Cardiac Sympathetic Denervation in the Failing Heart
A Role for Epicardial Adipose Tissue

Ian A. White

The pathophysiology of heart failure (HF) has long been linked to a neurohormonal imbalance because of excessive compensatory activation of the sympathetic nervous system (SNS).\textsuperscript{1-3} As HF develops, cardiac function is progressively lost prompting an increase in SNS activity in an attempt to maintain homeostasis and stabilize cardiac output. Although initially providing beneficial ionotropic support to the failing heart, the chronic increase of catecholamines is ultimately arrhythmogenic and causes cardiotoxicity by promoting interstitial fibrosis, myocyte apoptosis, left ventricular (LV) dilation, and a paradoxical desensitization of the heart to further adrenergic stimulation.\textsuperscript{4,5}

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The catecholamines norepinephrine and epinephrine bind to adrenergic receptors (ARs) in the membrane of cardiomyocytes where signals are coupled through interaction with heterotrimeric G proteins.\textsuperscript{7} There are at least 9 subtypes of AR in the human heart; however, the most relevant for biological function are $\beta_1$-AR and $\beta_2$-AR, which increase cardiac contractility and frequency, and $\beta_1$-AR, which antagonizes the activity of the former to mitigate against hyperionotropic and hyperchronotropic effects.\textsuperscript{8,9} During HF hyperactivation of the $\beta_1$- and $\beta_2$-AR pathways exacerbates disease progression, whereas therapeutic blockade of $\beta_1$- and $\beta_2$-AR signaling ($\beta$-blockers) has demonstrated efficacy in tempering SNS activity and reducing disease progression. Surprisingly though, the overuse of sympatholytics, such as $\beta$-blockers, has also been linked to pathological effects and can have a negative impact on patient with HF survival.\textsuperscript{10} Similar to the action of $\beta$-antagonists, overactivation of the $\beta_1$-AR pathway in HF progressively desensitizes nerves to $\beta_1$- and $\beta_2$-AR activation and decreases receptor density,\textsuperscript{11} resulting in a loss of ionotropic responsiveness to adrenergic stimulation. This loss of responsiveness, which is akin to a functional sympathetic denervation, is thought to contribute directly to disease progression and correlates with a poor patient prognosis.\textsuperscript{12-15}

It is widely appreciated that cardiac SNS hyperactivity in HF is primarily mediated through norepinephrine-releasing neurons and by circulating norepinephrine and epinephrine\textsuperscript{16}; however, other sources of catecholamines may also contribute to SNS hyperactivation and derangement. Epicardial adipose tissue (EAT), the visceral fat depot in the heart, contains intrinsic adrenergic and cholinergic nerves, which interact with the extrinsic cardiac sympathetic and parasympathetic nervous systems. These EAT nerves represent a significant source of several adipocytokines and other bioactive molecules,\textsuperscript{17} including norepinephrine and epinephrine. The production of these molecules is biologically relevant for the heart because abnormalities in EAT secretory properties are implicated in the development of pathological conditions, including coronary atherosclerosis, LV hypertrophy, LV diastolic dysfunction, and aortic stenosis.\textsuperscript{17} Because SNS hyperactivity and derangement is associated with HF and EAT contains adrenergic nerves competent in producing catecholamines, a logical question would be to explore the relationship between the accumulation of EAT in HF by asking whether a correlation exists between EAT volume and SNS derangement.

In this issue of Circulation Research, Parisi et al\textsuperscript{18} report the results of their study looking at the relationship between epicardial adipose density and cardiac sympathetic denervation in patients with HF. The study involved 110 patients with HF of ischemic and nonischemic pathogenesis enrolled at the HF clinic of Federico II University of Naples, Italy. All patients were clinically referred for cardioverter defibrillator implantation and within 7 days of enrollment patients underwent $^{123}$I-metaiodobenzylguanidine planar and single-photon emission computed tomography (SPECT) imaging and 2-dimensional echocardiography. Inclusion criteria included a left ventricular ejection fraction $\leq$50%, as documented by echocardiography, stable hemodynamic conditions, and no acute coronary syndromes within the previous 6 months. Exclusion criteria included hemodynamic instability, moderate to severe valvular disease, the presence of atrial fibrillation or flutter, ventricular-paced rhythm, myocardial inflammatory diseases, or suboptimal echocardiographic image quality. Also included in the study were 44 age-matched, healthy patients as controls for echocardiographic EAT thickness comparisons. Control subjects were excluded based on the presence of cardiovascular disease, cardiovascular risk factors, renal diseases, systemic inflammatory diseases, or any cardiovascular drug therapy. All measurements of EAT thickness were obtained from a parasternal long-axis view. Subject EAT thickness was measured perpendicularly to the free wall of right ventricle, at end systole over 3 cardiac cycles. Activity of the SNS was determined by cardiac imaging using planar and SPECT $^{123}$I-metaiodobenzylguanidine, an analog of norepinephrine.\textsuperscript{19}

Their key finding in patients with systolic HF identified a highly significant correlation between EAT thickness and
the extent of cardiac sympathetic denervation. Furthermore, the authors demonstrate that EAT thickness could be used as an independent predictor of SNS dysfunction, as assessed by $^{123}$I-metaiodobenzylguanidine planar and SPECT parameters, to complement clinical and LV functional data obtained for patients with HF. The authors also report a significant correlation between LV mass and both EAT thickness and cardiac sympathetic denervation in patients with HF. Simply put, as epicardial adipose becomes thicker cardiac SNS activity decreases and LV mass increases. The authors did not make a case for accentuated antagonism or reciprocal excitation as potential effectors as the increase in nerve activity, because of elevated EAT volume, was restricted to cardiac sympathetic nerves and no increase was seen in cardiac parasympathetic activity based on heart rate variability.

The significance of these results relies on the identification of previously unrecognized components of the disease process, which helps us generate a more comprehensive picture of the mechanisms behind HF. As the failing myocardium becomes depleted of norepinephrine stores because of reduced norepinephrine uptake, circulating catecholamines derived from peripheral organs may play a prominent role in perpetuating the progression of cardiac sympathetic denervation. In this study, the authors demonstrate that EAT represents a relevant source of catecholamines, as both norepinephrine and epinephrine were present in higher concentrations in EAT compared with subcutaneous adipose tissue (SCAT). In patients with HF, norepinephrine levels were increased 5.6-fold in EAT compared with SCAT and increased 2-fold compared with plasma. Epinephrine levels were also significantly elevated in EAT compared with SCAT, although in this study plasma levels of epinephrine were elevated over EAT. Importantly, the authors investigated whether catecholamine biosynthesis was occurring directly within EAT through the quantification of catecholamine biosynthetic enzyme (tyrosine hydroxylase [TH], dopamine-beta-hydroxylase [DBH], and phenylethanolamine N-methyltransferase [PNMT]) gene expression and protein levels. The mRNA levels of synthesizing enzymes TH and DBH was found to be significantly higher in EAT compared with SCAT (8.6- and 6.5-fold increase, respectively). Although the level of PNMT mRNA was comparable in both tissues, EAT demonstrated a significant increase in protein compared with SCAT (≈8-fold), which correlated with a comparable increase in TH protein (≈15-fold). The authors did not provide data on the levels of DBH protein; however, their data clearly identifies the EAT as a significant source of catecholamine biosynthesis during systolic HF. This means that, in the context of SNS hyperactivity in HF, the production of catecholamines within the EAT seems to play an additive role in generating the final net effect leading to cardiac sympathetic denervation (Figure). Such denervation of the SNS would have dramatic effects on the progression of HF not only because of a loss in responsiveness to ionotropic stimulation but also because of a loss of trophic support that we and others have demonstrated to be critical for the maintenance of cardiac homeostasis and repair. Although the authors present data to indicate that the density of SNS fibers is similar between EAT and SCAT, their data suggest that EAT is more biosynthetically active with regard to catecholamine production. This increase in activity, coupled with the progressive accumulation of additional epicardial adipose, and presumably a corresponding increase in the total number SNS fibers, would have an additive effect on total norepinephrine and epinephrine accumulation in the EAT.

In addition to these mechanistic insights, the authors also propose an application for measuring EAT volume as a novel approach to determining SNS derangement and HF.

Figure. Sympathetic hyperactivity and functional denervation in heart failure (HF). A. Increase in epicardial adipose tissue (EAT) volume correlates with hyperactive adrenergic signaling resulting from increased catecholamine biosynthesis. As a consequence increased adrenergic signaling SNS responsiveness progressively declines as HF progresses. B. Catecholamine production within the EAT, sympathetic nervous system (SNS), and peripheral circulation is additive in generating the final net effect leading to cardiac sympathetic denervation.
prognosis. Measurement of EAT by echocardiography is a low cost, noninvasive, and relatively simple procedure. The authors report excellent reproducibility with this technique and a high fidelity with measurements obtained from magnetic resonance imaging of EAT. As such, this report sets precedence for the potential future use of EAT thickness as an index of cardiac adrenergic nerve activity and derangement and for use in determining a rapid and noninvasive prognosis for patients with HF. Importantly, this study highlights EAT as a significant source of catecholamine production and for use in determining a rapid and noninvasive index of cardiac adrenergic nerve activity and derangement.

**Disclosures**

None.

**References**

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