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EDITORIAL COMMENT

Autophagy in the LVAD-Supported Heart

A Sign of Hope or a Marker of Unloading*

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Advanced heart failure is associated with very high morbidity and mortality, and left ventricular assist devices (LVAD) are the mainstay of therapy to prolong lifespan or sustain survival as a bridge to cardiac transplantation, given the limited supply of donor hearts. The goal of LVAD therapy as a "bridge to recovery" to permit LVAD explant without the need for transplantation remains elusive in nearly all patients with advanced heart failure, except in a few where the need for LVAD support may have been precipitated by a reversible etiology of cardiac dysfunction. Although multiple studies have documented that hemodynamic unloading with LVADs induces reverse ventricular remodeling and improves cardiac function, a deeper understanding of the biological pathways is required to uncover therapeutic targets to facilitate true "recovery" from heart failure.

Experimental studies in animal models to understand the cellular and molecular basis of reverse remodeling have uncovered a role of autophagy, a subcellular lysosomal degradative process to remove damaged proteins and organelles, generate nutrients, and recycle basic building blocks, as one such pathway.[1] In this issue of *JACC: Basic to Translational Science*, Martin et al[2] have carefully evaluated the state of activation of autophagy in paired left ventricular myocardial tissue samples from patients with dilated cardiomyopathy and end-stage heart failure, before and after LVAD support. Their findings support the conclusion that autophagy is "activated" upon hemodynamic unloading, along with increased function of other proteolytic pathways. Whether this represents "insufficient" activation of one or more therapeutically targetable pathways that can be harnessed to facilitate recovery of the LVAD-supported heart or represents activation of these pathways as markers of unloading similar to reverse remodeling and reversal of the pathologic hypertrophy-associated gene expression program[2] remains an open question.

The findings from Martin et al[2] conclusively demonstrate increase in autolysosomes and abundance of cathepsin D, a lysosomal enzyme, in addition to up-regulation of candidate autophagy gene transcripts (*BECN1* and *GABARAP1*), autophagy proteins (BECLIN-1 and autophagosome-bound LC3-II), and an autophagy-adaptor protein (p62). The increase in autolysosomes is consistent with up-regulation of autophagic flux, paralleling the observations with debanding to unload the failing heart in mice subjected to a combination of aortic banding (transverse aortic constriction) and myocardial infarction to model heart failure.[1] As discussed by the authors,[2] these findings clarify prior observations that solely evaluated levels of autophagic proteins and did not include readouts permitting assessment of autophagic flux. In animal studies, autophagic flux was reduced on induction of heart failure with transverse aortic constriction + myocardial infarction, and debanding to hemodynamically unload the failing heart increased autophagic flux back to baseline,[1] but polyubiquitinated proteins and damaged mitochondria (ie, autophagic cargo) persisted, suggesting

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"insufficient" autophagic flux. Indeed, further stimulation of autophagic flux after debanding with adeno-associated virus-mediated transduction of transcription factor EB, a member of the Mit/Tfe family of master regulators of autophagy and the lysosome biogenesis program, enhanced reverse remodeling with restoration of normal mitochondrial structure, lending support to this theory. This suggests that up-regulation of autophagic flux on LVAD support may be "insufficient" to drive recovery of myocardial function. Despite these encouraging results, experimental studies are required to determine whether up-regulation of autophagic flux is necessary for recovery of left ventricular function on unloading and rule out a deleterious role for autophagy via induction of autophagic cell death[3] that may suppress recovery.

Autophagy is a complex process that targets subcellular cargo for degradation via either nonselective sequestration within double membrane-bound autophagosomes, termed "general autophagy" or specific targeting of cellular components via unique receptors, termed "selective autophagy." Central to this process is the role of the lysosome, and fusion of the autophagosomes with the lysosome is often the rate-limiting step that is impaired in cardiac pathology, leading to accumulation of autophagosomes. In this regard, an increase in autolysosomes as observed by Martin et al[2] may also indicate restoration of lysosome function. Indeed, in addition to the previously described process of macro-autophagy, other lysosomal processes, namely, chaperone-mediated autophagy and micro-autophagy, also participate in clearance of damaged proteins. Accordingly, a limitation of this study is the lack of assessment of hemodynamic unloading on myocardial subcellular ultrastructure, which would shed light on selective autophagy as well as other lysosomal autophagy processes that can be tracked along with assessment of relevant markers. Indeed, up-regulation of p62 observed with LVAD support may point to induction of mitophagy,[2] a form of selective autophagy for removal of damaged mitochondria mediated by p62 as an adaptor. The authors' finding of reduced poly-ubiquitinated proteins, both with the lysine 48 and lysine 63 linkage, likely reflects their accelerated removal via up-regulation of proteasome activity and activation of autophagic flux, respectively. However, this may also reflect reduced damage and ubiquitination of cellular proteins in the setting of reduced hemodynamic overload, a premise that could be examined with assessment of chaperone-assisted selective autophagy, which targets damaged myofilament proteins for degradation and facilitates restoration of normal sarcomere and function.

As discussed,[2] the observation of increased autolysosomes and cathepsin D expression with LVAD support mirrors the findings in dilated cardiomyopathy patients that demonstrate a similar increase in these parameters in patients with guideline-directed medical therapy. These data lend support to the premise that stimulation of autophagic flux may facilitate recovery of the failing heart and even prevent progression to advanced heart failure. Assessment of autophagy in human tissues is limited by their availability, which necessitates the need for developing circulating biomarkers, to track the state of autophagy activation. One such candidate protein is diazepam-binding inhibitor/ acyl-CoA-binding protein (DBI/ACBP), which is secreted on induction of autophagy by stress stimuli, such as fasting.[4] Intriguingly, DBI/ACBP has also been proposed as an "autophagy check-point" and targeting DBP/ACBP with antibodies stimulated autophagic flux to reduce infarct size and protect against doxorubicin-induced cardiomyopathy.[4] Future studies are required to evaluate DBI/ACBP levels as a biomarker of autophagic flux in patients with heart failure and experimentally target DBI/ACBP in animal models to investigate its role in the failing heart.

Autophagy is regulated by alterations in nutrient availability, and stimulation of autophagic flux reciprocally regulates cellular metabolism via generation of nutrients that activate growth signaling via activation of lysosomal nutrient sensing complex and mammalian target of rapamycin (mTOR). mTOR activation counter-regulates the activity of the Mit/Tfe family of transcription factors and autophagy. Indeed, experimental studies demonstrate activation of mTOR in the failing heart that is reversed on debanding.[1] Accordingly, serial evaluation of circulating metabolites in patients supported with LVAD may uncover the upstream inputs to lysosome nutrient sensing that coordinately regulate the activity of mTOR kinase and the Mit/Tfe family of transcriptional regulators in patients with heart failure. Interestingly, evaluation of the circulating proteome in patients enrolled in the EMPEROR (EMPaglifozin OutcomE tRial in patients with chrOnic heaRt failure) clinical trials (which demonstrated the therapeutic efficacy and safety of sodium-glucose cotransporter-2 inhibitor, empagliflozin, in the treatment of heart failure) uncovered empagliflozin-induced up-regulation of proteins that stimulates autophagic flux, consistent with its proposed mechanism of action.[5] Taken together

with the findings of Martin et al,[2] these studies underscore the need to evaluate the efficacy of empagliflozin as a strategy to induce autophagy in the setting of LVAD support.

In summary, the findings of Martin et al[2] demonstrate activation of autophagic flux with LVAD support in patients with advanced heart failure, lending support to the premise that further stimulation of autophagy and lysosome function may be a viable strategy to achieve the long-cherished goal of "recovery" to heart failure-free survival after LVAD explant. Achieving this safely will require astutely designed clinical trials to "thread the needle" by avoiding potential adverse effects of autophagy.[1,3]

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