Omega-3 Fatty Acids in Cardiac Biopsies From Heart Transplantation Patients
Correlation With Erythrocytes and Response to Supplementation

William S. Harris, PhD; Scott A. Sands, PhD; Sheryl L. Windsor, MT; Hakim A. Ali, MD; Tracy L. Stevens, MD; Anthony Magalski, MD, Charles B. Porter, MD; A. Michael Borkon, MD

Background—Omega-3 fatty acids (FAs) appear to reduce the risk of sudden death from myocardial infarction. This reduction is believed to occur via the incorporation of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) into the myocardium itself, altering the dynamics of sodium and calcium channel function. The extent of incorporation has not been determined in humans.

Methods and Results—We first determined the correlation between red blood cell (RBC) and cardiac omega-3 FA levels in 20 heart transplant recipients. We then examined the effects of 6 months of omega-3 FA supplementation (1 g/d) on the FA composition of human cardiac and buccal tissue, RBCs, and plasma lipids in 25 other patients. Cardiac and RBC EPA+DHA levels were highly correlated ($r=0.82$, $P<0.001$). Supplementation increased EPA+DHA levels in cardiac tissue by 110%, in RBCs by 101%, in plasma by 139%, and in cheek cells by 73% ($P<0.005$ versus baseline for all; responses among tissues were not significantly different).

Conclusions—Although any of the tissues examined could serve as a surrogate for cardiac omega-3 FA content, RBC EPA+DHA was highly correlated with cardiac EPA+DHA; the RBC omega-3 response to supplementation was similar to that of the heart; RBCs are easily collected and analyzed; and they have a less variable FA composition than plasma. Therefore, RBC EPA+DHA (also called the Omega-3 Index) may be the preferred surrogate for cardiac omega-3 FA status. (Circulation. 2004;110:1645-1649.)

Key Words: biopsy ■ fatty acids, omega-3 ■ fish oils ■ myocardium

A link between omega-3 fatty acids (FAs) and mortality from coronary heart disease (CHD) was first observed in Greenland Inuits.1 The higher levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) found in the plasma2 and platelets3 of Inuits compared with Danes were inversely related to population rates of acute myocardial infarction. Experimental and clinical trial evidence has continued to accumulate, further supporting a cardioprotective effect for omega-3 FAs. Higher blood levels of EPA and DHA were associated with reduced risk for primary cardiac arrest,4 sudden cardiac death,5 and fatal ischemic heart disease.6 Total mortality was reduced in CHD patients advised to eat oily fish7 or given omega-3 FA supplements.8 The latter also reduced risk of sudden cardiac death by 45%. The American Heart Association has recently recommended that patients with known CHD consume $\approx 1$ g/d of EPA+DHA.9

Early efforts to understand the mechanism(s) by which omega-3 FAs reduce risk of death from CHD focused on their effects on classic CHD risk factors,9 but lowering of serum lipids and blood pressure does not appear to explain the observed reductions in risk for sudden cardiac death.10 Possible effects of $<1$ g EPA and DHA on platelet aggregation, endothelial function, heart rate variability, and inflammatory markers are poorly understood. Original observations in experimental myocardial infarction11 and later studies by McLennan et al12–14 in rats and monkeys suggested that omega-3 FAs had a direct protective effect on the heart itself. In a dog model of ventricular tachyarrhythmia,15 infused omega-3 FAs reduced the number of potentially fatal arrhythmias. Investigations using isolated cardiac myocytes revealed that EPA and DHA could prolong the refractory state of these cells by interaction with fast-acting sodium channels and L-type calcium channels.16,17 This antiarrhythmic effect is believed to be due to the release of EPA and DHA from myocardial membrane phospholipids by ischemia-activated phospholipase A$_2$, and the subsequent interaction of the free acids with ion channels.10 It has been demonstrated that omega-3 FA feeding increases the amount of EPA and DHA incorporated into the heart tissue of experimental animals, but the extent to which intakes of these FAs that are known to
reduce risk for sudden cardiac death after human cardiac FA composition is not known.

The present studies had 2 purposes. The first was to determine the EPA and DHA content of human myocardial tissues under normal and supplemented conditions. The second was to determine whether a readily available tissue [plasma, cheek, or red blood cells (RBCs)] could serve as a surrogate marker for cardiac EPA and DHA levels.

Methods

Protocols
This report describes the results of 2 separate but related studies conducted in stable cardiac transplant recipients. In the cross-sectional study, we examined the correlation between the EPA+DHA content of cardiac tissue and RBCs and how each of these tissues correlated with self-reported omega-3 FA intakes. For this study, all patients who were undergoing routine cardiac biopsies during the 2-month study period were invited to participate, regardless of their dietary omega-3 FA status. They were asked to consent to the harvesting of 1 extra tissue sample for FA analysis, and they provided information about background fish and fish oil consumption. Patients taking any dose of fish oil supplements or eating AHA-recommended amounts of fish (at least 2 fish meals per week) were considered high consumers of omega-3 FAs; those not supplementing or eating <2 fish meals per week were classified as low consumers.

In the second study (the supplementation study), we determined the effects of 6 months of supplemental omega-3 FAs on EPA and DHA levels in 4 human tissues: heart, RBCs, plasma, and cheek cells. Patients were required to meet the following criteria: be at least 3 months after transplantation; have no hospitalizations for transplant-associated infections or rejection episodes in the previous 3 months; be off fish oil supplements for at least 6 months; have a serum creatinine level <2.0 mg/dL; be on stable doses of medications, including steroids and immunosuppressive drugs; and be on a biopsy cycle of at least 2 per year. Patients were asked to take 2 capsules per day of a supplement (30/20 TG Fish Oil, Ocean Nutrition Canada, Ltd) containing 500 mg EPA+DHA per capsule (30% EPA and 20% DHA) as triglyceride.

Informed consent was obtained before initiation. The Saint Luke’s Hospital Institutional Review Board approved both studies.

Laboratory Methods

Tissue Collection Procedures
Heart biopsies were collected during right heart catheterization via the interventricular septum, placed immediately into cold saline, and frozen at −70°C.

Cheek cells were harvested by scraping the buccal membranes with a plastic spoon after 3 preliminary rinses with distilled water. The sample was briefly centrifuged; the supernatant was decanted; and the cells were frozen at −70°C.

RBCs and plasma were obtained from fasting blood collected into EDTA. The cells were sedimented by centrifugation; the plasma was removed and frozen; and the buffy coat was discarded. The packed RBCs were stored at −70°C. (Washing of RBCs was shown in preliminary experiments not to be necessary because it did not alter FA composition.)

Materials
Isopropanol, methanol, methylene chloride, hexane, 14% boron trifluoride-methanol (BF3), butylated hydroxytoluene, and L-α-phosphatidylcholine diheptadecanoate (internal standard) were obtained from Sigma-Aldrich. Butylated hydroxytoluene was added to all organic solvents at 50 mg/L.

Tissue Preparation/Lipid Extraction
Heart and cheek tissues were first lyophilized (Savant Speed-Vac Plus) overnight. Heart biopsies were further pulverized by grinding between 2 ground-glass slides. After lyophilization, all samples were resuspended in saline and subjected to 10 to 15 seconds of sonication (4710 Ultrasonic Homogenizer, Cole-Parmer). Lipids were then extracted with methanol (containing the internal standard) and methylene chloride as described,16 and the solvent was evaporated under nitrogen.

Thawed RBCs were extracted with isopropanol (containing the internal standard) and methylene chloride (1:30:14:4). After centrifugation of the stroma, the solvent was transferred and evaporated under nitrogen.

Plasma lipids were extracted with methanol, saline, and methylene chloride (1:25:75:50). After centrifugation, the aqueous layer was discarded, and the organic layer was transferred and evaporated under nitrogen.

Lipids extracted from heart, cheek, and RBC samples were methylated with BF3 at 100°C for 10 minutes. These conditions transmethylated glycerophospholipid but not sphingolipid FAs.19 Plasma lipid samples were heated with BF3, methanol, and benzene at 100°C for 45 minutes, conditions that transmethylate all FAs.19 After cooling, all samples were extracted with hexane and water (1:2:2). The hexane layer was removed and evaporated under nitrogen, and the FA methyl esters were reconstituted in hexane for analysis by flame ionization gas chromatography as previously described.20 FAs were identified by comparison with known standards, and FA composition is reported as weight percent of total FAs. The coefficient of variation for the RBC EPA+DHA assay was 10% to 12%; for whole-plasma EPA+DHA, 13% to 17%. Statistical Analysis

Fasting serum from all 25 subjects in study 2 was analyzed before and after supplementation for total cholesterol, triglycerides, and HDL cholesterol (LDL-C) on a Cobas Fara II (Roche) with enzymatic reagents. HDL-C was determined in the serum supernatant after precipitation of VLDL and LDL as described by Warnick et al.13 LDL-C was determined by the Friedewald equation.22

Statistical Analysis

The Microsoft Excel 97 Data Analysis Package was used to calculate correlation coefficients between tissues according to Pearson’s method. To test the hypothesis that 2 independent correlation coefficients differed significantly, each was first converted into a z score, and then a probability value was computed from a normal z table. Paired t tests were used to compare baseline and end-of-study values in the supplementation study, and unpaired t tests were used for comparisons between those in the cross-sectional study consuming high versus low amounts of omega-3 FAs. Differences between means were considered significant at P<0.05. Unless otherwise noted, results are presented as mean±SEM.

Results

Cross-Sectional Study
Cardiac and RBC samples were obtained from 20 consecutive cardiac transplantation patients. The average age of this group was 45±14 years; 15 were men. The average time from transplantation was 1.8 years (range, 0.3 to 9.7 years). There was a highly significant correlation between heart and RBC omega-3 levels (Figure 1) for all patients combined (r=0.82; P<0.001). Of the 20 patients, 13 were considered high omega-3 consumers, and 7 were considered low consumers. Although the correlation coefficients were virtually identical within each group (r=0.84; P<0.01), the relationships between the 2 tissues differed. The slope of the regression line was steeper in the low group than in the high group (Figure 1). The EPA+DHA as a percent of total RBC FA was
Figure 1. Correlation of omega-3 levels in cardiac tissue and RBCs in study 1 (n=20). Correlation between RBCs and cardiac EPA+DHA levels in group as a whole was 0.82 (P<0.001). When patients are separated according to estimated omega-3 intake (solid line, low intake; dashed line, high intake), correlation between RBCs and cardiac EPA+DHA levels remained essentially the same (r=0.84 in both groups; P<0.01). However, slope was greater in low than in high consumers (0.74 vs 0.35, respectively).

7.0±0.70% in the latter compared with 3.3±0.15% in the former (P=0.002). The values for cardiac tissue were 2.5±0.27% and 1.5±0.14%, respectively (P=0.003).

**Supplementation Study**

Twenty-five patients participated in the supplementation study, and samples from all 4 tissues were available from 21. The average age of this group was 55±9 years; 16 were men. The average time from transplantation was 5.2 years (range, 0.5 to 12.5 years). In all 4 tissues examined, a statistically significant increase in EPA+DHA content was observed after 6 months of fish oil supplementation (Table). The average increase in cardiac EPA+DHA was 110%, whereas that in RBC, cheek, and plasma was 101%, 73%, and 139%, respectively (Figure 2). There was no statistically significant difference among these responses. The mean percent increase in EPA and DHA individually were similar in all 4 tissues, although the rise in the former was generally much greater than in the latter. In the heart, EPA increased by 272±44% and DHA by 94±27%; in the cheek, 124±36% and 95±48%; in plasma, 365±52% and 104±16%; and in RBCs, 279±33% and 84±9%, respectively.

At baseline, correlations between cardiac tissue and the 3 potential surrogates were as follows: RBCs, r=0.47 and P=0.031; cheek, r=0.49 and P=0.023; and plasma, r=0.22 and P=NS. For RBCs (the only surrogate examined in both the supplementation and cross-sectional studies), the correlation tended (P=0.06) to be lower in the former (r=0.47) than in the latter (r=0.82).

In the 25 subjects in the supplementation study, there was no significant effect of 1 g/d EPA+DHA on serum lipids and lipoproteins: total cholesterol, 179±9 versus 179±8 mg/dL; triglycerides, 232±42 versus 197±30 mg/dL; HDL-C, 47±4 versus 46±4 mg/dL; and LDL-C, 87±6 versus 91±6 mg/dL.

**Discussion**

Current evidence suggests that the cardioprotective mechanism of omega-3 FAs depends on their presence in myocardial cell membranes. Thus, knowledge of cardiac omega-3 FA status may have clinical significance. Because it cannot be measured routinely, a surrogate tissue is needed that is both easily sampled and highly reflective of cardiac omega-3 FA levels.

**Surrogates for Cardiac Omega-3 FA Content**

Three tissues were examined as possible surrogates: RBCs, plasma, and cheek cells. An examination of baseline correlations between RBCs and cardiac tissue (study 1) and the responses of all 4 tissues to supplementation (Study 2), as well as practical and analytical issues, were taken into consideration to determine which of these 3 tissues could best serve as a surrogate for the heart.

**Cheek Cells**

Cheek cells have been used for noninvasive assessment of tissue omega-3 FA levels in infants and adults. In breast-fed infants, EPA+DHA accounted for 1.1% of total cheek cell phospholipid FAs; in adults, 0.9%. These values compare favorably with our presupplementation value of 1.6% (Table).

On a percentage basis, the cheek cell response was not statistically different from that seen in the other tissues; however, it was, on average, less than that seen in the heart (73% versus 110%). From a practical point of view, obtaining cheek cells is actually more time consuming and complicated than obtaining blood. It requires abstaining from food, tooth brushing, and using lipstick or lip balm on the morning of the test. It also involves three 30-second rinses and 2 episodes of buccal scraping, followed by further rinses. In addition, much less tissue is obtained by buccal scraping than by phlebotomy, making analysis more challenging.

**Plasma**

On a percentage basis, the plasma response was not statistically different from that seen in the other tissues; however, it was, on average, more than that seen in the heart (139% versus 110%). Plasma FAs are carried in several different lipid classes: cholesteryl esters, triacylglycerols, phospholipids, and nonesterified FAs. Because each of these classes has a unique FA composition, changes in plasma levels of a...
### Effects of Supplementation on Serum Lipid and Lipoprotein Concentrations

Consistent with many past studies, supplementation with \( \approx 1 \) g EPA+DHA did not materially alter serum lipid or lipoprotein levels.\(^{27}\) Most notably, in the GISSI-Prevenzione study,\(^ {26}\) 850 mg EPA+DHA had no effect on total or lipoprotein cholesterol levels, lowered triglycerides by only 6%, but decreased CHD events substantially. The reduction in triglycerides observed here was 15% (\( P=0.07 \)).

### Conclusions

RBC EPA+DHA content is highly correlated with and responds to omega-3 supplementation in a very similar manner as cardiac omega-3 FA levels. RBCs are easily isolated and may be analyzed in the fasted or fed state, and

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**Table:**

<table>
<thead>
<tr>
<th>FA</th>
<th>Cardiac Before</th>
<th>Cardiac After</th>
<th>Plasma Before</th>
<th>Plasma After</th>
<th>RBC Before</th>
<th>RBC After</th>
<th>Cheek Before</th>
<th>Cheek After</th>
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<tr>
<td>Palmitic</td>
<td>18.3±1.5</td>
<td>18.9±2.7</td>
<td>27.0±1.8</td>
<td>27.7±2.0</td>
<td>19.8±3.5</td>
<td>19.8±3</td>
<td>16.6±2.9</td>
<td>16.0±2.4</td>
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<td>Stearic</td>
<td>23.3±6.6</td>
<td>25.9±8.2</td>
<td>14.4±1.7</td>
<td>14.6±1.6</td>
<td>16.5±2.7</td>
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<td>22.6±5.4</td>
<td>21.1±4.5</td>
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<tr>
<td>Oleic</td>
<td>14.2±5.1</td>
<td>12.7±4.5</td>
<td>9.1±1.1</td>
<td>9.0±1.3</td>
<td>17.3±2.8</td>
<td>16.8±2.3</td>
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<td>Linoleic</td>
<td>9.1±2.8</td>
<td>7.8±3.3</td>
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<td>20.2±3.2</td>
<td>10.5±2.6</td>
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<td>8.2±2.9</td>
<td>8.3±2</td>
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<td>Linolenic</td>
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<td>0.4±0.5</td>
<td>0.1±0.04</td>
<td>0.2±0.05</td>
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<td>0.6±0.7</td>
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<td>Arachidonlc</td>
<td>9.1±3.6</td>
<td>7.7±2.7</td>
<td>12.3±2.4</td>
<td>11.0±2.6</td>
<td>17.3±2.7</td>
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<td>2.4±0.7</td>
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<td>DTA n-6</td>
<td>0.6±0.4</td>
<td>0.6±0.6</td>
<td>0.4±0.2</td>
<td>0.3±0.1†</td>
<td>5.1±1.3</td>
<td>3.0±0.7†</td>
<td>0.4±0.2</td>
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<tr>
<td>DPA n-6</td>
<td>0.3±0.2</td>
<td>0.2±0.1</td>
<td>0.3±0.1</td>
<td>0.2±0.1†</td>
<td>0.9±0.2</td>
<td>0.5±0.1†</td>
<td>0.1±0.1</td>
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<td>EPA</td>
<td>0.18±0.10</td>
<td>0.6±0.3‡</td>
<td>0.52±0.35</td>
<td>1.8±0.8‡</td>
<td>0.42±0.11</td>
<td>1.5±0.5‡</td>
<td>0.27±0.25</td>
<td>0.41±0.21*</td>
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<td>DPA n-3</td>
<td>0.81±0.46</td>
<td>0.84±0.37</td>
<td>0.71±0.20</td>
<td>0.97±0.32‡</td>
<td>2.7±0.5</td>
<td>3.9±0.7†</td>
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<td>0.51±0.38</td>
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<td>DHA</td>
<td>1.5±0.8</td>
<td>2.3±1.0‡</td>
<td>2.5±1</td>
<td>4.7±1.1†</td>
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<td>7.5±1.3‡</td>
<td>1.3±0.6</td>
<td>1.8±0.7*</td>
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<td>EPA+DHA</td>
<td>1.7±0.9</td>
<td>2.9±1.2‡</td>
<td>3.1±1.2</td>
<td>6.5±1.6‡</td>
<td>4.7±1.1</td>
<td>9.0±1.7‡</td>
<td>1.6±0.6</td>
<td>2.2±0.8‡</td>
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<tr>
<td>Total n-6 HUFA</td>
<td>10.0±3.7</td>
<td>8.4±2.6</td>
<td>13.0±2.4</td>
<td>11.5±2.7†</td>
<td>23.3±4.0</td>
<td>18.1±2.0‡</td>
<td>2.9±0.7</td>
<td>3.2±0.8</td>
</tr>
<tr>
<td>Total n-3 HUFA</td>
<td>2.5±1.2</td>
<td>3.7±1.5‡</td>
<td>3.8±1.3</td>
<td>7.5±1.8‡</td>
<td>7.3±1.4</td>
<td>12.9±2.2†</td>
<td>1.9±0.6</td>
<td>2.7±1.0†</td>
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<tr>
<td>n-6:n-3 HUFA</td>
<td>4.4±1.2</td>
<td>2.5±0.7†</td>
<td>3.8±1.3</td>
<td>1.7±0.7†</td>
<td>3.3±0.7</td>
<td>1.4±0.3‡</td>
<td>1.6±0.5</td>
<td>1.3±0.5‡</td>
</tr>
</tbody>
</table>

DPA indicates docosapentaenoic acid (C22:5); DPA, docosapentaenoic acid; and HUFA, highly unsaturated fatty acids (ie, those with \( \geq 20 \) carbons and \( \geq 3 \) double bonds). Values are mean±SD; n=21.

*\( P<0.05 \); †\( P<0.01 \) vs presupplementation within each tissue.
their EPA+DHA content reflects intakes over the past several weeks. We conclude that the Omega-3 Index may serve as a surrogate for cardiac omega-3 FA content.

Acknowledgments

This study was supported by grant from the Saint Luke’s Hospital Foundation and the Sara Morrison Bequest for Internal Medicine Research at the University of Missouri–Kansas City School of Medicine. The omega-3 capsules were a generous gift from Ocean Nutrition Canada. We thank the Cardiac Transplant Coordinators at Saint Luke’s Hospital, especially Kathy St. Clair, Elaine Russell, and Nancy Long, without whose support this study would not have been possible. The technical assistance of Lan Zhang and Phillip Mann was greatly appreciated, as was the statistical support of John House.

References

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An erratum has been published regarding this article. Please see the attached page for:
/content/110/19/3156.1.full.pdf

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Corrections

In the article “Omega-3 Fatty Acids in Cardiac Biopsies From Heart Transplantation Patients: Correlation With Erythrocytes and Response to Supplementation,” by Harris et al, which appeared in the September 21, 2004, issue of the journal (Circulation. 2004;110:1645–1649), the authors have identified 2 errors. On page 1646, under the heading “Plasma Lipids and Lipoproteins,” the abbreviation in parentheses on the third line should be HDL-C, not LDL-C. Also, in the final line in column 1 of page 1648, the word “not” was omitted. The sentence should read, “We found that RBC EPA+DHA was not altered in postprandial blood from 10 healthy volunteers.” The authors regret these errors.

Regarding the Correspondence page “Dietary Intervention Combined With Exercise Improves Vascular Dysfunction but Also Obstructive Sleep Apnea in Obese Children,” which appeared in the September 21, 2004 issue of the journal (Circulation. 2004;110:e314), it has been brought to our attention that this title is misleading. The 2 letters on this page pertained to an article published in the April 27, 2004, issue of the journal by Woo et al (Circulation. 2004;109:1981–1986) titled “Effects of Diet and Exercise on Obesity-Related Vascular Dysfunction in Children.” The second letter (available at http://circ.ahajournals.org/cgi/content/full/110/12/e314), written by Tsung O. Cheng, should have been titled “Childhood Obesity Among the Chinese.” We regret this error.

The article “Antibodies From Preeclamptic Patients Stimulate Increased Intracellular Ca²⁺ Mobilization Through Angiotensin Receptor Activation” by Thway et al, which appeared in the September 21, 2004, issue of the journal (Circulation. 2004;110:1612–1619), was inadvertently published without the authors’ corrections. The corrected version is available online at http://circ.ahajournals.org/cgi/content/full/110/12/1612. We regret these errors.

In the article “Critical Role of Macrophage 12/15-Lipoxygenase for Atherosclerosis in Apolipoprotein E–Deficient Mice” by Huo et al that appeared in the October 5, 2004, issue of the journal (Circulation. 2004;110:2024–2031), an error appeared in the legend of Figure 4. The following sentences should have been deleted: d, Serum-free cell medium conditioned by 12/15-LO⁺⁺ macrophages slightly increased endothelial VCAM-1 expression. e, In presence of LDL, 12/15-LO⁺⁺ macrophages cocultured with endothelial cells significantly increased expression of VCAM-1 on endothelial cells. n=4.

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