

# Myocardial efficiency in heart failure: non invasive imaging

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### Abstract

Any mechanical pump is far from efficient. Only a fraction of its input energy is ultimately converted to external work. In the case of the heart, this fraction is approximately 25%, and is defined as mechanical efficiency. Heart failure as a result of dilated cardiomyopathy is characterized by a reduction in efficiency, the extent of which serves as an important prognostic marker. Despite its relevance in studying disease and monitoring interventions, mechanical efficiency is not routinely determined, as it requires a highly invasive procedure. In recent years, however, advances in imaging techniques have made possible the non invasive assessment of this parameter. In this review, we discuss these currently available techniques, including their pitfalls, and place into clinical perspective the studies in which they have been applied.

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### Introduction

The heart is an aerobic organ, relying almost exclusively on the aerobic oxidation of substrates for generation of energy. Consequently, there is close coupling between myocardial oxygen consumption ( $m\dot{V}O_2$ ) and the main determinants of systolic function – ie, heart rate, contractile state, and wall stress [1]. As in any mechanical pump, not all the invested energy is converted to external power. In the case of the heart, the ratio of produced useful energy (stroke work) to consumed oxygen is defined as mechanical efficiency, and was originally defined by Bing et al [2]. Under normal conditions, this ratio is approximately 25%; the remaining energy mainly dissipates as heat [3]. 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 [4,5]. Moreover, therapeutic interventions

that enhance this particular relationship have proved to be beneficial with respect to outcome [6]. It is therefore desirable to quantify efficiency of the heart in order to study disease processes and monitor interventions.

### Invasive measurement of mechanical efficiency

In order to calculate the efficiency of the heart, input and output energy must be obtained. The first can be derived from measurements of  $m\dot{V}O_2$  ( $mL O_2 \cdot min^{-1}$ ), according to the Fick principle, by multiplying coronary sinus blood flow ( $mL \cdot min^{-1}$ ) with the arteriovenous (A–V) oxygen content difference [7]. Blood flow can be estimated with the use of the thermodilution or Doppler (electromagnetic flowmeter) method after access has been gained to the coronary sinus through right-sided heart catheterization. As oxygen dissolved

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in blood is negligible and hemoglobin concentrations in arterial and venous blood are similar, the A–V oxygen content difference can be obtained by determining the differences in oxygen saturation levels between arterial and coronary sinus blood. This method of determining oxygen utilization is currently considered to be 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  $m\dot{V}O_2$  can be assessed, which also includes oxidative metabolic demands of the right ventricle and both atria. In addition, an additional non invasive estimate of left ventricular mass is required to calculate oxidative metabolism per gram of tissue.

Output energy is defined as force times displacement, and is expressed in Joule (J). Energy generated by the heart can best be estimated by generating a pressure–volume (P–V) loop of the cardiac cycle by use of a conductance catheter placed in the left ventricle (Figure 1) to calculate external work (EW). EW is defined by the area contained within the pressure–volume loop [8]. Myocardial mechanical efficiency then equals EW divided by  $m\dot{V}O_2$  per gram of myocardial tissue.

In order to express efficiency in a dimensionless value or percentage,  $m\dot{V}O_2$  and EW must be converted from units of mL O<sub>2</sub> and mm Hg · mL, respectively, to units of energy (Joule). The caloric equivalent

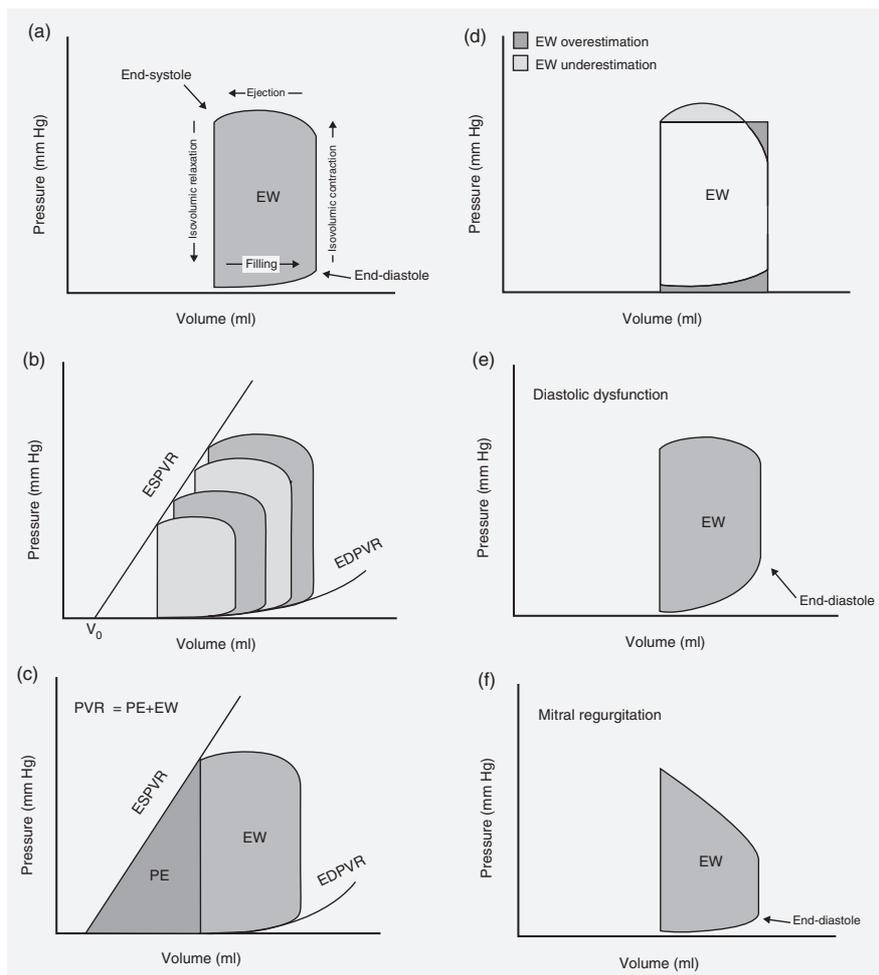


Figure 1. (a) Schematic graphic of a pressure–volume loop. With each heart beat, a full loop is described. Starting at end-diastole, isovolumic contraction occurs. When the aortic valve opens, ejection begins and during the ejection phase volume decreases, whereas pressure changes relatively little. After aortic valve closure, isovolumic relaxation takes place, characterized by a swift decrease in pressure. When the mitral valve opens, filling starts 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 pressure–volume loops under different loading conditions reveals the end-systolic (ESPVR) and end-diastolic (EDPVR) pressure–volume relationships. (c) The area to the left of the pressure–volume 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) Non invasive estimation of the pressure–volume loop based on estimation of stroke volume and end-systolic pressure results in a rectangle. Areas of over- and underestimation compared with the original pressure–volume loop are indicated. (e) Diastolic dysfunction is characterized by an augmented pressure increase during the diastolic filling phase. (f) Mitral regurgitation markedly influences the isovolumic contraction and ejection period characteristics of the pressure–volume loop. (From Knaapen et al [8], with permission).

of 1 mL of O<sub>2</sub> is approximately 20], and 1 mm Hg · mL equals 1.33 · 10<sup>-4</sup>] [9].

## Non invasive measurement of mechanical efficiency

### Input energy: oxidative metabolism

Non invasive assessment of m $\dot{V}$ O<sub>2</sub> is currently limited to positron emission tomography (PET) [10]. Carbon-11-labeled acetate ([<sup>11</sup>C]acetate) [11] is commonly used for this purpose. Acetate is a two-carbon-chain free fatty acid which is taken up by the heart and subsequently rapidly converted to acetyl coenzyme A (CoA) in the mitochondrial matrix. The primary metabolic fate of acetyl CoA is via the tricarboxylic acid (TCA) (Krebs) cycle, in which [<sup>11</sup>C] activity is transported to carbon-11-labeled carbon dioxide ([<sup>11</sup>C]CO<sub>2</sub>), which readily diffuses from myocardial tissue [11,12].

Figure 2 shows an example of a dynamic cardiac [<sup>11</sup>C]acetate PET acquisition and its matching 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,  $k_1$  and  $k_2$ , can be assessed through curve fitting. The rapid phase,  $k_1$ , represents the efflux of [<sup>11</sup>C]CO<sub>2</sub> produced by the TCA cycle. Because of the tight coupling between the TCA cycle and oxidative phosphorylation,  $k_1$  correlates closely with m $\dot{V}$ O<sub>2</sub>, as has been demonstrated under a wide range of conditions [12]. The slow phase,  $k_2$ , is caused by the clearance of [<sup>11</sup>C] activity, which is incorporated into amino acids and TCA cycle intermediates. This method of estimating m $\dot{V}$ O<sub>2</sub> has been further simplified by monoexponential fitting of the linear part of the time–activity curve ( $k_{\text{mono}}$ ), which correlates well with  $k_1$  [12]. Disregarding the slow wash-out phase,  $k_2$  reduces the duration of the scanning procedure to less than 30 min.

Despite the fact the myocardial turnover of [<sup>11</sup>C]acetate is most commonly used for non invasive assessment of m $\dot{V}$ O<sub>2</sub>, it has several disadvantages [10]. First, only semiquantitative estimates of oxidative metabolism are obtained. Even though there exist databases of findings from animal experiments and human studies for the conversion of clearance rate constants (units · min<sup>-1</sup>) to equivalents of absolute units (mL · g<sup>-1</sup> · min<sup>-1</sup>), the relationships found in those relatively small studies, performed under predominantly normal physiologic conditions, may not hold true in a variety of pathological disease states. Secondly, the metabolic fate of [<sup>11</sup>C]acetate depends, at least in part, on myocardial substrate metabolism and pathological conditions such as ischemia [12,13]. Thirdly, differences in the shape of the arterial input curve of tracer activity and artifacts of the spillover from blood pool to myocardium can significantly affect the observed rate of clearance of [<sup>11</sup>C] activity. 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 [<sup>11</sup>C] acetate kinetics have been developed [14]. The essence of these approaches is based on the incorporation of the arterial concentration of [<sup>11</sup>C]acetate and its principal contaminating metabolite, [<sup>11</sup>C]CO<sub>2</sub>, into a model, allowing the calculation of m $\dot{V}$ O<sub>2</sub> in absolute terms. By this means, variability of the input curve and spillover artifacts are taken into account. However, the need for arterial cannulation and repetitive sampling of arterial blood to measure radio-labeled metabolites makes this method cumbersome. In addition, corrections for the partial volume effect (underestimation of true radiotracer concentrations, depending on cardiac dimensions and motion) need to be carried out. As these corrections themselves may induce errors in estimating absolute m $\dot{V}$ O<sub>2</sub>, many groups resort to the simple, semiquantitative, but robust mono- or biexponential curve-fitting method.

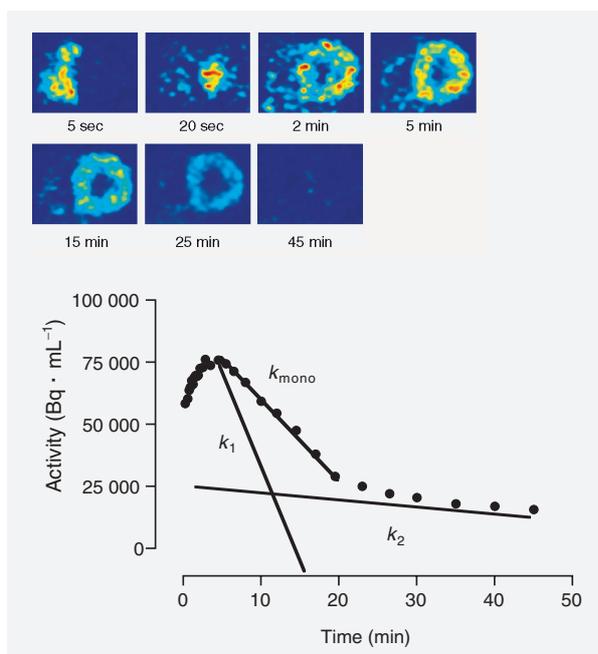


Figure 2. Short-axis view of a dynamic [<sup>11</sup>C]acetate positron emission tomography acquisition displays transit of radio-activity through the right and left ventricular cavities after a bolus injection. Subsequently, [<sup>11</sup>C]acetate is readily taken up by the myocardium and reaches a maximum after ~5 min. The matching myocardial time–activity curve demonstrates the bi- and monoexponential curve fitting of the wash-out phase of activity. The slopes of the fitting curves,  $k_1$  and  $k_{\text{mono}}$ , are correlated to myocardial oxygen consumption m $\dot{V}$ O<sub>2</sub>. (From Knaapen et al [8], with permission).

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### Output energy: external mechanical work

In contrast to oxidative metabolism, non invasive assessment of mechanical external work is relatively straightforward. To estimate the area contained within the pressure–volume loop, in essence, knowledge is required only of stroke volume (SV) – ie, left ventricular end-diastolic (LVEDV) and end-systolic (LVESV) volumes, and left ventricular end-systolic pressure (LVESP). Left ventricular volumes can routinely be derived by various imaging techniques, including magnetic resonance imaging (MRI), echocardiography, and nuclear imaging [15]. LVESP roughly corresponds to the mean arterial pressure (MAP) of the brachial artery and can be assessed by a simple sphygmomanometer [16]. The product of MAP and SV yields a fairly accurate estimate of external work (*Figure 1d*).

Although elegant in its simplicity, this approach has some inaccuracies that should be mentioned. First, the original pressure–volume loop is represented as a rectangle, resulting in some overestimation because it includes the area under the curve of the diastolic filling phase. This effect can be substantial, especially in patients with diastolic dysfunction (*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 pressure–volume loop. Secondly, valvular disease significantly hampers non invasive estimates of external work. In aortic stenosis, the systolic transvalvular pressure gradient results in underestimation of LVESP measured by a sphygmomanometer. Estimation of the transvalvular pressure gradient derived from echocardiography, however, can accurately correct for this underestimation [17]. 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 value of SV, this markedly diminishes external work by regurgitation of blood into the low-pressure atrium. Non invasive assessment of external work will therefore be overestimated in proportion to the magnitude of regurgitating volume (*Figure 1f*). This problem can partly be resolved by substituting total with forward SV, determined by aortic flow measurements derived echocardiographically [18] or by MRI [19] (*Figure 2*). However, subsequent calculation of the so-called ‘forward stroke work’ may not accurately reflect actual stroke work in these patients. Mitral regurgitation therefore remains an important source of error in non invasive quantification of external work.

### Mechanical efficiency

The combination of the non invasive estimates of  $m\dot{V}O_2$  and external work as described above allows

for the assessment of mechanical efficiency according to the following formula:

$$\text{efficiency} = \frac{\text{MAP} \cdot \text{SV} \cdot \text{HR} \cdot 1.33 \cdot 10^{-4}}{m\dot{V}O_2 \cdot \text{LVM} \cdot 20}$$

where HR is heart rate and LVM is left ventricular mass (grams); the conversion factors to units of Joule are as mentioned earlier. It needs to be emphasized that, in this formula,  $m\dot{V}O_2$  is expressed in absolute terms. The method most commonly used for estimating oxidative metabolism non invasively, however, remains the exponential curve-fitting procedure of [ $^{11}\text{C}$ ]acetate, which generally yields an index of  $m\dot{V}O_2$ . Beanlands et al [20] introduced an alternative efficiency index, the so-called work metabolic index (WMI):

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

where SBP is systolic blood pressure and SVI is stroke volume index. This equation is a modification of the minute work–oxygen consumption relationship originally defined as mechanical efficiency by Bing et al [2].

### Clinical studies of dilated cardiomyopathy

Heart failure as a result of dilated cardiomyopathy, regardless of its etiology, is characterized by an unfavorable mechano-energetic profile. There is growing support for the hypothesis that the increased energy expenditure relative to work leads to energy starvation of the failing heart [4,5]. A well-documented decline in the ratio of phosphocreatine to total ATP as an indicator of a poor cardiac energy status corroborates this notion [21]. The mechanisms underlying this process remain under investigation, but are believed to include abnormalities of creatine kinase shuttling [22], nitric-oxide-mediated mitochondrial respiration [23], oxidative stress [24], and coronary flow reserve [25]. The prognostic importance of reduced mechanical efficiency has recently been highlighted by Kim et al [26], who demonstrated that, in patients with idiopathic dilated cardiomyopathy, mechanical efficiency was the single most important and only independent predictor of cardiac death among various invasively measured left ventricular functional parameters, with an optimal discriminating cutoff value of 11%.

In the current era, therefore, attempting to alter the balance between myocardial oxygen utilization and work positively in patients with heart failure, without augmenting energy demand, seems a logical therapeutic goal. Initially, in an effort to optimize peripheral tissue perfusion, pharmacological approaches were

primarily designed to instigate an acute enhancement in systolic performance of the weakened heart muscle with the use of sympathomimetic agents [4,6]. Besides improving systolic cardiac performance, however, these agents increased heart rate, and hence  $m\dot{V}O_2$ . The effects on mechanical efficiency are less clear. Positive inotropic agents such as dobutamine increase the energetic costs of non mechanical work, which is often referred to as the oxygen-wasting effect [3,27]. Furthermore, increased contractility increases oxygen consumption per beat [28]. Conversely, dobutamine causes a reduction in systemic vascular resistance and thus left ventricular load, which may offset these increased energetic costs. Depending on the magnitude of each of these effects, mechanical efficiency may be increased, decreased, or unaltered [20,27,29]. Regardless of efficiency, the already inefficient, energy deprived, and failing heart is forced to increase its total energy expenditure further, with potential deleterious effects. Indeed, we now know from large-scale clinical trials that the short-term hemodynamic improvement and alleviation of symptoms of heart failure are actually achieved at the expense of increased long-term mortality [30,31]. The unfavorable mechano-energetic properties of these agents are most probably in part responsible for these observations.

In the meantime, it became increasingly apparent that the compensatory long-term activation of the renin-angiotensin and adrenergic systems results in accelerated disease progression and plays a central role in the process of ventricular remodeling [6,32]. Subsequent trials in which the neurohormonal system was pharmacologically antagonized with angiotensin-converting enzyme (ACE) inhibitors and  $\beta$ -blockers systematically showed an improvement in systolic left ventricular performance, the slowing/arresting or even the reversal of ventricular remodeling, and marked reduction in morbidity and mortality [33]. Even though the observed effects are to a certain extent related to the inhibition of the direct cardiotoxic effects of high circulating plasma concentrations of norepinephrine and angiotensin II, these agents also have a profound beneficial impact on ventricular mechanics and energetics. ACE inhibitors substantially reduce mean aortic pressure and systemic vascular resistance. As a result of the related reduction in left ventricular load, SV and stroke work immediately increase while decreasing  $m\dot{V}O_2$ , thereby augmenting mechanical efficiency [34]. More intriguing are the modes of action of  $\beta$ -blockers. Unlike vasodilators and inotropic drugs,  $\beta$ -blockers do not immediately improve the hemodynamics of a failing heart. Rather, upon their initiation, heart rate decreases and contractile function is further depressed, which frequently results in deterioration of hemodynamics and may have a negative impact on the well-being of the patient [35]. These effects have long served as an

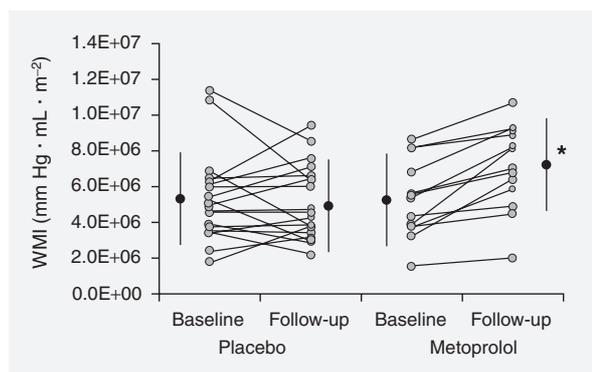


Figure 3. Work metabolic index (WMI), an estimate of mechanical efficiency, in patients with dilated cardiomyopathy treated with placebo ( $n = 19$ ) or metoprolol ( $n = 13$ ). [units?] Efficiency is enhanced in metoprolol-treated patients (\* $P < 0.02$ ). (From Beanlands et al [37], with permission).

argument against the use of  $\beta$ -blockers in dilated cardiomyopathy. The negative inotropic and chronotropic properties of these drugs, however, diminish the energy requirements of the heart. Of interest, in the ensuing months of therapy a seemingly paradoxical improvement in contractile function occurs, whereas oxygen utilization decreases. Consequently, mechanical efficiency improves, as has been demonstrated in placebo-controlled studies (Figure 3) [36,37]. The energy-sparing mechanisms of antiadrenergic therapy possibly allow for the restoration of cardiac energy reserves and actually reverse, at least in part, the process of cardiomyopathy. A secondary biological, rather than a direct pharmacological, hemodynamic effect explains this altered course of disease progression [6].

## Conclusions and future perspectives

An imbalance between oxidative metabolism and cardiac function appears to be a pivotal marker of disease progression in heart failure. Moreover, therapeutic interventions that improve outcome are associated with restoration of efficiency, highlighting the clinical significance of this parameter. Although some shortcomings must be acknowledged, recent advances in imaging techniques have made possible a reliable non invasive assessment of efficiency, with obvious advantages over the invasive method. Monitoring interventions that require serial measurements over longer periods of time benefit particularly from this non invasive 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 towards testing interventions in large clinical trials. New hybrid imaging tools, such as PET/computed tomography, will further improve this technique by registering function and metabolism almost simultaneously. ■

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