Assessment and clinical applications of myocardial efficiency

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Abstract

Myocardial work and its metabolic cost are important parameters in the pathogenesis and management of cardiovascular diseases. Myocardial efficiency, unlike other commonly used measures of cardiac function, accounts for both parameters. It has been demonstrated that myocardial oxygen demand can be reliably quantified using positron-emitting radionuclide tracers of oxygen flux, whereas cardiac work can be estimated from stroke volume and mean arterial pressure. Assessment of myocardial efficiency from these parameters has been shown to be very useful in providing an understanding of the pathogenesis of many cardiovascular diseases and the effects of therapeutic interventions.
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Introduction

Left ventricular myocardial efficiency is defined as the percentage of total energy expenditure by the myocardium that is converted into either total mechanical or external stroke work [1]. Assessment of the metabolic cost of left ventricular work is important in the management of cardiovascular diseases, because the heart is an aerobic organ with a limited oxygen supply. Myocardial extraction of oxygen from arterial blood is near maximal under basal conditions. Thus, an increase in myocardial oxygen supply requires an increase in coronary blood flow, which at times may be impaired because of atherosclerosis and other conditions.

Measurement of myocardial efficiency is superior to standard measures of ventricular performance, because it accounts for the metabolic cost of myocardial work. The heart requires a large amount of oxygen to generate high-energy phosphates, in the form of adenosine triphosphate (ATP), to meet the needs of mechanical contraction and regulation of rapidly changing ion gradients. The main substrates for myocardial metabolism include fatty acids, glucose, ketone bodies, and amino acids. Under normoxic conditions, the preferred substrates for myocardial metabolism are fatty acids. However, under conditions of ischemia, glucose becomes the preferred substrate. The fact that the heart generates high-energy phosphates from these substrates almost exclusively by aerobic pathways obviates the need to account for individual substrate pathways. Consequently, tracers of oxygen flux labeled with positron-emitting radionuclides are often used to quantify myocardial oxygen demand ($m\dot{V}O_2$).

Assessment of myocardial efficiency

Two positron emission tomography (PET)-based radionuclide tracers have been developed to track myocardial oxygen flux: oxygen-15-labeled oxygen ($[^{15}O]O$) and carbon-11-labeled acetate ($[^{11}C]$acetate). Assessment of myocardial oxygen flux with $[^{15}O]O$ is laborious, because it requires additional scans for blood volume and flow, correction for lung-to-heart

spillover, and conversion of labeled oxygen to labeled water of metabolism [2,3]. The approach with [^{11}C]acetate is more straightforward. The tracer is rapidly taken up by the myocardium, in proportion to the blood flow. Consequently, it can also be used for quantification of myocardial blood flow [4]. [^{11}C]Acetate is converted to [^{11}C]acetyl coenzyme A and undergoes oxidative phosphorylation through the Krebs cycle in the mitochondria. One of the metabolic end products of [^{11}C]acetate metabolism is [^{11}C]CO$_2$. It has been demonstrated that quantification of the egress of [^{11}C]CO$_2$ from the myocardium correlates well with directly measured m$\dot{V}$O$_2$ [5].

Assessment of [^{11}C]acetate metabolism is usually performed after an overnight fast. Approximately 0.2–$0.4 \, mCi \cdot kg^{-1}$ (7.4–$14.8 \, MBq \cdot kg^{-1}$) of [^{11}C]acetate is administered intravenously, followed by dynamic PET imaging. The clearance of [^{11}C]CO$_2$ from the myocardium is quantified either by performing a mono-exponential fit or by applying compartment model analysis. In general, under resting conditions, the clearance of [^{11}C]acetate from the myocardium follows a monoexponential pattern, because it predominantly represents the rapid oxidation of [^{11}C]acetate to carbon dioxide and water. However, during pharmacological stimulation with dobutamine, a second peak, which reflects slower incorporation of [^{11}C]acetate into amino acid pools and other Krebs cycle intermediates, is also noted [6–7].

When a single peak is present, monoexponential curve fitting (k_{mono}) is performed. However, when two peaks are discernible, a biexponential curve-fitting routine is applied, with calculation of the rapid and slow clearance rates (k_1 and k_2, respectively). The initial rapid clearance rate (k_1) represents the oxidation of [^{11}C]acetate to carbon dioxide and water, and the second slower clearance rate (k_2) represents incorporation of [^{11}C]acetate into amino acid pools. On the average, k_2 accounts for less than 5% of k_1 [8,9]. Both k_1 and k_{mono} have been shown to correspond with m$\dot{V}$O$_2$ during normoxia, hypoxia, and under varying ventricular loading conditions in experimental animal studies, and with double product in human [5–8,10]. The average rates of regional k_1 and k_{mono} are approximately 0.054–$0.058 \cdot min^{-1}$, corresponding to a biological half-time of approximately 12–13 min [9,10]. m$\dot{V}$O$_2$ is usually derived from either k_1 or k_{mono} using a regression equation [5–7].

Because of the limitations of curve-fitting routines, which include the fact that they do not account for tracer recirculation and [^{11}C]acetate contamination, some investigators have advocated compartment model analysis. However, this approach has not been shown to be clearly superior to curve-fitting routines [5,11].

In addition to quantifying m$\dot{V}$O$_2$, it is necessary to quantify myocardial mechanical work in order to estimate myocardial efficiency. Total mechanical work of the myocardium includes the potential energy needed for the development and sustenance of myocardial wall tension and external stroke work. Calculation of myocardial efficiency based on total mechanical work requires sophisticated invasive measurements of left ventricular pressure volume relationships. Consequently, this approach has been largely supplanted by calculations based on external stroke work.

Myocardial efficiency is estimated, as shown in the equation below, by calculating the percentage of total myocardial oxygen consumption that is used for left ventricular minute work. Myocardial oxygen consumption (mL/g/min) is derived from the clearance rate constant (K_{mono}) of [^{11}C] acetate and multiplied by left ventricular mass (LVM) to yield total myocardial oxygen consumption (mL/min). Total myocardial oxygen consumption is converted to a unit of energy (g.m^{-1}) by applying the conversion factor 2059, which is the energy equivalent of 1 ml of oxygen consumed. Left ventricular minute work is calculated from the product of mean arterial pressure (MAP mmHg), stroke volume (SV mL) and heart rate (HR beats/minute) and multiplied by 0.0136 to convert it into a unit of energy (g.m^{-1}).

$$\text{Efficiency}(\%) = MAP.SV.HR.0.0136/mVO_2.LVM.2059$$

In the original article by Bing et al [1], myocardial efficiency was reported as 25% under normal resting conditions. However, other investigators, using non invasive approaches, reported lower myocardial efficiency values that range between 14% and 19% [12–15].

Clinical applications

Quantification of myocardial efficiency is not only useful in the assessments of several cardiovascular pathophysiological conditions such as ischemic heart disease, congestive heart failure, and concentric left ventricular hypertrophy, but is also helpful in the evaluation of therapeutic interventions.

Several studies have assessed myocardial efficiency in patients with coronary artery disease. It is well documented that m$\dot{V}$O$_2$ is irreversibly decreased in infarcted myocardium [16]. However, in stunned or hibernating myocardium, it is maintained at near normal levels, whereas regional stroke work index is reduced, leading to a transient reduction in myocardial efficiency. With revascularization and recovery of regional systolic function in reversibly dysfunctional myocardium, efficiency improves [17]. Thus assessment of myocardial efficiency can be used to characterize myocardium that is dysfunctional as a result of coronary artery disease. Although assessment of

Main clinical article

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[^{18}F]2-fluoro-2-deoxyglucose (FDG) uptake by PET is believed to be the standard for assessment of myocardial viability, studies have shown that measurement of $m\dot{V}O_2$ by [^{11}C]acetate uptake may be superior to that of FDG uptake for predicting recovery of systolic function after revascularization [18,19].

It has been demonstrated that myocardial efficiency is reduced in congestive heart failure [20]. Assessment of myocardial efficiency has proved to be very useful in understanding the effects of various therapies on the failing heart. The negative impact of sympathomimetic drugs on prognosis in patients with congestive heart failure is believed to be attributable to their oxygen-wasting effects and the consequent reduction in myocardial efficiency caused by this class of drugs [21]. In contrast, β-blockers cause an initial decrease in both stroke work and $m\dot{V}O_2$, followed by an increase in myocardial efficiency as myocardial contractility improves while oxygen consumption remains depressed [22]. In addition, it has been demonstrated that ventricular resynchronization improves stroke work in patients with left ventricular systolic dysfunction, without a significant change in $m\dot{V}O_2$, leading to an increase in myocardial efficiency [23].

In patients with hypertension without left ventricular hypertrophy, $m\dot{V}O_2$ and stroke work are increased, causing myocardial efficiency to remain unchanged [24]. However, in hearts with concentric left ventricular hypertrophy, myocardial efficiency is reduced, because stroke work per gram of tissue is depressed, whereas $m\dot{V}O_2$ per gram of tissue is normal. Conversely, in eccentric hypertrophy, both stroke work and $m\dot{V}O_2$ are increased, and myocardial efficiency is normal [25].

Summary

Assessment of myocardial efficiency is clinically useful because it provides valuable insights into the pathophysiology of cardiovascular diseases. Furthermore, therapeutic interventions that improve efficiency have been shown to be beneficial. However, the requirement for an on-site cyclotron for generation of [^{11}C]acetate limits clinical application of the technique. It is hoped that, with increasing application of PET imaging in oncology and the availability of hybrid imaging systems such as PET–computed tomography systems that enable simultaneous assessment of metabolism and function, interest in clinical assessment of myocardial efficiency will be renewed. ■

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