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Review article

Coronary microvascular dysfunction as a chronic inflammatory state: Is there a role for omega-3 fatty acid treatment?

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ABSTRACT

Coronary microvascular dysfunction is a ubiquitous pathologic process that is operational in ischemia with no obstructive coronary artery disease and other cardiovascular disorders including heart failure with preserved ejection fraction. It may, in fact, be a manifestation of a multi-systemic condition of small vessel dysfunction that also affects the brain and kidneys. While the pathophysiology driving coronary microvascular dysfunction is multifactorial, chronic inflammation plays an important role. Resolution of inflammation is an active process mediated, in part, by a family of locally active mediators biosynthesized from omega-3 fatty acids, collectively referred to as specialized pro-resolving mediators. Omega-3 fatty acid treatment modulates inflammation and is associated with improved cardiovascular outcomes and attenuation of plaque progression on cardiovascular imaging. Whether omega-3 fatty acid treatment attenuates coronary microvascular dysfunction is unknown.

1. Introduction

1.1. Importance and prevalence of coronary microvascular dysfunction

Coronary microvascular dysfunction (CMD), defined as limited coronary flow reserve and/or endothelial dysfunction, is a ubiquitous pathologic process that contributes to myocardial ischemia and angina, and is associated with increased risk for major adverse cardiac events over long-term follow-up despite advances in the field [1–4]. While it is traditionally associated with women with symptoms of angina/ischemia with no obstructive coronary artery disease (CAD) (ANOCA, INOCA), it also affects men, people of different ethnicities [5], and has been documented in patients with prior technically successful percutaneous or surgical revascularization procedures [6], severe aortic stenosis [7], and hypertrophic [8] and dilated [9] cardiomyopathies. Recently, CMD has been implicated in the pathophysiology of heart failure with preserved ejection fraction (HFpEF), a disease associated with significant morbidity which has limited treatment options [10–13]. Whether CMD-related ischemia causes diffuse myocardial fibrosis, left ventricular diastolic dysfunction and the clinical manifestation of HFpEF is presently being studied in the NIH-funded Women's Ischemia Syndrome Evaluation Mechanisms of Coronary Microvascular Dysfunction Leading to Pre-Heart Failure with Preserved Ejection Fraction (WISE preHFpEF) project (NCT#03876223). When specifically assessed by coronary function testing in the cardiac catheterization laboratory, CMD is highly prevalent in symptomatic men and women undergoing coronary angiography that shows no evidence of flow-limiting epicardial artery lesions [14]. In the British Heart Foundation Coronary Microvascular Angina Study (BHF CorMicA), patients with INOCA were randomized to undergo invasive coronary function testing and receive stratified medical therapy guided by the results or usual care (coronary function testing results were not disclosed) [15]. These investigators found a significant improvement in both angina scores and quality of life assessment in those randomized to stratified medical treatment guided by coronary function testing.

A number of small, mechanistic, pilot studies assessing the effectiveness of medications including statins, aspirin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, anti-anginals, hormone replacement, and novel treatments to ameliorate symptoms and improve microvascular function have been published [16]. While the most promising medications thus far include potent statins in combination with high-dose angiotensin converting enzyme-inhibitors (ACE-I) or angiotensin receptor blockers (ARB), there is no standard proven therapy due to a paucity of large, randomized, long-

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term outcome trials, underscoring the need for well-designed clinical trials to aid in the development of effective therapies [17]. The Department of Defense-funded Women's Ischemia Trial to Reduce Events in Non-obstructive CAD (WARRIOR) (NCT# 03417388) is a multi-center randomized trial enrolling women with INOCA, MI with no obstructive coronary arteries (MINOCA), or ANOCA to usual care or intensive medical therapy (including high dose statin, aspirin, and either an ACE-I or an ARB) to address these knowledge gaps [18]. In addition, the MINOCA-BAT trial (NCT#03686695) is randomizing men and women with MINOCA to one of four arms, ACE-I/ARB and beta-blocker, beta-blocker alone, ACE-I/ARB only, and neither ACE-I/ARB or beta-blocker. This project is designed to determine whether these medications reduce the outcome of death from any cause or readmission due to acute myocardial infarction, ischemic stroke or heart failure [19]. Both the WARRIOR and MINOCA-BAT pragmatic trials should contribute important data regarding the effect of aspirin, statin, ACE-I and ARB on clinical outcomes.

1.2. Role of chronic inflammation in coronary microvascular dysfunction

While the pathophysiology of CMD is multi-factorial, emerging evidence supports chronic inflammation and ineffective efferocytosis as a crucial factor [6]. Several lines of evidence indicate that chronic inflammation plays a causal role in CMD: a) C-reactive protein (CRP) is elevated in patients with CMD [20–22], and correlates with the severity of CMD [23], b) individuals with chronic inflammatory diseases develop CMD [24,25], and have CRP levels that correlate with CMD severity [26], and c) in asymptomatic twins CRP levels were significantly higher in the twin with evidence of CMD assessed by coronary flow reserve (CFR) [27]. In a study of 86 subjects with INOCA and 48 controls, elevated peripheral blood levels of interleukin-6 and tumor necrosis factor-alpha were independent predictors of CFR of $\leq$2.5, further supporting a link between chronic inflammation and CMD [28]. Moreover, data from the WISE Program suggest that chronic inflammation may be an important mechanistic pathway leading to HFpEF in women with CMD [29]. In a cohort of 390 women with CMD followed for 6 years, circulating levels of interleukin-6 predicted mortality and heart failure hospitalization independent of traditional cardiac risk factors. CMD appears to be prevalent in chronic inflammatory rheumatologic diseases such as rheumatoid arthritis and systemic lupus erythematosus [25]. In a study of patients undergoing stress positron emission tomography myocardial perfusion imaging, the frequency of myocardial flow reserve $<$2.0, consistent with CMD, was higher in those with systemic lupus erythematosus compared to controls (57.1% *vs.* 33.3%, p = 0.017) [30]. Moreover, myocardial flow reserve was inversely related to disease activity (assessed by the systemic lupus erythematosus disease activity index) independent of traditional cardiac risk factors, atherosclerotic burden, and kidney disease. In 131 patients with single vessel CAD, mean pericoronary adipose tissue inflammation assessed by CT attenuation was an independent predictor of reduced global coronary flow reserve $<$2.0, underscoring the link between inflammation and coronary microvascular dysfunction [31]. Rethy and colleagues present data supporting the concept that CMD is not only more common in people living with HIV compared to controls but may serve as a key mediator of the increased risk of cardiovascular disease seen in this population [32]. If this is verified by large, well-designed studies, CMD may become an important target for treatment to attenuate cardiovascular risk not only in HIV but in other chronic proinflammatory diseases.

In summary, these findings support a key role for chronic inflammation as a driving mechanism for CMD and underscore the need to better identify heightened inflammatory pathways, which may lead to new/novel treatment strategies.

1.3. Resolution of inflammation and the specialized pro-resolving mediators

Eicosanoids, signaling molecules derived from arachidonic acid and polyunsaturated fatty acids, play a crucial role in inflammatory processes [33]. The term can be used to describe both classic eicosanoids (leukotrienes, prostaglandins, prostacyclins, and thromboxanes) and a family of locally active mediators biosynthesized from two main polyunsaturated omega-3 fatty acids (eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA)), collectively referred to as specialized pro-resolving mediators (SPMs) [34–37]. While classic eicosanoids are generally considered pro-inflammatory (although they can be pro- or anti-inflammatory depending on the receptor), SPMs are anti-inflammatory and actively mediate efferocytosis (Fig. 1). These small, lipid cell-signaling molecules resolve local inflammation by inhibiting neutrophil functions and promoting macrophage anti-inflammatory actions [38]. SPMs encompass several structurally distinct families of fatty acid-derived molecules that include lipoxins, resolvins, protectins, and maresins [36] (Fig. 1). It is plausible that disruptions in this endogenous proresolving system could lead to chronic inflammation. This concept is supported by data from a murine model of peritonitis where resolvin D1 regulated the activity of murine macrophages by suppressing tumor necrosis factor alpha production and restoring efferocytosis [39].

Evidence linking SPMs to the pathogenic mechanisms related to microvascular dysfunction include: a) anti-angiogenic effects [40], b) reduction of microvascular permeability [41], c) inhibition of smooth muscle migration and proliferation [42], d) inhibition of monocyte adhesion [42,43], e) reduction of ischemia-reperfusion injury [44,45], f) human macrophage switching from M1 to M2 phenotype [46,47], and g) augmentation of macrophage phagocytosis [48]. Unresolved inflammation can result in excessive fibrosis that impairs organ function. Animal studies have shown a reduction in both lung and kidney fibrosis with exogenous SPM administration [49–51]. To date, however, there is limited data regarding the potential role of SPM in HFpEF [52,53], a condition associated with increased myocardial stiffness due to excessive myocardial fibrosis and may involve microvascular inflammation [54]. The concept that omega-3 fatty acids are involved in the pathophysiology of CMD is supported by results of an interesting study focused on subjects with and without CMD in whom plasma lipidomic patterns were assessed [55]. These investigators reported a unique plasma lipidomic pattern in subjects with symptomatic CMD, namely, significantly lower amounts of long-chain omega-3 fatty acids (such as EPA and DHA).

Two studies have evaluated the relationship between EPA levels and coronary microvascular function (Table 1). In a study of 127 patients with INOCA, CFR assessed by phase-contrast cine CMR was significantly lower in patients with low serum EPA levels, and multivariate analysis showed that EPA level was an independent predictor of CFR [56]. In another study of 108 symptomatic patients with INOCA undergoing hyperemic microvascular resistance index testing (a wire-based method for invasively assessing coronary microvascular function), EPA/arachidonic acid (AA) ratio was an independent predictor of hyperemic microvascular resistance index [57] with the low EPA/AA ratio group having significantly higher hyperemic microvascular resistance index values compared to the high EPA/AA ratio group. These results suggest a lower serum EPA/AA ratio may result in CMD. While these studies suggest that EPA (the omega-3 fatty acid precursor for the E-series resolvins), may protect against CMD, it is important to note that resolvin levels were not measured. Therefore, the mechanism behind EPA's benefit was not fully investigated and may be related, at least in part, to the E-series resolvins effect on inflammation resolution.

Other investigators have assessed the relationship between blood levels of EPA and pericoronary adipose tissue (a marker of inflammation in coronary CT angiography) and coronary plaque progression by coronary CT angiography. In a cross-sectional study of 64 patients, higher

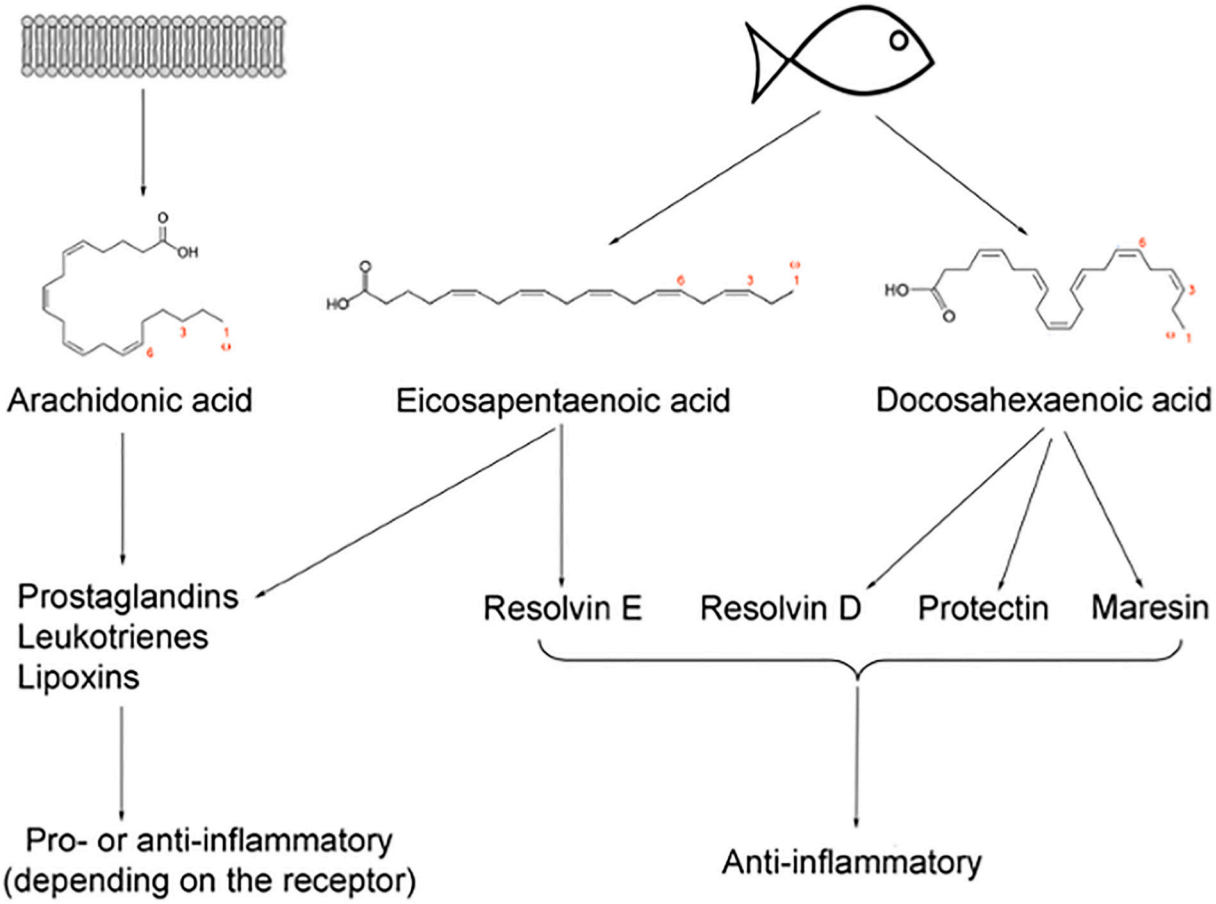

Fig. 1. Simplified schematic overview of classic eicosanoid and specialized pro-resolving mediator biosynthesis from polyunsaturated fatty acids.

Table 1
Studies evaluating association between circulating omega-3 fatty acid levels and coronary microvascular function.

Reference	Patient population	Measurement	Findings
Kato et al., 2013 (ref. [56])	127 patients with INOCA (116 men, 11 women) Mean age 72 years	CFR by cardiac magnetic resonance imaging	Serum levels of EPA and DHA positively correlated with CFR EPA was independent predictor of preserved CFR (>2.5)
Muroya et al., 2018 (ref. [57])	108 patients with INOCA (75 men, 33 women) Mean age 69 years	Hyperemic microvascular resistance index by cardiac catheterization	EPA/AA ratio was an independent predictor of hyperemic microvascular resistance index

AA, arachidonic acid; CFR; coronary flow reserve; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; INOCA, ischemia with no obstructive coronary artery disease.

levels of EPA were seen in patients with lower pericoronary adipose tissue [58]. Moreover, there was an inverse association between blood EPA level and pericoronary adipose tissue independent of age, sex, body mass index and traditional cardiovascular risk factors. In a substudy of the HEARTS trial (slowing heart disease with lifestyle and omega-3 fatty acids) [59,60], SPM were measured in 31 patients with stable CAD randomized to a combination of EPA + DHA or placebo for 30 months and correlated with coronary plaque volume on coronary CT angiography [61]. In this study, higher plasma levels of EPA + DHA were associated with significantly increased levels of resolvin E1, maresin1 and 18-hydroxy-eicosapentaenoic acid (HEPE), the precursor of resolvin E1. Moreover, patients with low EPA + DHA levels had significant coronary artery plaque progression, suggesting that SPM play a role.

SPM have been studied in patients with chronic inflammatory rheumatologic disease, a population that has a high prevalence of CMD [30]. In patients with systemic lupus erythematosus, resolvin D1 levels were significantly lower in peripheral blood compared to healthy subjects [62]. In patients with rheumatoid arthritis, peripheral blood concentrations of resolvin D1, resolvin E1, and lipoxin A4 were all significantly lower in patients with rheumatoid arthritis compared to healthy controls [63]. Similar results were reported in another study, with significantly lower levels of resolvin D3 in the serum of patients with rheumatoid arthritis compared to healthy controls [64].

In a pilot study we measured SPM acid by mass spectrometry in the peripheral blood of 31 women enrolled in WARRIOR who had confirmed CMD assessed by CFR and compared it to SPM levels from 12 sex and age-matched reference subjects. Compared to reference women, those with CMD had significantly lower plasma concentrations of resolvin D1 and maresin 1, and significantly higher levels of DHA and 18-HEPE, suggesting that insufficient SPM production may play a role in the pathophysiology of CMD [65].

We contend that these studies provide a proof of concept to investigate the effect of SPM in CMD and propose a hypothetical model wherein SPM is produced in the myocardium of patients with CMD but are qualitatively or quantitatively insufficient to attenuate inflammation. Omega-3 fatty acid therapy attenuates inflammation by augmenting SPM production and restoring a functional coronary microvasculature (Fig. 2).

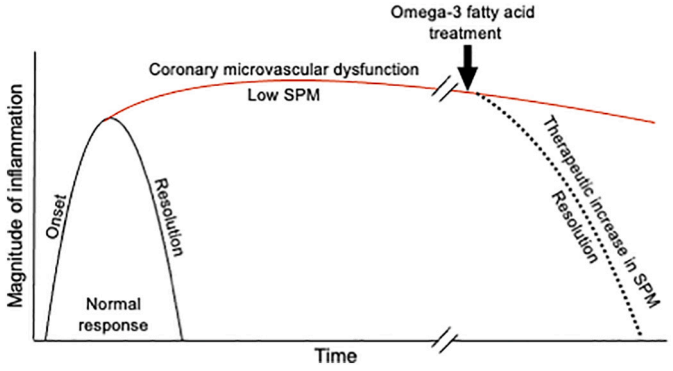

Fig. 2. Hypothetical model depicting a key role for specialized pro-resolving mediators in the pathophysiology of coronary microvascular dysfunction and the possible therapeutic effect of omega-3 fatty acid treatment.

1.4. Treatment with omega-3 fatty acids

Minimal data are available regarding effects of omega-3 fatty acid treatment on coronary function testing (Table 2). Among heart transplant recipients with coronary artery endothelial dysfunction, Fleischhaer and colleagues reported that treatment with omega-3 fatty acid for three weeks resulted in a normalization of the coronary artery endothelial response to acetylcholine [66]. The most convincing evidence, to date, comes from Oe and colleagues [67]. In this small, double-blind placebo-controlled study of healthy elderly subjects, treatment with omega-3 fatty acids for 3 months was associated with significantly improved coronary flow reserve measured by doppler echocardiography. In a study of 9 patients with INOCA and stress-induced ST segment depression, a 4-month course of omega-3 fatty acid resulted in normalization of ST segments during repeat stress testing in 7 of the 9 patients [68].

Results of 16 large randomized controlled trials (from 1989 to 2020) assessing the effect of omega-3 fatty acids treatment on cardiovascular outcomes have been summarized in a recent comprehensive review by Weinberg and colleagues [69]. The authors discuss the differences between these trials and the formulations of omega-3 fatty acids used (EPA alone or with DHA). Trials that used a combination of EPA and DHA were not associated with improved clinical outcomes while those that used EPA alone were. Although the coronary microvasculature was not directly assessed in these trials, we suggest that the benefits derived by EPA supplementation are likely to have been driven by improvements in the coronary microvasculature.

Supplementation with EPA and DHA increases SPM production in human serum of healthy volunteers, providing support for a counter-regulation of inflammation through endogenous production of these mediators [70]. In 6 patients with stable CAD randomized to open-label combination of EPA + DHA supplementation or no supplementation for one year, those randomized to supplementation with EPA + DHA had 2–5 times higher plasma levels of resolvin and protectin and significantly lower levels of prostaglandins than those who did not receive supplementation [48]. Moreover, EPA + DHA supplementation stimulated macrophages to increase phagocytosis *in vitro*. Of note, it is not known whether omega-3 fatty acid supplementation had any effect on CMD in these studies since it was not assessed.

1.5. Bigger picture, is small vessel disease a systemic disorder?

Small vessel dysfunction/disease not only affects myocardium, but it also affects the brain, retina and kidneys. Emerging data suggest that perhaps small vessel dysfunction/disease is a systemic process [71–75]. In a mouse model of stroke, endogenously produced DHA exerted a protective effect against reperfusion injury [76]. In a post-mortem study, investigators found lower levels of lipoxin A4 and maresin 1 in both hippocampal tissue and cerebrospinal fluid in patients with Alzheimer's disease compared to non-Alzheimer's disease patients, suggesting that chronic inflammation may lead be an important pathophysiologic process in this disease [77]. In a murine model, DHA supplementation attenuated Alzheimer's dementia-associated neuroinflammation and neuronal loss [78], and in a prospective cohort study of 1264 men and women over the age of 75 years, higher circulating EPA levels was associated with lower risk of incident Alzheimer's dementia [79]. While the evidence supporting omega-3 fatty acid treatment to prevent dementia in cognitively healthy individuals [80] and improve cognition in those with mild to moderate Alzheimer's disease [81] is currently lacking, longitudinal studies with longer follow-up are needed. There have been several published reports showing a high prevalence of abnormalities in cerebral blood flow in patients with CMD [82–84]. Lastly, we have previously proposed that long-standing mental stress during daily life, resulting in chronic activation of the sympathetic nervous system, contributes to a microvascular-myocardial diastolic dysfunctional state and the clinical manifestation of HFpEF [85].

These studies provide intriguing evidence to suggest a pathophysiological link between CMD and small vessel disease of the brain and support continued research into the possible role of SPM, and omega-3 fatty acid therapy as a novel treatment.

Table 2
Studies evaluating the effect of omega-3 fatty acid treatment on coronary reactivity testing.

Reference	Study design	PUFA formulation	Patient population	Measurement	Findings
Fleischhaer et al., 1993 (ref. [66])	Cohort	EPA (3.4 g) + DHA (2.3 g)	14 heart transplant recipients (13 men, 1 woman) PUFA (N = 7) No treatment (N = 7) 3-week duration	Acetylcholine vasodilatation during cardiac catheterization	PUFA treatment resulted in normal vasodilator response compared to vasoconstriction in the no-treatment group
Oe et al., 2008 (ref. [67])	Double-blind, placebo-controlled	AA (240 mg) + DHA (240 mg)	28 healthy elderly volunteers (19 men, 9 women) PUFA (N = 13) Placebo (N = 15) 3-month duration	CVFR by transthoracic doppler echocardiography	CVFR was significantly increased after PUFA treatment

AA, arachidonic acid; CFR; coronary flow reserve; CVFR, coronary volume flow reserve, DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; PUFA, polyunsaturated fatty acid.

1.6. Conclusions

Ineffective resolution of inflammation is likely to be a key pathologic process in CMD. Mechanistic and intervention trials are needed to more fully understand the inflammatory pathways involved and possible role SPM may play to inform novel pro-resolving therapies. We contend that there is sufficient data from small studies, to support a randomized, placebo-controlled trial of omega-3 fatty acids in subjects with CMD (Fig. 2).

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CRediT authorship contribution statement

Keeley: conceptualization, data curation, project administration, formal analysis, supervision, methodology, data collection, visualization, writing original draft of manuscript.

Handberg: project administration, resources, data collection, reviewing and editing of manuscript.

Wei: funding acquisition, reviewing and editing of manuscript.

Bairey Merz: data collection, resources, project administration, funding acquisition, reviewing and editing of manuscript.

Pepine: visualization, resources, supervision, project administration, funding acquisition, reviewing and editing of manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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