AFTER an acute myocardial injury, recruitment of stem cells may significantly influence the repair process. Studies have shown that serum stromal–derived factor-1 (SDF-1) levels rise significantly after an acute myocardial infarction, which increases homing of stem cells to the damaged tissue.1 In contrast, in patients with chronic heart failure, local homing signals may be less intense. This difference is especially pronounced in patients with nonischemic dilated cardiomyopathy (DCM), which involves significant downregulation of several homing factors, including SDF-1.2

The importance of homing is especially prominent when considering stem cell therapy in patients with heart failure.3 In a recent study of patients with nonischemic DCM, we demonstrated that the response to intracoronary CD34+ cell therapy is dependent on the degree of myocardial cell retention.4 These findings suggest that the efficacy of intracoronary cell therapy may be limited by the number of cells retained in the myocardium.

Compared with intracoronary delivery, intramyocardial (IM) cell delivery is consistently associated with higher myocardial retention rates in both early and late phases after acute myocardial infarction.5,6 In preclinical models of ischemic heart failure, IM injection of higher doses of bone marrow mononuclear cells was associated with incremental benefit,7 and late cardiac functional recovery was more prominent in patients with dilated cardiomyopathy, transendocardial CD34+ cell transplantation is associated with higher myocardial retention rates and greater improvement in ventricular function, N-terminal pro-brain natriuretic peptide, and exercise capacity compared with intracoronary route.

Conclusions—In patients with dilated cardiomyopathy, transendocardial CD34+ cell transplantation is associated with higher myocardial retention rates and greater improvement in ventricular function, N-terminal pro-brain natriuretic peptide, and exercise capacity compared with intracoronary route.

Key Words: cardiomyopathy, dilated □ heart failure □ stem cells

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cases with higher cell engraftment. In patients with ischemic heart failure, transendocardial cell delivery has been shown to be safe and was associated with enhancement of regional and global left ventricular function. Similarly, direct trans-thoracic IM injection of bone marrow mononuclear cells has been associated with global contractility increment in patients with DCM. At this time, it remains uncertain whether transendocardial stem cell delivery in patients with DCM is associated with greater retention and improvement in ventricular function than intracoronary delivery. To resolve this question, in this study, we sought to determine whether transendocardial stem cell delivery is associated with a greater retention rate and clinical improvement than intracoronary stem cell delivery in patients with DCM. Our second objective was to determine the relationship between retention rate and clinical improvement in patients with DCM.

Methods

Patient Population
This study consists of an open-label randomized study design conducted at the Advanced Heart Failure and Transplantation Center in Ljubljana between January 1, 2011, and January 1, 2012, in collaboration with the Methodist DeBakey Heart Center and Stanford University School of Medicine.

Patient inclusion criteria consisted of the following: age 18 to 65 years, diagnosis of DCM according to European Society of Cardiology position statement, optimal medical management for ≥ 6 months, left ventricular ejection fraction (LVEF) <40%, and New York Heart Association functional class III for ≥ 3 months before referral. Patients with acute multiorgan failure or a history of hematologic neoplasms were not included. Informed consent was obtained from all patients before participation in the study, and the study protocol was approved by the National Medical Ethics Committee. The trial was registered according to the Slovenian Drug Law and with clinicaltrials.gov.

Study Design
All patients received granulocyte colony-stimulating factor therapy (5 µg/kg BID); thereafter, CD34+ cells were collected via apheresis. Patients were randomly allocated in 1:1 ratio to receive either intracoronary (intracoronary group) or transendocardial (transendocardial group) stem cell therapy. Before intracoronary or transendocardial injections, cells were labeled with 99mTc-hexamethylpropyleneamine oxime. Nuclear imaging for quantification of myocardial retention rates of labeled cells was performed 2 and 18 hours after the procedure. Patients were followed for 6 months. The flowchart of study design, together with timeline, is presented in Figure 1.

At the time of enrollment and at 1, 3, and 6 months thereafter, we performed detailed clinical evaluation, echocardiography, and a 6-minute walk test and measured plasma levels of N-terminal pro-brain natriuretic peptide (NT-proBNP).

Echocardiography, 6-Minute Walk Test, and NT-proBNP Measurement
The echocardiogram data were recorded and analyzed at 6 months by an independent echosonographer who was blinded to both the randomization and timing of the recordings. Analysis of left ventricular dimensions and global and segmental function was performed in accordance with American Society of Echocardiography guidelines. All NT-proBNP assays were performed by a central independent laboratory blinded to the clinical data, using a commercially available kit (Roche Diagnostics, Mannheim, Germany).

Peripheral Blood Bone Marrow Cell Mobilization, Collection, and Labeling
Peripheral blood bone marrow cells were mobilized by daily subcutaneous injections of granulocyte colony-stimulating factor (5 µg/kg BID). On the fifth day, a full blood count and peripheral blood CD34+ cell count were performed. Peripheral blood stem cells were then collected

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Figure 1. Flow chart of the study design. After enrollment, all patients underwent bone marrow stimulation, apheresis, and immunomagnetic selection of CD34+ cells. Thereafter, they were randomized in a 1:1 ratio to either intracoronary or transendocardial CD34+ cell delivery. All patients were followed for 6 months.
with the Amicus cell separator (Baxter Healthcare, Chicago, IL), and immunomagnetic positive selection of CD34+ cells was performed with a magnetic cell separator Isolab 300i (Nexell Therapeutics Inc, Irvine, CA). CD34+ cells were labeled with 99mTc-hexamethylpropyleneamine oxime as described previously.4

Intracoronary Delivery

Before cell transplantation, patients underwent myocardial perfusion scintigraphy with 99mTc-sestamibi and nitrate augmentation (Figure 2). Resting myocardial perfusion imaging was performed according to a viability assessment protocol. After resting supine for 10 minutes, 2 puffs (0.4 μg each) of nitroglycerin were administered sublingually. The tracer (99mTc-sestamibi, 600 MBq) was injected after 10 minutes of repeated supine rest. Single-photon emission computed tomographic myocardial perfusion imaging was performed 40 minutes after tracer injection on a dual-head gamma camera (GE Millennium, GE Corporation, Fairfield, CT) using ECG gating (20% energy window =140 keV peak, 64×64 matrix, 36 projections, 20 seconds per projection, 8 bins per heart cycle). Data were reconstructed using filtered back-projection with a Butterworth filter (cutoff frequency 0.29, order 9) without attenuation correction. Tracer uptake in myocardium was quantified using a 20-segment model and normalized to maximum uptake in the heart muscle. Target areas for cell delivery were defined as viable segments of reduced tracer accumulation (tracer uptake <50% of maximum in the myocardium) and contractile dysfunction. Target coronary artery was defined as one of the major coronary arteries (left anterior descending artery, left circumflex artery, or right coronary artery) supplying segments of reduced tracer accumulation on scintigraphy. After full heparinization, a microcatheter (Progreat Microcatheter System, Terumo, Leuven, Belgium) was positioned in the midportion of the target coronary artery, and cells resuspended in saline were injected via the intracoronary route. Each patient received 10 injections (10 mL each; total volume of 100 mL). To avoid trauma of the target vessel, we performed no balloon inflations at any time during the procedure.

Transendocardial Delivery

Electroanatomic mapping was performed using the Biosense NOGA system (Biosense-Webster, Diamond Bar, CA) as described elsewhere.13 The mapping catheter was advanced into the left ventricle, and points were acquired when the catheter tip was stable on the endocardium; this occurred after the documentation of local activation time stability, location stability, loop stability, and cycle length stability. The catheter was removed from the left ventricle when all endocardial regions were represented on the reconstructed map. For each patient, color-coded unipolar voltage and linear shortening maps and their corresponding bull’s-eye maps, consisting of ≥150 sampling points, were created. Segments with high voltage and high linear shortening were defined as normal myocardium. Segments with low voltage and low linear shortening were defined as scarred myocardium. Segments with high voltage and low linear shortening were defined as hibernating myocardium and represent target areas for transendocardial cell delivery.

Figure 2. Tomographic images of myocardial perfusion before intracoronary cell injection and electroanatomic map of left ventricle with sites of transendocardial stem cell injections. **Top**, Representative example of tomographic images of myocardial perfusion scintigraphy with 99mTc-sestamibi and nitrate augmentation obtained before stem cell transplantation (A, short-axis view; B, vertical long-axis view). Radiotracer uptake in myocardium was quantified using a 20-segment model and normalized to maximum uptake in the heart muscle. Target areas for cell delivery were defined as viable segments of reduced tracer accumulation and contractile dysfunction. Target artery for intracoronary cell delivery was defined as one of the major coronary arteries (left anterior descending artery [LAD], left circumflex artery, or right coronary artery) supplying segments of reduced tracer accumulation on scintigraphy. In this case, because decreased perfusion is seen in the anterior of the left ventricle (arrows) on perfusion images, LAD was selected as the target coronary artery for cell delivery. **Bottom**, Representative example of 3-dimensional quantitative electroanatomic polar maps showing unipolar voltage (C) and linear local shortening (LLS, right, D). Segments with predominance of high unipolar voltage and high LLS (violet, blue, or green color on both panels) are defined as normal myocardium. Segments with predominance of low unipolar voltage and low LLS (red and yellow color on both panels) are defined as scarred myocardium. Segments with predominance of high unipolar voltage (violet, blue, or green on left) and low LLS (red or yellow on right) are defined as hibernating myocardium and represent target areas for transendocardial cell delivery. Brown dots represent the sites of transendocardial cell injections in the lateral wall.
points, were generated. The target area for cell delivery was defined as the myocardial segments with unipolar voltage potentials ≥ 9 mV, bipolar amplitudes >1.9 mV, and linear shortening <6%.

Intramyocardial delivery of cell suspension was performed with the MyoStar (BiosenseWebster, Diamond Bar, CA) injection catheter. After acquiring a stable mapping point with the tip of the catheter perpendicular to the endocardial surface, the needle was advanced into the myocardium, and IM injections were performed. Each patient received 20 injections (0.3 mL each; total volume of 6 mL). A representative electromechanical map displaying the sites of IM injections is presented in Figure 2. For segmental analysis of left ventricular function, the 9-segment model of electroanatomic mapping was converted into the standard 16-segment model.12

Assessment of Myocardial Retention
Two hours and 18 hours after delivery of the cells, cell imaging was undertaken to assess myocardial engraftment and distribution. Planar anterior and posterior projections and tomographic imaging of cardiac region were performed on a dual-head gamma camera (GE Millennium MG Dual Head Nuclear Gamma Camera, Fairfield, CT).

Follow-Up and End Points
Patients were followed for 6 months. The primary end point was the change in LVEF. Secondary end points included changes in left ventricular segmental function, left ventricular end-diastolic dimension, left ventricular end-systolic volume, exercise capacity, and NT-proBNP levels.

Statistical Analysis
Based on our previous findings on intracoronary injection in nonischemic DCM4 and the findings of studies investigating the effects of IM stem cell therapy in ischemic heart failure,9 the sample size calculation for this study was based on the 90% probability that the study will detect a treatment difference with a 5% 2-sided significance level, if the true difference in LVEF between the intracoronary group and the transendocardial group is 3.5% (assuming an SD of 6.5%). Continuous variables were expressed as mean±SD. Differences between the groups were analyzed by means of unpaired t test. Relationship of LVEF changes and myocardial homing was evaluated by Pearson correlation coefficient. Comparisons of categorical variables were made using a χ² test. All comparisons were performed on an intention-to-treat basis. A value of P<0.05 was considered significant.

Results

Patient Characteristics
Of the 40 patients enrolled, 20 received intracoronary and 20 received transendocardial stem cell injections. At baseline, the 2 groups did not differ with regard to age, sex, LVEF, left ventricular end-diastolic dimension, plasma sodium, serum creatinine, NT-proBNP, or medical/device management (Table 1).

Stem Cell Delivery and Retention
Target myocardial segments were defined according to American Society of Echocardiography guidelines,12 and their distribution did not differ between the groups (Table 2). The number of mobilized CD34⁺ cells used for injection was comparable (103±27×10⁶ in the intracoronary group versus 105±31×10⁶ in the transendocardial group, P=0.62). Viability

<table>
<thead>
<tr>
<th>Table 1. Baseline Patient Characteristics</th>
<th>All (n=40)</th>
<th>Intracoronary Delivery (n=20)</th>
<th>Transendocardial Delivery (n=20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55±10</td>
<td>54±8</td>
<td>56±7</td>
<td>0.72</td>
</tr>
<tr>
<td>Male</td>
<td>34 (85)</td>
<td>18 (90)</td>
<td>16 (80)</td>
<td>0.38</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>26.4±4.3</td>
<td>27.3±5.5</td>
<td>25.4±5.1</td>
<td>0.32</td>
</tr>
<tr>
<td>LVDD, cm</td>
<td>6.9±0.9</td>
<td>7.0±0.8</td>
<td>6.9±0.7</td>
<td>0.75</td>
</tr>
<tr>
<td>TAPSE, cm</td>
<td>1.37±0.44</td>
<td>1.40±0.41</td>
<td>1.33±0.49</td>
<td>0.71</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.45±0.62</td>
<td>1.42±0.42</td>
<td>1.49±0.47</td>
<td>0.40</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>136±8</td>
<td>137±6</td>
<td>136±9</td>
<td>0.62</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td>2450±1853</td>
<td>2378±1781</td>
<td>2522±1945</td>
<td>0.66</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>38 (95)</td>
<td>18 (90)</td>
<td>20 (100)</td>
<td>0.47</td>
</tr>
<tr>
<td>Digoxin</td>
<td>6 (15)</td>
<td>3 (15)</td>
<td>3 (15)</td>
<td>1.00</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>32 (80)</td>
<td>17 (85)</td>
<td>15 (75)</td>
<td>0.42</td>
</tr>
<tr>
<td>RAAS inhibitors</td>
<td>40 (100)</td>
<td>20 (100)</td>
<td>20 (100)</td>
<td>1.00</td>
</tr>
<tr>
<td>β-blockers</td>
<td>33 (83)</td>
<td>17 (85)</td>
<td>16 (80)</td>
<td>0.67</td>
</tr>
<tr>
<td>CRT</td>
<td>18 (45)</td>
<td>10 (50)</td>
<td>8 (40)</td>
<td>0.52</td>
</tr>
<tr>
<td>ICD</td>
<td>34 (85)</td>
<td>15 (75)</td>
<td>19 (95)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

All values, except for P values, represent either mean±SD or number of patients (%). CRT indicates cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; LVDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; RAAS, renin-angiotensin-aldosterone; and TAPSE, tricuspid annular plane systolic excursion.

<table>
<thead>
<tr>
<th>Table 2. Distribution of Target Myocardial Segments in Patients Receiving Intracoronary and Transendocardial CD34⁺ Cell Therapy</th>
<th>All (n=40)</th>
<th>Intracoronary Delivery (n=20)</th>
<th>Transendocardial Delivery (n=20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD territory</td>
<td>24 (60)</td>
<td>13 (65)</td>
<td>11 (55)</td>
<td>0.52</td>
</tr>
<tr>
<td>LCX territory</td>
<td>9 (23)</td>
<td>4 (20)</td>
<td>5 (25)</td>
<td></td>
</tr>
<tr>
<td>RCA territory</td>
<td>7 (17)</td>
<td>3 (15)</td>
<td>4 (20)</td>
<td></td>
</tr>
</tbody>
</table>

All values, except for P values, represent number of patients (%). LAD indicates left anterior descending artery; LCX, left circumflex artery; and RCA, right coronary artery.
of cells in the intracoronary group and the transendocardial group using methylene blue was 91.3% and 90.4%, respectively, which did not differ significantly \((P=0.4)\). Average early cell retention 2 hours after injection was 6.1±1.7% in the intracoronary group versus 21.3±5.2% in the transendocardial group \((P<0.01)\). Similarly, at delayed imaging (18 hours after injection), myocardial retention rates were significantly higher in the transendocardial group (19.2±4.8%) than in the intracoronary group (4.4±1.2%, \(P<0.01\)). Representative examples of myocardial cell retention in the intracoronary and transendocardial groups are shown in Figure 3.

**Clinical Outcome**

Time-related changes in LVEF, wall motion score index, left ventricular end-diastolic dimension, left ventricular end-systolic volume, NT-proBNP, and 6-minute walk test distance are presented in Figures 4 and 5. LVEF increased in both groups; however, the change at 6 months was significantly higher in the transendocardial group than in the intracoronary group. Furthermore, we observed a different course of improvement in LVEF. The intracoronary group principally improved their LVEF within the first month, whereas in the transendocardial group the main improvement occurred between months 1 and 3. A similar trend was observed when analyzing segmental wall motion. Left ventricular end-diastolic dimension did not change significantly in any of the groups, but we did find a trend toward a decrease in left ventricular end-systolic volume in both groups. NT-proBNP levels declined in both groups, more so in the transendocardial group than in the intracoronary group. Similarly, the 6-minute walk test distance increased more in the transendocardial group than in the intracoronary group.

**Cell Retention and Left Ventricular Function**

Relationship between change in LVEF at 6 months and myocardial cell engraftment is presented in Figure 6. LVEF improvement correlated significantly with the percent of cells retained in the myocardium 18 hours after intracoronary or transendocardial delivery \((r=0.53, P<0.001)\).

**Discussion**

This is the first study so far that directly compared clinical effects of intracoronary and transendocardial delivery of CD34+ cells in patients with nonischemic DCM. Compared with the intracoronary route, the transendocardial delivery was associated with greater myocardial cell retention and better clinical response. Confirming our previous findings, the results of the
present study show that CD34+ cell therapy improved LVEF and exercise capacity in patients with nonischemic DCM. Furthermore, the effects on left ventricular systolic function were found to directly correlate with the number of cells retained in the myocardium. We believe that the difference in retention rates partially explains the differences between intracoronary and transendocardial stem cell delivery.

Currently, the effects of CD34+ stem cells are thought to result from the direct incorporation of injected cells into the newly developing vasculature or the production and secretion of angiogenic cytokines that support an ischemia-induced angiogenic response. Consistent with the findings of preclinical studies, we found significant heterogeneity of myocardial viability and contractile dysfunction in patients with DCM. In our study, we chose the viable regions with the greatest perfusion defect or greatest decrease in linear shortening to target the region of interest, theoretically maximizing the response to stem cell therapy. In patients with ischemic heart disease, hibernating myocardium has been defined as a flow-metabolism mismatch in the presence of contractile dysfunction and is thought to represent the adaptation of the myocardial tissue to chronic or repetitive ischemia. Similarly, regions with flow abnormalities, increased glucose metabolism, and decreased aerobic metabolism have also been found in patients with nonischemic DCM. As the findings of electroanatomic mapping have been shown to closely correlate with myocardial perfusion, the presence of areas of myocardial hibernation (viable but dysfunctional areas) in patients with DCM from our study further supports the hypothesis that impaired vasculogenesis and angiogenesis may at least partly be responsible for disease development and progression in nonischemic DCM.

Improving myocardial retention in patients with DCM may be particularly important because homing mechanisms may not be optimal. Although there are multiple factors regulating myocardial homing or retention of injected CD34+ cells, SDF-1/chemokine receptor type 4 (CXCR4) axis is currently thought to be the most important homing mechanism for both acute myocardial infarction and ischemic cardiomyopathy. Myocardial homing factors, including SDF-1, were found to be upregulated in patients with ischemic heart failure but not in patients with nonischemic DCM. These data suggest that although the SDF-1/CXCR4 axis might represent an important mechanism of stem cell homing in patients with nonischemic DCM, its efficiency is significantly reduced by a lack of adequate upregulation of important myocardial homing factors. Combined with the evidence of hibernating myocardium on electroanatomic mapping, these findings suggest that the impaired perfusion in nonischemic DCM can be improved by administering CD34+ cells; additional direct validation will need to be performed to confirm this hypothesis. IM bone marrow cell injection has been shown to increase the SDF-1 gradient from bone marrow to peripheral blood and from peripheral blood to the myocardium. This may result in the reconstitution of the impaired SDF-1/CXCR4 axis in nonischemic DCM, thereby recruiting more stem cells for cardiac repair. Further studies are needed in nonischemic DCM to understand the precise mechanisms of functional improvement.

In the present study, we found cell retention rates that were higher than those reported in previous studies. There are multiple potential reasons for these differences, which may be related to the high numbers of stem cells collected by apheresis and immune selection methods, cell delivery techniques, and patient selection. In contrast to other studies using intracoronary cell therapy, we did not perform any balloon inflations during the procedure to avoid vessel trauma, which may lower myocardial retention in the target segments.
Furthermore, by applying slow intracoronary infusion only in the arteries supplying the predefined target myocardial segments, we maximized the cell numbers and prolonged their exposure time. By using electroanatomic mapping and transendocardial delivery, we were able to increase myocardial cell retention ≈5-fold, which is consistent with preclinical studies that consistently display significantly higher myocardial retention rates with the IM delivery route. Although this technique has been widely used in studying ischemic heart disease, this is the first clinical application of this technology in nonischemic DCM.

In the present study, we found transendocardial cell delivery to be superior to intracoronary route, but the magnitude of change in clinical parameters was somewhat lower than expected based on the substantially improved myocardial retention rates. Similarly, in a study investigating the effects of transendocardial CD34+ cell therapy in patients with refractory angina, the increase in cell dose was not associated with a parallel improvement in clinical outcome. Although the reasons for these discrepant findings remain undefined, they suggest that factors other than high myocardial cell retention (eg, mode of delivery, inflammatory response, scar quantity, and distribution) may also be important in defining the clinical response to CD34+ cell therapy.

The time course of changes in clinical parameters in our study was also different in the intracoronary versus transendocardial group. In the former, most of the clinical benefit occurred within the first month, whereas the latter group displayed most of the changes later (between months 1 and 3). This is consistent with the findings of preclinical studies, which found IM-injected CD34+ cells to persist in the heart ≤1 year after injection. Thus, transendocardial delivery may provide more sustained effects of cell therapy for nonischemic DCM patients.

Study Limitations

The results of our study are subject to several limitations. For instance, our patient population included patients with nonischemic DCM, but no biopsies were performed to exclude secondary cardiomyopathies. However, careful clinical history and coronary angiogram were obtained in all patients. Our sample size was relatively small (n=20 in each arm), but the groups were well matched at baseline. Consistent with several previous studies, we found no effect of radionuclide labeling on cell viability as assessed by methylene blue staining, but we did not measure cell proliferation and migration parameters to verify that the radioisotopes had no effect on cells. Although granulocyte colony-stimulating factor may independently affect left ventricular function, our previous experience in patients with DCM suggests that the incidence of such effect is low (<2% of patients). To further minimize its potential impact in our study, the granulocyte colony-stimulating factor stimulation protocol was standardized and performed in all patients before randomization. Our study protocol did not allow for direct evaluation of cell retention at the time of functional assessments; nevertheless, we were still able to demonstrate an indirect relationship between early cell retention and late response to cell therapy. Finally, we recognize that patients with DCM are a heterogeneous patient population, and dynamic changes in ventricular function may be multifactorial.

Conclusions

In patients with nonischemic DCM, transendocardial CD34+ cell transplantation is associated with higher myocardial retention rates and better improvement in ventricular function, NT-proBNP levels, and exercise capacity compared with the intracoronary route. Therefore, transendocardial delivery may represent a preferred method of stem cell transplantation in this patient cohort. Future studies investigating other factors that influence stem cell retention are needed.

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Disclosures

None.

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Comparison of Transendocardial and Intracoronary CD34+ Cell Transplantation in Patients With Nonischemic Dilated Cardiomyopathy
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