REPLY: Intracoronary Delivery of Mitochondria to Prevent Ischemia–Reperfusion Injury: Challenging Pathway From Bench to Bedside

In response to Dr. Aimo and colleagues, we used a pedigreed model of myocardial ischemia and reperfusion. The model mimicked acute myocardial infarction with no collaterals, with approximately 36% of the left ventricle (37.4 ± 1.9% and 35.4 ± 2.7%, respectively) being ischemic for 30 min. The ischemic cascade was initiated at 15 to 20 min following the onset of ischemia and was accurately measured at 2 h reperfusion by triphenyltetrazolium chloride staining (1).

We regret that Dr. Aimo and colleagues misinterpreted our findings about adenosine triphosphate (ATP) and uptake of mitochondria. We and others have shown that viable, respiration competent mitochondria are taken up by both ischemic and nonischemic tissue by endocytosis (2–4). Nonintact, respiration incompetent (unable to produce ATP) mitochondria are not taken up by cells and do not increase coronary blood flow when administered through the coronary arteries.

In this study, we used autologous mitochondrial transplantation to allow for comparison with our previous publications. However, we showed that mitochondrial transplantation could be performed using either single or serial injections of either autologous or heterologous mitochondria, with no direct or indirect, acute or chronic alloreactivity, allorecognition, or damage-associated molecular pattern molecules (5). We expect that the use of heterologous mitochondria will eventually become the primary source for mitochondrial transplantation.

Although left anterior descending artery occlusion represents only one of the many ischemic scenarios of ST-segment elevation myocardial infarction, it provides a clinically relevant experimental model to test new interventions. We encourage investigators to extend our findings to different models of coronary ischemia (different durations and distributions) using large animal models and will freely provide all of our accumulated knowledge base to aid in these endeavors.

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Please note: Dr. Emani has been a consultant for Medtronic. Drs. del Nido, Emani, and McCully have patents pending for the isolation and usage of mitochondria.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Basic to Translational Science* author instructions page.

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