Reply to “Letter to the editor: ‘Cyclosporin A in left ventricular remodeling after myocardial infarction’”

Andaleb Kholmukhamedov,1 Francis G. Spinale,2,4 Rupak Mukherjee,2 and John J. Lemasters1,3

1Department of Drug Discovery and Biomedical Sciences, Medical University of South Carolina, Charleston, South Carolina; 2Department of Surgery, Medical University of South Carolina, Charleston, South Carolina; 3Department of Biochemistry and Molecular Biology, Medical University of South Carolina, Charleston, South Carolina; and 4Department of Cell Biology and Anatomy, University of South Carolina School of Medicine, Columbia, South Carolina

REPLY: We thank Dr. Javadov (4) for providing feedback to our article published in American Journal of Physiology-Heart and Circulatory Physiology entitled “Cyclosporin A in left ventricular remodeling after myocardial infarction” (5).

We set up our study to determine whether and to what degree administration of cyclosporin A (CsA) after coronary artery ligation would prevent left ventricular (LV) dilation and pump dysfunction after myocardial infarction (MI). Specifically, CsA administration was initiated 48 h after coronary artery ligation so as not to interfere with early inflammatory/necrotic responses to sustained ischemia, since the extent of LV remodeling is proportional to infarct size (2). Therefore, our study design examined the effects of CsA exclusively on the “late” phase of LV remodeling post-MI and intentionally made the size of the necrotic area the same for the CsA-treated and vehicle groups.

Mitochondria isolated from cyclophilin D knockout (CypD−/−) mice are resistant to onset of the mitochondrial permeability transition (MPT), CsA does not inhibit MPT pores of CypD-deficient mitochondria, and myocardial necrosis after ischemia-reperfusion is diminished in CypD−/− mice (1, 9). In his letter, Dr. Javadov contends that the MPT can lead to only necrosis and not apoptosis. However, MPT onset is well established to cause large-amplitude mitochondrial swelling, rupture of outer membranes, and release of cytochrome c from the intermembrane space. Such cytochrome-c release leads to apoptotic protease activating factor-1 and caspase-9-dependent activation of the executioner caspase-3 as a committed step toward apoptotic cell death (8). Dr. Javadov is correct that caspase-3 activation by this mechanism requires ATP (or 2-deoxy-ATP), which becomes virtually completely depleted after severe ischemia-reperfusion. However, under less severe conditions, ATP may not become fully depleted, and enough ATP can remain to allow caspase-3 activation after cytochrome-c release, especially if glycolytic sources of ATP are available. Indeed, such glycolytic ATP prevents necrosis, but because of MPT onset, apoptosis occurs instead (6). The observation of increased apoptosis in cardiomyocytes of CypD-overexpressing mice provides further experimental support of MPT-initiated apoptosis (1).

After an MI, the LV regions that were not originally ischemic undergo “reactive” remodeling, resulting in hypertrophy secondary to an increase of workload of the surviving cardiomyocytes. After several weeks, this hypertrophy can give way to a dilated cardiomyopathy with loss of cell mass, leading to heart failure and death. Accordingly, our study examined the hypothesis that increased work by surviving viable myocardium post-MI causes a concomitant increase in intracellular Ca2+ loading and respiration-dependent reactive oxygen species (ROS) formation. Increased Ca2+ and ROS then predispose to CsA-sensitive MPT pore opening, leading to dysfunction and death of cardiomyocytes (7).

The question of apoptosis in ischemic myocytes raised by Dr. Javadov is moot as far as our study is concerned, because we measured apoptosis by terminal deoxynucleotidyltransferase-mediated dUTP nick end labeling and caspase-3 activation only in remote myocardium that had never experienced ischemia. Indeed, our aim was to determine whether CsA would alleviate apoptosis in remote myocardium and prevent LV dilation and pump dysfunction. However, contrary to the expectation of our hypothesis, even though CsA provided partial protection against apoptosis in remote nonischemic myocardium, CsA did not protect against LV dilation and pump dysfunction, which led us to the conclusion that a CsA-sensitive MPT was not an important pathophysiological mechanism in adverse postischemic remodeling in the weeks after an acute MI. Nonetheless, we cannot rule out that an unregulated, CsA-insensitive MPT was taking place to promote cell loss and adverse LV remodeling (3).

The dose of CsA that we used was comparable with doses previously employed to protect acutely against necrotic infarction after ischemia-reperfusion (10). Protection by CsA against apoptosis observed in our study confirmed that CsA had been previously employed to protect acutely against necrotic infarction after ischemia-reperfusion (10). Protection by CsA against apoptosis observed in our study confirmed that CsA had been administered at a pharmacologically effective dose, which was important to document since higher CsA caused nephrotoxicity and could not be used. In our study, we suggested that protection against apoptosis by CsA could have been due to MPT inhibition, but we also indicated that CsA could be acting by other mechanisms, including cyclophilin A-dependent immune suppression as argued by Dr. Javadov.

Dr. Javadov also suggested that in our experiments, CsA may not have been delivered to the border zone/MI region.
when administered after coronary occlusion. Although this may be true, our study focused on apoptosis and adverse remodeling in remote nonischemic myocardial regions where blood circulation was never compromised. Indeed, protection by CsA against apoptosis was strong evidence that CsA was effectively delivered to this tissue. Despite protection against apoptosis, CsA did not decrease ventricular dilation, pump dysfunction, and adverse LV remodeling at 4 wk post-MI. Thus we suggest that a CsA-sensitive MPT, although contributing to infarction in the early phase of ischemic injury, likely does not play a significant role in late adverse LV remodeling at 28 days post-MI.

REFERENCES


