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EDITORIAL COMMENT

Reverse Translation of Pericardial Access

Pericardial Catheter Implantation in Mice

Pedro Mendes-Ferreira, PhD,[a] André M. Leite-Moreira, MD, MS,[a,b] Adelino F. Leite-Moreira, MD, PhD[a,c]

Significant advances in heart failure (HF) therapies including noncoding ribonucleic acids, stem cells, and other biologic therapies require a localized delivery to increase on-target and avoid systemic off-target effects. Several approaches take advantage of catheter-based technologies to access the heart percutaneously,[1] including coronary and/or coronary sinus catheterization, endocardial injection, or pericardial access. The pericardial approach has been extensively developed due to its usefulness in electrophysiological studies and ablation therapy,[2] making it a common and safe procedure.

The pericardial fluid can have diagnostic value,[3] and whereas no clinical trials have delivered drugs to the pericardial space, a significant effort has been made to show this approach as a reliable and efficacious route in both large[4] and small animals.[5]

The pericardial space per se is not only crucial for modulating the cardiac response,[5] but also serves as a route for delivering biologics (cells and exosomes) into the pericardial space leading to cardiac repair in ischemia reperfusion injury.[6]

Intrapericardial injection as a tool is a major asset in developing new therapeutic strategies for HF. However, current research focuses mainly on a single (acute) intervention, without the possibility for repeated drug administration or diagnostic sampling. Its application offers clear advantages in comparison with the more commonly used delivery routes, namely intravenous, intracoronary, and intramyocardial delivery, which have a much lower retention of therapeutics in the heart. Intrapericardial injection offers a unique opportunity to deliver compounds directly in contact with the epicardium, with a long-lasting duration, in a minimally invasive way, which poses no additional costs.

Chronic pericardial access has only been tested in large animals, proving to be reliable and functional in both short[7] and long term (1 year[8]); however, large animal work is costly and time-consuming and does not allow for genetic manipulation and high-throughput studies.

In this issue of *JACC: Basic to Translational Science*, Rusinkevich et al[9] have developed a mouse model for pericardial catheter implantation, allowing for chronic intrapericardial drug delivery and sampling. This innovative method comes at a crucial time because it will not only facilitate the application of new therapeutic approaches, but very likely will optimize currently used methods, whose main limitation is the impossibility of repeated interventions to the pericardial space, leading to a more comprehensive understanding of the role and importance of the pericardial space as a route for treating HF.

Here, a reliable and reproducible technique involving the introduction of a small catheter (0.254 mm in outer diameter) in the pericardial space, through a mini-thoracotomy, that is secured in the subdermal space, is shown, and no complications related to the procedure were reported. The validity of this approach was demonstrated by the presence of fluorescent microparticles 4 days after injection into the pericardium. Rusinkevich et al[9] are to be commended for not only developing this apparently simple but extremely important new technique, but also for publishing its videographic record that will expedite its application in future studies, which we are sure will be many.

From the [a]Cardiovascular Research and Development Centre–UnIC@RISE, Department of Surgery and Physiology, Faculty of Medicine of the University of Porto, Porto, Portugal; [b]Department of Anesthesiology, Centro Hospitalar Universitário São João, Porto, Portugal; and the [c]Department of Cardiothoracic Surgery, Centro Hospitalar Universitário São João, Porto, Portugal.

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To understand its potential in the treatment of HF, Rusinkevich et al[9] applied the technique to a model of closed-chest ischemia/reperfusion injury (transient left anterior descending coronary artery occlusion) and demonstrated the feasibility of performing both procedures in the same surgical intervention, without any compromise in the recovery of the animals, when compared to left anterior descending coronary artery occlusion alone. By using ΔdblGATA1 mice, which lack eosinophils, Rusinkevich et al[9] demonstrated the ability to administer exogenous immune cells that not only localized to the pericardial space, but also migrated to the adjacent structures.

The value of the model and its minimal invasiveness could be pushed even further if Rusinkevich et al[9] would make the catheter accessible without the need for an additional surgical procedure, by coupling the pericardial implantation with the creation of an access port. This would facilitate sequential injections, reducing the need for several anesthetic inductions/surgical procedures, enhancing its usefulness as a chronic model.

Though extremely relevant, a few questions still remain regarding the model, namely whether the catheter is patent over longer periods of time, whether it can be used to aspirate pericardial fluid for diagnostic purposes, whether pericardial remodeling and/or inflammation (as noted by the investigators[9]) poses a limiting factor, and whether leakage of the injectate outside of the pericardial space can compromise its application. Despite these limitations, this comprehensive description of a new myocardial delivery approach in mice, which opens the door for several opportunities not available in large animals, sets the stage for several new applications that can accelerate the discovery of new treatments for HF.

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ADDRESS FOR CORRESPONDENCE: Dr Adelino F. Leite-Moreira, Faculdade de Medicina da Universidade do Porto, Departamento de Cirurgia e Fisiologia, Edifício Centro de Investigação Médica, Piso 06, Rua Dr Plácido da Costa, 4200-450 Porto, Portugal. E-mail: amoreira@med.up.pt.

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