Review

Metabolic remodelling of the failing heart: the cardiac burn-out syndrome?

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Abstract

It has been postulated that the failing heart suffers from chronic energy starvation, and that derangements in cardiac energy conversion are accessory to the progressive nature of this disease. The molecular mechanisms driving this ‘metabolic remodelling’ process and their significance for the development of cardiac failure are still open to discussion. Next to changes in mitochondrial function, the hypertrophied heart is characterized by a marked shift in substrate preference away from fatty acids towards glucose. It has been argued that the decline in fatty acid oxidation is not fully compensated for by a rise in glucose oxidation, thereby imposing an additional burden on overall ATP generating capacity. Several lines of evidence suggest that these metabolic adaptations are brought about, at least in part, by alterations in the rate of transcription of genes encoding for proteins involved in substrate transport and metabolism. Here, the principal metabolic changes are reviewed and the various molecular mechanisms that are likely to play a role are discussed. In addition, the potential significance of these changes for the aetiology of heart failure is evaluated.

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1. Introduction

Heart failure is a major cause of morbidity and mortality. Patients suffering from hypertension and surviving myocardial infarction in particular are at risk of developing cardiac failure. The development of heart failure is associated with a plethora of intracellular changes, including alterations in calcium handling, sarcomere function, extracellular matrix composition, and energy metabolism. Given the wide diversity of processes that are simultaneously affected, the establishment of clear cause–effect relationships is extremely cumbersome. Furthermore, often it is unclear whether the molecular changes taking place are to be considered adaptive or maladaptive responses. Accordingly, the identification of key processes setting off a cascade of detrimental cellular changes, ultimately leading to the development of cardiac failure, is still subject of intense research. The present review focuses primarily on alterations in cardiac energy metabolism and their potential significance for the development of cardiac failure, following pressure- or volume-overload, or regional myocardial infarction.

The majority of experimental and clinical studies indicates that the hypertrophied and failing myocardium is characterized by changes in energy and substrate metabolism, including alterations in high-energy-phosphate content, mitochondrial function and an increased dependence on glucose as substrate. Theoretically, these metabolic alterations could reflect either an increased energy demand of the cardiac muscle, or compromised capacity to generate sufficient amounts of ATP, or a combination of both. Since mitochondria are the principal sites of ATP regeneration, limitations in oxygen delivery or intrinsic defects in mitochondrial function, may well be responsible for the observed energetic alterations. The functional significance of the shift in substrate preference from fatty acids (FA) towards glucose is still enigmatic. Even more so, it is still being debated whether this metabolic shift should be considered adaptive or maladaptive.
2. The failing heart: an energy compromised organ?

2.1. Alterations in high-energy phosphate metabolism

The continuous resynthesis of ATP via mitochondrial oxidative phosphorylation is mandatory for the maintenance of the contractile process. The creatine kinase–phosphocreatine (CK–PCr) shuttle ensures delivery of ATP from mitochondria to the myofibrils. Preclinical as well as clinical studies, employing either biochemical or \(^{31}\)P-NMR techniques to monitor High-Energy Phosphate (HEP) content, indicated that energy metabolism is affected during compensated hypertrophy and cardiac failure, as evidenced by the decline in cardiac PCr content, whether or not in combination with a reduction in ATP content [1–3]. As a consequence, the ratio of PCr/ATP, being an index of energy reserve, is reduced. Indeed, it was reported that the PCr/ATP ratio correlated well with the severity of failure and may be of prognostic value [1]. It is of note that the changes in HEP content coincide with a diminished total CK activity and/or change in CK-isofrom distribution in the hypertrophied and failing heart [4]. The reduction in PCr along with a reduced CK activity will decrease CK flux rate, which in turn may limit the ability of the failing heart to respond to inotropic challenges [5].

2.2. Mitochondrial dysfunction

The decline in high-energy phosphates might be indicative for impaired mitochondrial function. Mitochondrial oxygen consumption rate was substantially reduced in an experimental model of post-infarction cardiac failure [6]. Similar observations were made in explanted hearts from patients with ischemic and idiopathic dilated cardiomyopathy [7]. Furthermore, reductions in the tissue content and activity of complex I through IV of the respiratory chain have been reported in animal models of cardiac failure and in end-stage human failing hearts [2,8,9]. It is important to realize that these observations were all made in failing hearts. No changes in mitochondrial function were found in hypertrophic ferret hearts [10]. Furthermore, in mitochondria isolated from volume-overloaded hearts state 3 and state 4 respiration remained unchanged suggesting that respiratory chain activity per se is not affected under these conditions [11]. Collectively, these findings suggest that abnormalities in mitochondrial oxidative phosphorylation represent a late, rather than early, phenomenon in the development of heart failure.

2.3. Shift in cardiac substrate utilization

Under normal conditions, the oxidation of FA and glucose covers approximately 65% and 30% of cardiac energy demand, respectively [12]. Pioneering studies of Geltman et al. [13] by means of positron emission tomography (PET) revealed marked spatial heterogeneity in uptake and depressed deposition of FA in the left ventricle of patients suffering from congestive cardiomyopathy. The application of PET or single photon emission computed tomography (SPECT) in later clinical studies [14–16] corroborated the more heterogeneous distribution of FA uptake and decline in FA utilization in various forms of left ventricular hypertrophic and dilated cardiomyopathy. Others, however, observed no abnormalities in FA uptake and utilization [17], or even reported an increase in FA uptake in failing human hearts [18]. Notwithstanding these conflicting data, detailed studies of De las Fuentes et al. [19] revealed a close quantitative relationship between the increase in left ventricular mass and the decline in FA oxidation rate. The direction of the alterations in glucose utilization in the human hypertrophied and/or failing heart is less consistent as decreased [17,18], unchanged [15] and increased [16,20] cardiac deposition of radiolabelled fluoroxyglucose has been reported.

Likewise, autoradiography studies on hypertension-induced cardiac hypertrophy in the rat revealed that the cardiac uptake of radiolabelled FA analogues was diminished and the uptake of 2-deoxyglucose was enhanced [21]. Subsequent studies with ex vivo perfused hypertrophic hearts from rats subjected to pressure overload [22,23], volume-overload [11,24], or regional myocardial infarction [25] almost consistently showed that FA oxidation was markedly depressed and glucose utilization increased. It is important to realize, however, that under these conditions a substantial part of the exogenous glucose was converted into lactate instead of being oxidized [22]. Given the central role of the pyruvate dehydrogenase complex (PDC) in destining pyruvate for either mitochondrial oxidation or conversion to lactate, alterations in PDC activity might be responsible for the reduced coupling of glycolysis and glucose oxidation.

Collectively, these observations indicate that the hypertrophied heart becomes more dependent on glucose as an energy-providing substrate. It is unknown, however, whether the rise in (anaerobic) glycolysis is sufficient to compensate for the decline in FA oxidation in terms of ATP production.

3. Metabolic remodelling: underlying mechanisms

Various biochemical and genomic mechanisms have been considered to contribute to the alterations in energy metabolism in the hypertrophied and failing heart (listed in Table 1). In this section, the evidence in favour or against these mechanisms is being evaluated.

3.1. Mitochondrial dysfunction due to DNA damage

Mitochondria contain a variable number of copies of their own DNA, encoding for transfer and ribosomal RNAs and several proteins of the respiratory chain. The mitochondrial DNA (mtDNA) appears to be more prone to
Putative mechanisms underlying energetic alterations during cardiac hypertrophy and failure

<table>
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<th>Reduced/impaired mitochondrial activity:</th>
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<tr>
<td>– Limitations in O$_2$ supply</td>
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<td>– Increased NO production$^a$</td>
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<tr>
<td>– Enhanced UCP activity</td>
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<td>– ROS-induced mitochondrial DNA damage</td>
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Increased glycolysis:

| – Reduced FA metabolism (Randle cycle)   |
| – Limitations in O$_2$ supply            |
| – Activation of AMPK                     |
| – Reduced NO production$^a$              |
| – Transcriptional upregulation (HIF-mediated) |

Reduced FA oxidation:

| – Increased glucose metabolism (Randle cycle) |
| – Limitations in O$_2$ supply               |
| – Impaired trans-sarcolemmal transport      |
| – Loss of carnitine                         |
| – Reduced mitochondrial activity            |
| – Transcriptional downregulation (via reduction PPAR activity) |

$^a$ As discussed in text, it is still being debated whether nitric oxide (NO) synthesis is increased or decreased during cardiac hypertrophy and failure. UCP—uncoupling protein; ROS—reactive oxygen species; AMPK—AMP-activated protein kinase; HIF—hypoxia-inducible factor; PPAR—peroxisome proliferator-activated receptor.

damage than nuclear DNA. The mitochondria lack both an effective DNA repair system and the protection afforded by histones, but above all mtDNA is in close proximity to the major source of intracellular reactive oxygen species (ROS), namely the respiratory chain itself. With ageing, the number of mutations in the mtDNA rises sharply, in particular in tissues with high rates of oxidative phosphorylation, among which the cardiac muscle. Several studies demonstrated an increased frequency of mutations in mtDNA in failing hearts [8,26]. Accordingly, it was postulated that an enhanced accumulation of mtDNA mutations over time contributes to the development of mitochondrial aberrations and, hence, to the progression of heart failure. Indeed, maternally inherited mtDNA mutations cause several genetic syndromes, among which cardiac failure [27]. Furthermore, in transgenic mice over-expressing a proofreading-deficient mitochondrial DNA polymerase (pol $\gamma$) in a cardiac-specific manner, the number of mtDNA mutations rapidly increases and the animals develop cardiomyopathy [28]. These observations substantiate the notion that mutations in mtDNA lead to cardiac dysfunction. On the other hand, changes in mitochondrial function in failing hearts of transplant patients have been reported without any evidence of an increase in mtDNA mutations [9].

Finally, it has been postulated that mitochondrial efficiency, i.e. ATP produced per oxygen atom consumed, is reduced due to increased activity of mitochondrial uncoupling proteins (UCPs), which may partly dissipate the mitochondrial electrochemical proton gradient that is normally used to regenerate ATP [29]. However, both increases [30] and decreases [31] in UCP2 and UCP3 expression were reported in animals with congestive heart failure and in patients with end-stage heart failure. Furthermore, the exact biological function of UCP2 and UCP3 is far from clear. Rather than mitochondrial uncoupling, these proteins have been postulated to be involved in the export of FA out of the mitochondrial matrix and inhibition of mitochondrial ROS production, implying beneficial instead of detrimental properties of these UCP isoforms [32].

3.2. Reactive oxygen species and nitric oxide

The ROS will inflict mitochondrial damage by attacking mtDNA and mitochondrial proteins, thereby compromising mitochondrial aerobic capacity. Conversely, dysfunction of the respiratory chain is believed to be associated with enhanced ROS production. For instance, genetic ablation of the cardiac-enriched isoform of the Adenine Nucleotide Translocase (ANT-1), facilitating the exchange of ATP against ADP across the mitochondrial inner membrane, disturbs mitochondrial energy production and increases mitochondrial ROS production [33]. In addition, extra-mitochondrial sources of ROS are also worth considering. The activity of xanthine oxidase, which generates superoxide anion during purine catabolism, is enhanced in the failing heart [34]. The xanthine oxidase inhibitor allopurinol was found to improve mechano-energetic coupling in pacing-induced heart failure [34,35]. By analogy, it is tempting to speculate that NADPH oxidase, which is activated during hypotrophy and failure, affects cardiac energetics as well [36].

Nitric oxide (NO) has also been implicated as a modulator of mitochondrial respiration as it competes with oxygen for binding to cytochrome-c oxidase (complex IV) [37]. Accordingly, the administration of NO generating reagents to isolated hearts lowers oxygen consumption, whereas inhibitors of NO synthesis stimulate oxygen consumption [38]. Interestingly, in the hypertrophic myocardium mitochondrial respiration appears to be more sensitive to inhibition by NO [37,39] and inhibition of NO production increases myocardial oxygen consumption in pacing-induced heart failure [40].

There is ongoing controversy whether the production of NO is either depressed or stimulated during cardiac failure. Various studies documented that expression of inducible NO synthase (iNOS) is enhanced in the failing heart [41], thereby suggesting that NO production will be increased. Conversely, others failed to measure increased NO formation, or actually observed a decline in NO production in the failing myocardium (for recent review, see Ref. [42]). To reconcile these conflicting results, it has been put forward that inhibition of endothelial NOS (eNOS) activity is quantitatively more important than the induction of iNOS under these conditions. As discussed later, NO production has also been linked to changes in substrate utilization.
3.3. Mismatch between oxygen supply and demand?

The drop in PCr/ATP ratio as well as the shift in substrate preference towards glucose are compatible with the notion of a mismatch between oxygen supply and demand in the failing heart. Although cardiac hypertrophy secondary to hypertension is associated with a reduced capillary density and, thus, an increase in the diffusion distance from capillary to mitochondrion, it is questionable whether the oxygen diffusion becomes limiting. In patients with idiopathic dilated cardiomyopathy myocardial blood flow at rest is similar to that of healthy controls, but dipyridamole infusion revealed that blood flow reserve is markedly reduced in these patients [43]. In other studies, however, oxygen supply seemed to match oxygen needs, even when workload was increased by dobutamine or exercise [44,45]. Imaging techniques that allow estimation of the ratio of deoxygenated/oxygenated myoglobin failed to detect derangements in intracellular oxygen availability in pressure overload hypertrophy [44], pacing-induced heart failure [45] and post-infarction failure [46]. These observations suggest that demand ischemia is of limited importance in the aetiology of cardiac failure and, by inference, that oxygen shortage is not the primary trigger for the shift in substrate preference towards glucose.

3.4. Enhanced glycolysis and hypoxia-inducible factor

The mechanism underlying the enhancement of glycolysis in the hypertrophied and failing heart is incompletely understood. Early findings that the activity and isoform distribution of a number of glycolytic enzymes (hexokinase, lactate dehydrogenase) were changed in the hypertrophied myocardium indicated that alterations in glucose metabolism might be related to changes in gene expression [47]. Subsequent studies showed that hypertrophy and failure are associated with a diminished expression of the insulin-dependent glucose transporter (GLUT4) and unchanged or increased expression of GLUT1 [48–50]. Interestingly, the expression of the monocarboxylate transporter-1 (MCT1), facilitating the sarcolemmal transport of lactate and pyruvate, increased substantially during heart failure [51].

In a rat model of monocrotaline-induced right ventricular pressure overload, immunohistochemical analysis revealed induction of the transcription factor hypoxia-inducible factor-1α (HIF-1α) [52]. The HIF-1α/HIF-1β dimer binds to the consensus DNA sequence (C/G/T)ACGTGC(G/T), present in the promoter regions of GLUT1 and the glycolytic enzymes aldolase (A-type), phosphoglycerate kinase (PGK), α-enolase (ENO1), and LDH-A [53,54]. In this respect, the enhanced expression of GLUT1 and LDH-A [55] is consistent with the idea that HIF-mediated transcriptional activation accounts for the increased reliance on glycolysis of the diseased myocardium. To date, however, the contribution of HIF-mediated transcription in enhancing glycolysis in the hypertrophic and failing heart is still questionable. As discussed above, oxygen shortage does not appear to be a common feature of cardiac hypertrophy and failure. More importantly, a large number of studies failed to observe increases or even reported decreases in the mRNA or protein content or enzyme activity ($V_{\text{max}}$) of glucose transporters and glycolytic enzymes both in animal models of hypertrophy [56–58] and in the failing human heart [2,31]. These observations suggest that the increase in glycolysis is brought about via post-translational, rather than transcriptional mechanisms.

3.5. AMP-activated protein kinase

In view of the changes in high-energy phosphate metabolism, it is conceivable that activation of AMPK, due to the rise in AMP/ATP ratio, is involved in the shift towards glucose utilization during cardiac hypertrophy and failure. Activation of AMPK with the AMP-analogue AICAR leads to the translocation of GLUT4 from intracellular stores to the sarcolemma [59]. The observation that patients with mutations in one of the AMPK subunits and mice over-expressing this activating AMPK mutant form suffer from pathological cardiac glycogen accumulation, underscores the importance of AMPK in cardiac carbohydrate homeostasis [60]. Furthermore, the AMPK-dependent phosphorylation of the enzyme 6-phosphofructo-2-kinase also stimulates glycolysis [61]. Indeed, cardiac hypertrophy was associated with a marked increase in AMPK activity and enhanced uptake of 2-deoxyglucose [62].

It is important to realize, however, that AMPK also activates FA uptake by stimulating the translocation of Fatty Acid Translocase (FAT/CD36) to the sarcolemma [63]. Furthermore, AMPK phosphorylates acetyl-CoA carboxylase (ACC), thereby inhibiting the conversion of acetyl-CoA into malonyl-CoA [64]. As malonyl-CoA is a potent allosteric inhibitor of carnitine palmitoyltransferase-1 (CPT1), the AMPK-mediated inhibition of ACC activity will promote FA utilization. Accordingly, the fact that activation of AMPK stimulates the uptake and metabolism of both glucose and FA is difficult to reconcile with a change in substrate preference to glucose in the hypertrophied and failing heart.

3.6. Nitric oxide and glucose utilization

Interestingly, there appears to be an, as yet poorly understood, relation between NO production and glucose utilization. Pharmacological inhibition of NO synthesis is associated with an increase in cardiac glucose utilization [42,65]. The enhanced uptake of glucose by ex vivo-perfused hearts from eNOS knockout mice corroborates this notion [66]. The observation that administration of cGMP analogues or NO-donors depressed cardiac glucose uptake by hearts from eNOS knock-out mice suggests that the effect of NO is cGMP-dependent.
3.7. Activity of pyruvate dehydrogenase complex

PDC plays a key role in the regulation of glycolysis and its activity largely determines the fate of the glycolytic product pyruvate, i.e. mitochondrial oxidation or anaerobic conversion into lactate. As such, it is tempting to speculate that uncoupling between glycolysis and glucose oxidation is based on changes in the regulation of PDC. The observation that total PDC content was not affected, whereas the active form of PDC is diminished in the hypertrophied myocardium is in line with this notion [67]. In addition to modulation by acetyl-CoA/CoA ratio and other metabolites, PDC activity is controlled by phosphorylation/dephosphorylation. Interestingly, the expression of one of the pyruvate dehydrogenase kinase isoforms (PDK4) is induced by peroxisome proliferator-activated receptors (PPARs: to be discussed in detail later) [68]. The PDK4-dependent phosphorylation of PDC inhibits the conversion of pyruvate into acetyl-CoA. Accordingly, the activation of PPAR promotes the utilization of FA, at the same time suppressing glucose oxidation (via PDK4 → PDC). Vice versa, it is conceivable that inhibition of PPAR activity, as has been demonstrated in the setting of cardiac hypertrophy, stimulates glucose oxidation by relieving the inhibition of PDC.

3.8. Impairment of fatty acid oxidation and peroxisome proliferator-activated receptors

Sack et al. [69] were the first to report a decrease in the expression of genes involved in mitochondrial β-oxidation in the hypertrophied and failing myocardium. Subsequent studies showed that the expression of a variety of genes involved in FA uptake and metabolism is diminished in experimental models of cardiac hypertrophy and failure [25,49,50,70] as well as in left ventricular tissue of human cardiac transplant recipients [71]. The finding that the exposure of cardiac myocytes to FA elicits a co-ordinated up-regulation of genes encoding for proteins involved in FA uptake and metabolism [72–74] and the subsequent elucidation of the role of PPARs herein [73,74] suggested that PPARs play a pivotal role in metabolic remodelling. Collectively, these data suggested that the reduction in FA oxidation in the hypertrophic and failing heart could be attributed to a down-regulation of the expression of genes involved in FA transport and metabolism as a result of a decline in PPAR activity.

The PPARα, β/δ, and γ isotypes form dimers with RXR and the PPAR/RXR heterodimers are capable of binding to the DNA consensus binding sequence (AGGTCA-nAGGTCA), referred to as peroxisome proliferator response element (PPRE) (for recent reviews, see Refs. [75,76]). The expression level of the three PPAR isotypes varies from tissue to tissue. In the intact heart all three isotypes are present, the RNA content of PPARα and PPARβ/δ being comparable and much higher than that of PPARγ [77]. The expression level of the PPAR isotypes, however, is likely to change under various pathological conditions. For both PPARα and RXRα, it has been shown that their content, at the mRNA as well as protein level, is decreased in the failing heart [70,78,79]. The reduction in the amount of functional PPARα/RXRα complexes offers an attractive explanation for the observed decline in the expression of genes involved in FA metabolism under these circumstances.

The transcriptional activity of PPAR/RXR is also modulated by a variety of co-repressor and co-activator proteins. The biological significance of the co-activator peroxisome-proliferator receptor-γ co-activator-1 (PGC-1), which is abundantly expressed in the cardiac muscle, has received widespread attention. PGC-1 also serves as co-activator of the nuclear respiratory factors (NRFs), transcription factors that control mitochondrial biogenesis [80]. Accordingly, PGC-1 is ideally suited to keep FA oxidation capacity and mitochondrial biogenesis in balance. Indeed, the over-expression of PGC-1 in skeletal muscle both increases FA oxidation rate and mitochondrial number [81]. Recently, it was shown that cardiac PGC-1 expression is reduced in a rat model of cardiac failure [82], further lending support to the importance of this co-factor in the metabolic remodelling of the failing heart.

In addition to PPARs several other nuclear receptors, among which chicken ovalbumin upstream promoter transcription factor (COUP-TF), are able to bind to the consensus PPRE sequence. In contrast to PPARα, the binding of COUP-TF to PPRE sequences suppresses transcriptional activity [83]. COUP-TF is increased in the hypertrophied heart [70], suggesting that competition between PPAR and COUP-TF for binding to promoter sequences might be responsible for the repression of the expression of FA-metabolising gene products.

Finally, evidence has been provided that PPARα is subject to phosphorylation by mitogen-activated protein (MAP) kinases. In cardiac muscle cells, p38 MAP kinase-dependent phosphorylation of PPARα led to an increase in PPARα activity [84]. However, the exact effect of the MAP kinase-dependent phosphorylation is far from clear as the phosphorylation of PPARα via another MAP kinase, i.e. via ERK, appeared to have opposite effects [85]. Given the fact that the activation of MAP kinases is an integral part of the cardiac hypertrophic response, it will be important to delineate the functional implications of PPAR phosphorylation for transcriptional activity in the heart.

Furthermore it is important to realize that, so far, research has been focussed exclusively on the role of PPARα in cardiac metabolic remodelling. In view of the fact that PPARβ/δ is likely to be equally important in the transcriptional control of cardiac FA metabolism [86], more research into the role of this subtype in the setting of cardiac hypertrophy and failure is warranted. Finally, it still remains to be established whether the PPAR-mediated down-regulation of these metabolic genes represents an early or late
phenomenon in the sequel of events ultimately leading to cardiac failure.

3.9. Impaired uptake of fatty acids

In addition to impaired mitochondrial FA oxidation, alterations in the transport of FA from the extracellular compartment to the sarcoplasm could lead to disturbances in FA utilization as well. The cellular uptake of FA is facilitated by membrane-associated proteins, including FAT/CD36, fatty acid transport protein (FATP) and plasma-membrane fatty acid-binding protein (FABPpm) [87]. Studies on patients carrying a mutated FAT/CD36 gene suggest that lack of the sarcolemmal FA transporter FAT/CD36 leads to hypertrophic cardiomyopathy [88]. Recently, it was shown that FAT/CD36 deficiency might play an important role in the aetiology of cardiac hypertrophy in spontaneously hypertensive rats (SHR) [89]. These findings collectively point towards a causal relationship between a reduced sarcolemmal capacity to transport extracellular FA and cardiac hypertrophy. So far, it is largely unknown if the activity of sarcolemmal FA transport proteins is affected during acquired hypertrophy and failure.

3.10. Loss of carnitine, the carnitine shuttle, and mitochondrial dysfunction

Carnitine is required for the import of activated long-chain FA into the mitochondrion via the carnitine shuttle. This co-factor is synthesized in the liver and taken up by the cardiac muscle cell by the organic cation transporter (OCT2N) primarily. In experimental and clinical studies on cardiac hypertrophy and failure, a decline in the tissue content of total and free carnitine has been observed [11,22,90], which is probably related to a reduction in carrier-mediated uptake [91]. In primary carnitine deficiency in man and in OCT2N-deficient mice, FA oxidation is severely disturbed, resulting in the accumulation of excessive amounts of intramyocardial triacylglycerols with potentially noxious effects (‘lipotoxicity’) [92]. Studies on mitochondria isolated from hypertrophic hearts indicated, however, that carnitine supplementation was insufficient to restore mitochondrial FA oxidation capacity [11]. The latter observation suggests that, although the loss of carnitine in hypertrophic hearts may be a contributing factor, it is not the principal factor responsible for the decline in FA oxidation capacity.

As indicated above, the activity of CPT1, and thus the carnitine shuttle, is inhibited by malonyl-CoA. Recently, it was shown that the expression of malonyl-CoA decarboxylase (MDC), the enzyme responsible for the degradation of malonyl-CoA, is controlled by PPAR [93]. Hence, the decline in PPAR activity as observed during hypertrophy may lead to a decline in MCD, resulting in a rise in malonyl-CoA levels and inhibition of mitochondrial FA import.

4. Metabolic remodelling: adaptive or maladaptive?

As discussed, the reduction of FA oxidation is not fully compensated for by an enhanced glucose oxidation, which would implicate a reduced overall rate of ATP regeneration in the hypertrophied and failing heart. Along with observed changes in mitochondrial function, the collective findings could be interpreted as such that the failing heart is an energy compromised organ that suffers from a progressive ‘burn-out syndrome’ eventually leading to functional deterioration.

The biological relevance of the shift in substrate utilization from FA to glucose remains largely elusive. It should be kept in mind that, as the foetal heart is also highly dependent on carbohydrates for energy production, the metabolic remodelling process could be considered part of the return to the foetal gene programme, a hallmark of cardiac hypertrophy. Interestingly, ventricular unloading also gives rise to the expression of foetal genes [49], which raises the question if metabolic remodelling during hypertrophy represents a purposeful cardiac response, or merely a fixed reaction to a homeostatic perturbation.

Although it is realized that there is a slight oxygen sparing effect (12%) in terms of ATP yield per oxygen atom invested when glucose instead of FA is oxidized, traditionally it has been assumed that metabolic therapies should be aimed to correct the decline in FA utilization. However, a number of observations suggest otherwise. ATP produced in the cytoplasm via glycolysis is used preferentially by ion pumps, including the sarcoplasmic reticular Ca$^{2+}$-ATPase, SERCA2 [94]. In this respect, the increased glycolytic rate might be considered an adaptive response attenuating the disturbances in Ca$^{2+}$-homeostasis associated with cardiac hypertrophy. In rats with pressure-overload-induced hypertrophy, the administration of the PPAR$\alpha$ ligand WY14,643, with the goal to increase FA oxidation, appeared to have adverse rather than beneficial effects [95]. Furthermore, the cardiac-specific overexpression of GLUT1 attenuated the development of cardiac failure [96]. Finally, drugs (ranolazine, trimetazine) that stimulate glucose utilization, have been shown to improve cardiac function in models of heart failure [97]. Accordingly, it is tempting to speculate that the shift towards glucose metabolism in the hypertrophied and failing heart is beneficial in several ways, the prize being however a reduced overall ATP production, the adverse effects of which might dominate in the end.

5. Concluding remarks

Cardiac failure is characterized by a spectrum of alterations in cardiac energy and substrate metabolism. Although defects in mitochondrial function in end-stage cardiac disease are apparent, it remains to be established whether these abnormalities are causally involved in the transition of
compensated hypertrophy to decompensated cardiac failure. With respect to FA metabolism, it is likely that the metabolic disturbances can be attributed to changes in the rate of transcription of the genes involved. In case of the enhancement of glucose metabolism, the mechanism responsible is less clear and several options need to be considered. At this moment, the functional consequences of metabolic remodelling in relation to the development of heart failure still remain elusive. Given the fact that redox state, adenine nucleotides, oxygen, FA and glucose derivatives, all serve important roles in signal transduction in the cardiac myocyte, alterations in cardiac metabolism will inevitably modulate cardiac phenotype and function. The challenge for the near future lies in the unravelling of the intricate relationship between energy metabolism, signal transduction and cardiac performance.

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References


Razeghi P, Young ME, Ying J, et al. Downregulation of metabolic...


