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Letters

RESEARCH CORRESPONDENCE

First-in-Human Use of a Retention-Enhanced Catheter for Endomyocardial Cell Delivery

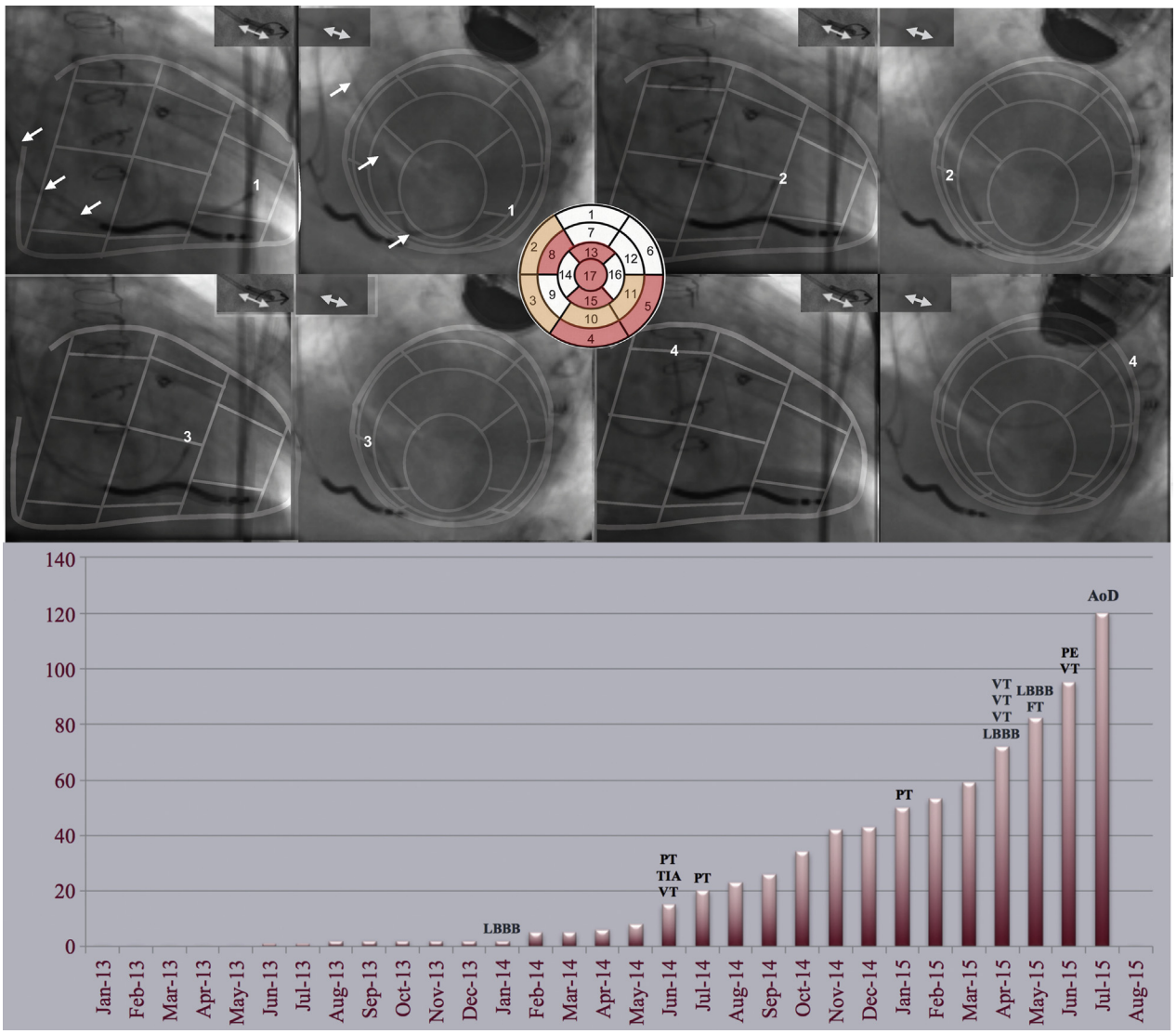
A novel deflectable-tip catheter (C-Cathez, Celyad, Mont-Saint-Guibert, Belgium) featuring a curved needle containing side holes developed to increase the retention of intramyocardial biotherapeutics (1) underwent first-in-human use in the CHART-1 (Congestive Heart Failure Cardiopoietic Regenerative Therapy) trial (2), which assessed autologous cardiopoietic bone marrow–derived mesenchymal stem cells in chronic ischemic heart failure (**Figure 1**). The method involved: 1) the creation of a left ventricular (LV) injection map from pre-procedural transthoracic echocardiography; 2) colocalization of the transthoracic echocardiographic map onto LV diastolic silhouettes from biplane contrast LV angiography taken immediately before injection; 3) retrograde placement of the C-Cathez into the left ventricle; and 4) device positioning for cell administration under real-time fluoroscopy. Confirmation of LV landmarks was routinely repeated throughout the procedure, after each set of 4 or 5 injections and following movements of patient, table, or gantry. Up to 20 injections of 0.5 ml cell product were delivered, each approximately 1 cm from adjacent injections. Unfractionated or low-molecular weight heparin was administered to maintain an activated clotting time in the range of 250 s. Operators were required to undergo comprehensive C-Cathez training before clinical use; experienced proctors were present for a minimum of 3 study cases before independent use. Serious adverse events occurring up to 24 h following the study intervention were reported through CHART-1's continuous safety monitoring program, requiring prompt assessment by the data safety monitoring board and adjudication by the events committee for device or procedure relatedness. Catheter procedure-related events are reported here.

One hundred twenty patients underwent study injections over a 24-month period at 30 centers, 10 having had prior experience in transendocardial injection procedures (4 in the antecedent study to CHART-1 [3]) or ventricular ablation or both. Accrual of successive 30-patient quartiles occurred over 15-, 5-, 3-, and 1-month intervals. The median procedure number per site was 2.5 (range 1 to 14). Fifteen patients experienced catheter procedure-related serious events: sustained ventricular tachyarrhythmia in 5 (4 during C-Cathez navigation or injection and 1 at 18 h post-procedure), pericardial effusion in 4, persistent left bundle branch block in 3 (1 first appearing during left ventriculography), ascending aortic dissection in 1 (with known dilatation of the thoracic aorta, requiring acute surgical repair), transient cerebrovascular event in 1, and femoral artery stenosis in 1. All but the dissection were treatment responsive.

Of the 15 events, 6% (5 of 30), 3% (1 of 30), 20% (6 of 30) and 10% (3 of 30) occurred during successive procedure quartiles at 12 of the 30 clinical centers, 9 of which were without previous transendocardial procedure experience. Eleven of the 15 events occurred during the first 3 procedures at individual sites. Aside from tamponade, ventricular tachycardia, and perhaps left bundle branch block, the distribution of other events was without a clear pattern across quartiles; the incidence rates of ventricular tachycardia and left bundle branch block could not be linked to specific patient or procedural characteristics.

The 4 pericardial effusive events were not evenly spread across quartiles (6.7%, 3.0%, 0.0%, and 3.0% rates, respectively) and demonstrated different characteristics. The first (case 12 of 120) followed a basilar injection and resulted in immediate tamponade; avoidance of basal target areas was implemented. The second and third tamponade cases (cases 20 and 47) occurred 1.5 and 2.5 h after effusion-free post-procedural transthoracic echocardiography. Review of injection maps from all 47 cases indicated that a "clustering" of injections may have occurred in cases 2 and 3, raising the hypothesis that increased cell retention, myocardial "oversaturation," disruption of tissue planes, the development of myocardial hematoma, and delayed emergence within the pericardial space may have occurred. On the basis of this assumption, optimization of spacing

FIGURE 1 **CHART-1 Injections and Patient Accrual**



(Top) Freeze-frame biplane images of injections 1 to 4 in a CHART-1 (Congestive Heart Failure Cardiopoietic Regenerative Therapy) patient. **Arrows** in images of injection 1 identify the shaft of the C-Cathez and **white numbers** the catheter tip. **Inset** depicts transthoracic echocardiography–derived left anterior oblique bull's-eye map of areas eligible **(white)**, ineligible **(red)**, or to be approached with caution **(orange)** for injection. **(Bottom)** Cumulative study interventions and events in CHART-1. Case accrual of C-Cathez injections of C3BS-CQR-1 over time. Events are listed by month of occurrence. AoD = aortic dissection; FT = femoral thrombosis; LBBB = left bundle branch block; PE = pericardial effusion without tamponade; PT = pericardial tamponade; TIA = transient ischemic attack; VT = ventricular tachyarrhythmias requiring treatment.

between adjacent injections was undertaken in the final 73 study procedures, without further tamponade. The fourth effusion was small to moderate and likely a result of device navigation during needle extension.

Comparing clinical outcomes of C-Cathez with those of other transcatheter intramyocardial devices is challenging, as published reports using this technique vary with respect to patient population, disease substrate, biotherapies administered, and injection regimen. The C-Cathez itself may provide advantages in the clinical setting compared with end-hole needle devices by limiting: 1) local pooling at the needle tip; 2) reflux of injectate on needle withdrawal; 3) the potential for trauma from linear flow (the "jet effect"); and 4) dependence on passive

distribution or active migration of injected agents. The last may be the most important, because the nature of the recipient tissue and the capacity of cells to attach to, and resist detachment from, native cells or extracellular matrix are major determinants of transplanted cell survival (4). It is here that the C-Cathez, by increasing myocardial dispersion, may have its greatest impact on biologic efficacy.

The use of the C-Cathez in CHART-1 is the largest and most detailed experience with intramyocardial injection and demonstrates 2 key attributes for adoption into the clinical arena: ease of use and efficiency of biologics retention (5). We have developed a method using common imaging modalities for this novel transendocardial device, thus providing a platform for the administration of biologics in patients with myocardial disease.

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REFERENCES

1. Behfar A, Latere JP, Bartunek J, et al. Optimized delivery system achieves enhanced endomyocardial stem cell retention. Circ Cardiovasc Interv 2013;6:710–8.

2. Bartunek J, Terzic A, Davison BA, et al. Cardiopoietic cell therapy for advanced ischemic heart failure: results at 39 weeks of the prospective, randomized, double blind, sham-controlled CHART-1 clinical trial. Eur Heart J 2017;38:648–60.

3. Bartunek J, Behfar A, Dolatabadi D, et al. Cardiopoietic stem cell therapy in heart failure: the C-CURE (Cardiopoietic Stem Cell Therapy in Heart Failure) multicenter randomized trial with lineage-specified biologics. J Am Coll Cardiol 2013;61:2329–38.

4. Copland IB. Mesenchymal stromal cells for cardiovascular disease. J Cardiovasc Dis Res 2011;2:3–13.

5. Dib N, Menasche P, Bartunek JJ, et al. Recommendations for successful training on methods of delivery of biologics for cardiac regeneration: a report of the International Society for Cardiovascular Translational Research. J Am Coll Cardiol Intv 2010;3:265–75.

RESEARCH CORRESPONDENCE

The COFFEE Trial (COmparison of Fractional Flow Reserve Measurements through 4 FrEnch versus 6 FrEnch Diagnostic Catheter)

Fractional flow reserve (FFR) measurement is a well-established pressure wire-based procedure that is used to assess the functional severity of coronary lesions (1). Various randomized trials have demonstrated that FFR-guided revascularization improves clinical outcomes in patients with ischemic heart diseases (2,3). On the other hand, transradial access (TRA) is widely performed worldwide and has become the main access method. A clinical benefit to TRA, including less vascular complications and improved patient comfort, compared with the transfemoral approach, has been previously revealed (4,5). Therefore, in the TRA era, a less invasive procedure needs to be established. Although 5-F or 6-F catheter-based FFR is routinely performed, the use of much smaller catheters has not been established. Furthermore, the standard approach for measuring FFR throughout the