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EDITORIAL COMMENT

Reduce, Reuse, Recycle…Unloading, Autophagy, and Myocardial Recovery*

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Autophagy is an essential part of nature's recycling system. It is a highly conserved process that maintains homeostasis in cells, balancing production of the new with removal of the old. Senescent or damaged organelles and proteins that accumulate with stress and disease are sequestered as cargo in double-membraned autophagosomes. These autophagosomes then fuse with lysosomes to facilitate degradation into metabolic precursors that can be reused by the cell.[1] The strict regulation of protein production and degradation by autophagy is important in maintaining the health of cardiomyocytes, because myocytes have limited ability to proliferate and high metabolic demand that drives continual turnover of intracellular contents. Autophagy is upregulated in the cell in response to a variety of stress conditions including nutrient depletion, accumulation of damaged proteins, and reactive oxygen species. Thus, it is not surprising that autophagy appears to be upregulated in heart failure (HF). However, what is not known is the precise role autophagy plays in the development of HF. Is it a cause of or a response to the disease? Is it adaptive or maladaptive?

In some instances, impaired autophagy appears to be the cause of myocardial dysfunction. Inactivation of *Atg5* (the gene required for autophagy) in an adult mouse model causes a rapid decline in heart function.[2] Similarly, in Danon disease, an X-linked sequence variation prevents autophagosome fusion with lysosomes, directly contributing to the development of cardiomyopathy.[2] In addition, there are examples where autophagy appears to be adaptive. Desmin-related cardiomyopathy is characterized by the accumulation of toxin protein aggregates. The upregulation of autophagy in mice models of this syndrome antagonizes disease progression, demonstrating a positive adaptive response.

By contrast, it is also possible that autophagy can rise excessively to maladaptive levels and instead contribute to disease progression. This was demonstrated in mice models of load-induced HF (achieved via constriction of the aorta), in which mice haplo-insufficient for *Becn1* (the gene required for autophagy) demonstrated a blunted increase in autophagic activity with diminished pathologic remodeling of the heart, and mice with overexpression of *Becn1* demonstrated an exaggerated increase in autophagic activity and greater pathologic remodeling.[2]

Finally, the role autophagy plays in reverse remodeling and recovery from HF is unclear. In advanced HF, adenosine triphosphate production is impaired and metabolic demands are high, thus autophagy may be maximally stimulated to mobilize amino acids as a last attempt to meet the energy demands of cardiomyocytes. With mechanical unloading of the heart, the energy demand is less, leading to a down-regulation of autophagy.[3] Despite down-regulation of what could be viewed as excessive or maladaptive levels of autophagy in end-stage HF, we rarely see left ventricular assist devices (LVADs) as an effective therapy for the bridge to recovery. On the contrary, a recent study by Kanamori et al[4] suggests autophagy may play a beneficial role in reverse remodeling. Using biopsy samples from patients with dilated cardiomyopathy, Kanamori et al[4]

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demonstrated that markers of autophagy were increased to a greater extent among those patients with evidence of reverse remodeling when compared to those without evidence of reverse remodeling.

It is with this background, that Evans et al[5] present their study that explores the role of the autophagy-lysosome pathway in a murine model of reversible HF in this issue of *JACC: Basic to Translational Science*. Evans et al[5] used a novel murine model of reversible HF, in which mice undergo moderate transaortic constriction (TAC) and distal left anterior descending ligation (MI), leading to a HF phenotype with progressive LV dilation and dysfunction—a pathophysiologic model of ischemic cardiomyopathy and pressure-volume overload. When the LV is unloaded by debanding the thoracic aorta, the HF phenotype is reversed with decrease of LV volumes, LV mass, and myocyte hypertrophy. Evans et al[5] used this model to study markers of autophagy in 3 groups: mice with HF who underwent TAC+MI (HF-mice); mice with reversal of HF who underwent TAC+MI followed by debanding (HF-recovery mice); and sham mice that served as control mice.

Autophagy was assessed through measurements of autophagic flux, the accumulation of damaged proteins and organelles, mitochondrial respiration, and mitophagy. Evans et al[5] found decreased autophagic flux in the HF-mice, resulting in the accumulation of damaged proteins and organelles. In the HF-recovery mice, the autophagic flux increases to normal, but the accumulation of damaged proteins and organelles persists, suggesting it is insufficient to restore myocytes protein homeostasis and organelle quality. They also demonstrated that the mitochondrial respiration was decreased in HF-mice and returned to normal in the HF-recovery mice. Mitophagy, on the other hand, was increased in HF-mice, but was unchanged compared to sham in HF-recovery mice despite the presence of damaged organelles, again suggesting inadequate protein quality control in HF-recovery mice.

Lastly, autophagic flux was experimentally augmented in the mice via a viral vector containing *Tfeb* (a master regular gene of the autophagy pathway) that leads to a 1.5- to 2-fold upregulation of *Tfeb* in the heart. Although there was no difference in LV ejection fraction (EF) in the HF-recovery mice, there was improved mitochondrial morphology and a decrease in LV volumes and mass, which was suggestive of improved mitochondrial protein control and further reverse remodeling. In striking opposition, upregulation of autophagy in the HF-mice did not lead to reverse remodeling but instead to 80% lethality.

Evans et al[5] should be congratulated for these thoughtful experiments that provide unique insights of the role of autophagy in the development of HF and subsequent myocardial recovery. They provide evidence that impairments in autophagic flux and mitochondrial respiration contribute to HF through the accumulation of damaged proteins and organelles. Furthermore, although unloading normalized autophagic flux was associated with reverse remodeling, this was insufficient to completely remove the damaged proteins and organelles. Taken together, these findings provide a mechanistic basis for the notion of remission in HF (as opposed to recovery), and they could explain why patients with HF and improved EF are at risk for worsening of cardiac function if guideline-directed medical therapy is discontinued.

Another novel finding is the potential synergistic role of mechanical unloading and augmentation of autophagy pathways as a therapeutic treatment in HF. The use of LVADs as a bridge to recovery is rarely actualized with successful LVAD explantations. As a result, a number of investigators have attempted to combine LVADs with additional treatments, such as HF medications, reloading protocols, and/or stem cells—all with underwhelming results. The concept of using LVADs plus a therapy to augment autophagy pathways as a means to recover the failing heart warrants additional investigation.

Finally, this study serves as a reminder of the importance of maintaining humility as we explore the therapeutic potential of manipulation of autophagy pathways in clinical disease. The dramatic increase in lethality when autophagy was augmented in the HF-failing mice (in the absence of unloading) suggests that such an intervention is highly conditional. The importance of preclinical studies cannot be overstated.

This study does have some important limitations. Evans et al[5] observed an inverse relationship between mammalian target of rapamycin activation and autophagic flux, but they correctly noted that the study did not specifically study the mechanistic pathways responsible for the regulation of autophagy. Also, whereas they found that augmenting autophagy in the HF-recovery mice resulted in enhanced reverse remodeling, this study cannot answer whether autophagy is required in reverse remodeling. Finally, Evans et al[5] have explored the role of autophagy in a murine model of ischemic cardiomyopathy and high afterload, whereby reverse remodeling is likely driven by a rapid reduction in afterload by aortic debanding. This most closely approximates a patient with ischemic cardiomyopathy and severe aortic stenosis that is treated with aortic valve replacement

with subsequent myocardial recovery. Future studies are needed to address the role of autophagy in other etiologies of HF as well as with other reverse remodeling treatments, such as quadruple medical therapy in HF with reduced EF and cardiac resynchronization therapy.

Despite these limitations, this study does emphasize the importance of autophagy as a key mediator of HF and reverse remodeling. Autophagic flux was impaired in HF with subsequent accumulation of damaged proteins and organelles. Mechanical unloading-induced reverse remodeling was associated with improvements in autophagic flux but incomplete reversal of cardiomyocyte proteostasis. Finally, escalation of autophagy in the select condition of mechanical unloading enhanced reverse remodeling. Taken together, these findings should prompt additional investigations of the therapeutic potential of leveraging nature's recycling system as a novel therapy in HF.

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