Letter to the editor: Infarct size measurements are critically important when comparing interventions affecting ventricular remodeling

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TO THE EDITOR: In the recent report by Singla et al. (8), the authors seek to determine the effect of transplanted embryonic stem cells (ESCs) on left ventricular remodeling after myocardial infarction in the mouse. They conclude that ESC treatment results in significantly less apoptosis, hypertrophy, and fibrosis. However, an interpretation is complicated by the difference in infarct size: 23 ± 3% in ESC-treated mice compared with 43 ± 8% in controls. The authors claim this difference is an effect of ESC treatment; however, this makes a major assumption, that the original pretreatment infarct size (area at risk) was identical in both groups. If by chance the area at risk was less in the ESC-treated group, then this alone could explain all of the beneficial effects attributed to ESC treatment. So, is this assumption valid? The coronary artery ligation model is well known for producing a wide range of infarct sizes, anywhere between 10–70%, even when the suture is placed in an identical location (3, 7). This is due to differences in coronary branching patterns that are evident even between littermates (2). Therefore, large-group sizes are necessary for this assumption to be reasonable, but with n = 5 mice in the ESC-treated group and only n = 4 in the control group, this clearly is not the case here.

There is also a question mark on the validity of the infarct size measurements that are performed at the end of the study. Sections cut at mid-papillary muscle level are assumed to be representative of the entire ventricle. Recent evidence suggests that at least seven slices from throughout the heart may be required to accurately determine infarct size (9). Another reason to doubt this approach is that mice commonly develop apical aneurysms (3) which contribute significantly to infarct size measurements that are performed at the end of the study. If by chance the area at risk was less in the ESC-treated group, then this alone could explain all of the beneficial effects attributed to ESC treatment. So, is this assumption valid? The coronary artery ligation model is well known for producing a wide range of infarct sizes, anywhere between 10–70%, even when the suture is placed in an identical location (3, 7). This is due to differences in coronary branching patterns that are evident even between littermates (2). Therefore, large-group sizes are necessary for this assumption to be reasonable, but with n = 5 mice in the ESC-treated group and only n = 4 in the control group, this clearly is not the case here.

Even if both of the above assumptions are correct, i.e., that the initial area at risk was identical and that the observed difference in infarct size is real and due to ESC treatment, there is then the important question of whether the observed reductions in apoptosis, fibrosis, and hypertrophy are simply knock-on effects of a smaller infarct size. Singla et al. (8) suggest a direct effect of ESC treatment since there was no correlation between infarct size and the number of apoptotic nuclei. This is a disingenuous argument, since there are insufficient numbers in either group for correlation analysis, and if the groups were combined, then there does appear to be a strong correlation. It also runs contrary to the literature where apoptosis has been previously shown to correlate with ventricular remodeling (1, 6), which, in turn, correlates with infarct size (4, 5, 7).

I believe that in a study such as this, where the entire message is dependent on several key assumptions, it is imperative that more consideration be given to whether these assumptions are indeed valid.

REFERENCES