Measuring cardiac efficiency: is it clinically useful?

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Have you ever wondered, in the management of patients with various cardiac diseases, what was the cardiac efficiency of your patient, and how treatment could possibly favorably change the cardiac efficiency of this patient? I, certainly, never considered this consciously, and I doubt that many of us do. Nevertheless, the concept of cardiac efficiency had already been proposed and studied by Bing et al [1] as long ago as 1949. Since then, cardiac efficiency has been studied in various cardiac diseases such as coronary artery disease, stunned and hibernating myocardium, and hypertrophic and dilated cardiomyopathy, during medical and resynchronization therapy for heart failure, and in hypertension. More importantly, from a clinical point of view, inefficiency is an important prognostic factor for patients. Kim et al [2], for example, showed that, in patients with dilated cardiomyopathy, inefficiency was the single, most important predictor of cardiac death.

Although the term “cardiac efficiency” may sound like a highbrow academic concept, in reality it is very simple: for work to be performed (whether by a car or by the heart), energy is needed, and the ratio between delivered work and input of energy is defined as “efficiency”. For the pumping function of the heart, energy is needed. This energy comes from the oxidation of several fuels, such as fatty acids and glucose. However, the concentration of these fuels may vary over time (eg, after a meal), and it may be quite laborious to measure and calculate the energy input from these nutrients. Because oxygen is required for the oxidation of the nutrients, the amount of oxygen consumed can substitute for the energy input of the nutrients. The other part of the efficiency equation is the work delivered by the heart. This is usually expressed as left ventricular external stroke work, and is calculated from stroke volume, heart rate, and the mean arterial pressure. Cardiac efficiency is therefore the ratio between stroke work and oxygen consumption. As one can read in this issue, the efficiency of the normal heart is approximately 20–25% and, although this may sound low, the heart is far more efficient than a car.

Because efficiency is an important factor in various cardiac diseases, and because it is a relatively unknown field, the editorial board of Heart and Metabolism decided to devote this issue of the journal to the topic.

In the Main Clinical Article, Akinboboye discusses in detail the measurement of cardiac efficiency in various diseases, and concludes that measurement of efficiency is useful because it provides valuable insights into the pathophysiology of cardiovascular disease and into the beneficial effects of therapeutic interventions. The efficiency and inefficiency found in cardiac disease have, of course, a molecular basis, and in the Basic Article, Bugger and Abel report some fascinating data on how efficiency may be changed in diabetic cardiomyopathy.

Cardiac efficiency can be determined invasively during cardiac catheterization and non invasively mainly using positron emission tomography (PET). These two methodologies are discussed, respectively, in Refresher Corner by Steendijk and ten Brinke, and...
in the Metabolic Imaging article by Knaapen and Germans.

Among the key features of heart failure are the dyssynchrony and inefficiency of cardiac contraction. In the New Therapeutic Approaches article, Ginks and Rinaldi highlight the improvement in both cardiac function and clinical outcome that result from resynchronization therapy in these patients. The effect of treatment on the improvement of cardiac efficiency is also nicely demonstrated in the Case Report by Germans et al. After septal alcohol ablation performed in a patient with an obstructive hypertrophic cardiomyopathy, cardiac efficiency was greatly enhanced.

Finally, in the Focus on Vastarel article, Belardinelli discusses the use of trimetazidine in combination with cardiac rehabilitation for the treatment of patients with heart failure. Although cardiac efficiency was not specifically studied, one may speculate that trimetazidine improves cardiac efficiency in patients with heart failure.

After reading this issue of Heart and Metabolism, you should have a clearer picture as to what cardiac efficiency is, how it is measured, and how treatment of various cardiac abnormalities counteracts inefficiencies of the heart. The question is: do we need to assess cardiac inefficiency in our daily clinical practice? Measurement of efficiency requires special methodologies for cardiac catheterization, or PET imaging, or both, which are expensive and not readily available. Because of this, measurement of cardiac efficiency may not be appropriate for routine patient management. Nevertheless, as stated above, assessment of cardiac efficiency does give valuable insight into the pathophysiology of various cardiac diseases, and into the beneficial effects of pharmacological and non pharmacological treatments.

Enjoy your reading!

REFERENCES

Molecular basis of cardiac efficiency

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Abstract
Cardiac efficiency is defined as the ratio between cardiac work and myocardial oxygen consumption. Impairment of cardiac efficiency is believed to contribute to contractile dysfunction in cardiac disease states such as diabetic cardiomyopathy, the hyperthyroid heart, and dilated cardiomyopathy. In diabetes, reduced cardiac efficiency is a common observation and is likely to result from alterations in cardiac energy-substrate metabolism. This review will discuss potential molecular mechanisms of reduced cardiac efficiency with a focus on diabetic cardiomyopathy, highlighting recent evidence that suggests mitochondrial uncoupling to be an underlying mechanism.

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Keywords: Myocardium, mitochondria, efficiency, molecular mechanisms, diabetic cardiomyopathy

Introduction
The heart is a highly oxidative organ. It relies almost exclusively on the oxidative generation of ATP from fatty acids, glucose, lactate, and other substrates, to maintain contractile function and cellular homeostasis. Under physiological conditions, oxidative production of ATP is relatively tightly coupled to mitochondrial oxygen consumption, thus making myocardial oxygen consumption (m$\dot{V}$O$_2$) a useful index of ATP turnover and metabolic activity by the heart. Cardiac efficiency is defined as the ratio between cardiac work and m$\dot{V}$O$_2$. Reduced cardiac efficiency is believed to contribute to contractile dysfunction in cardiac diseases such as diabetic cardiomyopathy, the hyperthyroid heart, and dilated cardiomyopathy [1–3]. As m$\dot{V}$O$_2$ is directly related to energy metabolism, it is not surprising that research revealed a link between impairment in cardiac efficiency and alterations in cardiac energy-substrate metabolism. This review will discuss potential molecular mechanisms of reduced cardiac efficiency, with a focus on mitochondrial uncoupling as a key underlying mechanism in diabetic cardiomyopathy.

Fatty acid induced mitochondrial uncoupling
Oxidation of energy substrates occurs in mitochondria and results in the generation of a proton gradient across the inner mitochondrial membrane that is used by the F$_0$F$_1$-ATPase to resynthesize ATP from ADP. Thus oxygen consumption is coupled to ATP synthesis (mitochondrial coupling). If protons bypass the ATP synthase when cycling across the mitochondrial inner membrane, heat is produced instead of ATP (mitochondrial uncoupling). Under physiological conditions, a certain proportion of protons always leaks through the membrane, in part as a result of slip reactions in the proton pumping machinery and other elusive mechanisms that do not result in ATP generation [4]. In addition, basal proton conductance is halved in muscle mitochondria from mice in which adenine nucleotide translocase 1 (ANT1)$^+$ has been ablated, also suggesting that a substantial part of basal proton leak is mediated by ANT1 [5].

Uncoupling proteins (UCPs)$^+$ belong to the superfamily of mitochondrial transport proteins and can also catalyze proton conductance across the mitochondrial membrane [6]. Neither UCP1, nor its
homologs UCP2 or UCP3, seem to catalyze basal proton conductance, as conductance remains the same in mitochondria from UCP isoform knockout mice [7,8]. Rather, UCPs comprise a system of inducible proton conductance. Echtay et al [6] demonstrated increased proton conductance in isolated mammalian mitochondria after the addition of exogenous superoxide for UCP1, UCP2, and UCP3 – an activation that required the presence of palmitate, thereby extending previous findings [9] that reactive oxygen species (ROS) cause fatty acid dependent uncoupling in plant mitochondria. Superoxide-induced UCP-mediated mitochondrial uncoupling also results from endogenously produced superoxide, and such an activation of UCPs was demonstrated to occur at the matrix side of mitochondria, thereby demonstrating that mitochondria-derived ROS can induce mitochondrial uncoupling [10]. Further studies demonstrated that the lipid peroxide 4-hydroxy-2-nonenal, a frequent byproduct of increased oxygen radical generation, can also trigger uncoupling activity of both UCPs and ANT [11].

In the mammalian heart, both UCP2 and UCP3 are expressed [12,13]. Their expression correlates with serum fatty acid concentrations and rates of myocardial fatty acid oxidation [14]. UCP3 and UCP2 (in part), are positively regulated by the transcriptional regulator of the fatty acid oxidative pathway, peroxisome proliferator-activated receptor α (PPARα), as indicated by reduced expression of UCP2 and UCP3 in PPARα null mice and increased expression of UCP3 in rats and mice treated with the PPARα agonist, WY-14,643 [12,15]. The physiological significance of changes in the abundance of cardiac UCPs remains to be elucidated, but the existence of UCP-mediated uncoupling in the heart has been demonstrated recently, as discussed below.

In the postnatal mammalian heart, ATP is generated mainly from the oxidation of fatty acids (60–70%) and to a lesser extent from glucose, lactate, and other substrates (30–40%). Early studies in healthy rats demonstrated that increasing the cardiac uptake of fatty acids by infusions of Intralipid resulted in increased mVO2, but no increase in cardiac mechanical activity – that is, reduced cardiac efficiency [16]. Similar observations have been made in obesity and type 2 diabetes, in which conditions the heart also oxidizes relatively more fatty acids and less carbohydrates, leading to reduced cardiac efficiency. Peterson et al [17] showed that impaired glucose tolerance correlated with increased fatty acid utilization, and that an increase in body mass index was associated with increased mVO2 and reduced cardiac efficiency in obese and insulin-resistant women. Similarly, increased myocardial fatty acid oxidation and oxygen consumption are associated with unchanged or reduced contractile function, resulting in reduced cardiac efficiency, in obese and diabetic ob/ob and db/db mice [1,18,19]. As both fatty acid oxidation and oxygen consumption occur in mitochondria, the findings of these studies suggest that the basis for impaired cardiac efficiency may be located within mitochondria. Work from our group showed that both ob/ob and db/db hearts pre-perfused with buffer containing glucose as the only substrate have impaired rates of ADP-stimulated mitochondrial oxygen consumption and ATP synthesis, probably caused by reduced expression of oxidative phosphorylation (OXPHOS) proteins, but show normal ATP: oxygen ratios, indicating normal mitochondrial coupling [13,20]. In contrast, the addition of high concentrations of palmitate to the perfusion medium resulted in an increase in palmitoyl-carnitine-supported mitochondrial respiration back to wildtype levels, accompanied by reduced ATP: oxygen ratios, suggesting that the “normalization” of oxygen consumption was the result of uncoupled respiration. These data suggest that mitochondrial uncoupling was induced by fatty acids in the perfusion buffer. Further studies using proton leak kinetics demonstrated that proton conductance was increased in mitochondria of db/db but not wildtype hearts, and that addition of the UCP inhibitor, guanosine diphosphate, reduced proton conductance in db/ db heart mitochondria, suggesting the presence of UCP-mediated uncoupling in db/db hearts [20]. Studies using the ANT inhibitor, atracyloside, showed that a small component of proton leak could also be attributed to ANT. Interestingly, the expression of UCP3 and that of ANT were not increased in db/db mice, suggesting an expression-independent mechanism of direct activation, consistent with the inducible nature of proton conductance by UCPs. Indeed, db/db hearts showed increased mitochondrial production of hydrogen peroxide and increased levels of 4-hydroxy-2-nonenal. As hydrogen peroxide production in isolated heart mitochondria is higher with palmitoyl carnitine as the substrate than with pyruvate, and because superoxide and 4-hydroxy-2-nonenal can directly activate UCPs, we propose the following mechanism for reduced cardiac efficiency in obesity and type 2 diabetes [6,11,21] (Figure 1).

Increased fatty acid oxidation in the diabetic heart may lead to increased production of mitochondrial ROS, resulting in activation of uncoupling proteins, which leads to increased oxygen consumption but reduced ATP synthesis. The deficit in ATP production may not allow an increase in cardiac work or may even lead to reduced cardiac work despite increased oxygen consumption, resulting in reduced cardiac efficiency. In combination with impaired mitochondrial oxidative capacity resulting from the downregulation of OXPHOS proteins, mitochondrial uncoupling may contribute to the development of contractile dysfunction as a result of a relative energy
deficit. The increase in fatty acid utilization in diabetic hearts may originate from increased uptake of fatty acid as a consequence of increased serum fatty acid concentrations or from reduced glucose utilization as a result of cardiac insulin resistance, which can reciprocally increase fatty acid utilization. Increased fatty acid oxidation (FAO) may result in increased mitochondrial generation of reactive oxygen species (ROS), which may induce mitochondrial uncoupling by activating uncoupling proteins (UCP) and adenine nucleotide translocase (ANT), ultimately resulting in reduced synthesis of ATP. Oxygen consumption may be increased as a result of mitochondrial uncoupling and increased oxygen cost for ATP production resulting from the preferential oxidation of fatty acids. Increased oxygen consumption in the absence of increased cardiac work caused by a relative energy deficit reduces cardiac efficiency (CE; white box). Acyl CoA, acyl coenzyme A; GO, glucose oxidation; , increased; , decreased; =/\#, the same or decreased.

The question remains why only db/db hearts, and not wildtype hearts, show increased ROS production and mitochondrial uncoupling when pre-perfused with high concentrations of fatty acids. This may result from differences in the enzymatic equipment (increased abundance or activity of the enzymes of fatty acid oxidation) or imbalances in the expression of OXPHOS subunits in diabetic animals, which may predispose diabetic heart mitochondria to increased generation of ROS [13,20]. Greater production of ROS, simply as a consequence of increased fatty acid oxidation, may alone not be sufficient to overwhelm the antioxidant defense and to activate UCPs. According to this hypothesis, in wildtype animals, increased m\(\dot{V}_O\)2 after lipid infusion would not result from fatty acid induced mitochondrial uncoupling (because these animals have no predisposition), but rather from the higher oxygen cost for ATP synthesis when fatty acids are preferentially oxidized.

Reduced cardiac efficiency is also observed in experimental hyperthyroidism [2,22]. Perfsusions of hyperthyroid rat hearts with glucose and palmitate, but not with a combination of glucose, pyruvate, and lactate, resulted in reduced cardiac efficiency that was accompanied by increased expression of UCP2 and UCP3 and increased mitochondrial consumption of oxygen in the presence of the ATP synthase inhibitor, oligomycin, suggesting that mitochondrial uncoupling had occurred [2]. These results support the concept that, similar to diabetic hearts, hyperthyroid hearts possess a predisposition that makes them prone to fatty acid induced mitochondrial uncoupling. Heart failure is another condition in which cardiac efficiency can be impaired [23]. The extent to which cardiac efficiency is reduced in dilated cardiomyopathy may even have prognostic value as a predictor of mortality in heart failure [24]. However, the molecular basis of impaired cardiac efficiency in failing hearts remains to be elucidated.

Substrate preference and oxygen cost

Alterations in the pattern of substrate utilization per se may also contribute to increased oxygen consumption.
and impaired cardiac efficiency in the heart. Theoretical calculations of the yield of ATP per atom of oxygen consumed show that fatty acids are a less efficient fuel than is glucose [25]. It is calculated that shifting from 100% palmitate to 100% glucose as substrate would increase the yield of ATP by 12–14%. Thus, if any heart, such as a diabetic heart, oxidizes relatively more fatty acids and less glucose, more oxygen is needed to generate the same amount of ATP compared with a healthy heart. As cardiac work would not change, the higher oxygen cost for ATP generation would also impair cardiac efficiency. In failing hearts, in which substrate preference seems to switch towards glucose, such an adaptation could be considered beneficial for the heart, because the amount of oxygen required to maintain ATP levels is reduced.

**Futile cycling**

Another mechanism that has been proposed to contribute to reduced cardiac efficiency in diabetes is “futile cycling” [26]. Cardiac expression of both cytosolic (cTE1) and mitochondrial (mTE1) thioesterase 1 is induced in diabetes [20,26]. Increased expression of cTE1 may increase hydrolysis of acyl coenzymes A (CoA) back to non esterified fatty acids before acyl CoAs can be utilized for oxidation or other pathways, thereby accumulating non esterified fatty acids in the cytosol. Increased expression of mTE1 may increase intramitochondrial hydrolysis of acyl CoAs and accumulation of nonesterified fatty acids, which may then be transported back into the cytosol via UCPs. In both cases, the acyl CoAs are reconverted to fatty acids instead of being utilized. Because esterification of fatty acids to acyl CoA requires ATP, the increase in esterification reactions that prepare the accumulated cytosolic fatty acids for subsequent utilization will consume more ATP than direct esterification and utilization of fatty acids after fatty acid uptake. Thus increased amounts of ATP are utilized for fatty acid re-esterification, instead of being used for oxidation and generation of ATP to support the energetic requirements of contraction in diabetic hearts, thereby potentially contributing to impaired cardiac efficiency.

**Summary**

We have discussed potential molecular mechanisms that may underlie impairment of cardiac efficiency. Good evidence exists to support the idea that fatty acid induced mitochondrial uncoupling may be an underlying mechanism for impaired cardiac efficiency in diabetic cardiomyopathy, thereby contributing to the development of contractile dysfunction.

Further studies will be required to identify additional molecular mechanisms that predispose diabetic hearts to fatty acid induced mitochondrial uncoupling. As both fatty acids and ROS appear to be required for mitochondrial uncoupling, lipid-decreasing strategies and antioxidant treatment may provide therapeutic options to prevent or delay the onset of contractile dysfunction. Partial fatty acid oxidation inhibitors such as trimetazidine and ranolazine have been shown to be efficacious in reducing symptomatic and asymptomatic ischemia in patients with diabetes, and to increase left ventricular function in diabetic individuals with ischemic cardiomyopathy [27–31]. As recently reviewed by Ashrafian and colleagues [32], trimetazidine has also been reported to increase left ventricular function in non diabetic individuals with heart failure. However, in some non diabetic patients with severe heart failure, significant inhibition of myocardial fatty acid oxidation as a result of the inhibition of substrate availability (by means of the lipolysis inhibitor, acipimox) might reduce left ventricular function further and may worsen cardiac efficiency [23]. These potentially conflicting results could reflect differences between the direct effects that partial fatty acid oxidation inhibition exerts on the heart and effects resulting from restriction of substrate availability. Thus the possibility remains that the beneficial effects of inhibitors of partial fatty acid oxidation in diabetic patients and nondiabetic individuals with angina or ischemic cardiomyopathy could result directly from an improvement in cardiac efficiency that is based on a relative shift in glucose utilization from fatty acid to glucose. However, this remains to be demonstrated definitively. In experimental and human studies [33], ranolazine has been shown to possess antiarrhythmic properties, and in animal studies [34,35], trimetazidine has been reported to alter membrane phospholipid metabolism and adrenergic receptor signaling. Thus additional studies are warranted to examine the mechanism of action of these compounds, particularly their contribution to changes in cardiac efficiency.

“See glossary for definition of these terms.”

**REFERENCES**

Basic article

Molecular basis of cardiac efficiency


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.


Keywords: Metabolism, myocardium, efficiency, work, clinical

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 ($\dot{m}V_{O2}$).

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) and carbon-11-labeled acetate ($^{11}$C acetate). Assessment of myocardial oxygen flux with $^{15}$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 $^{11}$Cacetate 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]. $^{11}$CAcetate is converted to $^{11}$Cacetyl coenzyme A and undergoes oxidative phosphorylation through the Krebs cycle in the mitochondria. One of the metabolic end products of $^{11}$Cacetate metabolism is $^{11}$CO$_2$. It has been demonstrated that quantification of the egress of $^{11}$C$\text{CO}_2$ from the myocardium correlates well with directly measured mVO$_2$ [5].

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

When a single peak is present, monoexponential curve fitting ($k_{\text{mono}}$) 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 $^{11}$Cacetate to carbon dioxide and water, and the second slower clearance rate ($k_2$) represents incorporation of $^{11}$Cacetate into amino acid pools. On the average, $k_2$ accounts for less than 5% of $k_1$ [8,9]. Both $k_1$ and $k_{\text{mono}}$ have been shown to correspond with mVO$_2$ 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 $k_{\text{mono}}$ are approximately 0.054–0.058·min$^{-1}$, corresponding to a biological half-time of approximately 12–13 min [9,10]. mVO$_2$ is usually derived from either $k_1$ or $k_{\text{mono}}$ 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 $^{11}$Cacetate 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 mVO$_2$, 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 ($k_{\text{mono}}$) 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$^{-1}$).

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 mVO$_2$ 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

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[18F]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 mVO2 by [13C]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 mVO2, 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 mVO2, leading to an increase in myocardial efficiency [23].

In patients with hypertension without left ventricular hypertrophy, mVO2 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 mVO2 per gram of tissue is normal. Conversely, in eccentric hypertrophy, both stroke work and mVO2 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 [13C]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.

### REFERENCES


Main clinical article

Clinical applications of myocardial efficiency


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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Keywords: Myocardium, efficiency, work, non invasive measurement, clinical

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$_2$·min$^{-1}$), according to the Fick principle, by multiplying coronary sinus blood flow (mL·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
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 $m\dot{V}_O2$ 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 $m\dot{V}_O2$ per gram of myocardial tissue.

In order to express efficiency in a dimensionless value or percentage, $m\dot{V}_O2$ and $EW$ must be converted from units of mL O2 and mmHg·mL, respectively, to units of energy (Joule). The caloric equivalent

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**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 O₂ is approximately 20 J, and 1 mm Hg · mL equals 1.33 \times 10^{-4} J [9].

**Non invasive measurement of mechanical efficiency**

**Input energy: oxidative metabolism**

Non invasive assessment of mVO₂ is currently limited to positron emission tomography (PET) [10]. Carbon-11-labeled acetate ([¹¹C]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 [¹¹C] activity is transported to carbon-11-labeled carbon dioxide ([¹¹C]CO₂), which readily diffuses from myocardial tissue [11,12].

Figure 2 shows an example of a dynamic cardiac [¹¹C]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 [¹¹C]CO₂ produced by the TCA cycle. Because of the tight coupling between the TCA cycle and oxidative phosphorylation, \( k_1 \) correlates closely with mVO₂, as has been demonstrated under a wide range of conditions [12]. The slow phase, \( k_2 \), is caused by the clearance of [¹¹C] activity, which is incorporated into amino acids and TCA cycle intermediates. This method of estimating mVO₂ 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 [¹¹C]acetate is most commonly used for non invasive assessment of mVO₂, 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⁻¹) to equivalents of absolute units (mL · g⁻¹ · min⁻¹), 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 [¹¹C]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 [¹¹C] 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 [¹¹C]acetate kinetics have been developed [14]. The essence of these approaches is based on the incorporation of the arterial concentration of [¹¹C]acetate and its principal contaminating metabolite, [¹¹C]CO₂, into a model, allowing the calculation of mVO₂ 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 mVO₂, many groups resort to the simple, semiquantitative, but robust mono- or biexponential curve-fitting method.
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 $\dot{V}O_2$ and external work as described above allows for the assessment of mechanical efficiency according to the following formula:

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

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, $\dot{V}O_2$ is expressed in absolute terms. The method most commonly used for estimating oxidative metabolism non invasively, however, remains the exponential curve-fitting procedure of $[^{11}C]acetate$, which generally yields an index of $\dot{V}O_2$. Beanlands et al [20] introduced an alternative efficiency index, the so-called work metabolic index (WMI):

$$\text{WMI} = \frac{\text{SBP} \cdot \text{SVI} \cdot \text{HR}}{(\text{mm Hg} \cdot \text{mL} \cdot \text{m}^{-2})}$$

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 β-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 cardio-toxic 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 β-blockers. Unlike vasodilators and inotropic drugs, β-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 argument against the use of β-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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Improvement of cardiac efficiency in heart failure by cardiac resynchronization therapy

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Abstract

Heart failure is a common and disabling condition. A large number of patients with heart failure have dyssynchronous and inefficient cardiac contraction. Cardiac resynchronization therapy (CRT) can improve mechanical function of the left ventricle by restoring synchronized contraction, resulting in positive remodeling. CRT has revolutionized the treatment of heart failure, with proven benefit in symptoms and a reduction in mortality. Unfortunately, up to 30% of patients undergoing CRT will be “non-responders”. Identifying patients who will improve as a result of CRT, and the development of new techniques that can ease the implantation procedure, remain the key areas of interest.

Keywords: Heart failure, cardiac resynchronization therapy, biventricular pacing

Introduction

Heart failure is frequently associated with intracardiac conduction delay, usually manifested on the surface electrocardiogram (ECG) as left bundle branch block [1]. Such conduction abnormalities may translate into mechanical “dyssynchrony”, with delayed stimulation and contraction of the lateral wall of the left ventricle. The uncoordinated contraction that arises causes the efficiency of the heart as a pump to be significantly reduced.

Cardiac resynchronization therapy (CRT) can be performed to normalize the timing of activation of the left ventricle and thereby restore coordinated contraction and mechanical efficiency. This is usually achieved by positioning a pacing lead on the epicardial surface of the left ventricle, via a tributary of the coronary sinus (Figure 1) [2]. Typically, empirical positioning of the lead in the posterolateral vein gives the best hemodynamic response [3].

Evidence for the benefit of CRT

Several large-scale randomized trials have shown CRT to be associated with improvements in New York Heart Association (NYHA) class, quality of life, 6-minute walk distance, and peak myocardial oxygen consumption (m\(\dot{V}O_2\)), in addition to a reduction in admissions to hospital because of heart failure [4–6]. More recently a mortality benefit has also been shown, in addition to the other positive effects of CRT [7]. CRT is able to improve cardiac output by correction of mechanical
dyssynchrony, and this increase in cardiac output appears to take place without an increase in metabolic demand, thereby representing improved cardiac efficiency [8].

In the long term, CRT may also give rise to reverse remodeling, whereby pathological dilatation is reversed and mechanics of the left ventricle are improved [9]. A reduction in mitral regurgitation may also improve cardiac efficiency, either acutely if papillary muscle dyssynchrony is the cause, or in conjunction with reverse remodeling in the setting of functional mitral regurgitation as a result of mitral annular dilatation [10]. Optimization of both atrioventricular and interventricular delays by programming of the CRT device improves atrial transport and enhances diastolic function.

In addition to improvements in cardiac efficiency, and symptomatic and mortality benefits, CRT may also reduce neurohumoral activation [11] and promote upregulation of genes encoding myocardial contractile proteins [12].

Selection of candidates for CRT

Current guidelines suggest that patients will derive benefit from CRT if they fulfill the following criteria: they are significantly symptomatic (NYHA Class III or IV), with dilated (ischemic or non ischemic) cardiomyopathy, despite optimal medical therapy, and have poor left ventricular function (ejection fraction < 35%), with evidence of dyssynchrony on the ECG (QRS duration > 120 ms) (Table I) with or without additional assessment with echocardiography (if QRS duration < 150 ms) [16]. Most patients who meet these criteria are also candidates for implantable cardioverter-defibrillator (ICD) therapy, especially if their symptoms have an ischemic etiology [17].

Response to treatment

There are numerous methods of assessing either acute or chronic response to treatment. Acute responses can be readily evaluated by hemodynamic parameters such as $\frac{dp}{dt}$ or by echocardiography using the left ventricular velocity–time integral. Symptomatic assessment can be performed by assessing NYHA class, quality-of-life questionnaires, 6-minute walk test, $\dot{m}V_{O_2}$ testing, and changes in echocardiographic parameters (such as left ventricular ejection fraction, end-diastolic dimension, and degree of mitral regurgitation). So-called “hard endpoints” include admission to hospital because of heart failure, adverse cardiac events, and death.

The challenge ahead: solving the problem of non response

Up to 30% of patients do not derive benefit from CRT, and this remains the driving factor behind much research in this field. Potential causes of non-response to treatment are outlined in Table II.

Improving patient selection

Improving patient selection is of paramount importance in identifying both the patients who will benefit from CRT and those who will not (who thus avoid the potential risks associated with device implantation).

The resting ECG has been used to select patients, with a broad QRS suggesting electrical and mechanical dyssynchrony. Echocardiographic methods have been used to try to assess mechanical dyssynchrony.
and predict which patients will have a favorable response. The current echocardiographic techniques for assessment of dyssynchrony include speckle tracking and tissue Doppler imaging. These techniques have the advantage that they are widely available and relatively easy to perform. The value of echocardiographically derived measures has been questioned by the recent Predictors of Response to Cardiac Resynchronization Therapy (PROSPECT) study [18], which did not lead to a consensus on the best parameters for the evaluation of dyssynchrony. Importantly, it showed that there was significant inter-operator variability in some of the measures, making them unreliable.

Magnetic resonance imaging (MRI) has emerged as a useful tool for the evaluation of myocardial viability.
and offers excellent quantification and localization of scar, which in the posterolateral position is associated with a less favorable outcome [19]. MRI also allows assessment of dyssynchrony using tagging techniques [20], although the temporal resolution is much poorer than that of echocardiography, and MRI studies cannot be repeated post-implantation. The ability of MRI to delineate coronary venous anatomy may in the future prove useful for the subsequent device implantation, but at present the gold standard for this remains cardiac computed tomography [21].

**Positioning of the left ventricular lead**

Perhaps the single most important factor affecting the outcome of CRT is the placement of the left ventricular lead. The main challenges of the implant procedure are coronary venous access, stability of the guide catheter, and variation in the anatomy of the coronary sinus. It is not always possible to achieve a favorable posterolateral position that is stable, with a good threshold, and avoids diaphragmatic pacing. In up to 10% of cases, transvenous placement of the left ventricular lead is not possible. The default option at present is surgical positioning of this lead, although, in the near future, multipolar left ventricular leads and percutaneous pericardial lead delivery systems may be able to overcome the need for this.

**Device optimization**

Device optimization is performed to attain the individual atrioventricular and ventriculoventricular delays that give rise to the optimal hemodynamic response to CRT. The gold standard is echo optimization, using the velocity–time integral and transmitral Doppler indices. Device manufacturers have developed algorithms that calculate optimal timings from intracardiac electrograms. An alternative approach is the use of hemodynamics (either invasive or non invasive) to achieve the optimal settings.

**Should the current criteria be extended?**

Controversy exists as to whether certain groups of patients with heart failure who fall outside current guidelines may benefit from CRT.

CRT in patients with a narrow QRS complex but echocardiographic evidence of dyssynchrony was evaluated in the Cardiac-Resynchronization Therapy in Heart Failure with Narrow QRS Complexes (RethinQ) study [22]. This included 172 patients with QRS duration <130 ms but mechanical dyssynchrony on the echocardiogram, who received CRT-defibrillator devices and were randomly assigned to CRT or no CRT for a 6-month period. This study did not show a significant improvement in the primary endpoint of peak oxygen consumption in the group who underwent CRT.

Studies involving less symptomatic patients with heart failure (NYHA Class II) have provided some evidence that such patients may derive benefit from CRT [14,23]. It is hoped that this question will be answered with the results of the current Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial [24]. It is entirely plausible that, even if symptomatic improvement is limited in this group, the progression of heart failure may be slowed – or indeed improved – by reverse remodeling as a result of CRT.

Patients with atrial fibrillation may benefit from correction of dyssynchrony by CRT, despite the fact that the potential for atrioventricular synchrony is absent. Treatment with biventricular pacing appears to be superior to right ventricular pacing in terms of functional status [13]. For CRT to be effective in this group of patients, however, it seems that ablation of the atrioventricular node is required to ensure continuous biventricular stimulation [25].

**Summary**

CRT offers new hope for many patients with heart failure. Its ability to improve cardiac efficiency has
transformed the outlook for this population, with demonstrated improvement in both symptoms and mortality. The aims of current work are to identify exactly which patients stand to benefit from the technique, and to optimize both positioning of leads and device programming in order to confer the maximum benefit possible.

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Abstract

Patients referred for cardiac rehabilitation may derive benefit from combining trimetazidine with exercise training, because both treatments produce similar effects in the cardiovascular system. Patients with viable myocardium should, in theory, obtain the greatest benefit, because trimetazidine improves the contractility of dysfunctional hibernating/stunned myocardium, whereas exercise has the documented ability to improve the endothelial vasomotor response of coronary arteries, to stimulate the coronary collateral circulation and small vessel growth, to improve left ventricular function, and to increase functional capacity. At present, however, there are no published reports on the efficacy of the combination of trimetazidine with exercise training.


Keywords: Trimetazidine, exercise training, ischemic cardiomyopathy, endothelial function

Introduction

Trimetazidine has been reported to improve functional capacity and the contractile response to dobutamine in patients with ischemic cardiomyopathy. In a group of patients with ischemic cardiomyopathy and with clinical characteristics similar to those of the population described below, Belardinelli and Purcaro [1] demonstrated that the addition of trimetazidine 20 mg three times daily to standard medications for 2 months improved peak $\dot{V}O_2$ by 19% and left ventricular ejection fraction by 16% ($P<0.001$ compared with placebo, for both). A shift toward glucose oxidation is likely to benefit hypoperfused myocardium, because the amount of ATP produced per mole of oxygen is approximately 12% greater when glucose is the preferential substrate. As a consequence, the contractility of dysfunctional myocardium improves, and this effect translates into enhanced left ventricular function. The improvement in contractility induced by trimetazidine can have potential therapeutic and prognostic implications. An important effect may be an increase in stroke volume during daily submaximal physical activities, which would make possible a more active lifestyle and might contribute to improving both functional capacity and quality of life.

There are also many studies demonstrating that cardiac rehabilitation improves the functional capacity of patients with ischemic heart disease and chronic heart failure. A recent meta-analysis [2] revealed improvements in peak $\dot{V}O_2$ ranging from 12% to 31% that were associated with lower rates of re-admission to hospital and of mortality. Such improvements are the result of adaptations induced by training and involve skeletal muscle, oxygen transport capacity, endothelial function, pulmonary oxygen diffusion, and myocardial perfusion and contractility [3–7].

Patients referred for cardiac rehabilitation may derive benefits from combining trimetazidine with exercise training, because both treatments produce similar effects in the cardiovascular system. Trimetazidine is a metabolic modulator that inhibits a key

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Benefits of the metabolic approach in cardiac rehabilitation

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enzyme in fatty acid oxidation, and shifts cellular energy substrate preference from oxidation of fatty acids to that of glucose [8]. As a result of this action, both left ventricular systolic function and diastolic filling are improved in patients with ischemic and diabetic cardiomyopathy [1,9,11]. Patients with viable myocardium should, in theory, benefit the most from either trimetazidine or exercise training, because both improve contractility of dysfunctional hibernating/stunned myocardium, the former through a series of induced adaptations in myocardial cells and coronary vessels, the latter through metabolic modulation of myocardial cells.

Rationale for using trimetazidine in cardiac rehabilitation

Trimetazidine is a piperazine derivative with anti-ischemic properties that is used in clinical practice to treat patients with stable angina and ischemic cardiomyopathy [8]. It shifts energy substrate preference from fatty acids to glucose oxidation through inhibition of the mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. A shift toward glucose oxidation is likely to benefit hypoperfused myocardium, because the production of ATP per mole of oxygen is higher when glucose is the preferential substrate.

There is evidence that trimetazidine, at doses of 20 mg three times daily orally, improves left ventricular function in patients with ischemic cardiomyopathy. In one study [1], 38 patients with postnecrotic left ventricular dysfunction and multivessel coronary artery disease were allocated randomly to two matched groups. One group received trimetazidine 20 mg three times daily for 8 weeks, and the second received placebo. Treated patients had significant improvements in systolic wall thickening score index at rest and at peak dobutamine infusion (13% and 21%, respectively, \( P < 0.001 \)), in left ventricular ejection fraction at rest and at peak dobutamine infusion (19.7% and 14.1%, \( P < 0.001 \)), and in peak VO\(_2\) (15%). These results are in agreement with the study by Brottier et al [9], who demonstrated an improvement in radionuclide ejection fraction after a 6-month treatment with trimetazidine at the same dose in 18 patients with ischemic cardiomyopathy in New York Heart Association Class III and IV. Similar improvements in left ventricular systolic performance and diastolic filling have been obtained more recently in patients with diabetic cardiomyopathy and in patients older than 75 years with coronary artery disease. No significant untoward events have been described, except for gastrointestinal symptoms [10].

More recently, interest has begun to focus on the antioxidant properties of trimetazidine and on its potential beneficial effect on endothelial function. As demonstrated by Fragasso et al [11], trimetazidine decreases the plasma concentrations of endothelin-1 in patients with ischemic cardiomyopathy and diabetes.

An antioxidant effect of trimetazidine is suggested by a reduction in systemic markers of oxidant stress, such as malondialdehyde and hydroperoxides. There is evidence from both experimental and clinical studies that free radicals are increased in chronic heart failure [12,13]. Prasad et al [14] found that leukocyte-mediated production of oxygen-derived free radicals was increased 4-fold in patients with heart failure as compared with controls. Recently, Belardinelli et al [15] demonstrated that trimetazidine improved endothelium-dependent vasodilation in a group of 51 patients (ages 51.4 ± 6 years) with ischemic cardiomyopathy and chronic heart failure, and that this effect was correlated both with decreased plasma concentrations of malondialdehyde and hydroperoxides and with enhanced functional capacity. No change in the endothelium-independent vasorelaxation was detected.

Clinical study of trimetazidine combined with exercise

Despite the potentially favorable premises suggested by the effects of trimetazidine or exercise training used separately, there are no published reports on the effects of trimetazidine in patients referred for cardiac rehabilitation. We studied 86 patients (72 men and 14 women, mean age 59 ± 9 years) with ischemic heart disease and left ventricular dysfunction who were referred for cardiac rehabilitation. Coronary risk factors were present in 72 of them (diabetes in 36). Patients were allocated randomly to three matched groups. One group (TMZ + training, \( n = 30 \)) received trimetazidine in a dose of 20 mg three times daily orally for 8 weeks in addition to standard medications, and underwent a supervised program of exercise training at 60% of peak VO\(_2\), three times a week for 8 weeks. A second group (TMZ + training, \( n = 30 \)) underwent supervised exercise training alone, and the third group (control, \( n = 26 \)) acted as controls.

Peak VO\(_2\) was significantly increased in both the TMZ + training group (from 16.4 ± 3.2 ml · kg · min\(^{-1}\) to 20.5 ± 3.4 ml · kg · min\(^{-1}\)) (Figure 1) and the exercise group (from 16.3 ± 3.3 ml · kg · min\(^{-1}\) to 18.8 ± 3.1 ml · kg · min\(^{-1}\)), whereas it was unchanged in controls (\( P < 0.001 \) for the TMZ + training group compared with the exercise group, and compared with controls). Left ventricular ejection fraction improved in the TMZ + training group (from 38 ± 7% to 43 ± 8%) and in the exercise group (from 35 ± 6% to 39.5 ± 5%), as a result of a reduction in end-systolic volume, but no changes were observed in controls (\( P < 0.05 \) for the TMZ + training group).
compared with the exercise group, and compared with controls). We speculate that trimetazidine potentiates the effects of exercise training on dysfunctional myocardium and on endothelial cells, as represented schematically in Figure 2.

In fact, in the presence of dysfunctional viable myocardium, trimetazidine, as a metabolic modulator, improves left ventricular function and cardiovascular efficiency, which may shift the balance between endothelial vasodilating and vasoconstricting substances in favor of the former. A reduction in oxidative stress may enhance endothelial function by decreasing the rate of inactivation of nitric oxide caused by the products of lipid peroxidation and reactive oxygen species [16]. Conversely, trimetazidine may exert a direct effect on endothelial cells,
acting as a chelator of the transition metals that are able to cross the lipid barrier, and thus protecting the endothelium from free radicals [17].

Summary

The findings of the investigation described above indicate that the combination of trimetazidine with exercise training potentiates the effect of exercise training and produces more marked improvements in functional capacity, left ventricular systolic function, and endothelium-dependent relaxation of the brachial artery than are achieved through exercise training alone, in patients with ischemic cardiomyopathy who are referred for cardiac rehabilitation. Patients with several coronary risk factors are those who may benefit most from a combination of trimetazidine with exercise training. Trimetazidine potentiates the effects of exercise training on the endothelium and functional capacity, possibly through its metabolic and antioxidant actions. As both endothelium-dependent relaxation and functional capacity are measures of outcome both in patients with coronary artery disease and in healthy individuals, improvements in one or both should reflect a better outcome or longer life expectancy, or both.

See glossary for definition of these terms.

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Improvement of myocardial efficiency in a patient with hypertrophic obstructive cardiomyopathy after alcohol septal ablation

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Abstract

A 70-year-old female patient presented with symptomatic hypertrophic obstructive cardiomyopathy (HOCM). Reduction of the left ventricular outflow tract obstruction by alcohol septal ablation is an established treatment strategy in patients with HOCM who remain symptomatic despite optimal medical treatment. Forward left ventricular stroke work, myocardial oxygen consumption, and myocardial efficiency were measured using cardiac magnetic resonance and positron emission tomography. Myocardial oxygen consumption was unchanged after reduction of the left ventricular outflow tract obstruction, but forward left ventricular stroke work per gram of myocardium was greater after the procedure. Alcohol septal ablation therefore improved the myocardial efficiency in this patient with HOCM.

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Keywords: Hypertrophic cardiomyopathy, alcohol septal ablation, myocardial efficiency, cardiac magnetic resonance, positron emission tomography

Case report

A 70-year-old female experienced dyspnea whilst cycling in 2001. At first, this exertional dyspnea was attributed to her moderate obesity (90kg, 1.70 m), but despite weight reduction, her symptoms slowly progressed. In 2006, she was unable to walk two flights of stairs without resting, because of severe shortness of breath. An electrocardiogram showed signs of left ventricular hypertrophy, so she was referred to a cardiologist for further evaluation. With cardiac magnetic resonance (CMR), hypertrophy of, mainly, the basal anteroseptal segment of the left ventricle was found, together with moderate-to-severe...
eccentric mitral regurgitation (Figure 1). In addition, a gradient over the left ventricular outflow tract (LVOT) of 30 mm Hg at rest increased to 80 mm Hg after 10 knee bends. The patient was diagnosed with hypertrophic obstructive cardiomyopathy (HOCM), and was initially treated with diltiazem SR 200 mg. However, her symptoms did not improve, and she was therefore referred for alcohol septal ablation (ASA), for relief of her symptoms.

Hypertrophic cardiomyopathy (HCM) is an inheritable disease that is caused by mutations in genes that mainly encode for sarcomeric proteins. It is characterized macroscopically by left ventricular hypertrophy in the absence of any disease likely to cause this hypertrophy, such as systemic hypertension or aortic stenosis. At the cellular level, the HCM mutations are believed to cause an increased calcium sensitivity of the sarcomeres. Although calcium homeostasis can be considered the driving force behind the contraction–relaxation cycle, the increased calcium sensitivity of sarcomeres is suggested to cause ‘hypercontractility’ and impaired relaxation, whereas actin and myosin myofilaments may remain able to interact even at very low diastolic concentrations of calcium [1]. This metabolically inefficient functioning of the sarcomere may cause the myocyte to be less adaptive to altered loading conditions, which is an important trigger for the development of hypertrophy [2].

When hypertrophy develops, increased extracellular collagen depositions are found (interstitial fibrosis) in the myocardium of carriers of the HCM mutation, together with disorganization of the myocardial architecture (myocyte disarray), and microvascular dysfunction [3]. These processes may further compromise myocardial function, and in turn might trigger more hypertrophy. Overall, the HCM mutations initiate a vicious cycle of molecular perturbations that, ultimately, lead to the clinical manifestation of disease.

The hypertrophy in HCM typically involves the interventricular septum and, when progressive, causes dynamic LVOT obstruction. The LVOT obstruction results in greater intracavitary wall stress and increased blood flow velocities within the LVOT tract during systole, through the Venturi effect, which subsequently causes systolic anterior motion of the anterior mitral valve leaflet towards the septum and eccentric mitral valve regurgitation (Figure 1). The

![Figure 1. Cardiac magnetic resonance three-chamber cine image in end-diastole (left) and end-systole (right) of a patient with hypertrophic obstructive cardiomyopathy before alcohol septal ablation. Note that the obstruction of the left outflow tract (red arrow) causes severe eccentric mitral regurgitation (yellow arrow).](image1)

![Figure 2. Cardiac magnetic resonance three-chamber cine image of a patient with hypertrophic obstructive cardiomyopathy after alcohol septal ablation. In the left panel, the induced infarct is clearly visible (blue arrow). Subsequently, left ventricular outflow tract obstruction is substantially reduced (middle panel, red arrow), and mitral regurgitation is almost completely resolved (right panel, yellow arrow).](image2)
increased external work, or stroke work, may further impair myocardial efficiency.

Although no definitive treatment of the disease is yet available, symptomatic relief of HCM may be provided by reduction of the LVOT obstruction, by either surgery or ASA [4]. The latter involves the percutaneous injection of a small amount of alcohol (1–5 ml) into one of the most proximal septal branches of the left coronary artery, causing a localized myocardial infarction and subsequent scarring at the level of the LVOT obstruction. This procedure has proven to be effective in reducing the LVOT obstruction and concomitant mitral regurgitation, which, importantly, results in relief of symptoms.

To monitor the effect of treatment on myocardial efficiency, CMR was performed before and 6 months after the procedure for measurement of mass, and to quantify flow in the aorta to determine forward left ventricular stroke volume. Stroke volume was measured in the aorta to avoid overestimation of effective volume through mitral regurgitation. In addition, scar tissue can be visualized with CMR by using late gadolinium enhancement imaging. Directly before the CMR acquisition, dynamic carbon-11-labeled acetate ([11C]acetate) positron emission tomography (PET) was performed. The transfer of [11C] activity from [11C]acetate to [11C]carbon dioxide is strongly related to oxidative metabolism, and the rate of clearance of [11C]acetate is regarded as an adequate index of oxygen consumption and is expressed as $k_{\text{mono}}$ [5]. Myocardial efficiency can be estimated from the ratio of forward left ventricular (LV) stroke work (systolic blood pressure $\cdot$ forward LV stroke volume $\cdot$ heart rate) and the rate of clearance of [11C]acetate per gram [6].

Six months after the procedure, the patient’s symptoms improved, and she was able to walk two flights of stairs again without taking a rest (“...and even do it again directly afterwards to get my keys if I have to...”). A significant reduction of the LVOT obstruction was observed on the CMR images, and a residual resting gradient of 7 mm Hg was measured (Figure 2). In addition, mitral regurgitation was almost completely resolved. On late gadolinium enhancement image, the localized iatrogenic infarct in the anteroseptal segment of the left ventricle was clearly visible.

Before the ASA, left ventricular mass index was 96 g $\cdot$ m$^{-2}$, forward left ventricular stroke work was 6.45 mm Hg $\cdot$ L $\cdot$ g$^{-1} \cdot$ min$^{-1}$, and $k_{\text{mono}}$ was 0.054 units $\cdot$ min$^{-1}$. After ASA, left ventricular mass index was reduced to 57 g $\cdot$ m$^{-2}$; forward left ventricular stroke work was increased to 7.85 mm Hg $\cdot$ L $\cdot$ g$^{-1} \cdot$ min$^{-1}$, and $k_{\text{mono}}$ was reduced to 0.047 units $\cdot$ min$^{-1}$. Consequently, myocardial efficiency was improved from 119 mm Hg $\cdot$ L $\cdot$ g$^{-1} \cdot$ min$^{-1}$ to 167 mm Hg $\cdot$ L $\cdot$ g$^{-1} \cdot$ min$^{-1}$. Merged dynamic [11C]acetate activity and late gadolinium enhancement CMR images obtained before and after ASA showed mildly reduced oxygen consumption in the lateral wall in the presence of the scar (Figure 3).

In the patient reported here, we expected to observe an increased level of oxygen consumption before ASA, as a result of the increased left ventricular intracavitary wall stress caused by the LVOT obstruction. However, myocardial oxygen consumption before and after ASA were relatively comparable. We observed that the “pseudonormalization” of oxygen consumption before ASA occurred at the expense of a further increase in left ventricular hypertrophy, and subsequent normalization of wall stress. However, this mechanism of compensation decreases myocardial efficiency. Therefore, we can postulate from the data obtained from this patient that LVOT obstruction in patients with HCM reduces myocardial efficiency, and is restored after ASA.

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Case report
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Invasive assessment of cardiac efficiency

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Abstract
The effective energy output divided by the total energy input defines the efficiency of a system. The heart burns substrates and, via several intermediate steps, ultimately produces external work. The efficiency of this process can be measured with invasive techniques that are briefly described in this paper. In addition, we discuss cardiac efficiency in the context of cardiac mechanics and energetics using the pressure–volume framework.


Keywords: Myocardial oxygen consumption, external work, stroke work, heat, efficiency, pressure–volume relationship, pressure–volume area

Introduction
The efficiency of a system is defined as the effective energy output from the system divided by the total energy input into the system. The cardiac pump (or the left ventricle) may be considered as a mechano-chemical transducer that converts chemical energy into heat and external work. The latter is also known as stroke work. In this process, adenosine triphosphate (ATP) is the carrier of chemical energy, which is released during the hydrolysis of ATP into adenosine diphosphate (ADP) and inorganic phosphate (Pi). Because, in the heart, ATP is regenerated almost entirely by oxidative metabolism, cardiac energy consumption can be estimated by measuring oxygen consumption. The metabolic substrates comprise lipids, carbohydrates, and proteins. These substrates have different caloric values (ie, heat liberated per gram of substrate oxidized), and also differ with respect to the amount of oxygen needed to metabolize a gram of substrate. However, when expressed per milliliter of oxygen consumed, their energy equivalents are very similar: approximately 20 J/mL O2 [1]. Consequently, the total energy input can be estimated by the energy equivalent of myocardial oxygen consumption (mVO2), and thus the energy balance of the cardiac pump can be written as:

\[ EE \cdot mVO_2 = H + EW \] (1)

where EE is energy equivalents, EW is external work, and H is heat.

If we consider EW as the effective energy output of the heart, cardiac efficiency (CE) is defined as:

\[ CE = EW/(EE \cdot mVO_2) \] (2a)

Considering equation (1), alternatives to this expression are:

\[ CE = 1 - H/(EE \cdot mVO_2) \] (2b)

\[ CE = 1/(1 + [H/EW]) \] (2c)

Thus, in principle, CE may be obtained by measuring (the ratio of) EW and mVO2, H and mVO2, or H and EW. In the following, we describe invasive methods of measuring each of these parameters, and briefly discuss cardiac efficiency in the context of cardiac mechanics and energetics.
Invasive measurement of myocardial oxygen consumption (mVO₂)

Oxygen consumption by the heart can be determined by the Fick principle as the product of coronary blood flow (CBF) and arterio–venous blood oxygen content difference (ΔAVcO₂) across the coronary bed:

\[
m\text{VO}_2 = \text{CBF} \cdot (\Delta \text{AVcO}_2) \quad (3)
\]

Determination of ΔAVcO₂ requires sampling of blood from the coronary sinus and a systemic artery. Oxygen content is then calculated as the product of hemoglobin concentration (Hb), oxygen saturation (SO₂), and a factor (1.36) representing the oxygen-binding capacity of Hb (free dissolved oxygen can generally be neglected) thus [2,3]:

\[
\Delta \text{AVcO}_2 = 1.36 \cdot \text{Hb} \cdot (\text{SaO}_2 - \text{SvO}_2) \quad (4)
\]

CBF may be determined invasively with reversed thermocatheter catheters in the coronary sinus [4,5]. Alternatively, intravascular Doppler techniques (Doppler flow wire) may be used to determine blood flow velocity, which should be combined with an estimate of cross-sectional area of the vessel(s) to calculate CBF [6]. Cross-sectional area may be estimated using quantitative coronary angiography or intravascular ultrasound.

Invasive measurement of cardiac heat (H)

Although heat measurements are used widely to study the energetics of isolated muscle preparations, heat liberated from the heart is difficult to measure in the intact circulation, and only a few attempts have been published [7]. Heat produced by the heart is removed from the myocardium by the coronary circulation (by convection, H_conv) or diffused into the mediastinum and the ventricular cavities (H_diff). In addition, a small proportion is used in endothermic chemical reactions of oxygen and carbon dioxide with hemoglobin (H_chem) [8]. Thus total heat liberated by the heart (H) equals:

\[
H = H_{\text{conv}} + H_{\text{diff}} - H_{\text{chem}} \quad (5)
\]

H_chem was estimated to amount to approximately 1.6 mJ/mL O₂ consumed, and thus to less than 10% of total heat [9]. H_conv may be calculated from the temperature difference between aortic and coronary sinus blood (ΔT_ao-cs), CBF, and the density (ρ_b) and specific heat capacity (C_b) of blood [10]:

\[
H_{\text{conv}} = \text{CBF} \cdot \rho_b \cdot C_b \cdot \Delta T_{\text{ao-cs}} \quad (6)
\]

Blood temperatures in the aorta and the coronary sinus can be measured with catheter-mounted thermistors, but, given the very small temperature differences (of the order of 0.2°C), a high accuracy and extremely careful calibration are required. An ingenious method of determining H_diff was developed that relies on the assumption that a small amount of heat (or cold) added exogenously to the coronary circulation diffuses in the same way as the endogenous heat produced by myocardial metabolism [9,11]. The ratio of heat recovered in the coronary sinus to the heat introduced into the coronary arteries can be determined experimentally by comparing the areas under the thermodilution curves in the aorta and coronary sinus (A_ao and A_cs, respectively) after an upstream bolus injection of cold saline. This so-called recovery ratio (R) equals:

\[
R = A_{\text{cs}}/A_{\text{ao}} \quad (7)
\]

and, as this also applies to endogenous heat:

\[
R = H_{\text{conv}}/(H_{\text{conv}} + H_{\text{diff}}) \quad (8)
\]

Thus, combining Eqs. (5), (6), and (8), and neglecting H_chem:

\[
H = (1/R) \cdot \text{CBF} \cdot \rho_b \cdot C_b \cdot \Delta T_{\text{ao-cs}} \quad (9)
\]

This approach makes it possible to estimate cardiac heat production with thermodilution techniques in humans [12].

Invasive measurement of external work (EW)

Work is defined as force times displacement, which, for the ventricle, translates into pressure (P) multiplied by volume changes (dV). Thus external work may be calculated by the integral:

\[
\text{EW} = \int P \, dV \quad (10)
\]

In addition to pressure–volume work, the accelerated blood in the aorta represents additional external kinetic work – which, however, is only a small fraction (~5%) and is generally ignored. An elegant way in which to visualize external work is to display the time-dependent pressure and volume signals in a so-called pressure–volume diagram (Figure 1a). A cardiac cycle is represented by a counter-clockwise loop and external work is defined by the enclosed area. Strictly speaking, calculation of external work requires the registration of ventricular volume and pressure signals during the cardiac cycle. These signals may be obtained from frame-by-frame analysis of left ventricular contrast angiography combined with pressure measurements using a fluid-filled catheter [13]. More elegantly and more accurately, a conductance catheter may be applied that contains a high-fidelity pressure sensor and several electrodes for conductance measurements to provide simultaneous

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Figure 1. Ventricular mechanics and energetics in the pressure–volume framework. EDPVR, end-diastolic pressure–volume relationship; ESPVR, end-systolic pressure–volume relationship; EW, external work; mVO$_2$, myocardial oxygen consumption; PE, potential energy; PVA, pressure–volume area.

Figure 2. Energy conversions and associated efficiencies (efficiencies indicated as percentages). ATP, adenosine triphosphate; BM, basal metabolism; EC, excitation–contraction; EW, external work; O$_2$, oxygen; PE, potential energy; PVA, pressure–volume area.

Cardiac efficiency, mechanics, and energetics

The pressure–volume framework provides an excellent tool with which to study and describe the complex relationship between cardiac mechanics, energetics, and efficiencies [16–18]. In this framework, total mechanical energy is represented by the area between the end-systolic pressure–volume relationship, the end-diastolic pressure–volume relationship, and the systolic trajectory of the pressure–volume loop (Figure 1b). This so-called pressure–volume area (PVA), consisting of external work and elastic potential energy (PE), was shown to be linearly related to mVO$_2$ (Figure 1c). The intercept of the mVO$_2$–PVA relationship, the unloaded mVO$_2$, represents the energy required for activation (excitation–contraction) and basal metabolism. The inverse slope of the mVO$_2$–PVA relationship is referred to as contractile efficiency. This pressure–volume framework illustrates that cardiac efficiency not only depends on intrinsic properties of the heart, but also, strongly, on the loading conditions [19]. In the extreme conditions of isovolumetric contractions (aortic clamping) or unloaded contractions (no pressure development), external work, and thus also cardiac efficiency, is zero. Actual cardiac efficiency is dependent on the ventricular–vascular coupling, and in normal conditions the heart works close to optimal cardiac efficiency [20]. This framework also clarifies the various steps from mVO$_2$ to, ultimately, production of external work. As illustrated in Figure 2, at each level part of the energy is dissipated into heat and thus each step codetermines the overall cardiac efficiency. Because disease conditions, in general, affect efficiencies at specific levels, and because interventions are generally targeted to optimize energy conversions at a specific level, these intermediate steps are important to consider when interpreting measurements of cardiac efficiency.
REFERENCES


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Nuclear receptors PPARβ/δ and PPARα direct distinct metabolic regulatory programs in the mouse heart

Diabetes predisposes to heart failure, particularly in combination with other comorbid conditions such as hypertension and coronary artery disease. Evidence has emerged that derangements in cardiac fuel metabolism, related to insulin-resistant and diabetic states, contribute to the development of diabetic cardiac dysfunction. The metabolic derangements in the diabetic heart involve gene regulatory programming via chronic activation of the nuclear receptor, peroxisome proliferator activated receptor α (PPARα). Chronic activation of the PPARα pathway drives excessive fatty acid oxidation, lipid accumulation, reduced glucose utilization, and cardiomyopathy. PPARα is a member of a fatty-acid-activated nuclear receptor family that includes PPARγ and PPARβ/δ. In contrast to PPARγ, which is expressed at low levels, PPARβ/δ is highly expressed in cardiac myocytes, similar to PPARα. The function of PPARα has been the subject of intense investigation; however, less is known about PPARβ/δ. To investigate the role of PPARβ/δ in the regulation of heart metabolism and function, the authors generated transgenic mice with cardiac-specific expression of PPARβ/δ driven by the myosin heavy chain (MHC-PPARβ/δ mice).

Commentary
The normal adult heart satisfies its energy requirements through the oxidation of both fatty acids and glucose. However, myocardial insulin resistance and increased rates of systemic lipolysis force the diabetic heart to rely almost exclusively on fatty acid as a fuel source – a loss of substrate flexibility. Over the long term, high rates of myocardial fatty acid utilization predispose to the development of a “lipotoxic” form of cardiomyopathy, characterized by accumulation of lipid in the myocytes, mitochondrial dysfunction, and generation of reactive oxygen species related to excessive substrate flux. In addition, the diabetic heart has a reduced capacity for glycolysis and glucose oxidation, which predisposes to postischemic damage. Recent evidence has implicated dysregulation of the nuclear receptor PPARα in the metabolic and functional derangements of the diabetic heart. PPARα activates transcription of genes involved in cellular pathways of lipid utilization, including fatty acid uptake and oxidation. The PPARα gene regulatory pathway is chronically activated in the hearts of insulin-deficient and insulin-resistant rodents. Transgenic mice with cardiac-specific overexpression of PPARα (MHC-PPARα mice) display a functional and metabolic phenotype that mimics the diabetic heart; specifically, MHC-PPARα mouse hearts exhibit increased rates of fatty acid oxidation, decreased glucose utilization, myocyte accumulation of triglyceride, and cardiomyopathy. Interestingly, the lipotoxic cardiomyopathy of MHC-PPARα mice is worsened with consumption of a high-fat diet. Consistent with observations in animal models, recent studies using positron emission tomography have shown that hearts of diabetic humans exhibit increased fatty acid uptake and utilization rates.

In the study by Burkart and colleagues, the authors describe the surprising finding that, in contrast to MHC-PPARα mice, MHC-PPARβ/δ mice did not develop myocyte accumulation of lipid or cardiomyopathy, even in the context of a high-fat diet. One likely explanation for this striking difference is that myocardial fatty acid uptake and esterification rates were increased in MHC-PPARα mice, but not in MHC-PPARβ/δ mice. The expression of genes involved in fatty acid uptake and triglyceride synthesis was activated in the hearts of MHC-PPARα mice, but not in MHC-PPARβ/δ mice. This differential gene regulation was also noted when PPARα and PPARβ/δ agonists were administered to wild-type mice. Collectively, these results suggest that the striking differences in
cardiac lipid metabolic phenotype exhibited by PPARα mice compared with PPARβ/δ transgenic mice are related to differential activation of a subset of gene-regulatory programs driving cellular transport and utilization of fatty acid. In striking contrast to MHC-PPARα mice, MHC-PPARβ/δ mice had increased myocardial glucose utilization, did not accumulate myocardial lipid, and had normal cardiac function. Consistent with these observed metabolic phenotypes, it was found that expression of genes involved in cellular fatty acid transport was activated by PPARα, but not by PPARβ/δ. Conversely, cardiac glucose transport and glycolytic genes were activated in MHC-PPARβ/δ mice, but repressed in MHC-PPARα mice. Furthermore, myocardial injury after coronary artery occlusion was significantly reduced in the MHC-PPARβ/δ mice compared with control or MHC-PPARα mice, consistent with an increased capacity for myocardial glucose utilization.

These results demonstrate that PPARα and PPARβ/δ drive distinct cardiac metabolic regulatory programs in the mouse heart, and identify PPARβ/δ as a crucial target for metabolic modulation therapy. If the same proves true in humans, selective activation of PPARβ/δ may then offer a potential therapeutic strategy for diabetic cardiac dysfunction.

Danielle Feuvray

Cardiac-resynchronization therapy in heart failure with narrow QRS complexes


Indications for cardiac resynchronization therapy (CRT) in patients with heart failure include a prolonged QRS interval (≥120 ms), in addition to other functional criteria. Some patients with narrow QRS complexes have echocardiographic evidence of left ventricular mechanical dyssynchrony and may also benefit from CRT. We enrolled 172 patients who had a standard indication for an implantable cardioverter-defibrillator. Patients received the CRT device and were randomly assigned to the CRT group or to a control group (no CRT) for 6 months. The primary endpoint was the proportion of patients with an increase in peak oxygen consumption of at least 1.0 mL per kilogram of body weight per minute during cardiopulmonary exercise testing at 6 months. At 6 months, the CRT group and the control group did not differ significantly in the proportion of patients with the primary endpoint (46% and 41%, respectively). In a prespecified subgroup with a QRS interval of 120 ms or more, the peak oxygen consumption increased in the CRT group (P = 0.02); it was unchanged in a subgroup with a QRS interval less than 120 ms (P = 0.45). There were 24 heart-failure events requiring intravenous therapy in 14 patients in the CRT group (16.1%) and 41 events in 19 patients in the control group (22.3%); this difference was not significant. We conclude that CRT did not improve peak oxygen consumption in patients with moderate-to-severe heart failure, providing evidence that patients with heart failure and narrow QRS intervals may not benefit from CRT. (ClinicalTrials.gov number, NCT00132977 [ClinicalTrials.gov].) Copyright 2007 Massachusetts Medical Society.

Commentary

Cardiac resynchronization therapy has been shown to improve survival and quality of life in patients with heart failure with a prolonged Q–T interval. Since the introduction of CRT, two conflicting observations have emerged: a fraction of patients presenting with large QRS complexes do not benefit from this treatment, and patients with narrow QRS complexes may present mechanical dyssynchrony. The study by Beshai and colleagues is the first prospective, controlled, double-blind randomized trial to evaluate CRT in patients with heart failure with a narrow QRS complexes and evidence of mechanical dyssynchrony at echocardiography. The conclusion was that CRT did not improve peak oxygen consumption (the primary endpoint) or other secondary endpoints, including quality-of-life scores and left ventricular volumes. Possible reasons for these disappointing results may relate to the echocardiographic methods applied to detect dyssynchrony, or to lead placement, or both, but may be the consequence of a simplistic approach to the problem. Mechanical dyssynchrony—that is, a disparity in regional contraction timing—may be secondary to electrical dyssynchrony or may express regional muscle dysfunction. Dyssynchrony may be limited to systole or may extend to diastole. The more sophisticated the echocardiographic methods used, the more frequent is dyssynchrony in patients with systolic or diastolic heart failure, whether with narrow or with large QRS complexes. The clinical significance of these observations is not always obvious. However, applying CRT to all patients presenting with mechanical dyssynchrony at echocardiography, independent of knowledge of the pathogenetic mechanism, would expose to risk a growing number of non responders.

Mario Marzilli
Adenine nucleotide translocase 1 (ANT1)

ANT-1 is an enzyme located in the mitochondrial membrane that is responsible for the transport of ATP out of the mitochondrial matrix. It is also a component of the mitochondrial permeability transition (MPT) complex, a protein aggregate connecting the inner with the outer mitochondrial membrane. Recent research interest has focused on the role of the role of this MPT complex in mediating apoptosis. ANT1 has also been implicated as a specific target for the autoantibody response in idiopathic dilated cardiomyopathy.

Cytosolic (CTE1) and mitochondrial (MTE1) thioesterase

Long chain acyl-CoA is both an intermediate in for the synthesis of complex lipids (phospholipids, triacylglycerol, etc) in the cytoplasm, and as a substrate for fatty acid oxidation in mitochondria and peroxisomes. However, an alternative fate of long chain acyl-CoA is to have the CoA group cleaved from the fatty acids by a thioesterase enzyme. This includes either a cytosolic thioesterase (CTE1) or a mitochondrial thioesterase (MTE1). Recent research interest has focussed on these thioesterases because of their potential to prevent the accumulation of potentially toxic levels of long chain acyl-CoA in the cytoplasmic and mitochondrial compartments of cells.

e-NOS

e-NOS stands from endothelial nitric oxide synthase. Nitric oxide synthase is the enzyme responsible for synthesizing nitric oxide. Nitric oxide has received considerable research attention, since it is not only a vasodilator but is also important in numerous other processes, including apoptosis. Nitric oxide synthase produced by e-NOPS in endothelial cells is an important source of nitric oxide.

ec-SOD

Superoxide is a free radical. It is an oxygen molecule that has an unpaired electron. This molecule can react with lipids, proteins, DNA, and RNA, causing tissue damage. Superoxide dimutase (SOD) is present in many cells to detoxify superoxide by converting it to hydrogen peroxide. An isoform of SOD present in endothelial cells called ec-SOCD.

F₀F₁-ATPase

F₀F₁-ATPase is a multisubunit enzyme located on the inner mitochondrial membrane that reversibly synthesizes adenosine triphosphate (ATP) from adenosine diphosphate (ADP). The energy necessary for ATP synthesis is derived from protons moving down a electrochemical gradient from the inter-membrane space into the mitochondrial matrix. Under certain conditions, the normal ATP synthase function can be reversed, resulting in an ATPase activity. The large multisubunit enzyme has an F₀ portion located within the membrane, and the F₁ portion located above the membrane. The F₀F₁-ATPase resembles a mushroom, with the head and stalk being the F₁ portion of the enzyme, and the the F₀ portion being the base embedded in the membrane.

OXPHOS proteins

Oxidative phosphorylation is a mitochondrial metabolic pathway that uses energy released by the oxidation of nutrients to produce adenosine triphosphate (ATP). Oxidative phosphorylation involves the transfer of electrons from electron donors to electron acceptors such as oxygen, in a redox reaction. These redox reactions release energy, which is used to form ATP. The redox reactions are carried out by a series of proteins located in the inner mitochondrial membrane, called oxidative phosphorylation proteins or “OXPHOS proteins”. Collectively the OXPHOS proteins constitute what is called the mitochondrial electron transport chain.

Peroxisome proliferator-activated receptor α (PPARα)

PPARα is a nuclear receptor involved in the transcriptional regulation of proteins. PPARα has many
functions, including regulating the expression of many enzymes involved in the control of fatty acid oxidation in muscle.

**Reactive oxygen species (ROS)**

ROS, or oxygen-derived free radicals, are highly reactive compounds that can react with and damage cellular components (lipid membranes, protein, and DNA/RNA). In order to protect the cell from ROS, cells have a number of different oxygen radical scavenger enzymes that are used to neutralize these free radicals.

**Uncoupling proteins (UCPs)**

Uncoupling proteins (UCP) are proteins that are present in the inner mitochondrial membrane of cells that dissipate the proton gradient across this membrane. As a result of this action, mitochondrial respiration produces heat instead of ATP. Heart and skeletal muscle contain two isoforms of UCPs, UCP2 and UCP3. The exact function of these UCP’s is not clear, but they may be involved in decreasing reactive oxygen species production by the mitochondria or transporting excess fatty acids out of the mitochondria. The expression of UCPs in the mitochondria is increased in muscle exposed to high fats.