Nonetheless, despite these limitations, establishing the role of autophagy in LV re-dilatation after LVP is paramount in the effort to eventually develop pharmacologic interventions that can alter myocardial metabolism and remodeling in ischemic cardiomyopathy.

References

1. Wu D, Zhang K, Hu P. The role of autophagy in acute myocardial infarction. *Front Pharmacol*. 2019;10:551.
2. Delbridge LMD, Mellor KM, Taylor DJ, Gottlieb RA. Myocardial stress and autophagy: mechanisms and interventional prospects. *Nat Rev Cardiol*. 2017;14:412-25.
3. Lavandro S, Chiong M, Rothermel BA, Hill JA. Autophagy in cardiovascular biology. *J Clin Invest*. 2015;125:55-64.
4. Sugimoto S, Shingu Y, Doenst T, Yamakawa T, Asai H, Wakasa S, et al. Autophagy during left ventricular redilatation after ventriculoplasty: insights from a rat model of ischemic cardiomyopathy. *J Thorac Cardiovasc Surg*. 2022;163:e33-40.
5. Toit AD, Hofmeyr JHS, Gniadek TJ, Loos B. Measuring autophagosome flux. *Autophagy*. 2018;14:1060-71.

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Commentary: Follow where the data take you

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Autophagy is a highly regulated process that eliminates misshapen, long-lived, excessive, or damaged proteins or organelles (eg, mitochondria) by lysosomal degradation or “self-digestion.” Autophagy is a normal housekeeping process in the baseline heart, but unbalanced autophagy—inadequate (heart failure), suppressed, or excessive (ischemia–reperfusion injury, heart failure)—can contribute to cardiac pathology. In some pathologies, autophagy can have either beneficial or deleterious effects and hence presents as a double-edged sword.

In this initial proof-of-concept study, Sugimoto and colleagues¹ hypothesize that autophagy “plays an important role” in redilatation after left ventriculoplasty (LVP), but they do not hypothesize whether autophagy limits or contributes to redilatation. The authors report that myocardial infarction (MI) was associated with larger early and late left ventricular (LV) diastolic dimensions and myocyte area, and less fractional shortening (FS) relative to a time sham group, thereby confirming the model of MI-induced maladaptive remodeling. Two days post-ventriculoplasty (early changes) LV diastolic dimensions and myocyte area

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CENTRAL MESSAGE

The first observations in a rat model of post-ventriculoplasty redilatation ventriculoplasty suggest that autophagy is triggered during redilatation, but does it play a deleterious or beneficial role?

were markedly reduced, and fractional shortening (FS) was increased relative to preoperative values. However, after 28 days post-ventriculoplasty, the LV had redilated, and early improvement in FS was lost. A marker of autophagy, LC3-II, decreased early after LVP but increased markedly during the later redilatation period after ventriculoplasty relative to the shams and MI/sham groups, consistent with enhanced autophagy.

This last observation provides the strongest support for the authors’ hypothesis. Administration of a phosphoinositide-3 kinase inhibitor (3-MA) for 21 days post-ventriculoplasty to inhibit autophagy was associated with only a slight increase in already dilated LV dimensions, a further reduction in FS, and an increase in myocyte area relative to the MI/LVP group, which strengthens

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support for their hypothesis and suggests that inhibition of autophagy suppresses beneficial adaptive changes. A more dramatic increase in LV dimensions by 3-MA would have made a stronger case for involvement of autophagy, but any further increase in LV dimensions may have led to mortality secondary to severe LV dilatation. The inclusion of a group receiving 3-MA without infarction would help to determine whether suppression of autophagy in the absence of LVP (ie, baseline effects) would, by itself, affect LV dimensions.

The data support the hypothesis that activation of autophagy acts to limit redilatation, but the response is inadequate. At this early stage, one must also ask whether activation of autophagy is contributing to redilatation (maladaptive, excessive autophagy) or limiting redilatation (adaptive cardioprotective response). Clearly, further investigations are needed using pharmacologic

enhancement of autophagy to further test the hypothesis. Furthermore, the authors need to confirm activation of autophagy using enhancers of autophagy, additional markers of autophagy, evidence of autophagosome and autolysosome formation, protein aggregation, and by measuring autophagic flux (rate). At some not-too distant point, translational studies must also be conducted in larger, close to human models incorporating the surgical environment used in ventriculoplasty, with the caveat that a rat is not a pig is not a human. The important discovery process has only begun; follow where the data take you.

Reference

1. Sugimoto S, Shingu Y, Doenst T, Yamakawa T, Asai H, Wakasa S, et al. Autophagy during left ventricular redilatation after ventriculoplasty: insights from a rat model of ischemic cardiomyopathy. *J Thorac Cardiovasc Surg*. 2022;163:e33-40.