Left atrial structural and functional response in kidney transplant recipients treated with mesenchymal stromal cell therapy and early tacrolimus withdrawal

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Left Atrial Structural and Functional Response in Kidney Transplant Recipients Treated With Mesenchymal Stromal Cell Therapy and Early Tacrolimus Withdrawal

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Background: Autologous bone marrow–derived mesenchymal stromal cell (MSC) therapy and withdrawal of calcineurin inhibitors (CNIs) has been shown to improve systemic blood pressure control and left ventricular hypertrophy regression in kidney transplant recipients. In the current subanalysis, we aimed to evaluate the impact of this novel immunosuppressive regimen on the longitudinal changes of left atrial (LA) structure and function after kidney transplantation.

Methods: Kidney transplant recipients randomized to MSC therapy—infused at weeks 6 and 7 after transplantation, with complete discontinuation at week 8 of tacrolimus (MSC group)—or standard tacrolimus dose (control group) were evaluated with transthoracic echocardiography at weeks 4 and 24 after kidney transplantation. The changes in echocardiographic parameters were compared between the randomization arms using an analysis of covariance model adjusted for baseline variable.

Results: Fifty-four participants (MSC therapy = 27; tacrolimus therapy = 27) were included. There was no significant interaction between the allocated treatment and the changes of indexed maximal LA volume (LAVImax) over the study period. Conversely, between 4 and 24 weeks post-transplantation, an increase in indexed minimal LA volume (LAVImin) was observed in control subjects, while it remained unchanged in the MSC group, leading to a significant difference between groups (P = .021). Additionally, patients treated with MSC therapy showed a benefit in LA function, assessed by a significant interaction between changes in LA emptying fraction and LA reservoir strain and the randomization arm (P = .012 and P = .027, respectively).

Conclusions: The combination of MSC therapy and CNIs withdrawal prevents progressive LA dilation and dysfunction in the first 6 months after kidney transplantation. LAVImin and LA reservoir strain may be more sensitive markers of LA reverse remodeling, compared with LAVImax. (J Am Soc Echocardiogr 2023;36:172-9.)

Keywords: Left atrium, Atrial function, Kidney transplantation, Mesenchymal stem cells, Immunosuppression

Current immunosuppressive treatments, and calcineurin inhibitors (CNIs) in particular, are associated with significant adverse effects, including nephrotoxicity and conventional cardiovascular risk factors (new onset of hypertension, dyslipidemia, and diabetes), which contribute to the high risk of cardiovascular complications in renal transplant recipients.[1] Therefore, there is a strong interest in alternative

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Abbreviations

CNIs = Calcineurin inhibitors

CKD = Chronic kidney disease

DBP = Diastolic blood pressure

eGFR = Estimated glomerular filtration rate

LA = Left atrial

LAEF = Left atrial emptying fraction

LAVImax = Maximal left atrial volume index

LAVImin = Minimal left atrial volume index

LV = Left ventricular

LVGLS = Left ventricular global longitudinal strain

MSC = Mesenchymal stromal cell

SBP = Systolic blood pressure

immunosuppressive therapies, which may have a better cardiovascular profile and preserve graft survival while being effective in the prevention of acute rejection. In the TRITON trial, a novel strategy with autologous bone marrow–derived mesenchymal stromal cell (MSC) therapy and complete discontinuation of CNIs was firstly tested in renal transplant recipients.[2] Interestingly, patients treated by MSC therapy showed better blood pressure control and reduction of left ventricular (LV) hypertrophy at 24 weeks post-transplantation compared with a standard tacrolimus-based regimen.[3] Nevertheless, the impact of this novel immunosuppressive strategy on left atrial (LA) remodeling, a strong predictor of cardiovascular outcomes in the general population[4] and in patients with chronic kidney disease (CKD),[5,6] has not been investigated. Thus, the purpose of this substudy of the TRITON trial was to assess the effects of MSC therapy combined with CNIs withdrawal on the longitudinal changes of LA structure and function, as evaluated by two-dimensional traditional and speckle-tracking echocardiography.

METHODS

Study Design and Population

In this echocardiographic subanalysis of the TRITON trial (NCT03398681),[2] patients who underwent transthoracic echocardiography with speckle-tracking analysis at 4 and 24 weeks post-transplantation were included. In brief, the TRITON trial was a 24-week randomized, prospective, single-center clinical study investigating the combination of MSC therapy and early tacrolimus withdrawal as a novel immunosuppressive strategy after kidney transplantation.[2] A total of 70 recipients of a first renal transplant from a living donor were randomized to receive either autologous bone marrow–derived MSCs with concomitant withdrawal of tacrolimus or standard tacrolimus dose (control group) in a 1:1 ratio. Detailed information on the study procedures and immunosuppressive treatment are reported in the Supplemental Material. The results of the main analysis showing the safety and feasibility of MSC strategy without increased graft rejection and with preserved renal function have been previously published.[2] In the present subanalysis, we evaluated and compared the longitudinal changes of echocardiographic variables over the study period between the 2 treatment groups. In addition, the correlation between structural and functional parameters of LA remodeling in the overall study population was assessed.

Echocardiographic Methodology

The transthoracic echocardiograms were performed using a commercially available ultrasound system (E95 system, General Electric Vingmed, Horten, Norway). Conventional electrocardiogram-triggered two-dimensional, pulsed-wave, continuous-wave, and color Doppler images were acquired and analyzed offline (EchoPAC ver. 203; General Electric Vingmed). Standard and speckle-tracking

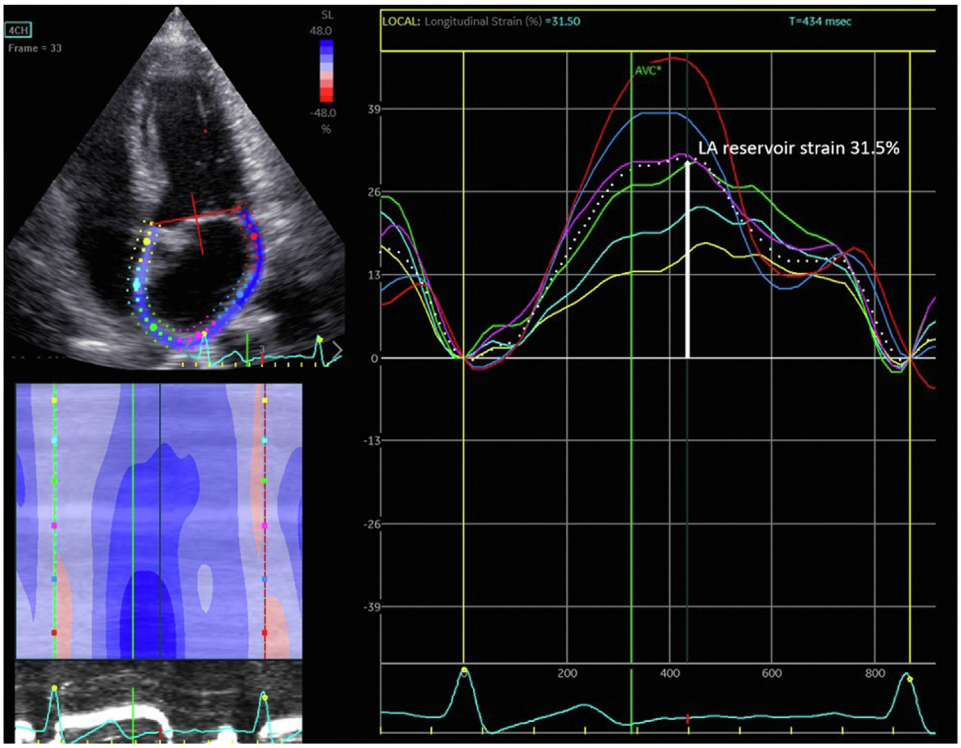

Figure 1 Assessment of LA reservoir strain by two-dimensional speckle-tracking echocardiography. The region of interest is shown in the upper left quadrant covering the left atrium from the apical 4-chamber view. The right of the image illustrates the segmental strain curves for each segment and the global LA strain *(white dotted line)*. In this case, the LA reservoir strain was 31.5%.

HIGHLIGHTS

- MSC therapy combined with CNIs withdrawal was tested in kidney transplant recipients.
- MSC therapy prevented an increase in LAVImin.
- There were no differences in the changes of LAVImax.
- MSC strategy was also associated with a benefit in LA functional parameters.
- Minimal LA volume and LA function are sensitive markers of LA reverse remodeling.

echocardiographic measurements were performed by experienced operators (M.C.M. and V.D.) who were blinded to the allocated treatment.

From the apical 2- and 4-chamber views zoomed on the left ventricle, the LV end-diastolic and end-systolic volumes were calculated and LV ejection fraction (LVEF) was derived using the biplane Simpson's method.[7] From dedicated apical 2- and 4-chamber views, LA volumes were measured at end systole and at end diastole using the biplane Simpson's method and then indexed for body surface area (LAVImax and LAVImin, respectively).[7,8] The LA emptying fraction (LAEF) was determined using the following formula and reported as a percentage: (LAVImax − LAVImin)/LAVImax.

Left ventricular diastolic parameters, including average e′ velocity and E/e′′ratio, were assessed by pulsed-wave Doppler at the tips of the mitral leaflets and tissue Doppler imaging at the level of the medial and lateral annulus.[8] Left ventricular stroke volume and cardiac output were calculated according to current recommendations.[9]

The assessment of LV global longitudinal strain (LVGLS) and LA reservoir strain by two-dimensional speckle-tracking echocardiography was performed offline using EchoPAC version 203 software. Images from the apical 4- and 2-chamber and long-axis views zoomed on the left ventricle and with a frame rate of ≥50 frames/sec were used for the measurement of LVGLS. The LV endocardial border was manually traced and then automatically tracked by the software through the cardiac cycle. The LVGLS was calculated by averaging all segmental strain values and later by averaging values of all apical views.[7] For the measurement of LA reservoir strain (Figure 1), the onset of the QRS wave was defined as the reference point (R-R gating).[10] After the manual definition of the LV endocardial border in the apical 4-chamber view, the region of interest was adjusted to cover the entire LA wall and divided into 6 segments by the software. Left atrial reservoir strain was defined as the average of the peak values during the cardiac cycle of all 6 segments.[10] According to current evidence,[4] LA dysfunction was defined by values of LA reservoir strain <35%. In this study, the values of strain measurements are reported as absolute values.

Statistical Analysis

Continuous data are reported as mean ± SD when normally distributed and as median (interquartile range) when not normally distributed. Categorical variables are presented as absolute numbers and percentages. The correlation of LAVImax and LAVImin with LA function, measured by LAEF and LA reservoir strain, was evaluated by the Spearman method, and the correlation coefficients were compared using a Fisher's *r* to z transformation.

Paired Student's *t* test and Wilcoxon test (for continuous data, as appropriate) and McNemar's test (for categorical variables) were used to evaluate the changes in clinical and echocardiographic parameters over the time within each study group.

The effect of the immunosuppressive treatment (MSC vs CNIs-based regimen) on the modifications of clinical and echocardiographic parameters was assessed using analysis of covariance adjusted for the baseline variable. In addition, for LA structural and functional echocardiographic parameters, a separate extension of the model was built including the changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), and estimated glomerular filtration rate (eGFR) as covariates. Finally, a sensitivity analysis was performed to confirm the treatment impact on the changes of LA dimensions and mechanics after excluding 2 patients with arteriovenous fistula. All statistical analyses were 2 sided, and $P < .05$ was considered statistically significant. SPSS version 25.0 (SPSS, Chicago, IL) was used for the data analysis.

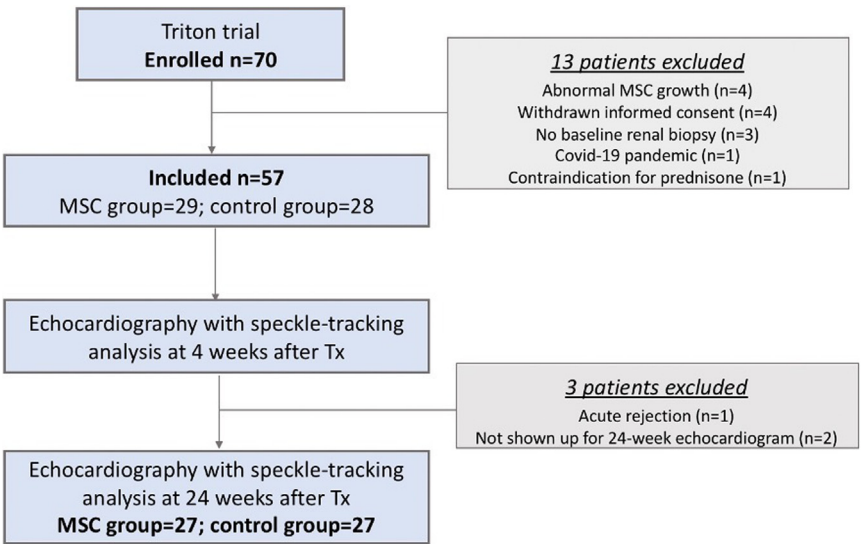

Figure 2 Flow chart of the echocardiographic subanalysis of the TRITON trial. *Tx*, Renal transplantation.

RESULTS

Of 70 patients initially enrolled in the trial, 13 subjects were excluded due to abnormal MSC growth ($n = 4$), contraindication for MSC therapy during the COVID-19 pandemic ($n = 1$), impossibility of obtaining a baseline renal biopsy ($n = 3$), withdrawal of the informed consent ($n = 4$), and contraindication for prednisone usage ($n = 1$). Therefore, the study population was composed by 57 patients, which were randomly assigned to the MSC group ($n = 29$) or control group ($n = 28$). Transthoracic echocardiographic data and feasible speckle-tracking analysis at 4 and 24 weeks after kidney transplantation were available in 54 patients, which constituted the study cohort of this subanalysis (Figure 2). Acute rejection under MSC therapy with the need of tacrolimus reintroduction ($n = 1$) and unavailable 24-week echocardiogram ($n = 2$) were additional exclusion criteria for the current study.

The baseline features of the study population are displayed in Table 1, while Table 2 shows the changes in clinical and echocardiographic parameters over the study period for each treatment group.

As described elsewhere,[5] patients randomized to MSC therapy achieved better blood pressure control at 24 weeks post-transplantation, as assessed by a significant interaction between the variations in DBP and the treatment group ($P = .005$). Notably, antihypertensive therapy was not significantly different between the 2 randomization arms at 24 weeks post-transplantation (Supplemental Table 1). In addition, there was a reduction in eGFR between 4 and 24 weeks after transplantation in the MSC group, whereas renal function did not change in controls ($P = .345$).

In the overall study cohort, LAVImin was significantly correlated with LA reservoir strain, whereas LAVImax was not (correlation coefficient $\rho = 0.38$, $P = .004$, vs $\rho = 0.11$, $P = .421$). Furthermore, LAVImin exhibited a closer correlation with LAEF compared with LAVImax ($\rho = 0.59$; $P < .001$ vs $\rho = 0.48$; $P < .001$), but this difference was not statistically significant ($P = .43$).

Between 4 and 24 weeks after transplantation, an increase in LAVImin was observed in the control group, whereas in the MSC group LAVImin did not change over time, leading to a significant difference between groups ($P = .021$; Table 2, Figure 3). The LAEF was reduced at 24 weeks post-transplantation in patients treated with tacrolimus and increased in patients treated with MSCs, and these opposite responses resulted in a significant difference between groups ($P = .012$). Notably, the association between changes in LAVImin and LAEF and the randomization arm remained significant after adjustment for the variation in SBP, DBP, and eGFR over the time ($P = .036$ and $P = .042$, respectively; Figure 4). A significant interaction was also observed between the variations of tricuspid regurgitant jet velocity and the randomization arm ($P = .001$). Conversely, the changes of LAVImax, average e′ velocity, and E/e′ ratio did not differ between the treatment groups (Table 2).

At 24 weeks post-transplantation, LVEF and LVGLS values were lower in control subjects compared with baseline, while these parameters remained unchanged in the MSC group. However, these differences were not statistically significant. On the contrary, patients randomized to MSC therapy showed a beneficial effect on LA function, as demonstrated by a significant interaction between changes in LA reservoir strain and the treatment group ($P = .012$). This finding was also confirmed after adjustment for the changes in SBP, DBP, and eGFR over the time ($P = .047$; Figure 4). In addition, the prevalence of LA dysfunction decreased at 24 weeks in the MSC therapy group (48% vs 70%, $P = .060$), whereas it remained unchanged in controls (78% vs 63%, $P = .219$).

Table 1 Baseline characteristics after randomization

Variable	MSC group (n = 27)	Control group (n = 27)
Recipient:		
Age, years	50.2 ± 14.0	50.0 ± 15.5
Gender, male gender, *n* (%)	24 (89)	20 (74)
Body mass index, kg/m^2	25.8 ± 3.6	25.8 ± 4.0
Cause of CKD, *n* (%):		
Hypertensive disease	3 (11.1)	9 (33.3)
Polycystic kidney disease	9 (33.3)	3 (11.1)
IgA nephropathy	6 (22.2)	3 (11.1)
Diabetic nephropathy	5 (18.5)	0 (0)
Reflux nephropathy	0 (0)	2 (7.4)
Membranous glomerulonephritis	1 (3.7)	1 (3.7)
Lupus nephritis	1 (3.7)	0 (0)
Other	1 (3.7)	3 (11.1)
Unknown	1 (3.7)	6 (22.2)
Renal replacement therapy, *n* (%):		
None	21 (78)	20 (74)
Hemodialysis with central venous catheter	4 (15)	4 (15)
Hemodialysis with arteriovenous fistula	1 (4)	1 (4)
Peritoneal dialysis	1 (4)	2 (7)
eGFR,* mL/min/1.73 m^2	9.2 ± 3.8	10.9 ± 4.8
Donor:		
Age, years	54.4 ± 12.7	50.6 ± 11.0
Gender, male, *n* (%)	13 (48)	10 (37)
Predonation eGFR, mL/min/1.73 m^2	109.7 ± 12.0	109.3 ± 12.7
Transplantation:		
Type, related, *n* (%)	12 (44)	14 (52)
HLA A/B mismatch, mean (SD)	2.3 ± 1.3	2.5 ± 0.9
HLA DQ/DR mismatch, mean (SD)	1.3 ± 0.6	1.3 ± 0.5
Cardiovascular medications, *n* (%):		
Calcium-channel blocker	18 (67)	19 (70)
ACE-I/ARB	11 (40)	4 (15)
Beta-blocker	10 (37)	10 (37)
Thiazide diuretic	0 (0)	4 (15)
Alpha-blocker	3 (11)	1 (4)
Statin	7 (28)	10 (37)
Insulin	6 (22)	0 (0)

The eGFR was calculated by the CKD-EPI formula. *ACEI*, Angiotensin-converting enzyme inhibitors; *ARB*, angiotensin receptor blocker; *HLA*, human leucocyte antigen.
*eGFR assessed before the transplantation.

The changes in LA dimensions and mechanics were not significantly correlated with the variations in SBP and DBP over the study period. In contrast, the modifications of antihypertensive therapy (categorized as increased, stable, or decreased number of antihypertensive drugs at 24 weeks compared with the baseline;

Table 2 Changes of clinical and echocardiographic parameters in each treatment group between 4 and 24 weeks post-transplantation

Variables	MSC treatment (n = 27)		Tacrolimus-based treatment (n = 27)		P value*
	4 Weeks	24 Weeks	4 Weeks	24 Weeks	
Clinical parameters:					
SBP, mm Hg	143.7 ± 14.7	137 ± 16.1	145.5 ± 12.9	143.2 ± 17.3	.192
DBP, mm Hg	87.2 ± 11.0	82.8 ± 8.9	87.3 ± 10.8	90.6 ± 11.0	.005
Weight, kg	77.3 ± 12.1	81.5 ± 12.5	81.4 ± 13.5	83.5 ± 15.1	.737
eGFR, mL/min/1.73 m^2	60.8 ± 16.1	55.6 ± 15.2†	45.9 ± 10.9	46.5 ± 15.6	.345
Echocardiographic parameters:					
LVEDVI, mL/m^2	56.5 ± 15.4	58.8 ± 17.2	52.9 ± 12.9	56.4 ± 11.6†	.857
LVESVI, mL/m^2	21.1 ± 7.5	24.0 ± 10.0	18.4 ± 6.7	22.3 ± 7.8†	.886
LVEF, %	63.0 ± 6.5	60.5 ± 7.9	65.0 ± 8.5	60.9 ± 7.7†	.973
LVGLS, %	17.6 ± 2.7	17.5 ± 2.8	18.1 ± 2.5	17.3 ± 3.0†	.325
Stroke volume index, mL/m^2	45.6 ± 10.9	45.2 ± 8.4	42.1 ± 12.9	42.2 ± 11.9	.564
Cardiac output, L/min	7.0 ± 1.8	6.8 ± 1.3	6.6 ± 2.1	6.0 ± 1.1	.474
LAVImax, mL/m^2	34.1 ± 10.5	35.1 ± 11.1	31.5 ± 9.3	34.0 ± 10.5	.730
LAVImin, mL/m^2	11.9 ± 3.1	11.4 ± 4.6	11.3 ± 4.1	13.4 ± 6.5†	.021
LAEF, %	64 (56-70)	69 (63-73)	66 (60-70)	64 (55-69)	.012
LA reservoir strain, %	30.6 ± 7.1	32.4 ± 8.4	31.7 ± 8.6	29.2 ± 8.1†	.027
Average e'velocity, cm/sec	11.0 ± 3.2	12.3 ± 3.8†	10.4 ± 3.4	11.1 ± 3.7	.334
E/e' ratio	7.2 ± 2.6	7.1 ± 2.8	7.0 ± 2.8	6.9 ± 2.1	.582
TR jet velocity, m/sec	2.5 ± 0.4	2.3 ± 0.3	2.1 ± 0.3	2.4 ± 0.3	.001

The eGFR was calculated by the CKD-EPI formula. *LVEDVI*, LV end-diastolic volume indexed for body surface area; *LVESVI*, LV end-systolic volume indexed for body surface area; *TR*, tricuspid regurgitation.
*Calculated using analysis of covariance model with baseline adjustment.
†$P < .05$ versus baseline within each randomization arm.

Supplemental Table 1) were associated with the changes of LAVImin ($P = .007$), LAEF ($P = .019$), and LA reservoir strain ($P = .053$). Nevertheless, MSC strategy was consistently associated with a reduction of LAVImin ($P = .046$) and improvement of LA functional parameters ($P = .027$ for LAEF and $P = .050$ for LA strain), after adjustment for the changes in antihypertensive treatment.

Finally, a sensitivity analysis was performed excluding 2 patients (1 randomized to MSC therapy and 1 randomized to tacrolimus) with arteriovenous fistula, but in the absence of echocardiographic signs suggestive of high cardiac output. Of note, this analysis confirmed the favorable response of LA structural and functional parameters in patients randomized to MSC therapy (Supplemental Figure 1).

DISCUSSION

The present study showed that MSC therapy combined with early discontinuation of CNIs prevents progressive LA dilation and dysfunction in recipients of kidney transplantation compared with a tacrolimus-based regimen. Notably, LAVImin and LA reservoir strain emerged as more sensitive markers of LA reverse remodeling in comparison to LAVImax.

Patients with CKD as well as kidney transplant recipients are at increased risk of cardiovascular disease.[11] Current immunosuppressive treatments, particularly CNIs, are important contributors to the high risk of cardiovascular complications in kidney transplant recipients. Nevertheless, CNI-withdrawal immunosuppressive strategies, despite being effective in reducing cardiovascular side effects, resulted in higher rates of acute rejection.[12] Thus, alternative immunosuppressive regimens, such as MSC strategy, that may exert potential cardioprotective effects while preserving the graft survival represent an urgent, unmet clinical need for this population.

In patients with CKD, LA dimensional and functional parameters allow the detection of early stages of myocardial involvement, with changes in LAVImax and LA reservoir strain preceding alterations in LV parameters, including LVEF and LVGLS.[13]

Left atrial enlargement and its progression over the time are established prognostic biomarkers in several cardiovascular conditions[4] and in patients with CKD.[5] Particularly, the increase in LAVImax has been associated with the occurrence of cardiovascular events in end-stage CKD, with an independent value from the corresponding baseline measurement and the changes in LV hypertrophy.[5] Of note, although most of the studies reporting the prognostic importance of LA size have measured LAVImax, recent investigations suggested that

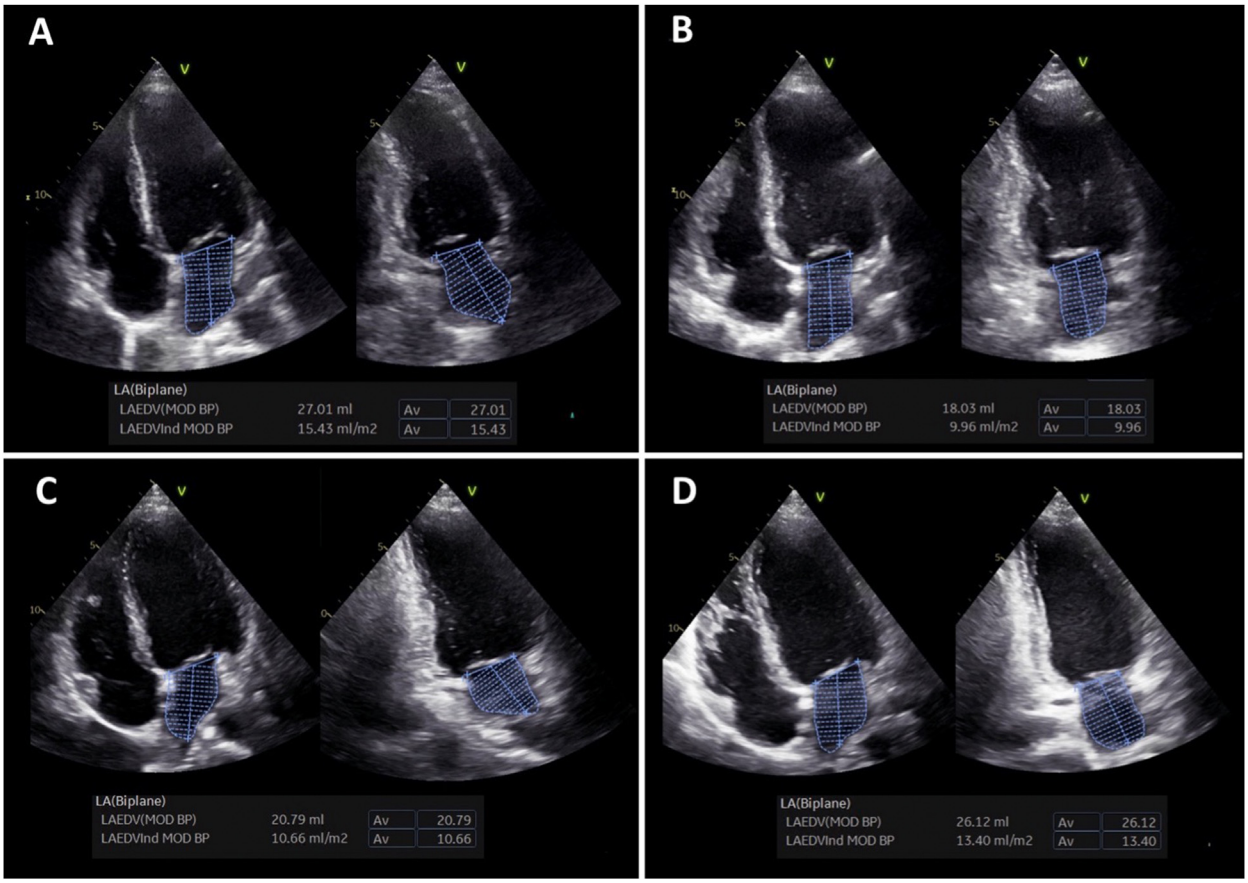

Figure 3 Iconographic example of the LAVImin variations during the study period in each randomization arm. A case of LA reverse remodeling (decrease of LAVImin from 15.4 to 10.0 mL/m^2) in a patient treated with MSC is illustrated in the upper panels **(A and B)**. The lower panels **(C and D)** show the progression of LA remodeling in a subject of the control group (increase of LAVImin from 10.7 to 13.4 mL/m^2).

LAVImin may be a stronger predictor of adverse outcomes in comparison to LAVImax.[4] Indeed, LAVImin is calculated in the end-diastolic phase, when the LA is more directly exposed to LV pressure. Accordingly, LAVImin has been reported to have a stronger correlation with invasive LV filling pressure and N-terminal pro-brain natriuretic peptide levels compared with LAVImax.[14,15] In addition, an analysis from the Multi-Ethnic Study of Atherosclerosis[16] showed the increase of LAVImin as a more robust predictor of cardiovascular events than the changes of LAVImax in patients without a history of cardiovascular disease.

Parameters of LA function, particularly LA reservoir strain, have recently emerged as sensitive markers of LV diastolic dysfunction,

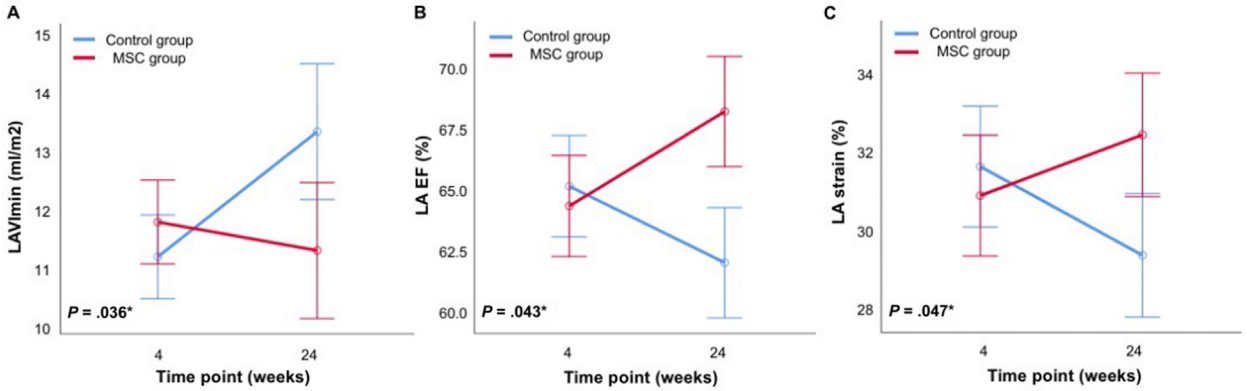

Figure 4 Changes in estimated marginal means of LAVImin **(A)**, LAEF **(B)**, and LA reservoir strain **(C)** between 4 and 24 weeks post-transplantation for each randomization arm. Standard errors of the mean are displayed as *error bars*. **P* value calculated using analysis of covariance model adjusting for the baseline variable and for the changes in SBP, DBP, and eGFR.

with additive diagnostic and prognostic value in comparison to LA size.[4] Notably, LA reservoir strain was a stronger predictor of mortality and cardiac events compared with LAVImax and LV parameters (LV mass index and LV GLS) in patients with CKD.[6]

In the present study, MSC therapy combined with early CNIs discontinuation prevented LA structural remodeling, as assessed by the changes in LAVImin, compared with a standard tacrolimus-based regimen. Conversely, there were no significant differences in the changes of LAVImax over time between the treatment groups. Consistent with previous findings,[17] we reported a stronger correlation of LAVImin with LA reservoir function, as assessed by LAEF and LA strain, compared with LAVImax. The closer relationship of LAVImin with LV filling pressure and LA function may likely explain the different results regarding the changes of LAVImin and LAVImax. Indeed, the favorable changes of LAVImin observed in the MSC group were accompanied by an improvement in LA functional measurements, namely, LAEF and LA reservoir strain. It has been demonstrated that LA functional recovery may happen independently or precede LA structural reverse remodeling (evaluated as LAVImax) in response to the reduction of LV filling pressure associated with medical or surgical therapy.[18] In this regard, there is a growing interest in the potential value of LA reverse remodeling, evaluated by LA strain, as a sensitive biomarker of response to specific therapeutic interventions, particularly in the setting of heart failure.[19]

In the present study, the improvement of LA structural and functional parameters in the MSC group may be, at least partially, consequent to the better blood pressure profile and the regression of LV hypertrophy, as suggested by the significant association with the up- or down-titration of the antihypertensive therapy. Nevertheless, a direct antiremodeling effect of MSC therapy or tacrolimus discontinuation may also have played a role. Left atrial fibrosis represents the underlying substrate of LA dysfunction,[4,20] although the loading conditions may also influence LA function. In patients with CKD, neurohormonal abnormalities, primarily the upregulation of the renin-angiotensin-aldosterone system, contribute to LA dysfunction independently from the effects of LV hypertrophy and diastolic dysfunction, enhancing the activity of TGF-beta 1 and other profibrotic signaling pathways.[6,21] In this context, MSCs may exert an antifibrotic action via several mechanisms, downregulating the myocardial expression of angiotensin II receptor type I and stimulating the production of antifibrotic molecules including metalloproteinases and adrenomedullin.[22,23] Furthermore, a direct profibrotic action of CNIs therapy has also been suggested by a recent trial conducted in recipients of cardiac transplantation.[24] In this study, subjects treated with the combination of low-dose tacrolimus and everolimus showed a reduction of LV myocardial fibrosis and improvement in LVGLS assessed by cardiac magnetic resonance at 1 year post-transplantation compared with patients treated with standard dose tacrolimus, despite the similar blood pressure control in the 2 groups. Of interest, it has been suggested that both the profibrotic and antifibrotic myocardial changes can manifest earlier in the LA mechanics (as opposed to the LV mechanics), due to the small atrial myocardial mass.[6,25]

Variations in the loading conditions over the study period may also have influenced the differential responses of LA dimensions and mechanics, but it is worth highlighting that there were no relevant modifications in noninvasive LV filling pressures (assessed by E/e′ ratio) in both the treatment groups. Finally, LA reservoir function is determined, to a large extent, by the LV deformation.[26] Nevertheless, since there were no differential treatment effects on LVGLS, the increase of LA reservoir strain in the MSC group may not be explained by an improvement in LV myocardial mechanics.

Study Limitations

The present study was conducted in a single center, with a small size population and a relatively short follow-up time. Thus our findings should be validated in larger trials, and further studies are needed to investigate the relationship between LA structural and functional reverse remodeling and outcomes in kidney transplant recipients. Minimal LA volume can be foreshortened and thereby underestimated by two-dimensional echocardiography, while three-dimensional echocardiography has been demonstrated to be more accurate and reproducible than two-dimensional echocardiography.[27] Moreover, LA strain measurements were not performed using an LA dedicated tracking software, which has been associated with a higher reproducibility,[28] since this was not available at the time in which the study was conducted.

CONCLUSION

The combination of MSC therapy and early CNIs withdrawal may prevent LA structural and functional remodeling in the first 6 months after kidney transplantation compared with a standard tacrolimus regimen. The early response of LAVImin and LA reservoir strain in patients treated by MSC strategy supports their value as more sensitive markers of LA reverse remodeling compared with LAVImax.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.echo.2022.10.022.

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