To the Editor:

We have read with interest the editorial1 about our article on intracoronary cardiosphere infusion.2 In his editorial, Ishikawa1 proposes 4 different mechanisms that might explain the absence of microinfarctions after cardiosphere injection: (1) adhesion and transmigration of cardiospheres in the large vessels, (2) passage of the cardiospheres through the capillaries, (3) transient microvascular occlusion followed by quick transmigration across the capillaries, and (4) distal perfusion maintained by collateral capillaries. We think that yet another possibility is likely to be operative.

From measurements of reactive hyperemia and fractional flow reserve, it is known that coronary flow is far from maximal under basal conditions. Recruitment of coronary reserve can increase coronary blood flow \( \leq 5\)-fold.3 Moreover, collateral capillaries exist (even in healthy myocardium) and are recruited as soon as 1 minute after occlusion.4 Thus, a large fraction of microvessels are closed under basal conditions; these vessels can be occluded without undermining resting coronary flow and therefore without microinfarction.

Do the occluded vessels remain occluded forever or do they recanalize over time? Cardiospheres undergo active extravasation5; after infusion, they first lodge within the microvasculature, causing vessel occlusion. Afterward, cardiospheres transmigrate via the creation of endothelial pockets and breakdown of the adjacent vessel wall. This process takes 24 to 72 hours, resulting in eventual (but not immediate) recanalization of the occluded vessel.

Therefore, we propose that carefully titrated cardiosphere infusion does not cause microinfarction because reserve nonoccluded microvessels and collateral vessels are promptly recruited to supply the distal myocardium. Moreover, those microvessels that are occluded acutely will recanalize over time, causing no lasting reduction in coronary flow or flow reserve.

Disclosures

Dr Marbán owns equity in Capricor Inc. Dr Gallet reports no conflicts.

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References

Letter by Gallet and Marbán Regarding Article, "Intracoronary Injection of Large Stem Cells: Size Matters"
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