Myocardial oxygenation is critical for improving regeneration capacity

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Despite significant strides in improving prevention and treatment, cardiovascular disease continues to be a leading cause of death in the United States with an estimated cost of ~$300 billion per year. One of the leading causes of mortality and morbidity from cardiovascular diseases is myocardial infarction (7). Decreased oxygen and nutrient delivery to myocardial tissue compromises function, resulting in localized necrosis. Despite aggressive revascularization approaches through catheterization and stent placement or coronary artery bypass grafting, there are limitations to targeted increases in blood flow and oxygen delivered to the susceptible myocardium. Another attractive alternative is cell-based therapy to repopulate and subsequently regenerate the myocardium. The initial results of the improved function of the injured myocardium when treated with various cell types (3, 4, 6) is lost at 6 month postinfarction (4), and there is a lack of an increase in tissue quantity. This implies that a paracrine mechanism is the leading candidate for cellular restoration; however, further questions remain as to whether an optimal oxygen supply is required for cellular viability.

The preferred approach to treating injured myocardial tissue in the setting of an infarct is based on traditional medical and surgical strategies of restoring blood flow; however, this often does not lead to an optimal recovery. To overcome this limitation, a variety of cell-based approaches (termed “cellular cardiomyoplasty”) have been proposed for improving the function of the injured myocardium. These approaches typically involve various bone-derived cell types, resident cardiac stem cells, and skeletal muscle cells (reviewed in Ref. 8), with a common goal of improving myocardial performance in the hostile environment of the infarcted myocardium (2). However, it is not clear to what extent oxygen delivery to the infarcted myocardium plays a role in these cell-based therapies. Is there a critical oxygen tension required for cell viability to allow for other factors to contribute to recovery? Moreover, the lack of a real-time, active-tracking approach is required to document the level of oxygen present in the infarcted myocardium.

Chacko et al. (1) report in the American Journal of Physiology-Heart and Circulatory Physiology a novel and systematic method of monitoring the oxygen requirement of transplanted mesenchymal stem cells (MSCs) using a live-tracking oxygen-sensing spin probe (OxySpin) that follows myocardial tissue preservation in real time in infarcted rat hearts treated with MSCs. These findings add to the promise of MSC transplantation for improving myocardial function following infarction and indicate that the level of oxygen is critical for myogenic functional recovery.

Chacko et al. (1) hypothesized that oxygen tension plays a critical role in the microenvironment of the infarcted myocardial tissue. This methodology was based on previous studies by the authors showing that the OxySpin probe measures changes in oxygen saturation by electron paramagnetic resonance. The strength of this methodology relies on the real-time tracking of oxygen consumption. Previously, the strength of using OxySpin probes had been shown with skeletal muscle cells, which demonstrated an improved oxygen tension within the rat infarct compared with controls (5).

The authors tested their hypothesis using MSCs containing a variety of mesenchymal-derived differentiation markers and labeled OxySpin probe cells, which were shown to proliferate and differentiate appropriately in vitro. They also showed that the internalized probe had no effect on the innate ability of the cells. To validate their approach in vivo, MCSs with the internalized OxySpin probe were injected into the infarcted myocardium and showed improvement in overall cardiac performance as assessed by echocardiography. In contrast to infarcted rats injected with medium alone, MSC-injected rats had an increase in oxygen tension within the infarcted myocardium. Tissues collected from MSC-treated rats exhibited an increase in angiogenesis shown by increased VEGF levels and capillary density in the infarct region.

The ability of the OxySpin probe to measure an increase oxygen tension within the infarcted myocardium to such a great extent is surprisingly significant. This implies that blood vessel growth is stimulated and sustained within the infarcted myocardium. Since the OxySpin probe has no side effects on the injected cells in vitro, this methodology could potentially be applied to humans for monitoring the transplanted cells and measuring a “live” recovery of the myocardium, which may have theoretical advantages over existing monitoring studies for myocardial performance. Other noninvasive studies have focused on flow heterogeneity or regional alterations in myocardial metabolism, which are all limited to indirect assessments of the ischemic myocardium. In contrast, the best indicator may in fact be direct measurements of oxygen tension in the hypoxic myocardium. In this way, the OxySpin probe is one of the most promising modalities for tracking injected cells within the damaged myocardium and allows for a better understanding of the mechanisms of cellular regeneration.

Previous efforts to revascularize the myocardium have focused on simply improving oxygen tension of the myocardial tissue. However, it is possible that the level of oxygen tension requires a critical set point, and anything beyond that level requires other modalities, such as growth factors to stimulate the formation of new vessels. The findings in Chacko et al. (1) are novel and intriguing; however, they must be taken in context with the animal model studied and the duration of the
experiments. The authors report striking data for reestablishing appropriate oxygen tension of the myocardium within 4 weeks of the study, but longer studies are clearly required to ascertain whether these results are sustainable. In addition, larger animal models are needed to validate the usefulness of this technique as well as the benefit of measuring in vivo oxygen tension. Finally, the specific mechanisms underlying the positive findings must be delineated, given that MSCs may not differentiate into the endothelial cells that line blood vessels which supply the infarcted myocardium.

The findings of Chacko et al. (1) will likely add more fuel to the current debate over the use of cell-based therapies for improving function in the infarcted myocardium. A rapidly accumulating body of evidence indicates that appropriately targeted cells can overcome the harsh environment of the infarcted myocardium (3, 4, 8). While exact mechanisms remain unknown, the methods employed in Chacko et al. have shown that oxygen tension is critical in the recovering myocardium.

REFERENCES