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Effect of Aging on Human Mesenchymal Stem Cell Therapy in Ischemic Cardiomyopathy Patients

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ABSTRACT

BACKGROUND The role of patient age in the efficacy of mesenchymal stem cell (MSC) therapy in ischemic cardiomyopathy (ICM) is controversial.

OBJECTIVES This study sought to determine whether the therapeutic effect of culture-expanded MSCs persists, even in older subjects.

METHODS Patients with ICM who received MSCs via transendocardial stem cell injection (TESI) as part of the TAC-HFT (Transendocardial Autologous Cells in Ischemic Heart Failure) (n = 19) and POSEIDON (Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis) (n = 30) clinical trials were divided into 2 age groups: younger than 60 and 60 years of age and older. Functional capacity was measured by 6-min walk distance (6MWD) and quality of life using the Minnesota Living With Heart Failure Questionnaire (MLHFQ) score, measured at baseline, 6 months, and 1 year post-TESI. Various cardiac imaging parameters, including absolute scar size, were compared at baseline and 1 year post-TESI.

RESULTS The mean 6MWD was similar at baseline and increased at 1 year post-TESI in both groups: 48.5 ± 14.6 m ($p = 0.001$) for the younger and 35.9 ± 18.3 m ($p = 0.038$) for the older participants (p = NS between groups). The older group exhibited a significant reduction in MLHFQ score (−7.04 ± 3.54; $p = 0.022$), whereas the younger than 60 age group had a borderline significant reduction (−11.22 ± 5.24; $p = 0.058$) from baseline (p = NS between groups). Although there were significant reductions in absolute scar size from baseline to 1 year post-TESI, the effect did not differ by age.

CONCLUSIONS MSC therapy with TESI in ICM patients improves 6MWD and MLHFQ score and reduces myocardial infarction size. Importantly, older individuals did not have an impaired response to MSC therapy. (J Am Coll Cardiol 2015;65:125–32) © 2015 by the American College of Cardiology Foundation.

Based on pre-clinical studies and clinical trials, bone marrow-derived mesenchymal stem cells (MSCs) (1-3) have been shown to mitigate left ventricular (LV) remodeling associated with acute myocardial infarction (MI) (2,4,5) and chronic (1,6-8) ischemic cardiomyopathy (ICM). Although the data are encouraging, evidence suggesting a deleterious effect of aging on autologous MSC transplantation has been highly controversial (9). Telomere length and shortening play crucial roles in the cellular molecular aging process (10,11), and there is a strong correlation between human mesenchymal stem cell (hMSC) proliferative capacity and telomere length in culture and with donor age (12). In addition to their diminished proliferative potential, aging hMSCs tend to have a compromised homing capability

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ABBREVIATIONS AND ACRONYMS

6MWD = 6-min walk distance

CI = confidence interval

EDV = end-diastolic volume

EF = ejection fraction

ESV = end-systolic volume

hMSC = human mesenchymal stem cell

ICM = ischemic cardiomyopathy

LV = left ventricular

MI = myocardial infarction

MLHFQ = Minnesota Living With Heart Failure Questionnaire

MSC = mesenchymal stem cell

TESI = transendocardial stem cell injection

(13–16). Accordingly, these age-related impairments suggest that MSC therapy might produce a reduced effect when the cells are derived from older individuals.

SEE PAGE 148

Although some proponents believe that advanced stem cell donor age results in diminished function (17–21), other studies raise a clinically relevant issue as to whether *recipient* age is a crucial factor limiting the response to cell therapy (22–24). This has led to the notion that MSC therapy outcome depends not only on stem cell age, and thus function, but also recipient age and comorbidities (9,22). Indeed, reduced responsiveness as a function of donor age would be a major limitation to the emerging development of cell therapy for heart disease, given the increasing incidence and morbidity of heart disease with age (25). Here, we tested the hypothesis that improvements in functional capacity, quality of life, and reverse remodeling by transendocardial injection of hMSCs in patients with ICM is actually preserved with recipient age. Our data here derive from the phase I/II randomized trials of TAC-HFT (Transendocardial Autologous Cells in Ischemic Heart Failure) (26) and POSEIDON (Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis) (27) trials.

TABLE 1 Baseline Characteristics

	Age Group		
	<60 yrs (n = 23)	≥60 yrs (n = 26)	p Value
Age at transplantation, yrs	51.95 ± 7.33	68.86 ± 4.51	<0.0001
Time from MI to therapy, yrs	6.26 ± 6.42	15.43 ± 9.23	0.0002
Sex			1.000
Male	21 (42.9)	23 (46.9)	
Female	2 (4.1)	3 (6.1)	
Race			0.1547
White	12 (24.5)	19 (38.8)	
European	0 (0.0)	1 (2.0)	
White North American	3 (6.1)	1 (2.0)	
Western European	0 (0.0)	1 (2.0)	
Black	2 (4.1)	0 (0.0)	
Indian/South Asian	0 (0.0)	1 (2.0)	
Filipino (Pilipino)	1 (2.0)	0 (0.0)	
Native American	0 (0.0)	1 (2.0)	
White Caribbean	5 (10.2)	2 (4.1)	
Ethnicity			0.0629
Hispanic or Latino	9 (18.4)	4 (8.2)	
Not Hispanic or Latino	14 (28.6)	20 (40.8)	
Unknown	0 (0.0)	2 (4.1)	
6MWD	418.30 ± 71.57	372.12 ± 93.01	0.0561
MLHFQ total score	42.33 ± 28.84	31.58 ± 27.81	0.2013
Scar size as absolute value	26.93 ± 15.35	21.47 ± 13.29	0.2080
Scar size as % of LV mass	22.09 ± 13.55	11.79 ± 6.06	0.0041
EF	31.96 ± 6.22	29.49 ± 12.65	0.3945
EDV	289.36 ± 81.65	274.40 ± 86.66	0.5525
ESV	199.50 ± 68.53	199.29 ± 86.15	0.9930
SI	0.50 ± 0.07	0.47 ± 0.11	0.3077

Values are mean ± SD or n (%).

6MWD = 6-min walk distance; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; LV = left ventricular; MI = myocardial infarction; MLHFQ = Minnesota Living With Heart Failure Questionnaire.

METHODS

Data from the TAC-HFT and POSEIDON trials were collected in a similar fashion in a central electronic data system. All ICM patients who received hMSCs from these trials were pooled together and dichotomized into 2 age groups, younger than 60 years of age and 60 years of age and older. The associations between age and both clinical and imaging parameters were assessed. Values of $p < 0.05$ were considered significant. Comprehensive statistical methods can be found in the Online Appendix.

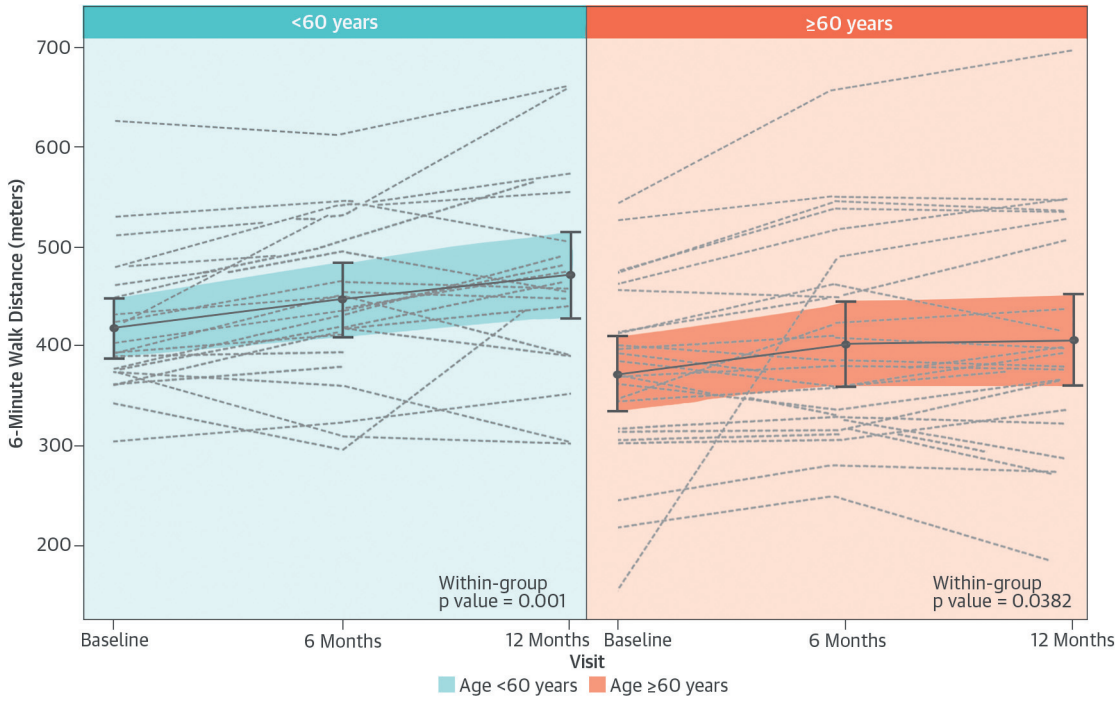
RESULTS

A total of 49 patients who received hMSCs from both trials are included in this analysis. Thirty patients received hMSCs in the POSEIDON trial, of whom 11 patients (36.7%) were younger than 60 years of age and 19 patients (63.3%) were 60 years of age and older. In the TAC-HFT trial, a total of 19 patients received hMSCs, with 12 (63.2%) younger than 60 years of age and 7 patients (36.8%) were 60 years of age and older. The average age at transplantation was 51.95 ± 7.33 years (range: 32.48 to 59.91 years) in the younger than 60 years age group and 68.86 ± 4.51 years (range: 62.84 to 79.01 years) in the older group. The mean time from MI to cell therapy was 6.26 ± 6.42 years for younger patients and 15.43 ± 9.23 years for the older group ($p = 0.0002$).

Baseline characteristics are shown and compared between age groups in Table 1. The majority of the cohort was male (89.8%). A borderline statistically significant difference was observed between age groups for the baseline 6MWD test ($p = 0.0561$). Scar size as a percentage of LV mass was significantly different between age groups at baseline ($p = 0.0041$). No other statistically significant differences were observed for demographic characteristics, Minnesota Living with Heart Failure Questionnaire (MLHFQ), or other cardiac imaging parameters.

There was a statistical trend toward reduced functional capacity at baseline in the older age

CENTRAL ILLUSTRATION **Patient Functional Capacity: 6-Min Walk Distance**



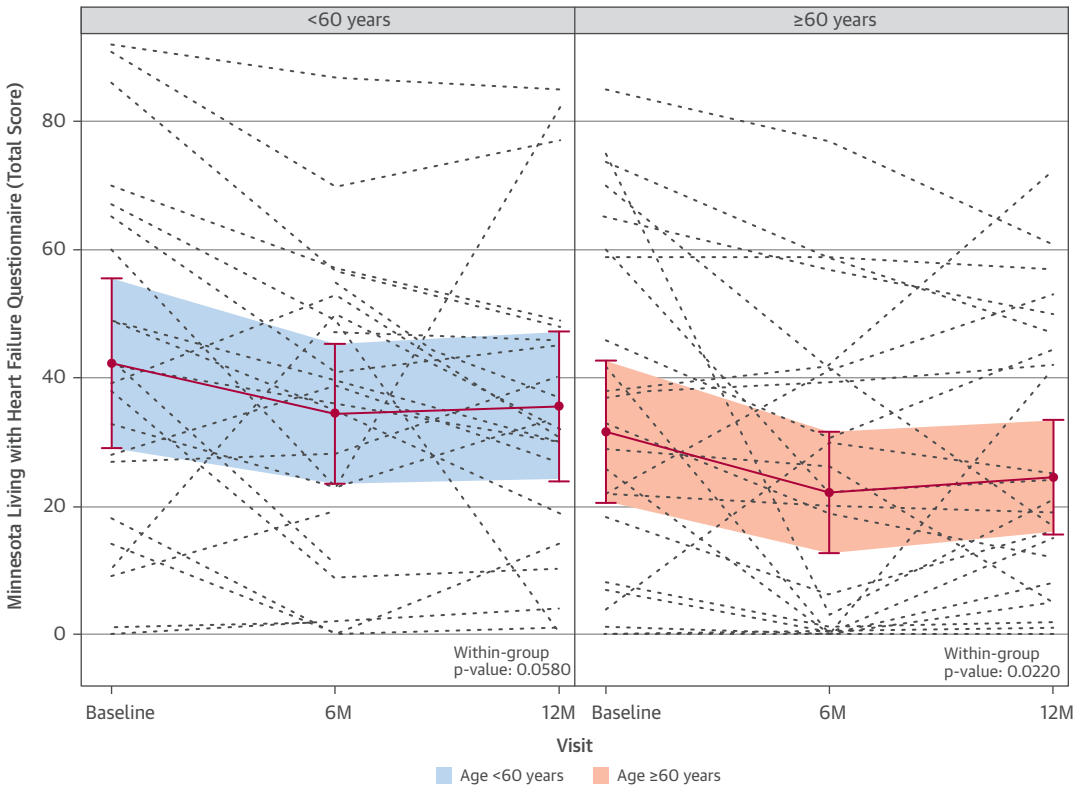
Golpanian, S. et al. J Am Coll Cardiol. 2015; 65(2):125–32.

This graphic representation shows the estimated mean 6-min walk distance values and individual patient values in each age group at each time point, using a repeated-measures model. Both age groups increased similarly until 6 months post-TESI. Although the older age group plateaus by 1 year post-TESI, average distances between age groups do not differ significantly ($p = 0.954$ and $p = 0.288$ at 6 months and 1 year post-TESI, respectively; between-group comparison). TESI = transendocardial stem cell injection.

group, with 6MWD at baseline (418.30 ± 14.92 m vs. 372.12 ± 18.24 m, <60 years vs. ≥60 years, respectively; $p = 0.056$). A repeated-measures model was used to estimate 6MWD at 6 months and 1 year after transendocardial stem cell injection (TESI), which is shown in the **Central Illustration**. The 6MWD increased significantly over time in both the younger and older age groups ($p = 0.001$ and $p = 0.038$, respectively). A repeated-measures model adjusting for baseline 6MWD showed no significant difference in 6MWD between age groups across time ($p = 0.5621$). Using the estimates from the model, we tested whether there were differences between age groups at each of the follow-up time points. The estimated difference at 6 months post-TESI was −1.01 (95% confidence interval [CI]: −35.51 to 33.49; $p = 0.9538$) and at 1 year 18.61 (95% CI: 15.95 to 53.17; $p = 0.2882$).

Quality of life measured by the MLHFQ was compared between age groups. A repeated-measures model was used to estimate MLHFQ total score at 6 months and 1 year post-TESI, which is displayed in **Figure 1**. Patients younger than 60 years of age showed an improvement in MLHFQ total score over time, although of only borderline significance ($p = 0.0580$), whereas those 60 years of age and older exhibited a more significant improvement in MLHFQ total score over time ($p = 0.0220$). A repeated-measures model adjusting for baseline MLHFQ total score showed no significant difference in total score between age groups over time ($p = 0.5859$). Estimated differences between groups at 6 months and 1 year post-TESI were not significant (2.74; 95% CI: −5.74 to 11.23; $p = 0.5237$ and −0.72; 95% CI: −9.51 to 8.07; $p = 0.8711$, respectively). When 6MWD and MLHFQ were analyzed using the repeated-measures model using age as a continuous covariate, neither outcome demonstrated a significant change with increase in age ($p = 0.137$ and $p = 0.535$, respectively).

FIGURE 1 Patient Quality of Life: Minnesota Living With Heart Failure Questionnaire



In this graphic representation of the estimated mean Minnesota Living With Heart Failure Questionnaire, the total score values and individual patient values in each age group at each time point are depicted, using a repeated-measures model. The total scores of both age groups improved in a parallel fashion at 6 months post-TESI. Both groups plateaued by 1 year post-TESI with similar mean total scores on between-group comparison ($p = 0.524$ and $p = 0.871$ at 6 months and 1 year post-TESI, respectively; between-group comparison). TESI = transendocardial stem cell injection.

Next we examined the impact of age on reduction in MI scar size. Both age groups had a similar absolute scar size at baseline. MI size was 26.93 ± 15.35 g in the younger than 60 years of age group and 21.47 ± 13.29 g in the 60 years of age and older group ($p = 0.208$). When testing within-group changes from baseline to 1 year post-TESI, patients younger than 60 years of and 60 years of age and older, both had a significant decrease in absolute scar size ($p < 0.0001$ and $p < 0.0001$, respectively). Furthermore, this percentage of change over time was not significantly different between groups (−33.44 ± 5.41% in the younger vs. −32.89 ± 5.25% in the older age group; $p = 0.945$) (Figures 2A and 3). Scar size as a percentage of LV mass was significantly higher at baseline in the younger group (22.09 ± 13.55 g) compared with older patients (11.79 ± 6.06 g; $p = 0.004$). However, at 1 year post-TESI, the percentage of change from baseline was significant within both age groups ($p = 0.0013$ in the younger age group and $p < 0.0001$ in the older age group). There was no significant difference in scar size as a percentage of LV mass when comparing percentage of change from baseline to 1 year post-TESI between age groups ($p = 0.197$) (Figure 2B).

Cardiac computed tomography- or cardiac magnetic resonance imaging-measured end-diastolic volume (EDV) and sphericity index were similar between age groups at baseline ($p = 0.553$ and $p = 0.508$, respectively). At 1 year post-TESI, within-group changes in EDV ($p = 0.024$) and sphericity index ($p < 0.0001$) significantly decreased in the 60 years of age and older group, but no significant change was observed in the younger group. Neither EDV nor sphericity index, as a percentage of change from baseline, differed between age groups at 1 year post-TESI ($p = 0.434$ and $p = 0.077$, respectively) (Figures 3C and 3D). Although the mean ejection

fraction (EF) and end-systolic volume (ESV) between groups were not different at baseline ($p = 0.395$ and $p = 0.993$, respectively) or at 1 year post-TESI ($p = 0.143$ and $p = 0.417$, respectively), there was a borderline significant decrease over time in ESV within the older age group ($p = 0.054$), that was not replicated in the younger group. There was no significant increase in EF in either age group. Linear regression analyses, using age as a continuous variable, did not indicate any significant association between cardiac structure or function and age (**Table 2**).

DISCUSSION

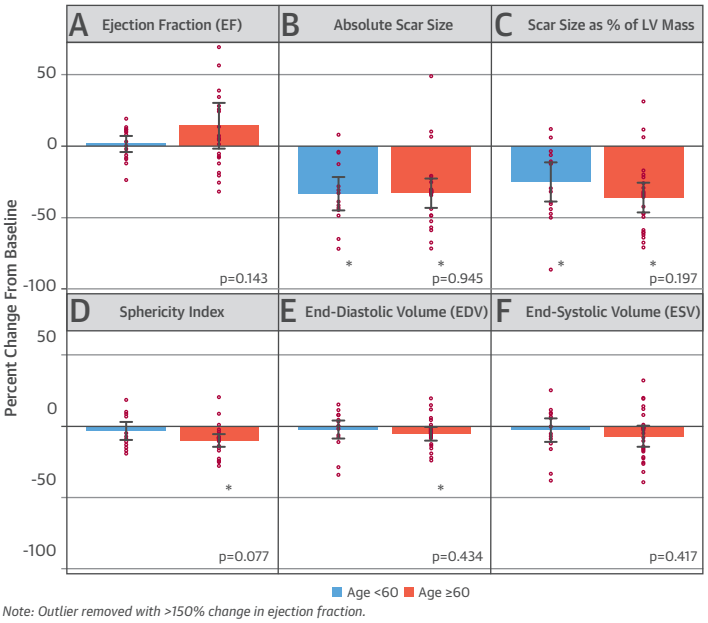
The major new finding of this study shows that therapeutic responses to culture-expanded MSCs are not impaired in subjects of older age. This is particularly important to the emerging field of cell therapy for chronic heart failure due to ICM, a disorder that increases dramatically in incidence with age (28). If cell therapy responses were impaired with age, this would affect patients at greatest risk. Our findings suggest that culture expansion of MSCs overcomes any limitation that endogenous cells might have, and the age of the host is not a limiting factor. These data support developing this strategy for individuals of advanced age, and, thus, they have major public health implications.

Here we analyzed efficacy outcomes from the TAC-HFT (26) and POSEIDON (27) trials to test whether older patients with chronic ICM receiving transendocardial MSC therapy have impaired outcomes relative to young individuals. Notably, improvements in functional capacity were evident at 6 months after injection and persisted to 1 year after TESI to similar degrees in both age groups. To date, although several studies have examined whether donor cell age and function influence responses to cell therapy (17,19,20), no study has tested the hypothesis that recipient age diminishes the efficacy of MSC transplantation. Moreover, although previous studies examining aging and stem cell potency have tested bone marrow mononuclear cells (29–31) and peripheral blood progenitor cells (32), this relationship in culture-expanded MSCs has not previously been explored.

The 6MWD test has been widely used to assess functional capacity in patients with advanced heart failure (33) and is an independent predictor of all-cause mortality (34). We found a significant improvement in 6MWD in both age groups (**Central Illustration**), a result that parallels the overall results of the TAC-HFT and POSEIDON trials. More importantly, the change from baseline at both 6 months and 1 year after TESI did not differ significantly between age groups. Such an improvement in functional capacity highlights the test's prognostic value (35) and strongly suggests that older cell recipients functionally recover just as well as younger patients.

Findings from the TAC-HFT and POSEIDON trials suggest that MSCs reduce infarct size over time. We found a similar significant decrease in absolute scar size irrespective of age groups at 1 year post-TESI (**Figures 2 and 3**). These results corroborate findings from the POSEIDON trial in which both autologous and allogeneic MSCs reduced infarct size over time. It is known that MSCs secrete antifibrotic matrix metalloproteinases (36) via paracrine signaling. Although the reason remains mechanistically unclear, our study demonstrates that aging in stem cell recipients does not appear to influence the antifibrotic effects of MSC therapy. Interestingly, scar size as a percentage of LV mass in the younger age group was almost twice

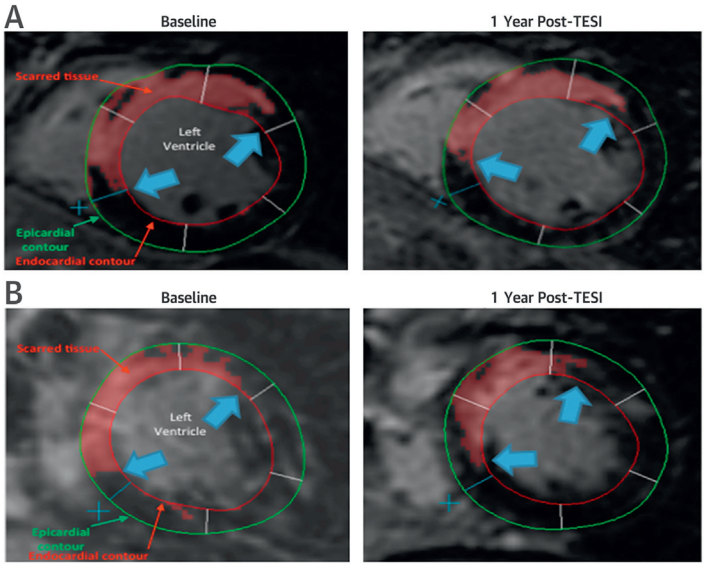
FIGURE 2 Changes in Cardiac Structure and Function 1 Year Post-Mesenchymal Stem Cell Injection



Note: Outlier removed with >150% change in ejection fraction.

(A) Neither age group demonstrates significant improvement in ejection fraction. **(B)** Both younger and older patients show a significant decrease in absolute scar size, with no difference at 1 year post-TESI. **(C)** Scar size as a percentage of LV mass decreases in both age groups and do not differ at 1 year. **(D, E)** Sphericity index and end-diastolic volume significantly improve only in the older age group; however, there are no between-group changes 1 year post-TESI. **(F)** The older age group shows a trend in decreased end-systolic volume; neither end-systolic volume or ejection fraction were significantly different between groups at 1 year post-TESI. *$p < 0.05$ within-group repeated-measures analysis of variance. LV = left ventricular; TESI = transendocardial stem cell injection.

FIGURE 3 Impact of TESI on Scar Reduction



(A) Short-axis views of the mid-ventricular area of a younger patient's heart show delayed enhancement delineated at the anterior and septal walls. After mesenchymal stem cell injection, the scar size in a patient younger than 60 years of age decreased from 30.9 g at baseline to 21.2 g at 1 year with a −31.4% reduction. **(B)** Short-axis views of the mid-ventricular area of the heart of a patient 60 years of age and older, with delayed enhancement shown at the anterior and septal walls. Delayed tissue enhancement corresponds to scarred tissue and is depicted brighter than the nonscarred tissue (automatically detected and delineated in **red** using the full width at half-maximum technique). **Red, green, and white lines** demarcating the endocardial and epicardial contours and borders of the segments, respectively, were drawn manually. The extent of the scar is represented by **blue arrows**. After mesenchymal stem cell injection, scar size in the patient 60 years of age and older decreased from 36.2 g at baseline to 24.5 g at 1 year, with a similar −32.3% reduction in myocardial infarction size. TESI = transendocardial stem cell injection.

as large as in the older age group at baseline (Table 1). This cannot be accounted for except possibly by the small sample size used in the study, which was further narrowed when focusing on the younger than 60 years of age group. More importantly, the change from baseline to 1 year post-injection was similar between the 2 groups.

Quality of life in each age group was similar at baseline, and comparisons of MLHFQ total score changes at both 6 months and 1 year from baseline did not differ significantly between groups (Figure 1). The questionnaire has been deemed a valid and effective instrument in measuring quality of life in heart failure patients (37). Composed of 21 items that sum up a total score, ranging from 0 (no effect) to 105 (strong effect of heart failure on daily life), the MLHFQ is a commonly used assessment tool in heart failure studies (38,39). Our analysis demonstrated a significant improvement in MLHFQ score in older patients and a trend, with borderline significance, toward an improved total score in patients younger than 60 years of age.

Past studies (1,2) established the role of MSC therapy in LV reverse remodeling. We found that LV chamber volumes between age groups were similar at baseline as well as 1 year post-injection, albeit a significant improvement in EDV only in patients age 60 years and older. Correspondingly, sphericity index was reduced in the older age group, despite being the same between groups at baseline and 1 year post-TESI. Although these findings may not completely corroborate those of the POSEIDON and TAC-HFT trials, they do raise the important concept of recipient age not having an influence on MSC therapy efficacy. Improvements in EF have been inconsistent throughout clinical trials of stem cell therapy (40), and we did not find significant increases in either age group. Still, 1 year post-injection, EF between older and younger age groups was not different. Notwithstanding these data, it is important to note that infarct size is a stronger predictor of future adverse cardiac events than EF (41).

TABLE 2 Association Between Cardiac Structure and Age Using a Linear Regression Model

Cardiac Imaging Parameter	Regression Parameter Estimate	SE	p Value
Scar size as absolute value	−0.25	0.38	0.5009
Scar size as percentage of LV mass	−0.58		0.1501
EF*	–	–	0.5414
EDV	−0.25	0.18	0.1639
ESV	−0.28	0.26	0.2777
SI	−0.19	0.18	0.2831

*Due to the highly skewed distribution of the EF, a nonparametric Spearman rank correlation coefficient test was used to determine whether a significant association was present. Correlation coefficient between age and EF = 0.0957.

Abbreviations as in Table 1.

STUDY LIMITATIONS. First, this work had a relatively small sample size, which may limit conclusions from certain measurements such as time to therapy. Although a formal power or sample size calculation was not performed prospectively given that the patient population originates from a fixed cohort, we note that the sample size in each of the age groups would have 84% power to detect a difference in the distance walked in 6 min from 33 to −10 using a 2-sided alpha of 0.05, a relatively large difference. Second, because this analysis is a composite of 2 different clinical trials, data from 2 different imaging modalities were used; multidetector computed tomography scanning in the POSEIDON trial and both cardiac computed tomography and cardiac magnetic resonance in the TAC-HFT trial. We corrected for

this by calculating the percentage of changes for cardiac imaging measurements. Finally, the issue of biological versus chronological age merits comment. Researchers generally believe that biological age predominates over chronological age and can be assessed with molecular assays such as telomere length (10–12). We did not incorporate this assessment, as telomere length assays were not part of either the POSEIDON or TAC-HFT study design. Importantly, whereas most telomere studies have correlated cellular and chronological age of donor cells, our study does not incorporate cellular characteristics of donor cells, but rather the chronological age of recipients. Future studies are planned to measure telomere length in both donors and recipients.

CONCLUSIONS

Our study suggests that recipient age does not reduce the effects of MSC therapy in patients with ICM. Importantly, comparisons of the 6MWD test and absolute scar size between age groups did not differ. Our findings document for the first time the relationship between advanced age and clinical outcomes in heart failure and show an important preservation in responses to cell therapy in a group of recipients of advanced age. These data support ongoing clinical trials on cell-based therapy and the need for future clinical investigation of MSC use in individuals of older age groups.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Aging patients respond similarly to younger patients after receiving human mesenchymal stem cell therapy for ischemic cardiomyopathy. Functional capacity, quality of life, and several cardiac function parameters may improve in these patients, even long after myocardial infarction, highlighting their ability to yield to mesenchymal stem cell antifibrotic and pro-myogenic effects.

TRANSLATIONAL OUTLOOK: Older patients should be included in future clinical stem cell therapy trials. Future randomized studies are required to further demonstrate equivalence in responsiveness between older and younger recipients.

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APPENDIX For a supplemental methods section, please see the online version of this paper.