Reply to “Letter to the editor: Characterizing preclinical model of ischemic heart failure: difference between LAD and LCx infarctions”

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REPLY: We thank Dr. Katz and colleagues (7) for their interest and comments on our recent study (3). The study was conducted to develop and characterize a large animal model of chronic heart failure (HF) associated with large myocardial infarction (MI).

In the six-lead electrocardiography, ST-segment elevation was observed in all the animals, usually in the lateral electrodes, in both the left anterior descending coronary artery (LAD) and the left circumflex artery (LCx) MIs. In addition, as shown in Fig. 3 (3), all the infarctions had similar transmurality, which is not likely to be found in non-ST-segment elevation MI.

In terms of the scar size, we believe the question arose from the different methods to analyze this index. While Katz et al. probably consider the scar size as a percent surface area, we calculated it as a percent volume of the left ventricle (LV). Infarct expansion occurs in both circumferential and longitudinal directions, while there is a significant thinning in the radial direction. Therefore, even though the scar increases in surface area, scar volume decreases (11). Additionally, scar volume relative to total LV myocardial volume further decreases as the remote myocardium becomes more hypertrophic. We estimated the scar/myocardium volumes by planimetry of the short-axis cross sections. Although we do not have MRI data on scar size at this time, our method shows a strong relationship to the measured scar/myocardium weight in explanted hearts.

We fully agree with the comments by Katz et al. that dP/dtmax is highly dependent on hemodynamic conditions and load-independent measures of contractility would add more information. In fact, we found significant differences in echocardiographic longitudinal strain among the groups, which is consistent with the present finding, we have previously demonstrated that LV ejection fraction was a better indicator than dP/dtmax to indicate the presence of systolic dysfunction in post-MI pigs (4).

One of the major aims in our study was to develop a large-animal model of HF that mimics HF in ischemic patients who require novel therapeutic approaches. Thus achieving advanced LV remodeling was one of our goals in developing this model. Presumably in sheep based on their publications, Katz et al. report that their animals experience HF symptoms after LCx MI that require daily diuretics and β-blocking agents. In contrast, we did not observe such HF symptoms in LCx MI pigs, whereas a few pigs after LAD MI died from HF.

The difference in HF severity is likely because of the development of ischemic mitral regurgitation after LCx MI in sheep. Llaneras et al. (10) reported the development of ischemic mitral regurgitation after LCx ligation in sheep, which has been replicated in multiple laboratories (1, 6). However, this was not the case in our pigs, because none of the LCx MI pigs developed more than moderate mitral regurgitation at 3 months after MI induction, probably because of the smaller size of the LCx compared with sheep. Large-animal models that recapitulate ischemic mitral regurgitation are extremely interesting and provide a more complex pathophysiology of post-MI HF, despite a markedly higher reported mortality, particularly in swine (5).

As Katz et al. suggest, we found that LV long-axis length was greater in LAD MI pigs (7.18 ± 0.69 cm) than in LCx MI pigs (6.46 ± 0.69 cm). Greater infarct expansion in the longitudinal direction may be one of the mechanisms for greater long-axis length after LAD MI. We agree that further study is necessary to examine this hypothesis, since our study was underpowered to show statistically significant differences in sphericity index after LAD and LCx MIs. Meanwhile, it is of note that sphericity index is higher in animal models with ischemic mitral regurgitation (8), which predominantly occurs after LCx MI in both humans (9) and sheep (1, 10).

Because promising novel therapeutic approaches are now being developed, large-animal studies are becoming increasingly important for translating these approaches to bedside. Large-animal models that closely reproduce clinical-type HF are essential to examine the safety and efficacy of novel therapies. Characterizing these models will facilitate the ability of researchers and clinicians to interpret the results of preclinical studies.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

REFERENCES

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