Omega-3 PUFA attenuate mice myocardial infarction injury by emerging a protective eicosanoid pattern

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\textbf{A B S T R A C T}

Omega-3 polyunsaturated fatty acid (n-3 PUFA) supplementation is a recommended preventive approach against cardiovascular diseases, but its mechanism of protection against myocardial infarction (MI) injury is not fully understood. Eicosanoid metabolomics demonstrated an abnormal eicosanoid profile was in the plasma of mice receiving MI surgery. 19,20-EDP, 17,18-EEQ, 14,15-EET and 9,10-EpOME were decreased, and PGE\textsubscript{2} was increased by the surgery. N-3 PUFA-rich diets feeding or transgenic of Fat-1 shifted the eicosanoid profile to an n-3 PUFA dominant style and attenuated the myocardial infarction injury. Multiple logistic regression analysis suggested the degree of MI injury was related with an eicosanoid pattern, composed by eicosanoids derived from both n-3 and n-6 PUFA in the three enzymatic pathways. These results suggested the benefits of n-3 PUFA on MI was achieved synergistically.
how does n-3 PUFA influence the eicosanoid profile when it is applied as an intervention approach to MI is entirely unknown. In this work, we used the targeted metabolomic method to study the plasma eicosanoid profile which was altered by MI surgery and shifted by n-3 PUFA intervention. Generally, the protective epoxides, derived from both n-3 and n-6 PUFA, were decreased in plasma of the mice receiving MI surgery. In contrast, PGE₂ was increased by MI surgery. These alterations were partially reversed by n-3 PUFA-rich diets feeding or transgene of Fat-1, which encode the enzyme converting n-6 PUFA to n-3 PUFA. It was suggested that the benefits of n-3 PUFA was achieved synergistically by affecting the eicosanoid metabolic status. A multiple logistic regression model was constructed to depict the relationship between the injury degree of MI and the combination of 7 critical eicosanoids, including, PGE₂, 14,15-EET, 17,18EEQ, 9,10-EpOME, 19,20-EDP, 15-HETE, 17-HDoHE. The metabolic pattern constituted by these eicosanoids would be an explanation of the protective effect of n-3 PUFAs on MI.

2. Materials and methods

2.1. Animal experiments

All procedures of animal handling were approved by the Institutional Animal Care and Use Committee of Peking University Health Science Center. Fat-1 tg mice were provided by Dr Alan Zhao from Guangdong University of Technology [10]. All mice were maintained under a 12-h light/dark cycle and controlled temperature with free access to water. Mice were fed a standard diet (MD12016 (Medili, IL, USA)). Gene expression was normalized to that of β-actin.

2.2. TTC staining

Mice were killed with anesthetic seven days after MI operation. Hearts were frozen at −20 °C for 20 min and then were sectioned into 5 mm thick slices. Five continuous slices from apex to the occlusion site were incubated with triphenyl tetrazolium chloride (TTC) at 37 °C for 5 min. After fixation with 4% paraformaldehyde overnight, each slice was weighed (w) and photographed with a digital camera. Infarct areas (IR) were indicated as the area not stained by TTC. The IR and left ventricular size (LV) were evaluated by Photoshop. Percentage of infarct area was calculated as IR/LV = (IR(per slice) × w(per slice)) / (LV(per slice) × w(per slice)).

2.3. Quantitative RT-PCR (qPCR)

Real-time PCR with primers was conducted as previously described [12]. Total RNA from mouse liver was isolated by use of RNAiso Plus reagent (Takara Bio, Japan) as instructed and reverse-transcribed by using the first-strand cDNA synthesis kit (Thermo Scientific, Rockford, IL, USA). Gene expression was normalized to that of β-actin.

2.4. Sample preparation for metabolomics

Plasma was extracted by solid-phase extraction (SPE) using Waters Oasis-HLB cartridges. Before extraction, cartridges were washed with methanol (1 mL) and Milli-Q water (1 mL). Samples were spiked with IS mixture (including 6-keto-PGF₁α-d₄, PGE₂-d₄, LTB₄-d₄, 11,12-DHET-d₁₁, 9-HODE-d₄, 20-HETE-d₆, 5-HETE-d₈, 8,9-EET-d₁₁, ARA-d, EPA-d₅, and DHA-d₅) and loaded onto cartridges. Cartridges were washed with 1 mL of 5% methanol. The aqueous plug was pulled from the SPE cartridges under high vacuum, and SPE cartridges were further dried under high vacuum for 20 min. Analytes were eluted into tubes with 1 mL of methanol and evaporated to dryness. The dried residue was dissolved in 100 μL of 30% acetonitrile and filtered by centrifuge tube filters (nylon membrane, 0.22 μm) before LC-MS analysis.

2.5. LC–MS method for metabolomics

Metabolomic analysis by LC–MS/MS for eicosanoids was performed as we previously described [13]. BEH C18 column (1.7 μm, 50 × 2.1 mm i.d., Waters, Milford, MA) was used for ultra-performance liquid chromatographic separation. Solvent A was water and solvent B was acetonitrile. The mobile-phase flow rate was 0.25 mL/min. The gradient was 0–3 minutes 30% B; 3–20 min B to 60%; 20–24 min B to 80% and maintained for 3 min; and 27–29 min B reduced to 30% and maintained for 1 min. The column was maintained at 25 °C, and the injection volume was set to 10 μL. Targeted profiling of n-6 and n-3 PUFA metabolites involved use of a 5500 QTRAP hybrid triple quadrupole linear ion trap mass spectrometer (AB Sciex, Foster City, CA) equipped with a turbo ion spray electrospray ionization source. Analytes were detected by MRM scans in negative mode. The dwell time used for all MRM experiments was 25 ms. The ion source parameters were CUR = 40 psi, GS1 = 30 psi, GS2 = 30 psi, ISP = −4500 V, CAD = MEDIUM, and TEMP = 500 °C.

2.6. Data analysis

LC–MS raw data processing involved the use of Analyst 1.6 (AB Sciex, Foster City, CA). Eicosanoids were quantified with use of MultiQuant 2.1 (AB Sciex, Foster City, CA). Metaboanalyst 3.0 [14] (http://www.metaboanalyst.ca) was used for metabolomic data analysis, interpretation and visualization, including Wilcoxon Mann-Whitney test, partial least squares discriminant analysis (PLS-DA), clustering and presenting as a heatmap. Spearman’s correlation analysis and multiple logistic regression analysis were performed using R (3.0.3). The correlation network was constructed and analyzed with use of Cytoscape 3.5.1 [15].

3. Results

3.1. The influence of MI surgery on eicosanoid profile

To study the metabolic status of eicosanoids in plasma of mice undergoing MI, a mice MI surgery model was established. The left anterior descending (LAD) artery which below the tip of the left auricle was tied with a 6 sterile silk suture. The sham subjects underwent the same operation except that the LAD was not ligated. After the operation, echocardiography was performed with a Vevo 710 RMV-707B (VisualSonics, Toronto, Ontario, Canada).
in Sham group and MI group could be clustered into two clusters perfectly by the top 25 changed eicosanoids. PLS-DA was used to develop a classification model which categorize the 2 type of samples based on MI and Sham surgery. The 2-dimensional score plot of PLS-DA proved the classification model could perfectly separate the samples by their groups (Fig. 1C). Variable importance for prediction (VIP) scores were calculated, and the top 10 eicosanoids mostly contributing to the classification were shown on the Y-axis (Fig. 1D). Univariate statistical analysis (Wilcoxon Mann-Whitney Test) for each eicosanoid was also performed. The significance and the magnitude of changes in eicosanoids between MI and Sham group were visualized by a volcano plot (Fig. 1E), and the level of each significantly changed eicosanoid in the two groups was shown as boxplot (Fig. 1F). Four cardiovascular protective epoxides, both derived from n-3 and n-6, decreased in the MI group. PGE2, the COX metabolite of AA, significantly increased in the MI group. Likely all the epoxides are influenced by a common factor, so

Fig. 1. Myocardial infarction surgery led to an abnormal eicosanoid profile in mice plasma. (A) Parameters determined by echocardiography reflecting the decreased heart function after MI surgery. LV, left ventricle; LVID, left ventricle internal diameter; Vol, volume; FS, fraction shortening; EF, ejection fraction; d, diastole; s, systole. *P < 0.05 versus Sham. (B) Heatmap showing the altered eicosanoid profile after MI surgery. Class 1 and 2 represented the Sham and MI group respectively. (C) PLS-DA score plot and (D) features (variables) of top 10 most significant metabolites based on VIP scores from loading 1 of PLS-DA. Color bars showed the relative intensities of variables in respective groups. (E) Volcano plot screening out eicosanoids with significant change in level (x-fold change > 2 or < 50%, *P < 0.05 versus Sham) in plasma. (F) Boxplot showing the five significantly changed eicosanoids by MI.
Table 1
The levels of the eicosanoids in the plasma of mice (ng/mL, mean ± SEM).

<table>
<thead>
<tr>
<th>Eicosanoid</th>
<th>Sham, FO, FAT-1tg, Sham</th>
<th>MI, MI + FO, FAT-1tg</th>
<th>MI, MI + FO, FAT-1tg</th>
<th>Δ</th>
<th>FAT-1tg Sham, MI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epoxy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5,6-EET</td>
<td>0.04 ± 0.04</td>
<td>0.02 ± 0.04</td>
<td>N.D.</td>
<td></td>
<td>N.D.</td>
</tr>
<tr>
<td>8,9-EET</td>
<td>0.07 ± 0.05</td>
<td>0.04 ± 0.03</td>
<td>0.02 ± 0.02</td>
<td>0.01 ± 0.01</td>
<td>0.03 ± 0.01</td>
</tr>
<tr>
<td>11,12-EET</td>
<td>0.36 ± 0.25</td>
<td>0.09 ± 0.03</td>
<td>N.D.</td>
<td>0.01 ± 0.01</td>
<td>0.04 ± 0.01</td>
</tr>
<tr>
<td>14,15-EET</td>
<td>1.51 ± 0.67</td>
<td>0.32 ± 0.11</td>
<td>0.24 ± 0.07</td>
<td>0.27 ± 0.12</td>
<td>0.23 ± 0.03</td>
</tr>
<tr>
<td>9,10-EpoE</td>
<td>7.01 ± 4.97</td>
<td>1.53 ± 0.36</td>
<td>0.52 ± 0.11</td>
<td>0.65 ± 0.22*</td>
<td>1.47 ± 0.2</td>
</tr>
<tr>
<td>12,13-EpoE</td>
<td>4.40 ± 39.11</td>
<td>5.67 ± 1.01</td>
<td>0.85 ± 0.12</td>
<td>1.22 ± 0.48**</td>
<td>5.35 ± 0.83</td>
</tr>
<tr>
<td><strong>Prostaglandin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PG and others</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6k-PGF2α</td>
<td>0.23 ± 0.08</td>
<td>0.24 ± 0.14</td>
<td>0.13 ± 0.03</td>
<td>0.09 ± 0.01</td>
<td>0.18 ± 0.06</td>
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<td>PGD2</td>
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<td>N.D.</td>
<td>N.D.</td>
<td></td>
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</tr>
<tr>
<td>PGF2A</td>
<td>N.D.</td>
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<td>N.D.</td>
<td></td>
<td>N.D.</td>
</tr>
<tr>
<td>TXA2</td>
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<td>N.D.</td>
<td>N.D.</td>
<td></td>
<td>N.D.</td>
</tr>
<tr>
<td><strong>Thromboxane</strong></td>
<td></td>
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<td></td>
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<tr>
<td>TXB2</td>
<td>0.58 ± 0.16</td>
<td>1.27 ± 0.14</td>
<td>0.63 ± 0.38</td>
<td>0.51 ± 0.25</td>
<td>0.48 ± 0.14</td>
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<tr>
<td>TXB3</td>
<td>N.D.</td>
<td>N.D.</td>
<td>N.D.</td>
<td></td>
<td>N.D.</td>
</tr>
<tr>
<td>5-oxoET</td>
<td>N.D.</td>
<td>N.D.</td>
<td>0.06 ± 0.05</td>
<td>0.26 ± 0.12*</td>
<td>0.68 ± 0.09</td>
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<tr>
<td>15-oxoET</td>
<td>0.02 ± 0.03</td>
<td>0.09 ± 0.06</td>
<td>0.26 ± 0.12</td>
<td>0.12 ± 0.04</td>
<td>0.12 ± 0.04</td>
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<tr>
<td>5R-LXA4</td>
<td>0.14 ± 0.1</td>
<td>0.05 ± 0.03</td>
<td>0.17 ± 0.06</td>
<td>1.35 ± 0.82**</td>
<td>0.55 ± 0.08</td>
</tr>
<tr>
<td>10,17-DiHETDiF</td>
<td>N.D.</td>
<td>1.5 ± 0.44</td>
<td>0.95 ± 0.48</td>
<td></td>
<td>N.D.</td>
</tr>
</tbody>
</table>

* Significance level for the comparison between Sham and MI using Wilcoxon Mann-Whitney test, p < 0.05. ** p < 0.01.
† Significance level for the comparison between MI and MI + FO using Wilcoxon Mann-Whitney test, p < 0.05. # p < 0.01.
‡ Significance level for the comparison between MI and FAT-1tg MI using Wilcoxon Mann-Whitney test, p < 0.05.
Fig. 2. N-3 PUFA supplementation protected mice against myocardial infarction injury and shifted the eicosanoid profile. (A) Parameters determined by echocardiography reflecting the reversed heart function by n-3 PUFA supplementation. *P < 0.05 versus Sham, #P < 0.05 versus MI. (B) TTC staining showing the diminished infarction area by n-3 PUFA supplementation. *P < 0.05 versus Sham, #P < 0.05 versus MI. (C) Heatmap showing the shifted eicosanoid profile by n-3 PUFA supplementation. Class 1, Sham group fed with normal diet; Class 2, MI group fed with normal diet; Class 3, Sham group fed with high n-3 PUFA diet; Class 4, MI group fed with high n-3 PUFA diet. (D) 3D PLS-DA score plot and (E) features (variables) of top 10 most significant metabolites based on VIP scores from loading 1 of PLS-DA. Color bars showed the relative intensities of variables in respective groups. (F) Boxplot showing the level of the 5 MI altered eicosanoids changed by n-3 PUFA supplementation. *P < 0.05 versus Sham, #P < 0.05 versus MI.
we tested transcription level of the epoxide related genes in mice liver, where the epoxides mainly produced. qPCR experiment indicated the decrease of the four epoxides could be caused by the down-regulation of CYP2C40 transcription (Fig. S1).

3.2. N-3 PUFA supplementation protected mice from MI injury and shifted the eicosanoid profile

To determine the effect of n-3 PUFAs on myocardial infarction, we fed mice with an FO diet or a normal diet for three weeks before MI surgery. The data of “Sham” and “MI” groups presented in Fig. 1 were used as control groups in this section of the analysis. Echocardiography revealed the heart function was greatly ameliorated by n-3 PUFA (Fig. 2A). The image of TTC staining also showed the area of myocardial infarction diminished in the n-3 PUFA-rich group (Fig. 2B). We applied the metabolomic method to study the eicosanoid profile in the mice fed with FO diet. The levels of the eicosanoids were listed in Table 1. The heatmap showed FO diet shifted the eicosanoid profile to an n-3 PUFA dominant style (Fig. 2C). Hierarchical clustering analysis showed the eicosanoid profiles of mice fed with FO mice and normal diet were in two separated clusters. PLS-DA was also performed with the eicosanoid profile of the 4 groups (Sham, MI, Sham + FO and MI + FO). The 3-dimensional score plot of PLS-DA showed the mice fed with FO or normal diet could be separated by Component 1, and mice receiving MI surgery or not in each diet fed group could be further separated by Component 2 (Fig. 2D). It meant FO supplementation shifted the alteration on eicosanoid profile induced by MI surgery. VIP scores showed the top 10 eicosanoids contributing to the classification based on Component 1 (Fig. 2E). Univariate statistical analysis for each eicosanoid was performed, and the boxplots of the five eicosanoids significantly changed by MI surgery were shown as Fig. 2F. Wilcoxon Mann-Whitney Test performed between the MI and MI + FO group indicated the level of 19,20-EDP and 17,18-EEQ, the two n-3 PUFA derived eicosanoid, were significantly reversed by FO diet and even higher than the Sham group. For n-6 PUFA derived epoxides, the level of 9,10-EpOME were decreased by FO diet, but the proportion of decrease in these two eicosanoids is less than the proportion of the increase in 19,20-EDP and 17,18-EEQ. The levels of 14,15-EET (p = 0.164) and PGE₂ (p = 0.063) did not reach the significance.

3.3. Fat-1 transgenic mice have a resistance on MI injury and an n-3 PUFA dominant eicosanoid profile

To further validate the effect of n-3 PUFA on myocardial infarction. Fat-1 transgenic mice expressing the C. elegans Fat-1 gene received the MI surgery. The Fat-1 gene encodes an n-3 fatty acid desaturase which converts n-6 to n-3 fatty acids (which is absent in mammals). The data of “Sham” and “MI” groups presented in Fig. 1 were used as control groups in this section of the analysis. Echocardiography and TTC staining showed Fat-1 transgenic mice had a stronger heart function and a smaller infarction area compared with WT mice receiving the MI surgery (Fig. 3A and 3B). Eicosanoid metabolomics also demonstrated Fat-1 mice had an intrinsic n-3 PUFA dominant eicosanoid profile (Fig. 3C and Table 1). PLS-DA analysis indicated the increase of n-3 PUFA derived eicosanoids were still the most important factor contributing to the difference of eicosanoid profile (Fig. 3D and E). The boxplots of the five eicosanoids significantly changed by MI surgery were shown in Fig. 3F. Wilcoxon Mann-Whitney Test performed between the MI and Fat-1 MI group indicated only PGE₂ was significantly reversed in the Fat-1 MI group, and all the epoxides did not reach the statistical significance. These results suggested both n-3 PUFA supplementation and Fat-1 transgene had a protective effect on MI and produced an n-3 PUFA dominant eicosanoid profile, but the specific significantly changed eicosanoids between these two n-3 PUFA intervention approaches were different (Table 1).

3.4. Correlation between eicosanoids and the protective eicosanoid pattern on MI

Firstly, we tested if the levels of PUFAs in plasma were changed by MI and n-3 PUFA supplementation or Fat-1 transgene. As shown in the boxplot (Fig. 4A), n-3 PUFA supplementation significantly increase the level of EPA and DHA and decrease the level of AA. However, Fat-1 transgene only increased the level of EPA significantly, but the change of the DHA and AA level did not reach the significance statistic level. Compared the MI group with the Sham group, the change of PUFAs did not reach the significance statistic level either. These results couldn’t prove if the protective effect of the two n-3 PUFA intervention approaches on MI was related to the level change of the PUFAs. According to the metabolomics results, we proved both supplementation and Fat-1 transgene shifted the eicosanoid profile (Fig. 2C and 3C). However, the five significantly changed eicosanoid by MI were not reversed by the two intervention approaches consistently. We still couldn’t identify the specific eicosanoids contributed to the protective effect on MI. Considering the eicosanoids are derived from a same metabolic network, we wanted to study the interaction between eicosanoids and the position of the five significantly changed eicosanoids in the metabolic network. We also wanted to know which parts of the metabolic network were influenced by the two intervention approaches and found the eicosanoid pattern which contributes to the protective effect. We calculated the Spearman’s correlation coefficient for each correlation between eicosanoids based on the amount of whom in the six groups. A network of eicosanoid was constructed to present the overall correlations (Fig. 4B), from which we found most n-3 PUFA derived eicosanoids were negatively correlated with the n-6 PUFA derived ones (shown by blue edge) and eicosanoids derived from the same PUFA were positively correlated with each other (shown by black edge). The eicosanoids influenced by either intervention approach were with red borders. To understand the protective metabolic state, we dissected the eicosanoid network. The network was constituted by five modules, which contain LOX and CYP metabolites derived from n-3 PUFA and COX, LOX and CYP metabolites derived from n-6 PUFA. The eicosanoids in the same module positively correlated with each other. The five significantly altered eicosanoids (PGE₁, 19,20-EDP, 17,18-EEQ, 14,15-EET and 9,10-EpOME, shown by yellow nodes) by MI surgery belonged to 3 modules including CYP n-3, CYP n-6 and COX n-6. The two n-3 PUFA interventions not only reversed four eicosanoids significantly changed by MI but also changed lots of eicosanoids in all the five modules. We could not ascertain if the protective effect n-3 PUFA comes from the reverse of the five eicosanoids of from the regulation of other eicosanoids.

Although the specific function of eicosanoids in the process of omega-3 PUFA’s protection on MI could not be identified, we tried to find which eicosanoids could be the effective factors on cardiac function. Whether the ejection fraction (EF) exceeds 50% was a criterion of cardiac dysfunction. Logistic regression analysis was used to measure the influence of each eicosanoid on cardiac function. The area under curve (AUC) of the receiver operating characteristic (ROC) for each eicosanoid was listed in Table S2. Most of the AUCs for eicosanoids were below 0.7. Furthermore, we tested the combinational effect of the five significantly changed eicosanoids by MI on cardiac function using a multiple logistic regression model (Model 1), in which each eicosanoid was an independent variable and whether cardiac dysfunction occurs was the dependent variable. The ROC curve suggested this model have good efficacy in the classification of cardiac function, of which the AUC was 0.817 (Fig. 4C). Considering the correlation among eicosanoids, we further inspected the efficacy by other combinations of eicosanoids. 15HETE and 17-HDoHE had the highest connection degree in the LOX n-6 and LOX n-3 modules respectively, so these two representative eicosanoids were added to the logistic model (updated as Model 2). Thus, eicosanoids in Model 2 covered all the five modules in the eicosanoid network. The ROC curve of Model 2 indicated the efficacy of
classification was increased when the 2 LOX metabolites were included (Fig. 4D). The increased efficacy on the classification of cardiac function by multiple logistic regression indicated the factor contributing to the protective effect of omega-3 PUFA on MI was the eicosanoid pattern but not a specific eicosanoid.

4. Discussion

Although much work reported the cardiovascular protective effect of n-3 PUFA, no studies focused on the perspective from eicosanoid profile which contains the main metabolite in the three major enzymatic pathways. Targeted metabolomics method provided
comprehensive information about eicosanoids in plasma of mice fed with n-3 PUFA-rich diet and Fat-1 transgene. The significant eicosanoids changed by these two kinds of n-3 intervention approach were not the same. Most of the significant eicosanoids changed by Fat-1 transgene were the decreased n-6 PUFA derived ones, whereas n-3 PUFA supplementation not only decreased n-6 PUFA derived eicosanoids, but also increased lots of n-3 PUFA derived eicosanoids (Table 1). Also, the fold-changes of n-3 PUFA derived eicosanoids increased by n-3 PUFA supplementation were higher than that increased by the Fat-1 transgene. One possible reason was that n-3 PUFA intake from food made the level of n-3 PUFA in plasma rise sharply, which lead to a lot of n-3 PUFA entered tissues and cells and be rapidly metabolized into eicosanoids by the corresponding enzymes. Whereas Fat-1 transgene converses n-6 PUFA to n-3 PUFA in a mild manner, the increase of the n-3 PUFA derived eicosanoids is less obvious. The level of EPA and DHA, which was not remarkably changed by the Fat-1 transgene, also supported this deduction (Fig. 4A).

Many eicosanoids changed by n-3 PUFA intervention have a definite function on the cardiovascular system. For example, EEQs and EDPs were increased by n-3 PUFA intervention. Besides the anti-inflammatory effect which was broadly reported, both 17,18-EEQ and 19,20-EDP were reported to inhibit the calcium-induced arrhythmias in cardiomyocytes [16,17]. PGE2 was increased after seven days of MI surgery and decreased by n-3 PUFA intervention. In most instances, PGE2 was recognized as an inflammation mediator [18]. Deletion of microsomal prostaglandin E2 synthase-1 (mPGES-1) reduced plaque burden in fat-fed LDLR(-/-) mice, which suggested PGE2 would be a pro-atherogenic factor [19]. However, some work reported the potential protective effect of PGE2 on myocardial infarction injury. Deletion of mPGES-1 leads to eccentric cardiac myocyte hypertrophy, LV dilatation, and impaired LV contractile function after acute MI [20]. Therefore, the actual effects of PGE2 on prevention and repair phases of myocardial infarction need to be comprehensively considered. N-3 supplementation also elevated most of the monohydroxy-eicosanoid, despite the functional studies of these compounds in the heart is lack. Bone marrow transplantation experiments revealed 18-HEPE from Fat-1 transgenic macrophages exhibited resistance to pressure overload-induced inflammation and fibrosis and ameliorated cardiac function [21]. N-3 PUFA derived specialized pro-resolving mediators (SPM) were not detected in this work, which could be related to the time point we selected. SPMs are usually produced in the resolution phase [22].

After acquiring the eicosanoid profile, logistic regression analysis was applied to depict the relation of eicosanoids and the recovery of cardiac function after MI surgery. The ROC curve of the logistic models indicated the classification efficacy on cardiac function using a combination of eicosanoids was better than using each eicosanoid or PUFAs themselves, which suggested n-3 PUFA synergistically exerted its protective effect. This viewpoint is supported by lots of works in which specific eicosanoid metabolites were proved to play a role in different biological processes related to MI injury or recovery respectively. The eicosanoids are derived from a same metabolic network. As a result, the increase of the substrates could influence lots of metabolites’ level. A pattern composed of seven eicosanoids was suggested to be highly related to the cardiac function. The discovery of this pattern could afford some inspiration for clinical application, which is the influence on eicosanoids should be comprehensively considered when using n-3 PUFA intervention. This pattern could also be an explanation of why some clinical trial of n-3 PUFA supplementation on MI acquired negative results [23,24]. Although the specific function of eicosanoids in the pattern need to be further demonstrated, it still suggested the regulation of muti-eicosanoids in a combinational manner would be a new perspective in clinical application.
Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.prostaglandins.2018.09.002.

References


