Assessment of Predictors of Left Atrial Volume Response to a Transcatheter InterAtrial Shunt Device (from the REDUCE LAP-HF Trial)

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In patients with heart failure and preserved or mildly reduced ejection fractions (EF ≥40%), implantation of an interatrial shunt device (IASD) resulted in heterogenous changes of the left atrial (LA) volume. Baseline characteristics that correlate with a favorable decrease in LA volume are unknown. We hypothesized that a larger ratio of left to right atrial volume at baseline would correlate strongly with LA volume decongestion following IASD implantation. Reduce Elevated LA Pressure in Patients With Heart Failure was a multicenter study of the safety and feasibility of IASD implantation. Sixty-four patients with EF ≥40% underwent device implantation along with baseline conventional echocardiograms, speckle tracking echocardiography, and resting and exercise hemodynamics. Higher LA compliance (−4.2%, p = 0.048) and right atrial reservoir strain (−0.8%, p = 0.005) were independently associated with a percent decrease in the systolic LA volume index from baseline to 6-months. In conclusion, greater LA volume reduction following IASD implantation is associated with higher baseline compliance of the left atrium and higher reservoir strain of the right atrium. **(Am J Cardiol 2019;124:1912−1917)**

Heart failure with preserved or mid-range ejection fraction (HFpEF/HFmrEF) accounts for more than half of all cases of heart failure,[1] but pharmacologic therapies for the disease have had limited success.[2−4] An interatrial shunt device (IASD, Corvia Medical Inc., Tewksbury, Massachusetts) that could mechanically offload the left atrium (LA) at rest and during exercise was developed as an alternative treatment strategy.[5,6] In the open-label Reduce Elevated Left Atrial Pressure in Patients with Heart Failure (REDUCE LAP-HF) study, the impact of the IASD on clinical end points, LA pressure, and LA volume overload was evaluated.[7] The IASD was associated with an increase in exercise time and 6-minute walk distance,[7−10] but LA volume had a heterogeneous response at 6-months. Because (1) a large LA volume correlates with a higher incidence of hospitalization for HFpEF/HFmrEF,[11−13] and (2) decreased LA volume following the IASD may represent reverse LA remodeling better than isolated measurements of left atrial (LA) pressure or volume,[14] we sought to determine if a patient's baseline echocardiographic, hemodynamic, or other clinical characteristics predict the LA volume response to device implantation.

Methods

Study design, patient selection, echocardiographic and hemodynamic measurements, inclusion and exclusion criteria, and the device implantation procedure for REDUCE LAP-HF have been previously described.[7] The REDUCE LAP-HF trial was a multicenter, prospective, open-label, single-arm study that evaluated safety and efficacy end points. Men and women greater than 40 years old were eligible if they had evidence of chronic symptomatic heart failure (NYHA class II-IV), a left ventricular ejection fraction greater than 40%, normal right ventricular function,

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See page 1916 for disclosure information.

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and an increased Pulmonary Capillary Wedge Pressure (PCWP) at rest (>15 mm Hg) or during exercise (>25 mm Hg) measured by right heart catheterization. Study measurements were obtained at baseline and 6 months later at a follow-up visit. The primary end point of the current analysis is the percent change in LA volume index during ventricular systole (LAVI), which reflects maximal atrial volume distension and has been shown to correlate with progressive heart failure.[15] A decreased or unchanged LAVI at 6 months (echocardiographic responders) is favorable, compared with patients with an increased LAVI at 6 months (echocardiographic nonresponders).

All patients underwent baseline right heart catheterization at rest and during supine bicycle exercise, and again at 6-month follow-up. Bicycle exercise commenced at 20 watts (W) with 20-W increments every 3 minutes until the patient achieved maximum effort. Hemodynamic traces were analyzed at an independent core laboratory (PVLoops LLC, New York). Cardiac output was assessed by thermodilution (rest and exercise) and Fick methods (rest only).[16] PCWP was measured at end-expiration.

Conventional resting echocardiograms from baseline and at 6-month follow-up were analyzed per protocol at an independent core laboratory at the University of Pennsylvania (PA, USA). Right ventricular diastolic and systolic volumes were obtained by 2D echocardiography through the area-length estimation method and used to calculate the right ventricular ejection fraction (RVEF). LA and right atrial (RA) volumes in this study were obtained from the apical 4 chamber position by method of discs and timed to the end of ventricular systole or diastole. LA and RA compliance were defined as the ratio of the unindexed left or right atrial volume during ventricular systole divided by the PCWP or central venous pressure (CVP). All volumes were indexed to body surface area other than those used in calculation of atrial compliance, a property independent of body surface area. Speckle tracking echocardiography was analyzed in the core lab at Northwestern University using a customized software package (2D Cardiac Performance Analysis, TomTec v4.5, Munich, Germany). LA and RA strain were calculated using the onset of the QRS complex as the zero reference, so that all longitudinal atrial strain values are positive. LA and RA reservoir strain were defined as the peak longitudinal strain in the respective atria. LA and RA booster strain were measured in patients without atrial fibrillation as the maximal longitudinal strain between the onset of the P wave and onset of the QRS complex. This value was indeterminate in patients with atrial fibrillation. Conduit strain was defined as reservoir minus booster strain. In patients in atrial fibrillation at the time of measurement, reservoir strain = conduit strain due to the lack of booster function. Optimized apical 4 chamber images were used to measure global longitudinal strain of the left ventricle. Speckle tracking was not performed in patients with inadequate image quality, defined as >1 segment dropout, missing views, or significant foreshortening of the left ventricle (LV), LA, or RA.

Normally distributed and nonparametric baseline demographics were compared between echocardiographic responders and nonresponders using Student's *t* test and the Wilcoxon Rank Sum test, respectively. Univariate linear regression was used to screen for baseline variables associated with decreased 6-month LAVI. In order to avoid regression to the mean, the change in LAVI from baseline to 6-month follow-up was calculated as a percent difference (e.g., 100% × [6-month LAVI − baseline LAVI]/(baseline LAVI). Variables significant in univariate models to a p value <0.05 were included in a multivariable linear regression model to identify independent predictors of response, as was atrial fibrillation given an a priori concern for its impact on LA mechanics in response to the device. In the final model, multicollinearity was assessed with the variance inflation factor and variables resulting in multicollinearity were dropped. All analysis was performed using STATA IC 15.1 (Stata Corp LP, Texas).

Results

One hundred two patients were enrolled from 21 centers between February 8, 2014 and June 10, 2015, in whom 66 qualified, 64 underwent successful IASD implant, and 43 had measurements of LAVI at baseline and 6-month follow-up. The remainder was either missing echocardiographic studies or had inadequate LA image quality at one or both timepoints. Reasons for study exclusion were detailed previously,[7] noting that most of the 38 patients who were not implanted had either PCWP that was too low or CVP that was too high. The distribution of LAVI percent change from baseline to 6 months was skewed slightly to the right (Figure 1). Table 1 shows baseline characteristics in all 43 implanted patients with complete LA volume measurements, stratified by the response in LA volumes at 6 months (i.e., Responder vs Nonresponder). Responders had a higher LAVI and LA compliance at baseline, but all other clinical parameters were balanced between the 2 groups. There were no differences in baseline clinical or available echocardiographic variables between patients with or without 6-month LAVI follow-up images.

Table 2 shows all univariate associations between baseline covariates and percent change in LAVI from baseline to 6-month follow-up, divided into echocardiographic (Table 2a), hemodynamic (Table 2b), and laboratory or demographic parameters (Table 2c). As seen in Table 2a, each unit increase in the baseline ratio of LA to RA volume

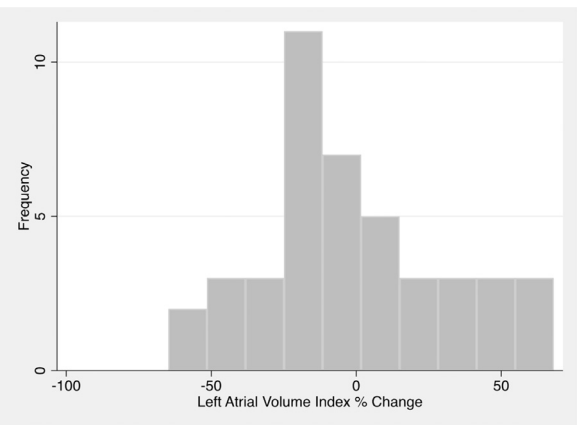

Figure 1. Percent change in left atrial volume index across subjects from baseline to 6-month follow-up.

Table 1
Comparison of baseline covariates among responders (decreased or unchanged left atrial volume index at 6 months) vs nonresponders (increased left atrial volume index)

Variable	Responders (n = 25)	Nonresponders (n = 18)	p Value
Baseline LAVI (ml/m^2)	49.0 (38.3, 57.8)	39.1 (34.7, 48.5)	0.06
Age (years)	69 (66, 75)	70 (68, 76)	0.4
BMI (kg/m^2)	33.8 (28.1, 36.4)	31.7 (28.3, 37.5)	0.8
NT-pro BNP (pg/ml)	298 (169, 1330)	546 (218, 1084)	0.7
Hemoglobin (g/dl)	13.0 (12.5, 14.1)	12.8 (11.9, 14.2)	0.4
eGFR (ml/min/1.73 m^2)	63 +/- 23	57 +/- 19	0.4
Atrial fibrillation	8 (32%)	6 (33%)	0.9
LVEF (%)	46 +/- 7	46 +/- 5	0.9
LA compliance (mL/mmHg)	5.9 (5.1, 7.6)	5.1 (3.9, 5.1)	0.002
LA reservoir strain (%)	26.2 (13.2, 44.1)	28.4 (12.2, 28.4)	0.2
LA booster strain (%)	9.2 (0, 20.9)	8.3 (0, 12.0)	0.4
LA conduit strain (%)	14.8 (12.4, 21.7)	11.5 (9.1, 14.3)	0.06
RA reservoir strain (%)	31.5 (21.7, 50.0)	25.3 (19.2, 33.8)	0.1
RA booster strain (%)	13.7 (0, 28)	8.2 (0, 20.8)	0.6
RA conduit strain (%)	18.2 (14.9, 25.2)	17.8 (11.4, 10.0)	0.3

Variables are displayed as mean +/− SD when normal, median (interquartile range) when nonparametric, and number (%) when categorical. BMI = body mass index; eGFR = estimated glomerular filtration rate; LA = left atrium; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction.

was significantly associated with a decrease in LAVI from baseline to 6 months. However, neither baseline LAVI nor RA volume index alone was associated with this favorable response. Increased baseline RA volumes tended to correlate with higher resting and peak exercise CVP at baseline, although increased resting LA volumes were only seen in patients with higher peak exercise PCWP. Analysis of strain parameters revealed a significant decrease in LAVI at 6 months associated with higher baseline RA reservoir and conduit strain. Two patients had RA reservoir strain >1.5 × the interquartile range above the 3rd quartile that drove this effect (Figure 2): in a sensitivity analysis excluding both of these patients, higher RA reservoir strain was not significantly associated with a decreased LAVI (−33%, p = 0.63). No association was seen with baseline LA strain parameters or global longitudinal strain of the LV.

Higher LA compliance (ratio of LA systolic volume to PCWP) at baseline was associated with a larger decrease in LAVI from baseline to 6 months (Table 2b and Figure 3). The range of LA compliance was 2.5 to 13.9 ml/mm Hg, and higher LA compliance was significantly related to a higher LA/RA volume ratio at baseline. Moreover, while neither resting nor exercise PCWP-CVP gradient were themselves associated with decreased 6-month LA volumes, patients in the highest 50th percentile of compliance (>5.34 ml/mm Hg) and resting PCWP-CVP gradient (>7 mm Hg) had significantly larger decrease in LAVI at 6 months compared with patients below median in both measures (−40%, p = 0.01).

Baseline RVEF was associated with an increase in LAVI from baseline to 6 months (Table 2a). This relation did not hold for other measurements of RV function: baseline tricuspid annular plane systolic excursion showed no

Table 2
Univariate linear regression—association of baseline covariates with % change in left atrial volume index from baseline to 6 months following implantation of an interatrial shunt device

2a. Baseline echocardiographic covariates

Variable	% Change in LAVI (95% CI)	p Value
LVEF (%)	−0.4 (−2.0, 1.2)	0.6
RVEF (%)	1.1 (0.1, 2.0)	0.03
TAPSE (mm)	−6.8 (−31.0, 17.3)	0.6
RA volume index (ml/m^2)	−0.2 (−0.9, 0.6)	0.7
LA volume index (ml/m^2)	−0.3 (−0.6, 0.04)	0.09
LA/RA volume ratio	−27.7 (−52.3, −3.2)	0.03
LV end diastolic volume index (ml/m^2)	−0.4 (−0.4, 1.2)	0.30
RV end diastolic volume index (ml/m^2)	−0.5 (−1.0, 1.9)	0.5
Transmitral E/A	4.0 (−10.7, 18.7)	0.6
Tricuspid regurgitation severity	−1.1 (−14.4, 16.7)	0.9
LV global longitudinal strain (%)	−1.5 (−3.6, 0.7)	0.2
LA reservoir strain (%)	−0.5 (−1.2, 0.2)	0.2
LA booster strain (%)	−0.4 (−1.4, 0.6)	0.4
LA conduit strain (%)	−1.5 (−3.0, 0.03)	0.056
RA reservoir strain (%)	−0.5 (−0.7, −0.2)	0.001
RA booster strain (%)	−0.3 (−1.1, 0.5)	0.4
RA conduit strain (%)	−0.9 (−1.5, −0.4)	0.003

2b. Baseline hemodynamic covariates

Variable	% Change in LAVI (95% CI)	p Value
Heart Rate, rest (bpm)	−0.6 (−1.3, 0.1)	0.08
MAP rest (mm Hg)	0.3 (−1.1, 0.4)	0.4
CVP rest (mm Hg)	2.2 (−0.5, 4.9)	0.1
CVP peak exercise (mm Hg)	1.2 (−0.9, 3.3)	0.3
mPAP rest (mm Hg)	0.89 (−0.6, 2.3)	0.2
mPAP peak exercise (mm Hg)	−0.3 (−1.5, 0.9)	0.6
PCWP rest (mm Hg)	1.2 (−0.8, 3.1)	0.2
PCWP peak exercise (mm Hg)	−0.03 (−1.4, 1.3)	1.0
PCWP-CVP gradient, rest (mm Hg)	0.1 (−2.3, 2.6)	0.9
PCWP-CVP gradient, peak exercise (mm Hg)	−0.8 (−2.3, 0.8)	0.3
CO rest, thermodilution (L/min)	2.3 (−3.7, 8.3)	0.4
CO exercise, thermodilution (L/min)	−1.1 (−4.8, 2.7)	0.6
CO rest, fick (L/min)	10.9 (1.3, 20.5)	0.03
PVR (WU)	2.0 (−14.3, 18.4)	0.8
LA compliance (LASV/PCWP) (ml/mm Hg)	−3.7 (−7.3, -0.1)	0.04
RA compliance (RASV/CVP) (ml/mm Hg)	−1.2 (−3.7, 1.4)	0.4
LA/RA compliance ratio	−16.3 (−54.3, 21.9)	0.4

2c. Baseline clinical covariates

Variable	% Change in LAVI (95% CI)	p Value
Age	0.8 (−.6, 2.2)	0.2
Atrial Fibrillation (presence)	−0.6 (−22.0, 20.7)	1.0
BMI (kg/m^2)	1.0 (−0.8, 2.8)	0.3
Hemoglobin (g/dL)	−0.4 (−0.8, 0.01)	0.06
NT-proBNP (pg/mL)	−0.002 (−0.02, 0.01)	0.8
Serum Creatinine (umol/L)	0.20 (− 0.04, 0.44)	0.09

LA = left atrial; LV = left ventricle; LVEF = left ventricular ejection fraction; RA = right atrial; RV = right ventricle; RVEF = right ventricular ejection fraction; TAPSE = tricuspid annular plane systolic excursion; CO = cardiac output; CVP = central venous pressure; LASV = left atrial volume during ventricular systole; MAP = mean arterial blood pressure; mPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RASV = right atrial volume during ventricular systole; BMI = body mass index.

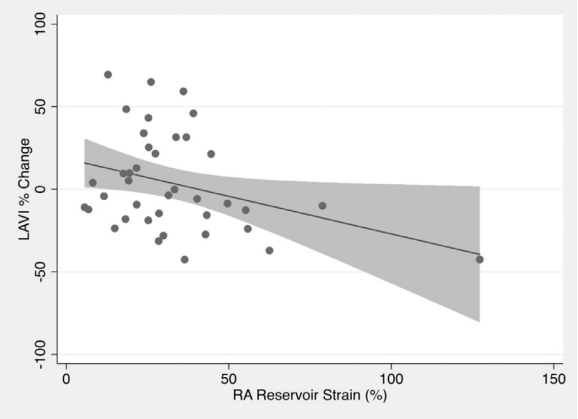

Figure 2. Percent change in left atrial volume index from baseline to 6-month follow-up in relation to baseline RA reservoir strain.

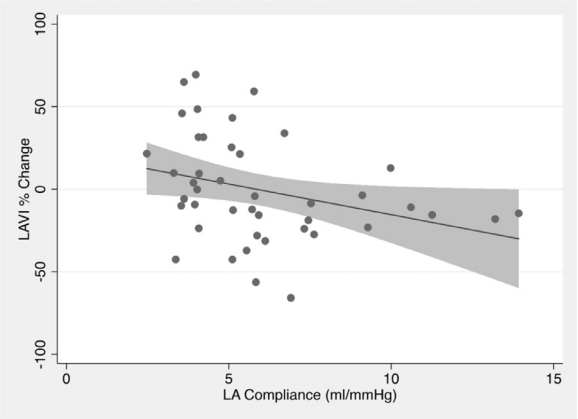

Figure 3. Percent change in left atrial volume index from baseline to 6-month follow-up in relation to baseline LA compliance.

significant relation with LAVI change. Nor did patients with a drop in LAVI have any difference in baseline pulmonary vascular resistance or change in pulmonary vascular resistance at 6 months that could explain the impact of RVEF. There was, however, a significant increase in LAVI associated with higher baseline cardiac output by Fick estimation (Table 2b). This relation did not hold for cardiac output measured by thermodilution at rest or exercise. No association with change in LAVI was seen with baseline serum creatinine, diuretic dose, NT-pro BNP, age, or hemoglobin (Table 2c).

All variables with univariate p $\leq$0.05 in association with 6-month percent change in LAVI were included in an initial multivariable logistic regression model. These included baseline RVEF, the ratio of LA to RA volumes, resting Fick cardiac output, LA compliance, and RA reservoir and conduit strain. However, given that RA reservoir and conduit strain were equivalent in all patients with atrial fibrillation, conduit strain generated excessive multicollinearity and was dropped from the model. Finally, atrial fibrillation was included in the multivariable model due to its important a priori contribution to LA mechanics. Table 3 shows that a percent decrease in LAVI from baseline to 6 months remained independently associated with a higher baseline LA compliance as well as higher baseline RA reservoir strain.

Discussion

HFpEF and HFmrEF have proven difficult to treat in a number of large trials of neurohormonal inhibition.[2–4,17] The safety, feasibility, and potential clinical efficacy of an IASD in HFpEF/HFmrEF was demonstrated in the REDUCE LAP-HF study,[7,10] but the effect on LAVI over a 6-month follow-up period was heterogeneous. In this study, we sought to determine baseline characteristics that would predict a favorable reduction in LAVI following IASD, a surrogate end point for reversal or stabilization of chronic LA remodeling.

In the multivariable analysis, higher baseline LA compliance predicted a greater decrease in LAVI from baseline to 6 months. The change in LAVI was greatest in patients with baseline PCWP-CVP gradient above the median. Thus, patients with a greater initial driving pressure from LA to RA and a more compliant LA had the greatest LA volume reduction, corroborating recent data that the PCWP dropped more after IASD in patients with a larger PCWP-CVP gradient.[18]

Higher baseline RA reservoir strain also independently predicted a decrease in LAVI at 6 months in a small number of patients with particularly high baseline RA reservoir strain. Strain imaging, which detects subtle changes in tissue relaxation properties, may predict response to device therapy by discriminating impaired versus preserved RA relaxation at baseline. The RA acts as a reservoir during ventricular systole, a conduit during early diastole, and a contractile pump during late diastole if atrial contraction occurs. During the reservoir phase, the RA stretches to accommodate incoming blood from the great veins and, in the setting of an IASD, the LA. Thus, RA reservoir strain acts as a summative measure of both RA compliance and relaxation properties. Patients with exceptionally robust RA reservoir strain may have an improved ability to accept the increased volume load created by a left-to-right shunt, translating into greater load-dependent volume reduction or durable LA remodeling after IASD. Conversely, RA conduit and booster strain primarily reflect RV compliance and RA contractility.[19] Although improved RA conduit and booster function could hypothetically improve LA volume, this was not seen in this study—with the caveat that atrial fibrillation greatly impedes measurement of these 2 parameters.

It is notable that neither LV global longitudinal strain nor any LA strain parameters predicted LA volume response, whereas LA compliance did. Although indices of

Table 3
Multivariable linear regression—independent association of significant baseline covariates with % change in left atrial volume index at 6 months following implantation of an interatrial shunt device

Variable	% Change in LAVI (95% CI)	p Value
RVEF (%)	0.2 (−0.8, 1.3)	0.7
LA/RA volume ratio	−19.8 (−52.7, 13.2)	0.2
CO rest, fick (L/min)	8.8 (−0.3, 17.9)	0.057
LA compliance (ml/mm Hg)	−4.2 (−8.4, −0.05)	0.048
RA reservoir strain (%)	−0.8 (−1.3, −0.3)	0.005
Atrial fibrillation (presence)	−15.4 (−42.0, 11.1)	0.2

LA = left atrial; RA = right atrial; RVEF = right ventricular ejection fraction.

LA mechanics—particularly LA reservoir strain—have been shown to predict adverse outcomes in patients with HFpEF,[20] LA compliance appears here to be more important than LA strain in determining volume offloading. LA compliance more directly represents the expected relation between pressure unloading and a change in volume, whereas LA relaxation mechanics measured by LA reservoir strain may be less important in the longitudinal volume response to an IASD.

The IASD assessed in the REDUCE LAP-HF study is a promising tool in the efforts to reduce morbidity and mortality in HFpEF/HFmrEF. Given the diverse presentation of this disease, it is important to develop an understanding of baseline parameters that may predict success with the device in order to optimize patient selection both clinically and for future trials. In this analysis, higher LA compliance and RA reservoir strain at baseline predicted a larger decrease in LAVI from baseline to 6 months, both of which are mechanistically plausible. This analysis lacked statistical power to analyze associations between the change in LAVI at 6 months as a surrogate end point and more direct measures of clinical improvement. Further work examining these granular parameters of atrial function in a larger cohort of randomized patients is necessary to validate their role in patient selection for the IASD.

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.09.019.

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