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Even subtle variations in the efficiency of energy generation or utilization may have a profound impact on cellular energy levels. Different cardiac pathologies can alter cardiac efficiency, both as a result of a decrease efficiency of producing ATP or alterations in the efficiency of using ATP to produce contractile work. Given that the requirement for ATP for all metabolic processes and for cell viability is absolute, a renewed interest in metabolism has led to identification of the molecular links between physiological and metabolic stimuli and the regulation of gene expression in the heart. Metabolism remolds in the failing heart leading to the inability to increase ATP supply. Ultimately, this may lead to a fall in ATP. The likely time line is decreased energy production via the phosphotransferase reactions (creatine kinase and adenylate kinase) leading to increases in ADP and AMP. As heart failure evolves, ATP synthesis from oxidation of metabolic substrates by mitochondria, the major source of ATP in the heart, falls. Remodeling of the failing myocardium is controlled by energy sensors, such as AMP-activated protein kinase (AMPK) that regulates energy substrate metabolism and regulates transcription of metabolic genes. This issue of Heart and Metabolism addresses the important topic of energetics in heart disease.

In the Basic Article, Dr. Aasum offers a concise review of myocardial energetic mechanisms, focusing on alterations in processes related to energy production and energy utilization in the failing heart. The Main Clinical Article by Dr. Ashrafian gives a clear and elegant overview of successful metabolic therapies presently available, especially for chronic ischemic heart disease. While considering the likely future directions for metabolic therapy, Dr. Ashrafian also points out the need for greater experience with the existing metabolic therapies, which could benefit most to those patients with concomitant metabolic disease, such as metabolic syndrome or diabetes mellitus.

In this context the Refresher Corner article by Drs. Fillmore and Lopaschuk provides a didactic summary of the state of the art, showing notably how metabolic substrates compete at myocardial cell level for energy production and how they may affect cardiac efficiency. Alterations in the balance between fatty acid and glucose use are known to occur in certain heart pathologies such as during ischemia and in the failing heart. This leads to decreased cardiac efficiency through a number of mechanisms that are reviewed and discussed herein, among which are intracellular ionic (H+, Na+, Ca2+) disturbances and their deleterious consequences. Measuring metabolic substrate utilization in humans has been difficult. The Metabolic Imaging article by Dr. Camici underlines that although the quantification of glucose utilization rates in patients encounters many difficulties, positron emission tomography with the glucose
analogue 18F-fluorodeoxyglucose (FDG) may help to establish values of the metabolic rates of glucose utilization in normal and pathologic conditions.

Furthermore, Drs. Baskin and Taegtmeyer provide an authoritative New Therapeutic Approaches article that broadens the role of energy substrate metabolism from a provider of ATP to a regulator of self-renewal of cardiac myocytes. They highlight the exciting new concept of how heart muscle cells can renew themselves from within by the identification of certain metabolic signals as a root cause for altered rates of intracellular protein turnover and, hence, self-renewal of cardiac myocytes. Metabolic remodeling precedes, triggers and sustains structural and functional remodeling of the heart. As mentioned before, AMPK supports energy provision in the cell by sensing changes in the ratio [ATP]/[AMP]. In addition, decrease in [ATP]/[AMP] and the subsequent activation of AMPK regulate protein degradation. Since individual proteins are degraded through the ubiquitin proteasome system Drs. Baskin and Taegtmeyer investigated the role of AMPK in proteasome-mediated protein degradation. They found that proteasome-mediated protein degradation in the heart is indeed increased with AMPK activation. They therefore speculate that the activation of AMPK results in enhanced availability of intracellular amino acids for either ATP production or the synthesis of new proteins as the heart adapts to a new physiological state. These most recent data advance a new understanding of cardiac metabolism. They should also set us on the path to develop novel strategies aimed at optimizing metabolic therapy in heart disease. •
Myocardial energetics and efficiency

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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

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 (mVO_{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 mVO_{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 {superscript}31P 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 myofilibrils and sarcoplasmatic 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 PPARα), 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 sarcoplasmatic reticulum function, notably calcium pumping, and basal metabolism (BM), and is consequently referred to as the work-independent mVO2. 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 mVO2 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.
The failing heart shows increased oxygen cost for non-mechanical processes

The y-intercept of the work-mVO₂ relationship reflects the oxygen cost for non-mechanical processes (unloaded mVO₂) [12], which is reported to be increased in several models of heart failure. Altered unloaded mVO₂ may be related to altered myocardial Ca²⁺ handling, altered substrate utilization and/or induction of oxygen wasting processes. Decreased sarcoplasmic reticulum (SR) Ca²⁺-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⁺-Ca²⁺ exchange activity is increased, which energetically will lead to a less efficient Ca²⁺ transport during excitation-contraction coupling. In addition, increased sarcoplasmic reticulum Ca²⁺ leak, as well as desynchronised Ca²⁺ release via SR calcium channels may also contribute to increased oxygen cost for Ca²⁺ 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 mVO₂ 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]. Mjos and coworkers demonstrated more that 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 mVO₂ 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 mVO₂. Fatty acids are ligands for PPARα 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

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**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 mVO₂, where the y-intercept defines the work-independent mVO₂, and the inverse of the slope of the relationship will indicate the efficiency of oxygen to TME (contractile efficiency). Adapted from Suga (1990) [12].
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

Modulation of cardiac energetics as a target in ischemic heart disease

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Abstract
Substantial advances in mechanical and adjunctive pharmacological therapies have reduced the consequences of ischemic heart disease. Despite these advances, cardiovascular disease and its major contributor coronary artery disease continue to accrue substantial morbidity and mortality. Metabolic therapies (ranging from insulin to fatty acid oxidation inhibitors and late sodium channel current inhibitors) represent a novel and immediately clinical relevant class of therapies that can contribute to improving patient outcomes. In the current article, I will discuss the basic biology of cardiac metabolism and the clinical efficacy of agents, some of which have direct clinical applicability. As well as outlining the considerations that may culminate in the effective deployment of these agents in the care of patients, I also consider the likely future directions for metabolic therapy in cardiovascular disease.

Keywords: cardiac energetics; ischemic heart disease; metabolic therapies; cardiac metabolism

Introduction
Cardiovascular disease remains the leading cause of mortality in the developed world and has emerged as a major cause of morbidity and mortality in the developing world [1]. Ischemic heart disease resulting from coronary artery disease, along with hypertensive heart disease, represents the engine of cardiovascular mortality and is consequent upon the lifestyle changes occurring with increasing “development” (e.g., smoking, obesity, psychosocial factors and sedentary lifestyle) [2]. Advances in mechanical interventions (e.g., percutaneous coronary intervention and coronary artery bypass surgery) that augment the oxygen supply to the myocardium coupled with therapies that reduce cardiac oxygen demand (e.g., β-blockers and ivabradine, which reduces heart rate exclusively by acting on the sinus node-I_{f} current) are the mainstay of current therapy. However, despite the use of these therapies, many patients remain symptomatic, expanding the reservoir of aging patients who, having undergone the demographic transition, aill with angina and chronic heart failure. To combat the morbidity and mortality associated with these conditions, novel therapies are urgently required—therapies that modify cardiac metabolism represent a hitherto practically unexplored group of treatments that are increasingly recognized to have promise in addressing the chronic consequences of cardiac disease [3].
Metabolic changes in the ischemic myocardium

It is frequently stated that the heart is capable of metabolizing a range of substrates, including free fatty acids (FFA), glucose and other carbohydrates (e.g. pyruvate and lactate) and even amino acids. The consequence of changing this substrate is less frequently considered.

A striking exemplification of the influence of metabolism on myocardial structure, albeit in the reptile hearts, can be adduced from the influence of metabolism on Burmese python hearts. These reptile hearts hypertrophy by >40% after the snakes’ monthly meal [4]. This entirely physiological—and likely reversible—structural change derives from the metabolism of a combination of three fatty acids: myristic, palmitic, and palmitoleic acids. Importantly, mice hearts also undergo cardiac hypertrophy (~10%) when exposed to the same cocktail of FFA. Thus while the mammalian heart is therefore a metabolic omnivore [5], the choice of substrate has profound consequences on cardiac structure, energetics and function. For example, theoretically a complete switch from FFA metabolism as an energy source to glucose can save 11–13% of myocardial oxygen use based on stoichiometric considerations (and by ~50% as measured experimentally in pig and canine hearts).

The healthy adult myocardium, especially during fasting, preferentially metabolizes FFA and their derivatives (60–100%) [3]. In hypertrophy and heart failure, it is believed (though not unanimously accepted) that a downregulation of fatty acid metabolism is compensated for by increased carbohydrate metabolism in an attempt to spare oxygen. Although far from experimentally confirmed, during myocardial ischemia a rapid activation of AMP-activated protein kinase (AMPK) occurs, resulting in an activation of both glucose uptake and an increase in fatty acid oxidation [6]. It is therefore presumed that the ischemic myocardium continues to rely on FFA metabolism with the attendant inefficiency of this substrate. Not only do FFA confer an oxygen utilization penalty on the heart at a time of blood/oxygen deficiency, but inappropriately high FFA metabolism may, as Randle proposed, compromise coupled glucose metabolism and have especially adverse sequelae on ischemic hearts (e.g., due to the influence of excess FFA on calcium transients in ischemia).

Accordingly, substantial emphasis has been placed on physiological or therapeutic strategies designed to suppress FFA uptake and/or oxidation in order to stimulate coupled myocardial glucose utilization. Although this substrate switch continues to be the primary focus for metabolic therapies, it is increasingly recognized that redox and aldehyde-induced stress responses can effect a shift in glucose metabolism from glycolysis to the pentose phosphate pathway [7]. Such studies provide a rationale for investigating other such signaling pathways with a broader view to elaborating resistance against acute oxidative stress induced by ischemia/reperfusion through metabolism.

Metabolic therapies

Glucose-insulin

In an attempt to recapitulate and exaggerate “physiological” glucose uptake into myocardium, Sodi-Pallares et al., in 1962, successfully applied “polarizing solution”, i.e., glucose-insulin-potassium infusion (GIK), for treatment of acute myocardial infarction. GIK infusion was initially thought to confer benefit primarily by increasing glycolysis and by reducing in FFA uptake and metabolism. More recently, we have demonstrated that GIK treatment also engenders a number of signaling changes (e.g., increased signaling protein phosphorylation and O-GlcNAcylation) likely to contribute to myocardial protection [8].

A number of early studies supported this early promise, for example the ECLA (Estudios Cardiológicos Latinoamérica) Collaborative Group were able to show a dramatic reduction of death rate of acute myocardial infarction from 11.5% in the control group to 6.7% in patients treated with GIK. However the negative results of large trials such as the CREATE-ECLA trial, which studied 20,201 patients with ST-elevation acute myocardial infarction, mostly in India and China, have questioned the role of GIK in the context of modern reperfusion therapy [9]. The conclusions of the latter study are moderated by the observation that GIK may have been given too late to be effective [10], its efficacy may have depend on the dose, its efficacy may have been limited by pharmacokinetics and pharmacodynamics and may depend on the exact population studied (including the nature of the adjunct pharmacology/coronary revascularisation).

Nevertheless, the current evidence suggests that GIK provision as performed in existing trials does not reduce mortality in patients with AMI but that tight
glycemic control is beneficial [11]. One way in which these limitations of insulin have been overcome is by the use of the incretin glucagon-like peptide-1 (GLP-1), which has demonstrable cardioprotective properties in experimental models and patients with cardiac ischemia [12]. Indeed, there is accumulating evidence suggests that albiglutide, a novel longer lasting GLP-1, rather akin to the early GIK studies, may protect the heart against from ischemic injury by altering substrate use and ameliorating cardiac energetics [13].

Partial fatty oxidation (pFOX) inhibitors
In order to achieve a more enduring and practicable switch between FFA and carbohydrate metabolism, a number of inhibitors of fatty acid oxidation have been sought and executed. CPT-1 is the rate-limiting enzyme that transports FFA into the mitochondria. Pharmacological inhibition of CPT-1 by etomoxir, oxfenecine and perhexeline and experimental malonyl CoA decarboxylase inhibitors (which augments the native CPT-1 inhibitor - malonyl CoA) have been investigated in pre-clinical models and human studies of cardiac ischemia. Similarly, the β-oxidation enzymes downstream of CPT-1, such as mitochondrial 3-ketoacyl-CoA thiolase inhibited by trimetazidine, are recognized to be therapeutic targets in the treatment of ischemic heart disease. Notably, despite the challenges of dose monitoring and intellectual property issues, both perhexiline and trimetazidine continue to be used successfully in the clinical setting [14].

It is important to recognize that the more potent pFOX inhibitors (inhibitors) tend to be limited by their side effect of cardiac lipotoxicity arising from excess cardiac lipid accumulation (etomoxir, oxfenecine). In contrast, competitive inhibitors of these enzymes such as perhexilene and trimetazidine, which allow excess endogenous FFA to break through the inhibition, do not show such effects. It is likely, therefore, that any successful cardiac metabolic therapy should be carefully moderated in order to prevent extreme inhibition of any single metabolic pathway, highly likely to be harmful to an organ.

Late sodium channel current
In the ischemic myocardium, inhibition of the energy-requiring Na+/K+ ATPase and other ATP dependent currents results in excess of myocellular sodium loading through failure of sodium efflux. The late sodium current, as a result of its persistent flow throughout the action potential, may make a substantial contribution to this ischemic sodium loading [15]. Excess sodium loading increases oxidative stress, increases myocellular calcium loading perhaps through the influence of sodium on calcium countertransport through NCX and depletes mitochondria of their calcium (which reduces the mitochondrial Kreb’s cycle activity and exacerbates energy deficiency) [16]. The mechanism through which blocking late inward sodium currents, leads to a reduction in angina remains the subject of active investigation but ranolazine, a late inward sodium current blocker with pFOX activity [17] does exhibit some anti-anginal properties [18].

The Future
A number of successful metabolic therapies are therefore presently available for clinical therapy, especially for chronic ischemic heart disease. Two directions remain to be pursued.

Greater experience with existing therapies
Substantial advances have been made in developing and demonstrating the safety and efficacy of a number of metabolic agents for the treatment of ischemic heart disease. Indeed a number of these agents, e.g., ranolazine and trimetazidine, have been tested in clinical trials. The paucity of use of these agents partially reflects the requirement for further education of clinical colleagues. However, perhaps a more trenchant reason for the lack of extensive use of these agents derives from a lack of clarity about the ideal context for their use. Existing agents such as β-blockers, nitrates, calcium channel antagonists and specific rate-limiting agents, such as ivabradine, all successfully mitigate the consequences of ischemia in many patients. One of the challenges for many practitioners is, to identify the population in which these products will offer them the most adapted benefits, e.g., those with concomitant metabolic disease such as the metabolic syndrome/diabetes mellitus or those with ventricular dysfunction, whose cardiac metabolic dysfunction may respond especially well to metabolic modulation.

Novel metabolic therapies
While inhibition of FFA oxidation continues to represent a credible strategy for the treatment of chronic ischemia, there is substantial potential for identifying novel metabolic nodes for treatment. Existing interesting
metabolic therapies such as dichloroacetate which, through liberating pyruvate dehydrogenase from its kinase inhibitors, augments carbon flux into the Kreb’s cycle have been disappointing by virtue of their pharmacokinetics and their potential side effects. However, there are a number of novel avenues to pursue. Firstly, it is increasingly recognized that as well as their roles in energy generation, metabolites can marshal a wider group of biological responses that are amenable to therapeutic modulation. For example, the Kreb’s cycle intermediate, succinate, acting through G protein-coupled receptor-91, can determine angiogenesis as a response to chronic ischemic stress. This observation supports the contention that a broader vision of metabolic manipulation is likely to elevate metabolic therapy beyond energy modulation [19]. Pursuing this theme further, established metabolic therapies such as GLIK and more specifically agents such as glucosamine post-translationally modify serine and threonine residues of proteins by the O-linked attachment of the monosaccharide β-N-acetyl-glucosamine (i.e., O-GlcNAc) [20]. As well as subserving metabolic benefits, metabolic therapies also have profound influences on other aspects of cardiac biology as diverse as contractility and clock function [21].

Conclusion

Accordingly, the future of metabolic therapies likely lies in a redoubling of clinical efforts to apply existing therapies to patients likely to benefit most from them, and to recognize the potentially beneficial consequences of metabolic therapies on exciting novel biological pathways, a better understanding and application of which holds promise for conferring additional benefits to patients with acute or chronic cardiac ischemia.

Acknowledgements

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References


Glucose metabolism as a marker of myocardial ischemia

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Abstract
Although the heart is omnivorous, glucose becomes the key substrate under conditions of stress. The utilization of exogenous glucose by the myocardium can be assessed non-invasively using positron emission tomography (PET) with the glucose analogue 18F-fluorodeoxyglucose (FDG). Several studies have demonstrated that glucose utilization is increased at peak stress and during conditions of reduced oxygen supply. Moreover, glucose utilization remains elevated after an episode of transient ischemia, which constitutes a sort of "metabolic memory". PET with FDG also permits the identification of "hibernating myocardium". This allows a more accurate stratification of patients with post-ischemic left ventricular dysfunction and identification of those that might benefit most from coronary revascularization.

Keywords: coronary artery disease; myocardial metabolism; myocardial ischemia; positron emission tomography.

Introduction
The human heart in the fasting state extracts free fatty acid (FFA), glucose, lactate, pyruvate, and ketone bodies from the systemic circulation. A small but consistent net uptake of circulating glucose by the heart is normally demonstrable in the fasting state with a reported arterial-venous (AV) difference ranging from 0.15 to 0.23 mmol/l, corresponding to a fractional uptake of only 3% and to an average oxygen extraction ratio of ~27%. Measurements of the rate of glucose oxidation by radiolabelled techniques in healthy volunteers have shown that, at the most, only about 30% of the glucose uptake is rapidly oxidized, and about 15% is converted to lactate [1].

Cardiac glucose metabolism during fasted and fed states
There is a general consensus that FFA is the major fuel for cardiac muscle in the fasting, post-absorptive state. In various studies using the coronary sinus (CS) catheterization technique, net uptake of FFA from the arterial circulation has been found consistent. At arterial FFA levels in the 0.5 to 0.9 mmol/l range, the reported AV differences is 0.14 to 0.20 μmol/ml, which correspond to oxygen extraction ratios of up to 40%. If a total coronary blood flow of ~250 ml/min is assumed, then the heart of fasting subjects at rest consumes up to about 50 μmol/min of FFA, or up to 10% of the whole body FFA turnover (8 μmol/min/kg), despite receiving only 5% of cardiac output. In general, the fate of FFA is largely complete oxidation in the Krebs’ cycle with a lesser component undergoing re-esterification to tissue triglycerides. The fact that the
respiratory quotient of the heart in the fasting state is on average 0.74 indicates that the greater part of the extracted FFA is oxidized [1] (Fig. 1).

The oxidative use of lipid (FFA) and carbohydrate (glucose and lactate) fuel is reciprocally regulated through the operation of Randle’s cycle [2]. Feeding, by increasing both insulin and glucose concentrations shifts myocardial metabolism towards preferential carbohydrate usage, both for oxidative energy generation and for glycogen synthesis (Fig. 1).

Cardiac glucose metabolism during conditions of reduced oxygen supply

During conditions of reduced oxygen supply, the oxidation of all substrates is decreased while anaerobic metabolism is activated (Fig. 2). In patients with coronary artery disease (CAD) and stable angina pectoris, net lactate release in the CS can be demonstrated during pacing stress. However, this occurs in only 50% of patients, and no relationship can be demonstrated between lactate production and the severity of ischemia [3]. In patients with chronic angina, a significant release of alanine in the CS and an increased myocardial uptake of glutamate could be demonstrated at rest and following pacing [4–5]. These two phenomena result from increased transamination of excess pyruvate to alanine with glutamate serving as NH₂ donor. In addition, release of citrate (a known inhibitor of glycolysis) in the CS can be demonstrated following pacing in patients with stable angina.

Positron emission tomography

The utilization of exogenous glucose by the myocardium can be assessed using positron emission tomography.

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Fig. 1 Left panel: Inhibited glycolysis in fasted state. Overall control of pathways of glycolysis, which is taken as the conversion of G-6-P to P. The inhibition of glycolysis at the level of phosphofructokinase is the result of accumulation of excess citrate during oxidation of FFA. Pyruvate dehydrogenase is inhibited by accumulated NADH₂, the result of β-oxidation of fatty acids. Right panel: Overall patterns of glycolysis in the fed state. Besides direct acceleration of glucose uptake as a result of high circulating levels of glucose and insulin, there is indirect acceleration of glycolysis as blood FFA levels decrease, and the inhibition of phosphofructokinase by citrate is removed. G-6-P glucose-6-phosphate, P pyruvate, G glucose, F-6-P fructose 1,6 phosphate, PFK phosphofructokinase, F 1,6 bis P fructose1,6 diphosphate, GAPDH glyceraldehyde phosphate dehydrogenase, NADH₂ reduced form of nicotine edenine dinucleotide, PDH pyruvate dehydrogenase.
(PET) with the glucose analogue $^{18}$F-fluorodeoxyglucose (FDG). FDG is transported into the myocyte by the same trans-sarcolemmal carrier as glucose and is then phosphorylated to FDG-6-phosphate by the enzyme hexokinase. This is essentially a unidirectional reaction and results in FDG-6-phosphate accumulation within the myocardium, as no glucose-6-phosphatase (the enzyme that hydrolysates FDG-6-phosphate back to free FDG and free phosphate) has yet been identified in cardiac muscle. Thus, measurement of the myocardial uptake of FDG is proportional to the overall rate of trans-sacolemmal transport and hexokinase-phosphorylation of exogenous (circulating) glucose by heart muscle.

A number of kinetic modeling approaches have been used for the quantification of glucose utilization rates using FDG. The major limitation of these approaches is that quantification of glucose metabolism requires the knowledge of the lumped constant, a factor that relates the kinetic behavior of FDG to naturally occurring glucose in terms of the relative affinity of each molecule for the trans-sarcolemmal transporter and for hexokinase. Unfortunately, the value of the lumped constant in humans under different physiological and pathophysiological conditions is not known, thus making precise in vivo quantification of myocardial metabolic rates of glucose practically impossible. Still current measurements of the uptake of FDG (particularly if obtained under standardized conditions) allow comparison of absolute values from different individuals and may help to establish the absolute rates of glucose utilization (in FDG units) in normal and pathologic myocardium.

**FDG uptake in patients with CAD and stable angina**

Different patterns of myocardial glucose utilization have been observed in patients with CAD studied using FDG. In patients with stable angina studied at rest, after overnight fast, regional myocardial glucose utilization was homogeneously low and comparable with that in normal subjects. In contrast, in patients with unstable angina, myocardial glucose utilization at rest was increased even in the absence of symptoms and electrocardiographic signs of acute ischemia [6]. In patients with stable angina, a prolonged increase in FDG uptake could be demonstrated in post-ischemic myocardium in the absence of symptoms or perfusion abnormalities, which suggests a sort of post-ischemic "metabolic memory" [7]. Subsequent studies in animals have indicated that this increased post-ischemic glucose utilization is mainly finalized to replenish myocardial glycogen stores which were depleted during ischemia [1].

**PET with FDG for the identification of hibernating myocardium**

In the current era of coronary revascularization and thrombolysis, it has become increasingly apparent that restoration of blood flow to asynergic myocardial segments may result in improved regional and global LV function [8–10]. The greatest clinical benefit is seen in those patients with the most severe forms of dysfunction. Initial studies indicated that myocardial ischemia and infarction could be distinguished by analysis of PET images of the perfusion tracer $^{13}$NH$_3$ and the glucose analogue FDG acquired after an oral glucose load. Regions which showed a concordant reduction in both myocardial blood flow and FDG uptake ("flow-
metabolism match") were labeled as predominantly infarcted, whereas regions in which FDG uptake was relatively preserved or increased despite having a perfusion defect ("flow-metabolism mismatch") were considered to represent jeopardized viable myocardium [11]. The uptake of FDG by the myocardium, however, depends on many factors such as dietary state, cardiac workload, and response of the tissue to insulin, sympathetic drive and the presence and severity of ischemia. These factors contribute to variability in FDG imaging in the fasted or glucose-loaded state, confusing data interpretation.

With the recent suggestion that semi-quantitative and quantitative analyses of FDG uptake may enhance detection of viable myocardium, there was an urgent need to rigorously standardize the study conditions. Furthermore, many patients with coronary artery disease are insulin resistant, i.e., the amount of endogenous insulin released after feeding will not induce maximal stimulation due to partial resistance to the action of the hormone. This may result in poor FDG image quality after an oral glucose load. To circumvent the problem of insulin resistance, an alternative protocol has been recently applied to PET viability studies. The protocol is based on the use of the hyperinsulinemic euglycemic clamp, essentially the simultaneous infusion of insulin and glucose acting on the tissue as a metabolic challenge and stimulating maximal FDG uptake (see Fig. 3). This leads to optimization of image quality and enables PET studies to be performed under standardized metabolic conditions, which allows comparison of the absolute values of the metabolic rate of glucose (μmol/g/min) amongst different subjects and centers [12].

Conclusion

Although the heart is omnivorous, glucose becomes the key substrate under conditions of stress. Several studies have demonstrated that glucose utilization is increased at peak stress and during conditions of reduced oxygen supply. Moreover, glucose utilization remains elevated after an episode of transient ischemia, which constitutes a sort of "metabolic memory". PET with FDG also permits the identification of "hibernating myocardium". This allows a more accurate stratification of patients with post-ischemic left ventricular dysfunction and identification of those that might benefit most from coronary revascularization.
References

An expanded role for AMP kinase: self-renewal of the cardiomyocyte

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Abstract
Our work on atrophic remodeling of the heart has caused us to appreciate a simple principle in biology: from the cell cycle to the Krebs cycle, there is no life without cycles. While the potential for cellular regeneration receives much attention, the dynamics of intracellular protein turnover have received only selective consideration. Although the concept of the “dynamic state of body constituents” has existed since the 1940s, the idea that heart muscle cells renew themselves from within is relatively new. The rationale is as follows. For the last 30 years, we (and many others) have elucidated the interaction of metabolic pathways for energy provision and contraction of the heart. Work in the field has uncovered novel metabolic regulators of enzyme action, yet much less attention has been given to the impact of myocardial energy metabolism on myocardial protein turnover. We therefore began to consider metabolic signals as putative regulators of myocardial protein synthesis and degradation. In a broad sense, we sought to establish mechanisms underlying the self-renewal of intact cardiomyocytes, because we have observed that atrophic remodeling of the heart simultaneously activates pathways of intracellular protein synthesis and degradation. We determined how metabolic signals regulate protein degradation, and tested the hypothesis that there is a direct link between intermediary metabolism and protein degradation and that the specific molecular mechanisms involve 5’ AMP-activated protein kinase (AMPK) regulation of ubiquitin ligases. We review our first results on metabolic signals as regulators of myocardial protein turnover that seek to broaden the role energy substrate metabolism from a provider of ATP to a regulator of self-renewal of the cardiomyocyte.

Keywords: AMPK; protein degradation; cardiac metabolism

Introduction
Our work on atrophic remodeling of the heart has led us to appreciate a simple principle in biology: from the cell cycle to the Krebs cycle, there is no life without cycles. While cellular regeneration of the heart receives much attention [1], the dynamics of intracellular protein turnover have received only selective consideration [2]. Undoubtedly stem (or precursor) cells contribute to the replacement of cardiomyocytes after injury, but they contribute little to cardiomyocyte renewal during normal aging [3]. Although Schoenheimer’s concept of the “dynamic state of body constituents” has existed for some time [4], the idea that heart muscle cells renew themselves from within is relatively new. We will begin to address this concept with a review on the...
transcriptional role for 5’ AMP-activated protein kinase (AMPK) on protein degradation pathways.

For the last 50 years many laboratories have elucidated the interaction of metabolic pathways for energy provision and contraction in the heart. Work in the field has uncovered novel metabolic regulators of enzyme action, yet the impact of myocardial energy metabolism on myocardial protein turnover has not been considered. After we discovered that cardiac atrophy is not a simple mirror image of hypertrophy [5], we are now proposing that metabolic signals are putative regulators of myocardial protein synthesis and degradation. In a broad sense we seek to establish mechanisms underlying the self-renewal of the intact cardiomyocyte. The rationale arises from our observation that atrophic remodeling of the heart simultaneously activates pathways of intracellular protein synthesis and degradation [5] and the following considerations.

First, a large number of models already exist that identify molecular targets of myocardial hypertrophy and atrophy [6,7]. Secondly, metabolism is the first responder to any form of stress [8]. We have evidence suggesting that the process of metabolic remodeling precedes, triggers and sustains both structural and functional remodeling of the heart [9]. We propose that modulation of metabolic stresses provides a means to remove damaged or redundant proteins and replace them with new, functional proteins (Fig. 1). Furthermore, the identification of metabolic signals which govern cardiac remodeling will set us also on the path to develop novel strategies aiming at specific metabolic intermediaries as modulators of cardiomyocyte size.

**Intracellular protein turnover in perspective**

The depressing statistics on heart failure are widely known [10]. Yet in spite of broad and formidable efforts, there is no cure in sight because the cellular and molecular mechanisms are still not completely understood. Accepted features in the development of heart failure are cardiac hypertrophy and impaired ATP production, which develop in response to both endogenous (genetic) and exogenous (environmental) changes. We propose that metabolic remodeling (which is potentially reversible) precedes, triggers and sustains structural and functional remodeling [11]. In order for the heart to adapt to various types of stress, individual heart muscle cells change or “remodel” both metabolically and structurally. Excessive remodeling results in the enlargement of cardiomyocytes, which translates into an overall increase in heart size. The transition from hypertrophy to heart failure, or the transition from adaptation to maladaptation of the heart, remains elusive. Consequently it seems to us critical to know more about the mechanisms that control the rebuilding of the cardiomyocyte.

Our most recent ideas advance a new understanding of cardiac metabolism as an integral part of the self-renewing myocyte as highlighted below. These ideas result from our investigations on switching of metabolic genes and atrophic remodeling of the cardiomyocytes in response to mechanical unloading.

We are operating under the premise that during steady state conditions rates of myocardial protein synthesis (PS) and protein degradation (PD) are equal [12,13]. The intrinsic mechanism of self-renewal of the cardiomyocyte requires the regulated degradation of damaged, misfolded, or useless proteins and their replacement by new and functional proteins (Fig. 1). Protein turnover therefore constitutes a major line of defense for protein quality control of the cardiomyocytes [14]. The rate of myocardial protein turnover is much faster than it is generally assumed, with the half-life of individual myocardial proteins ranging from several hours to several days [12]. The term “self-
renewal of the cardiomyocyte” gives exciting new meaning to the concept of “cardiac plasticity” [6].

We do not know at present to what extent biochemical signals regulate protein degradation and protein synthesis. We have preliminary evidence which suggests that metabolic signals, i.e., changes in intracellular metabolite levels in response to stress, may activate pathways of protein degradation and protein synthesis [5,15].

Lastly, and perhaps most importantly, for nearly a century the study of cardiac metabolism has concerned itself with energy substrate metabolism and contraction of the heart [16,17]. This focus has culminated in a recent review proclaiming that the failing heart is an “engine out of fuel” [18]. We have questioned this concept because the non-ischemic, failing heart is always well supplied with nutrients, and the heart is actually drowning in fuel [19]. Not surprisingly, attempts to restore normal contractile function in the failing heart by metabolic interventions have not been consistently successful [20,21]. It is much more likely that intermediary metabolism, rather than impaired fuel supply, is the culprit. We consider altered fuel metabolism (leading to either a decrease or an increase of certain metabolic signals) as a root cause for altered rates of intracellular protein turnover and, hence, self-renewal of the cardiomyocyte.

Taken together, we propose that the “metabolic” approach to myocardial protein synthesis and degradation provides a new framework that will expose new regulators driving self-renewal of cardiomyocytes from within. We focus on the ubiquitin proteasome system (UPS).

The ubiquitin proteasome system and AMPK

Intracellular protein degradation is a complex and highly controlled process that is integrated with the environment of the cell. We have recently identified a metabolic signal that regulates protein degradation in the heart and the corresponding mechanisms by which it does so, specifically pertaining to the ubiquitin proteasome system (UPS). Our studies suggest that the adenine nucleotides ATP and AMP are metabolic signals that regulate protein degradation. AMP-activated protein kinase (AMPK) supports energy provision in the cell by sensing changes in the ratio [ATP]:[AMP]. Therefore, our working hypothesis was that metabolic signals (decrease in [ATP]:[AMP]) and the subsequent activation of AMPK, regulate protein degradation. We have tested the hypothesis by modulating AMPK in vitro and in vivo to define the mechanisms by which AMPK is involved in protein degradation [22].

Intracellular protein degradation in cardiomyocytes is controlled by independent but interrelated processes: UPS-mediated proteolysis and autophagy. While autophagy can degrade whole organelles, individual proteins are degraded through the UPS [13]. Ubiquitin ligases confer specificity to the system by the selective ubiquitination of target proteins which are then degraded by the proteasome [2]. Two muscle-specific ubiquitin ligases, muscle atrophy F-box (MAFbx/atrogin-1) and muscle ring finger-1 (MuRF1), are critical regulators of cardiac protein degradation and myocardial mass. Studies in vivo have demonstrated that overexpressing atrogin-1 in the heart attenuates the development of hypertrophy [23], while the deletion of MuRF1 results in increased hypertrophy [24]. These experiments highlight the importance of atrogin-1 and MuRF1 in regulating heart size. However, the mechanisms by which the ligases themselves are regulated are not completely understood.

Early studies in the heart in vivo demonstrated that nutrient deprivation decreases protein synthesis and increases fractional rates of protein degradation [25]. Starvation decreases the intracellular concentration of ATP and, consequently, AMPK is activated in order to provide energy to maintain normal cellular function. It is well established that AMPK regulates energy substrate metabolism, inhibits protein synthesis [26], and regulates transcription of metabolic genes [27]. Although it has recently been reported that starvation induces autophagy in cardiomyocytes through AMPK [28], a role of AMPK in the cardiac UPS had never been considered before.

In order to investigate the role of AMPK in the UPS, we first verified that substrate deprivation in cardiomyocytes (CM) enhances protein degradation (PD), as has been shown already in vivo [25]. Protein degradation was enhanced in CM during starvation, but decreased with bortezombi, a proteasome inhibitor, or with 3-methyladenine (3-MA), an inhibitor of autophagy. These results suggest that, like autophagy [28], proteasome-mediated degradation is important during nutrient starvation in CM. Given the importance of atrogin-1 and MuRF1 in regulating protein degradation.
and cardiac size [23,24], we quantified their expression in parallel experiments. Atrogin-1 and MuRF1 levels were significantly increased with starvation, which also correlated with enhanced AMPK activity (Fig. 2). We also found that direct AMPK activation, independent of nutrient starvation, increased both atrogin-1 and MuRF1 expression, which was significantly impaired with AMPK inhibition. Consequently, protein degradation in the heart is increased with AMPK activation, but proteasome-mediated protein degradation downstream of AMPK requires MuRF1 [22]. The conclusions are shown in the schematic (Fig. 3).

**Perspective**

We have shown that AMPK regulates ubiquitin ligases in the rodent heart. The present work extends the long established concept of the “dynamic state of body constituents” [4] to a specific situation when the heart adapts to changes in its metabolic environment. Protein turnover constitutes a major line of defense for protein quality control of the cardiomyocytes [14] and is a major mechanism of adaptation in the heart. Therefore it is of interest to understand how protein degradation is regulated under various circumstances in the heart. Markers of the UPS are upregulated in the heart in several settings of cardiac remodeling [13], but it is not clear exactly how the markers themselves are regulated. AMPK regulates cellular homeostasis in part by inhibiting the mTOR pathway [26] and thus by decreasing protein synthesis, while at the same time AMPK activates autophagy [28].

It is well known that AMPK is a central regulator of fuel homeostasis, but studies have until now predominantly focused on the effects of AMPK activation on energy substrate metabolism [29]. The active subunit of AMPK is highly expressed in the heart, and is preferentially localized to the nucleus [30]. It is therefore not surprising that AMPK also transcriptionally regulates metabolic gene expression. Earlier reports in liver show that AMPK activation represses transcription, but little is known about AMPK-regulated transcription in the heart. AMPK activates transcription [27], and the activation of PGC1α by AMPK leads to increased mitochondrial gene expression [31]. Still, the importance of AMPK in transcription is only now coming into focus. AMPK regulates entire transcriptional programs, and not only transcription of individual genes, by regulating histone 2B [32]. We have now expanded the role of AMPK in both cellular homeostasis and transcriptional regulation in the heart [22].

The AMPK activator and anti-diabetic drug metformin has proven to have beneficial outcomes in heart failure patients with diabetes [21]. The role of protein turnover in hearts of these patients could not be investigated. However, based on our experimental findings, AMPK-regulated protein degradation may be

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**Fig. 2** Nutrient deprivation increases expression of ubiquitin ligases and enhances protein degradation. (A) Atrogin-1 and MuRF1 mRNA expression in nutrient deprived NRVM. (B) Relative protein levels and quantification in NRVM after 24 hours of nutrient deprivation. (C) Protein degradation in NRVM after 24 hours of nutrient deprivation with 1μmol/L Bortezomib or 10μmol/L 3-methyladenine treatment. Data are mean ± SEM of 3 independent experiments performed in triplicate. *P<0.01 vs control or untreated, †P<0.01 vs control or complete nutrients (reprinted with permission from [22] ©2011 Wolters Kluwer Health).
protective because of enhanced protein quality control [14]. Activation of AMPK results in increased rates of protein degradation, and consequently leads to remodeling of the heart. The immediate cardiometabolic environment may determine whether the remodeling is beneficial or detrimental. We speculate that the activation of AMPK results in enhanced availability of intracellular amino acids for either ATP production or the synthesis of new proteins as the heart adapts to a new physiologic state. This self-renewal of the cardiomyocytes would mean an expanded role for 5′AMP-activated protein kinase in the heart.

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References

Beneficial effects of trimetazidine (Vastarel®MR) in patients with chronic heart failure

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Abstract
The possibility of modifying cardiac metabolism by switching the fuel used by the myocardium could become increasingly important, especially in clinical conditions characterized by reduced energy availability, such as heart failure. Trimetazidine (Vastarel®MR), an inhibitor of free fatty acid (FFA) oxidation, holds the characteristics to play a fundamental role in the therapeutic strategy of patients with heart failure. More specifically, shifting the energy substrate preference away from FFA metabolism and toward glucose metabolism has been shown to be an effective adjunctive treatment in terms of myocardial metabolism and left ventricular function improvement. These effects seem operative in heart failure syndromes regardless of their etiopathogenetic cause and are not confined to those of ischemic origin. In this paper, the recent literature on the beneficial therapeutic effects of trimetazidine on left ventricular dysfunction and heart failure is reviewed and discussed.

Keywords: systolic-dysfunction heart failure; left ventricular function; metabolic therapy; energy expenditure

Introduction
Trimetazidine (TMZ) (1-[2,3,4-trimethoxybenzyl] piperazine dihydrochloride) (Vastarel®MR) has been reported to exert anti-ischemic properties without affecting myocardial oxygen consumption and blood supply [1]. The beneficial effect of this agent has been attributed to preservation of phosphocreatine and ATP intracellular levels [2] and reduction of cell acidosis [3–4], calcium overload [4] and free-radical-induced injury caused by ischemia [5]. More importantly, TMZ MR affects myocardial substrate utilization by inhibiting oxidative phosphorylation and by shifting energy production from free fatty acids (FFA) to glucose oxidation [6–7]. This effect appears to be predominantly caused by a selective block of long chain 3-ketoacyl CoA thiolase activity, the last enzyme involved in β-oxidation [8].

Effects of TMZ in patients with chronic heart failure
In chronic heart failure therapeutic strategies have traditionally focused on the modification of hemodynamic alterations that occur in the failing heart. However, in addition to hemodynamic
alterations, heart failure causes deep changes both in systemic and in cardiac metabolic milieu. In this context, recent studies performed in small groups of patients with post ischemic left ventricular dysfunction, have shown that TMZ may be beneficial in terms of left ventricular function preservation and control of symptoms [9–15]. On this basis, it has been shown that this pharmacological approach could also be useful in the treatment of patients with heart failure of various etiologies [16–19].

The beneficial effect of TMZ on left ventricular function has been attributed to preservation of intracellular phosphocreatine (PCr) and adenosintriphosphate (ATP) [2]. Previous clinical studies using phosphorus-31 magnetic resonance spectroscopy to measure PCr/ATP ratios in human myocardium have shown that this ratio is reduced in failing human myocardium [20]. The PCr/ATP ratio is a measure of myocardial energetics, and its reduction may depend on imbalance of myocardial oxygen supply and demand [21] and reduction of the total creatine pool, a phenomenon known to occur in heart failure [22]. In a recent study performed in patients with heart failure of different etiologies who were receiving full standard medical therapy, TMZ-induced improvement of functional class and left ventricular function was associated with a 33% improvement of the PCr/ATP ratio, supporting the hypothesis that TMZ probably preserves myocardial high-energy phosphate intracellular levels [23]. These results appear particularly interesting in view of previous evidence indicating that the PCr/ATP ratio is a significant predictor of mortality [24].

Effects of TMZ on whole body energy metabolism of patients with heart failure

A higher resting metabolic rate has been observed in patients with heart failure [25–27], and this factor probably contributes to progressive worsening of the disease. Rate of energy expenditure is related to increased serum FFA oxidation and both energy expenditure and serum FFA oxidation are inversely correlated with left ventricular ejection fraction and positively correlated with growth hormone concentrations, epinephrine and norepinephrine [28]. Norepinephrine increases whole body oxygen consumption, circulating FFA concentrations, and FFA oxidation [29]. These changes have been attributed to stimulation of hormone-sensitive lipase in adipose tissue, and to stimulation of oxygen consumption independent of lipolysis by norepinephrine [30]. This data, together with close correlations between plasma norepinephrine concentrations, energy expenditure at rest and FFA oxidation, make increased sympathetic activity the most likely explanation for alterations in fuel homeostasis in patients with HF [30]. Therefore, intervention strategies aimed at optimizing global and cardiac metabolism, could be useful for interrupting the vicious circle of reduced function at greater metabolic expenses in different cardiac conditions [31]. In a very recent study, it has been shown that 3 months of treatment with TMZ added to usual treatment consistently reduces whole body resting energy expenditure along with improved functional class, quality of life and left ventricular function in patients with systolic heart failure, regardless of its etiology and diabetic status [32] (Fig. 1). The observation that the beneficial effect of TMZ on left ventricular function is also paralleled by a reduction of whole body rate of energy expenditure when compared to patients on conventional treatment underlies the possibility that the effect of TMZ may be mediated through a reduction of metabolic demand at the level of the peripheral tissues and, in turn, in some sort of central (cardiac) relief. Therefore, reduction of whole body energy demand could be one of the principal mechanisms by which TMZ could improve symptoms and left ventricular function in patients with heart failure.

**Fig. 1** Rate of energy expenditure (Kcal/die) measured by indirect calorimetry at baseline and 3 months follow-up in patients with heart failure receiving conventional therapy alone (left histograms) or conventional therapy plus trimetazidine (right histograms) (adapted with permission from reference [32]).
Additional potential beneficial pharmacological effects of TMZ in heart failure

It has been observed that TMZ could reduce endothelin release in cardiac patients [12, 33–34]. Growth factors, vasoactive substances and mechanical stress are involved in the endothelin-1 (ET-1) increase in heart failure patients. Despite the known adaptive aspect of supporting contractility of the failing heart, persistent increases in cardiac ET-1 expression in the failing heart have a pathophysiological maladaptive aspect and are associated with the severity of myocardial dysfunction [35].

TMZ-induced reduction of intracellular acidosis in ischemic myocardium could not only influence myocardial but also endothelial membranes [5]. By decreasing endothelial damage, TMZ could inhibit ET-1 release that, in turn, will finally decrease myocardial damage. A second hypothesis is that, by just decreasing the effects of chronic myocardial ischemia, TMZ could inhibit ET-1 release. Therefore, the observed decrease in ET-1 release with TMZ, could likely be linked to TMZ-induced reduction of myocardial ischemia. Finally, keeping in mind the close relation between endothelium and insulin sensitivity, the observed effects of TMZ on endothelial function could also explain the beneficial action of TMZ on glucose metabolism. In fact, apart from improving left ventricular function in cardiac patients, it has been recently shown that TMZ could also improve overall glucose metabolism in the same patients, indicating an attractive ancillary pharmacological property of this class of drugs [12, 33]. In fact, the known insulin resistant state in most cardiac patients is certainly aggravated in those patients with overt diabetes. This is particularly relevant in patients with both diabetes and left ventricular dysfunction. In this context, the availability of glucose and the ability of cardiomyocytes and skeletal muscles to metabolize glucose are grossly reduced. Indeed, since a major factor in the development and progression of heart failure is already a reduced availability of ATP, glucose metabolism alterations could further impair the efficiency of cardiomyocytes to produce energy. By inhibiting fatty acid oxidation, TMZ stimulates total glucose utilization, including both glycolysis and glucose oxidation. The effects of TMZ on glucose metabolism could therefore be dependent by a) improved cardiac efficiency; b) improved peripheral glucose extraction and utilization. Both mechanisms could definitely be beneficial in heart failure patients.

Systematic literature search on the beneficial effect of TMZ in heart failure

A systematic search of the literature was recently conducted by Gao et al. to identify randomized controlled trials of TMZ for heart failure [36]. They considered reports of trials comparing TMZ with placebo control for chronic heart failure in adults, with outcomes including all-cause mortality, hospitalization, cardiovascular events, changes in cardiac function parameters and exercise capacity. The results of the search identified 17 trials with data for 955 patients. TMZ therapy was associated with a significant improvement in left ventricular ejection fraction in patients with both ischemic (7.37%; 95% CI 6.05 to 8.70; p<0.01) and non-ischemic heart failure (8.72%; 95% CI 5.51 to 11.92; p<0.01). With TMZ therapy, New York Heart Association classification was also improved (p<0.01), as was exercise duration (p<0.01). More importantly, TMZ had a significant protective effect for all-cause mortality (RR 0.29; 95% CI 0.17 to 0.49; p<0.00001) and cardiovascular events and hospitalization (RR 0.42; 95% CI 0.30 to 0.58; p<0.00001). These data confirm that TMZ might be an effective strategy for treating heart failure and that a large multicenter randomized controlled trial should be performed, in order to clarify its therapeutic role in this setting.

Conclusion

TMZ could have an important role in the therapeutic strategy of patients with heart failure. More specifically, shifting the energy substrate preference away from fatty acid metabolism and toward glucose metabolism appears as an effective adjunctive treatment in patients with heart failure, in terms of left ventricular metabolism and function improvement. These effects are operative in heart failure syndromes regardless of their etiopathogenetic cause and are not confined to those of ischemic origin.

However, despite a very recent meta-analysis has evidenced that these benefits also translate into improved survival, a randomized placebo controlled multicenter trial is definitely warranted in order to objectively investigate the role of TMZ in the therapeutic armamentarium of heart failure.
References

Myocardial power delivery is impaired in progressive left ventricular pump failure: a case report

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Abstract
The driving force for the flow of blood is the total energy imparted to it that corresponds to the mechanical, external work performed by the ventricle. In the cardiovascular system, the pumping power of the heart can be determined by cardiac power output, which is the product of cardiac output and mean blood pressure. Similarly to power-to-weight ratio, that is a measurement of the actual performance of any engine, maximal left ventricular power output-to-left ventricular mass is an index of cardiac performance potentially useful in patients with heart failure. In this case report, an example of the usefulness of this parameter is described in a patients with advanced heart failure secondary to dilated cardiomyopathy.

Keywords: heart failure; dilated cardiomyopathy; echo stress

Introduction
In attempting to characterize a system composed of an energy source and pipes conducting this energy, the usual parameters used for this purpose are the power of the energy generator and the resistance of the conducting pipes [1]. In the cardiovascular system, the pumping power of the heart can be determined by cardiac power output, which is the product of cardiac output (CO) and mean blood pressure (BP). By incorporating both flow and pressure in a single entity, cardiac power output represents the amount of energy imparted by the left ventricle to the volume of blood ejected per second [2]. Cardiac power output can be invasively and noninvasively assessed during maximal exercise or pharmacological stress test [3–7].

Power-to-weight ratio is a measure that is widely applied to mechanical engines to compare the performance of vehicles, aircrafts, and other mobile power sources. Similarly to power-to-weight ratio, peak power output-to-left ventricular (LV) mass (peak power-to-mass) is an index of LV performance potentially useful in patients with cardiac diseases. This parameter allows us to assess the relationship between cardiac power measurements and most of the recruitable myocardial reserve available at maximum workload. As a result, peak power-to-mass may be interpreted as a measure of myocardial efficiency, that is a ratio that incorporates the degree of the external work per unit of time and the maximal work possible.
Although the denominator of this equation cannot be measured, it can be argued that in normal ventricles the amount of LV mass is comparative to myocardial power delivery, whereas a disproportion between LV performance and mass is suggestive of the maladaptive features of LV remodeling [1]. To date, peak power-to-mass can be easily assessed during exercise or dobutamine stress echocardiography and resulted to be valuable to measure cardiac pumping capacity especially in patients with cardiomyopathies. In the following case report, the clinical significance of peak power-to-mass is described.

**Case report**

The clinical, biochemical and echocardiographic data of a 64-year-old man with idiopathic dilated cardiomyopathy hospitalized because of symptoms of congestive heart failure (HF) are reported. After stabilization, cardiac right-sided catheterization was carried out using a 7F MPA1 catheter (Cordis, Miami, FL). Mean pulmonary capillary wedge pressure was determined automatically by the monitoring system (Horizon 9000 WS, Mennen Medical Ltd, Israel). LV end-diastolic pressure was recorded using a 6F 145° pigtail catheter (Cordis, Miami, FL). Hemodynamic measurements were acquired before any injection of the contrast medium. LV end-systolic and end-diastolic meridional wall stresses were estimated using invasive measurements of LV pressures. The patient was submitted to a comprehensive transthoracic echocardiography using commercially available Acuson Sequoia C256 ultrasound instrument (Mountain View, CA) with 2nd harmonic imaging and a 3.5-MHz transducer. Two-dimensional and color-flow Doppler images were obtained in standard parasternal and apical views. The LV mass was determined by using the M-mode method according to the recommendations of the European Society of Echocardiography [2]. A symptom-limited graded bicycle semi-supine exercise was performed at an initial workload of 20 watts lasting for one minute; thereafter the workload was increased stepwise by 10 watts every minute. A 12-lead electrocardiogram and blood pressure determination were performed at baseline and every minute thereafter. At baseline and at peak exercise, Doppler-derived CO at LV outflow tract, heart rate (HR) and arterial systolic blood pressure (BP) and diastolic BP (by cuff sphygmomanometer) were measured. Mean BP was estimated as follows: diastolic BP + 1/3 (systolic BP – diastolic BP). Stroke volume (SV) was calculated as stroke distance × LV outflow tract area and CO as SV × HR as previously described [3]. LV power output was measured as the product of CO and mean BP. In meter-kilogram-second units, the conversion is 106 ml/m3 for SV, and 133 pa (pascal)/mmHg for pressure. Power-to-mass was calculated as LV power output per 100 gram of LV mass: 100 × LV power output divided by LV mass (watt/100 g).

The characteristics of the patient during the hospitalization are shown in Table 1 and Table 2. He was in NYHA class III and his LV ejection fraction (EF) was 21%. The electrocardiogram showed a sinus rhythm and a complete left branch bundle block. B-type natriuretic peptide (BNP) level was 498 pg/ml. The workload reached at the end of the stress test performed the day before discharge was 70 watts. At maximum exercise, mean BP was 107 mmHg, SV was 80 ml and HR was 145 beats per minute; entering these values in the above formulas, we get: BP = 133 × 103 = 13,699 pa, SV = 35 × 10⁻⁶ m³ and then we can calculate power as (13,699 × 35 × 145 × 10⁻⁶)/60 = 1.15 watt. LV mass was 349 g. A simplified formula to calculate power output-to-mass is: 0.222 × CO (l/min) × mean BP (mmHg)/LV mass (g) = (0.222 × 5 × 103)/349 = 0.33 watt/100 g. The patient underwent cardiac resynchronization therapy and was implanted with an automatic cardioverter defibrillator. Then, he was discharged with a therapy that included furosemide, angiotensin converting inhibitors, aldosterone antagonists, beta-blockers and digoxin. Six months later, he

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Table 1 Clinical and hemodynamic characteristics of the patient described in the case report.
was re-hospitalized for worsening HF. LV EF was not different with respect to the previous hospitalization and no relevant changes were apparent for most of the other echocardiographic and Doppler parameters. Pre-discharge BNP was 1072 pg/ml. The exercise stress test was repeated before discharge. Peak power output-to-mass at exercise stress test was 0.16 watt/100 g. Four months later the patient died due to refractory progressive pump failure.

**Discussion**

This case report describes a case of dilated cardiomyopathy accompanied by a severe deterioration of cardiac pumping capacity. The patient developed a progressive refractory heart failure, which was clearly evident at the time of the first exercise stress test, where peak cardiac power output showed only a blunted increase during the exercise. Neither optimized medical treatment nor cardiac resynchronization therapy were able to retard the progression of the disease.

This report shows the importance of measuring cardiac pumping capacity during exercise stress echocardiography for risk stratification of patients with advanced HF. It is interesting to note that resting LV EF did not change between the first and the second hospitalization. LV EF is the most frequently used index of LV performance, but it may not accurately reflect myocardial contractility and provides little prognostic information in patients with advanced HF. The interpretation of an EF less than 30% in a NYHA class I patient with mild LV dilation may be quite different from that an individual with class III symptoms associated with a severely dilated left ventricle. Both EF declines reflect chamber remodeling despite relative preserved stroke volume. However, in one instance, LV remodeling dominates this decline, with a near normal residual myocardium capable of providing adequate cardiac reserve. In the other, the entire LV myocardium is depressed with little reserve pumping capacity. These two situations may look similar when assessed by conventional measures, such as EF or wall motion score index, yet be very different by alternative methods, such as cardiac power output performed under stress.

Although cardiac power output is a well-established parameter of ventricular function that can be noninvasively acquired during exercise testing, it does not consider alterations in cardiac size and structure that may have an impact on the outcome of patients with HF. The novelty of peak power-to-mass (and peak mass-to-power) is that it encompasses LV mass, that is a major feature of the alterations in ventricular structure that occurs as a part of normal growth or due to a pathologic process, and similarly to EF, that is the ratio between the stroke volume and LV end-diastolic volume, provides integrate information on cardiac function and ventricular remodeling. The amount of LV mass may be equated to the energy stored in the myocardium according to the principle of equivalence of mass and energy as affirmed by Einstein’s theory of relativity. An example of this is physiological hypertrophy that is induced by exercise training, whereas the phenotypes that appear in chronically overloaded ventricles are pathological because they are accompanied by maladaptive changes [4,5]. The discrepancy between a severely depressed cardiac power output

<table>
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<th>Table 2</th>
<th>Clinical and echo-Doppler-derived hemodynamic characteristics of the patient described in the case report.</th>
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<tbody>
<tr>
<td><strong>Before</strong></td>
<td><strong>After</strong></td>
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<tr>
<td>Heart rate (bpm)</td>
<td>81</td>
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<tr>
<td>Mean blood pressure (mmHg)</td>
<td>89</td>
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<tr>
<td>End-diastolic volume (ml)</td>
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<tr>
<td>End-systolic volume (ml)</td>
<td>162</td>
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<tr>
<td>Stroke volume (ml)</td>
<td>43</td>
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<tr>
<td>Stroke volume index (ml/m²)</td>
<td>23</td>
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<tr>
<td>Ejection fraction (%)</td>
<td>21</td>
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<tr>
<td>Cardiac output (l/min)</td>
<td>3.5</td>
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<tr>
<td>Cardiac index (l/min/m²)</td>
<td>1.8</td>
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<tr>
<td>Power output (watt)</td>
<td>1.15</td>
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<td>Power output-to-mass (watt/100 g)</td>
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<tr>
<td>Workload (watt)</td>
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</tr>
<tr>
<td>Heart rate (bpm)</td>
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<tr>
<td>Mean blood pressure (mmHg)</td>
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<tr>
<td>End-diastolic volume (ml)</td>
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<tr>
<td>End-systolic volume (ml)</td>
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</tr>
<tr>
<td>Stroke volume (ml)</td>
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<tr>
<td>Stroke volume index (ml/m²)</td>
<td>18</td>
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<tr>
<td>Ejection fraction (%)</td>
<td>21</td>
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<tr>
<td>Cardiac output (l/min)</td>
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<tr>
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<tr>
<td>Power output (watt)</td>
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</tr>
<tr>
<td>Power output-to-mass (watt/100 g)</td>
<td>0.33</td>
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Heart Metab. (2011) 53:29–32
albeit an increased LV mass is likely to reveal the presence of maladaptive LV remodeling and this may reflect the inefficiency of the system to comply with the body’s metabolic needs. Adverse or maladaptive LV remodeling is a major factor that affects the outcome of patients with advanced HF due to LV systolic dysfunction [6].

The effects of intervening LV hypertrophy on recruitable cardiac power output are important to establish the significance of LV remodeling. When the recruitable power output per unit of LV mass decreases due to progressively decreasing ability of the myocardium to generate force to overcome the load, LV function rapidly deteriorates. Furthermore, the high LV end-diastolic volume and pressure promote subendocardial ischemia that aggravates LV dysfunction and neurohormonal activation, decreases exercise capacity and increases the risk of ventricular arrhythmias. Another factor that may contribute to maladaptive LV remodeling is the inadequate growth of myocardial microvasculature accompanying myocardial hypertrophy [7].

Peak power-to-mass provided incremental prognostic information over resting LV EF as well as other LV parameters recorded under stress. In our experience, the cutoff value for peak cardiac power-to-mass that accurately predicts all-cause mortality or HF hospitalization is 0.58 watt/100 g, but its impact on prognosis is clearer if the patient achieves a peak cardiac power-to-mass less than 1.0 watt/100 g after optimal tailored therapy or myocardial revascularization with interventional cardiac procedures or resynchronization therapy [8].

By coupling peak exercise LV power output and LV mass, peak power-to-mass is useful to identify patients with adverse LV remodeling during stress echocardiography and may provide additional prognostic information either in association with resting echocardiographic studies or cardiopulmonary exercise testing. LV hypertrophy is almost always present in patients with chronic systolic HF accompanied by LV dilatation and low EF, is typically eccentric, and is frequently associated with a normal or lower than normal LV wall thickness [8]. Despite that changes in LV geometry and wall thickness may be temporarily useful in maintaining myocardial pump function, they occurs at significant high cost and are commonly followed by the unfavorable consequences of dilation. LV enlargement increases the force that must be generated to exceed end-diastolic wall stress and to achieve a given level of cavity pressure.

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Impact of fatty acid oxidation on cardiac efficiency

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Abstract
Alterations in energy substrate preference by the heart can lead to significant changes in cardiac efficiency. Cardiac efficiency, which is the amount of work produced by the heart per energy (O2) consumed, is dependent not only on the efficiency of producing energy (ATP), but also on the efficiency of using energy to produce contractile work. Using fatty acids as a source of fuel has the potential to alter both of these pathways. The mitochondrial oxidation of fatty acids utilizes more O2 per molecule of ATP produced than most other sources of fuel. High rates of fatty acid oxidation also inhibit glucose oxidation in the heart, which can result in alterations in ionic homeostasis, such that more of the ATP produced in the heart is used for non-contractile purposes. Combined, the excessive use of fatty acids by the heart can result in a significant decrease in cardiac efficiency. In certain heart pathologies, such as during and following ischemia or in the failing heart, cardiac efficiency is also decreased. Alterations in the balance between fatty acid and carbohydrate use contribute to these alterations in cardiac efficiency. In this review we will focus on how alterations in cardiac energy metabolism alter cardiac efficiency, as well as on how alterations in energy metabolism that occur in heart failure and ischemia result in decreased cardiac efficiency.

Keywords: fatty acid β-oxidation; uncoupling proteins; mitochondrial thioesterase; glucose oxidation; glycolysis

Introduction
The heart has a very high energy demand, while essentially having no energy reserves. For example, consumption of the main energy currency of the heart, adenosine triphosphate (ATP), is so high that in the contracting heart the entire pool of ATP turns over approximately 6 to 8 times a minute [1]. In order to produce this large amount of ATP, the heart consumes a number of different energy substrates, including fatty acids (FAs), glucose, lactate, ketones, pyruvate, and amino acids. Most of the ATP produced requires the consumption of O2 for mitochondrial oxidative metabolism (Fig. 1) [1]. However, the efficiency of producing ATP can vary dramatically depending on the type of energy substrate used. An example of this is the utilization of FAs, which while being a plentiful source of energy, is also a particularly inefficient source of energy [1]. Different cardiac pathologies can also alter cardiac efficiency, both as a result of a decreased efficiency of producing ATP or alterations in the efficiency of using ATP to produce contractile work [1].
Cardiac efficiency is often expressed as a measure of the amount of cardiac work produced per amount of energy (O_2) consumed by the heart (cardiac work/MVO_2 ratio) [2]. It is not surprising that alterations in energy metabolism can alter cardiac efficiency, since cardiac work requires ATP and production of ATP via mitochondrial oxidative metabolism requires O_2. The type of substrate utilized in the production of ATP via oxidative metabolism affects cardiac efficiency. In addition, metabolic by-products produced during ATP production also have the potential to alter cardiac efficiency.

Energy metabolism and cardiac efficiency

Efficiency of ATP production
A major determinant of cardiac efficiency is the type of fuel being utilized for ATP production. The efficiency with which FAs and glucose are utilized to produce ATP differs [1]. The production of 31 ATP by one glucose molecule going through glycolysis and glucose oxidation (GO) requires 6 O_2. For the production of 105 ATP by palmitate oxidation, 23 O_2 are required. Therefore, more oxygen is used per ATP produced during fatty acid oxidation (FAO) compared to coupled GO, making FAs a
less efficient substrate than glucose for energy production. In addition, FAO inhibits GO [1]. When the FA supply to the heart rises, assuming O\(_2\) availability, the rate of FAO increases and GO decreases. This explains why under conditions in which circulating free FAs are elevated (such as heart failure [HF], ischemia, and type II diabetes) cardiac efficiency is decreased.

**Futile cycling**
In addition to being less efficient at ATP production per O\(_2\) consumed, FAs can also decrease cardiac efficiency through a number of other mechanisms. This is evident from the fact that there is a large discrepancy between the degree of inefficiency observed in ATP production/O\(_2\) consumed, and actual measurements of cardiac efficiency in the heart (cardiac work/MVO\(_2\)) [1]. At most, elevated FAO should decrease efficiency by 10 to 12% [1]. In reality, cardiac efficiency has been shown to be decreased by as much as 30% [3]. One possible mechanism to explain this is long-chain FA activation of Ca\(^{2+}\) channels in the sarcolemma [4]. A rise in cytosolic Ca\(^{2+}\) results in more energy being expended to keep cytosolic Ca\(^{2+}\) levels normal. Another mechanism that has been proposed involves FA inhibition of ATP removal from the mitochondria by inhibition of adenine nucleotide transferase [1]. Yet another potential mechanism involved in FA-induced inefficiency is the presence of futile cycles.

One such futile cycle involves the uncoupling proteins. The uncoupling proteins UCP2 and UCP3 are present in ventricular muscle [2]. These proteins are classically believed to work by dissipating the intermembrane proton gradient (Fig. 2). FAs are believed to work through UCP2 and UCP3 to mediate the uncoupling of oxidative phosphorylation [2,5]. Further, UCP2 and UCP3 expression correlate positively with circulating FA levels in the failing human heart [6]. UCP3 may also contribute to cardiac efficiency by transporting FA anions out of the mitochondrial matrix [2,7].

FAs in the cytoplasm can also cycle between their acyl-coenzyme A (CoA) moieties and intracellular triacylglycerol pools [1]. Two high energy phosphates are required to esterify FA to CoA, which can then either be directed to mitochondrial FA \(\beta\)-oxidation or complex lipid synthesis in the heart (such as triacylglycerols). FAs liberated from the triacylglycerol pool prior to subsequent \(\beta\)-oxidation create a futile cycle, potentially contributing to a decreased cardiac efficiency.

**Fatty acid inhibition of glucose oxidation**
Another pathway by which FAs may decrease cardiac efficiency is secondary to GO inhibition [1]. FAO products can inhibit GO (i.e., the Randle Cycle) (Fig. 1). This FA inhibition of GO is more dramatic than the effects of FAs on glycolysis [1]. This can result in a scenario where glycolysis is uncoupled from GO, which

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**Fig. 2** Mechanisms of uncoupling protein reduction of cardiac inefficiency. Uncoupling proteins dissipate the high proton concentration in the mitochondrial intermembrane space by transferring the hydrogen back into the mitochondrial matrix. UCP3 may also reduce cardiac efficiency by transferring fatty acid anions out of the mitochondrial matrix. CoA coenzyme A, UCP uncoupling protein
can result in elevated lactate and proton levels causing intracellular acidosis [2,8]. The co-transport of protons with pyruvate into the mitochondria is decreased because pyruvate is not taken into the mitochondria when glycolysis is uncoupled from GO. Although glycolysis produces ATP without consuming O$_2$, an increase in glycolysis in the presence of low GO rates can result in the accumulation of metabolic byproducts in the heart, that include both lactate and protons [1] (Fig. 1). The clearance of these protons can result in Na$^+$ and Ca$^{2+}$ accumulation in the heart (Fig. 1), requiring ATP to remove these ions [1]. This can lead to a decrease in cardiac efficiency, as ATP is redirected away from contractile function and towards ionic homeostasis [1].

**Altered energy metabolism in ischemic heart disease**

Prominent alterations in energy metabolism occur in the setting of myocardial ischemia and reperfusion that result in reduced cardiac efficiency (Fig. 3a) [1]. In the ischemic heart, energy metabolic rates are dependent upon the degree of ischemia. Because of the reduced oxygen availability both GO and FAO are reduced in the ischemic heart [2,9,10]. Interestingly, during mild ischemia FAO predominates as the source of oxidative metabolism in the heart [2,11,12]. This is likely explained by the exposure of ischemic hearts to high plasma FAs and to direct changes in the intracellular control of FAO, which combine to inhibit GO [11,11]. It is important to note that unlike the normal heart, exposure of the ischemic heart to FAs does not inhibit glycolysis, and that glycolytic rates are increased in the ischemic heart [11].

Increased glycolysis and impaired GO in the ischemic heart result in lactate and proton accumulation in the ischemic myocardium. Indeed, uncoupling of glycolysis from GO can largely explain the acidosis observed in the severely ischemic heart. As described above, accumulation of protons can lead to Na$^+$ and Ca$^{2+}$ overload in the heart, resulting in decreased cardiac efficiency as ATP is used to attempt to restore ionic homeostasis [1].

Lack of recovery of cardiac function and efficiency upon reperfusion is also explained by the alterations in metabolism during ischemia and reperfusion [2,13,14]. Return of intracellular pH to normal upon reperfusion can be deleterious. This is because, by modulating the Na$^+$/H$^+$ transporter and the Na$^+$/Ca$^{2+}$ exchanger, changes in intracellular ion concentrations occur that contribute to impaired cardiac function and efficiency.

**Fig. 3** Cardiac inefficiency in the ischemic heart and the failing heart. A. During ischemia and reperfusion fatty acid levels rise resulting in elevated fatty acid oxidation. This results in decreased glucose oxidation and elevated glycolysis. As a result of glycolysis and glucose oxidation being uncoupled, proton levels rise causing an overload of sodium and calcium. More energy is expended to maintain ionic homeostasis resulting in a decrease in cardiac efficiency. Through other mechanisms, fatty acids also reduce cardiac efficiency. B. In heart failure, a reduction in overall oxidative metabolism results in elevated uncoupled glycolysis resulting in decreased cardiac efficiency through similar mechanisms as described for ischemia.
The large trans-sarcolemmal proton gradient that forms increases the exchange of the Na\(^+\)/H\(^+\) transporter resulting in further elevation of intracellular Na\(^+\). In response, the Na\(^+\)/Ca\(^{2+}\) exchanger reverse mode is activated. The movement of calcium into the cell via the Na\(^+\)/Ca\(^{2+}\) exchanger results in an overload of intracellular calcium and thus more energy being expended to maintain calcium homeostasis.

As would be expected, cardiac efficiency and function is reduced in mildly ischemic hearts exposed to high levels of FAs [11]. If a heart is subjected to global ischemia, FA β oxidation decreases secondary to a lack of O\(_2\) availability for mitochondrial oxidative phosphorylation [15]. During reperfusion FAO recovers, resulting in GO remaining low [2,8,13,14]. Therefore, while glycolysis can remain high during reperfusion, it can still be uncoupled from GO resulting in elevated lactate and proton production [2,13]. Changes in FA supply, the type of oxidative metabolism, and increased glycolysis are responsible for the cardiac inefficiency observed during ischemia and reperfusion.

**Energy metabolism and cardiac efficiency in heart failure**

Alterations in energy substrate metabolism accompanying HF are extremely complex, in part due to the heterogeneous nature of HF [1]. In general, however, as HF progresses, what is observed is a decrease in overall mitochondrial oxidative capacity and an increase in glucose uptake and glycolysis [1]. FAO rates have been shown to be elevated, unchanged or decreased in HF (see [1] for review). The increase in glycolysis in HF is an adaptive response to compensate for decreased mitochondrial oxidative capacity. This increase in glycolysis with a low mitochondrial capacity to oxidize glucose can exacerbate lactate and proton production, in a manner similar to that seen in the ischemic heart (Fig. 3b). Since FAO competes with GO, FAs can further exacerbate this uncoupling. Support for this concept comes from a number of clinical studies in which FAO inhibition in HF improved both cardiac efficiency and function.

**Conclusions**

Alterations in cardiac energy metabolism can profoundly affect cardiac efficiency. Excessive use of FAs has been shown to be especially important, either by decreasing the efficiency of producing ATP, or by decreasing ATP availability for contractile function. Strategies aimed at optimizing cardiac energy metabolism have the ability to improve cardiac efficiency and function. For example, the Randle cycle is being targeted in order to increase GO and decrease FAO [1]. Therefore, understanding how energy metabolism affects cardiac efficiency is important for improving the treatment of heart disease.

**Acknowledgements** Gary D. Lopaschuk is a Scientist of the Alberta Heritage Foundation for Medical Research.

**References**

With a few exceptions [1], in the past two decades the benefit of statin therapy has been reproducible irrespective of the individual drug, population subset or prevention strategy (i.e., primary or secondary) used [2]. In addition to the established benefits, the decision to use statin therapy has recently been reinforced by the introduction of generic formulation drugs (i.e., simvastatin, lovastatin and pravastatin) in the market. Accordingly, the need for expanding the indications was met in the 2011 European Society of Cardiology (ESC) guidelines for the management of dyslipidemia [3]. These guidelines confirm that patients with a risk score of ≥10%, those with established cardiovascular disease (CVD), type II or I diabetes or chronic kidney disease have a class I indication, level of evidence (LoE) A to receive aggressive statin treatment in order to achieve low density lipoprotein cholesterol (LDL-C) levels of less than 70 mg/dl. In these guidelines, it is also recommended that a drug therapy with statins be considered in patients with a risk score of <1% who have LDL-C levels of ≥190 mg/dl (Class IIa, LoE A), and in those patients with a risk score from 1 to 5% who have LDL-C levels of 100–190 mg/dl (Class IIa recommendation, LoE A), or ≥190 mg/dl (Class I recommendation and LoE A).

However, recent data suggest that statin therapy is associated with an increased incidence of new-onset diabetes. The incident finding in large clinical trials [4–6] of increased new-onset diabetes was in fact confirmed recently in two well-conducted metanalysis [7,8]. The first one [7], including 91,140 patients, showed that, as compared to patients receiving placebo, patients receiving statin therapy had a 9% increase in relative risk for developing diabetes (odds ratio [OR] 1.09, 95% confidence interval [CI] 1.02–1.17). More specifically, 1 out of 255 patients would develop diabetes during a 4-year period of statin therapy. The second metanalysis [8] assessed whether, among those patients receiving statins, an intensive-dose treatment regimen would further increase the incidence of new-onset diabetes. Data from five clinical trials including 32,752 patients showed that, as compared to moderate-dose therapy, an intensive treatment strategy was associated with a further 12% increase in relative risk for developing new-onset diabetes (OR 1.12, 95% CI 1.04–1.22). Therefore, during a year of statin treatment, one out of 498 patients would develop new-onset diabetes if in the intensive treatment arm. However, on the other hand, 1 out of 155 of the same patient population would experience less cardiovascular events because of the intensive treatment. Although no plausible biological effects can yet be identified, the dose-dependence relationship observed in the
latter study further confirmed that statin therapy is associated with an increased risk for new-onset diabetes.

The status quo of statin therapy can therefore be summarized as follows: on one hand, as supported also by the availability of generic formulations and establishment of new guidelines, there is a strong willingness to extend treatment indications; however, on the other hand, there is also an increasing concern regarding the incidence of new-onset diabetes, particularly for the low risk patient population.

Given such statements, how is the clinician supposed to weight the benefits and risks of statin treatment in the individual patient?

Following the recent meta-analysis, another, very elegant study, that might actually help answer this question was published [9]. This study used an established computer simulation model to project cost-effectiveness of statin therapy in an era where a more aggressive statin treatment is being sought, low cost generic formulations are available and side effects such as new-onset diabetes are better defined. The authors found that lowering LDL-C thresholds to <130 mg/dl for patients with no risk factors and to <100 mg/dl for patients with one risk factor and treating all moderate and moderately high risk patients regardless of LDL-C levels would provide additional health benefits. Most importantly, these benefits were not negatively affected by the inclusion in the analysis of statin-associated diabetes or other severe hypothetical side effects.

In conclusion, as outlined by the recently published ESC guidelines [3], broadening of the indications to statin therapy appears reasonable. With regards to the individual patient, one should keep in mind that the odds of developing diabetes from statin therapy are lower than those of reducing cardiovascular events. Therefore, if the former occurs, statin therapy is theoretically supposed to provide a payback by reducing the risk for cardiovascular events, one of the major complications of diabetes.

References

AMP-activated protein kinase (AMPK)
AMPK is a key kinase that controls many cellular processes, particularly pathways involved in cellular energy status. AMPK is activated during metabolic stress, where it then can either activate energy-producing pathways or inhibit energy-consuming pathways. For these reasons, it has been termed a “fuel gauge” of the cell.

mTOR pathway
Mammalian target of rapamycin (mTOR) is a kinase that is a member of the phosphatidylinositol kinase family. The mTOR pathway functions as a key signaling pathway involved in the control of cell growth and proliferation. mTOR is activated in response to a number of upstream signaling molecules, including insulin and growth factors such as IGF-1 and IGF-2. The term mTOR arose since rapamycin was originally shown to inhibit the mTOR pathway.

PGC-1α
Peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) is a transcription co-activator that plays a key role in the regulation of cellular energy metabolism. Activation of PGC-1α increases mitochondrial biogenesis. In muscle PGC-1α activation results in a muscle that is more oxidative and less glycolytic.

PPARα
Peroxisome proliferator-activated receptor α (PPARα) is a nuclear receptor involved in the transcriptional regulation of proteins. This includes the transcription of key proteins involved in the control of fatty acid oxidation.

Proteosomes
Proteosomes are large protein complexes inside cells that function to degrade damaged proteins. Proteases in the proteasome degrade these proteins into short amino acid peptides.

SERCA2
Sarcoplasmic/endoplasmic reticulum calcium ATPase 2 (SERCA2) is the enzyme primarily responsible for the transport of calcium into intracellular sarcoplasmic reticulum (SR) and endoplasmic reticulum (ER). SR is an intracellular organelle in heart and skeletal muscle that stores calcium. During excitation-contraction coupling, release of calcium for the SR is the major source of calcium that initiates contraction. SERCA2 initiates relaxation of muscle by re-sequestering the calcium back up into the SR.

Ubiquitination
Ubiquitination is a process in cells in which proteins are “tagged” with a small protein called ubiquitin. This can lead to further ubiquitination of the protein, which then targets the protein for degradation by proteasomes.

Ubiquitin ligases
Ubiquitin ligases are enzymes in cells that catalyze the ubiquitination reaction. These ubiquitinated proteins are then targeted for degradation by proteasomes. As a result, ubiquitine ligases are key enzymes involved in cellular protein degradation.