The heart is an aerobic organ that relies almost exclusively on the aerobic oxidation of substrates for generation of energy. Consequently, there is close coupling between myocardial oxygen consumption (MV$_{O2}$) and the main determinants of systolic function: heart rate, contractile state, and wall stress. As in any mechanical pump, only part of the energy invested is converted to external power. In the case of the heart, the ratio of useful energy produced (ie, stroke work [SW]) to oxygen consumed is defined as mechanical efficiency, as originally proposed by Bing et al. Under normal conditions this ratio is $\approx 25\%$, and the residual energy mainly dissipates as heat. In pathophysiological disease states, such as heart failure, mechanical efficiency is reduced, and it has been hypothesized that the increased energy expenditure relative to work contributes to progression of the disease. Moreover, therapeutic interventions that enhance mechanical efficiency have proven to be beneficial with respect to outcome. It is therefore desirable to quantify efficiency of the heart to study disease processes and monitor interventions.

Both cardiac oxidative metabolism and mechanical work, and thus efficiency, can be quantified through invasive measurements. Although these measurements are accurate and currently considered the gold standard, in clinical practice they are limited because of the need for dual-sided heart catheterization and selective catheterization of the coronary sinus. Recent advances in imaging techniques, however, offer the possibility to noninvasively estimate MV$_{O2}$ and mechanical work by positron emission tomography and echocardiography or by magnetic resonance imaging, respectively.

This review discusses the principles of mechanical efficiency, together with its invasive and noninvasive assessment, as well as their strengths and pitfalls. Finally, results from clinical pathophysiological studies are discussed.

**Invasive Measurement of Mechanical Efficiency**

To calculate the efficiency of the heart, input and output energy must be obtained. The first can be derived from MV$_{O2}$ (mL O$_2 \cdot$ min$^{-1}$) measurements according to the Fick principle by multiplying coronary sinus blood flow (mL$^{-1}$ min$^{-1}$) by the arteriovenous oxygen content difference. Blood flow can be estimated with the use of thermodilution or Doppler (electromagnetic flowmeter) methods after accessing the coronary sinus through right-sided heart catheterization. As oxygen dissolved in blood is negligible and hemoglobin concentrations in arterial and venous blood are similar, arteriovenous oxygen content difference can be obtained by determination of the differences in oxygen saturation levels between arterial and coronary sinus blood. This method to determine oxygen utilization is currently considered the gold standard, although it should be noted that it is limited by its invasive nature, susceptibility to sampling errors, and the fact that only global MV$_{O2}$ can be assessed, which also includes oxidative metabolism of the right ventricle and both atria. Furthermore, thebesian left ventricular (LV) flow (1% to 2% of total coronary flow) is unaccounted for, and an additional noninvasive estimate of LV mass is required to calculate oxidative metabolism per gram of tissue.

Output energy is defined as force $\cdot$ displacement and is expressed in joules (J). Energy generated by the heart can be divided into actual produced energy (ie, external work [EW] or SW) and potential energy. These parameters can best be estimated by generation of a pressure–volume (PV) loop of the cardiac cycle by use a conductance catheter placed in the left ventricle (Figure 1A). EW is defined by the area contained within the PV-loop. Potential energy can subsequently be estimated when a family of PV loops is acquired during different loading conditions, eg, by transient vena cava occlusion (Figure 1B). Connection of the end-systolic and end-diastolic points in the PV loops gives the end-systolic and end-diastolic PV relations, respectively. The slopes of these relations in turn function as indices of LV contractility and stiffness, respectively (Figure 1C). The area under the curve on the left side of EW and confined by the slopes of the end-systolic pressure–volume relation and the end-diastolic pressure–volume relation represents potential energy. The total pressure–volume area (PVA) (ie, the sum of EW and potential energy) equals total mechanical energy generated by the heart per beat.

**Reference**

From the Department of Cardiology (P.K., T.G., P.A.D., C.P.A., F.C.V.), the Laboratory of Physiology (W.J.P.), and the Department of Nuclear Medicine & PET Research (A.A.L.), VU University Medical Center, Institute for Cardiovascular Research, Amsterdam, The Netherlands, and the Turku PET Center (J.K.), University of Turku, Turku, Finland.

Correspondence to Dr Paul Knaapen, Department of Cardiology, 6D 120, VU University Medical Center, De Boelelaan 1117, 1081 HV, Amsterdam, The Netherlands. E-mail p.knaapen@vumc.nl

(Circulation. 2007;115:918-927.)

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Circulation is available at http://www.circulationaha.org

DOI: 10.1161/CIRCULATIONAHA.106.660639
It is important to realize that 2 stages can be distinguished in the process of \( \text{MV} \cdot \dot{O}_2 \) conversion to mechanical energy: (1) efficiency of energy transfer from \( \text{MV} \cdot \dot{O}_2 \) to total PVA-area and (2) efficiency of energy transfer from PVA area to EW. The product of the 2 stages yields the mechanical external efficiency and is most commonly used in clinical studies as it represents the conversion of \( \text{MV} \cdot \dot{O}_2 \) to “useful” EW. For the sake of clarity and brevity, only (noninvasive) assessment of mechanical external efficiency will be discussed in this review.

To express efficiency in a dimensionless value or percentage, \( \text{MV} \cdot \dot{O}_2 \) and EW must be converted from units of mL O\(_2\) and mm Hg · mL, respectively, to units of energy (J). The caloric equivalent of 1 mL of O\(_2\) is \( \approx 20 \text{ J} \), whereas 1 mm Hg · mL equals \( 1.33 \times 10^{-4} \text{ J} \). Figure 2 schematically illustrates the myocardial energy conversion process. Invasive studies in normal controls have demonstrated that \( \approx 25\% \) of consumed oxygen is finally converted to external work.\(^2,9,10\) The residual energy is used for nonmechanical activity of basal metabolism and excitation-contraction coupling, although the majority is converted to heat.\(^3,11\)

**Noninvasive Measurement of Mechanical Efficiency**

**Input Energy, Oxidative Metabolism**

Noninvasive assessment of \( \text{MV} \cdot \dot{O}_2 \) is currently limited to positron emission tomography.\(^12\) Two \( \text{MV} \cdot \dot{O}_2 \) tracers have been developed: carbon-11–labeled acetate (\(^{11} \text{C}\)-acetate)\(^13\)

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**Figure 1.** A, Schematic graphic of a pressure–volume loop. With each heart beat a full loop is described. At end-diastole, isovolumic contraction occurs. When the aortic valve opens, ejection begins and during the ejection phase volume decreases, whereas pressure changes relatively little. After aortic valve closure, isovolumic relaxation takes place, characterized by a swift pressure drop. When the mitral valve opens, the chamber begins to fill, and volume increases with a very small increase in left ventricular pressure until the end-diastolic volume is reached. The area contained within the loop is external work (EW). B, A family of PV-loops under different loading conditions reveals the end-systolic pressure–volume relation (ESPVR) and the end-diastolic pressure–volume relation (EDPVR). C, The area on the left side of the PV-loop and confined by the ESPVR and EDPVR represents potential energy (PE). EW and PE together (pressure–volume area, PVA) represent total generated mechanical energy. D, Noninvasive estimate of the PV-loop based on stroke volume and end-systolic pressure estimation results in a rectangle. Areas of under- and overestimation compared with the original PV-loop are indicated. E, Diastolic dysfunction is characterized by an augmented pressure rise during the diastolic filling phase. F, Mitral regurgitation markedly influences the isovolumic contraction and ejection period characteristics of the PV-loop.

**Figure 2.** Energy flow diagram from O\(_2\) consumption to EW. Efficiency from O\(_2\) to ATP and PVA are \( \approx 60\% \) to 70%. Efficiency transfer from PVA to EW depends on contractile function and loading conditions. EC indicates excitation contraction coupling; BM, basal metabolism. Adapted from Suga.\(^3\) Used with permission of the publisher. Copyright © 1990, the American Physiological Society.
and oxygen-15–labeled molecular oxygen (15O2).14,15 As shown in detail in Figure 3, acetate is a 2-carbon chain free fatty acid, which is taken up by the heart and subsequently rapidly converted to acetyl-coenzyme A in the mitochondrial matrix. The primary metabolic fate of acetyl-coenzyme A is via the tricarboxylic acid (TCA) cycle, where 11C-activity is transported to carbon-11–labeled carbon dioxide (11CO2), which readily diffuses from myocardial tissue.13,16 Figure 4 shows an example of a dynamic cardiac 11C-acetate positron emission tomography acquisition and its corresponding myocardial time–activity curve. Within a few minutes after intravenous injection, tracer activity in myocardium reaches a maximum level that is directly proportional to myocardial blood flow. Thereafter, activity is cleared in a biexponential fashion, and the rate constants k1 and k2 can be assessed through curve fitting. The rapid phase, k1, represents the efflux of 11CO2 produced by the TCA cycle. Because of the tight coupling between the TCA cycle and oxidative phosphorylation, k1 correlates closely with MVO2, as has been demonstrated under a wide range of conditions, and therefore functions as an index of oxygen use.16 The slow phase, k2, represents clearance of 11C-activity, which is incorporated into amino acids and TCA cycle intermediates. This method of MVO2 estimation has been further simplified by monoexponential fitting of the linear part of the time–activity curve (kmono), which correlates well with k1.16 To reduce the length of the scanning protocol to <30 minutes, the slow wash-out phase k2 can be disregarded.

The use of the second available tracer to determine MVO2 (ie, 15O2 gas) expands on the well-defined measurements of myocardial blood flow by use of oxygen-15–labeled water (H215O).14,15 Inhalation of 15O2 causes 15O2 to bind to hemoglobin and, after transport to peripheral tissues, 15O2 is converted by cellular metabolism to H215O.17 A tracer kinetic model has been developed to account for recirculating H215O, which allows for oxygen extraction fraction to be estimated (Figure 5). Additional corrections, however, are required for substantial spillover effects from radioactivity in adjacent ventricular blood and lung tissue, which necessitates an additional blood pool scan with oxygen-15–labeled carbon monoxide (C15O) and a transmission image to calculate lung volume. Finally, the combination of a transmission, 15O2, H215O, and C15O scan, displayed in Figure 6, allows the
quantification of both myocardial blood flow and oxygen extraction fraction. Subsequently, by multiplying arterial oxygen content of blood with myocardial blood flow and oxygen extraction fraction, \( \dot{V}O_2 \) can be expressed in absolute terms per gram of myocardial tissue (mL O2 · g \(^{-1}\) · min \(^{-1}\)).

**Output Energy, External Mechanical Work**

In contrast to oxidative metabolism, noninvasive assessment of mechanical EW is relatively straightforward. To estimate the area contained within the PV-loop, only knowledge of stroke volume (SV) (ie, LV end-diastolic and end-systolic volumes and end-systolic LV pressure [LV-Pes]) is required. LV volumes can routinely be derived by various imaging techniques, which include magnetic resonance imaging, echocardiography, and nuclear imaging. \(^{18}\) LV-Pes roughly corresponds to the mean arterial blood pressure of the brachial artery and can be assessed by a simple sphygmomanometer. \(^{19}\) The product of mean arterial blood pressure and SV yields a fairly accurate estimate of EW (Figure 1D).

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**Figure 5.** Simplified schematic representation of the compartment model to measure oxygen extraction fraction and \( \dot{V}O_2 \) by use of PET and \(^{15}\)O2 inhalation. The defined region of interest (ROI) comprises radioactivity in the myocardial tissue as well as spillover activity from the LV cavity blood pool and lung. Spillover corrections can be made with the use of LV blood pool and lung volume imaging with \(^{15}\)O and a transmission image, respectively, as depicted in Figure 6. Hemoglobin-bound \(^{15}\)O2 is extracted from the intravascular space to the tissue space (myocardium) where it is instantaneously converted into H\(^2\){\(^{15}\)O}. The latter is freely diffusible across the capillary membrane and is washed out in proportion to myocardial blood flow. Therefore, shortly after \(^{15}\)O2 inhalation is started, radiolabeled water that is recirculating must be corrected for to measure the oxygen extraction fraction. This requires arterial blood sampling to determine the relative contribution of \(^{15}\)O2 and H\(^2\){\(^{15}\)O} to total arterial radioactivity. Alternatively, in steady-state conditions during continuous inhalation of \(^{15}\)O2, the proportion of recirculating H\(^2\){\(^{15}\)O} to total arterial radioactivity has been shown to be relatively constant at \(\approx 18\%\) and can therefore be fixed in the compartment model, which obviates the need for arterial blood sampling. \(^{17}\) Finally, a separate H\(^2\){\(^{15}\)O} scan is performed to measure myocardial blood flow. \( \dot{V}O_2 \) equals the product of oxygen extraction fraction, myocardial blood flow, and the oxygen content of blood. MBF indicates myocardial blood flow; OEF, oxygen extraction fraction. Adapted from Iida et al\(^{14}\) with permission of the publisher. Copyright © 1996, the American Heart Association.

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**Figure 6.** Examples of a transmission (Tx), steady state oxygen (\(^{15}\)O2), and blood pool (\(^{15}\)CO) image obtained by positron emission tomography in a transaxial view. Through a weighted subtraction technique, lung volume and ventricular blood pool are subtracted from the \(^{15}\)O2 image. The lower panel, \(^{15}\)O2-myo, visualizes the myocardial \(^{15}\)O2 activity that can be used to calculate the oxygen extraction fraction. Courtesy of H. Laine, Turku PET Center, Turku, Finland.
Mechanical Efficiency

The combination of the noninvasive estimates of $\dot{MV}_O$ and EW as described above allows for the assessment of mechanical efficiency according to the equation below,$^{20}$

$$\text{Efficiency} = \frac{\text{MAP} \cdot \text{SV} \cdot \text{HR} \cdot 1.33 \cdot 10^{-4}}{\dot{MV}_O \cdot \text{LVM} \cdot 20}$$

where HR is heart rate and LV mass (LVM) is measured in grams, the conversion factors to joules are as mentioned earlier. It needs to be emphasized that in this equation $\dot{MV}_O$ is expressed in absolute terms. The most commonly employed method to estimate oxidative metabolism noninvasively, however, remains the exponential curve-fitting procedure of $^{11}$C-acetate, which yields an index of $\dot{MV}_O$. Therefore, Beanlands et al$^{21}$ introduced an alternative efficiency index, the so-called work metabolic index (WMI):

$$\text{WMI} = \frac{\text{SBP} \cdot \text{SVI} \cdot \text{HR}}{\text{clearance rate of } ^{11}\text{C-acetate}} \text{ (mm Hg} \cdot \text{mL} \cdot \text{m}^{-2})$$

where SVI is stroke volume index and SBP is systolic blood pressure. This equation is a modification of the minute work-to-oxygen consumption relationship originally defined as mechanical efficiency by Bing et al.$^2$ Traditionally, systolic blood pressure instead of mean arterial blood pressure is used to calculate the work metabolic index, although this is based solely on the personal preferences of the investigators who first proposed this index and is of little clinical significance.$^{21}$

Strengths and Limitations of the Noninvasive Approach

Oxidative Metabolism

Despite the fact that myocardial turnover of $^{11}$C-acetate is most commonly used to noninvasively assess $\dot{MV}_O$, it has several limitations.$^{12}$ First and most important, only a semi-quantitative index of oxidative metabolism is obtained. Even though databases exist from animal experiments and studies in humans to convert the clearance rate constants (units · min$^{-1}$) to equivalents of absolute units (mL · g$^{-1}$ · min$^{-1}$), the relationships found in those relatively small studies, which were performed under predominantly normal physiological conditions, may not hold true in a variety of pathological disease states. Second, the metabolic fate of $^{11}$C-acetate depends, at least in part, on pathological conditions such as ischemia and hibernation.$^{16,22}$ In such conditions the initial myocardial $^{11}$C-acetate clearance rate $k_1$ or kmono slightly overestimates actual $\dot{MV}_O$ because of alterations in the TCA amino acid pool sizes. Third, fluctuations in the arterial input curve of tracer activity and spillover artifacts caused by alterations in cardiac output and recirculation of $^{11}$C-activity, respectively, can significantly affect tracer kinetics that are unrelated to oxygen utilization.$^{21,24}$ Finally, selection of data points from the time–activity curve for subsequent analysis is susceptible to observer variability. To circumvent some of these drawbacks, compartment modeling approaches for myocardial $^{11}$C-acetate kinetics have been developed.$^{13,24}$ The essence of these approaches lies in the correction of the arterial input curve of $^{11}$C-acetate for contaminating metabolites, predominantly $^{13}$CO$_2$. The major advantage of this modeling approach is the fact that $\dot{MV}_O$ is quantified in absolute terms. Furthermore, variability of the input curve and spillover artifacts are taken into account. However, the need for arterial cannulation, repetitive sampling of arterial blood to measure radiolabeled metabolites, and its subsequent implementation in the modeling procedure make this method cumbersome. In addition, corrections for the partial volume effect (underestimation of true radiotracer concentrations that is based on cardiac dimensions and motion) need to be carried out. As these corrections themselves may induce errors in the estimation of absolute $\dot{MV}_O$, many groups return to the simple, but robust semiquantitative monoexponential or biexponential curve fitting method.

$^{15}$O$_2$ is theoretically the most suitable tracer to assess oxidative metabolism, as oxygen is the final electron acceptor in all pathways of aerobic metabolism. This approach is independent of cellular metabolic changes that occur in pathological conditions and conveys absolute values of $\dot{MV}_O$. Unfortunately, only a few centers worldwide are currently equipped to perform the combination of these specific $^{15}$O-scans, and the multiple tracer usage makes this method prone to motion artifacts. In addition, the data analysis, which includes the modeling procedure, is very challenging, and it has been applied only in small series of subjects. Nevertheless, it should be considered the gold standard for noninvasive quantification of $\dot{MV}_O$.

Regardless of the methodology used to assess $\dot{MV}_O$, substrate metabolism affects the ratio of adenosine triphosphate (ATP) produced per oxygen molecule consumed. From Figure 3, one can calculate this ratio for various substrates and conclude that glucose metabolism yields 11% to 13% more ATP per unit of oxygen consumption compared with free fatty acid metabolism, irrespective of cardiac workload.$^{13,22}$ Therefore, substrate metabolism affects mechanical efficiency and metabolic standardization (ie, during a fasting state, it is required when these measurements are performed).

External Mechanical Work

Although external mechanical work calculation derived from SV and mean arterial blood pressure is elegant in its simplicity, some inaccuracies of this approach should be mentioned. First, the original PV-loop is represented as a rectangle, which results in some overestimation by including the area under the curve of the diastolic filling phase. Especially in patients with diastolic dysfunction, this effect can be substantial (Figure 1E). Furthermore, the parabolic shape of the systolic ejection phase of the loop is disregarded, which may result in over- or underestimation, depending on the characteristics of the individual PV-loop. Second, valvular disease significantly hampers noninvasive estimates of EW. In aortic stenosis, the systolic transvalvular pressure gradient results in underestimation of LV-Pes measured by a sphygmomanometer. Echocardiography-derived transvalvular pressure gradient estimation, however, can accurately correct for this underestimation.$^{26}$ More complex are the discrepancies caused by mitral regurgitation. The systolic bidirectional flow of blood into the left atrium and aorta causes the isovolumic contraction phase to be shortened. For a given SV, this
markedly diminishes EW by regurgitation of blood into the low-pressure atrium. Noninvasive assessment of EW will therefore be overestimated in proportion to the magnitude of regurgitating volume (Figure 1F). This problem can partly be resolved by substitution of total with forward SV determined by aortic flow measurements derived by echocardiography or magnetic resonance imaging. The subsequent calculation of the so-called forward SW, however, may not accurately reflect actual SW in these patients. Mitral regurgitation, therefore, remains an important source of error in noninvasive quantification of EW.

A more general disadvantage lies in the fact that LV volumes are usually derived by echocardiography, which is hampered by a poor ultrasound window in a fairly large percentage of patients. Furthermore, geometric assumptions, made when 1- or 2-dimensional echocardiography is used, can lead to substantial inaccuracies in patients with, for example, severe LV remodeling and/or aneurysms. Magnetic resonance imaging overcomes these limitations but is less widely available, is contraindicated in patients with implanted devices, and ideally requires a regular heart beat for gating purposes, which excludes a reliable assessment in the presence of arrhythmias. More recently, 3-dimensional echocardiography has also proven to overcome some of the aforementioned limitations, particularly when images are enhanced with the use of contrast agents.

Mechanical Efficiency
Table 1 lists results of efficiency studies in healthy controls. A few remarks are in order. The noninvasively obtained mechanical efficiency values are somewhat lower than those found with invasive methods. This discrepancy is probably related to differences in loading conditions and contractile state, which affect mechanical efficiency, in combination with methodological issues as already discussed. It should be further noted that the number of both invasive and noninvasive studies in normal physiology is rather small and the accuracy and reproducibility of efficiency measurements have not yet been adequately demonstrated. Although validation studies are available for the assessment of noninvasive oxidative metabolism and external mechanical work separately, validation studies of noninvasive versus invasive efficiency estimation in human subjects are lacking. Clearly, more studies are warranted to more reliably define normal limits and reproducibility of mechanical efficiency in humans.

Of interest, the noninvasive approach surpasses the invasive method in its unique possibility to quantify myocardial efficiency at a regional level, which is of specific relevance in coronary artery disease and cardiomyopathies that display marked regional disease expression as can be appreciated in the clinical studies described in the next section. Various noninvasively determined regional work parameters, which are based on regional wall stress estimation, systolic wall thickening, and myocardial deformation that can be related to regional oxidative metabolism, have been proposed (Figure 7).

A final pitfall that must be addressed is the dual-imaging approach in the quantification of efficiency, which is confounded by potential discrepancies in hemodynamic conditions between imaging sessions. Moreover, particularly in regional efficiency assessment, accurate alignment of myocardial segments must be ensured. Coregistration software for image-fusion during postprocessing may be of use, but dual-imaging tools will ultimately be required to optimize regional alignment and simultaneous assessment of metabolism and function.

Clinical Studies in Cardiovascular Disease
Coronary Artery Disease
Coronary artery disease is the most common cause of compromised myocardial perfusion. The accompanying limited supply of oxygen frequently results in ischemia, which in turn causes a rapid decline in ATP production and immediately induces contractile dysfunction. In the acute phase of ischemia, therefore, reduction in MVo2 and contractile function are matched. After a transient period of ischemia, when oxygen delivery has already been restored, however, prolonged reversible contractile dysfunction can be observed without signs of cellular necrosis. This condition is referred to as myocardial stunning. Gerber et al and Barnes and colleagues showed that oxidative metabolism of stunned myocardium exhibited a slight and nonsignificant reduction compared with baseline values and remote myocardium, which seemed to parallel levels of perfusion. Regional oxygen use in stunned myocardium, however, was relatively high compared with contractile function, which yielded a marked (transient) reduction of mechanical efficiency. As a

TABLE 1. Mechanical Efficiency Studies in Normal Controls

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No.</th>
<th>Method</th>
<th>PET Tracer</th>
<th>ME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bing et al</td>
<td>1949</td>
<td>4</td>
<td>Invasive</td>
<td></td>
<td>22±2</td>
</tr>
<tr>
<td>Nichols et al</td>
<td>1986</td>
<td>8</td>
<td>Invasive</td>
<td></td>
<td>29±6</td>
</tr>
<tr>
<td>Arnoult et al</td>
<td>1997</td>
<td>11</td>
<td>Invasive</td>
<td></td>
<td>26±6</td>
</tr>
<tr>
<td>Vanoverschelde et al</td>
<td>1993</td>
<td>8</td>
<td>Noninvasive</td>
<td>11C-acetate</td>
<td>35±6</td>
</tr>
<tr>
<td>Porenta et al</td>
<td>1999</td>
<td>11</td>
<td>Noninvasive</td>
<td>11C-acetate</td>
<td>16±6</td>
</tr>
<tr>
<td>Takala et al</td>
<td>1999</td>
<td>11</td>
<td>Noninvasive</td>
<td>15O2</td>
<td>14±4</td>
</tr>
<tr>
<td>Laine et al</td>
<td>1999</td>
<td>10</td>
<td>Noninvasive</td>
<td>15O2</td>
<td>18±4</td>
</tr>
<tr>
<td>Akinboboye et al</td>
<td>2004</td>
<td>10</td>
<td>Noninvasive</td>
<td>11C-acetate</td>
<td>16±3</td>
</tr>
<tr>
<td>Peterson et al</td>
<td>2004</td>
<td>12</td>
<td>Noninvasive</td>
<td>11C-acetate</td>
<td>19±7</td>
</tr>
</tbody>
</table>

ME indicates mechanical efficiency (%±SD); PET, positron emission tomography.
systolic performance of the weakened heart muscle with the primarily designed to instigate an acute enhancement in

sion, initial pharmacological approaches in heart failure were considered a noninvasive parameter of regional contractility. It should be emphasized, however, that systolic wall thickening and strain analysis cannot be used to calculate actual external work and therefore do not allow quantification of mechanical efficiency in absolute terms.

Figure 7. End-diastolic (upper panels) and end-systolic (lower panels) cine (A to D) and tagging (E to F) magnetic resonance images in a short axis view of a patient with a previous myocardial infarction of the anterior wall. Endocardial and epicardial borders can be delineated to allow accurate estimation of wall thickness. In combination with measurements of LV diameter and end-systolic pressure, regional wall stress can be calculated in absolute terms (g · cm⁻²) according to Laplace’s law. Relative work parameters can also be obtained by estimation of regional systolic wall thickening (C and D) and myocardial deformation (E and F). The magnetic resonance imaging tissue tagging technique to quantify systolic deformation alters the magnetic properties of the myocardial tissue for a short period of time and appears as black lines on the images. The relative change between these lines from end-diastole to end-systole can be quantified in 3 dimensions, and relative deformation (ie, strain) can be calculated (expressed in %). Strain is generally considered a noninvasive parameter of regional contractility. It should be emphasized, however, that systolic wall thickening and strain analysis cannot be used to calculate actual external work and therefore do not allow quantification of mechanical efficiency in absolute terms.

Dilated Cardiomyopathy
Heart failure produced by dilated cardiomyopathy, regardless of that cardiomyopathy’s cause, is characterized by an unfavorable mechanoenergetic profile (ie, diminished mechanical efficiency). In an effort to optimize peripheral tissue perfusion, initial pharmacological approaches in heart failure were primarily designed to instigate an acute enhancement in systolic performance of the weakened heart muscle with the use of sympathomimetic agents. Apart from improving systolic cardiac performance, however, these agents elevate heart rate and hence $\dot{MV}O_2$. The effects on mechanical efficiency, however, are less clear. Positive inotropic agents like dobutamine increase energetic costs of nonmechanical work, which is often referred to as the oxygen-wasting effect. Furthermore, increased contractility increases oxygen consumption per beat. On the other hand, dobutamine causes a reduction in systemic vascular resistance and thus LV load, which may offset these increased energetic costs. Depending on the magnitude of each of these effects, mechanical efficiency may either be increased, decreased, or unaltered. Regardless of efficiency, the already inefficient and failing heart is forced to further increase its total energy expenditure, with potential deleterious effects.

Meanwhile, it has become apparent that compensatory long-term activation of renin-angiotensin and adrenergic systems results in accelerated disease progression and plays a central role in the process of ventricular remodeling. Pharmacological antagonism of the neurohormonal system with angiotensin-converting enzyme inhibitors and β-blockers have a profound beneficial effect on ventricular mechanics and energetics. Angiotensin-converting enzyme inhibitors substantially reduce mean aortic pressure and systemic vascular resistance. Because of the related reduction in LV load, stroke volume and SW immediately increase while $\dot{MV}O_2$ is lowered, thereby augmenting mechanical efficiency.

Unlike vasodilators and inotropic drugs, β-blockers do not immediately improve hemodynamics of a failing heart. In contrast, on initiation heart rate decreases, and contractile function is further depressed, which frequently results in
deterioration of hemodynamics. The negative inotropic and chronotropic properties, however, diminish the energy requirements of the heart. It is of interest that in the ensuing months of therapy a seemingly paradoxical improvement in contractile function occurs, whereas oxygen use decreases. Consequently, mechanical efficiency improves, as has been demonstrated in invasive and noninvasive placebo-controlled studies.

Mechanical Dyssynchrony
Left bundle-branch block is a common finding in dilated cardiomyopathy and is associated with poorer prognosis. The slow propagation of myocardial depolarization typically induces mechanical dyssynchrony (ie, contraction of the interventricular septum and of the lateral free wall occur at different points in the time of the cardiac cycle). This type of contraction is characterized by waste of myocardial work as energy is lost in shifting blood within the heart itself instead of contributing to ejection. Left bundle-branch block therefore renders the already failing heart even more inefficient. Recently, in an attempt to counteract the detrimental impact of mechanical dyssynchrony, cardiac resynchronization therapy has emerged as a new treatment for a subgroup of patients with drug-refractory symptomatic dilated cardiomyopathy and mechanical dysynchrony. Cardiac resynchronization therapy restores ventricular synchrony by simultaneously pacing the interventricular septum and lateral free wall. In doing so, systolic LV performance is enhanced immediately (ie, within a few heartbeats after initiation of therapy). Moreover, augmented LV work occurs without increasing energy requirements, thereby inducing a more favorable mechanoenergetic profile. Furthermore, the effects on mechanical efficiency are maintained over time and disappear immediately on cessation of long-term cardiac resynchronization therapy, which stresses the beat-to-beat therapeutic effect.

Left Ventricular Hypertrophy
When the heart is subjected to high mechanical load, LV hypertrophy frequently occurs as an adaptive physiological response to lower wall stress and maintains systolic function. Recently, Laine et al have provided more insight into the mechanoenergetic effects of hypertrophy. In hypertensive patients without LV hypertrophy, MV\(\text{O}_2\) was increased in response to augmented metabolic demand caused by a higher workload, which leaves efficiency unaltered, although a nonsignificant reduction was observed. In hypertrophy, however, oxygen utilization per gram of myocardium was normalized and comparable to controls. Total SW did not change in the presence of hypertrophy, but work delivered per gram of hypertrophied tissue was disproportionately depressed relative to the changes observed in MV\(\text{O}_2\). Therefore, the apparent normalization of oxygen utilization per unit of weight induced by hypertrophy occurred at the expense of mechanical efficiency. It should be noted, however, that these observations could not be reproduced in hypertrophy caused by aortic valve stenosis or in patients with hypertensive eccentric hypertrophy. This underscores the complexity of various adaptive processes that occur in hypertrophy under different pathological loading conditions. Clearly, more studies in carefully selected subgroups of patients are warranted.

Conclusions and Future Perspectives
An imbalance between oxidative metabolism and cardiac function appears to be a sensitive marker of myocardial pathology, albeit rather unspecific. In this respect, impaired mechanical efficiency may represent a final common pathway in cardiomyopathy, regardless of cause, and provides important prognostic information. Moreover, as summarized in Table 2, therapeutic interventions that improve outcome are associated with restoration of efficiency, which highlights the clinical significance of this parameter. Although some shortcomings must be acknowledged, recent advances in imaging techniques have enabled reliable noninvasive methods to assess efficiency with obvious advantages over invasive methods. In particular, monitoring interventions that require serial measurements over longer periods of time should benefit from a noninvasive approach. Evaluation of new treatment strategies in this manner in a relatively small number of patients can provide important insight and is an important step toward testing interventions in large clinical trials.

**TABLE 2. Mechanoenergetic Characteristics in Myocardial Pathology and Effects of Interventions in Humans**

<table>
<thead>
<tr>
<th>Condition</th>
<th>MV(\text{O}_2)</th>
<th>EW</th>
<th>ME</th>
<th>Intervention</th>
<th>MV(\text{O}_2)</th>
<th>EW</th>
<th>ME</th>
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<tbody>
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<td>Ischemia</td>
<td>↓</td>
<td>↓</td>
<td>←</td>
<td>...</td>
<td>...</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Stunning</td>
<td>←/↓</td>
<td>↓</td>
<td>↓</td>
<td>Time</td>
<td>↑</td>
<td>↑</td>
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</tr>
<tr>
<td>Hibernation/repetitive stunning</td>
<td>←/↓</td>
<td>↓</td>
<td>↓</td>
<td>Revascularization</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Dilated cardiomyopathy</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>β-Agonists</td>
<td>↑</td>
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<td></td>
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<td>β-Blockers</td>
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<td>↑</td>
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<td></td>
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<td></td>
<td>Vasodilators</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Ventricular dyssynchrony</td>
<td>←</td>
<td>↓</td>
<td>↓</td>
<td>CRT</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Hypertensive concentric LVH</td>
<td>←</td>
<td>↓</td>
<td>↓</td>
<td>Antihypertensive drugs</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

EW indicates external work; ME, mechanical efficiency; CRT, cardiac resynchronization therapy; LVH, left ventricular hypertrophy; and NA, not available. MV\(\text{O}_2\) and EW are adjusted for heart rate and left ventricular mass. Changes are relative to normal controls for each condition. Chronic changes are reported for interventions and are relative to baseline conditions.
New hybrid imaging tools, such as positron emission tomography/computed tomography, will provide further improvements through accurate and nearly simultaneously registration of function and metabolism. Furthermore, algorithms have recently been developed to noninvasively assess both end-systolic pressure–volume relations and end-diastolic pressure–volume relations. These algorithms facilitate quantification of myocardial contractility and relaxation and may offer the possibility to estimate the entire PVA noninvasively (Figure 1C). Thereafter, efficiency can be calculated at different levels of energy transfer (eg, from MVO2 to PVA and from PVA to EW). Future studies will certainly focus on development and validation of these promising and clinically valuable tools.

Disclosures

None.

References


Myocardial Energetics and Efficiency: Current Status of the Noninvasive Approach

Circulation. 2007;115:918-927
doi: 10.1161/CIRCULATIONAHA.106.660639
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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