

Myocardial energetics and efficiency

Ellen Aasum, Cardiovascular Research Group Faculty of Health Sciences, University of Tromsø, Norway

Correspondence: Ellen Aasum, Cardiovascular Research Group,
Institute of Medical Biology, Faculty of Health Sciences,
University of Tromsø, N-9037 Tromsø, Norway.
Tel: +47 77646486 fax: +47 77645440, e-mail: ellen.aasum@uit.no

Abstract

In addition to structural and functional abnormalities, it is well established that energy homeostasis is impaired in the failing heart. As the heart requires large amounts of energy to sustain its continuous pumping activity, it is highly dependent on an optimal substrate metabolism with efficient ATP generation and utilization. Alterations in processes related to energy production as well as energy utilization in the failing heart may lead to energetic imbalance, an inefficient hearts with impaired contractile reserve.

Keywords: cardiac energy metabolism; oxygen consumption; mechano energetics; heart failure

■ Heart Metab. (2011) 53:5–8

Introduction

The heart maintains its pumping action by converting chemical energy in metabolic substrates into mechanical energy, and because of its high energy requirement and relatively low content of high energy compounds (ATP and creatine phosphate [PCr]) ATP must be continuously generated at a high rate. Thus, the heart must adjust energy production to energy utilization, and at the same time secure an efficient energy transfer. These processes involve substrate uptake, breakdown and entry into the Krebs cycle, as well as mitochondrial oxidative phosphorylation, ATP transfer (e.g., the creatine kinase energy shuttle), and hydrolysis at the energy consuming sites. The metabolically healthy heart has the capacity to switch between lipids and carbohydrates as energy substrates, and the fuel selection is to a large extent governed by the availability of plasma substrates, as well as the levels of hormones (insulin and catecholamines) in the circulation. Since the majority (>90%) of ATP production is derived from mitochondrial oxidative phosphorylation, myocardial oxygen consumption ($m\dot{V}O_2$) in the normoxic heart can be used as a measure of the total myocardial energy utilization. Mechanical efficiency, which connote the ability of the heart to perform its functions, is the ratio between external (stroke) work and $m\dot{V}O_2$ [1]. Decreased mechanical efficiency has been suggested to play a leading role in the pathogenesis of a number of cardiovascular conditions leading to heart failure. The imbalance between energy demand and availability will ultimately lead to an energetically compromised heart with reduced working capacity. As decreased efficiency will be particularly disadvantageous under conditions of reduced oxygen availability, it will also contribute to the increased susceptibility of the failing myocardium to acute ischemia or hypoxia.

The failing heart is energetically compromised

In accordance with this notion, clinical and experimental studies on heart failure, using ^{31}P magnetic resonance spectroscopy (MRS), have revealed a decreased cardiac PCr:ATP ratio.

Decreased PCr:ATP ratio has been shown to correlate with the severity of heart failure in patients with idiopathic dilated cardiomyopathy [2] and to be a predictor of mortality in these patients [3]. Decreased PCr:ATP ratio is also found in hearts from type 2 diabetic patients [4], which show increased prevalence and worsened prognosis of heart failure [5].

Impaired ATP homeostasis in the failing heart is obviously multifactorial and complex, including reduced ATP production, loss of the total adenine nucleotide pool and changes in the creatine kinase system, which in turn affect the energy transport to the energy consuming sites, such as myofibrils and sarcoplasmic reticulum (SR) [2,6–8]. The failing heart is also characterized by altered energy substrate utilization. The mechanisms behind these metabolic changes are complex due to the heterogeneous etiology of heart failure, as well as to differences in the progression of the disease. Experimental models of heart failure generally report decreased fatty acid oxidation and increased reliance on glucose oxidation and glycolysis, with a depressed overall oxidative metabolism in end-state failure [9]. Changes in human hearts show less consistency with respect to fuel selection, likely due to the complexity and diversity of the metabolic status of these patients. Patients with heart failure often have increased plasma noradrenalin and free fatty acid concentrations reflecting stress hormone-induced lipolysis [10]. In addition, co-morbidities such as obesity, insulin-resistance and type 2 diabetes will influence myocardial substrate utilization. In the uncompensated state, the fatty acid oxidation pathway is generally down-regulated (metabolic remodeling due to a decline in the activation of the transcription factors PPAR α), and glucose uptake and oxidation is insufficient to secure an adequate energy production. Altered mitochondrial mass, structure, and functional capacity have also been demonstrated in failing myocardium. Whether inadequate oxygen availability or metabolic substrate supply are limiting factors for oxidative capacity is not clear. Several studies have, however, shown decreased activity of the complexes of the respiratory chain, Krebs' cycle enzymes and the ATP synthase (F₀F₁) [8], and functional studies also suggest that mitochondria from failing hearts are less coupled [11]. As there is a clear correlation between oxidative ATP production and heart work, decreased mitochondrial oxidative

capacity and/or loss of functional coupling with sites of energy utilization, can limit the heart's ability to generate work and thus contribute to cardiac dysfunction.

Myocardial efficiency and mechano-energetics

Decreased myocardial mechanical efficiency in the failing heart is a consistent and early finding both clinically and in experimental models. Assessment of myocardial mechanical efficiency is an important clinical tool for evaluation of the outcome of therapies. As illustrated in the Fig. 1, energy is used for both mechanical and non-mechanical processes in the heart. The latter deals with energy used in excitation-contraction coupling (ECC), i.e., cardiac sarcoplasmic reticulum function, notably calcium pumping, and basal metabolism (BM), and is consequently referred to as the work-independent $m\text{VO}_2$. Energy for the mechanical processes (total mechanical energy, TME), includes generation of myocardial force and pressure in the ventricular wall (potential energy) and for ejection of blood against an afterload pressure (external work, EW). Oxygen cost for mechanical work is therefore work-dependent and correlates closely with TME of the heart (panel B). This principle implies that each step co-determines the overall mechanical efficiency, and that mechanical efficiency not only depends on intrinsic properties of the heart, but also strongly on hemodynamic conditions (loading conditions) [12]. Assessment of the relationship between $m\text{VO}_2$ and TME in experimental models of heart failure can reveal the underlying mechanisms leading to mechanical inefficiency by identifying mechano-energetic changes in the heart. Failing hearts in different experimental models (pressure/volume overload, coronary microembolisation, rapid ventricular pacing, diabetes, infarcted hearts) have generally reveal unchanged or decreased slope of this relationship, which suggest unchanged or improved efficiency of the chemo-mechanical energy transduction (contractile efficiency) [12]. These changes may reflect an adaptive response to the impaired energy balance, and has been associated with a shift from the myosin heavy chain (MHC) α isoform to the slower, but more economical, β isoform in rodent models. The functional role of such a shift in MHC isoform in larger mammals (including human) is, however, less clear.

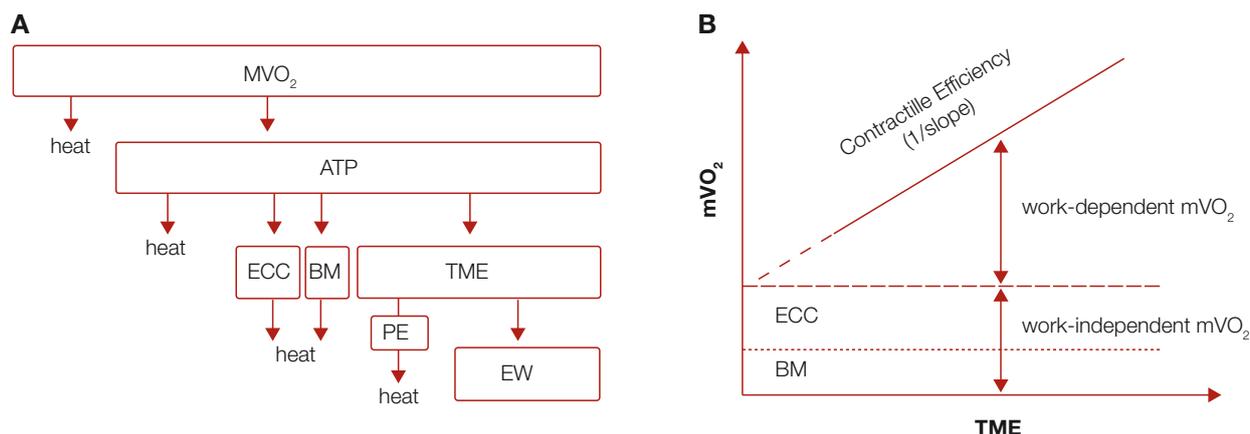


Fig. 1 Panel A. Energy flow diagram from oxygen consumption to external work (EW) via ATP. ATP in the heart is used for non-mechanical activity (excitation-contraction coupling, ECC) and basal metabolism (BM), and for generating total mechanical energy (TME) which includes generation of myocardial tension in the ventricular wall (potential energy, PE) within the ventricular wall and pressure in the left ventricle for ejection of blood against an afterload pressure (external work, EW). **Panel B.** A linear relationship exists between total mechanical energy (TME) and mVO_2 , where the y-intercept defines the work-independent mVO_2 , and the inverse of the slope of the relationship will indicate the efficiency of oxygen to TME (contractile efficiency). Adapted from Suga (1990) [12].

The failing heart shows increased oxygen cost for non-mechanical processes

The y-intercept of the work- mVO_2 relationship reflects the oxygen cost for non-mechanical processes (unloaded mVO_2) [12], which is reported to be increased in several models of heart failure. Altered unloaded mVO_2 may be related to altered myocardial Ca^{2+} handling, altered substrate utilization and/or induction of oxygen wasting processes. Decreased sarcoplasmic reticulum (SR) Ca^{2+} -ATPase (called SERCA2 in the heart) expression and activity are generally accepted as important mediators of cardiac dysfunction in the failing heart. As a compensatory mechanism, sarcolemmal Na^+ - Ca^{2+} exchange activity is increased, which energetically will lead to a less efficient Ca^{2+} transport during excitation-contraction coupling. In addition, increased sarcoplasmic reticulum Ca^{2+} leak, as well as desynchronised Ca^{2+} release via SR calcium channels may also contribute to increased oxygen cost for Ca^{2+} handling in these hearts. The pivotal role of SERCA2 in ventricular dysfunction is supported by studies demonstrating enhanced contractile function via either transgenic approaches or adenoviral gene transfer. Hence, supportive SERCA2 gene therapy is a potential treatment strategy for heart failure. There are, however, controversies with regard to the energetic consequence of such interventions [13].

Since fatty acids is an energetically less efficient energy substrate compared to glucose (i.e. require a

higher oxygen consuming due to a lower ATP:oxygen ratio), the switch towards glucose in the failing heart is generally regarded an adaptive mechanism. On the other hand, the predominant myocardial fatty acid oxidation in diabetes has been associated with increased mVO_2 and decreased mechanical efficiency [9]. Based on this, reduction of fatty acid oxidation by inhibiting fatty acid transport into the mitochondria, or fatty acid β -oxidation, has proven beneficial in animal models of heart failure and in clinical trials [9,10,14,15]. Mjøs and coworkers demonstrated more than 40 year ago, that elevation of circulating fatty acids induced oxygen wastage and decreased mechanical efficiency in an open chest dog model [16]. This fatty acid-induced increase in mVO_2 is due to increased oxygen cost for non-mechanical purposes [17], and cannot solely be ascribed to increased fatty acid oxidation rate, as a shift from glucose to fatty acid oxidation can only account for approximately 1/3 of the increased mVO_2 . Fatty acids are ligands for PPAR α that regulate the expression of uncoupling proteins (UCPs), and although the role of mitochondrial uncoupling in heart failure is not definitively established, UCP expression has been shown to correlate to circulating fatty acid concentrations in human and animal samples [11,18]. In experimental studies the presence of fatty acids has also been shown to decrease cardiac mechanical efficiency, not only in the normal heart [17] but also in the chronically infarcted rat heart [11]. Finally there are

evidence linking fatty acids and oxidative stress to mitochondrial uncoupling in several models of heart failure [10,19].

Despite favorable effects of current therapies, the high mortality rate in heart failure indicates the need for developing new and more targeted therapeutic strategies [20]. While the current treatments of heart failure (ACE inhibitors, cardiac β -blockers and resynchronization therapy) aim to decrease energy demand, future strategies could focus on re-establishing the energetic balance by also improving energy production and/or reducing processes leading to the mechano-energetic uncoupling in the failing heart. •

References

- Bing RJ, Hammind MM, Handelsman JC, Powers SR, Spencer FC, Eckenhoff JE, Goodal MD, Hafkenschiel JH, Kety SS (1949) The measurement of coronary blood flow, oxygen consumption, and efficiency of the left ventricle in man. *Am Heart J* 38(1):1–24
- Neubauer S (2007) The failing heart--an engine out of fuel. *N Engl J Med* 356(11):1140–1151
- Neubauer S, Horn M, Cramer M, Harre K, Newell JB, Peters W, Pabst T, Ertl G, Hahn D, Ingwall JS, Kochsiek K (1997) Myocardial phosphocreatine-to-ATP ratio is a predictor of mortality in patients with dilated cardiomyopathy. *Circulation* 96(7):2190–2196
- Scheuermann Freestone M, Madsen PL, Manners D, Blamire AM, Buckingham RE, Styles P, Radda GK, Neubauer S, Clarke K (2003) Abnormal cardiac and skeletal muscle energy metabolism in patients with type 2 diabetes. *Circulation* 107(24):3040–3046
- Kannel WB, McGee DL (1979) Diabetes and cardiovascular disease. The Framingham study. *JAMA* 241(19):2035–2038
- Ventura-Clapier R, Garnier A, Veksler V, Joubert F (2011) Bioenergetics of the failing heart. *Biochim Biophys Acta* 1813(7):1360–1372
- Ingwall JS, Weiss RG (2004) Is the failing heart energy starved? On using chemical energy to support cardiac function. *Circ Res* 95(2):135–145
- Ingwall JS (2009) Energy metabolism in heart failure and remodelling. *Cardiovasc Res* 81(3):412–419
- Lopaschuk GD, Ussher JR, Folmes CD, Jaswal JS, Stanley WC (2010) Myocardial fatty acid metabolism in health and disease. *Physiol Rev* 90(1):207–258
- Opie LH, Knuuti J (2009) The adrenergic-fatty acid load in heart failure. *J Am Coll Cardiol* 54(18):1637–1646
- Murray AJ, Cole MA, Lygate CA, Carr CA, Stuckey DJ, Little SE, Neubauer S, Clarke K (2008) Increased mitochondrial uncoupling proteins, respiratory uncoupling and decreased efficiency in the chronically infarcted rat heart. *J Mol Cell Cardiol* 44(4):694–700
- Suga H (1990) Ventricular energetics. *Physiol Rev* 70(2):247–277
- Pinz I, Tian R, Belke D, Swanson E, Dillmann W, Ingwall JS (2011) Compromised myocardial energetics in hypertrophied mouse hearts diminish the beneficial effect of overexpressing SERCA2a. *J Biol Chem* 286(12):10163–10168
- Abozguia K, Elliott P, McKenna W, Phan TT, Nallur-Shivu G, Ahmed I, Maher AR, Kaur K, Taylor J, Henning A, Ashrafian H, Watkins H, Frenneaux M (2010) Metabolic modulator perhexiline corrects energy deficiency and improves exercise capacity in symptomatic hypertrophic cardiomyopathy. *Circulation* 122(16):1562–1569
- Fragasso G, Perseghin G, De CF, Esposito A, Palloschi A, Lattuada G, Scifo P, Calori G, Del MA, Margonato A (2006) Effects of metabolic modulation by trimetazidine on left ventricular function and phosphocreatine/adenosine triphosphate ratio in patients with heart failure. *Eur Heart J* 27(8):942–948
- Mjøs OD (1971) Effect of fatty acids on myocardial function and oxygen consumption in intact dogs. *J Clin Invest* 50:1386–1389
- Korvald C, Elvenes OP, Myrmet T (2000) Myocardial substrate metabolism influences left ventricular energetics in vivo. *Am J Physiol Heart Circ Physiol* 278(4):H1345–H1351
- Murray AJ, Anderson RE, Watson GC, Radda GK, Clarke K (2004) Uncoupling proteins in human heart. *Lancet* 364(9447):1786–1788
- Echtay KS, Pakay JL, Esteves TC, Brand MD (2005) Hydroxynonenal and uncoupling proteins: a model for protection against oxidative damage. *Biofactors* 24(1–4):119–130
- Mudd JO, Kass DA (2008) Tackling heart failure in the twenty-first century. *Nature* 451(7181):919–928