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Commentary: An innovative “CABG-patch”

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CENTRAL MESSAGE

The authors present a model of hibernating myocardium treated with CABG and an epicardial mesenchymal stem cell patch. This model shows improved ventricular function but its real-world use is limited.

After myocardial ischemia, hibernating myocardium consists of ischemic cells that remain viable but can lead to decreased contraction and ventricular dysfunction.¹ Because the myocardial cells are still viable, hibernating myocardial function improves after coronary revascularization.² In addition to coronary revascularization to improve ventricular function, there is growing interest in the use of mesenchymal stem cells (MSCs) to aid in the recovery of infarcted ventricular muscle. The first published report of cellular cardiomyoplasty was in 1999 from the University of Toronto.³ Further studies suggest that injecting MSCs into infarcted cardiac myocardium leads to differentiation of MSCs into cardiomyocytes^{4,5} but the clinical benefit of cellular cardiomyoplasty is still debated.⁵⁻⁹

Stone and colleagues¹⁰ aim to investigate the utility of MSCs applied as an epicardial patch at the time of coronary artery bypass graft (CABG). In a swine model, they mechanically stenosed the left anterior descending artery; after 12 weeks, a single vessel left internal thoracic artery–left anterior descending artery CABG was performed in addition to placing an epicardial patch containing MSCs on hibernating myocardium. They found improved contractile function when tested with inotropes and on a microscopic level there were increased number and size of mitochondria suggesting a potential mechanism for the improved myocardial function.

The authors should be congratulated on their study and its novel findings. But we have several concerns that we believe limit the applicability of their findings. The first is the disease model used. Although a single vessel disease model is easily reproducible, the real-world applicability

of single-vessel coronary disease without infarction undergoing CABG is quite limited. More commonly, our patients present with triple-vessel disease that complicates the technical aspect of patch placement and calls into question whether the burden of dysfunctional myocardium would overwhelm the improvement seen from the MSC patch application. Secondly, all of these operations were performed under normothermic off-pump conditions. With on-pump CABG, would the conditions of cardiopulmonary bypass such as hypothermia and the heightened inflammatory response affect the MSCs and limit the improvements in myocardial function? Finally, the authors chose to use an allogeneic MSC patch as their mode of delivery of MSC to hibernating myocardium citing improved delivery of viable MSC over intramyocardial or intracoronary injection. This method is limited by both cell type and incubation time. Their source of MSCs was sternal bone marrow—which in a human model would not be feasible. Additionally, the time from cell collection to patch implantation of more than 1 week limits its practical application.

The authors present an elegant model for inducing hibernating myocardium and provide a thorough investigation on a macro- and microscopic level of the changes induced from applying an MSC patch during CABG. Although these results are promising, further study is certainly needed to make this model more real-world applicable.

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Commentary: Awakening the hibernating myocardium: The pristine business of mesenchymal stem cells

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CENTRAL MESSAGE

Mesenchymal stem cells restore the functional activity of hibernating myocardium by upregulating the mitochondrial proteomic profile.

Hibernation is a natural phenomenon adopted by many warm-blooded animals to survive adverse environmental situations (especially extreme winter) by minimizing their metabolic demands. The process of hibernation sustains the survival of those animals to restart their active life after surviving the period of adversity. Likewise, myocardial tissue undergoes a so-called clinical hibernation due to chronic ischemia following reduced coronary blood flow. Hibernating myocardium (HM) displays increased

regenerative capacity, decreased tissue mortality, and low risk of future failure suggesting the increased survival capacity of myocardial tissue following a coronary artery bypass graft (CABG) procedure.¹ The term *hibernating myocardium* was coined by renowned cardiologist Shahbuddin H. Rahimtoola in 1984 at the National Heart, Lung, and Blood Institute Workshop on the Treatment of Coronary Artery Disease.² Since then, HM has gained clinical attention in therapeutic and regenerative cardiology. Because HM is critically associated with myocardial energetics, the mitochondrial adaptations in HM tissue provoked research interests across the globe and led to several outstanding discoveries.

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