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EDITORIAL COMMENT

Charting New Real Estate

Leveraging the Therapeutic Potential of the Pericardial Space

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The pericardial space provides a reservoir of biologically active mediators, including cytokines, chemokines, and growth factors.[1] We once thought that the singular function of the pericardium and its contents was to protect the heart and provide balanced hemodynamics, which optimized cardiac function. More recently, some think that the contents of the pericardial space can exhibit dynamism and reflect the adjacent cardiovascular pathology of the organ resting within its cradle. For example, using pericardial fluid collected from patients undergoing cardiac surgery, our group has shown that acute ischemic events can alter the immune cell composition of the pericardial space.[2] These findings imply that the pericardial space and its altered contents may carry prognostic value for underlying cardiac disease states. Further research may uncover diagnostic and prognostic biomarkers.

The space does not simply mirror cardiac disease states—it can actively participate in cardiac repair processes. We and others have shown that pericardial macrophages are able to translocate to injured myocardial regions and attenuate fibrosis,[3] and it has been established that cells in the pericardial space are substantially altered after cardiac surgery.[4,5] Importantly, pericardial content changes after surgery are distinct from systemic postsurgical inflammatory responses.[6] These findings may have clinical relevance because inflammatory processes have been implicated in complications such as postoperative atrial fibrillation[7] and postoperative pericardial adhesion formation.[8] Collectively, these studies suggest that the pericardial space is responsive and dynamic and may influence health and disease.

The therapeutic potential of the pericardial space is the exciting corollary of these recent advances in pericardial biology. In a preclinical study, using a rodent model, our group has shown that micronized biomaterials can be delivered into the pericardial space resulting in enhanced postinfarct repair mediated by eosinophil activity.[9] One of the major obstacles limiting our ability to research the therapeutic potential of the pericardial space is developing a model delivery system that is safe, reproducible, and effective.

In this issue of *JACC: Basic to Translational Science*, Rusinkevich et al[10] report the development and successful implementation of a permanent pericardial catheter in mice. The investigators used a transgenic rodent model and implanted a catheter that facilitates intrapericardial delivery of therapeutics. The model can be used in ischemic and nonischemic mice. They further showed that delivered agents can be tracked after being tagged with fluorescent beads. Finally, they demonstrated that cells (eosinophils) can be delivered into the pericardial space via the inserted catheter.

The study is notable for a few reasons. First, a microsurgical approach has been developed and applied. Second, the delivery system did not damage or kill cells. Third, the catheter was effective in a closed chest model, where the outcomes of treatment in the setting of chronic ischemia/reperfusion was possible.

This approach is simple and elegant. They show the safety and efficacy of the catheter implantation and the delivery of agents (cells, beads) into the pericardial space. While not an objective of the study,

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it would have been interesting to see if the mice who received eosinophils had improved hemodynamics compared with the control animals. As acknowledged by the team, it is also important to recognize the potential permeability of the pericardium in the treatment group. Given that the Evans Blue dye stained the lungs, further modifications and assessments are needed to ensure that agents delivered into the pericardial space remain in the pericardial space.

This study can provide a foundation for future work. In addition to addressing the above limitations, further research can be done in assessing the efficacy of the catheter in larger animal models. This will be important for translating preclinical observations to clinical applicability. Groups should also consider whether intrapericardial delivery of therapeutics is more effective in mitigating the sequelae of a myocardial infarction, such as fibrosis.

The pericardial space is a confined, but enriched, milieu of biologically active factors. These factors provide a microenvironment that facilitates optimal cardiac function. They also offer unique insight into an isolated ecosystem that closely mirrors heart health and disease. As we move toward developing treatment strategies with lower side-effect profiles, the local delivery of therapeutics provides a compelling alternative to systemic administration of medications. The pericardial space is precious real estate that has not been extensively charted to date. Utilizing its diagnostic, prognostic, and therapeutic potential represents a new frontier in cardiovascular medicine, and Rusinkevich et al show that there is great promise in developing this highly exclusive piece of real estate.

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