REPLY: Apoptosis, A Double-Edge Sword!

We appreciate the comments of Drs. Rossello and Yellon regarding our recent paper (1), and we agree that activation of pro-survival pathways in viable myocytes after brief periods of ischemia likely occurs alongside apoptotic myocyte death to provide protection against subsequent ischemic injury. Aside from the severe transmural ischemia associated with an acute transient occlusion that we used in our study, apoptosis-induced myocyte cell loss with compensatory myocyte cellular hypertrophy can arise in response to reversible subendocardial ischemia and can ultimately affect regional as well as global left ventricular function. Thus, modulating this dynamic interplay between myocyte survival and death may be most important with repetitive ischemia similar to angina in chronic coronary artery disease that can contribute to the development of ischemic cardiomyopathy. For example, we previously demonstrated that chronic repetitive subendocardial ischemia distal to a chronic coronary artery stenosis in swine leads to a progressive increase in apoptosis as the physiological significance of a coronary stenosis increases (2,3). This is followed by regional myocyte loss, compensatory cellular hypertrophy, and physiological features consistent with hibernating myocardium. Interestingly, proteomic profiling has demonstrated that this is accompanied by an up-regulation of a variety of pro-survival proteins as well as a down-regulation in mitochondrial metabolism (4,5). This is functionally significant, as hibernating myocardium exhibits depressed mitochondrial respiration and a reduced rate of ATP depletion during simulated zero flow ischemia in vitro (6). Others have also demonstrated activation of pro-survival pathways during repetitive nontransmural ischemia (7). These cardioprotective adaptations are reversed by alleviating demand-induced ischemia with coronary revascularization (8). Collectively, these findings support the notion that hibernating myocardium becomes ischemia-tolerant to prevent a supply-demand imbalance and reduce mitochondrial oxidative stress as a counter-regulatory process to attenuate myocyte loss from apoptosis in a fashion similar to that proposed by Rossello and Yellon for ischemic pre-conditioning and infarction. We agree that further work is needed to understand whether favorable manipulation of the balance between pro- and anti-apoptotic signaling pathways can have a long-term effect on myocyte loss after ischemia and prevent the development of ischemic cardiomyopathy.

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REFERENCES

1. Weil BR, Young RF, Shen X, et al. Brief myocardial ischemia produces cardiac troponin I release and focal myocyte apoptosis in the absence of pathological infarction in swine. J Am Coll Cardiol Basic Trans Science 2017;2:105–14.

2. Lim H, Fallavollita JA, Hard R, Kerr CW, Canty JM Jr. Profound apoptosis-mediated regional myocyte loss and compensatory hypertrophy in pigs with hibernating myocardium. Circulation 1999;100:2380–6.

3. Fallavollita JA, Lim H, Canty JM. Myocyte apoptosis and reduced SR gene expression precede the transition from chronically stunned to hibernating myocardium. J Mol Cell Cardiol 2001;33:1937–44.

4. Page B, Young R, Iyer V, et al. Persistent regional downregulation in mitochondrial enzymes and upregulation of stress proteins in swine with chronic hibernating myocardium. Circ Res 2008;102:103–12.

5. Duan XT, Young R, Straubinger RM, et al. A straightforward and highly efficient precipitation/on-pellet digestion procedure coupled with a long gradient nano-LC separation and Orbitrap mass spectrometry for label-free expression profiling of the swine heart mitochondrial proteome. J Proteome Res 2009;8:2838–50.

6. Hu Q, Suzuki G, Young RF, Page BJ, Fallavollita JA, Canty JM Jr. Reductions in mitochondrial O(2) consumption and preservation of high-energy phosphate levels after simulated ischemia in chronic hibernating myocardium. Am J Physiol Heart Circ Physiol 2009;297:H223–32.

7. Depre C, Tomlinson JE, Kudej RK, et al. Gene program for cardiac cell survival induced by transient ischemia in conscious pigs. Proc Natl Acad Sci U S A 2001;98:9336–41.

8. Page BJ, Banas MD, Suzuki G, et al. Revascularization of chronic hibernating myocardium stimulates myocyte proliferation and partially reverses chronic adaptations to ischemia. J Am Coll Cardiol 2015;65:684–97.