Changes in Substrate Metabolism and Effects of Excess Fatty Acids in Reperfused Myocardium

A. James Liedtke, Luc DeMaison, Alice M. Eggleston, Larry M. Cohen, and Stephen H. Nellis

The purpose of these studies was to characterize the rates of fatty acid oxidation in reperfused myocardium and test the influence of excess fatty acids (FA) on mechanical function in the extracorporeally perfused, working swine heart model. Seventeen animals were prepared. Eight were untreated (LOW FA group; serum FA averaged 0.55 ± 0.07 μmol/ml) and nine received a constant infusion of 10% Intralipid with heparin to raise serum FA to about 1.4 ± 0.21 μmol/ml (HIGH FA group). Coronary flow in both groups was held at aerobic levels for an equilibration period of 40 minutes, acutely reduced regionally in the anterior descending circulation by 60% for 45 minutes, and acutely restored to aerobic levels for 60-minute reflow. Appreciable mechanical depression (−47 Δ%) from aerobic values; p < 0.01) during reperfusion was noted in both groups. This was associated with modest reductions in myocardial oxygen consumption (p < 0.05) and losses of total tissue carnitine stores (p at least < 0.02). Reperfused myocardium showed a strong preference for and aerobic use of FA during reflow such that 14CO2 production from labeled palmitate exceeded preischemic levels (+89 Δ%) in LOW FA hearts; +111 Δ% in HIGH FA hearts). This suggested relative preservation or restoration of certain elements in mitochondrial function during reflow. The findings argue for uncoupling between substrate metabolism and energy production, accelerated but useless energy drainage, or some impairment between energy transfer and function of contractile proteins as possible explanations for the persistent depression of mechanical function (stunning) during reperfusion. Excess FA affected a modest decline in mechanical efficiency at aerobic flows but was without further influence during moderate-to-severe ischemia or reflow. Stunning was not associated with significant tissue accumulations of acyl CoA or carnitine. (Circulation Research 1988;62:535–542)

Fatty acids in excess are known to exacerbate a number of injuries in ischemic myocardium and have been shown both clinically and experimentally to promote and accelerate life-threatening arrhythmias,1–3 impair membrane integrity and suborganellar performance,4–7 and depress myocardial contractility.8–10 Their effects on mechanical function during reflow following reversible ischemia remain contested. Ichihara and Neely10 noted no correlation between hemodynamic recovery during reperfusion and the presence of excess fatty acids in the perfusate under conditions of severe ischemia (0 and 0.5 ml/min) in isolated rat hearts. Conversely, Paulson et al11 reported a further buildup of fatty acid amphiples with excess fatty acids, which was associated with a significant decrease in recovery of cardiac work at conditions of less-severe ischemia (1.2 ml/min). This persistent stunning of contractility has been proposed to relate in some way to the enhanced rates of peroxidation provided by the lipid excess during conditions when free radical formation is accelerated.12,13

Little is currently known regarding metabolic fuel consumption and oxidation during reperfusion. When imaged with positron emission tomography, fatty acid utilization appears distinctly altered following periods of severe ischemia and is replaced by preferred use of glucose in viable tissue. Schwaiger et al14 observed in a canine model that a 20-minute coronary occlusion caused a significant delay in the clearance of [14C]palmitate activity after 90 minutes’ reflow. Increasing the time of occlusion to 3 hours caused more sustained delays in [14C]palmitate clearance for up to 1 week,15 presumably from prolonged impairments of β-oxidation in the fatty acid utilization pathway together with tissue accumulations of triacylglycerols. These trends were also noted in a different experimental model of coronary thrombosis using [14C]palmitate16 and were confirmed recently in another rat heart preparation after severe ischemia (0.1 ml/min) using [14C]palmitate.17 No data are available as yet characterizing these parameters at lesser levels of ischemia.

The purpose of these studies is to further detail metabolic trends with respect to substrate preference and utilization in reperfused myocardium using the extracorporeally perfused, intact, working swine heart model. Emphasis is placed on documenting changes in fatty acid oxidation during reperfusion following moderate-to-severe regional ischemia. Since the presence of excess fatty acid previously has been shown to adversely affect myocardial performance during ischemia in our model system, we extended these observations to include similar measurements during reperfusion. Our hypothesis is that excess fatty acids should delay mechanical recovery.

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Materials and Methods

Adolescent swine, weighing 40–69 kg (average 56.3 ± 2.4 kg), were studied following general anesthesia with pentobarbital (35 mg/kg i.v.), intubation with positive pressure ventilation using oxygen-supplemented room air (60–70% O₂), and administration of heparin (3 mg/kg i.v.). The preparation used in this study has been extensively reported and critiqued elsewhere. 9-18 Briefly, all three coronary arteries were perfused separately via an arterioarterial shunt connected extracorporeally. Blood was withdrawn from a femoral artery and returned by three low-flow perfusion pumps to proximally cannulated right, main left, and left anterior descending (LAD) coronary arteries. Included in the LAD circuit was a 150-ml mixing chamber used to receive a constant infusion of labeled palmitate (approximately 50–55 µCi/animal study) for mixing with the coronary perfusate prior to its infusion into the anterior myocardium. Aerobic flows were adjusted so that coronary perfusion pressures approximated arterial pressures, and the coronary venous oxygen saturation was maintained at or about 30%. Venous canulas were inserted into the great cardiac vein anteriorly and, together with ports in the arterial lines, were used to sample for gases and metabolites.

Global mechanical function (i.e., left ventricular pressure and its maximal first derivative) was measured by a high fidelity manometer-tipped pressure device (Millar Instruments, Houston, Texas) placed in the left ventricle. Regional function was estimated from motion changes and shortening in myocardial segment lengths as measured from pairs of ultrasonic crystals placed at midmyocardial depth in the LAD and left circumflex (LCF) perfusion systems. Segment shortening and elongation or recoil were used to characterize regional contractility and motion abnormalities after the methods of Akashi et al. 20-21

Regional myocardial oxygen consumption (MVO₂ in milliowles per hour per gram dry weight) and fatty acid oxidation (in micromoles of 14CO₂ per hour per gram dry weight) acquired across the LAD perfusion bed, together with serum fatty acids (in micromoles per hour per gram dry weight) and long-chain esters of carnitine from a modified method of Ingebretsen et al. 9-24 All analysis. Tissue was prepared for measurements of fatty acid uptake. Data were gathered at 5-10-minute intervals throughout the perfusion trials and stored for later review on a Digital MINC-23 computer (Digital Equipment, Marlboro, Massachusetts).

At the conclusion of the 145-minute perfusion run, tissue samples from normal (LCF bed) and ischemic-reperfused (LAD bed) myocardium were frozen with Wollenberger clamps and stored at −80° C for further analysis. Tissue was prepared for measurements of free, short-chain, and long-chain esters of carnitine according to methods of Parvin and Pandé 25 and others. 19 Long-chain acetyl CoA was determined using high-performance liquid chromatography (HPLC) from a modified method of Ingebretsen et al. 9 All metabolite data from LCF and LAD myocardium were expressed in nanomoles normalized by dry weight. The size and distribution of the right coronary and LCF beds from the LAD bed were determined at the conclusion of each study by injecting dye into the LAD cannula and dissecting free and weighing the appropriate ventricular myocardium.

The purpose of the studies was to characterize the rates of recovery of mechanical and metabolic function in ischemia-reflow protocols with and without the presence of excess fatty acids. Right coronary and LCF flows were held at aerobic levels throughout the experiments. LAD flow was maintained at aerobic levels for the first 40 minutes of perfusion, reduced acutely by 60% for the next 45 minutes, and then returned to aerobic levels for the remaining 60 minutes. To set a condition of near constant myocardial oxygen demand in all hearts, blood volumes were augmented periodically with 6% dextran to maintain systemic pressures at about 100 mm Hg. This augmentation resulted in a slight but acceptable 11% decrease in hemoglobin. Serum glucose was continuously monitored and maintained above 90 mg/100 ml with intravenous injections of dextrose. [β-14C]Palmitate with 4% bovine serum albumin was infused selectively into the LAD coronary circulation at 0.5 ml/min during control and reperfusion periods and 0.2 ml/min during ischemia. This tagged substrate was infused for 40 minutes before inducing ischemia to ensure both steady-state incorporation of fatty acids from the perfusate into heart muscle and steady-state production of 14CO₂ from fatty acid oxidation by the myocardium.

Seventeen animals were studied. In eight, no exogenous fatty acids were administered (LOW FA group). In nine others (HIGH FA group), unlabeled Intralipid (an emulsion of triglycerides courtesy of Kabi Vitrum, Inc., Alameda, California) with additional heparin was infused systemically throughout the studies (1.0–1.2 ml/min) beginning at 0 minutes’ perfusion. Mechanical, metabolic, and tissue data were collected as above. Statistical comparisons were made within groups using paired Student’s t tests and between groups using nonpaired Student’s t tests. Statistical significance was defined by two-tailed probability values of less than 5%. 25 Data are shown as mean ± SEM.

Results

The controlled variables are shown in Figure 1. In the LAD perfusion bed (upper panel), flow in both LOW and HIGH FA groups was held at aerobic levels; that is, flow was held at 6.6 ± 0.4 ml/min/g dry wt for 40 minutes, reduced acutely to 2.7 ± 0.2 ml/min/g dry wt for the next 45 minutes, and then acutely restored to control values for the final 60 minutes of reflow. To ensure aerobic conditions in adjacent myocardium, right coronary plus LCF flows in both groups were maintained at 12.1 ± 0.6 ml/min/g dry wt throughout. Over the entire perfusion period in the HIGH FA group, exogenous fatty acids were administered by means of a constant infusion of Intralipid with heparin. After 20
Liedtke et al
Substrate Metabolism During Coronary Reperfusion

537

LAD BED

LOW FA ○
HIG FA X--X

CORONARY FLOW (mL/min/g dry)

LOW FA ○
HIG FA X--X

FIGURE 1. Controlled variables, left anterior descending (LAD) flow and serum-free fatty acids, for LOW FA (○—○) and HIGH FA (X—X) groups. Comparisons were made between groups and statistical symbols include *p<0.05; **p<0.02; ***p<0.01; ****p<0.001.

Regional mechanical data are displayed in Figure 2. Percent systolic shortening (%SS) and recoil (late shortening in protodiastole to mid-diastole) were normalized to aerobic values (20, 30, and 40 minutes of perfusion). In the LAD bed, ischemia caused the expected declines in %SS and increases in percent recoil. There was a trend toward worsened performance in the HIGH FA group, but the differences did not reach statistical significance. Significant mechanical stunning was evinced in both groups during reflow as shown by the persistent decreases in %SS (−47 Δ%; p<0.01) and increases in percent recoil (3.7%; p<0.001) compared with preischemic values. Mechanical stunning in this context is used to indicate the depression of mechanical function resulting from ischemia that persists after flow has returned to normal in reversibly stressed myocardium. In the LCF bed (also shown in Figure 2), %SS was not different between groups. No compensatory augmentation in normal motion was observed during the period of mechanical stunning in the adjacent LAD bed. In the LCF bed, some differences in recoil values were noted between groups, which may have reflected greater recoil in the HIGH FA group or a decrease in recoil in the LOW FA group. Left ventricular max dP/dt was not different between groups.

Regional mechanical events were generally unassociated with tissue intermediates of carnitine and CoA as listed in Table 1. Shifts in intermediates caused by ischemia in the LAD bed were largely reversed after 60 minutes of reperfusion and washout. Depletion of total tissue carnitine stores in the LAD bed was noted in both groups even after reflow and was explained by losses of free carnitine from cytosol. Accumulations of short-chain esters of carnitine were noted in LOW FA hearts, but these were masked in HIGH FA hearts due to the higher values in aerobic myocardium. No important differences remained in long-chain acyl carnitine or CoA levels between reperfused and aerobic myocardium in either group. Differences in percent recoil in the LCF bed in the HIGH FA group were associated with significant increases in short- and long-chain esters of carnitine.

Slight but significant reductions in oxygen consumption values (see Figure 3) were noted between reflow and aerobic conditions in both LOW and HIGH FA groups (−20 Δ% and −17Δ%; p<0.05 and p<0.01, respectively). These were more modest than the previously noted declines in %SS and suggested that oxygen was being consumed but was not contributing to useful mechanical work.

Rates of 14C0₂ production from labeled fatty acids were of particular interest (Figure 4). Fatty acid oxidation showed appreciable "rebound" during reflow compared with aerobic values in both heart groups. These increases (89 Δ% in LOW FA hearts; +111 Δ% in HIGH FA hearts) were much more impressive than the slight declines effected by ischemia and were particularly evident in the HIGH FA group. These data, together with the MVo₂ data above, suggested a preservation or appreciable restoration in elements of mitochondrial function pertaining to substrate metabolism in reperfused heart muscle.

As an estimate of substrate preference and oxidative utilization, a ratio of M Vo₂ CO₂ production from fatty acids to M Vo₂ (mole fatty acids per mole oxygen) was calculated and compared for aerobic and reflow conditions within each group (Figure S). Oxidative utilization of fatty acids during reflow was at least equal to preischemic values in both groups and exceeded preischemic values (p<0.02) in LOW FA hearts. This suggested a restored capability and heightened preference for oxidizing long-chain fatty acid substrate either from endogenous or exogenous sources.

A mechanical efficiency based on preferred substrate utilization was also constructed and displayed in Figure 6. The ratio of systolic shortening to 14C0₂ production from fatty acid oxidation was calculated for the two

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heart groups. The presence of excess fatty acids impaired mechanical efficiency in the HIGH FA group during aerobic conditions as evidenced by the 40-minute intergroup comparison. Thereafter, efficiency declined comparably in both groups during ischemia and remained depressed during reflow.

**Discussion**

The purpose of this study was to detail the use of fatty acid substrate in the intact swine heart at conditions of reflow following moderate-to-severe ischemia and to describe the influence of excess fatty acids in the coronary perfusate. Appreciable mechanical stunning

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Free Carnitine</th>
<th>Short-Chain Carnitine Ester</th>
<th>Long-Chain Carnitine Ester</th>
<th>Total Tissue Carnitine</th>
<th>Long-Chain Acyl CoA</th>
</tr>
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<tbody>
<tr>
<td><strong>A. Aerobic (LCF)</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Low FA</td>
<td>3,787 ± 229</td>
<td>642 ± 133</td>
<td>157 ± 18</td>
<td>4,586 ± 267</td>
<td>143 ± 16</td>
</tr>
<tr>
<td>High FA</td>
<td>3,010 ± 371</td>
<td>1,371 ± 194</td>
<td>366 ± 87</td>
<td>4,746 ± 218</td>
<td>173 ± 8</td>
</tr>
<tr>
<td><strong>B. Statistical comparisons (LCF)</strong></td>
<td></td>
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<tr>
<td>Low FA vs. high FA</td>
<td>NS</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td><strong>C. Ischemic/reperfused (LAD)</strong></td>
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<tr>
<td>Low FA</td>
<td>2,894 ± 215</td>
<td>978 ± 186</td>
<td>223 ± 45</td>
<td>4,094 ± 298</td>
<td>168 ± 12</td>
</tr>
<tr>
<td>High FA</td>
<td>2,532 ± 313</td>
<td>1,604 ± 129</td>
<td>329 ± 45</td>
<td>4,465 ± 273</td>
<td>162 ± 17</td>
</tr>
<tr>
<td><strong>D. Statistical comparisons (LAD)</strong></td>
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<tr>
<td>Low FA vs. high FA</td>
<td>NS</td>
<td>p &lt; 0.02</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td><strong>E. Statistical comparisons</strong></td>
<td></td>
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<tr>
<td>Low FA: LCF vs. LAD</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.05</td>
<td>NS</td>
<td>p &lt; 0.02</td>
<td>NS</td>
</tr>
<tr>
<td>High FA: LCF vs. LAD</td>
<td>p &lt; 0.01</td>
<td>NS</td>
<td>NS</td>
<td>p &lt; 0.01</td>
<td>NS</td>
</tr>
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</table>

LCF, left circumflex bed; LAD, left anterior descending bed; NS, not statistically different. Data are listed as mean ± SEM, and each entry represents the measurements from 8–9 heart samples per animal group. Statistical comparisons are by paired (section E) and nonpaired (sections B and D) Student’s t tests.
Figure 3. Levels of regional oxygen consumption in the left anterior descending perfusion bed for the LOW (O—O) and HIGH (X—X) FA groups. MVO₂ was higher in HIGH FA hearts (intergroup comparisons) but only modestly reduced (intragroup comparisons) during reflow (−175%, p < 0.01). MVO₂ was low in LOW FA hearts and did not return to preischemic values during reflow (−20 %, p < 0.05). *p < 0.05.

During recovery was observed in the myocardium rendered ischemic following a 45-minute exposure to 60% reduction in coronary flow. Comparable changes occurred in animals either receiving or not receiving excess exogenous fatty acids. This stunning was associated with slight reductions in oxygen consumption, significant losses of total tissue carnitine stores, and a trend toward significant recovery of the aerobic utilization of fatty acids during reflow. The latter finding is of interest, has not previously been reported, and would not be predicted from previous observations with positron emission tomography. This disparity between substrate oxidation and mechanical recovery in our intact working heart model suggests an uncoupling of fuel consumption with energy production, an accelerated but useless energy drainage, or an impairment of energy transfer or availability with contractile proteins.

Figure 4. Regional ¹⁴CO₂ production from labeled palmitate in the left anterior descending perfusion bed in LOW (O—O) and HIGH (X—X) FA groups (symbols as before). Rates of fatty acid oxidation were higher in HIGH FA hearts (intergroup comparisons) at aerobic (p < 0.05), ischemic (p at least < 0.05), and reflow conditions. During reperfusion in both groups fatty acid oxidation exceeded aerobic levels (+89.4% in LOW FA hearts; +111.8% in HIGH FA hearts). *p < 0.05; **p < 0.02; ***p < 0.01.

Figure 5. Rates of fatty acid oxidation to total oxygen consumption (expressed as moles per mole), as an estimate of preferred substrate oxidative utilization, are shown for the LOW FA (Panel A) and HIGH FA (Panel B) groups. Data are grouped by condition, averaged, and compared within each group. Aerobic use of fatty acids during reperfusion was at least equal to preischemic values in HIGH FA hearts and exceeded preischemic values in LOW FA hearts.

Myocardial stunning during reperfusion has been well characterized in the past, and reports have focused on the prolonged impairment to mechanical recovery, unanticipated from the level and extent of the ischemia that preceded it. Heyndrickx and workers and Theroux et al showed in conscious dogs that a 2-minute transient occlusion of coronary flow resulted in motion abnormalities for 45 minutes or longer; a 5-minute occlusion caused mechanical depression for at least 3 hours; and a 15-minute occlusion caused dysfunction for 6 hours and beyond.

The mechanism or mechanisms for this event remain contested. Initial interest centered on depletions of high-energy phosphate and total adenine nucleotide pools. Reibel and Rovetto reported a close correlation between ventricular performance and remaining tissue ATP stores in postischemic and postanoxic rat hearts. DeBoer and Klöner and workers expanded this notion by reporting prolonged depressions in ATP and total purines for up to 72 hours following 15-minute transient coronary occlusion. This correlated nicely with prolonged decreases in regional segment length.
shortening. However, recent disparate results were obtained by Neely and Grotyohann\(^\text{49}\) who noted a lack of dependency between ATP levels and mechanical recovery that was more related to the level of glycolytic intermediates including lactate, hydrogen ion, and reduced nicotinamide adenine dinucleotide.

Other evidence has implicated free radical formation. Ferrari and colleagues\(^\text{32}\) in reperfused rabbit hearts described metabolic trends suggesting oxidative damage above the neutralizing capacity of select tissue defense systems. A variety of studies using superoxide "scavengers," principally catalase and superoxide dismutase, have shown benefits in either improved ventricular performance or lessened infarct size\(^\text{33-38}\).

Still other information has suggested preservation in key elements of contractile reserve during the stunning phenomenon. Perturbations with reactive hyperemia,\(^\text{39-40}\) diltiazem,\(^\text{41}\) dopamine,\(^\text{42-43}\) epinephrine and postextrasystolic potentiation\(^\text{44}\) have all demonstrated an ability of the heart muscle to improve function under various conditions and stimuli.

No one to our knowledge has previously reported on metabolic uncoupling. Based on data from positron emission tomography, there is unanimity of opinion that fatty acid utilization during reflow is depressed\(^\text{44-48}\) and is slowly restored at varying intervals (90 minutes to one week)\(^\text{49-50}\) depending on the length and severity of the preceding ischemia. Rates of fatty acid oxidation using \([^{14}\text{C}]\)palmitate are not known. Positron emission tomography gives only generic information on metabolic function and has not traditionally been used to focus on specific elements in the utilization pathways. Indeed, exponential decay kinetics from time-activity curves using \([^{14}\text{C}]\)palmitate have been interpreted differently\(^\text{51-52}\) with only the UCLA group suggesting a relation between oxidation and the early rapid clearance phase.\(^\text{53-54}\) Preliminary data with \([^{14}\text{C}]\)palmitate have confirmed the depression in fatty acid utilization during early reflow\(^\text{55-56}\) but have shown relative preservations in fatty acid oxidation. Myears et al\(^\text{57}\) showed in dogs that, after an hour of severe ischemia, oxidation of this substrate during reflow accounted for 63% of the total oxygen consumed, despite diminished uptake of palmitate. Our data extend these observations and suggest preservations or restorations of essential elements of intramitochondrial function. This is argued from the preferred aerobic use of fatty acids during reflow and the higher than normal rates of \(^4\text{CO}_2\) production from labeled fatty acids. Melding these data with the older findings of decreased ATP stores suggests either an accelerated but useless drain of ATP production or an intramitochondrial uncoupling between substrate oxidation and energy production. As an explanation for mechanical stunning, these mechanisms, as well as other possible impairments in energy transfer between cellular compartments, must await further investigations.

A final goal of this study was to test the influence of excess fatty acids in the coronary perfusate on mechanical recovery during reflow. In the present studies, deterioration in relative motions during ischemia and reflow was moderately comparable between LOW and HIGH FA hearts, with only minor trends toward worsened performance in the HIGH FA group. This is in contrast to previous data from our laboratory that showed better-defined impairments in mechanical function as a result of excess fatty acids in the perfusate.\(^\text{5}\) The most logical explanation for this difference in our opinion is the much more dramatic insult caused by regional hypoperfusion on regional performance in the present data. The relations between regional and global function in response to regional and global restrictions in coronary flow are highly complex. Pagani et al\(^\text{1}\) noted a close correlation between global ischemia and global dysfunction and between regional ischemia and regional dysfunction in the conscious dog model. Correlations between global ischemia and regional dysfunction and between regional ischemia and global dysfunction were not nearly as consistent or predictable. This has been our experience as well. In our previous report,\(^\text{4}\) the 35.7% decrease in global flow over 30 minutes caused only a 20% change in regional performance. This is contrasted with the 75% or greater change in regional performance effected by a 60% reduction in regional flow over 45 minutes in this report. With these regional response characteristics to regional ischemia, which essentially eliminated all motion in the present data, any added effects of fatty acids were lost or appreciably masked. We also were very close to causing probable irreversible necrosis in swine, which has a deficit of inherent collateral circulation.\(^\text{51}\) This no doubt further attenuated any expression of possible fatty acid effects. The present data do show a decline in mechanical efficiency caused by excess fatty acids at aerobic conditions only. This is confirmatory of our previous findings and also supports those of Paulson et al.\(^\text{11}\).

We previously reported in addition a close association between mechanical dysfunction during ischemia and the accumulation of certain fatty acid amphiphiles,
which was further exacerbated at high fatty acid conditions. These trends were not evident in the current study because the 60 minutes of reperfusion and washout essentially reversed the accumulation of fatty acid esters. Such findings are in agreement with those of Ichihara and Neery. Only one association between mechanical dysfunction (percent recoil) and amphi-

phile concentration remained as noted in the long-chain carnitine ester accumulations in the HIGH FA group in aerobic myocardium. All in all, however, mechanical stunning based on the present data appears better explained by some defect in energy production, deg-

radation, or transfer rather than in buildup of fatty acid intermediates.

Acknowledgments

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