Metabolic remodelling of the failing heart: beneficial or detrimental?

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1. Introduction

Cardiac diseases are a major cause of morbidity and mortality in the Western World. Hypertension and myocardial infarction (MI), in particular, predispose to the development of heart failure, a debilitating syndrome with poor prognosis. Changes in cardiac substrate utilization and energy metabolism, including a decline in high-energy-phosphate content, mitochondrial dysfunction, and an increased dependence on glucose as substrate, are hallmarks of the hypertrophied and failing heart.1,2 These findings have led to the concept that, following chronic pressure and volume overload and after regional MI, the heart gradually develops a diminished capacity to generate adenosine triphosphate (ATP) required for the heart to maintain cardiac output at an adequate level. These metabolic changes are thought to contribute to the development of cardiac failure.3-5

Theoretically, limitations in oxygen delivery or defects in mitochondrial substrate oxidation may be responsible for inadequate ATP generation. The functional significance of the shift in substrate preference from fatty acids (FAs) towards glucose is still enigmatic. Even more so, it is still being debated whether this metabolic shift should be considered beneficial or detrimental. Despite all research efforts, it is still unclear in which phase from compensated hypertrophy, via early mechanical dysfunction to end-stage congestive heart failure, alterations in cardiac metabolism become apparent. This issue is crucial for the understanding of a possible causative role of metabolic derangements in the development of cardiac failure.

In this review, we will briefly discuss the fundamentals of cardiac substrate utilization and techniques used to assess metabolic remodelling. Strictly speaking, the term metabolic remodelling refers to the metabolic changes that are caused by genomic alterations.6 However, in this review, we use the frequently used broader definition which encompasses all chronic metabolic alterations, whether they are transcriptional or post-transcriptional in nature. Subsequently, we will discuss current findings and ideas on the significance of metabolic remodelling in cardiac hypertrophy and failure.

2. Cardiac substrate metabolism

2.1 Carbohydrates and lipids

Under resting conditions, the oxidation of FAs covers more than 70% of the cardiac energy need. The remainder is accounted for by the oxidation of carbohydrates, principally glucose.2,7 In the healthy heart, this fuel selection is primarily governed by plasma substrates and hormone (insulin, catecholamines) levels, rather than an intrinsically determined substrate preference of the myocardium. When the circulating concentrations of alternative substrates such as ketone...
bodies or lactate rise, for instance, as a result of fasting or strenuous exercise, the cardiac muscle switches to these alternative substrates. As discussed later, during hypertrophy and failure intrinsic changes within the myocardium appear to affect this so-called metabolic flexibility.

FAs are delivered to the heart as non-esterified FAs bound to plasma albumin and as esterified FAs containing lipoproteins. The significance of lipoprotein-derived FAs for the cardiac muscle has long been overlooked. Recent studies, however, showed that triglycerides (TGs) are a major source of FAs for the murine heart.8,9 If this also holds for the human heart, then the reported alterations in FA utilization, as measured clinically after infusion of FA analogues, may underestimate the true change in FA utilization during cardiac hypertrophy and failure.

2.2 Measuring cardiac metabolism: pros and cons of different techniques

The answer to the question whether metabolic alterations in the hypertrophied and failing heart are beneficial or detrimental is hampered by the fact that the interpretation of experimental and clinical data strongly depends on the methodology applied to assess cardiac metabolic parameters and use of different experimental models and species.

The classical way to measure cardiac substrate utilization is the assessment of arterio-venous differences of oxygen, glucose, and FAs, along with coronary blood flow, in larger animal species including human. Clinical application of advanced imaging techniques, like positron emission tomography (PET) and single-photon emission tomography (SPECT), has allowed the measurement of FA and glucose utilization non-invasively by following the fate of tracers via PET (11C-glucose, 18F-fluorodeoxy-glucose [18F-FDG], and 11C-palmitate) or via SPECT (123I-iodophenylpentadecanoic acid or 123I-BMIPP). In addition, 11C-acetate PET is frequently applied. As acetate is readily taken up and oxidized via the tricarboxylic acid cycle, 11C-acetate serves as a measure of oxidative metabolism and, indirectly, of myocardial oxygen consumption (MVO2). In contrast, tracers like 18F-FDG and 123I-BMIPP actually measure the uptake and initial conversion step, rather than the oxidation of glucose and FAs. These restrictions should be kept in mind when interpreting PET and SPECT data.

For smaller animal species (rats, mice, etc.), ex vivo perfusion of the hearts with 3H and 14C tracers has been frequently applied to determine the fate of glucose and FAs utilized by the heart.10-12 This allows the simultaneous measurement of the rates of glycolysis and glucose and FA oxidation in control, hypertrophic, or failing hearts under identical conditions with respect to loading (fixed pre- and after-load, fixed heart rate) and substrate supply (FAs, glucose, and insulin concentrations of the perfusion buffer). At the same time, the outcome is highly dependent on the perfusate concentrations chosen.12 Moreover, as substrate use and selection also depend on workload, intrinsic differences in cardiac function between control hearts and hypertrophic/failing hearts complicate the interpretation of alterations in substrate preference. One remarkable feature of ex vivo perfused mouse and rat hearts is that glycolysis and glucose oxidation appear to be loosely coupled, the rate of glycolysis being about five times higher than the rate of glucose oxidation.10,11 As the majority of studies indicate that the healthy as well as failing heart of larger mammals (including human) consume, rather than produce, lactate,13,14 the net lactate production by ex vivo perfused hearts most likely reflects the limited oxygen-carrying capacity of the crystalloid perfusion buffer.

Next to monitoring cardiac substrate utilization in vivo or ex vivo, one can also determine mitochondrial function in skinned muscle bundles or mitochondria isolated from healthy and diseased heart.15,16 Furthermore, the activity of individual enzymes can be measured in tissue homogenates. When assessed under optimal conditions, the activity equals Vmax and is a good approximation of the amount of active enzyme. Alternatively, the flux through an entire metabolic pathway can be determined under optimal conditions [co-factors, ATP/adenosine diphosphate (ADP)]. Degens et al.17 and Cheng et al.18 have applied this approach to monitor changes in FA oxidation and glycolytic capacity in murine and rat cardiac homogenates. However, given the nature of the assay one cannot assess the potential significance of alterations in membrane transport, the impact of the loss of co-factors like carnitine, and the presence of competing substrates. So, this assay is useful when one assumes that changes in the expression of metabolic genes are primarily responsible for the observed changes in cardiac metabolism.

Finally, the tissue content of enzymes can be analysed at the protein or mRNA level by western blotting or quantitative polymerase chain reaction. Notably, in the case of transport proteins (GLUT1, GLUT4, CD36) it should be realized that they also exist in an inactive intracellular pool and are transported to the sarcolemma in response to a variety of stimuli.19 The determination of changes in cardiac mRNA levels is the closest estimate of alterations in the transcription of metabolic genes. However, the extent to which such alterations ultimately translate into changes in cardiac energy metabolism is subject of continuous debate.

The differences in assay techniques, and their respective pros and cons, may explain part of the controversies in literature as to whether cardiac hypertrophy and failure are associated with a shift in substrate preference away from FAs. Furthermore, it is of note that per unit of mass the murine heart requires four times more energy than the human heart. The latter is also reflected by a substantially higher fractional volume of mitochondria in the murine myocardium.20 This raises the question whether the murine heart might be even more dependent on FAs than the human heart and whether cardiac energy reserve, i.e. the capacity of the myocardium to generate ATP in excess of its normal rate of utilization, will differ between mice and human.

3. Metabolic remodelling

One of the prevailing concepts is that the failing heart is an energy-compromised organ. Theoretically this could be due to a diminished ATP-generating capacity or an increased energy demand, related to the changes in wall stress, or a combination of both. As most of ATP is generated by mitochondrial substrate oxidation (>90%), hypertrophy and failure-related changes in mitochondrial function have been the subject of intense research. The biological
significance of alterations in mitochondrial substrate oxidation and high-energy phosphate (HEP) metabolism are extensively reviewed elsewhere and will be addressed very briefly in this review.

3.1 Mitochondrial ATP generation

The maximal oxygen consumption rate of isolated mitochondria was found to be reduced in experimental models of cardiac failure\textsuperscript{15,21–23} and in explanted hearts from patients with cardiomyopathy.\textsuperscript{16} Consistent with this, reductions in tissue content and activity of complexes I–IV of the mitochondrial respiratory chain have been reported in animal models of cardiac failure and in end-stage human failing hearts.\textsuperscript{24–27} Notably, in mitochondria from volume-overloaded\textsuperscript{28} and pressure-overloaded hearts that did not display signs of failure\textsuperscript{29,30} respiration parameters remained unchanged. Similarly, after regional MI in rats, oxygen consumption during state 3 and state 4 respiration were preserved in mitochondria isolated from the surviving myocardium.\textsuperscript{31} The only difference was a decline in amount of mitochondrially generated ATP over oxygen consumed (ATP/O ratio), indicative of mitochondrial uncoupling, in a subgroup of rats showing overt failure after MI. Apparently, abnormalities in mitochondrial function represent a late, rather than early, phenomenon in the development of heart failure. This contention is supported by elegant studies of the group of Bache\textsuperscript{32,33} who determined the HEp content, and MVO\textsubscript{2} in swine with either compensated uncoupling by 2,4-dinitrophenol (DNP) on cardiac function, the effect of catecholamine stimulation and of mitochondrial oxidative capacity under these conditions. In contrast, in swine with congestive heart failure, DNP failed to increase MVO\textsubscript{2} and reduced the PCr/ATP ratio, indicating that the reserve for converting chemical energy into mechanical work had become exhausted in the failing hearts.

As to the cause of the mitochondrial dysfunction, several hypotheses have been put forward. The observed decline in the expression level of crucial factors involved in mitochondrial biogenesis (Figure 1), such as PGC-1\textsubscript{α} (PPARγ-coactivator-1α), nuclear respiratory factors (NRF1/2), and mitochondrial transcription factor A (Tfam), has been held responsible for the decrease in mitochondrial capacity in the failing heart.\textsuperscript{15,27} It should be noted, however, that not all studies were able to detect a decline in regulatory factors, such as PGC-1\textsubscript{α}, in the failing heart.\textsuperscript{34} Also the increased generation of reactive oxygen species (ROS) that is seen in failing hearts is regarded as a possible cause of mitochondrial dysfunction. ROS will inflict mitochondrial damage by damaging mitochondrial DNA (mtDNA) and proteins, thereby compromising mitochondrial function.\textsuperscript{35} It was postulated that enhanced accumulation of mtDNA mutations over time also contributes to the progression of heart failure. Indeed, increased frequencies of mtDNA mutations in failing hearts were reported by several groups.\textsuperscript{35,36} Nitric Oxide (NO) synthases have also been implicated as modulators of mitochondrial function. NO is known to compete with oxygen for binding to cytochrome-c oxidase (complex IV).\textsuperscript{37} Perhaps even more harmful are ROS produced via uncoupled NO synthases. Recently, it was shown that oral administration of the obligate cofactor tetrahydrobiopterin (BH4) restored endothelial NOS (eNOS) coupling in mice subjected to trans-aortic constriction. This was associated with marked improvement of cardiac geometry and function.\textsuperscript{38}

Several studies point to a change in mitochondrial coupling, as reflected by the reduction in ATP/O ratio.\textsuperscript{31} It has been suggested that mitochondrial uncoupling proteins (UCPs), which dissipate the mitochondrial electrochemical proton gradient that is normally used to regenerate ATP,\textsuperscript{39} are largely responsible for this phenomenon. Consistent with this, enhanced UCP2 or UCP3 expression has been observed in animal models of heart failure and in patients with end-stage heart failure.\textsuperscript{31,40,41} However, several other studies found no evidence of changes in UCP expression, or even reported decreased UCP expression,\textsuperscript{34,42,43} thereby questioning the importance of UCPs as a causative factor for mitochondrial dysfunction. Very recently, evidence was provided that an improper organization, rather than a diminished expression or activity of the individual electron transport chain complexes, may be responsible for the reduced mitochondrial respiration rate observed in the failing heart.\textsuperscript{23}

3.2 Cardiac HEP content

Many clinical and preclinical studies have shown that HEP content is reduced during compensated hypertrophy and cardiac failure, as reflected by the decline in cardiac PCr content, whether or not in combination with a decline in ATP level.\textsuperscript{14,44–46} As a consequence, the ratio of PCr/ATP, an index of energy reserve, is reduced. The PCr/ATP ratio was found to correlate well with the severity of cardiac

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\caption{Hypothetical role of genomic alterations as causative factors in the chain of events leading from compensated hypertrophy to cardiac failure. Reductions in PGC1\textsubscript{α} and Nrf1/2 (left side) impair mitochondrial replication and the expression of genes constituting respiratory chain complexes. Concurrently, the expression/activity of PPARs (right side) is reduced leading to diminished expression of FA oxidation (FAO) genes. For details of the proposed mechanisms, existing controversies, and explanation of abbreviations, see text.}
\end{figure}
failure in patients and thus may be of prognostic value.\textsuperscript{64} Comparable observations were obtained in hypertrophic murine hearts, in which the drop in PCR/ATP ratio correlated with the end-systolic volume.\textsuperscript{47} The decline in PCR/ATP ratio supports the idea that the capacity to convert chemical energy into mechanical work is compromised in the failing heart.

### 3.3 Shift in cardiac substrate utilization during hypertrophy and failure

Various clinical PET or SPECT studies demonstrated a decline in FA utilization in different forms of left ventricular hypertrophic and dilated cardiomyopathy.\textsuperscript{48–51} Others, however, failed to observe abnormalities in FA uptake and utilization,\textsuperscript{52} or even reported an increase in FA uptake in failing human hearts.\textsuperscript{53–55} Also with respect to glucose uptake, the outcome of clinical studies is far from consistent. Both decreased,\textsuperscript{52,53,55} unchanged,\textsuperscript{49,56} and increased\textsuperscript{14,50,57} cardiac deposition of \textsuperscript{18}F-FDG and glucose oxidation has been reported in hypertrophied and failing hearts. This stirred much debate as to the role of patient selection as a confounding factor. Indeed, cardiac failure is a syndrome with varying aetiology. In addition, the effect of co-morbidity has to be taken into account. Cardiac failure is primarily a pathological syndrome of the elderly and is quite frequently associated with obesity, insulin resistance, or established type-2 diabetes. The group of Knuuti\textsuperscript{58} was one of the first to investigate the role of co-morbidity more systematically. Although patient numbers were quite small, the investigators could show that, relative to healthy controls, in patients with idiopathic dilated cardiomyopathy (IDCM) the reduction in myocardial FA uptake \textsuperscript{(13}C-palmitate) was significantly greater in ‘uncomplicated’ IDCM patients than in IDCM patients with insulin resistance. It is far from clear that whether these differences can solely be explained by alterations in plasma FA and glucose levels (mass effects) or that intrinsic changes in cardiac metabolism are involved.

Pre-clinical studies both using dogs with pacing-induced heart failure\textsuperscript{13,59,60} and isolated hearts from rats subjected to pressure overload\textsuperscript{10,61} or volume overload\textsuperscript{28,62} showed that myocardial FA oxidation was depressed, whereas glucose uptake was increased. As indicated earlier, it is important to note that in ex vivoperfused hearts, only a small part of glucose taken up was oxidized which, as discussed earlier, could be an anomaly of the red-blood-cell-deficient buffer-perfused heart.\textsuperscript{10} More recently,\textsuperscript{13}C NMR spectroscopy was applied to study changes in cardiac metabolism after aortic constriction in rats.\textsuperscript{63} Analysis of \textsuperscript{13}C NMR spectra of control and mildly hypertrophic, compensated hearts showed that in the hypertrophic myocardium, FA oxidation was suppressed, whereas lactate and glucose oxidation were unaffected and pyruvate oxidation was increased. Of note in this study is the exceptionally high rate of lactate oxidation (almost 10 times higher than that of palmitate) in both control and hypertrophic hearts. The increased pyruvate oxidation suggests that mitochondrial function was not impaired, but well preserved and, hence, that the reduction in FA oxidation is at the level of \(\beta\)-oxidation or more upstream (cellular uptake or activation of FA). This led the authors to conclude that FA metabolism is already compromised in the early stages of hypertrophy.

In contrast, in a comparable rat model of mild, compensated hypertrophy induced by supraprenal aortic banding, we were unable to detect a significant decline in FA oxidation capacity, as measured by the maximal flux rate in cardiac homogenates, whereas glycolytic capacity was increased when hypertrophy was more pronounced.\textsuperscript{17} In another study in which the ascending aorta of rats was banded to induce hypertrophy, in the \textit{ex vivo}perfused hypertrophic heart only glucose oxidation was increased to a significant extent (when expressed as \% of MVO\textsubscript{2}).\textsuperscript{51} Pellieux \textit{et al.}\textsuperscript{64} used transgenic mice with cardiac-specific overexpression of angiotensinogen as a model of cardiac hypertrophy which progresses to congestive heart failure in a subgroup of mice. FA oxidation rate was compromised in the subgroup of mice with congestive heart failure, but not in those with compensated hypertrophy. Also in larger animal species such as in the dog, it was noted that in microembolization-induced compensated heart failure neither FA oxidation nor glucose oxidation was affected, which strongly suggesting that changes in substrate metabolism are confined to more severe, congestive heart failure.\textsuperscript{65}

In both rat and mouse models of regional MI, time-dependent changes in cardiac metabolism in the remote, surviving myocardium have been studied.\textsuperscript{66,67} Changes in FA oxidation rate in the surviving myocardium were not observed in animals with healed infarcts (2–3 months post-MI) irrespective of the method chosen, i.e. via the assessment of maximal FA oxidation capacity in tissue homogenates,\textsuperscript{67} or by measuring FA oxidation rate in \textit{ex vivo}perfused hearts.\textsuperscript{66} In the latter study, however, a marked increase in glucose oxidation was observed.

Collectively, these observations indicate that the failing heart is more dependent on glucose as an energy-providing substrate. It is well conceivable that, at least in human, this metabolic change can be partly obscured by the high incidence of co-morbidity, type 2 diabetes, in particular, which in itself is associated with a reverse shift (i.e. more FAs, less glucose uptake).\textsuperscript{58} With respect to the pre-stages of congestive heart failure, i.e. when cardiac hypertrophy is still compensatory in nature or when clinical signs of congestion are still absent, the literature is divided and a clear conclusion cannot be drawn. Nonetheless, an unambiguous answer is needed, as it is one of the cornerstones required to solve the issue as to whether changes in cardiac metabolism are causally involved in the transition from compensated hypertrophy to overt failure, or whether metabolic remodelling is just an epiphenomenon of end-stage failure.

### 3.4 Mechanisms underlying the shift in substrate preference

Various mechanisms have been proposed to explain the switch in substrate preference from FAs to glucose often observed in the hypertrophied and failing heart.\textsuperscript{2,3} Impairment of FA oxidation may be secondary to mitochondrial derangements. Alternative explanations include changes in the activity of pyruvate dehydrogenase (PDH) and carnitine palmitoyltransferase-1 (CPT-1), being responsible for the mitochondrial entry of glucose-derived acetyl units and of FAs, respectively. However, studies failed to detect changes in PDH activity in the hypertrophic myocardium\textsuperscript{68} or reported a decrease in PDH activity, despite increased glucose oxidation rate.\textsuperscript{60}
CPT-1 is known to be inhibited by malonyl-CoA, which is formed by acetyl-CoA carboxylase (ACC). Phosphorylation of ACC by AMP-kinase (AMPK) inhibits its activity and thus indirectly activates FA oxidation. Currently, it is unclear whether changes in AMPK activity and tissue malonyl-CoA levels can be held responsible for CPT-1 inhibition as different studies reported increased, unchanged, and decreased AMPK activity in models of hypertrophy and failure. Similarly, cardiac malonyl-CoA levels were found to be increased, unchanged, or diminished in failing hearts.65

An alternative, more appealing concept is that the decline in FA oxidation in the hypertrophic and failing myocardium is the direct consequence of a reduction in the expression of the FA-handling genes concerned (Figure 1).6,73 As the foetal heart is also highly dependent on carbohydrates for energy conversion, the metabolic remodelling has also been considered part of the recapitulation of the foetal gene programme, a characteristic of cardiac hypertrophy. Indeed, the expression of a variety of genes involved in FA uptake and metabolism was shown to be diminished in experimental models of cardiac hypertrophy and failure.59,63,64,74–76 The decreased expression of genes involved in FA transport and metabolism was believed to be due to a decline in the activity of the nuclear hormone receptor PPARα, the transcription factor that plays a crucial role in the transcriptional regulation of genes involved in FA metabolism (Figure 1).1,77 Again, the changes observed in cardiomyopathic patients lack consistency as both diminished78 and increased79 cardiac expression of PPARα and FA oxidation genes were reported.

Several studies on hypertrophic and failing hearts, however, observed discrepancies between PPARα expression, the expression of FA oxidation enzymes, and FA oxidation rates.43 One puzzling observation is that for several FA oxidation enzymes the decline in mRNA is already seen during compensated hypertrophy, but that only in advanced stages of heart failure this was accompanied by a decline in their corresponding protein content.64,74 The time window is much too large to explain this discrepancy in terms of protein half-life, suggesting that post-transcriptional mechanisms contribute somehow. Although post-transcriptional and post-translational mechanisms certainly cannot be ignored, it is noteworthy that in these studies medium-chain acyl-CoA dehydrogenase (MCAD) is frequently used as a typical FA oxidation gene.43,66

3.5 Cause or consequence?
The question as to whether altered substrate metabolism is a cause or consequence of cardiac failure is still unsolved. Theoretically, the decline in cardiac function could be caused (in part) by a diminished substrate oxidation. Alternatively, the decreased mechanical performance of the heart could be caused by factors unrelated to cardiac metabolism, in which case the decline in substrate (FAs) oxidation merely follows the decrease in cardiac function.

Evidence in favour of a causal relationship between defects in cardiac metabolism and impaired mechanical work is primarily derived from clinical studies with patients with inherited deficiencies in enzymes crucial to cardiac metabolism, the so-called ‘inborn errors of metabolism’84 and is supported by studies with genetically modified mice developing cardiomyopathy subsequent to the deletion of FA oxidation enzymes or factors needed for proper mitochondrial function.85,86 Such genetic modifications generally lead to overt cardiomyopathy. Can this, however, be taken as a proof for a causal relationship between metabolic remodelling and the progression of acquired cardiac disease? It only tells us that inactivation of a critical enzyme leads to energy starvation and hence cardiac dysfunction. Notably, the changes in mitochondrial density and structure and the expression of mitochondrial genes were shown to be clearly different in patients with inherited mitochondrial cardiomyopathies and in patients with dilated cardiomyopathy.87 However, studies showing a positive effect of metabolic interventions on mechanical function of the failing heart88–90 seem to support the notion that in this setting impaired energy metabolism might be one of the causes of the decline in cardiac hemodynamic performance.

3.6 Beneficial or detrimental?
The collective findings from both clinical and experimental studies generally indicate that the failing heart is characterized by a diminished capacity to convert chemical energy into mechanical work due to mitochondrial derangements (both in quantitative and qualitative terms). Along this line of thinking, the shift in substrate preference away from FAs can be considered a switch towards a more anaerobic substrate. Consistent with this idea is that in genetically modified mice with primary defects in mitochondrial function, the subsequent changes in gene expressions also are reminiscent of an increase in glucose utilization at the expense of FAs.86

At this point, some quantitative aspects deserve consideration. In terms of oxygen cost, the oxidation of glucose is more efficient (ATP/O~3.1) than that of FAs (ATP/O~2.8). As such, switching from FAs to glucose oxidation is approximately 11% more economical in terms of cardiac oxygen cost. However, in absolute terms the oxidation of one molecule of FAs, with palmitate as example, yields far more ATP (~129) than glucose (~36). Hence, a relatively modest reduction of cardiac FA oxidation would require a very pronounced increase in glucose oxidation in order to maintain ATP synthesis rate constant. Although most studies point to a rise in myocardial glucose uptake and oxidation in failing hearts, in terms of ATP yield the decrease of cardiac FA oxidation is not compensated for by the increase in glucose oxidation.13,14 Accordingly, the failing heart is an energy-compromised organ suffering from a progressive ‘burnout syndrome’ precipitating further functional deterioration.

Although insufficient in terms of ATP yield, the shift from FA towards glucose utilization may still be advantageous for
the challenged heart. In this respect, it is important to realize that mitochondrial ATP is utilized for cardiac contraction mainly, whereas glycolytically derived ATP is used for other purposes primarily. Indeed, the ATP produced by glycolysis is used preferentially by ion pumps, including the Na⁺/K⁺-ATPase and the sarcoplasmic reticulum Ca²⁺-ATPase SERCA2. Intriguingly, glycolytic ATP was reported to be important in the regulation the Ca²⁺/calmodulin-dependent kinase II (CaMKII), suggesting that depending on their subcellular localization the activity of phosphokinases is controlled by glycolytic ATP. There is also evidence that ATP-sensitive K⁺-channels utilize glycolytically derived ATP preferentially (see Dhar-Chowdhury et al. for review). As K<sub>ATP</sub> channels also act as sensors of the energy status (ATP/ADP) and are important in cell survival and protection, it is conceivable that the increased preference for glucose and enhanced rate of glycolysis are part of cell-survival pathways activated during hypertrophy and failure.

Originally, the changes in substrate metabolism in failing hearts were considered as perturbations of normal cardiac metabolism. Hence, it was reasoned that normalization of substrate preference should be the therapeutic goal. One way to accomplish this is by stimulation of cardiac FA oxidation by administration of synthetic PPAR ligands. Results so far, however, are not unequivocal as both beneficial, neutral, and deleterious effects on cardiac function have been reported in different models of cardiac hypertrophy and failure.

To date sufficient evidence has been gathered to attest that during cardiac failure, stimulation of glucose utilization, either directly or indirectly via (further) inhibition of FA oxidation, has salutary effects. Cardiac-specific overexpression of the glucose transporter GLUT1 in mice attenuated the development of cardiac failure after aortic constriction. Moreover, inhibition of FA oxidation at the level of mitochondrial FA transport (the CPT-1 inhibitors etomoxir and perhexiline), or at the level of mitochondrial β-oxidation (the 3-keto-acyl-CoA thiolase inhibitors ranolazine and trimetazidine) exerts salutary effects.

Some of these drugs were tested in the clinical setting recently, the results being encouraging. It should be noted, however, that the beneficial effects reported in these clinical trials may actually be due to mechanisms not directly related to the inhibition of their target enzymes in the failing heart. Blocking of cardiac FA metabolism at the level of mitochondria induces accumulation of upstream FA intermediates that may act as ligands for PPARs. This would give rise to an ambivalent condition, whereby FA oxidation is simultaneously stimulated via genomic mechanisms and blocked pharmacologically. As FA transport proteins are also regulated by PPARs, this condition may aggravate the imbalance between FA uptake and oxidation. Conversely, given their pleiotropic effects, activation of PPARs may also activate anti-inflammatory pathways that may be beneficial for the challenged heart. Furthermore, studies with isolated cardiomyocytes and hypertrophied rat hearts were unable to demonstrate effects of trimetazidine on β-oxidation and on FA and glucose oxidation. Notwithstanding these gaps in our current knowledge, it seems that the shift towards glucose oxidation in the hypertrophied and failing heart is beneficial, rather than detrimental.

4. Conclusion

The majority of studies indicate that mitochondrial dysfunction and the shift in substrate utilization away from FAs are late phenomena that are seen predominantly in failing hearts. Nonetheless, it is too simple to state therefore that metabolic remodelling merely represents an epiphenomenon that is of limited importance. Indeed, a number of experimental and patient studies suggest that metabolic interventions may improve cardiac function, even when signs of heart failure are already evident. Consequently, interventions in cardiac metabolism still are an attractive option for adjuvant therapy, perhaps also in earlier stages of the development of cardiac failure.

Although definitive proof is still awaited for, recent findings suggest that a further stimulation of cardiac glucose metabolism may be more beneficial than promoting FA metabolism to restore the physiological balance between FA and glucose utilization. Nonetheless, a number of issues still warrant further investigation. The pharmacological inhibition of mitochondrial FA oxidation may further enhance the accumulation of TGs and potentially toxic FA intermediates, resulting in lipotoxicity. Furthermore, metabolic interventions lack specificity and as such will affect most organs and hence total body substrate utilization and energy conversion. Consequently, it remains to be established if metabolic interventions are tolerated by the heart as well as other organs in the long-term.

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