Are the Epoxyeicosatrienoic Acids (EETs) at the Heart of the B’EET’ in Obesity Induced Cardiomyopathy

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Obesity and metabolic syndrome are approaching epidemic proportions in the western societies. Significant complications of obesity and metabolic syndrome are diabetes and resulting obesity- and diabetic-induced cardiomyopathy (CM). The exact etiology or mechanisms responsible for these cardiomyopathies are under intense investigation. Clinically, using epidemiological and other clinical data, most considered the etiology of diabetic CM as secondary to ischemia from atherosclerotic coronary artery disease (CAD). A series of elegant studies over the past several years questioned that as the sole theory (2,6) and spurred significant investigation into other underlying mechanisms. Despite the approach to obtain new information related to obesity-induced CM, there are several key commonalities which are maintained. First, the condition is precipitated by or worsened by a state of generalized increased inflammation (4). Second, increased oxidative stress, likely secondary to heightened inflammation, is found in those individuals or models with worsening cardiac function (6). Third, effective and targeted clinical treatment or prevention of the condition remains elusive (7).

Epoxideicosatrienoic acids (EETs) are a family of lipid moieties generated via the cytochrome P450 metabolism of arachidonic acid. EETs produce potent vasodilatory effects on the coronary microvasculature (8) through hyperpolarization (4). In addition, multiple pleiotropic effects have been noted (7). These compounds can produce potent anti-inflammatory, fibrinolytic, and anti-apoptotic effects. EETs are shown to affect multiple signaling pathways including PI3K and KATP channels (2). Several investigators assessed the role of EETs in improving diabetes, metabolic syndrome and ischemia reperfusion injury (4,7). The recent literature suggests that manipulation of EETs or their downstream effector messaging system could have a significant impact on either prevention or amelioration of obesity-induced CM.

In this issue of the American Journal of Physiology: Heart and Circulatory Physiology, Cao, et al describes a series of elegant studies in obese mice to further define the signaling pathway of EETs in the
setting of cardiomyopathy of obesity (3). Using an EET analog, EET-A, they found reduced body weight, improved glucose tolerance, reduced fasting glucose and blood pressure. Additionally, cardiac function in vivo using echocardiography, respiratory quotient and oxygen consumption was improved. When EET-A was given with lentivirus PGC-1α(sh), the improvements were ameliorated. EET-A administration increased expression of Wnt1 and β-catenin in both cardiac and adipose tissues. Most notably, they found that NOV protein expression was decreased in EET-A treated mice and less impaired in the PGC1α deficient mice. EET-A increased cardiac expression of PGC1α and HO-1 among other signaling proteins. Interestingly, the expression of NOV in adipose tissue was significantly higher compared to heart tissue in db/db mice. EET-A also increased Mfn2 and MnSOD expression several-fold while lentiviral suppression of PGC1α reversed the effect of EET-A. This report identified that EET is a regulator of NOV which in turn is a negative regulator of cardiac function and potentially pericardial fat abnormalities. The studies, while elegant in their design, do provide difficulty in ascertaining the contribution of EET-A on the metabolic pathways resulting in the changes in second messenger signaling from the direct effects of EET-A since the PGC-1α(sh) did not completely reverse the effects. Despite this limitation, the combination of post-mortem tissue analysis and in vivo measures of metabolic state, cardiac function, oxygen consumption and respiratory quotient suggest that these pathways may become therapeutic targets for the treatment of obesity-induced CM.

In the setting of myocardial damage, there is increased sympathetic tone and activation of the renin-angiotensin aldosterone systems resulting in fibrosis. This results in the clinical conditions of accelerating fibrosis, increased vasoconstriction and salt and water retention. Based upon these results (3), the use of EETs as a modulator of treatment may affect the pathophysiology of heart failure as shown in the Figure. EETs are shown to reduce NF-κB, which produces an anti-inflammatory response. In addition through BKCa, vasodilation occurs. More recently, important pleiotropic effects have been shown to increase adiponectin, PGC1α, and HO-1. These pathways lead to increased GLUT4
translocation and a decrease in plasma glucose. Additionally, they produce decreased mitochondrial fatty acid oxidation, increased mitochondrial biogenesis, and increased nitric oxide bioavailability. Cao et al., added to our knowledge that EETs also increased Wnt1/β-catenin and decreased NOV. Increases in Wnt1/β-catenin lead to reduced inflammation and fibrosis. The decrease in NOV as shown in this study increased myocardial contractility. Thus, EETs in their multitude of signaling pathways are potential targets for therapeutic intervention in patients with heart failure.

As a clinician, these findings may substantially impact care of those with obesity-induced CM in the future. The health care costs, not to mention the mortality and morbidity associated with obesity, diabetes and cardiac failure are significant. Over the last several decades we saw substantial improvements in morbidity and mortality from the standard treatment of heart failure using β-adrenergic blockade, angiotensin converting enzyme inhibitors as well several newer approaches which target aldosterone and fibrosis. Despite these advances made in those with CHF, mortality and morbidity remains high. Thus, it is important to identify additional targets for therapeutic intervention which may prevent the development or ameliorate the severity of the CM. The set of elegant experiments by Cao, et al. suggest administration of EET-A agents could improve function. With a leap of faith, perhaps earlier intervention before the CM is severe, may prevent the development of significant LV dysfunction and the attendant abnormal neurohumoral responses. Based on the results of this study, EET analogs or NOV appears to be a potential targets given its role in the development of CM. As with any hypothesis for translation to humans, the barriers are great, especially with signaling pathways that exist throughout the body. Can we package the compound into a formulation to get to the intended target without affecting other vital tissues? Are the delivery mechanisms sufficiently long enough to provide consistent drug levels? Is there an effect of tachyphylaxis that renders long-term treatment ineffective? Certainly, additional studies are necessary to develop a therapeutic agent, but we need additional studies to these to further our understanding into the mechanisms of these unique
lipid compounds and their messenger system(s). Given our technological advances in the last 1-2 decades, it is highly likely continued work in this area will provide insight into important therapeutic targets to reduce death and disability from obesity-induced cardiomyopathy.

References


Figure Legend

Figure. The schematic diagram above demonstrates the multi-factorial impact of EETs on metabolic, vascular and cardiac function. The study by Cao et al. demonstrates the novel impact on Wnt1/β-catenin and NOV (dashed box).
EETs

Vasodilation

↑BKca

↑Adiponectin

↓Plasma Glucose

↑GLUT4 Translocation

↑Mitochondrial Biogenesis

↓Mitochondrial FA oxidation

↑AMPK/AKT

↑HO-1

↑PGC1α

↑NO

↓NF-κB

↑NO Bioavailability

↑β-catenin

↑Wnt1

↑NOV

↓Inflammation

↓Fibrosis

↑LV Contractility