an underestimation of $\text{MVO}_2$. Although it is not typically a problem in normal hearts, spillover may become a problem in situations in which recirculation of tracer may be significant or in which lung activity is increased, as may be seen in patients with marked LV dys-function. The spillover effect may be even more problematic when curve fitting is performed on the RV, because of the relative thinness of the RV myocardium. Finally, the curve-fitting method provides only an estimate of $\text{MVO}_2$. To compare $k_{\text{mono}}$ values with previously reported values for $\text{MVO}_2$, $k_{\text{mono}}$ (in units of per min) is converted to its equivalent value for $\text{MVO}_2$ (usually in $\mu$mol/g per min), based on the relationship between these two values measured directly in either dogs or humans. However, this relationship was usually measured under normal physiologic conditions. It is unknown whether the relationship between $k_{\text{mono}}$ and $\text{MVO}_2$ is altered under abnormal conditions in which marked alterations in the blood curve could occur.

To circumvent many of the problems associated with exponential curve fitting, approaches that utilize compartmental modeling of the myocardial $^{11}$C-acetate kinetics have been developed. The advantages of compartmental modeling are that the effects of variability in the blood curve and spillover from blood (or lung) to the myocardium can be taken into account. Moreover, depending on the model used, $\text{MVO}_2$ can be estimated directly, as opposed to converting rate constants estimated by the model to $\text{MVO}_2$ using a previously measured relationship. Indeed, measurements of $\text{MVO}_2$ have been shown to be more accurate when the compartmental modeling method is used as opposed to exponential curve fitting (6). That being said, there are several disadvantages associated with compartmental modeling of myocardial $^{11}$C-acetate kinetics. First, this method is more complex and time-consuming than exponential curve fitting. The blood curve must be corrected for $^{11}$CO$_2$ so that an accurate measurement of $^{11}$C-acetate blood activity is obtained. Other physical factors, such as under-estimation of true tissue activity due to partial volume effects, can significantly degrade the accuracy of the estimates obtained with compartmental modeling and thus must be accounted for. Finally, because of the number of parameters being estimated, the need for high-quality images is greater with compartmental modeling than exponential curve fitting. Despite these complexities, numerous groups have used compartmental modeling of myocardial $^{11}$C-acetate kinetics to measure $\text{MVO}_2$ under a variety of normal and abnormal cardiac states (7–9).

Because oxygen is the final electron acceptor in all pathways of aerobic myocardial metabolism, PET with $^{15}$O-oxygen has also been used to measure $\text{MVO}_2$. Administration of $^{15}$O-oxygen is generally performed by inhalation of the gas, which results in marked spillover of radioactivity from the lungs to the heart (10). Tracer kinetics are further complicated by the need to account for the conversion of $^{15}$O to $^{16}$O-water and blood to myocardial spillover. Consequently, four different scans have to performed: a transmission scan to calculate lung volume; a $^{15}$O-carbon monoxide scan to measure blood volume; a scan using a PET perfusion tracer to quantify myocardial blood flow; and the $^{15}$O-oxygen scan. However, despite these complexities, a compartmental modeling approach has been devised that quantifies the myocardial oxygen extraction fraction. Thus, with the knowledge of the arterial oxygen content and myocardial blood flow, $\text{MVO}_2$ can be accurately calculated (10,11). The major advantage of the approach is that it provides a measure of myocardial oxygen extraction and measures $\text{MVO}_2$ directly. Its major disadvantage is the need for a multiple-tracer study and fairly complex compartmental modeling to obtain the measurements. Despite these limitations, the $^{15}$O-oxygen method has provided unique insights into the changes in $\text{MVO}_2$ that occur in a variety of abnormal cardiac conditions (12,13).

Because of the close coupling between $\text{MVO}_2$ and myocardial mechanical function, separate measurements of LV function, in addition to the PET measurements of $\text{MVO}_2$, are usually required to obtain a more comprehensive understanding of myocardial energetics and efficiency. The separate measurements of LV function are usually performed with a different imaging method, such as echocardiography or cardiac magnetic resonance imaging (cMRI). The disadvantage of this dual-imaging approach is that differences in hemodynamic conditions between the two imaging sessions may confound the interpretation of the relationship between $\text{MVO}_2$ and function. Moreover, particularly when regional assessments are being performed, accurate co-registration of the images is necessary to ensure that $\text{MVO}_2$ and mechanical function are being measured in the same myocardial segment. It has been proposed that by obtaining electrocardio-
graphically gated PET data of myocardial $^{11}$C-acetate kinetics, one can simultaneously acquire measurements of myocardial work and $MVO_2$ and thus measure efficiency (14). Consequently, the concerns regarding hemodynamic differences and image co-registration would be allayed. Although the initial results in normal volunteers look promising, confirmation of the accuracy of the method, when compared with more invasive methods and in patients with abnormal LV function, is lacking.

In the future, cMRI may play a significant role in the noninvasive measurement of $MVO_2$ by utilizing the blood oxygen level–dependent, or BOLD, effect (15). The basic principle underlying the BOLD effect is that oxyhemoglobin contains no unpaired electrons and is diamagnetic. In contrast, deoxyhemoglobin has unpaired electrons and is paramagnetic. Because water and proteins are diamagnetic, inhomogeneity will occur in the local magnetic field surrounding deoxyhemoglobin. Thus, as the fraction of deoxyhemoglobin in the blood increases, there will be signal loss in blood and tissue on T2- and T2*-weighted images. The major application for measurements of the BOLD effect has been in functional brain imaging. Compared with the brain, the myocardium has a greater blood volume (~10% vs. ~4%). Moreover, at baseline, the myocardium extracts more oxygen, leading to a lower oxygen saturation in the coronary sinus blood (~30%) than in the venous blood in the brain (~60%). Consequently, the myocardium has a wider dynamic range of signal change than does the brain. The feasibility of using BOLD imaging to detect differences in myocardial blood oxygenation has been demonstrated using a variety of interventions. For example, there is signal enhancement in response to dipyridamole: coronary sinus blood oxygenation increases due to luxuriant perfusion (16). No change in signal is observed during dobutamine use: oxygen supply and demand are matched, and thus no change in coronary sinus blood oxygenation occurs. By contrast, with ischemia there is signal loss as oxygen extraction increases (17). With the use of approaches devised for measuring oxygen extraction in the brain, measurements of myocardial oxygen extraction will probably be developed. As is done with the PET with $^{15}$O-oxygen method, with knowledge of the arterial oxygen content and level of myocardial blood flow, $MVO_2$ can be calculated. However, before myocardial oxygen extraction and $MVO_2$ can be measured in humans, numerous hurdles must be overcome. Some of these difficulties include image degradation due to cardiac and respiratory motion, the inherent low signal-to-noise ratio, and the relatively low sensitivity of magnetic resonance contrast to myocardial oxygenation that is seen with commercial 1.5-tesla systems. Finally, accurate measurements of myocardial oxygen extraction and $MVO_2$ require a priori knowledge of both myocardial blood flow and volume. Therefore, both myocardial blood flow and volume need to be quantified independently. If these problems can be overcome, then measurements of $MVO_2$ can be obtained nearly simultaneously with measurements of myocardial wall stress, strain, and work, using well-established cMRI methods. This would offer the advantage of the measurements being obtained under similar hemodynamic conditions and would remove the need to apply image fusion techniques to ensure accurate image co-registration.

**References**