Fatty acid transporter levels and palmitate oxidation rate correlate with ejection fraction in the infarcted rat heart

Lisa C. Heather, Mark A. Cole, Craig A. Lygate, Rhys D. Evans, Daniel J. Stucy, Andrew J. Murray, Stefan Neubauer, Kieran Clarke

Objectives: Cardiac fatty acid uptake occurs predominantly via sarcolemmal transporter proteins; fatty acid translocase (FAT/CD36), plasma membrane fatty acid binding protein (FABPpm) and fatty acid transporter proteins (FATP) 1 and 6. We hypothesised that levels of the fatty acid transporters would be reduced in the chronically infarcted rat heart, in parallel with reduced dependence on fatty acid utilisation.

Methods and results: In vivo left ventricular ejection fractions, measured using echocardiography, were 36% lower in rats six months after coronary artery ligation than in sham-operated control rats. In isolated, perfused, infarcted hearts, 3H-palmitate oxidation was 30% lower, and correlated with in vivo ejection fractions. As myocardial lipid incorporation was also reduced by 25%, total palmitate utilisation was 29% lower in the infarcted rat heart. The protein levels of the cardiac fatty acid transporters were reduced in the infarcted rat heart; FAT/CD36 by 36%, FABPpm by 12%, FATP6 by 21% and FATP1 by 26%, and the cytosolic fatty acid binding protein (cFABP) was 47% lower than in sham-operated rat hearts. Fatty acid transporter levels correlated with both palmitate oxidation rates and cardiac ejection fractions.

Conclusions: Reductions in fatty acid oxidation and lipid incorporation rates were accompanied by downregulation of the cardiac fatty acid transporters. The metabolic shift away from fatty acid utilisation was proportional to the degree of functional impairment in the chronically infarcted rat heart.

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Keywords: Heart failure; Infarction; Lipid metabolism; Energy metabolism

1. Introduction

The healthy adult heart is a “metabolic omnivore”, able to utilise a range of substrates [1]. Under normal physiological conditions the heart derives 60–70% of its energy requirement from the oxidation of fatty acids [2]. Changes in fatty acid metabolism have been detected in various models of cardiac hypertrophy and failure, with aortic banded or volume-overloaded rat hearts exhibiting reduced cardiac palmitate oxidation rates [3,4]. In heart failure, many mitochondrial β-oxidative enzymes have reduced activity, and are partly responsible for the overall decrease in fatty acid metabolism [5]. However, it is plausible that decreased sarcolemmal fatty acid uptake may limit entry of the fatty acid moieties into the β-oxidation cycle and thus contributes to the downregulation of this pathway.

Sarcolemmal free fatty acid (FFA) uptake is proposed to occur via two mechanisms; protein mediated transport and passive diffusion, and in isolated cardiomyocytes the contribution of these two processes is believed to be 80% and
20%, respectively [6,7]. A number of proteins have been implicated in sarcolemmal fatty acid uptake; fatty acid translocase (FAT/CD36), plasma membrane fatty acid binding protein (FABPpm), fatty acid transport proteins (FATP) 1 and 6; and cytosolic fatty acid binding protein (cFABP) [8–12]. The significance of these proteins in fatty acid metabolism has been highlighted using knockout models, in which cardiac fatty acid uptake and oxidation were significantly impaired [13,14]. The mechanism by which these proteins co-ordinate fatty acid uptake remains unclear, although they may act in combination to facilitate transfer of the fatty acid moiety across the sarcolemma and to the site of metabolic utilisation within the cytosol [15].

Following uptake, fatty acids can either enter the mitochondrial β-oxidation pathway for production of ATP or be incorporated into intramyocardial lipids as substrate reserves or for phospholipid synthesis [16]. Measurement of both of these pathways is necessary to estimate total palmitate utilisation and hence give an indirect measurement of fatty acid uptake within the intact, contracting heart.

We hypothesised that in the chronically infarcted rat heart, decreased myocardial fatty acid utilisation may be related to the downregulation of the fatty acid transporters. We tested this hypothesis by examining several stages of the fatty acid utilisation process, from the protein levels of the fatty acid transporters to fatty acid oxidation and lipid incorporation rates.

2. Methods

2.1. Rat model of myocardial infarction

Male Wistar rats (∼200 g; n=23) were obtained from a commercial breeder (Harlan, UK) and kept under controlled conditions of temperature, light and humidity, with ad libitum access to rat chow and water. Left coronary artery ligation was performed in rats (n=12), as previously described [17]. In sham-operated rats (n=11), the same procedure was followed, but the ligation suture was not placed in the heart. Rats, at 6 months post-infarction, had reduced ejection fraction with some displaying overt heart failure. The investigation conforms with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

2.2. Echocardiography

Echocardiography was performed post-surgery to ensure successful infarction, and repeated one week prior to perfusion to determine ejection fraction. Animals were anaesthetised with isoflurane and echo as previously described [17]. Ejection fractions were calculated as fractional area change at papillary muscle level, calculated using; ejection fraction (%) = (end diastolic cavity area – end systolic cavity area)/(end diastolic cavity area) × 100.

2.3. Isolated Langendorff perfusion

Infarcted and sham rats (n=6 per group) were fasted overnight and terminally anaesthetised with intraperitoneal sodium pentobarbital (150 mg.kg−1 bodyweight; Euthatal, Merial, UK). Hearts were rapidly excised and placed in ice-cold modified Krebs–Henleit (KH) buffer containing 11 mM glucose. Hearts were cannulated via the aorta and perfused in Langendorff mode with KH buffer (gassed with 95% O2, 5% CO2) at 37 °C, at a constant perfusion pressure of 100 mmHg. After an initial 15 min stabilisation period, hearts were perfused with 250 ml recirculating KH buffer containing 1.0 mM palmitate bound to 1.5% fatty acid-free bovine serum albumin (Sigma, USA) and containing 0.2 µCi.ml−1 [9,10−3H] palmitate for 1 h. To measure functional changes during the perfusion protocol a fluid filled, PVC balloon inflated to 4 mmHg was inserted into the left ventricle and attached via a polyethylene tube to a bridge amplifier (ADInstruments, Oxfordshire, UK) and PowerLab data acquisition system. Left ventricular developed pressure was determined as systolic pressure minus end diastolic pressure. Rate pressure product (RPP) was calculated as the product of developed pressure and heart rate. Post-perfusion, the infarcted region was dissected out and discarded, and the remaining left ventricular tissue was rapidly frozen in liquid nitrogen (N2) for subsequent analysis.

2.4. Palmitate oxidation rates

Aliquots of recirculating buffer were collected every 8 min during the perfusion protocol and palmitate oxidation rates were determined [18]. Briefly, 3H2O was separated from 3H-palmitate in the buffer samples using a chloroform:methanol Folch extraction, with the upper aqueous phase counted for radioactivity. Steady state palmitate oxidation rates were calculated from the linear increase in 3H2O, expressed as μmol.gram whole heart wet weight (gww−1).min−1.

2.5. Incorporation of 3H palmitate into myocardial lipid

Myocardial lipid incorporation is the conversion of exogenous palmitate into the intramyocardial lipid pool. Myocardial 3H lipid content was measured according to the previously published protocol [16]. Frozen left ventricle was powdered under N2 and lipids were extracted using Folch extraction. After drying under air, the lipids were resolubilised in chloroform and separated by thin-layer chromatography (TLC) using a hexane–diethylether–acetic acid aqueous phase. Separated lipid bands were visualised with rhodamine 6G under ultraviolet light and the 3H counted in each isolated lipid group. Total palmitate utilisation was the sum of palmitate oxidation and myocardial lipid incorporation.

2.6. Western blotting

Levels of cardiac proteins were measured in left ventricular whole cell homogenates using SDS-PAGE and Western
Proteins were separated on 12.5% SDS-PAGE gels, incubated in transfer buffer with Immobilon-P membranes (Millipore, UK) and extra thick chromatography paper (BioRad, UK) for 30 min, and transferred using semidry transfer apparatus (BioRad, UK) at 0.07 A per gel for 1 h. Membranes were incubated with primary antibodies overnight, diluted in Tris-buffered saline containing 5% (wt/vol) milk powder. FAT/CD36 was detected with the monoclonal antibody MO25 diluted 1:25,000, a gift from Dr Narendra Tandon (Otsuka Maryland Medicinal Laboratories, MD). The anti-FATP6 antibody (diluted 1:10,000) was donated by Dr Andreas Stahl (Palo Alto Medical Foundation, CA). Primary antibodies raised against FATP1 (diluted 1:200) and cFABP (diluted 1:2,500) were purchased from Santa Cruz Biotechnology (Santa Cruz, CA). The anti-FATP6 antibody (diluted 1:10,000) was donated by Dr Jorge Calles-Escandon (Wake Forest University School of Medicine, NC). Appropriate horseradish peroxidase-conjugated secondary antibodies (Santa Cruz, CA) were detected in left ventricular tissue, by following manufacturer’s instructions. FABPpm was detected using a primary antibody (diluted 1:10,000) donated by Dr Jorge Calles-Escandon (Wake Forest University School of Medicine, NC). Appropriate horseradish peroxidase-conjugated secondary antibodies (Santa Cruz, USA) were diluted 1:3,500 in Tris-buffered saline containing 5% (wt/vol) milk.

2.7. Enzyme assays

Medium chain acyl-coenzyme A dehydrogenase (MCAD) activity was measured in left ventricular tissue, by following the decrease in ferricinium ion absorbance as described by Lehman et al. [20]. Citrate synthase activity was measured in left ventricular tissue, by following decrease in absorbance at 340 nm. Appropriate horseradish peroxidase-conjugated secondary antibodies (Santa Cruz, USA) were diluted 1:200 and cFABP (diluted 1:2,500) were purchased from Santa Cruz (Autogen Bioclear, UK) and Abcam (Cambridge, UK), respectively. FABPpm was detected using a primary antibody (diluted 1:10,000) donated by Dr Jorge Calles-Escandon (Wake Forest University School of Medicine, NC). Appropriate horseradish peroxidase-conjugated secondary antibodies (Santa Cruz, USA) were diluted 1:3,500 in Tris-buffered saline containing 5% (wt/vol) milk.

2.8. Plasma metabolites

Post-heart excision, blood was immediately collected from the chest cavity and plasma was separated by centrifugation and stored at −80 °C. Analysis of plasma glucose and triacylglycerol (TAG) concentrations was carried out using an automated spectrophotometric analyser (Monarch Laboratories, Maumee OH, USA). Aliquots of plasma were stored in the presence of 2% BHT lipoprotein lipase inhibitor (Xenical, Roche, USA) and assayed for FFA (NEFA assay kit, Wako Chemicals, Germany).

2.9. Statistical analysis

Data are presented as means ±SEM. Data were analysed using an unpaired t-test (SPSS 12.0 for windows, USA). Significance was taken at $p < 0.05$.

3. Results

3.1. Cardiac function

Cardiac function was significantly impaired in the infarcted rats, with the mean ejection fraction reduced to 33±4% from 69±3% in sham control rats (Table 1). Six months post-myocardial infarction, body weights of sham and infarcted Wistar rats were the same at 447 g. Infarcted hearts were significantly hypertrophied, with heart weights and heart to body weight ratios 38% higher than shams. Plasma FFA, glucose and TAG concentrations were the same in sham and infarcted rats at 6 months post-surgery (Table 1).

3.2. Palmitate oxidation

Infarcted and sham rat hearts were perfused in the Langendorff mode with 1 mM palmitate, a concentration chosen to mimic the physiologically elevated plasma concentrations seen in patients post-myocardial infarction [22]. Contractile function was impaired in the isolated perfused infarcted hearts, with the rate pressure product 33% lower than sham control hearts (Table 1). There was a positive correlation between the ejection fraction and the rate pressure product measurements, indicating that the ex vivo perfusion conditions closely mimic the in vivo physiological situation ($r^2 = 0.86$, $p < 0.0001$). Palmitate oxidation rates were 30% lower in infarcted rat hearts compared with sham-operated hearts (0.12 ± 0.02 μmol.ggdw$^{-1}$.min$^{-1}$ in infarcted hearts vs. 0.17 ± 0.01 μmol.gww$^{-1}$.min$^{-1}$ in shams, $p < 0.01$). Wet to dry weight ratios did not differ between groups, with the decrease in palmitate oxidation in the infarcted rat hearts maintained when expressed per gram dry weight (1.01 ± 0.13 μmol.gww$^{-1}$.min$^{-1}$ in infarcted hearts vs. 1.36 ± 0.07 μmol.gww$^{-1}$.min$^{-1}$ in shams, $p < 0.05$). Palmitate oxidation rates correlated positively with in vivo ejection fraction and ex vivo rate pressure product measurements, indicating that those hearts with the greatest functional deficit had greater impairment of FFA oxidative capacity (Fig. 1).

Table 1

<table>
<thead>
<tr>
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<th>Sham</th>
<th>Infarct</th>
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<tr>
<td>Physiological characteristics</td>
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<tr>
<td>Ejection fraction (%)</td>
<td>69±3</td>
<td>33±4$^\dagger$</td>
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<tr>
<td>Body weight (g)</td>
<td>447±15</td>
<td>447±13</td>
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<tr>
<td>Heart weight (g)</td>
<td>1.61±0.07</td>
<td>2.22±0.19$^\dagger$</td>
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<tr>
<td>HW/BW ratio (mg.g$^{-1}$)</td>
<td>3.60±0.09</td>
<td>4.97±0.39$^\dagger$</td>
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<tr>
<td>Plasma metabolites (mmol.l$^{-1}$)</td>
<td></td>
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<tr>
<td>FFA</td>
<td>0.46±0.05</td>
<td>0.50±0.03</td>
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<tr>
<td>Glucose</td>
<td>8.18±0.52</td>
<td>9.00±0.97</td>
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<tr>
<td>Triacylglycerol</td>
<td>0.68±0.08</td>
<td>0.76±0.10</td>
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<tr>
<td>Perfusion heart function</td>
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<tr>
<td>Developed pressure (mmHg)</td>
<td>132±5</td>
<td>103±15</td>
</tr>
<tr>
<td>Heart rate (beats.min$^{-1}$)</td>
<td>296±8</td>
<td>270±32</td>
</tr>
<tr>
<td>Coronary flow (ml.min$^{-1}$)</td>
<td>26±1</td>
<td>26±1</td>
</tr>
<tr>
<td>Rate pressure product×10$^{-3}$ (mmHg.min$^{-1}$)</td>
<td>39±1</td>
<td>26±3$^*$</td>
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HW/BW, heart weight to body weight ratio. Physiological characteristics and plasma metabolites, $n=11$ for sham, 12 for infarcts; perfused cardiac function, $n=6$ per group. $^\dagger p<0.05$ vs. sham, $^\ast p<0.01$ vs. sham.
3.3. Total palmitate utilisation

Total palmitate utilisation, the sum of lipid oxidation and myocardial lipid incorporation \[16\], is an indirect measurement of fatty acid uptake. In addition to a 30% reduction in palmitate oxidation rates, infarcted rat hearts had a 25% lower myocardial lipid incorporation \[16\], (Fig. 2). Thus, total palmitate utilisation was 29% lower in the infarcted rat hearts, compared with sham controls \((0.16 \pm 0.02 \ \mu\text{mol.gww}^{-1}.\text{min}^{-1} \ \text{in infarcts} \ vs. \ 0.22 \pm 0.01 \ \mu\text{mol.gww}^{-1}.\text{min}^{-1} \ \text{in shams})\). Myocardial lipid incorporation correlated positively with palmitate oxidation rates \(\left(r^2=0.59, \ p<0.01\right)\) and in vivo ejection fraction \(\left(r^2=0.71, \ p<0.001\right)\). Oxidation and incorporation, expressed as a percentage of total lipid utilisation, were found to be the same in both groups, as palmitate oxidation accounted for 78% and 76%, and incorporation accounted for 22% and 24%, in sham and infarcted hearts, respectively. Palmitate was incorporated into 5 classes of myocardial lipids; — phospholipids (PL), diacylglycerol (DAG), FFA, TAG and cholesterol ester (CE). There was no significant difference in the distribution to the different lipid classes in the infarcted hearts compared with sham-operated hearts (Fig. 2).

3.4. Activity of key mitochondrial enzymes

MCAD activity, a marker of mitochondrial \(\beta\)-oxidative capacity, was reduced by 33% post-myocardial infarction compared with sham hearts (Table 2). Citrate synthase (CS) activity was 14% lower in the infarcted hearts, suggesting lower mitochondrial content. Reductions in MCAD and citrate synthase activities revealed a generalised down-regulation of the fatty acid oxidation pathway in the 6 month post-infarction rat heart.

3.5. Cardiac fatty acid transporters

Total cardiac levels of the fatty acid transporters FAT/CD36, FATP6, FATP1 and FABPpm were measured in left ventricular homogenates. FAT/CD36 was reduced by 36% in the infarcted hearts compared with shams (Fig. 3). The cardiac specific FATP6 and the ubiquitously expressed FATP1 were reduced by 21% and 26%, respectively.

Table 2

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<th>Sham</th>
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<tbody>
<tr>
<td>MCAD activity</td>
<td>7.63 \pm 0.31</td>
<td>4.91 \pm 0.43⁹</td>
</tr>
<tr>
<td>CS activity</td>
<td>148 \pm 8</td>
<td>127 \pm 6*</td>
</tr>
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\(n=6 \ \text{per group}, \ *p<0.001 \ \text{vs. sham}, \ *p<0.05 \ \text{vs. sham.}\)
FABPpm was reduced by 12% and the cytosolic fatty acid binding protein, cFABP, was reduced by 47% in the infarcted rat hearts. Palmitate oxidation rates were found to correlate positively with FAT/CD36, FATP1, FATP6 and cFABP protein levels (Fig. 4). In addition, *in vivo* ejection fractions were found to correlate positively with the protein levels of the fatty acid transporters FAT/CD36 ($r^2=0.62$, $p<0.01$), FATP6 ($r^2=0.52$, $p<0.05$), FATP1 ($r^2=0.42$, $p<0.05$), FABPpm ($r^2=0.36$, $p<0.05$) and cFABP ($r^2=0.45$, $p<0.05$).

4. Discussion

In this study we have shown that palmitate oxidation rates were reduced in the infarcted rat heart, and that the transition away from fatty acid metabolism correlated with the degree of cardiac impairment, in that those hearts with the lowest ejection fractions oxidised the smallest proportion of fatty acids. Decreased palmitate oxidation rates have been observed in both aortic banded and volume-overloaded rat hearts [3,4]. Using the rat model of myocardial infarction, Remondino et al. were unable to show a decrease in palmitate oxidation rates or differences in the mRNA levels of the β-oxidation enzymes [23]. This apparent contrast to our results may have arisen because of varying degrees of cardiac impairment in the two studies. Our correlation of...
palmitate oxidation rates with ejection fraction would suggest that, even with slight cardiac impairment there is an accompanying small reduction in fatty acid oxidation. Studies in humans have also generated apparently conflicting data, Wisneski et al. demonstrated no difference in the rate of myocardial palmitate or oleate oxidation in ischaemic heart disease patients, compared with controls [24]. In contrast, Davila-Roman et al. found decreased fatty acid oxidation rates in patients with idiopathic dilated cardiomyopathy [25]. This apparent contradiction could be explained by differences in ejection fraction seen in these two subsets of patients, with the former study averaging 66% and the latter 27%.

A potential limitation of our study is that the Langendorff retrograde-perfused heart may not accurately represent in vivo cardiac metabolism. However, our palmitate oxidation rates are comparable to those published for the working heart [18]. Allard and co-workers have shown that perfusing hearts at a reduced workload has no significant effect on palmitate oxidation rates in either control or aortic banded hypertrophied hearts [4]. In addition, the close correlation between rate pressure product and ejection fraction suggests that ex vivo perfusion represents in vivo physiology.

Under perfusion conditions in which sufficient metabolic substrates are provided, hearts are able to concurrently oxidise and incorporate appreciable quantities of fatty acids [16]. In the normal healthy heart, 70–90% of fatty acid is diverted to oxidation whilst 10–30% is incorporated into the cardiac tissue [26]. We have shown that, in addition to the reduced palmitate oxidation rates, myocardial lipid incorporation was also reduced in the infarcted rat hearts. This may indicate a depletion of intracellular substrate reserves which, in turn, may jeopardise the heart’s ability to generate sufficient energy during times of increased metabolic demand, such as increased workload. However, to fully characterise changes in triglyceride metabolism in the infarcted heart, measurement of endogenous fatty acid lipolysis is necessary. Interestingly, although both oxidation and myocardial incorporation are reduced in our infarct model, the percentage distribution between these two pathways was maintained. This highlights the possibility of a joint regulatory step upstream of both of these pathways determining the metabolic partitioning of the fatty acids.

Another novel observation in this study is the reduction in the fatty acid transporter levels in the failing heart. Protein levels of FAT/CD36, FATP1, FATP6, and cFABP were lower in the infarcted rat heart and correlated positively with palmitate oxidation rates and ejection fraction. Our observation that changes in transporter levels correlated with fatty acid metabolism is in agreement with studies using modified cell systems and sarcolemmal preparations. Protein levels of FAT/CD36 in genetic models and cell systems change in the same direction as fatty acid uptake and oxidation rates [27,28]. An elegant study by Luiken et al. showed a positive correlation between palmitate uptake into cardiac giant vesicles and the protein levels of FAT/CD36 and FABPpm in a rodent model of type 1 diabetes [29]. In the present study there was a significant decrease in FABPpm protein levels in the infarcted hearts, however the percentage reduction was smaller than in the other transporters, and did not correlate with palmitate oxidation rates. A study by Chabowski et al. showed similar discordance between FAT/CD36 and FABPpm protein levels in response to acute insulin treatment, with the conclusion that the two transporters may be differently regulated [30].

Precisely how these transporters facilitate fatty acid uptake has not yet been determined, but the favoured model suggests they operate synergistically to transfer the fatty acid moiety across the sarcolemma to its site of utilisation in the cytosol [15]. A positive correlation has been shown between palmitate oxidation rates and arterial palmitate concentrations in individuals treated with heparin, indicating that in the acute situation there is a large degree of flexibility in the fatty acid uptake mechanisms within the heart [24]. The present study indicates that in the long term other regulatory factors exist, as plasma fatty acid concentrations were the same in both our sham and infarcted rats, but cardiac fatty acid transporter and oxidation rates were reduced in the infarcted group. Thus, the decrease in fatty acid transporter levels in the failing hearts may account for the decrease in fatty acid utilisation by restricting entry of fatty acids to the cardiomyocyte. Taken together, the decrease in fatty acid transporter levels and the well characterised decrease in MCAD and citrate synthase activity in heart failure would suggest a generalised down-regulation of fatty acid oxidation controlled by a common mechanism [5,31].

Whereas FAT/CD36, FABPpm and FATPs are associated with the sarcolemma and are involved in the fatty acid uptake process [32], cFABP is an intracellular protein that is thought to transfer fatty acids around the cytosolic compartment [14]. In isolated soleus muscle from cFABP null mice, decreased palmitate oxidation was accompanied by decreased TAG and PL synthesis [33]. This suggests that cFABP may be responsible for shuttling the fatty acid moieties from the sarcolemma to the site of esterification or to the mitochondria for oxidation. Our data support this observation, as the decreased palmitate oxidation and incorporation in the present study were accompanied by a 47% decrease in cFABP.

It is possible that the decrease in fatty acid transporters is important in the metabolic switch from fatty acid to carbohydrates in heart failure and that, by limiting fatty acid uptake, the heart has to switch to an alternate available substrate. In FAT/CD36 null mouse hearts, palmitate oxidation rates were reduced with a compensatory increase in glucose oxidation [34], whilst mice over-expressing FATP1 in the heart showed increased cardiac palmitate oxidation and decreased glucose oxidation [35]. Whilst we did not measure glucose metabolism in the present study, we have shown a decrease in insulin-stimulated glucose uptake and a reduction in the protein levels of the insulin-stimulated glucose transporter, GLUT4, in the rat heart 10 weeks post-infarction [36]. Whether this is a transient decrease at
10 weeks, or a sustained decrease in glucose uptake to 6 months, the age of the infarcted rats studied here, remains to be seen. This would indicate whether a “metabolic switch” or an overall suppression of metabolism had occurred in the progression to heart failure [26].

In conclusion, this study demonstrated that the levels of cardiac fatty acid transporters were significantly lower in the intact, infarcted rat heart, and correlated positively with palmitate oxidation, myocardial lipid incorporation rates and cardiac function. There was a parallel decrease in cardiac ejection fraction and total palmitate metabolism, with those hearts with greatest functional impairment exhibiting lowest fatty acid utilisation rates. Although palmitate utilisation was reduced in the infarcted heart, the percentage distribution between oxidation and myocardial incorporation was maintained. These findings suggest that the fatty acid transporters may be involved in the transition away from fatty acid metabolism in heart failure.

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References


