Reply to Katlandur, Ozbek, and Keser

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TO THE EDITOR: we appreciate the opportunity to respond to the comments by Katlandur et al. (5a) regarding our recent paper entitled “Glucose uptake and Lipid metabolism are impaired in epicardial adipose tissue from heart failure patients, with or without diabetes” (1). We agree that there may be other mechanisms at play leading to the significant decrease in lipolysis and insulin-stimulated fatty acid uptake observed in epicardial fat (EAT) during isoproterenol stimulation compared with subcutaneous fat in heart failure patients with and without diabetes, including the contribution of the autonomic nervous system. The authors refer to a number of papers that seem to further reinforce the important connection between EAT and the sympathetic and parasympathetic regulation of cardiac function. In fact, many studies have now indicated that the increase in body fat, and thus body mass index, is a strong predictor of atrial fibrillation. Carnevali et al. (2) presents evidence that the fat mass and obesity-associated gene (FTO) are involved in cardiac remodeling. However, animals that have global deletion of FTO are leaner than normal animals, and therefore, they have less fat around the heart to contribute to arrhythmias. In addition, rodents appear to have very little or no EAT surrounding the heart, indicating perhaps the existence of yet other mechanisms at play besides accumulation of EAT around the heart. It has been shown that heart-specific deletion of glucose transporter 4 (GLUT4) causes cardiac hypertrophy, insulin resistance, and increased oxidative stress, possibly due to decreased glucose uptake and increased fatty acid uptake by the heart and likely independent of local EAT effects (3). The same is true in hearts of skeletal muscle GLUT4 knockout animals (Carvalho E, Kotani K, Peroni OD, and Kahn BB, unpublished observations), where adipose-specific overexpression of GLUT4 reverses insulin resistance and cardiomyogal (4). Furthermore, recent studies indicate that EAT is composed of both white and brown adipocytes, and it presents the capacity to convert from one cell type to the other (5, 6). Therefore, dysfunctional BAT or BAT-like cells around the heart may also affect myocardial injury and remodeling, which has been shown by Thoonen et al. (7). On the other hand, a recent paper by Zeng et al. (8) beautifully shows that sympathetic neurons that innervate adipocytes can mediate the lipolytic effects of leptin. Although not directly shown in EAT cells, these neuro-adipose junctions may directly mediate fat breakdown. As such, we agree with Katlandur et al. (5a) that impaired autonomic nervous system could contribute to the potential role of EAT in contributing to arrhythmogenesis. However, as demonstrated in our study, it is also clear that direct alterations in insulin signaling and β-adrenergic responsiveness at the level of the EAT may also have an important role as well.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

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REFERENCES


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