

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 non-transmural 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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