Response to Letter Regarding Article, “Leptin Signaling in the Failing and Mechanically Unloaded Human Heart”

Response:
In response to our publication, Drs Macrea and Martin pointed out the potential role of hypoxia in regulating leptin expression in the failing human heart. Some degree of tissue ischemia, hypoxia, and the increased generation of reactive oxygen species are a likely occurrence in the failing human heart regardless of ischemic or nonischemic etiology.1 As Drs Macrea and Martin discuss, hypoxia induces expression of the transcriptional regulator HIF-1α, and hypoxia induces leptin expression via HIF-1α, in a variety of cell types and tissues. However, whether HIF-1α is increased in the failing human heart remains unclear. Specifically, studies have demonstrated both increases2 and decreases3 in HIF-1α expression in failing human hearts. Mechanical unloading has also been shown to decrease cardiac HIF-1α expression,4 possibly through alterations in tissue perfusion and a reduction in ischemia and/or hypoxia. Interestingly, HIF-1α expression can also be induced by mechanical stress independent of hypoxia.4 Thus, it is plausible that increased cardiac leptin expression in the failing heart could arise from elevated cardiac HIF-1α expression that is consequent to cardiac hypoxia/ischemia and/or mechanical stress. Likewise, mechanical unloading could reduce mechanical stress and improve perfusion. The relative roles of mechanical signals and ischemia/hypoxia in altering leptin expression in the failing heart remain incompletely understood. For example, we did not observe differences in the quantitative expression of cardiac leptin between samples arising from ischemic or nonischemic failing hearts. Increases in HIF-1α expression may induce processes beneficial to the failing heart, including increased angiogenesis, enhanced glucose uptake, and glycolytic enzyme activity.1 Conversely, chronic activation of HIF-1α in ischemic hearts might also contribute to heart failure progression.5 Despite these uncertainties regarding HIF-1α expression and activity in the failing human heart, our data would nonetheless continue to suggest that exogenous leptin may be of benefit in heart failure by activating downstream (relative to HIF-1α) cardioprotective signal transducer and activator of transcription-3 and adenosine monophosphate-activated protein kinase pathways.

Disclosures
None.

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References
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