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Optimized Catheter System Demonstrates Utility for Endomyocardial Delivery of Cardiopoietic Stem Cells in Target Patients With Heart Failure

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Introduction

Regenerative therapies are under evaluation in clinical trial settings to assess their potential in fostering the structural and functional recovery of failing myocardium. Notably, however, a low and unreliable level of cell retention after treatment delivery has hindered adequate dosing.[1] This shortcoming is a recognized contributor to mixed outcomes in cell-treated patients. This limitation is, in part, related to the highly vascularized, spongelike structure and the heterogenous texture of cardiac tissue. Accordingly, cells—even when directly delivered into the myocardium itself—may escape into the systemic circulation or pericardial space. Cell retention after endomyocardial delivery is significantly hampered by tissue compliance and pressure generated at the needle tip, with potential backflow at the site of needle penetration into the tissue. These limitations associated with the use of traditional methodology warrant close consideration to guide the evolution of next-generation, optimized delivery systems.

Recent Developments

A deflectable-tip catheter (C-Cath$_{EZ}$, Celyad SA) has been developed to improve myocardial cell retention while assuring safety and ease of use.[2] The implemented design, characterized by a curved 28G needle, uses mathematical modeling to minimize backflow and reduce the risk of perforation while enabling stable needle anchoring in the beating heart without imposing additional tissue trauma (Fig. 1).[2,3] Side holes of incremental sizes in the distal curved portion of the needle were incorporated to reduce tissue pressure caused by the injectate and ensure an even distribution along the injection track, thereby increasing myocardial dispersion by exploiting a favorable biologic-tissue interplay.[2] The in silico predictions were translated into practice and tested in vivo in various preclinical settings, including healthy and chronically infarcted porcine models. Endomyocardial delivery using the C-Cath$_{EZ}$ catheter was consistently associated with a superior outcome—namely, a 3-fold increase in myocardial cell retention in either normal or infarcted myocardial tissue compared with the traditional straight end-hole catheter needle. The enhanced retention was documented without an increase in cardiac troponin levels.

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The C-Cath$_{EZ}$ catheter underwent its first-in-human use in the Congestive Heart Failure Cardiopoietic Regenerative Therapy (CHART-1) trial, which investigated the use of autologous cardiopoiesis-guided injection of bone marrow–derived mesenchymal stem cells in patients with chronic ischemic heart failure.[4,5] The procedural planning included creation of a left ventricular (LV) injection map derived from preprocedural transthoracic echocardiogram according to the 17-segment "bull's-eye" model from the American Society of Echocardiography[6] (Fig. 2). Apical, basal inferior, and basal inferolateral segments near the mitral subvalvular apparatus were ineligible for injection, irrespective of wall thickness. The mid-inferior and mid-inferolateral areas were targeted with caution to minimize potential adverse effects of increased column strength with the device in the undeflected position. The basal anteroseptal and inferoseptal areas were also cautiously targeted to minimize potential adverse effects on the conduction system.[6,7] In addition, regions with wall thickness less than 8 mm were designated as "no-go zones." A predefined transthoracic echocardiogram map was colocalized onto LV diastolic silhouettes from biplane contrast LV angiography taken prior to injection, and the ensuing procedure was performed under real-time fluoros-

Abbreviations and Acronyms

LV left ventricular

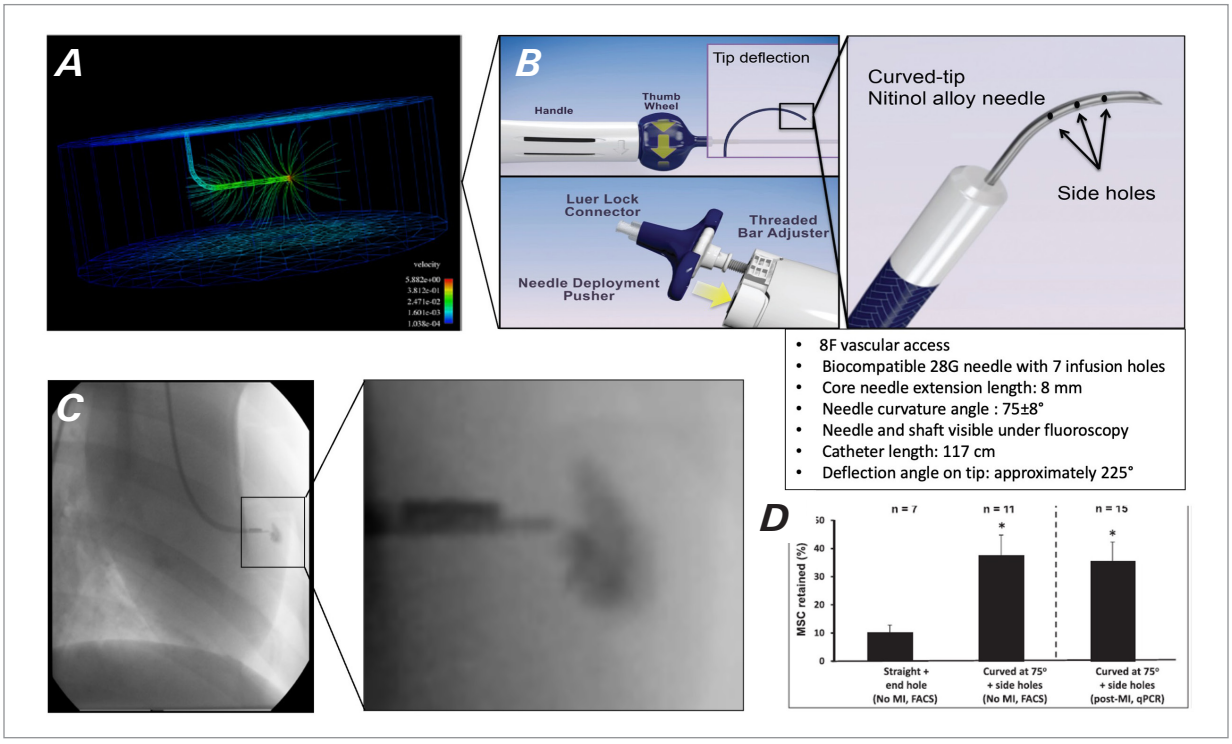

Fig. 1 Review of the retention-enhanced catheter delivery system. **A**) Predicted uniform dispersion of the injectate along the injection track using the C-Cath$_{EZ}$ modeled design. **B**) Actual C-Cath$_{EZ}$ catheter injection system featuring a curved needle with side holes (inset). **C**) Imagery of a fluoroscopy-guided endomyocardial delivery shows in vivo tissue retention of the contrast dye, with the curved needle with side holes visible in close-up. **D**) The superiority of the C-Cath$_{EZ}$ curved catheter over a traditional straight needle counterpart is seen in the quantification of myocardial retention following C-Cath$_{EZ}$ delivery of mesenchymal stem cells into healthy porcine hearts. Results were further validated in sex-mismatched infarcted porcine hearts.

FACS, fluorescence-activated cell sorter; MI, myocardial infarction; MSC, mesenchymal stem cells; qPCR, quantitative polymerase chain reaction.

Figures 1A and 1D used with permission from Behfar A, Latere JP, Bartunek J, et al. Optimized delivery system achieves enhanced endomyocardial stem cell retention. *Circ Cardiovasc Interv.* 2013;6(6):710-718.
Figure 1B adapted from Bartunek J, Davison B, Sherman W, et al. Congestive Heart Failure Cardiopoietic Regenerative Therapy (CHART-1) trial design. *Eur J Heart Fail.* 2016;18(2):160-168. Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

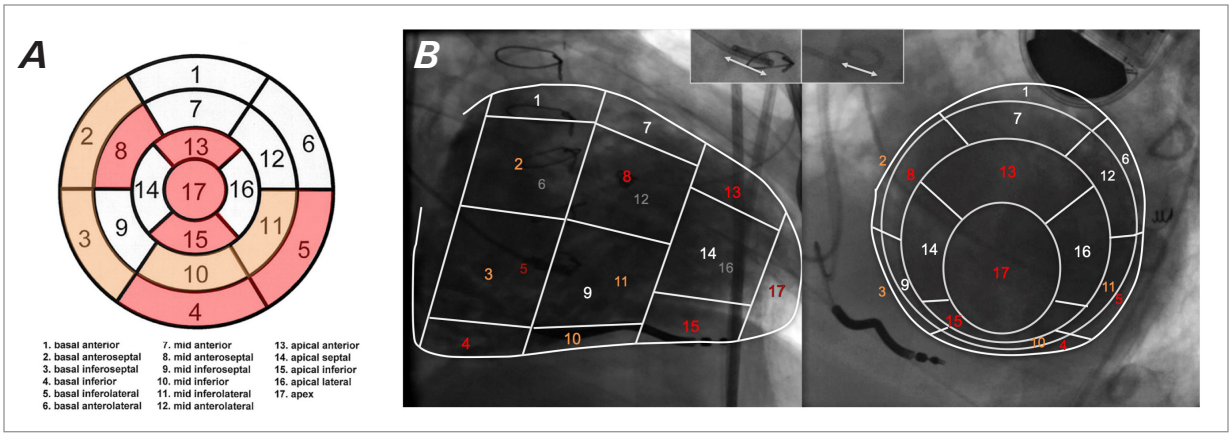

Fig. 2 Target scheme for region selection as implemented in the clinical trial setting. **A**) "Bull's-eye" display, on a circumferential polar plot, of the 17 left ventricular myocardial segments used to determine injection targets. Segments shaded in red denote "no-go" zones; orange shading designates regions to "approach with caution." **B**) Images from biplane left ventriculography with corresponding segment numbers marked from the bull's-eye map. Cardiac landmarks include this patient's right ventricular intracardiac defibrillator lead and epicardial lead over the mid anterolateral segment (segment 12 on the map). The bidirectional arrow in the inserts denotes the diameter of the pigtail catheter in each view.

copy after retrograde insertion of the catheter into the LV while maintaining standard interventional procedural measures. Up to 20 injections of 0.5 mL of cell product were delivered, each approximately 1 cm from adjacent injections. Confirmation of LV landmarks and map position were routinely repeated throughout the procedure.[6,7]

All CHART-1 trial participants demonstrated reduced LV ejection fraction (<35%) and received standard-of-care treatment for heart failure secondary to ischemic heart disease.[4,8,9] Patients were randomized to receive either 600×106 autologous cardiopoietic stem cells[10] administered endomyocardially via the retention-enhanced injection catheter or a sham procedure. Long-term follow-up documented the procedure's overall safety. Although the overall ischemic heart failure population showed a neutral efficacy composite readout, post hoc analysis suggested a sustained benefit by way of reduced risk of death and lower rates of hospitalization for heart failure in subpopulations defined by the degree of LV enlargement (LV end-diastolic volume of 200-370 mL) and tolerable cell dosing (≤19 injections).[5,9,11]

Conclusion

This article presents a prototype system optimized for enhanced endomyocardial stem cell delivery. Compared with conventional end-hole needle devices, the C-Cath$_{EZ}$ platform offers apparent advantages in a clinical setting. Notably, it may limit confined injectate pooling at the needle tip and its reflux, reduce risk of the "jet effect" caused by trauma of the linear flow, and ease dependency on passive distribution or active migration of injected agents. This reduced dependency may be particularly relevant because the complexion of the recipient myocardial tissue and the capacity of cells to attach to or resist detachment from native cells or extracellular matrix are major determinants of transplanted cell survival. By increasing myocardial dispersion along the injection tract, C-Cath$_{EZ}$ may have a significant impact on biologic efficacy.

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