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Myocardial substrate metabolism in heart disease

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1. ABSTRACT

Cardiac disease is commonly associated with changes in energy substrate metabolism. Fatty acid and glucose represent the main fuels used by the heart, and characteristic alterations in substrate preference and utilisation occur early in many cardiac disease processes. Different substrate classes (lipids, carbohydrates) have different metabolic efficiencies, both in terms of energy (ATP) yield and in terms of oxygen requirement; changes in metabolic efficiency may affect, positively and negatively, cardiac function. Furthermore, metabolic diseases alter substrate supply to the heart, which may have an impact on cardiac function. One challenge is to establish whether a primary metabolic abnormality in myocardial fuel utilisation leads to cardiac dysfunction, or whether changes in substrate selection are a consequence of the disease state. The distinction is important as the ability to manipulate cardiac substrate utilisation may offer a therapeutic opportunity for cardiac disease.

2. INTRODUCTION

The heart consumes large amounts of energy. This is required both for myofibre contraction and for maintenance of ionic gradients, and energy transduction involves a rapid turnover of high energy phosphate groups (ADP/ATP and creatine/phosphocreatine). The heart is unique in providing its own energy supply, via the coronary arteries, which is potentially precarious as coronary blood flow occurs principally in diastole. Hence, with limited coronary perfusion pressure and flow, there is a resulting high oxygen extraction. It is also unusual in the quantity of energetic substrate consumed. Also, unlike other tissues, the heart must continue its function uninterrupted. Available energy transduction/yielding pathways include both oxidative and non-oxidative processes; given the large requirement for energy, it is unsurprising that the heart derives most of this energy (> 90%) from oxidative pathways (oxidative phosphorylation), although glycolysis, despite its relatively low ATP yield, may have a vital role

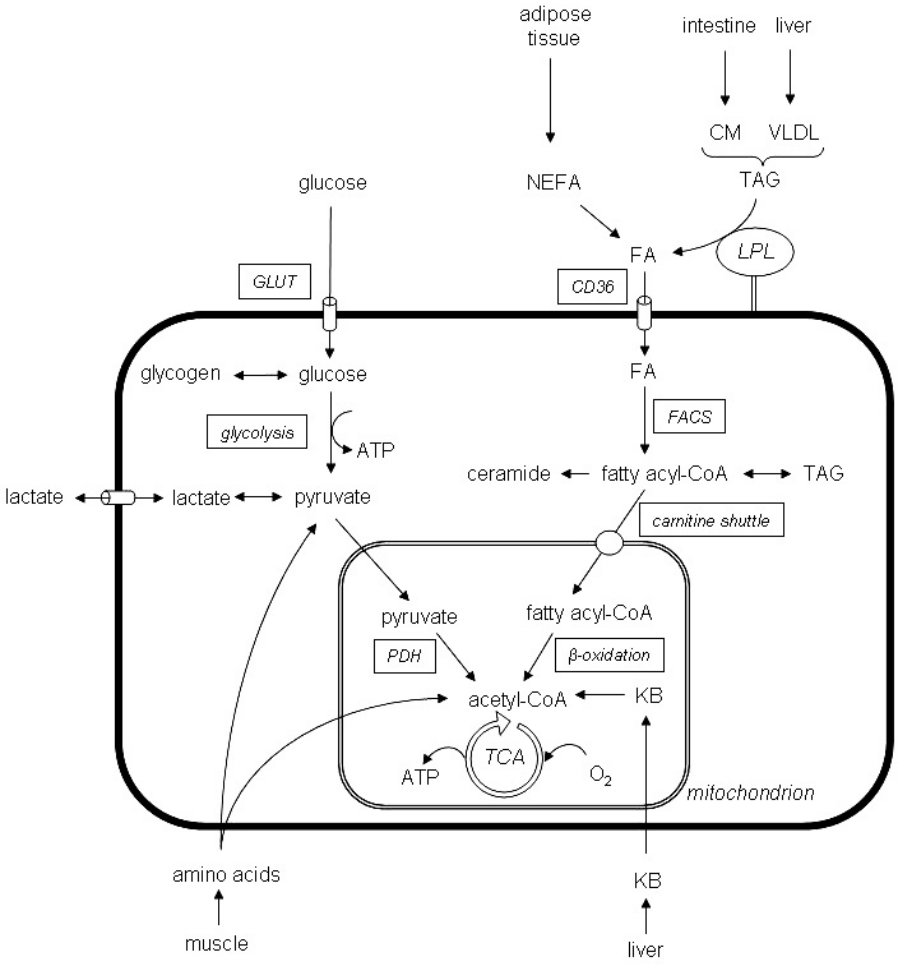

Figure 1. Overview of principal metabolic pathways in the heart. Fatty acids, glucose and lactate are taken up into the cardiomyocyte; some ATP is derived from glycolysis in the cytosol, but most ATP is generated by oxidative phosphorylation in the mitochondrion. NEFA: non-esterified fatty acids, TAG: triacylglycerol, CM: chylomicrons, VLDL: very-low-density lipoprotein, LPL: lipoprotein lipase, CD36: fatty acid translocase, FA: fatty acid, FACS: fatty acyl-CoA synthase, GLUT: glucose transporter, PDH: pyruvate dehydrogenase complex, TCA: tricarboxylic acid cycle, KB: ketone bodies.

in myocardial function by virtue of its intracellular compartmentation (1-8). The energy transduction pathway involves energy production (substrate utilisation and metabolism), energy transfer (oxidative phosphorylation), and energy utilisation (high energy phosphate metabolism)(9). Integrity of all three processes is required for optimal function (10). This review will focus on substrate utilisation and metabolism.

3. ENERGY METABOLISM IN THE HEALTHY HEART

Some organs, such as brain, are specialised to utilise a limited selection of energetic substrates, yet the heart is adapted to use any of the classes of energetic substrate available, possibly an evolutionary requirement to maintain function at all times. Substrates include all the major energetic biomolecular classes – lipids (fatty acids (FA), triacylglycerols (TAG)) and their derivatives (ketone bodies), carbohydrates (glucose, lactate) and amino acids (3, 4, 11-16). Limited intracellular storage is provided by TAG and glycogen (Figure 1). However, although the heart is capable of using any plasma-borne substrate available for energy provision, its substrate preference, and hence substrate selection, is well defined, and varies according to prevailing physiological and pathological state. Furthermore, the substrate that the heart chooses, or is obliged to utilise, may impact on its resulting performance, emphasising the intimate relationship between cardiac metabolism and function (15, 16). It is the relationship between substrate utilisation and mechanical function that makes this area of fundamental importance to cardiac disease.

Glucose is assimilated via glucose transporters, principally insulin-sensitive glucose transporter (GLUT4) (but also through insulin-insensitive GLUT1), and lactate via the monocarboxylate transporter, MCT. Besides being

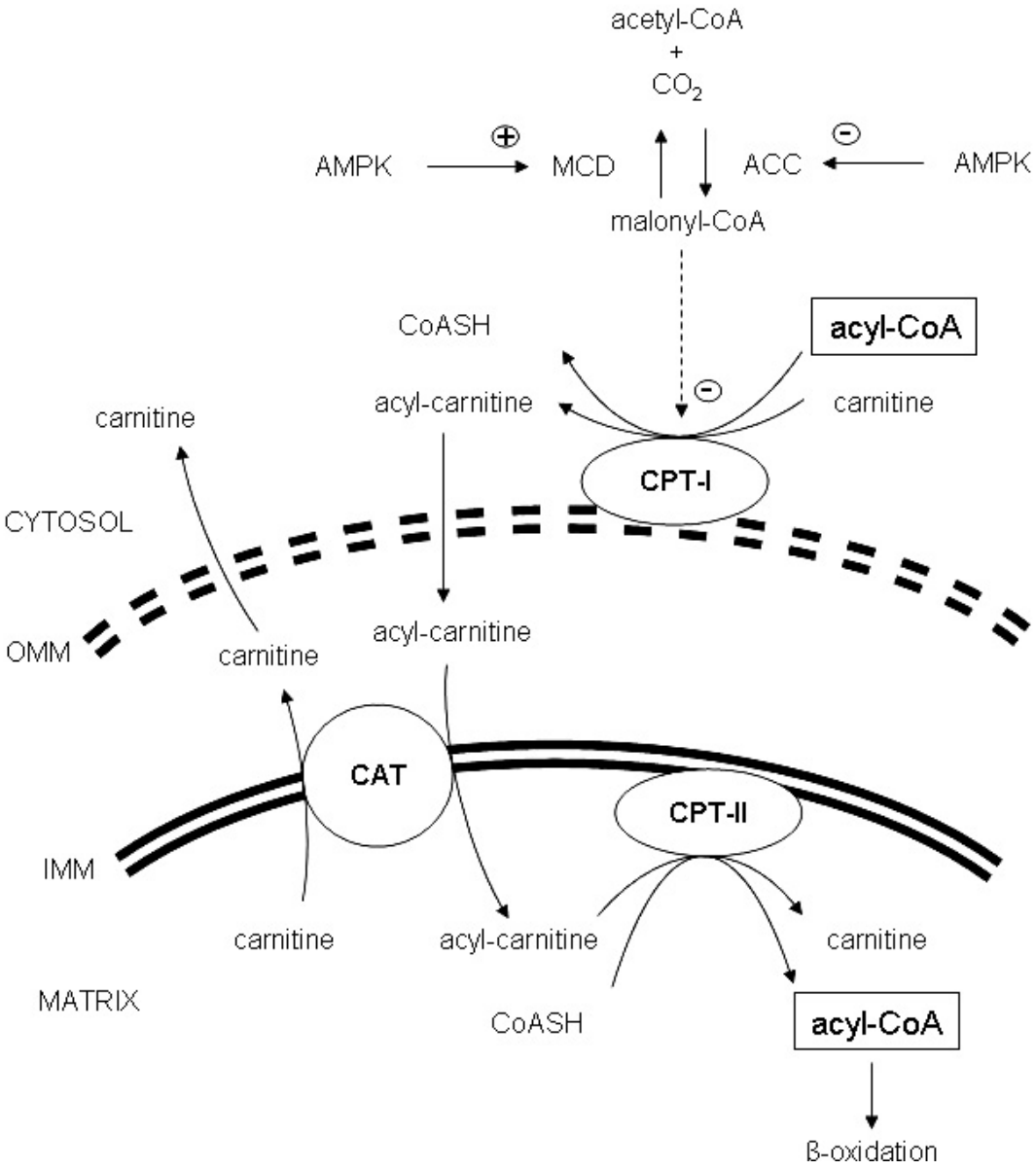

Figure 2. Mitochondrial carnitine shuttle. Fatty acids in the form of acyl-CoAs are transported into the mitochondrion for β-oxidation by the carnitine shuttle. CPT-I is inhibited by malonyl-CoA, providing a link between glucose and fatty acid oxidation. OMM: outer mitochondrial membrane, IMM: inner mitochondrial membrane, MCD: malonyl-CoA decarboxylase, ACC: acetyl-CoA carboxylase, AMPK: AMP-activated protein kinase, CPT-I: carnitine palmitoyl transferase-I, CPT-II: carnitine palmitoyl transferase-II, CAT: carnitine-acylcarnitine translocase, CoASH: coenzyme-A.

used to synthesise myocardial glycogen, glucose is split in glycolysis yielding limited ATP and pyruvate; following oxidative decarboxylation by pyruvate dehydrogenase complex (PDH) to acetyl-CoA in the mitochondrion, pyruvate may then be oxidized by the tricarboxylic acid (TCA) cycle to produce NADH and $FADH_2$ for the electron transport chain, if sufficient oxygen is present. If not oxidized, pyruvate is converted to lactate (8, 11). Like glucose, lactate can be oxidized only if sufficient oxygen is available to permit TCA cycle activity (17). Lipids are delivered to the heart in plasma as non-esterified fatty acids (NEFA) bound to albumin, and are assimilated through the FA transporters CD36/FAT (fatty acid translocase), FATP (fatty acid transport protein) and FABPpm (plasma membrane fatty acid binding protein)(18-20). Following acylation to coenzyme-A and transport into the mitochondrion via the carnitine shuttle, FAs undergo β-oxidation to acetyl-CoA then oxidation though the TCA cycle and electron transport chain to generate ATP (2, 7, 8). Plasma NEFA is derived primarily from TAG lipolysis in white adipose tissue, which is stimulated by "catabolic" hormones such as catecholamines, and inhibited by insulin.

Plasma FAs are also provided esterified in the form of TAG, present within the core of TAG-rich lipoproteins (TGRLP): endogenously-synthesised TAG from the liver within very-low-density lipoproteins (VLDL) and exogenous (dietary) TAG assembled as chylomicrons (CM) by the gut (21-23). TAG in the core of these lipoproteins is hydrolyzed to FA by the endothelial enzyme lipoprotein lipase (LPL) (24-26); LPL activity may liberate substantial amounts of "free" fatty acids into the circulation (27-30). Whole-particle assimilation also occurs through lipoprotein receptor-mediated uptake mechanisms (31, 32). Whether the uptake and subsequent intracellular channelling of NEFA- and TAG-derived FA are identical is currently uncertain (33-35). Some assimilated FA is re-esterified and incorporated into the intracellular lipid pool (10-25% of the assimilated TAG; mostly into TAG and phospholipid) whilst the remainder is oxidized (75-90%); this proportion varies according to the FA source (21, 35). The intracellular TAG pool is extremely labile and has a highly dynamic relationship with FA destined for β-oxidation; although the physiological significance of this pool, and its relationship to cellular lipid toxicity (see below), remains uncertain (36), it is probably an obligatory step in intracellular lipid buffering (> 10% of myocardial energy is derived from endogenous TAG stores in hearts perfused *ex vivo*, even when FA is present in the perfusate (37)). TAG are a potentially quantitatively important source of FA, given their high plasma concentration (≈ 10 x that of NEFA) and efficient and multiple uptake mechanisms; they may be the major cardiac fuel under physiological conditions (21, 25, 26, 38-40). Ketone bodies derived from the liver in catabolic states associated with TAG mobilisation and ketogenesis (e.g. starvation, diabetes) are also readily oxidized by the heart (8, 41-43). Amino acids (principally the branched chain amino acids) can be oxidized by the heart, although they are quantitatively less important than carbohydrates and lipids and relatively little is known of their metabolic significance and regulation (44-51)(Figure 1).

Hence, TAG, NEFA and glucose constitute the principal energy substrates for the healthy heart *in vivo* and this is partly a function of their availability (prevailing plasma concentrations), but also reflects myocardial preference.

One of the problems in studying cardiac metabolism is that much work has been performed on the isolated perfused heart with typically only one or two substrates (e.g. glucose and FA) present in the perfusate. Although this technique has important advantages, (e.g. workload can be defined and fixed, and the substrates and effectors prescribed), these studies do not address the complex milieu of multiple substrates and hormones/mediators to which the heart is exposed *in vivo*. Some recent studies have addressed this by examining multiple substrates in the form of stable isotopes using positron emission tomography *in vivo* (52).

3.1. Fetal cardiac metabolism

The fetal heart exhibits a pattern (program) of gene expression coding both metabolic and contractile proteins that differ from those seen in the adult heart – specific fetal isoforms of many contractile and metabolic enzymes and other proteins exist, reflecting the differing physiological status of the fetal heart. The fetal heart has a relatively low workload and, in addition, fetal plasma lipid levels are low (53), limiting FA availability (54, 55), and the PO_2 is also relatively low (56). Probably for this reason, fetal myocardial metabolism relies principally on (anaerobic) glycolysis to provide ATP by substrate-level phosphorylation (56-61). Oxidative mitochondrial metabolism is mostly confined to lactate oxidation (62) with notably low rates of glucose and FA oxidation (61, 63). The fetal heart expresses the fetal form of myosin heavy chain (β-MHC), and the liver form of carnitine palmitoyl transferase-1 (lCPT-1) predominates over the muscle form (mCPT-1) (64, 65), hence malonyl-CoA sensitivity is high, with resulting limited FA β-oxidation (Figure 2).

3.2. Adult cardiac metabolism

Following birth and in the neonatal period, cardiac work increases, as do plasma lipids and arterial oxygen tension. The heart responds with a shift to an adult pattern of isoenzyme expression. A wide variety of metabolic and contractile protein adult isoforms are now expressed (66), including the adult form of myosin heavy chain (α-MHC) and the muscle form of CPT-1 (mCPT-1) together with decreased malonyl-CoA (14). The resulting metabolic profile is decreased glycolysis with increased glucose (pyruvate) oxidation, decreased lactate oxidation, and most notably, increased ketone body and FA oxidation (8, 58, 62, 63, 67, 68). In the adult heart under normal workload, FA oxidation accounts for about 60-70% of ATP synthesis, whilst glucose oxidation accounts for 25-35% of ATP synthesis, with the remainder derived from glycolysis. The relative contribution of NEFA and TAG-FA to myocardial FA utilisation *in vivo* is still uncertain (20, 21, 33), though LPL is very active in cardiac tissue and recent evidence suggests that TAG is a quantitatively important source of myocardial FA *in vivo* (26, 38, 39). Of the two forms of plasma TGRLP, CM, being larger, are better substrates for LPL and dietary TAG is likely an important source of myocardial FA (21). Increases in workload result in increased FA oxidation, but a striking finding is the accompanying increase in glycogen metabolism and pyruvate oxidation (69). Amino acid and ketone body utilisation and metabolism are low in the fed state, reflecting their limited plasma concentrations and hence availability.

Substrate selection by the healthy heart changes under varying physiological conditions, a reflection of the varying requirements as well as supply. Hence, when decreased plasma insulin levels lead to increased plasma NEFA concentrations during fasting, cardiac metabolism will shift away from glucose utilisation and towards FA oxidation (70, 71). The inverse relationship between glucose and FA utilisation was originally defined by Randle and co-workers (72) and is now termed the Randle cycle: increased FA utilisation inhibits glucose utilisation via increased acetyl-CoA and citrate levels inhibiting PDH, phosphofructokinase and GLUT – a classical glucose-

sparing mechanism. The role of TAG in energy provision in either starvation (when CM are low, but VLDL still provides endogenously synthesised FA) or increased workload is not known. However, in the physiological state of lactation in the rodent, suppression of cardiac LPL redirects VLDL and CM TAG away from heart and towards assimilation by the lactating mammary gland for export as milk lipid (73); cardiac function is maintained despite increased cardiac output in this state, implying increased cardiac work and hence energy demand and altered myocardial substrate selection.

4. ENERGY METABOLISM IN HEART DISEASE

Alterations in cardiac metabolism may be categorised as maintaining or increasing cardiac functional efficiency ("adaptive" changes) or decreasing functional efficiency ("maladaptive" changes) (15, 16). Substrate selection and utilisation changes in the diseased heart in a characteristic way, and a key question is whether the cardiac disease process causes the change in substrate utilisation, or whether a change in cardiac metabolism is a primary etiological event and, if the change decreases cardiac efficiency, whether this leads to cardiac mechanical dysfunction (heart failure). The order of these two events is still unknown; it is likely however that, in some instances, a shift in metabolism is secondary to a primary cardiac disease process, whereas in other instances the change in substrate utilisation is the primary event, impacting on cardiac performance and leading to cardiac dysfunction. In the former case the change may be adaptive, serving to preserve cardiac function; in the latter case, a maladaptive change in substrate selection adversely affects cardiac pump function. Regardless of primacy, the relationship between cardiac metabolism and mechanical function is probably so intimate that the distinction becomes irrelevant.

The basis for the potentially beneficial or detrimental impact of substrate selection on cardiac performance hinges on the concept of metabolic efficiency. Cardiac efficiency may be expressed in several ways, including the ratio of external cardiac power to cardiac energy expenditure (2). As myocardial metabolism is predominantly (> 95%) oxidative, myocardial energy expenditure may be estimated from myocardial oxygen consumption. Because FAs are more reduced than carbohydrates, they yield more ATP per mol when oxidized (palmitate: 104 mol ATP/mol; glucose: 34 mol ATP/mol)(74) but this comes at a greater oxygen cost (P:O ratio; palmitate: 2.80 mol ATP/mol O_2; glucose: 3.17 mol ATP/mol O_2)(74-76). It is possible that the difference *in vivo* is even greater than this, partly due to the effect of mitochondrial uncoupling proteins (UCPs)(77). Hence, glucose can be regarded as a more "efficient" oxidative fuel than FA, at least in terms of oxygen consumption, and this may be critical in cardiac metabolism where oxygen supply through the coronary circulation is limited and precarious, and typically decreased in many cardiac diseases. Furthermore, whilst glucose metabolism is undoubtedly more flexible than FA metabolism, providing limited energy even anaerobically by glycolysis, the relationship between glycolysis and glucose oxidation may be critical in cardiac disease. Coupling of glucose (pyruvate) oxidation to glycolysis is thought to be necessary to prevent the generation of intracellular acidosis, although this mechanism has been challenged (78-80). Finally, glucose can be considered a more metabolically efficient fuel than FAs by virtue of its ability to replenish TCA cycle intermediates through anaplerosis (81-85), in contrast to cataplerotic (in the case of even chain carbon number) FAs and ketone bodies (43, 86).

4.1. Cardiac hypertrophy

Hypertrophy of the cardiac ventricle involves a structural remodelling of the cardiomyocyte (87) and may be an adaptive process to physiological stimuli (e.g. exercise), or maladaptive to diverse pathological stimuli, which may be categorised as pressure overload (causing concentric hypertrophy with ventricular wall thickening) and volume overload (causing eccentric hypertrophy and ultimately leading to ventricular dilatation) (88). The natural progression of both these maladaptive processes is towards cardiac failure (inability to maintain an adequate cardiac output). Pressure overloading with ventricular thickening leads principally to diastolic dysfunction, whereas volume overloading with ventricular dilatation leads mainly to systolic dysfunction; primary cardiac muscle disease tends to cause uncompensated wall stretch: idiopathic dilated cardiomyopathy. Adaptive (physiological) and maladaptive (pathological) states have different phenotypes, including the remodelling of metabolic profiles (88-94). Whilst adaptive physiological hypertrophy normalises wall stress and oxygen consumption, the changes in pathological hypertrophy ultimately lead to heart failure and an inability to cope with stress, including ischemia and reperfusion. Attempts have been made to relate observed changes in myocardial metabolism to changes in cardiac function: adaptive metabolic remodelling preserves cardiac function, whilst maladaptive metabolic remodelling compromises cardiac function and may be the trigger for progression to heart failure (95).

In physiological hypertrophy, increased long chain FA oxidation is observed, presumably a reflection of the increased workload (88, 93). However, glycolysis is decreased whilst glucose oxidation is increased, indicating more coupled glucose metabolism (88, 93, 96), an adaptation considered beneficial as glucose uncoupling increases cytosolic acidification (97) and disrupts sodium and calcium handling (see below)(2). Myocardial lactate oxidation is also increased in exercise/physiological hypertrophy: indeed, lactate may be oxidized preferentially to FAs (69, 98-104). The increase in long chain FA oxidation is mediated by increased peroxisome proliferator-activated receptor-α (PPARα) and PPAR-γ coactivator-1α (PGC-1α) activity. By contrast, changes occurring in pathological hypertrophy are variable and time-dependent, according to the conditions leading to the hypertrophy. These changes have been interpreted as initially adaptive, but eventually render the ventricle less able to cope with additional stress (e.g. ischemia-reperfusion) when they become maladaptive, as they may contribute to the disease process itself. The pattern of metabolic phenotype observed

in pathological cardiac hypertrophy has been summarized as reverting to the fetal situation (105), with a recapitulation of the fetal metabolic gene expression program (66, 106). The patterns are similar, but not identical. Long chain FA oxidation is decreased (107-109) (though medium chain FA oxidation is unaffected (108, 110) – medium chain FAs do not require carnitine shuttling for transport into mitochondria); there is an early decrease in FA oxidation gene expression, but decreases in proteins of FA oxidation are only seen late in the disease progression, when heart failure supervenes (111). Decreased FA oxidation in hypertrophy can be interpreted as an adaptive mechanism because of the inherent inefficiency of FAs as substrates (see above); however, the (im)balance between glycolysis and glucose oxidation (glucose coupling) is likely to have a significant impact on resulting cardiac efficiency (91). Strikingly, there is increased glucose uptake and glycolysis, but unchanged or even decreased glucose oxidation (88, 91, 93, 107). Hence glucose metabolism is more uncoupled with potentially deleterious consequences (see below). Despite the inherent inefficiency of FA as energetic substrate, it is notable that primary (genetic) defects in FA oxidation result in hypertrophic cardiomyopathy (112-116). The decrease in FA oxidation enzymes in hypertrophy may be mediated by increased FA gene transcription repressors (e.g. the chicken ovalbumin upstream promoter transcription factor (COUP-TF), Sp1, Sp3)(106) together with decreased expression of PPARα and PGC-1α and potentially other transcription factors(66). A potential consequence of decreased FA oxidation is lipid accumulation within the cardiomyocyte, especially if FA supply and uptake is maintained or increased (and it is noteworthy that unlike the low plasma NEFA in the fetus, plasma NEFA concentrations are sometimes increased in cardiac failure) (117-119).

4.2. Cardiac failure

It has proved extremely difficult to categorize changes in myocardial metabolism with cardiac function in the development of heart failure (inability to maintain an adequate cardiac output; for review see (2, 8, 9, 120, 121). This is likely to be due to the variety of the multiple etiologies leading to the final outcome of cardiac failure; indeed, the distinction between hypertrophy and failure may be specious, as hypertrophy ultimately leads to failure, and many causes of failure (e.g. myocardial infarct) are associated with compensatory myocardial hypertrophy. Hence, the diversity of cardiac conditions leading to heart failure may be expected to be associated with diverse metabolic phenotypes and, within the limitations of the number of ways in which the heart is able to respond, this is found to be the case. Hence there are widely varying reports in the literature as to the characteristic changes in metabolism associated with heart failure, and the issue of whether heart failure leads to "metabolic failure" or, conversely, whether primary changes in metabolism are the primary cause of heart failure, remains uncertain.

Heart failure is associated with increased circulating NEFA (117-119), a reflection of the stimulation of the sympatho-adrenal axis in low cardiac output states with resultant increased catecholamine activity and hence increased adipose tissue lipolysis. NEFA availability is increased and, as FA availability regulates the rate of myocardial β-oxidation (122), increased FA utilisation would be anticipated; however, increased (117), decreased (107, 108, 123-128) and unchanged (129, 130) rates of FA uptake and oxidation have all been reported in human patients and animal models of heart failure, and these have largely been associated with reciprocal changes in glucose metabolism (see (2). The observed rates of FA utilisation/oxidation probably reflect prevailing plasma NEFA levels. Plasma ketone body concentrations will also be increased in heart failure if NEFA concentrations are high, and preferential cardiac utilisation of ketones may also influence (decrease) FA and glucose utilisation and metabolism (131). It is likely that, in early heart failure, changes in metabolism are modest, which may argue against altered metabolism as a primary cause of heart failure; however, in advanced disease there is a general decrease in all metabolic enzymes (132), with decreased myocardial capacity for β-oxidation (decreased PPARα activity (133, 134)), together with decreased mitochondrial function and capacity (10, 135-137) (probably as a result of decreased PGC-1α activity (138)) – despite increased plasma NEFA concentrations – leading to suggestions that heart failure causes disruption of the PPARα/RXR/PGC-1α nuclear transcription complex (139, 140). The defects in metabolism in heart failure, including decreased mitochondrial and electron transport chain capacity (i.e. decreased oxidative capacity) result in decreased ATP, increased ADP (decreased energy charge and phosphorylation potential) and decreased creatine phosphate (119, 141). These changes impact on energy-dependent mechanisms of contraction (excitation-contraction coupling through myosin-ATPase) and relaxation (sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA2a)). The decrease in FA oxidation in severe heart failure has been interpreted as an adaptive mechanism, based on the intrinsic inefficiency of FA as a metabolic fuel, and has led to a variety of strategies to decrease FA oxidation and/or increase glucose oxidation (increase glucose coupling) in the treatment of heart failure (2, 120, 142-148). These interventions include: 1. inhibitors of FA oxidation, including CPT-1 inhibitors (e.g. etomoxir, oxfenicine, perhexiline), partial β-oxidation inhibitors (e.g. trimetazidine, ranolazine), inhibitors of lipolysis and agents to lower plasma lipids (e.g. nicotinic acid, insulin, β-blockers, PPARγ agonists (e.g. thiazolidinediones) and PPARα agonists (e.g. fibrates) to stimulate extracardiac FA oxidation and hence decrease plasma lipids), and 2. direct stimulators of glucose oxidation such as dichloroacetate (DCA), which inhibits PDH kinase (PDK), increasing PDH activity. In general, these strategies have demonstrated that partially decreasing oxidation of energetically inefficient FAs, and stimulating pyruvate oxidation, hence increasing glucose coupling, improves cardiac contractile function, although results to date have been modest and inconsistent, and their role in the clinical management of heart failure in humans is relatively limited (149), with fatty acids remaining a vital energy resource (121).

GLUT1 and GLUT4 expression are both decreased in heart failure (105, 119, 150), implying

decreased basal and insulin-stimulated glucose uptake, together with decreased PDH activity (151), but PDK4 is also decreased (105, 150) (a PPARα-dependent enzyme) which may account for the observed increase in glucose metabolism in advanced heart failure (125, 150); it is possible that glucose utilisation increases in response to decreased FA oxidative capacity, rather than as a primary mechanism. Therefore, it seems likely that decreases in enzymes of oxidative metabolism (including FA β-oxidation and electron transport chain complexes (136)) in heart failure result in increased reliance on glucose for energy (notably glycolysis) by the failing heart. One possible explanation for the reversion to a fetal pattern of metabolism in the hypertrophied and failing heart, with decreased oxidative metabolism and increased reliance on glycolysis, is the potentially unifying mechanism of hypoxia: the fetal heart is hypoxic (56) and its gene expression pattern and metabolic phenotype reflect this (58, 61, 105, 152, 153). The pathologically hypertrophied ventricle, with its thickened wall muscle and increased distance from epicardial coronary vascular supply to subendocardial regions increased, together with increased wall tension, may have critically limiting coronary blood flow especially in the subendocardial region, with resulting hypoxia, conditions that could also pertain to the dilated and thinned ventricular wall in the volume overload of late-stage cardiac failure. The resulting hypoxia would trigger reversion to a glycolytic energy economy, resulting in the observed increase in lactate production; such a mechanism may be mediated by induction of the oxygen-sensing transcription factor hypoxia-inducible factor (HIF). Physiological hypertrophy allows adequate neovascular growth, and hence adequate oxygen delivery is maintained to permit increased FA and glucose oxidation. The prevailing difference between fetal and adult hypertrophy/failure phenotypes would be the plasma NEFA concentration – low in the fetus and athletes, high in failure, which may account for some of the differences seen in physiological and pathological states.

4.3. Ischemia-reperfusion injury

Profound changes in substrate metabolism are also seen during ischemia and subsequent reperfusion (154), but again these are variable and highly condition-dependent. An acute fall in cardiac output, secondary to myocardial ischemia, activates the sympathoadrenal axis and hence adipose tissue lipolysis is activated, leading to a rise in plasma NEFA levels and FA availability (155); however, cardiac substrate utilisation will critically depend on coronary flow (156). Total ischemia results in increased glycolysis from endogenous glycogen stores and cessation of oxidative metabolism, with rapid onset of necrosis and cell death. However, partial ischemia, in which some limited coronary blood flow remains, is characterized by increased glycolysis, plus some preservation of pyruvate oxidation (albeit at a decreased rate) and hence uncoupling of glucose metabolism (157, 158) with intracellular lactate and proton production. FA oxidation is decreased at this time due to the relative lack of oxygen availability; this may account for an accumulation of FA intermediates (including fatty acyl-CoA)(159), leading to mitochondrial damage. On restoration of coronary flow (reperfusion), cellular energy-sensing mechanisms (such as 5'AMP-activated protein kinase (AMPK)(160), acting on acetyl-CoA carboxylase and malonyl-CoA decarboxylase to decrease malonyl-CoA levels; Figure 2) stimulate FA oxidation to excessively high rates (161-163), and AMPK inhibition may improve cardiac functional recovery on reperfusion (164). This may be further aggravated by increased LPL activity in reperfusion (165), although LPL activity has been reported to be decreased in ischemia (166). FAs, both as oxidative substrates and tissue lipid substrates, have consistently been found to impair cardiac function in reperfusion (167, 168); cardiac function correlates with phosphorylation potential, which is decreased in ischemia-reperfusion (169). The combination of uncoupled glucose metabolism (glycolysis > pyruvate oxidation) and an oxidative balance favoring FA oxidation over glucose oxidation in reperfusion (170) is energetically inefficient and also leads to intracellular acidification, which is suggested to be central to the abnormalities of Na^+, and hence Ca^{2+}, handling which result in intracellular calcium overload in these hearts (171), causing contractile dysfunction ("stone heart"), further mitochondrial damage, and apoptosis (see (2)). Again, the balance between glycolysis, pyruvate oxidation, and FA oxidation, is critical to cardiac function and outcome.

4.4. Unloading

The structural and metabolic changes observed in cardiac hypertrophy, and the ultimate progression of hypertrophy to heart failure, have been termed "ventricular remodelling" and have obvious clinical importance (172, 173). Recently, the phenomenon of "reverse ventricular remodelling" in the unloaded myocardium has attracted considerable interest (174). The prevalence of heart failure has prompted the development of mechanical "ventricular assist" devices in clinical practice that pump blood in parallel with the native heart, resulting in pressure and volume unloading of the failing ventricle (175). This intervention was conceived as a "bridge to transplant" for cardiac failure patients awaiting heart transplant, but it became clear that partial recovery of cardiac function occurred following explantation of devices in some patients (176), a surprising finding given that the structural and functional changes observed in cardiac failure were thought to be irreversible (177). Clinically, this has led to the concept of ventricular assist devices as bridges to recovery, but has also prompted considerable research interest in the structural and metabolic changes that occur in the unloaded myocardium (178).

The changes seen may be categorised as structural (trophic), cellular, metabolic/molecular and, ultimately functional (177, 178). Although the changes may be considered atrophic in nature (179, 180), recovery of function suggests alternative mechanisms. The changes are multifaceted and complex, but a striking feature is a partial reversion to the fetal gene expression program (64, 65, 181-183). In unloading, fetal isoforms of contractile proteins (e.g. MHCα to MHCβ) and metabolic enzymes (e.g. GLUT4 to GLUT1; mCPT-1 to lCPT-1) are re-expressed, together with enhanced expression of characteristically fetal growth factors (e.g. transforming growth factor-β

(TGFβ), insulin-like growth factor-1 (IGF-1), fibroblast growth factor-2 (FGF-2) and proto-oncogenes (e.g. c-fos) (64, 65, 184). In addition, calcium handling machinery (SERCA2a, ryanodine receptor (RyR), Na^{+}/Ca^{2+} exchanger (NCX))(185) and calcium transients (177, 186-188) improve; these changes are associated with improved contractile function. Furthermore, hypertrophy of failing hearts regresses (186). The observation that re-expression of a fetal pattern of components of energy metabolism precedes changes of MHC and trophic factors has led to the concept that the changes may be primarily related to energy provision. This would complement the situation in heart failure, where there is a general decrease in components of energy release, suggesting energy "starvation" itself leads to contractile dysfunction (10, 110, 189). Expression of fetal isoforms of metabolic enzymes, and hence patterns of metabolism (i.e. reversion to a glucose-based energy supply) may indicate that the metabolic strategy in this state is concerned with energy sparing rather than contractile efficiency (64) (though see comments on relative efficiencies of glucose and FA utilisation); furthermore, a particularly striking observation is that a similar recapitulation to the fetal pattern of metabolism seen in unloading also occurs in pressure-overload hypertrophy - the opposite extremes of cardiac workload and trophic response, yet having a similar metabolic transcriptional profile and phenotype, together with similar signalling mechanisms (179). Whilst this may simply reflect the limited ways in which the myocardium can respond to "stress", a teleological explanation would suggest a concerted molecular mechanism to spare energy, rather than optimise contractile efficiency (64). Hence the changes in metabolism seen in both hypertrophy and unloading are adaptive in nature; however, one major difference between the two conditions is that unloading does not progress beyond a limited state (atrophy) whereas hypertrophy will eventually progress to heart failure. In this case, there is down regulation of all metabolic machinery (see, e.g. (2, 8, 120, 173, 183, 189) resulting in inadequate energy supply (energy starvation), culminating in loss of contractile function (132, 190).

Whilst the underlying signalling mechanisms responsible for the rapid change to fetal isoenzyme gene expression are still being investigated, it has become clear that downregulation of PPARα expression mediates at least some of the changes, both in relation to lipid and glucose metabolism (179, 183, 191): there is simultaneously decreased expression of many PPARα-regulated metabolic components, including medium chain acyl-CoA dehydrogenase (MCAD), uncoupling protein-3 (UCP3) and PDK4 (184), a mechanism likely mediated by the transcription factor NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells). Hence, both increased and decreased cardiac work increase glucose and decrease FA utilisation, likely to have been orchestrated by the decreased PPARα occurring in hypertrophy and unloading, with decreased PDK4, MCAD and UCP3 protein expression. The central importance of PPARα in orchestrating these changes, and their adaptive nature, is emphasised by the severe contractile dysfunction which results following reactivation of PPARα in hypertrophy (192).

Not all the changes seen in unloading have been interpreted as beneficial – the issue of atrophy with decreased contractile reserve has been raised (180, 183, 193), together with controversy regarding cellular calcium regulation and increased myocardial collagen and fibrosis (178, 194). However, progression to full fibrosis does not occur, and the changes in protein metabolism reported (increased protein synthesis and simultaneously increased protein degradation, based on mammalian target of rapamycin (mTOR) and ubiquitin proteosome proteolysis (UPP) levels)(195, 196) suggest an active remodelling process, dissimilar in nature to the true atrophy seen in skeletal muscle denervation (decreased mTOR and increased UPP)(196).

Increased caveolin expression occurs in unloading and is associated with increased CD36/FAT expression (197) and, while this latter finding seems unexpected in the context of decreased FA oxidation, it may contribute to improved lipid metabolism; it may also improve cardiomyocyte insulin sensitivity: $CD36^{-/-}$ knockout hearts are insulin-resistant and develop hypertrophic cardiomyopathy (197). This is a particularly striking finding, given the putative relationship between caveolins and integrins (caveolin-1 is involved in integrin signalling). In turn, integrins may form the basis of mechanoreception, sensing contraction through the extracellular matrix. The relationship between cardiac contraction and insulin sensitivity is also suggested by the finding that myocardial glycogen levels are increased in unloading, together with decreased active glycogen synthase (GS-I), slower glycogen synthesis and less activation of GS by infused insulin (198) – contraction is required to maintain insulin responsiveness. Some investigators have reported unchanged levels of cardiac glycogen in unloading (182), but their finding of decreased active GS is consistent, and therefore also argues for the importance of contraction, and myocardial glycogen levels, in cardiac insulin sensitivity (182, 199). The shift from GLUT4 (insulin sensitive; decreased) to GLUT1 (constitutive; increased) expression in unloading also results in a loss of insulin responsiveness in this state.

Besides the observed relationship between FA oxidation rate and contractile function in unloaded (as well as pressure overloaded) hearts *ex vivo* (182), the importance of lipid metabolism in cardiac function is also demonstrated by the finding of increased cardiolipin levels in unloaded hearts, a finding associated with improved mitochondrial function in these hearts (200); this may also account for the observed decrease in apoptosis in unloaded hearts compared to the increased apoptosis which is considered a central feature of heart failure (178) – although Bugger *et al* (180) report atrophy and decreased electron transport chain complexes 1 and 2, and decreased state 3 respiration in 8 day unloaded rat hearts. Glucose metabolism is also linked to cell survival (199).

4.5. Diabetes

Diabetes mellitus is the classic metabolic disease and, as such, would be expected to involve changes in substrate metabolism in many tissues, including heart, which has consistently been found to occur in both type 1 (insulin-deficient) and type 2 (insulin-resistant) diabetes. The observation that cardiac contractile function may be decreased in this disease ("diabetic cardiomyopathy") in the absence of associated coronary vascular or hypertensive disease (201-203) has stimulated a

large effort to define the underlying mechanism (203-209). Whilst decreased mitochondrial function, impaired calcium signalling and dysfunctional contractile machinery have all been described in the diabetic myocardium (210-212), it is possible that there is a central role for altered metabolism in diabetic cardiac dysfunction, which has led to the suggestion that the etiology may be primarily based on the changes in substrate flux and cardiac utilisation that characteristically occur.

Although plasma insulin levels vary in diabetes (decreased in type 1 diabetes, increased early, but decreased late, in type 2 diabetes), as do blood glucose levels (increased in type 1 diabetes, normal in early, but increased in late type 2 diabetes), changes in plasma lipids are more consistent. Diabetic dyslipidemia is characterised by increased plasma NEFA levels (mainly a result of increased adipose tissue lipolysis secondary to decreased insulin action in this tissue)(213-215) and hypertriglyceridemia (increased plasma VLDL levels)(214, 216-218). Increased VLDL is due to increased hepatic production (219, 220), and also decreased uptake by certain tissues (220), a consequence of tissue-specific changes in LPL activity in diabetes (221), but also a result of the abnormal composition of TGRLP in diabetes (220, 222). The complex pattern of prevailing substrate availability (glucose, NEFA, TAG, ketone bodies) together with changes in hormonal milieu (insulin, leptin) *in vivo* make studying cardiac substrate utilisation by the diabetic heart, and relating this to cardiac mechanical function, problematic, and caution must be applied when interpreting studies that have examined diabetic cardiac metabolism *ex vivo*. This is especially true when considering the role of other quantitatively important substrates in diabetes, such as ketone bodies (and amino acids). Furthermore, it has proved difficult to assess the degree of insulin sensitivity/resistance in the heart compared to other tissues (e.g. skeletal muscle)(119, 121, 223-228). However, a consensus pattern of changes in cardiac metabolism in the diabetic heart has emerged.

Diabetic heart may be characterised as having increased reliance on FA as energetic substrate; *ex vivo* studies have indicated that, when perfused with glucose and FA, FA oxidation accounts for > 90% of ATP generation (see (2, 207, 229-233)). Some dissenting studies have failed to demonstrate this effect (234, 235), but most studies in both insulin-deficient and insulin-resistant diabetes show increased FA oxidation. Furthermore, this increased FA utilisation and oxidation by the diabetic heart is associated with decreased cardiac efficiency (the relationship between contractile power and myocardial oxygen consumption)(231, 236), which may provide a mechanistic basis for diabetic cardiomyopathy. The decreased efficiency is only partly accounted for by the fact that FAs are more reduced than carbohydrates and therefore require more oxygen for complete oxidation; increased FA utilisation also results in increased ATP hydrolysis for non-contractile purposes (237) (including mitochondrial uncoupling of oxidative phosphorylation and increased substrate cycling(2)).The driving force behind this effect is likely the increased plasma NEFA perfusing the heart from increased adipose tissue lipolysis: FA availability determines FA utilisation (including regulation of β-oxidation)(122). However, increased NEFA levels also stimulate cardiac PPARα (238-242), resulting in up-regulation of lipid metabolising pathways (including FA transport proteins, β-oxidation components, and mitochondrial uncoupling proteins). Indeed, it is striking that PPARα-overexpressing mice have a phenotype very similar to diabetes (36, 203, 207, 243, 244). Inhibition of glucose utilisation and pyruvate oxidation by increased FA oxidation, a mechanism based on the Randle cycle, also contributes to dysregulation and decreased efficiency in these hearts in diabetes; the importance of glucose metabolism to metabolic efficiency via anaplerotic reactions has been demonstrated (81, 82, 85, 245, 246).

In addition, it is found that diabetes is accompanied by increased PGC-1α levels (138, 243, 247), a co-activator of PPARα, strongly suggesting upregulation of FA utilising mechanisms and accounting for the (generally) observed increase in cardiac FA utilisation in this state. The reciprocal nature of glucose and FA oxidation in hypertrophy and diabetes is emphasised by the finding that PGC-1α is downregulated in hypertrophy (66, 138), coincidentally with the decreased lipid (and increased glucose) utilisation, compared with the opposite pattern in diabetes, suggesting a role for PGC-1α as a central energy regulator (248-251).

Furthermore, the increased cardiac FA uptake seen in diabetes is also associated with increased accumulation of intracellular lipids (205, 207, 252-256). Since cardiomyocytes are not specialised to store lipid, this finding suggests a deleterious effect, and cellular lipid overloading underlies the concept of "lipotoxicity" as a potential mechanism for impaired cardiac function (36, 257-259). The importance of the cellular lipid (TAG) pool was highlighted by studies by Saddik *et al* (37, 254, 260), who demonstrated the dynamic nature of this intracellular pool. The disjunction between increased FA uptake and increased cellular lipid deposition, despite increased FA oxidation, has led to controversy regarding the importance of the balance between uptake and disposal (oxidation) in determining cardiac lipid accumulation; for example, PPARα downregulation leading to decreased FA oxidation, and hence decreased intracellular FA disposal, in some rat studies has been proposed as a mechanism leading to cellular lipid accumulation in diabetes (16, 235).

Whilst some FA provision appears essential for normal cardiac function (261), excess FA utilisation clearly has the capacity to be deleterious to cardiac function (256, 262). It is unlikely that TAG itself is cytotoxic, but some other intracellular FA derivative, increased in hyperlipidemic conditions, including (but not limited to) diabetes, may be responsible for the observed impaired cell function. One suggestion is fatty acyl-CoA (205, 263-265), and in this respect it is noteworthy that mitochondrial uncoupling proteins (increased in diabetes (229)) have been suggested as mechanisms to transport FA anions, via activity of mitochondrial thioesterase-1, to replenish intramitochondrial coenzyme-A (266-268). Another

suggestion is that sphingolipid derivatives may be involved: excess FA leads to increased ceramide levels (269, 270), causing increased apoptosis with subsequent impairment of cardiac function, an effect observed in the diabetic heart (258, 259, 271). By contrast, FAs may exert protective effects on the diabetic myocardium: although the diabetic myocardium is more susceptible to ischemia-reperfusion injury than healthy hearts (272), FAs are protective during low-flow ischemia (273).

The role of TAG in cardiac energy provision and (dys)function in diabetes has been difficult to define (274, 275), partly because of the conflicting results in animal models and uncertainty regarding the regulation of cardiac LPL activity, and partly because the physiological role of TGRLP in energy provision in the healthy heart is still uncertain (Figure 1)(21, 34). Increased (276-282), unchanged (22, 283-286) and decreased (280, 282, 287-292) myocardial LPL activity have all been reported in response to diabetes or nutritional manipulations that alter insulin; these results reflect the complex nature of LPL biology (27, 29). That TAG is a major cardiac fuel (24, 34) and LPL is essential for heart function are demonstrated by the loss of cardiac function observed in heart-specific LPL knockouts (26, 38, 39) – NEFA cannot replace TAG-derived FA *in vivo* (despite increased glucose utilisation (39)); its importance is emphasised by the fact that hearts overexpressing LPL accumulate cellular lipid and show mechanical dysfunction (256, 293). Furthermore the importance of cardiac LPL for whole body TAG metabolism (and the quantitative importance of heart LPL as a TAG "sink" (38, 40, 294)) is demonstrated by the finding that heart LPL rescue in $LPL^{-/-}$ knockout mice normalises plasma TAG concentration (38, 294). However, on the balance of published studies, the current consensus view is that fasting and diabetes increase heart LPL activity (i.e. the opposite effect to that seen in white adipose tissue) (28, 29) although this effect is modest. Increased cardiac LPL activity in diabetes would account in part for the lipotoxicity and cardiomyopathy seen in the diabetic heart (22, 29, 229, 295, 296), although this is difficult to reconcile with the hypertriglyceridemia that is characteristic of the diabetic state. It is possible that CM-TAG, but not VLDL-TAG, utilisation is increased in diabetic hearts (22) (since CM are a better substrate for LPL than VLDL) and compositional changes to CM in diabetes may enhance this effect. However, VLDL, and in particular diabetic VLDL, is a relatively poor substrate for cardiac LPL (219) and undergoes significant compositional change in diabetes (220, 222, 274, 297, 298). Recent evidence that AMPK regulates cardiac LPL may provide a clue as to the (dys)regulation of cardiac LPL in diabetes (and other disease states) – it is possible that PPARα provides "chronic" regulation of cardiac LPL activity (and TAG-FA derived from cardiac LPL is known to act as a PPARα ligand (299-301)), whilst AMPK acts to regulate the enzyme acutely (278, 302, 303). However, AMPK inhibition by siRNA does not decrease LPL protein or activity (304). A further mechanism likely to be involved in cardiac TAG metabolism is lipoprotein receptor-mediated uptake. Several lipoprotein receptors have been implicated in cardiac FA uptake, including the apo-E-binding VLDL receptor (VLDL-R)(31) and the apo-B-binding TGRLP receptor (305). These receptors provide the cell with cholesterol, but also account for significant bulk uptake of TAG-FA, both by particle and remnant uptake and by selective core uptake (34, 35), and it is possible that FA assimilated by this route is differentially channelled between tissue deposition and oxidation (35). Indeed, evidence suggests that LPL-derived FAs also enter a different intracellular metabolic pool (and may enter the cell through distinct FA transporters) than NEFA (35), although it is striking that both LPL and CD36/FAT seems to be similarly regulated (including by AMPK, PPARα and insulin). The putative role of muscle contraction in LPL expression, stimulating CD36/FAT (306), remains to be elucidated. Intracellular channelling may direct FA from different sources (NEFA; LPL; lipoprotein receptors) to different metabolic fates, and this may account for some aspects of myocellular lipid accumulation and subsequent lipotoxic cardiomyopathy. Besides hydrolysis of TGRLP, LPL has an important "bridging" function, facilitating TGRLP-lipoprotein receptor binding (307, 308); the effect of diabetes on this process is not known. However, VLDL-R is downregulated in STZ-treated (insulin-deficient) rats (309); VLDL-R is involved in LPL transcytosis from parenchymal cells to the active site on the endothelium (310, 311). LPL is also regulated by angiopoietin-like protein-4 (angPTL-4; an LPL inhibitor)(312) but again the significance of this in diabetes is uncertain. Stress does upregulate cardiac LPL (313), and this may be related to glucocorticoid secretion (314) although catecholamines do not directly alter the activity of cardiac LPL *in vivo* (315) or *in vitro* (316).

Whilst the issue of insulin sensitivity/resistance in diabetic cardiomyocytes remains controversial, with rat studies generally suggesting myocardial insulin resistance in type 2 diabetes (227, 228, 317) but human studies demonstrating little or no cardiac insulin resistance in this condition (318), it is apparent that glucose oxidation is decreased in the diabetic myocardium, despite high glucose exposure (319, 320). This may be a reflection of the decreased GLUT4 expression seen in these hearts (321). The issue of insulin sensitivity is central to the resulting cardiac metabolic phenotype. Type 1 (insulin-deficient) diabetic hearts retain insulin sensitivity and hence the ability to switch metabolic substrates ("metabolic flexibility"): the prevailing high lipid (NEFA; TAG) concentrations, together with PPAR-stimulated lipid metabolic pathways (LPL, CD36/FAT, fatty acyl-CoA synthetase (FACS), MCAD, UCP &c.), and downregulated glucose utilising machinery (322), ensure that the resulting metabolism is principally lipid based, with lipotoxicity if FA uptake pathways exceed FA oxidation/uncoupling mechanisms. Metabolic flexibility is however maintained – these hearts are capable of increasing glucose utilisation (228). Type 2 diabetic hearts, however, demonstrate metabolic inflexibility *in vivo* (227), which may represent insulin resistance in the cardiomyocyte itself. The issue of insulin resistance in the diabetic heart remains controversial however – cardiomyocytes, but not hearts, isolated from db/db diabetic mice are insulin sensitive *in vitro*. Again, the importance and complexity of the hormone and substrate

milieu *in vivo* demands cautious interpretation of *ex vivo* data.

5. PERSPECTIVE

Significant advances have been made in characterizing energetic substrate utilisation by the heart in both health and disease, and in defining the regulatory mechanisms controlling substrate selection by the myocardium under varying pathophysiological conditions. The importance of multiple levels of regulation, from substrate supply to the regulation of transcription of substrate transport components and metabolic enzymes is now apparent, together with the fact that they change profoundly in heart disease. However, the fundamental question of whether cardiac pathology causes changes in myocardial metabolism, or whether a primary alteration in substrate utilisation is responsible for cardiac dysfunction, remains uncertain. Regardless of this, the ability to manipulate cardiac metabolism is a promising therapeutic intervention.

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