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Protecting the Heart in Obesity: Role of ACE2 and Its Partners



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Heart failure, which is among the most common and disabling forms of cardiovascular disease, is closely associated with obesity (1). This is not a new observation, and as highlighted in a historical treatise on the heart and obesity by Alexander (2), in the 1700s the relationship of excess fat deposition involving the heart in obese individuals was reported. In the early 1800s, the fatty heart as an entity was described, and in 1847, William Harvey reported in a postmortem examination of a morbidly obese man that the heart was “large, thick and fibrous, with a considerable quantity of adhering fat” (2). Although the association between obesity and heart disease is well accepted, underlying pathophysiological processes remain elusive, and it is unclear whether obesity cardiomyopathy is due to increased adiposity itself or due to the effects of obesity-associated comorbidities, including hypertension, metabolic syndrome, and diabetes.

In obesity, the heart undergoes structural remodeling due to interstitial fibrosis, cardiomyocyte hypertrophy, and cardiac steatosis, leading to functional alterations (3). Molecular mechanisms associated with these processes include oxidative stress, natriuretic peptides, endothelin-1, advanced glycation end products, and activation of the renin-angiotensin-aldosterone system (RAAS) (4,5). In addition, inflammation is now considered to be important in obesity-related heart disease, especially in the context of diabetes and insulin resistance (6). In support of this are studies demonstrating that adipocyte-derived factors (adipokines) directly influence proinflammatory signaling in the heart (7).

Common in many of the above processes is activation of the RAAS, which is upregulated in obesity (5). Angiotensin (Ang) II, through the angiotensin type 1 receptor (AT1R), promotes cardiovascular fibrosis, inflammation, and insulin resistance and plays a role in the cardiovascular complications of diabetes and obesity. Recent evidence indicates that cardiac steatosis amplifies the injurious actions of Ang II through reactive oxygen species (8), thereby creating a feed-forward system where Ang II

promotes obesity cardiomyopathy, which enhances Ang II actions. Although Ang II/AT1R promotes cardiovascular injury and inflammation, there is growing evidence that these actions are counterregulated by the protective arm of the RAAS, comprising angiotensin-converting enzyme 2 (ACE2), Ang 1-7 (produced from Ang II by ACE2), and the Mas receptor through which Ang 1-7 signals (9). Members of the dual RAAS (ACE/Ang II/AT1R and ACE2/Ang 1-7/Mas) have been identified in many cell types, including adipocytes (10). This is of particular relevance in obesity where adipocytes possess a local RAAS that contributes to adipose inflammation, characteristically observed in experimental and human obesity (11). This has pathophysiological significance in the cardiovascular system because perivascular adipose tissue is an important player in vascular dysfunction in obesity-associated cardiovascular disease (12). Whether a similar relationship exists between epicardial adipose tissue and cardiac function is unclear and until now has not been comprehensively examined.

In this issue of *Diabetes*, Patel et al. (13) provide novel data demonstrating that epicardial adipose tissue in obese mice has a proinflammatory phenotype with associated cardiac dysfunction, features that are exaggerated in mice lacking ACE2. Associated with the marked inflammatory response in fat-fed ACE2-deficient mice was decreased myocardial adiponectin (protective adipokine), reduced AMPK signaling, myocardial insulin resistance, and increased cardiac steatosis and lipotoxicity with worsening of cardiac function; effects that were normalized by Ang 1-7 administration. This study identifies the ACE2/Ang 1-7/Mas system as a negative modulator of obesity cardiomyopathy. Although the cardioprotective actions of ACE2/Ang 1-7 are well known, the current study highlights its role in epicardial adipose tissue. In fact, the importance of “fatty epicardium” in obesity was described over 80 years ago when postmortem cardiac findings in obese individuals showed excess epicardial fat (14). What we now learn from Patel et al. (13) is that this fat depot is biologically active and that in obesity it is inflamed and influences myocardial

signaling and metabolism as well as cardiac function through processes that are ameliorated by ACE2/Ang 1-7/Mas (Fig. 1).

Although Patel et al. (13) have discovered an important role for epicardial adipose tissue and ACE2/Ang 1-7 deficiency in obesity-related cardiomyopathy, there are some aspects that warrant further consideration. First, although it is clearly shown that in the absence of ACE2, epicardial adipose tissue differentiates into a proinflammatory phenotype, the authors do not reveal whether other adipose depots and organs also become inflamed in the model studied. This is important because it may be possible that ubiquitous ACE2 knockout leads to a generalized inflammatory response, including in the myocardium, which could directly impact on cardiac dysfunction independently of epicardial inflammation. However, cross talk between inflamed epicardial adipocytes and cardiomyocytes/fibroblasts may amplify underlying cardiac injury in ACE2 knockout mice. Such cross talk is evidenced by the findings that epicardial inflammation is linked to aberrant myocardial AMPK signaling and insulin resistance (13). To fully appreciate the exact role of epicardial adipose tissue in obesity cardiomyopathy, experiments in mice where ACE2 is knocked down in an epicardial-specific manner are necessary.

Second, there appears to be some discordance between epicardial ACE2 and cardiac function in obesity, because in fat-fed obese wild-type mice with epicardial inflammation

and cardiac dysfunction, ACE2 expression was increased, yet in mice with ACE2 deletion, epicardial adipose tissue also had an inflammatory phenotype and exaggerated cardiac changes (13). How can obesity cardiomyopathy and epicardial inflammation be associated with both increased and reduced ACE2 activity? While this enigma is not discussed by the authors, it could be speculated that in obesity upregulation of ACE2 and its partners may compensate for increased activation of the injurious arm of the RAAS and that at a critical time point when the protective axis is overwhelmed the ACE2/Ang 1-7/Mas system is decompensated with consequent cardiac failure. This notion is supported by other studies in mice fed high-fat diets, where with increasing obesity, adipose ACE2 activity was blunted with a shift in the RAAS to favor high Ang II levels (15).

Third, the study by Patel et al. (13) was performed in male mice. Considering the fact that clinically heart failure with a preserved ejection fraction occurs more often in obese females (16), one wonders whether epicardial adipose inflammation and associated cardiac changes in ACE2-deficient fat-fed male mice would be exaggerated in females. This may be especially relevant with respect to ACE2/Ang 1-7/Mas because estrogens influence the RAAS. In particular, Ang II/Ang 1-7 balance is differentially regulated in obese male and female mice and contributes to diverging susceptibilities to obesity-related cardiovascular

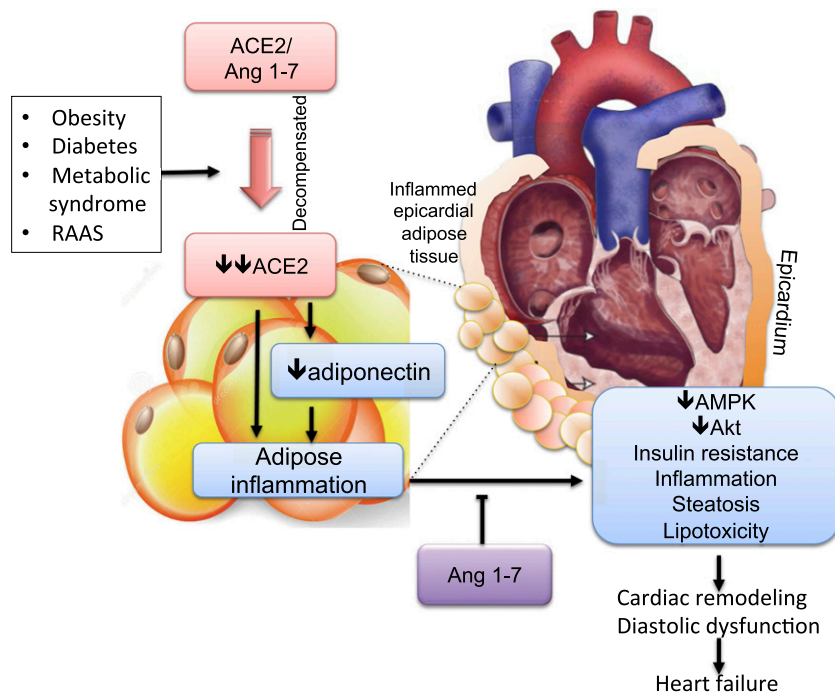


Figure 1—Diagram demonstrating possible mechanisms whereby ACE2 negatively regulates epicardial adipose tissue and cardiac function. In obesity, diabetes, metabolic syndrome, or conditions where there is activation of the RAAS, the cardioprotective arm of the RAAS may be decompensated, leading to a proinflammatory phenotype of the epicardial adipose tissue. Cross talk between the epicardium and myocardium leads to reduced myocardial AMPK and Akt signaling, insulin resistance, steatosis, and lipotoxicity, processes that underlie cardiac dysfunction, which ultimately leads to heart failure. Administration of Ang 1-7 prevents these changes and protects against cardiac injury and heart failure.

disease (17). Further studies exploring the relationship between epicardial adipose tissue, the RAAS, and cardiomyopathy in female models of obesity may shed light on why heart failure with a preserved ejection fraction is more common in obese women.

Finally, an intriguing finding is the observation that epicardial inflammation, cardiac metabolism, and heart dysfunction were worse in high-fat diet-fed ACE2 knockout mice than in fat-fed controls, despite ACE2-deficient mice being less obese than their wild-type counterparts, indicating an inverse association between adiposity cardiomyopathy and body weight (13). The data suggest that while obesity leads to cardiac dysfunction, as long as ACE2 is present, there is some cardioprotection, a phenomenon that is lost when ACE2 is absent. These observations may have important clinical relevance and may explain, at least in part, the “obesity paradox,” where overweight/obese patients with cardiovascular disease have a more favorable outcome with less cardiovascular events than lean individuals (18). Perhaps upregulation of the ACE2/Ang 1-7/Mas system in obese subjects may be related to “healthy” cardioprotective epicardial adipose tissue, whereas in leaner individuals, this is blunted, leading to worse cardiac outcomes. Further investigation of this paradigm may unravel some putative mechanisms underlying the obesity paradox.

In summary, the findings by Patel et al. (13) raise some thought-provoking ideas, such as the possible role of ACE2 in the obesity paradox and the potential for differential ACE2/Ang 1-7 regulation in sex-linked obesity cardiomyopathy, and provide new insights into cardioprotective mechanisms of ACE2/Ang 1-7/Mas in obesity. Specifically, the study advances the field by identifying epicardial adipose tissue as an important target for ACE2 and its partners, which when deficient lead to an inflammatory response that promotes impaired myocardial metabolism and cardiac dysfunction. Considering the growing clinical interest in orally active Ang 1-7 as a potential therapeutic agent in many diseases (19,20), perhaps obesity-related cardiac heart disease should be added to the list of conditions that may benefit from such an approach.

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Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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