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Cardiac membrane fatty acid composition modulates myocardial oxygen consumption and postischemic recovery of contractile function

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Abstract
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Salvatore Pepe, PhD; Peter L. McLennan, PhD

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Key Words: myocardium ■ oxygen ■ ischemia ■ fatty acids ■ fish oils

Epidemiology and human intervention trials consistently show inverse associations between dietary fish or fish oil intake and mortality from heart disease.1–5 Because of the importance of ischemic coronary artery disease in myocardial infarction, sudden arrhythmic death, and heart failure, research has largely focused on the influence of dietary fats on blood pressure, plasma lipids, atherosclerosis, and thrombosis.6–8

Animal studies demonstrate that dietary fats not only modulate platelet and vascular function but also determine the fatty acid composition of myocardial cell membranes. Fish oils are rich sources of the long-chain ω3 (n-3) polyunsaturated fatty acids (PUFA) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Eating fish oil leads to high incorporation of DHA into myocardial membrane phospholipid.9–14 Hearts with high DHA content have very low in vivo and in vitro vulnerability to arrhythmia, which is reflected in a low incidence of ventricular fibrillation induced by ischemia, reperfusion, programmed electrical stimulation, or other stimuli.10–14 This cannot be attributed to reduced coronary atherosclerosis.15

Human intervention trials in postinfarction patients demonstrate reduced mortality with regular intake of fish or fish oil, without changes in blood pressure, blood lipids, or new cardiac events.2,5 The Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico (GISSI)-Prevenzione Trial,5 with >11 000 postinfarction subjects, found that fish oil intake reduced the risk of both sudden and nonsudden death. These reports support the animal data that indicate that fish oil may prevent fatal arrhythmias, and they raise the possibility that further direct effects on heart function may contribute to the cardioprotective effects of n-3 fatty acids. In support of this premise, fish oil feeding increases left ventricular end-diastolic volume and ejection fraction in nonhuman primates and reduces rate pressure product, which may be indicative of low myocardial oxygen consumption (MVO2).16

We tested the hypothesis that n-3 PUFA incorporation into myocardial membranes has direct effects on heart function, particularly after ischemia, additional to previously reported effects on arrhythmia, thrombosis, and vascular function. We
used the erythrocyte-perfused isolated working heart, which provides optimal oxygen delivery and permits assessment of hemodynamic function and metabolism under controlled physiologically relevant conditions.10,17

Methods

Animals and Diets

Four-month-old male Wistar rats (University of Adelaide, Adelaide, Australia) were fed a fish oil (n-3 PUFA)—supplemented diet, a saturated fat (SAT)—supplemented diet, or a reference diet (REF) rich in n-6 PUFA for 16 weeks (n=55 per diet). The REF diet was commercially available, unrefined rat pellets (Milling Industries). The SAT and n-3 PUFA diets were prepared as previously reported10 by adding sheep peri-renal fat or fish oil to the dry mix components of the unrefined pellets. The fatty acid profile of each diet was published previously.10 In brief, the n-3 PUFA diet contained 25% saturated fatty acids and 45% PUFA (39% n-3 PUFA as EPA [20:5] and DHA [22:6]), the SAT diet contained 55% saturated fat and 10% PUFA (7% n-6 PUFA), and the REF diet contained 29% saturated fat and 46% PUFA (34% n-6 PUFA). All diets were consumed iso-energetically, delivering a similar total fat intake to all groups.10 Experiments were conducted according to the National Health and Medical Research Council Australia Guidelines for the Use of Experimental Animals.

Perfusion Protocol

At least 1 rat was used from each dietary group each experimental day, and was fasted overnight. The experimenter was blind to the diet of each rat. Animals were killed by cervical dislocation and hearts were removed and prepared for working heart perfusion with porcine erythrocyte buffer (40% hematocrit).17 Briefly, after 10-minute equilibration in Langendorff mode, hearts were switched to working heart mode (preload, 10 mm Hg; afterload, 75 mm Hg; coronary perfusion pressure, 75 mm Hg; paced heart rate, 300 bpm). Arterial and venous blood gas partial pressures and pH were measured every 5 minutes. MVO2 was derived from arteriovenous oxygen differences per unit coronary flow, and external work was derived from cardiac output (CO) and developed pressure.17

In separate experiments, we performed the following: (1) preload was changed over the range 5 to 20 mm Hg by altering ventricular filling pressure. (2) Global ischemia was induced by lowering the coronary pressure to 35 mm Hg for 15 minutes while maintaining afterload at 75 mm Hg and pacing throughout.23 Reperfusion was initiated by restoring coronary perfusion pressure to 75 mm Hg. (3) Basal MVO2 was determined in control and reperfused hearts arrested in diastole by perfusion with 30 mmol/L KCl. Hearts were continuously perfused with (1) the direct-acting vasodilator hydralazine (1 mmol/L), (2) the selective inhibitor of mitochondrial Ca++ uptake ruthenium red (3.4 μmol/L), or (3) the inhibitor of sarcoplasmic reticulum Ca++ release ryanodine (1 mmol/L). At completion, hearts were blotted dry and weighed. A segment of ventricle was retained for dry weight estimation, and the remainder was frozen in liquid nitrogen and stored at −60°C.

Coronary Creatine Kinase, Lactate, and Potassium Analysis

Creatine kinase (units per liter per minute) was measured spectrophotometrically (340 nm, 37°C) using creatine kinase N-acetyl-L-cysteine reagent (Behring). Lactate (millimoles per liter per minute) was analyzed (340 nm, 37°C) by Cobass Bio (Hoffman-La Roche). Creatine kinase and lactate release were adjusted for coronary flow and expressed per gram ventricle (dry weight). Extracellular K+ concentration (mmol/L) was measured by flame photometry.

Statistical Analysis

CO, external work, coronary flow, oxygen extraction, MVO2, and metabolites were expressed per gram ventricle dry weight.15 Results were expressed as mean±SD. The effect of diet was tested by 1-way ANOVA with Scheffe’s post-hoc F test for multiple comparisons of individual means. Effects of ischemia/reperfusion and altered preload were tested by repeated-measures ANOVA. The incidence of ventricular fibrillation in reperfusion was compared using the χ2 test. Values in text sharing the same symbol were not significantly different from other dietary groups. The level of significance was considered at P<0.05.

Results

Normoxic Function

Figures 1 and 2 (n=55 per diet) summarize the hemodynamic function of all hearts at equilibration, before subsequent diversion to individual experiments (6 separate experiments with individual groups of n=5 to 10). There were no differences between dietary groups in cardiac output (REF, 182±14; SAT, 183±15; n-3 PUFA, 188±15 mL · min⁻¹ · g⁻¹) or external work (Figure 1A). SAT hearts had significantly higher coronary flow, percent oxygen extraction (Figure 2A and 2B), and MVO2 (Figure 1B). Although coronary flow was similar in n-3 PUFA and n-6 PUFA-rich REF, the percent oxygen extraction and MVO2 were significantly lower in n-3 PUFA hearts (Figures 2B and 1B). Body weights (REF, 504±10; SAT, 525±5; n-3 PUFA, 513±9 g), and ventricle dry weights (REF, 0.25±0.01; SAT, 0.25±0.01; n-3 PUFA, 0.27±0.01 g) were not different.

Frank-Starling Relationship

The maximum CO (REF, 210±7; SAT, 201±3; n-3 PUFA, 272±18 mL · min⁻¹ · g⁻¹) was significantly higher in n-3 PUFA hearts. In the REF and SAT hearts, CO was not
sustained at high preload. The same pattern was seen in external work (Figure 3A). Coronary flow was significantly higher in SAT hearts at low (5 mm Hg) preload (REF, 30 ± 3; SAT, *87 ± 1; n-3 PUFA, †21 ± 2 mL · min⁻¹ · g⁻¹), whereas the percent oxygen extraction was significantly lower in the n-3 PUFA hearts (REF, 28 ± 1%; SAT, 31 ± 2%; n-3 PUFA, 18 ± 1%). Coronary flow increased with preload in n-3 PUFA and REF hearts only (maximum REF, 58 ± 3; SAT, *90 ± 4; n-3 PUFA, †44 ± 2 mL · min⁻¹ · g⁻¹). The percent oxygen extraction increased with preload, but in the n-3 PUFA hearts, this was only seen at the highest preload (max extraction: SAT, 57 ± 4%; REF, 39 ± 1%; n-3 PUFA, 40 ± 2%). MVO₂ increased with preload in all groups, especially at the higher filling pressures (Figure 3B) and was significantly greater in SAT and less in n-3 PUFA at all preloads. The efficiency of oxygen conversion into external work increased with preload but declined at the high filling pressures as external work stabilized or declined (Figure 3C). Efficiency was significantly higher in n-3 PUFA and lower in SAT hearts at all preloads. Lactate washout into the coronary perfusate increased with preload and was significantly higher in SAT and lower in n-3 PUFA hearts (at 20 mm Hg preload: REF, 230 ± 10; SAT, *295 ± 5; n-3 PUFA, †125 ± 12 µmol · min⁻¹ · g⁻¹, n = 10).

Ventricular Function and MVO₂ in Ischemia and Reperfusion
Coronary flow decreased during ischemia (Figure 4A), barely exceeded by CO (Figure 4B). After reperfusion, CO returned to 83% of preischemic output in n-3 PUFA, 73% in REF, and 62% in SAT hearts (Figure 4B). Myocardial external work decreased during ischemia in all groups (Figure 5A), and recovery of external work after reperfusion was lowest in SAT and highest in n-3 PUFA hearts.

Despite reduced work, MVO₂ was not diminished in reperfusion. Reperfused SAT hearts exhibited the highest, whereas n-3 PUFA hearts had the lowest MVO₂ (Figure 5B).
This resulted in lower energy utilization efficiency in SAT hearts (ratio of work output energy/energy input from MVO₂), whereas n-3 PUFA hearts had significantly higher postischemic energy efficiency than did n-6 PUFA-rich REF hearts (Figure 5C).

Coronary venous pH fell during ischemia, (REF, 7.14±0.01; SAT, 7.03±0.02; n-3 PUFA, 7.20±0.01) and K⁺ concentration increased (REF, 7.82±0.27; SAT, 8.63±0.42; n-3 PUFA, 5.36±0.23 mmol/L). These effects were least pronounced in n-3 PUFA hearts, and the acidosis was greatest in SAT hearts. The coronary venous washout of lactate (REF, 210±20; SAT, 300±40; n-3 PUFA, 140±30 μmol·min⁻¹·g⁻¹) and creatine kinase (REF, 12.1±0.5; SAT, 17.4±4.4; n-3 PUFA, 13.0±0.1 IU·min⁻¹·g⁻¹) was significantly lower in n-3 PUFA hearts.

**Ischemia at High Preload**

During reperfusion at 20 mm Hg preload, oxygen extraction (REF, 62.2±3.2%; SAT, 83.8±3.2%; n-3 PUFA, 58.1±1.5%) increased in all hearts, whereas MVO₂ was significantly increased in REF (26%) and SAT (24%) hearts but not in n-3 PUFA hearts (11%) (n=10 per diet (Control: REF, 3.99±0.23; SAT, 7.54±0.53; n-3 PUFA, 9.26±0.17 mL·min⁻¹·g⁻¹). Reperfusion: REF, 5.04±0.42; SAT, 9.38±0.76; n-3 PUFA, 3.28±0.19 mL·min⁻¹·g⁻¹). Cardiac energy efficiency was correspondingly decreased during reperfusion in REF and SAT hearts but not significantly in n-3 PUFA hearts. (Control efficiency: REF, 2.93±0.34%; SAT, 1.28±0.07%; n-3 PUFA, 1.71±0.77%). Reperfusion efficiency: REF, 1.94±0.27%; SAT, 0.92±0.05%; n-3 PUFA, 7.48±0.36%). Reperfusion release of lactate (REF, 369±34; SAT, 420±45; n-3 PUFA, 150±39 μmol·min⁻¹·g⁻¹) and creatine kinase (REF, 19.0±0.8; SAT, 24.3±0.8; n-3 PUFA, 15.2±0.7 IU·min⁻¹·g⁻¹) were significantly greater than after ischemia at low preload but lower in n-3 PUFA hearts than in REF or SAT hearts.

**Basal MVO₂**

Hearts arrested in diastole by 30 mmol/L KCl infusion after reperfusion (n=5 per diet) or time-matched control perfusion (n=5 per diet) had very low MVO₂, representing noncontractile (basal) metabolism (Table). No significant effect of diet or reperfusion was observed after KCl arrest.

**Coronary Flow**

Hydralazine increased coronary flow in REF and n-3 PUFA hearts but not in SAT hearts and abolished the dietary differences. (n=10 per diet. Control: REF, 51±10; SAT, 77±5; n-3 PUFA, 51±4 mL·min⁻¹·g⁻¹. Hydralazine: REF, 67±12; SAT, 71±10; n-3 PUFA, 74±10 mL·min⁻¹·g⁻¹).

**Intracellular Calcium Modulation**

At a concentration that did not affect CO (data not shown) or external work (Figure 6A), ruthenium red reduced MVO₂ in REF and SAT hearts to similar levels as those in n-3 PUFA hearts (Figure 6B). Ryanodine had no effect on CO, external work (Figure 6A), or MVO₂ (Figure 6B) but totally abolished ventricular fibrillation in reperfusion (Figure 6C). Ruthenium red had no significant effect on reperfusion arrhythmias (P>0.05, χ²).

**Discussion**

Dietary fish oil reduced MVO₂ while sustaining cardiac output and external work, revealing an increase in the efficiency of oxygen use under conditions of constant heart rate, preload, and afterload. When hearts were put under stress, such as increased filling pressure or acute myocardial ischemia and reperfusion, this low oxygen demand was associated with enhanced hemodynamic function and reduced production of markers of ischemic damage.

Changes in both coronary flow and oxygen extraction contributed to the differences in MVO₂ seen in these hearts.

**Effects of Dietary Lipids on Working and Basal MVO₂ After Arrest With 30 mmol/L KCl (37°C), Under Control Conditions or During Reperfusion After 15 Minutes of Acute Low-Flow Global Ischemia**

<table>
<thead>
<tr>
<th></th>
<th>MVO₂, mL·min⁻¹·g⁻¹ dry weight</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>REF (n-6 PUFA)</td>
</tr>
<tr>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>Working</td>
<td>3.24±0.25</td>
</tr>
<tr>
<td>Basal</td>
<td>0.57±0.18</td>
</tr>
<tr>
<td>Reperfusion</td>
<td></td>
</tr>
<tr>
<td>Working</td>
<td>3.92±0.26</td>
</tr>
<tr>
<td>Basal</td>
<td>0.69±0.21</td>
</tr>
</tbody>
</table>

Values are mean±SD (n=5 per group). *P<0.05; significantly different compared with n-6-rich REF (ANOVA with Schefte’s comparison).
The low coronary flow in n-3 PUFA hearts contrasted to the vasodilator and antihypertensive properties of fish oil\textsuperscript{9} and reflected a low oxygen demand. This afforded the n-3 PUFA hearts a high vasodilator reserve, which was revealed by both high workloads and the vasodilator hydralazine. In contrast, the high coronary flow in SAT hearts was not responsive to hydralazine or high workload and represented maximal vasodilation as an adaptive response to increased metabolic requirements, rather than any direct vascular effect. The high MVO\textsubscript{2} and high washout of lactate in SAT hearts under control or high preload conditions and after ischemia further support this supposition. These data highlight further potential adverse cardiovascular effects of dietary saturated fat that are also independent of effects on atherosclerosis and thrombosis.

In view of the low MVO\textsubscript{2} and low lactate release in n-3 PUFA hearts, we tested the hypothesis that they would exhibit reduced vulnerability to ischemic stress. Typical responses of venous acidosis and myocardial K\textsuperscript{+} loss were elicited by low-flow global ischemia. Together with the increase in lactate and creatine kinase washout recorded when coronary perfusion pressure and flow were restored in reperfusion, these indicators of acute ischemic stress were greatly attenuated in the n-3 PUFA hearts at high or low workloads. The n-3 PUFA hearts also had better postischemic recovery of hemodynamic and metabolic function, supporting reports of cardioprotective properties in ischemia-reperfusion.\textsuperscript{14,18} These observations extend the range of effects on cardiac function observed in vivo that are associated with dietary-induced changes in myocardial fatty acid composition.\textsuperscript{16} Dietary n-3 PUFA reduced the susceptibility to arrhythmias in the present study, as in other studies.\textsuperscript{10–15} The reduced loss of K\textsuperscript{+} during ischemia may be indicative of effects on ion channels or exchange mechanisms that lead to changes in K\textsuperscript{+} conductance\textsuperscript{26} and altered arrhythmic potential.\textsuperscript{27} Alternatively, the lower MVO\textsubscript{2} in n-3 PUFA hearts suggested a metabolic reserve, which may contribute to the reduced arrhythmia vulnerability by ensuring energy for maintenance of transmembrane potentials.

Underlying changes in mitochondrial metabolism may contribute to the high oxygen energy utilization efficiency of n-3 PUFA hearts. Reduced rates of mitochondrial respiration are seen in hearts from fish oil–fed rats.\textsuperscript{28,30} Paradoxical increases in MVO\textsubscript{2} during reperfusion may in turn be driven by increased energy requirements to regulate intracellular Ca\textsuperscript{2+}, which is raised during ischemia.\textsuperscript{25–30} Spontaneous Ca\textsuperscript{2+} release from sarcoplasmic reticulum and impaired contractility after ischemic injury\textsuperscript{29} suggest the ability of sarcoplasmic reticulum to deal with elevated intracellular Ca\textsuperscript{2+} may also be impaired.

There is direct evidence of elevated intracellular (mitochondrial) Ca\textsuperscript{2+} in hearts fed saturated fat or REF diets, whereas n-3 PUFA are associated with less activation of Ca\textsuperscript{2+}-dependent pyruvate dehydrogenase at rest and after stimulation by catecholamines.\textsuperscript{30} Lower oxygen consumption by mitochondria isolated from n-3 PUFA hearts, most notably during uncoupled respiration, suggests that augmented n-3 PUFA content in inner mitochondrial membranes may minimize thermodynamic inefficiency because of high rates of proton motive force and proton leak that may underlie futile consumption of excess oxygen after ischemia-reperfusion.\textsuperscript{30} State III respiration may also be influenced by n-3 PUFA.\textsuperscript{21} The findings of the present study—in which excess MVO\textsubscript{2} was abolished by ruthenium red (blocks mitochondrial uniporter Ca\textsuperscript{2+} uptake) but not by ryanodine (blocks sarcoplasmic reticulum Ca\textsuperscript{2+} release), although ryanodine but not ruthenium red abolished postischemic cardiac arrhythmias—promote the hypothesis that n-3 PUFA prevent intracellular Ca\textsuperscript{2+} overload.

The fatty acid composition of myocardial membrane phospholipid is sensitive to the type of fatty acids consumed in the diet.\textsuperscript{9–14,18–20,30–32} Although fish oils often contain mainly EPA, the myocardium, including mitochondrial membrane, accumulates DHA as the principal n-3 PUFA, even after feeding purified EPA.\textsuperscript{13} We previously reported the effects of the very diets used in the present study,\textsuperscript{10} demonstrating high incorporation of DHA with fish oil feeding. Membrane fatty

\begin{figure}[h]
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\caption{Effects of dietary lipids, ruthenium red (3.4 μmol/L), and ryanodine (1 mmol/L) on cardiac external work (A), MVO\textsubscript{2} during control perfusion (B), and incidence of ventricular fibrillation (C) during reperfusion in isolated working heart: REF (open bars), SAT (cross-hatched), and n-3 PUFA (filled bars). Values are mean±SD; n=10 per group. *P<0.05 vs REF; #P<0.05 vs control, ANOVA (external work and MVO\textsubscript{2}) and χ\textsuperscript{2} (ventricular fibrillation).}
\end{figure}
acid modulation may modify a wide variety of intracellular and membrane events, such as ion flux, respiratory electron transport, carrier-mediated transport, membrane-bound enzyme activity, receptor function, intracellular lipid-based second messengers, and eicosanoid synthesis.²⁵,³⁴ Thus, membrane modification of phospholipid properties may impact on many lipid-protein interactions, membrane protein function, and membrane-dependent signaling and metabolism. It is therefore not surprising that dietary lipid-induced modulation of Ca²⁺ handling³⁰–³³ via altered cardiac membrane composition may drive both excessive oxygen use and arrhythmia vulnerability.

Diet-induced augmentation of cardiac membrane n-3 PUFA improved ventricular function by reducing the oxygen required to produce any given work output compared with either saturated fat or n-6 PUFA. This was particularly evident at high workloads and was not attributable to altered vascular function. Increased n-3 PUFA incorporation made the myocardium less susceptible to ischemic injury and aided posts ischemic recovery. These findings provide further support for epidemiological and intervention studies that show associations between n-3 PUFA intake and low incidence of death from coronary heart disease, even after myocardial infarction.¹⁻⁵ The results suggest direct cardioprotective effects of fish oil, beyond the acknowledged antithromogenic and antiarrhythmic actions.

References