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Trans-myocardial omega-3 fatty acid gradient in coronary microvascular dysfunction

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Abstract

Background: Cardiac remodeling is a process mediated, in part, by 18-hydroxyeicosapentaenoic acid (HEPE), a metabolite of the omega-3 polyunsaturated fatty acid, eicosapentaenoic acid (EPA). We hypothesized that trans-myocardial levels of 18-HEPE could inform the pathophysiologic processes involved in heart failure with preserved ejection fraction (HFpEF).

Methods: We measured the concentration of 18-HEPE and EPA in trans-myocardial plasma samples from 10 subjects enrolled in The Women's Ischemia Syndrome Evaluation [WISE] Mechanisms of Coronary Microvascular Dysfunction Leading to Pre-HFpEF project.

Results: Concentrations of 18-HEPE were significantly lower in coronary venous compared to the aortic plasma (270.5 pg/mL [212.8–480.8] vs. 430.5 pg/mL [299.5–655.8], $p = 0.0039$). There was a significant correlation between the concentrations of coronary venous EPA and aortic 18-HEPE ($r = 0.94$, $p = 0.0002$), and aortic EPA and aortic 18-HEPE ($r = 0.82$, $p = 0.0058$).

Conclusions: Results of this small pilot study support the suggestion that 18-HEPE is synthesized outside the heart and utilized within the myocardial bed.

Keywords

Omega-3 fatty acid; Coronary microvascular dysfunction

1. Introduction

Coronary microvascular dysfunction (CMD) is an inflammatory condition that limits coronary blood flow independent of epicardial arterial disease and is a key contributor to cardiac ischemia and heart failure with preserved ejection fraction (HFpEF) [1]. Maladaptive cardiac remodeling is an active process mediated, in part, by 18-hydroxyeicosapentaenoic

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Declaration of competing interest

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acid (HEPE), a metabolite of the omega-3 polyunsaturated fatty acid, eicosapentaenoic acid (EPA) produced by macrophages, by attenuating inflammation and fibrosis in the heart [2]. Previously, we reported significant differences in peripheral blood plasma levels of EPA and 18-HEPE in women with CMD compared with reference subjects [3]. We hypothesized that subjects with CMD are unable to resolve inflammation occurring locally within the heart related to insufficient production or ineffective activity of omega-3 fatty acids resulting in progressive left ventricular fibrosis and HFpEF. The ability to directly measure the concentration of omega-3 fatty acids and their metabolites in the heart could inform the pathophysiologic processes involved in CMD.

2. Methods

The Women's Ischemia Syndrome Evaluation [WISE] Mechanisms of Coronary Microvascular Dysfunction Leading to Pre-Heart Failure with Preserved Ejection Fraction [Pre-HFpEF] (ClinicalTrials.gov NCT03876223) is a prospective cohort study evaluating the effect of CMD on the development of HFpEF. All subjects enrolled in the WISE pre-HFpEF study gave written informed consent. As part of the protocol, subjects undergo blood sampling across the myocardial bed with simultaneous collection of aortic and coronary sinus (venous) blood. After the University of Florida institutional review board approval, we measured EPA and 18-HEPE levels in trans-myocardial blood samples from 10 subjects using liquid chromatography with tandem mass spectrometry. (LC-MS-MS) according to established techniques [4,5]. Quantitation was performed on a Thermo TSQ Altis triple quadrupole mass spectrometer at the University of Florida-Southeast Center for Integrated Metabolomics. Plasma concentrations of EPA and 18-HEPE were compared between aortic and coronary venous blood samples using Wilcoxon matched-pairs sign rank test, and correlations were performed using Spearman correlation coefficient. All analyses were performed using (GraphPad Prism 9.1.0). A 2-sided p value <0.05 was considered statistically significant.

3. Results

The subjects were women with a median age of 52 years [interquartile range 49–63]. We observed a highly significant reduction in the concentration of 18-HEPE levels in paired coronary venous compared with aortic samples ($p = 0.0039$) (Fig. 1, panel A), suggesting uptake and utilization of 18-HEPE by myocardium. There was no significant difference in the trans-myocardial concentration gradient of EPA (Fig. 1, panel A). The concentration of aortic EPA correlated with the concentration of aortic 18-HEPE (correlation coefficient 0.82, $p = 0.0058$), and the concentration of coronary venous EPA correlated with the concentration of 18-HEPE in aortic samples (correlation coefficient 0.94, $p = 0.0002$) (Fig. 1, panel B). In coronary venous blood there was no such correlation between 18-HEPE levels in the coronary sinus and EPA levels in the coronary sinus (correlation coefficient 0.59, $p = 0.0806$), or 18-HEPE levels in the coronary venous and EPA levels in the aortic blood (correlation coefficient 0.27, $p = 0.4483$). Our findings suggest that the synthesis of 18-HEPE from EPA likely occurs systemically and not in the myocardial bed. A representative chromatogram showing 18-HEPE levels in the calibrator and representative patient sample appears in Fig. 2.

4. Discussion

In a prior report we found that subjects with CMD had higher levels of 18-HEPE and EPA in their peripheral blood compared to age-matched reference subjects [2]. Results from our current first in human pilot study extend our hypothesis by suggesting that 18-HEPE, a product of EPA which is a potent anti-inflammatory and anti-fibrotic mediator, is synthesized outside the heart and utilized within the myocardial bed. This finding supports the hypothesis that 18-HEPE is recruited to the heart in response to a chronic inflammatory milieu, which propagates CMD. There are at least 2 scenarios that may explain our findings in subjects with CMD: First, quantitatively there is insufficient 18-HEPE produced from EPA to resolve the inflammation, or second, qualitatively 18-HEPE is functionally abnormal rendering it ineffective to resolve the inflammation.

In an animal model of HFpEF, higher levels of 18-HEPE were found in the macrophages of fat-1 mice, a model that has high levels of omega-3 fatty acids in all tissues and are protected from adverse cardiac remodeling [2]. Moreover, in the same study, in vivo administration of 18-HEPE to wild type mice was associated with attenuation of cardiac remodeling, effectively reproducing the fat-1 mouse phenotype (2). Abnormal EPA metabolism, namely production of 18-HEPE, and insufficient uptake across the myocardial bed may contribute to linking ineffective resolution of inflammation to CMD and the subsequent development of HFpEF.

Several limitations include: a) this is a small, hypothesis-generating pilot study that requires validation in a larger cohort that should also include men, b) the source and utilization of EPA is not elucidated, and c) due to the invasive approach required for coronary venous blood collection, we did not include healthy controls.

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References

[1]. AlBadri A, Lai K, Wei J, et al. , Inflammatory biomarkers as predictors of heart failure in women without obstructive coronary artery disease: a report from the NHLBI-sponsored Women's ischemia syndrome evaluation (WISE), PLoS ONE 12 (2017), e0177684. [PubMed: 28542263]

[2]. Endo J, Sano M, Isobe Y, et al. , 18-HEPE, an n-3 fatty acid metabolite released by macrophages, prevents pressure overload-induced maladaptive cardiac remodeling, J. Exp. Med. 211 (2014) 1673. [PubMed: 25049337]

[3]. Keeley EC, Li HJ, Cogle CR, et al. , Specialized proresolving mediators in symptomatic women with coronary microvascular dysfunction (from the Women's ischemia trial to reduce events in non-obstructive CAD [WARRIOR] Trial), Am. J. Cardiol. 162 (2022) 1. [PubMed: 34728061]

[4]. Colas RA, Shinohara M, Dalli J, et al. , Identification and signature profiles for proresolving and inflammatory lipid mediators in human tissue, Am J Physiol Cell Physiol 307 (2014) C39. [PubMed: 24696140]

[5]. Dalli J, Colas RA, Walker ME, et al. , Lipid mediator metabolomics via LC-MS/MS profiling and analysis, Methods Mol. Biol 1730 (2018) 59. [PubMed: 29363065]

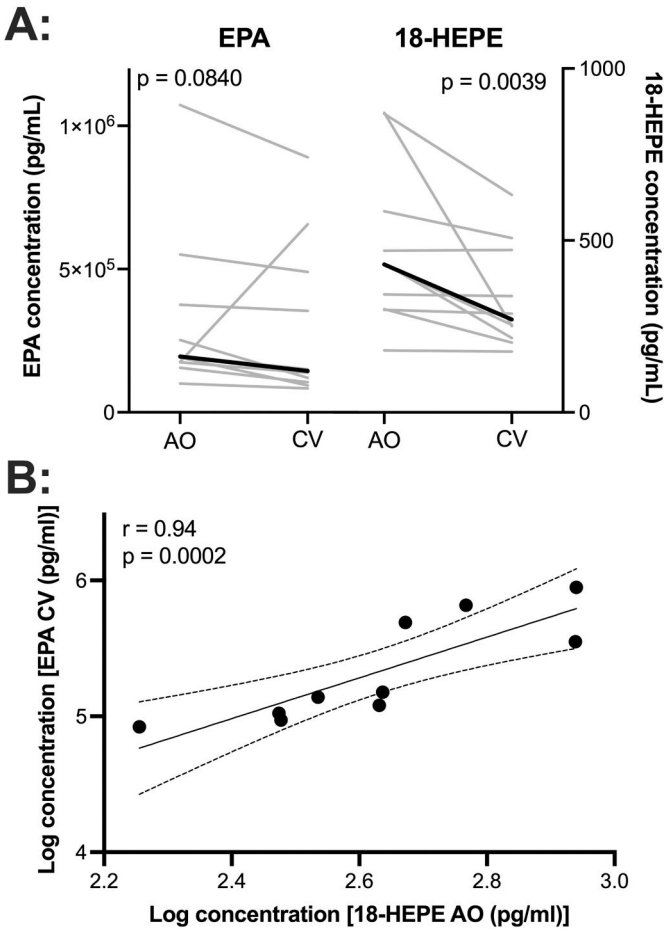

Fig. 1.

Paired aortic and coronary venous blood levels of EPA and 18-HEPE (A), and correlation between aortic 18-HEPE levels and coronary venous EPA levels (B). AO, aorta; CV, coronary venous; EPA, eicosapentaenoic acid; HEPE, hydroxyeicosapentaenoic acid.

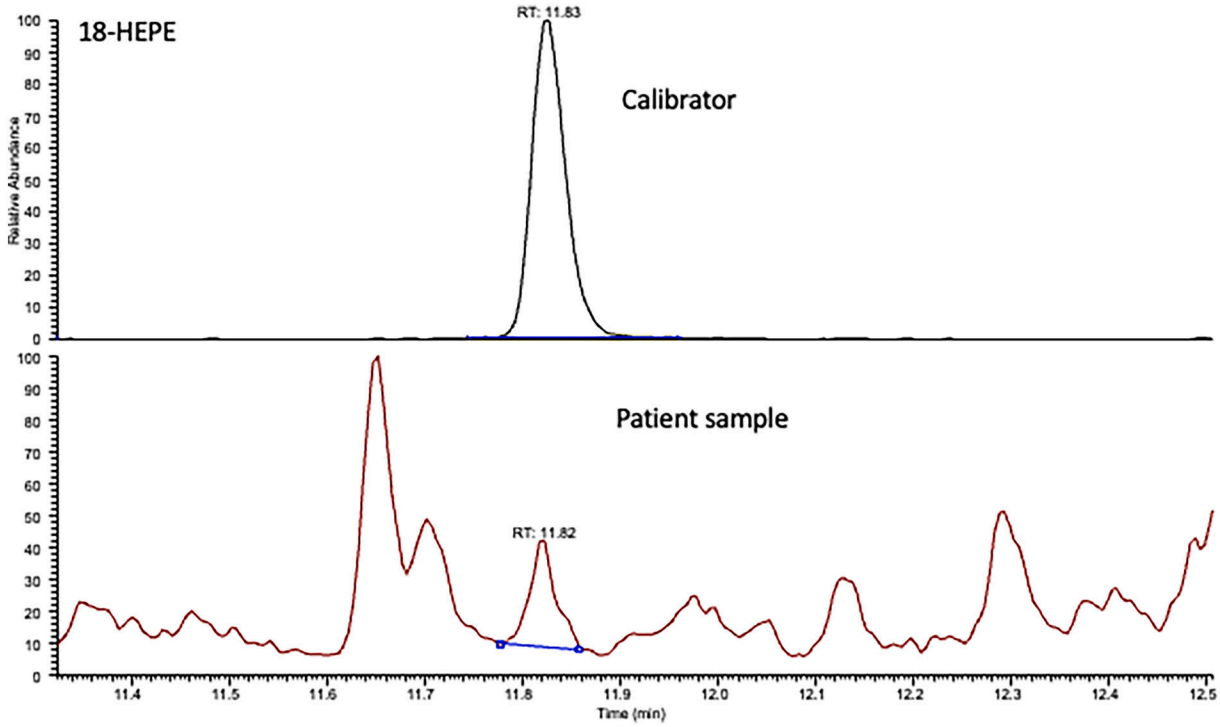

Fig. 2.

Selected reaction monitoring extracted ion chromatogram for 18-HEPE. Top panel is the calibrator, bottom panel is a patient sample. RT, retention time (in minutes); HEPE, hydroxyeicosapentaenoic acid.