Trans-endocardial intramyocardial delivery systems for biotherapeutics to treat heart failure, ischemia, and infarction: having the right delivery solution should enhance clinical results

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Local intramyocardial delivery (IMD) expands the therapeutic window of cell, gene, and protein based therapies by maximizing dosage where targeted and minimizing dosage at remote sites where toxic effects may occur. Intracoronary artery (ICA) infusion delivers agents to the well perfused tissues of the heart. For agents that are small (gene therapies, proteins, and many cells), these agents will pass rapidly through the heart having little local benefit. For agents that are larger, such as culture expanded mesenchymal stem cells or cell aggregates, these larger agents will be stopped in the first capillary bed they enter achieving microvascular obstruction in well perfused regions of the heart.

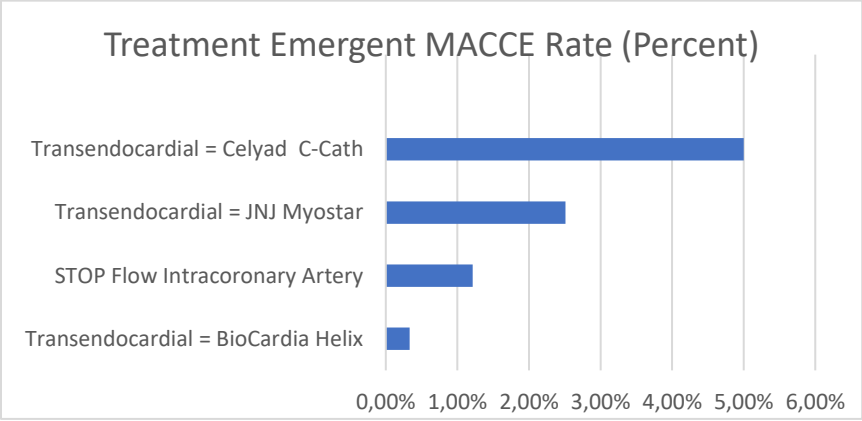
Because most animal research on local delivery of cell, gene, and protein therapy utilized IMD delivery and most clinical research on these agents used coronary artery infusion, much has been lost in translation from animals to humans. Many of the past clinical trials using ICA delivery in the past two decades could be significantly enhanced with IMD.

Interventional cardiologists realized that they could minimally invasively deliver biotherapeutics into the heart muscle with special transendocardial IMD catheters from within the heart to avoid the limitations of ICA infusion. Motivation was to enhance local biodistribution where needed – not just where the cells or genes would go after infusion into a blood vessel. Here, a catheter is advanced retrograde through the aortic valve and is deliveries to certain heart segments relative to areas of infarction or ischemia are performed.

Transendocardial IMD (TE-IMD) development continues to address the issue of catheter over all safety, efficiency of delivery and avoiding back leak of injectate to the ventricular chamber, navigation within the left ventricle of the heart in terms of device control and imaging. A number of previous investigational devices are no longer available as these each have challenges.

Reviews of delivery system safety for cell and gene based therapy to the heart with treatment emergent major adverse cardiac and cerebrovascular event (MACCE) profile are shown below where each delivery approach had been utilized in hundreds of patients[i].

Figure 1 – Treatment emergent MACCE rates from published clinical trial results (Duckers 2018)



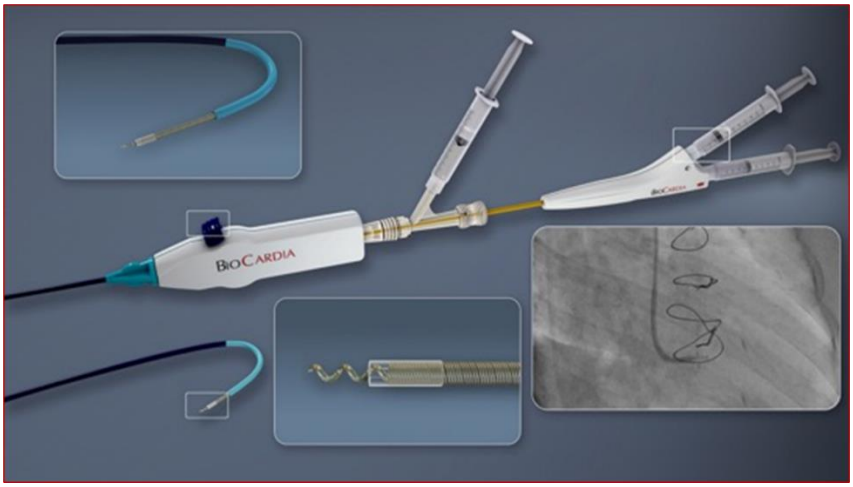
The primary cause of MACCE with TEIMD was reported as cardiac perforation. The primary cause of MACCE for the Stop Flow ICA technique was reported as vascular obstruction. There was also mortality with STOP FLOW and other approaches not seen with Helix. An additional review by Raval (2021)[ii] also showed that the Helix Catheter had 1/3 the MACCE reported relative to its next closest catheter the JNJ Myostar. In the setting of only post-acute myocardial infarction, where there have been two smaller studies, one each with the Myostar and with the Helix TEIMD systems, there have been zero treatment emergent MACCE.

Delivery efficiency is also important and Mitsutake[iii] has reported elegant experimental results using PET/CT to quantify deliveries of 18F-FDG labeled mononuclear cells (containing CD34+ cells) that have been radio-labelled. The quantification approach was enhanced by normalizing the signal with a vial of the same cells taped to the animal chest. Results show an average of three times the efficiency with the Helix TEIM catheter when compared to a straight needle transepicardial intramyocardial delivery and eighteen times the retention achieved with ICA. The enhanced retention due to the helical needle is hypothesized to be due to its longer self-sealing pathway through the tissue while engaged to the heart and these results have been confirmed by other groups with other agents.

Figure 2 Efficiency of Delivery Quantified for Three Delivery Approaches (Mitsutake 2017)

This engagement to the heart provides the physician with the ability to control the time course of infusion and is believed to reduce back leak into the ventricular chamber which has been shown with other straight needle TEIM catheter platforms. Those considering cell aggregates and biopolymers may benefit significantly from these aspects as enhanced retention may correlate well with enhanced safety.

Figure 3. The Helical Infusion System, CE Marked in EU and Investigational in USA utilizes a steerable is an 8 French introducer compatible retrograde TEIMD catheter system. It is navigated using fluoroscopy with pre-procedure echo or MRI guidance and requires no capital equipment.



Today the Helix TEIM catheter system is being advanced in clinical trials of autologous and allogenic cell therapies for heart failure and chronic myocardial ischemia by BioCardia and in post-acute myocardial infarction by CellProThera. Succesful delivery has potential to significantly enhance the therapeutic efficacy outcomes of each of these programs. For BioCardia's programs, there are other similar straight needle programs from which we can infer what a threefold dosage increase due to delivery efficiency may contribute. For CellProThera's program, an eighteen-fold targeted dosage has great promise over

the limitations of ICA infusion. CellProThera may also advance their therapy for chronic myocardial ischemia ahead – a second large indication where BioCardia is also active. Significant enhancements to the Helix platform are also underway which are intended to benefit all of the ongoing programs and those of other therapeutic partners ahead.

Disclosures: Peter Altman is CEO of BioCardia and Mathieu Kalbermatten is CEO of CellProThera.

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[i] Duckers H, Raval A, Pepine C, et al. Performance of Helix transendocardial biotherapeutic delivery system after 300 cases, TCT 2018 (poster).

[ii] Raval AN and Pepine CJ. Clinical Safety Profile of Transendocardial Catheter Injection Systems: A Plea for Uniform Reporting, Cardiovascular Revascularization Medicine 22 (2021) 100–108.

[iii] Mitsutake Y, Pyun WB, Rouy D. et al. Improvement of Local Cell Delivery Using Helix Transendocardial Delivery Catheter in a Porcine Heart, Int Heart J 2017; 58: 1-6.