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# Left Atrial Function Dynamics During Exercise in Heart Failure

## Pathophysiological Implications on the Right Heart and Exercise Ventilation Inefficiency

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**ABSTRACT**

**OBJECTIVES** The hypothesis of this study was that left atrial (LA) dynamic impairment during exercise may trigger right ventricular (RV)-to-pulmonary circulation (PC) uncoupling and ventilation inefficiency.

**BACKGROUND** LA function plays a key role in the hemodynamics of heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). Extensive investigation of LA dynamics, however, has been performed exclusively at rest.

**METHODS** A total of 49 patients with HFrEF, 20 patients with HFpEF, and 32 healthy subjects with normal LA size and reservoir function (LA volume index $<34$ ml/m$^2$ and peak left atrial strain [LA-strain] during LA relaxation $>23\%$) were prospectively enrolled. They underwent cardiopulmonary exercise testing and contemporary echo-Doppler assessment of LA-strain and LA-strain rate and of RV-to-PC coupling (pulmonary arterial systolic pressure/tricuspid annular peak systolic excursion ratio), measured at rest, at 40% of predicted peak oxygen consumption, and during recovery.

**RESULTS** In control subjects, LA-strain increased during exercise and recovery. Patients with HFpEF exhibited some LA-strain increase during exercise and recovery, whereas no changes occurred in those with HFrEF. The baseline LA-strain rate was greater in control subjects; a significant enhancement during recovery was observed only in this group. In both the HFpEF and HFrEF cohorts, RV-to-PC uncoupling and LA-strain at rest, exercise, and recovery significantly correlated with pulmonary arterial systolic pressure/tricuspid annular peak systolic excursion, as well as ventilation versus carbon dioxide slope, in a continuous fashion across groups ($r = -0.63$ and $r = -0.59$, $r = -0.65$ and $r = -0.50$, and $r = -0.70$ and $r = -0.53$ for control subjects, HFpEF, and HFrEF, respectively; $p < 0.05$).

**CONCLUSIONS** In heart failure, an impaired LA-strain response is a key hemodynamic trigger for RV-to-PC uncoupling and exercise ventilation inefficiency with some overlap between HFpEF and HFrEF phenotypes. Reversibility of LA dynamics seems to be an unmet target of specific therapeutic interventions. (J Am Coll Cardiol Img 2017;■:■–■)


In heart failure (HF), left atrial (LA) dysfunction is a mediator of impaired cardiac dynamics well recognized since the pioneering observations of Braunwald et al. (1) >50 years ago. Growing evidence suggests that LA dysfunction is actively involved in symptoms and disease progression.

The left atrium is extremely sensitive to sustained volume and pressure overload secondary to increased left ventricular (LV) filling pressures (2), and the stepwise backward effects of loss in LA functional properties are a reduction in lung vessel compliance and vascular remodeling that may trigger

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**ABBREVIATIONS AND ACRONYMS**

**2DSTE** = 2-dimensional speckle-tracking echocardiography

**$CO_2$** = carbon dioxide

**CPET** = cardiopulmonary exercise test

**HFpEF** = heart failure with preserved ejection fraction

**HFrEF** = heart failure with reduced ejection fraction

**LA-strain** = left atrial strain

**LA-SRa** = left atrial strain rate

**LAVI** = left atrial volume index

**LV** = left ventricular

**LVEF** = left ventricular ejection fraction

**MR** = mitral regurgitation

**PASP** = pulmonary artery systolic pressure

**PC** = pulmonary circulation

**RV** = right ventricular

**TAPSE** = tricuspid annular plane systolic excursion

**$VE/VCO_2$** = ventilation to carbon dioxide production rate

**$VO_2$** = oxygen consumption

right ventricular (RV) overload and dysfunction (3). Accordingly, the evolving stages of heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF) are associated with RV-to-pulmonary circulation (PC) uncoupling, gas exchange impairment, and exercise ventilation inefficiency (4,5).

Recent studies of LA function by using 2-dimensional speckle-tracking echocardiography (2DSTE) (6) have shown an association between LA function at rest and LV filling pressure, LV diastolic function, atrial fibrillation, mitral regurgitation (MR), HF symptoms, exercise capacity, and cardiovascular outcomes (7,8). Nonetheless, these studies have not systematically addressed the LA function contribution to the pathophysiology of exercise performance. 2DSTE and tissue-Doppler imaging combined with exercise stress echocardiography offer the opportunity to study the left and right heart functional adaptations during exercise by analyzing the specific role of the left atrium. This approach seems relevant considering that a true contribution of LA dysfunction in the dyspnea sensation and early exercise intolerance in HF has never been investigated. To this purpose, combining stress echocardiography with measures of gas kinetics, including lung mechanics and ventilation by using a cardiopulmonary exercise test (CPET), seems attractive. We hypothesized that the left atrium is a fundamental key player in determining exercise limitation, ventilation inefficiency, and RV-to-PC uncoupling in patients with HF. Along with this hypothesis, our goal was to define differences in LA dynamics between patients with HFpEF and HFrEF.

## METHODS

**STUDY POPULATION.** Consecutive patients with or without HF, referred to our center between January 2013 and September 2015 for functional assessment, were considered for recruitment in this prospective study. A total of 76 patients with HF and 38 non-HF subjects with normal LV function, LA size, and reservoir function (left ventricular ejection fraction [LVEF] >50%, left atrial volume index [LAVI] <34 ml/$m^2$, and left atrial strain [LA-strain] peak during LA relaxation >23%) (6,9), underwent CPET combined with simultaneous echocardiography. Eligible patients were patients with HFrEF or HFpEF. HF was defined by a cardiologist-adjudicated HF diagnosis of >6 months' duration. Specifically, patients with HFrEF were recruited on the basis of LVEF <40% and signs and symptoms of HF according to the Framingham criteria. A diagnosis of HFpEF was made on the basis of signs and symptoms of HF and echocardiography findings according to the criteria of Paulus et al. (10). The ability to perform maximal exercise testing with gas exchange was taken as a mandatory inclusion criterion.

Exclusion criteria were recent myocardial infarction (<3 months), unstable angina, inducible myocardial ischemia, aortic stenosis, atrial fibrillation, peripheral artery disease, significant anemia (hemoglobin <10 g/dl), and respiratory diseases of at least moderate degree. All patients with HFrEF and 5 HFpEF underwent coronary angiography. All patients signed 2 informed consent forms, 1 for the execution of the test and the other for the research use of clinical and instrumental data, approved by our local ethical committee. Habitual therapy was maintained during the study.

**EXERCISE ECHOCARDIOGRAPHY.** A complete echocardiographic evaluation was performed at rest, recording standard images to assess LV systolic, diastolic, and valvular function. The Online Appendix provides a description of this evaluation.

Based on previous validated studies and guidelines on myocardial mechanisms of the American Society of Echocardiography/European Association of Cardiovascular Imaging, LA dynamics was evaluated by using LA-strain and left atrial-strain rate (LA-SRa) (11), the first for assessing reservoir function and the second for booster pump function. These measurements were derived from the myocardial analyses of the left atrium in a longitudinal direction in the apical 4-chamber and 2-chamber views and using QRS onset as the reference point. During exercise and in the recovery period, LA-strain was obtained by averaging all segment strain values from the apical 4-chamber views. Because there is no standardized method for atrial analysis, the kernel was narrowed as much as possible to optimally adapt to the thinner LA wall (12). We analyzed LA-strain and LA-SRa during exercise at a similar level of oxygen consumption ($VO_2$) (40% of maximal exercise based on a previous reference test). The intraobserver variability was 9% and 6%, respectively, for LA-SRa and LA-strain, based on a sample size of 20 subjects.

**CARDIOPULMONARY EXERCISE TEST.** A symptom-limited CPET was performed on a cycle ergometer by all subjects. Incremental ramp protocols were

**TABLE 1 Clinical Characteristics and Therapy Distribution**

| | Non-HF | HF (n = 69) | | p Value | |
|---|---|---|---|---|---|
| | LA Control (n = 32) | HFrEF (n = 49) | HFpEF (n = 20) | LA Control Versus HF | HFrEF Versus HFpEF |
| Age, yrs | 56.5 ± 14.6 | 63.1 ± 12.9 | 72.6 ± 10.3 | 0.002 | 0.005 |
| Male | 38 | 69 | 40 | 0.03 | 0.03 |
| Body mass index, kg/m$^2$ | 25.6 ± 4.3 | 26.7 ± 4.5 | 28.3 ± 5.0 | 0.10 | 0.20 |
| Systolic blood pressure, mm Hg | 127 ± 14 | 123 ± 15 | 131 ± 14 | 0.60 | 0.06 |
| Heart rate, beats/min | 74 ± 13 | 70 ± 11 | 69 ± 12 | 0.10 | 0.50 |
| Hypertension | 66 | 63 | 74 | >0.99 | 0.60 |
| Ischemic heart disease | 0 | 52 | 10 | 0.001 | 0.05 |
| Diabetes mellitus | 6 | 35 | 42 | 0.001 | 0.60 |
| Dyslipidemia | 41 | 67 | 58 | 0.03 | 0.60 |
| Current or ex-smoker | 22 | 37 | 42 | 0.10 | 0.80 |
| Previous episodes of paroxysmal atrial fibrillation | 0 | 24 | 30 | 0.02 | 0.06 |
| Therapy | | | | | |
| ACE inhibitors or ARBs | 55 | 80 | 68 | 0.04 | 0.40 |
| Beta-blockers | 23 | 86 | 74 | <0.001 | 0.30 |
| Calcium-channel blockers | 13 | 6 | 16 | 0.70 | 0.30 |
| Loop diuretics | 29 | 78 | 63 | <0.001 | 0.20 |
| Aldosterone blockers | 3 | 47 | 26 | <0.001 | 0.20 |
| Ivabradine | 3 | 8 | 5 | 0.70 | >0.99 |
| Statins | 32 | 69 | 47 | 0.005 | 0.10 |
| Nitrates | 3 | 14 | 11 | 0.20 | >0.99 |

Values are mean ± SD or %.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; LA = left atrial.

designed to obtain a standard of exercise. The Online Materials provide a description.

**STATISTICAL ANALYSIS.** Qualitative variables were summarized as percentages and quantitative variables as mean ± SD. Parametric unpaired Student *t* tests were used to compare quantitative variables. The chi-square test or Fisher exact test was used to compare qualitative variables. One-way analysis of variance or Kruskal-Wallis tests were used to compare >2 groups. When a significant difference was found, post hoc testing with Bonferroni comparisons for identified specific group differences was used. Paired Student *t* tests or Wilcoxon tests were used to compare differences within groups. Pearson's correlation coefficient was used to examine the relationship between continuous variables. For all tests, a p value <0.05 (2-sided) was considered significant. Data were analyzed by using open source statistical software (R version 3.1.1, R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

**STUDY GROUPS.** From a cohort of 76 patients with HF undergoing a CPET combined with simultaneous exercise echocardiography, 7 (10%) patients were excluded because of poor echocardiographic image quality for LA-strain analysis in the apical 4-chamber view during exercise or in the recovery period. For the same reasons, 6 (16%) non-HF patients with a

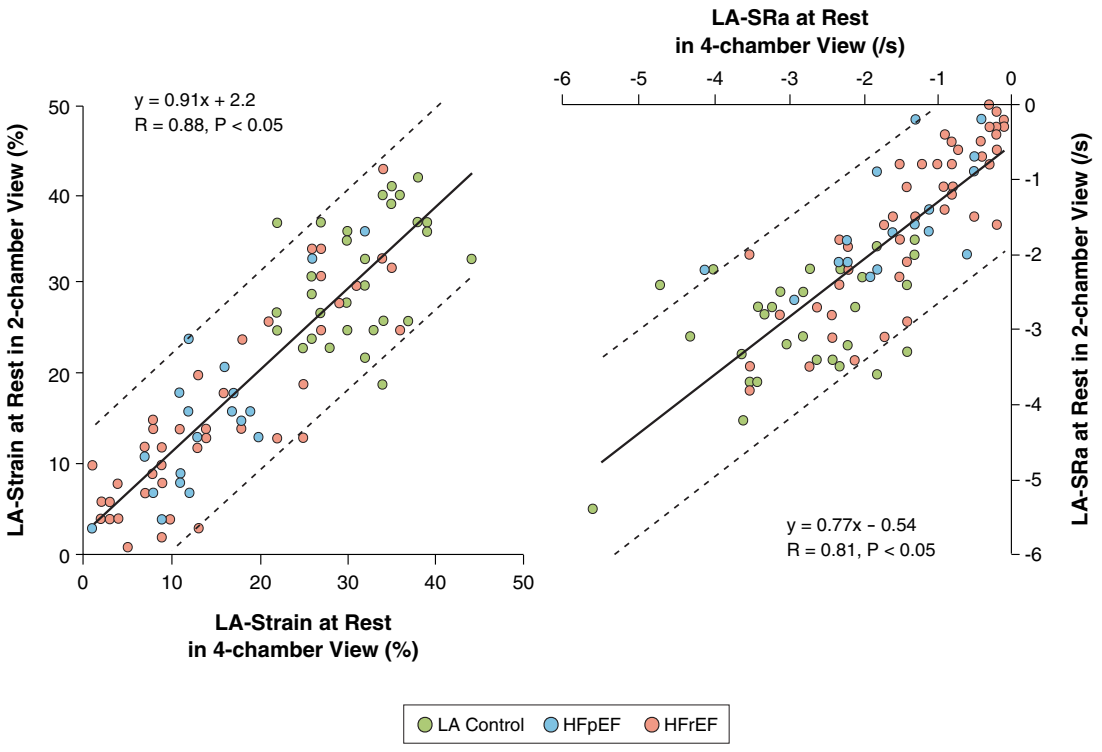
**TABLE 2 LA-Strain and LA-SRa According to Groups at Rest, During Exercise, and in Recovery Period**

| | LA Control (n = 32) | HFrEF (n = 49) | HFpEF (n = 20) | p Value |
|---|---|---|---|---|
| LA-strain, % | | | | |
| Apical 2- and 4-chamber views at rest | 31.1 ± 5.0 | 15.1 ± 10.1 | 14.7 ± 7.4 | <0.001 |
| Apical 2-chamber view at rest | 31.2 ± 6.4 | 15.3 ± 10.6 | 15.1 ± 8.6 | <0.001 |
| Apical 4-chamber view at rest | 31.1 ± 5.6 | 14.9 ± 10.3 | 14.3 ± 6.8 | <0.001 |
| Apical 4-chamber view during exercise | 39.8 ± 11.2 | 14.9 ± 11.5 | 19.5 ± 9.0 | <0.001 |
| Apical 4-chamber view in recovery period | 41.9 ± 10.2 | 16.9 ± 13.5 | 21.8 ± 9.8 | <0.001 |
| LA-SRa, per s | | | | |
| Apical 2- and 4-chamber views at rest | −2.82 ± 0.80 | −1.41 ± 0.99 | −1.42 ± 0.83 | <0.001 |
| Apical 2-chamber view at rest | −2.82 ± 0.80 | −1.51 ± 1.07 | −1.40 ± 0.78 | <0.001 |
| Apical 4-chamber view at rest | −2.77 ± 1.03 | −1.3 ± 0.98 | −1.43 ± 1.00 | <0.001 |
| Apical 4-chamber view during exercise | −3.09 ± 0.88 | −1.21 ± 1.01 | −1.52 ± 1.09 | <0.001 |
| Apical 4-chamber view in recovery period | −3.75 ± 1.33 | −1.34 ± 1.10 | −1.55 ± 1.03 | <0.001 |

Values are mean ± SD.

LA-strain = left atrial strain; LA-SRa = left atrial strain rate; other abbreviations as in Table 1.

**FIGURE 1** Correlations Between LA-Strain and LA-SRa Measurements in the Apical 4-Chamber and 2-Chamber Views



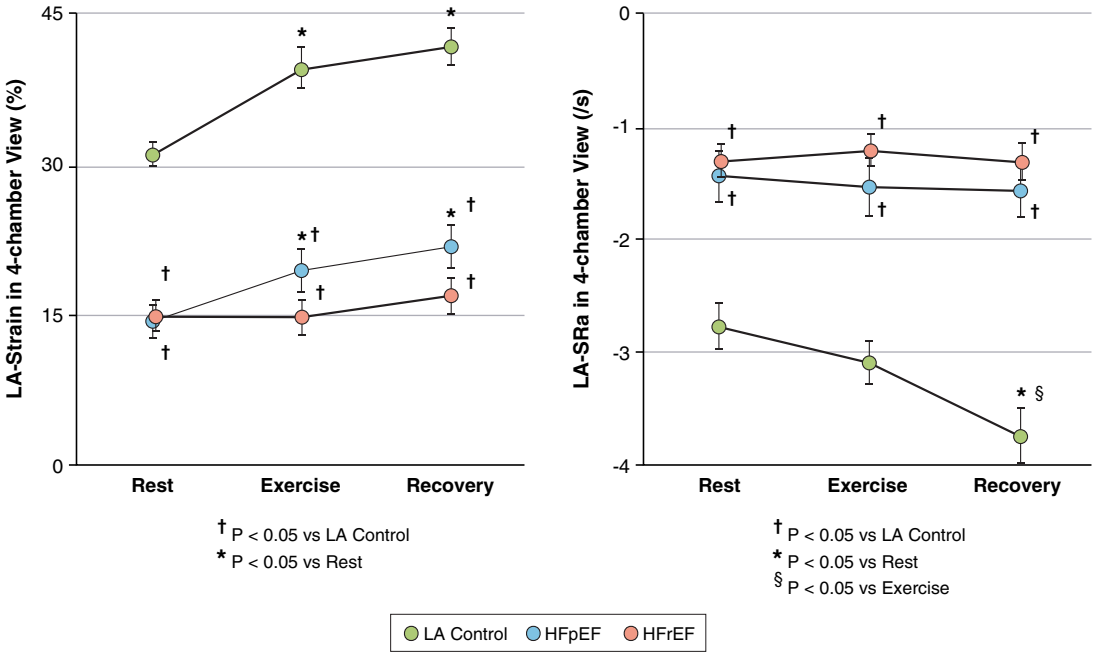

**Dotted lines** indicate 95% prediction bands. HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LA = left atrial; LA-strain = left atrial strain; LA-SRa = left atrial strain rate.

normal left atrium were excluded. Therefore, 69 patients with HF and 32 non-HF subjects with a normal left atrium (LA control) were included in the final analysis.

Patients with HF were divided into 2 groups according to LVEF at rest: HFpEF ≥50% (n = 20) versus HFrEF <40% (n = 49). Patients were older and prevalently male compared with control subjects. Patients with HFpEF were older and mainly female compared with HFrEF patients. No differences in prevalence of hypertension or smoking were found, whereas patients with HF were more likely to have diabetes mellitus and dyslipidemia and to be treated with renin-angiotensin system inhibitors, β-adrenergic receptor antagonists, loop diuretics, aldosterone antagonists, and statins. Fifty-two percent of patients with HFrEF had post-myocardial infarction dilated cardiomyopathy and 2 patients with HFpEF had microvascular angina. Ten patients with HFrEF and 6 with HFpEF had experienced a single episode of paroxysmal atrial fibrillation; in 2 patients with HFrEF, 2 episodes occurred. In all cases, paroxysmal atrial fibrillation occurred no more than 2 months before study enrollment (Table 1).

**LA-STRAIN AND LA-SRa ANALYSIS.** Significant differences were observed in LA-strain and LA-SRa at rest, during exercise, and in the recovery period among the 3 groups (Table 2). Percent predicted $VO_2$ for strain analysis during exercise was similar (control subjects, 37 ± 13%; HFpEF, 42 ± 13%; and HFrEF, 38 ± 16%; p = 0.50), but the corresponding heart rate was significantly different (control subjects, 102 ± 13 beats/min; HFpEF, 85 ± 12 beats/min; and HFrEF, 94 ± 14 beats/min; p < 0.001) among the 3 groups. The correlation coefficient between LA-strain at rest in the apical 4-chamber and 2-chamber views was 0.88 (p < 0.05). The correlation coefficient between LA-SRa at rest in the apical 4-chamber and 2-chamber views was 0.81 (p < 0.05) (Figure 1). In both the control subjects and patients

**FIGURE 2** Changes in LA-Strain and LA-SRa at Rest, Exercise, and Recovery in the 3 Groups



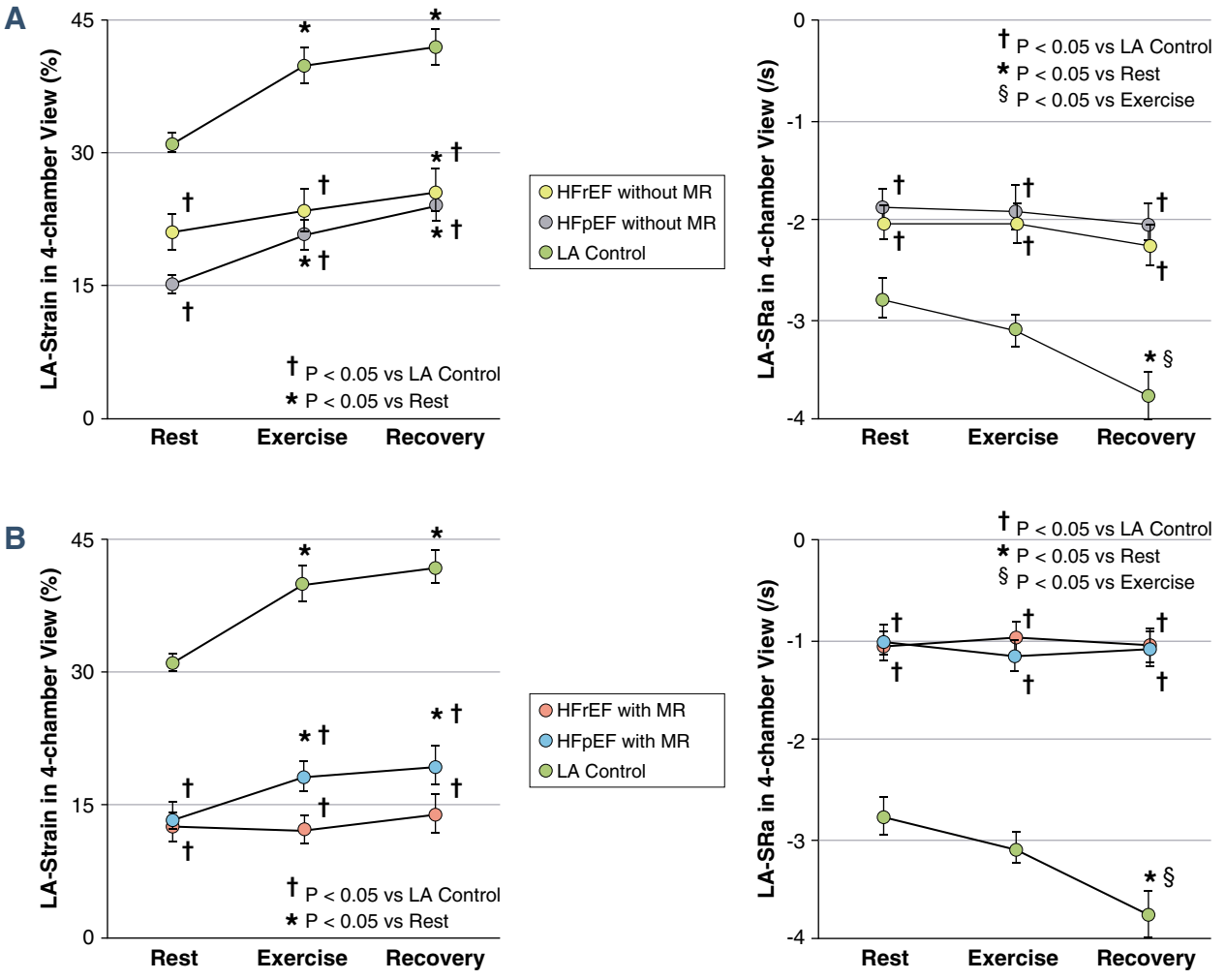

**Error bars** indicate standard error of the mean. Abbreviations as in Figure 1.

with HFpEF, 4-chamber LA-strain during exercise and in the recovery period was significantly increased compared with rest. LA-SRa on exercise and recovery did not vary from baseline in HFrEF and HFpEF (Figure 2). Similar findings were recorded when patients with HF were divided according to the presence of moderate to severe MR or no MR. Although either HFrEF (n = 24) and HFrEF (n = 6) with MR had a slightly worse pattern in LA-strain increase during exercise and recovery compared with no MR, it did not reach statistical significance (Figure 3A). The same is true for the LA-SRa pattern (Figure 3B). In control subjects but not in patients, LA-SRa in the recovery period was significantly enhanced compared with rest. Representative cases of LA-strain and LA-SRa patterns in control subjects, patients with HFpEF, and patients with HFrEF at rest, exercise, and the recovery phase are reported in Figure 4.

**CARDIOPULMONARY EXERCISE VARIABLES.** Compared with control subjects, patients with HF had lower maximal workload, peak $VO_2$, percent predicted peak $VO_2$, peak respiratory exchange ratio, heart rate recovery, and end-tidal carbon dioxide ($CO_2$), and a higher ventilation to carbon dioxide production rate ($VE/VCO_2$) slope and prevalence of $\Delta VO_2/\Delta$ work rate flattening (Table 3). Between HF groups, there were no differences in maximal workload, peak $VO_2$, peak respiratory exchange ratio, peak $O_2$ pulse, heart rate recovery, $VE/VCO_2$ slope, end-tidal $CO_2$ and exercise oscillatory ventilation prevalence, or $\Delta VO_2/\Delta$ work rate flattening. Despite similar levels of peak $VO_2$, patients with HFpEF presented with a significantly higher percent predicted peak $VO_2$.

**EXERCISE HEMODYNAMICS AND ECHOCARDIOGRAPHY.** No differences in systolic and diastolic blood pressure were observed among groups, while patients with HF had a lower systolic blood pressure response during exercise (Table 4). Heart rate at peak exercise was significantly lower in both the HFpEF group and the HFrEF group. Between groups, those with HFrEF had a higher LV end-diastolic volume index and LAVI and a lower relative wall thickness, LVEF, stroke volume index, and tricuspid annular plane systolic excursion (TAPSE) at rest. Patients with HFpEF and HFrEF had similar increases in estimated LV filling pressure (E/e′) and bigger RV

**FIGURE 3 Changes in LA-Strain and LA-SRa at Rest, Exercise, and Recovery in Patients With HF Divided According to the Presence of Significant MR or no MR Versus Control Subjects**

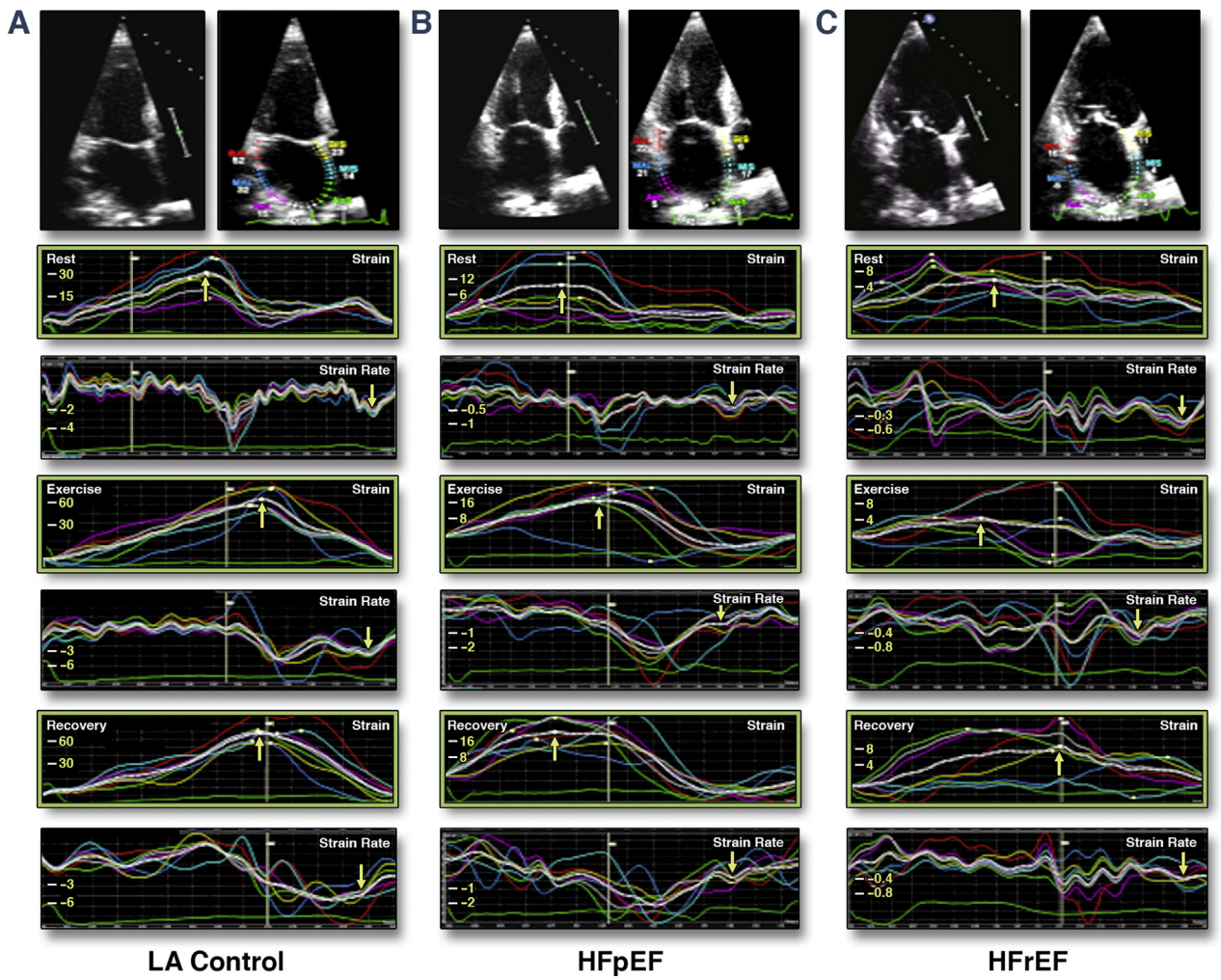



**Error bars** indicate standard error of the mean. HF = heart failure; MR = mitral regurgitation; other abbreviations as in Figure 1.

area and right atrial volume than control subjects. During exercise, patients with HFrEF had a higher prevalence of moderate/severe MR and lower LVEF, stroke volume index, and TAPSE. Significant increases in LVEF and prevalence of moderate/severe MR at peak exercise were observed only in patients with HFrEF.

As to RV-to-PC coupling, values of pulmonary artery systolic pressure (PASP)/TAPSE in patients were significantly higher than in control subjects both at rest and during exercise (control subjects, 1.12 ± 0.26 and 1.55 ± 0.41 mm Hg/mm; HFpEF, 1.78 ± 0.81 and 2.57 ± 1.08 mm Hg/mm; HFrEF, 2.53 ± 1.77 and 3.47 ± 1.7 mm Hg/mm, respectively; $p < 0.001$) and the increase in PASP/TAPSE at peak exercise was also greater in patients than in control subjects ($p < 0.05$). Among the HF groups, patients with HFrEF had a significantly higher PASP/TAPSE at peak exercise ($p = 0.03$) but not at rest ($p = 0.07$). Figure 5 describes the PASP/TAPSE versus LA-strain changes from rest to exercise. Interestingly, in both groups, despite a similar change in PASP/TAPSE, the reserve in LA strain was exhausted in HFrEF and partially preserved in HFpEF, with a progressive leftward shift in the relationship from control to HFrEF. Significant inverse correlations were observed between LA-strain at rest, during exercise, and recovery phase and the $VE/VCO_2$ slope ($R = -0.59$, $R = -0.5$, and $R = -0.53$,

**FIGURE 4** Representative Cases of 2DSTE LA Study Analysis




The myocardial reservoir and pump function of the left atrium were analyzed according to LA-strain and LA-SRa, respectively. The **fragmented white curve** indicates the average of LA-strain and LA-SRa from all segments of the left atrium. **(A)** LA control. LA-strain and LA-SRa increase during exercise (LA-strain, 31% to 59%; LA-SRa, −2.1 to −3.7/s). **(B)** In the case of HFpEF, LA-strain and LA-SRa increased during exercise (LA-strain, 10% to 16%; LA-SRa, −0.3 to −0.3/s). **(C)** In the case of HFrEF, LA-strain and LA-SRa remained unchanged during exercise (LA-strain, 6% to 5%; LA-SRa, −0.5 to −0.4/s). 2DSTE = 2-dimensional speckle-tracking echocardiography; other abbreviations as in Figure 1.

respectively; $p < 0.05$) (Figure 6A) among all groups. Similarly, LA-strain inversely correlated with PASP/TAPSE at rest, exercise, and the recovery phase ($R = -0.63$, $R = -0.65$, and $R = -0.70$, respectively; $p < 0.05$) (Figure 6B).

**LA SIZE AND STRAIN PHENOTYPE SUBDIVISION.** Irrespective of LVEF, patients with HF were divided into 4 groups according to baseline LA size (<34 ml/m$^2$>) and LA-strain (<23%>). Fifty-one patients (73% of the HF population) presented with an enlarged left atrium and impaired LA reservoir function (group A, LAVI >34 ml/m$^2$ and LA-strain ≤23%), and 11 (16%) had LA dimension and function (group B) similar to the control group. Among patients with HF, 4 patients (6%) had normal LA size and impaired LA reservoir function (group C, LAVI <34 ml/m$^2$ and LA-strain ≤23%) and 3 patients (4%) had enlarged LA size and normal LA reservoir function (group D, LAVI ≥34 ml/m$^2$ and LA-strain >23%) (Figure 7A). There were significant differences in age and sex (group A, 55 ± 12 years and 55% male; group B, 68 ± 11 years and 65% male; group C, 68 ± 20 years and 0% male; and

**TABLE 3 CPET Variables**

| | Non-HF | HF (n = 69) | | p Value | |
|---|---|---|---|---|---|
| | Control (n = 32) | HFrEF (n = 49) | HFpEF (n = 20) | Control Versus HF | HFrEF Versus HFpEF |
| Maximal work, W | 95.7 ± 40.0 | 61.4 ± 23.4 | 71.4 ± 22.2 | <0.001 | 0.10 |
| Peak $VO_2$, ml/kg/min | 18.5 ± 6.0 | 12.5 ± 3.8 | 13.5 ± 3.5 | <0.001 | 0.30 |
| Percent predicted peak $VO_2$, % | 67 ± 20 | 51 ± 16 | 67 ± 23 | 0.01 | 0.001 |
| Peak RER | 1.19 ± 0.12 | 1.11 ± 0.12 | 1.17 ± 0.12 | 0.02 | 0.09 |
| Peak $O_2$ pulse, ml/beats | 9.9 ± 2.9 | 8.9 ± 3.0 | 9.7 ± 3.2 | 0.20 | 0.30 |
| HRR, beats/min | 14.8 ± 7.9 | 9.6 ± 7.4 | 9.8 ± 8.5 | 0.003 | 0.90 |
| $VE/VCO_2$ slope | 26.9 ± 3.8 | 34.7 ± 11.1 | 30.2 ± 6.9 | 0.001 | 0.09 |
| Peak end-tidal $CO_2$, mm Hg | 38.0 ± 4.3 | 33.0 ± 5.6 | 35.4 ± 5.1 | <0.001 | 0.10 |
| EOV | 16 | 35 | 25 | 0.10 | 0.60 |
| $\Delta VO_2/\Delta WR$ flattening | 3 | 19 | 35 | 0.01 | 0.20 |

Values are mean ± SD or %.

$\Delta VO_2/\Delta WR$ = Δ oxygen consumption/Δ work rate; $CO_2$ = carbon dioxide; CPET = cardiopulmonary exercise test; EOV = exercise oscillatory ventilation; HRR = heart rate recovery; RER = respiratory exchange ratio; $VE/VCO_2$ = ventilation over carbon dioxide; other abbreviations as in Table 1.

group D, 62 ± 19 years and 100% male, respectively; $p < 0.05$). Compared with groups A and D, groups B and C had a tendency to increase LA-strain and presented with a lower PASP/TAPSE at exercise. Patients with moderate/severe MR at rest and peak exercise were distributed between group A (95%) and group D (5%). Figure 7B describes the PASP/TAPSE versus LA-strain changes from rest to exercise in the 4 groups versus control subjects.

Online Table 1 reports the clinical characteristics of control subjects and HFrEF enrolled patients versus subjects excluded for poor image qualities. Online Figure 1 illustrates the setting of our laboratory while performing a combined echo-Doppler and CPET.

## DISCUSSION

A thorough analysis of LA dynamics by speckle tracking assessment during rest, exercise, and recovery provided evidence that in HF, of either normal or reduced ejection fraction, LA reservoir function is impaired and plays a key role in the abnormal right heart hemodynamic response during exercise. Specifically, the lack of LA reservoir function is per se associated with RV-to-PC uncoupling, both at rest and on exertion along with exercise ventilation inefficiency. At variance with HFrEF, patients with HFpEF maintained some ability to increase LA-strain during exercise and recovery, whereas no reserve in LA contractility (LA-SRa) was observed in either HF phenotype. To the best of our knowledge, this study is the first that addresses the dynamics of the LA response during exercise in a

**TABLE 4 Physiological and Echocardiographic Parameters According to HF Groups at Rest and Peak of Exercise**

| | Non-HF | | HF (n = 69) | | | | p Value | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | LA Control (n = 32) | | HFrEF (n = 49) | | HFpEF (n = 20) | | LA Control Versus HF | | HFrEF Versus HFpEF | |
| | Rest | Peak | Rest | Peak | Rest | Peak | Rest | Peak | Rest | Peak |
| Systolic BP, mm Hg | 127 ± 14 | 190 ± 29 | 123 ± 15 | 155 ± 26 | 131 ± 14 | 179 ± 28 | 0.60 | <0.001 | 0.06 | 0.001 |
| Diastolic BP, mm Hg | 77 ± 5 | 80 ± 7 | 78 ± 7 | 77 ± 7 | 80 ± 5 | 79 ± 6 | 0.97 | 0.30 | 0.40 | 0.30 |
| Heart rate, beats/min | 74 ± 13 | 131 ± 24 | 70 ± 11 | 107 ± 19 | 69 ± 12 | 107 ± 21 | 0.10 | <0.001 | 0.50 | 0.90 |
| LV mass index, $g/m^2$ | 79 ± 16 | | 135 ± 33 | | 125 ± 31 | | <0.001 | | 0.30 | |
| LV end-diastolic volume index, $ml/m^2$ | 41 ± 7 | | 98 ± 31 | | 57 ± 22 | | <0.001 | | <0.001 | |
| Relative wall thickness | 0.39 ± 0.06 | | 0.31 ± 0.11 | | 0.43 ± 0.15 | | 0.05 | | <0.001 | |
| LA volume index, $ml/m^2$ | 24 ± 6 | | 55 ± 29 | | 52 ± 24 | | <0.001 | | 0.70 | |
| E/A | 1.05 ± 0.29 | | 1.55 ± 1.14 | | 1.27 ± 0.9 | | 0.04 | | 0.40 | |
| E/e′ | 11 ± 3 | | 24 ± 13 | | 20 ± 8 | | <0.001 | | 0.20 | |
| LV ejection fraction, % | 67 ± 6 | 74 ± 5 | 31 ± 8 | 34 ± 11 | 56 ± 11 | 57 ± 16 | <0.001 | <0.001 | <0.001 | <0.001 |
| Cardiac output, l/min | 4.1 ± 1.1 | 8.8 ± 2.5 | 3.5 ± 1 | 5.8 ± 2.1 | 3.8 ± 0.8 | 6.7 ± 1.6 | 0.02 | <0.001 | 0.20 | 0.09 |
| Stroke volume index, $ml/m^2$ | 31.6 ± 5.6 | 38 ± 6.3 | 27.4 ± 7.5 | 29.9 ± 8.7 | 32.3 ± 8.7 | 36.2 ± 8.8 | 0.09 | 0.001 | 0.01 | 0.007 |
| Mitral regurgitation ≥3 | 0 | 0 | 49 | 55 | 29 | 35 | 0.001 | <0.001 | 0.40 | 0.01 |
| Systolic PAP, mm Hg | 26.1 ± 5.9 | 43.1 ± 10.7 | 35.6 ± 13.8 | 53.9 ± 12.6 | 33.5 ± 10.2 | 54.9 ± 14.2 | <0.001 | <0.001 | 0.50 | 0.80 |
| TAPSE, mm | 23.6 ± 3.3 | 28.0 ± 2.9 | 16.6 ± 4.9 | 17.7 ± 5.3 | 20.5 ± 4.9 | 23.1 ± 5.5 | <0.001 | <0.001 | 0.004 | <0.001 |
| RV fractional area change, % | 50 ± 8 | 55 ± 6 | 42 ± 14 | 41 ± 13 | 43 ± 8 | 45 ± 10 | 0.003 | <0.001 | 0.70 | 0.20 |
| RA area, $cm^2$ | 15.9 ± 3.5 | | 19.7 ± 5.1 | | 20.3 ± 5.8 | | <0.001 | | 0.70 | |
| RA volume, ml | 44.3 ± 16 | | 62.4 ± 26.1 | | 65.6 ± 29.2 | | <0.001 | | 0.70 | |

Values are mean ± SD or %.

BP = blood pressure; E/A = the ratio of the mitral peak velocity of the early filling (E) wave to the atrial contraction (A) wave; E/e′ = the ratio of E to early diastolic mitral annular velocity (e′); LV = left ventricular; PAP = pulmonary artery pressure; RA = right atrial; RV = right ventricular; TAPSE = tricuspid annual plane systolic excursion; other abbreviations as in Tables 1 and 2.

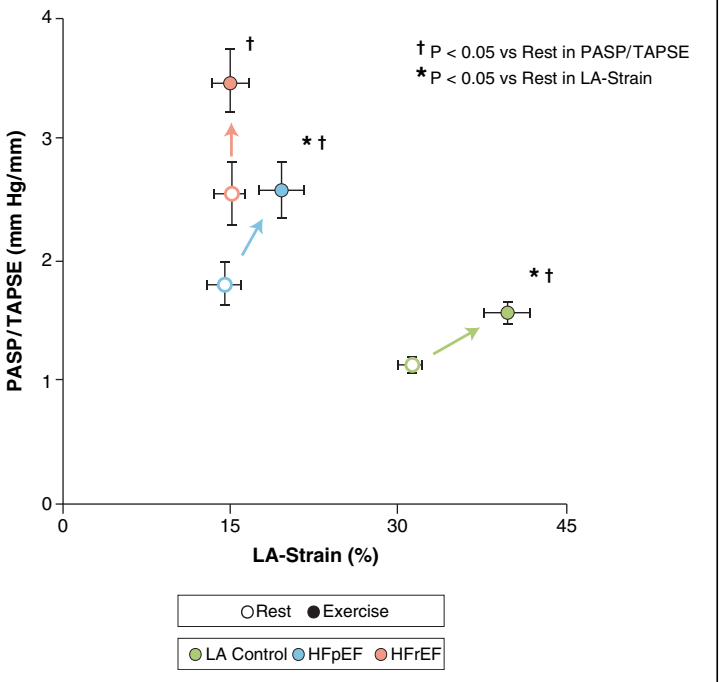
population of HF patients of both systolic and diastolic origin.

**CONTRIBUTORY ROLE OF ALTERED LA DYNAMICS TO FUNCTIONAL PERFORMANCE AND EXERCISE VENTILATION INEFFICIENCY.** Experimental studies have established that, under physiological conditions, LA reservoir and pump functions are augmented during exercise, whereas the conduit function does not change (13). The increased reservoir property is considered functional to the speed of LV filling by keeping the atrioventricular diastolic pressure gradient enhanced and increasing LA pump function through a preload mechanism. LA reservoir and pump functions have also been reported to be augmented in patients with early-stage LV filling impairment but to be blunted in patients with HFrEF and a restrictive LV filling pattern (14). Studies using 2DSTE at rest have identified LA-strain as a major correlate of exercise intolerance (15). In the present study, LA size and function were evaluated by LA volume indexed to body surface area and strain analysis using 2DSTE according to guideline recommendations (9,11). LA-strain also has a weak negative correlation with age and body mass index, and LA-SRa has a weak positive correlation with age (16).

The present data show that in HF, despite similar levels of aerobic efficiency, patients with HFpEF may still have some reserve of increasing LA-strain during exercise, whereas those with HFrEF do not. Nonetheless, compared with control subjects, patients with both HF phenotypes failed to increase LA-SRa in the recovery phase. The observed significant association between LA-strain at rest and $VE/VCO_2$ slope, a consolidated strong prognosticator in HF (17), is noteworthy because it prospects direct implications of LA impaired hemodynamics in the abnormal ventilatory response during exercise, a finding new in itself.

**LA DYSFUNCTION AND RV-TO-PC UNCOUPLING.** Multiple hemodynamic factors underpin a loss of RV contractile reserve and RV-to-PC uncoupling during exercise in patients with HF. Before the development of a lung vascular remodeling process, the main determinant of an impaired right heart hemodynamic adaptation to exercise is the backward transmission of LA pressure, which is commonly due to impeded LV filling, otherwise defined as increased pulsatile loading (3). An impaired LA reservoir function may translate into a loss of pulmonary vessel compliance, as reported in previous observations by Melenovsky et al. (18).

**FIGURE 5 Changes From Rest to Exercise in RV-to-PC Coupling (PASP/TAPSE) Versus LA-Strain in the 3 Groups**

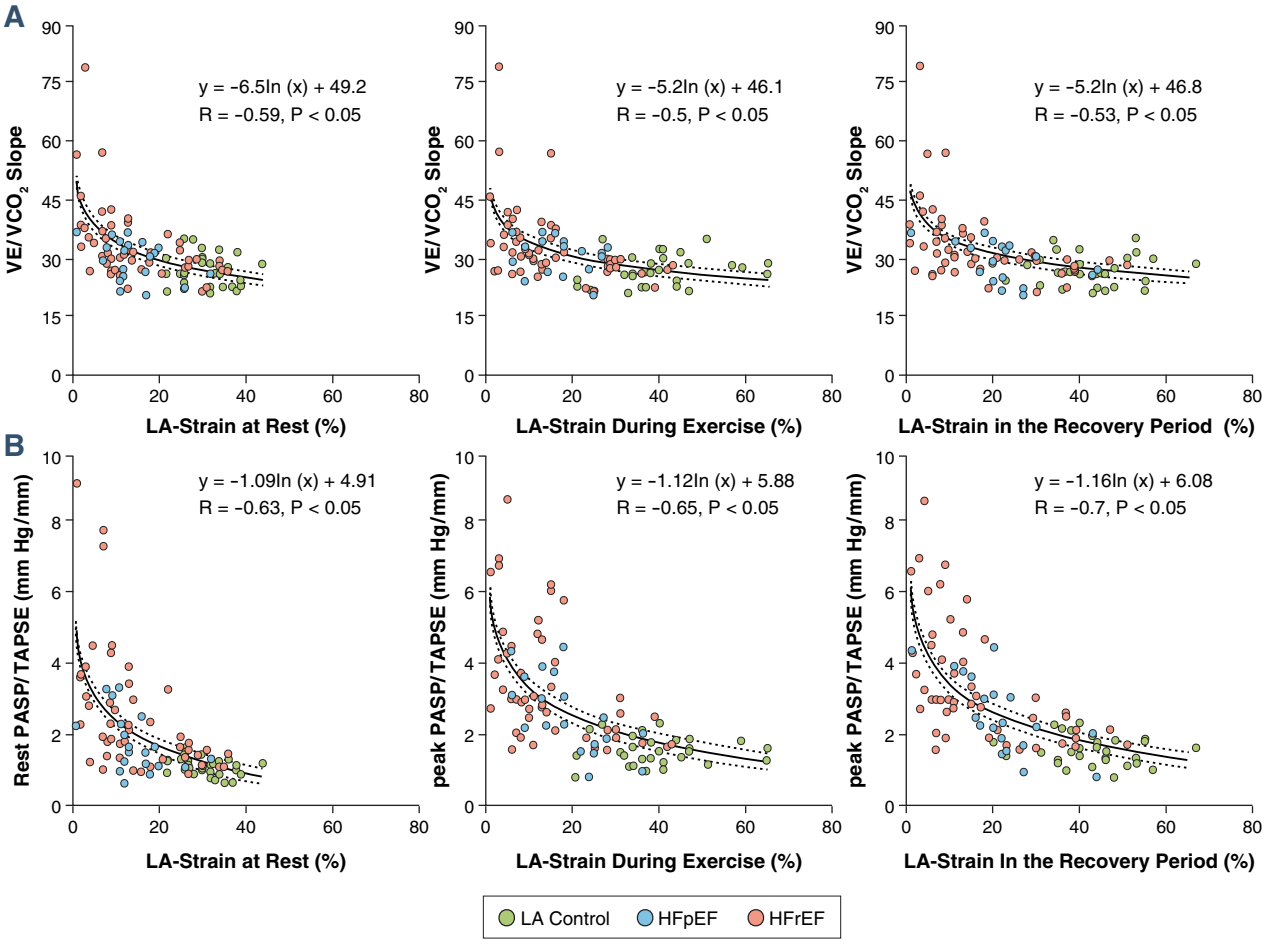



**Error bars** indicate SEM. PASP = pulmonary artery systolic pressure; PC = pulmonary circulation; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion; other abbreviations as in **Figure 1**.

Overall, an analysis of the LA dynamics may define the role of an abnormal atrial pulsatile loading in the right heart maladaptation to exercise. Findings of our study move into this direction. Indeed, LA-strain showed a strong hyperbolic correlation with the PASP/TAPSE ratio, a variable reflecting RV-to-PC coupling (19,20), at rest, exercise, and recovery. Even though the influence of MR on LA function cannot be precisely evaluated because of the biphasic response of LA reservoir function to different degrees of MR (21), a relevant question is to define the role of MR in the present findings. The subanalysis performed in the MR versus non-MR subgroups of HFrEF and HFpEF showed a similar pattern of LA-strain and LA-SRa, suggesting that an increased LAVI, whatever the reason may be, is the main driver of an impaired LA dynamics and contractility.

Future studies are warranted to clarify the relative contribution of this important relationship. Although patients with HFrEF exhibited the more unfavorable RV-to-PC uncoupling with no atrial

**FIGURE 6 Correlations Between Ventilation to Carbon Dioxide Production Rate ($VE/VCO_2$) Slope and PASP/TAPSE at Rest During Exercise and Recovery**



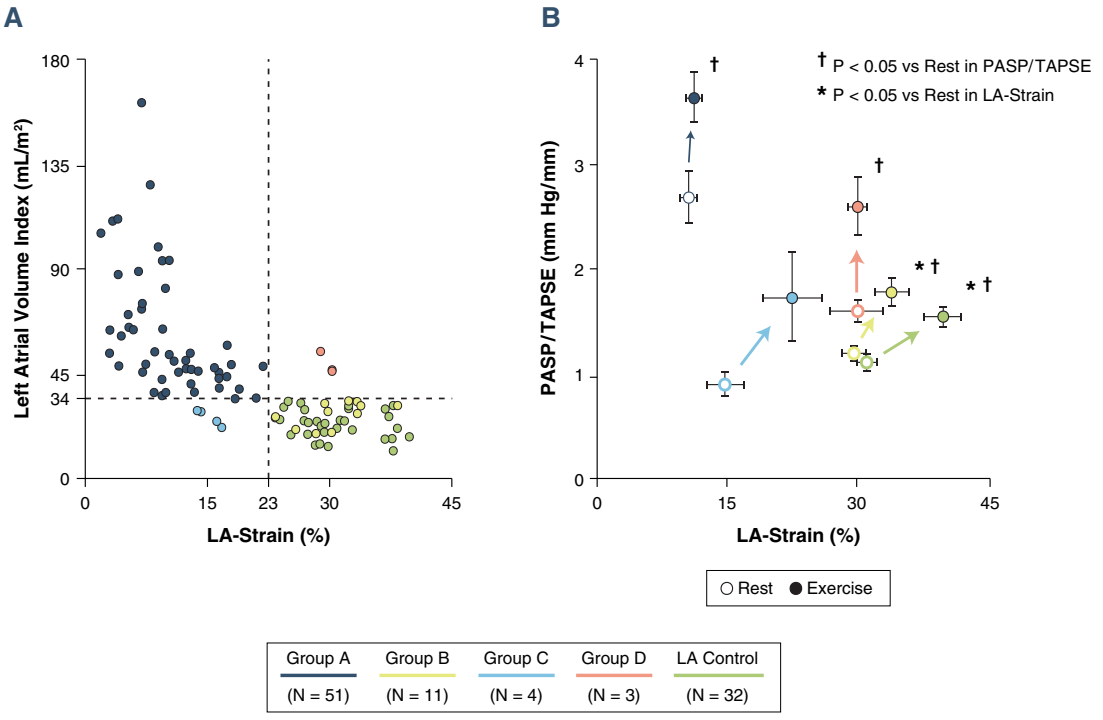

**(A)** Correlations between LA strain at rest, during exercise and in the recovery phase with $VE/VCO_2$ slope. **(B)** Correlations between LA strain at rest with rest PASP/TAPSE; LA strain during exercise with peak TAPSE/PASP and LA strain in the recovery phase with peak PASP/TAPSE. Control subjects were distributed in the most favorable portion of the curve at variance with patients with HFrEF, who were in the most unfavorable relation. Patients with HFpEF were distributed in the middle between control subjects and patients with HFrEF. **Dotted lines** indicate 95% confidence bands. Abbreviations as in Figures 1 and 5.

reserve function, those with HFpEF exhibited a pattern of PASP/TAPSE versus LA-strain intermediate between control subjects and patients with HFrEF. Furthermore, LA reservoir function seems to be a determinant of the slope of PASP/TAPSE changes from rest to exercise.

An interesting analysis is provided by the 4-quadrant subdivision in LAVI and LA-strain phenotype combinations. Compared with control subjects, the vast majority of patients with HF (71%) were distributed in the upper left hand (i.e., increased LAVI [>34 ml/m$^2$] and a reduced LA-strain [<23%]). Nonetheless, a minority of patients with HF (15%) may still have atrium size and function similar to control subjects and associated with a very good performance concerning the RV-to-PC coupling and the slope of changes of PASP/TAPSE from rest to exercise. A small minority of patients then exhibited a reduced LA-strain but still preserved LAVI or an increased LAVI with preserved LA-strain. The former, at variance with the latter, still maintains a physiological adaptive slope of increase in rest to peak PASP/TAPSE. Overall, these observations underlie the importance of recognizing these phenotypes early as far as preventive strategies and therapeutic interventions may be concerned.

**STUDY LIMITATIONS.** As a single-center study, these results suffer from the limitation of a small study size. The lack of a comparative invasive hemodynamic

**FIGURE 7** Subdivision of Study Groups According to LAVI Versus LA-Strain Cutoff and PASP/TAPSE Versus LA-Strain




According to this distribution, 51 patients (73% of the heart failure [HF] population) presented with an enlarged left atrium and impaired LA reservoir function (group A, left atrial volume index [LAVI] >34 ml/m$^2$ and LA-strain <23%) and 11 (16%) had LA dimension and function (group B) similar to the control group. Among the patients with HF, 4 patients (6%) had normal LA size and impaired LA reservoir function (group C, LAVI <34 ml/m$^2$ and LA-strain <23%), and 3 patients (4%) had enlarged LA size and normal LA reservoir function (group D, LAVI >34 ml/m$^2$ and LA-strain >23%) **(A)**. The worse pattern of changes in PASP/TAPSE versus LA strain were observed in Group A and Group D **(B)**. **Error bars** indicate standard error of the mean. Abbreviations as in Figures 1 and 5.

evaluation is another important limitation. However, we used a pre-specified strict echocardiographic protocol rejecting data without good quality to limit potential errors. The 2DSTE was used for LA function evaluation; it must be recognized, however, that 3-dimensional speckle-tracking echocardiography is considered a better approach to eliminate the effects of through-plane motion. Although unable to record the LA 2-chamber views during exercise and recovery phases, we limited the analysis to 4-chamber views. The observed strong correlation between LA-strain obtained in 4-chamber and 2-chamber views seems reassuring for a precise assessment of the whole LA dynamics. Our approach may not be an easy application in daily clinical practice. A technically simpler LA reservoir analysis should be performed by measuring the LA emptying fraction as LA maximal volume - LA minimal volume/LA maximal volume × 100. Obviously, this approach during exercise would require validation against LA-strain and LA-SRa.

## CONCLUSIONS

In patients with HF, LA dysfunction seems to be a hemodynamic key mediator of RV-to-PC uncoupling and impaired ventilation efficiency during exercise. Monitoring LA-strain during exercise is feasible, and its maladaptive response during physical stress represents a novel and additional target of interventions to prevent/avoid the negative evolution toward RV-to-PC uncoupling.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** LA function plays a key role in the hemodynamics of HFrEF and HFpEF. Extensive investigation of LA dynamics, however, has been performed exclusively at rest. The LA is extremely sensitive to sustained volume and pressure secondary to increased LV filling pressure. The effects of loss in LA functional properties on lung vessel compliance and vascular remodeling may trigger RV overload and dysfunction. The objective of this study was to elucidate the effect of this on exercise RV-to-PC uncoupling and impaired ventilation efficiency. In patients with HF, LA dysfunction emerged as a key hemodynamic mediator of RV-to-PC uncoupling and impaired ventilation during exercise. Monitoring LA-strain during exercise is feasible, and the LA-strain maladaptive response during physical stress represents a novel and additional target for intervention.

**TRANSLATIONAL OUTLOOK:** Starting from the present observations, further studies are needed to determine the direct implications in developing therapies that may benefit LA function and the unfavorable load imposed on the right heart when impairment of LA reservoir reserve occurs. These observations may therefore shift the paradigm toward a key LA role in determining exercise limitation in HF.

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**KEY WORDS** heart failure, left atrial function, right heart

**APPENDIX** For an expanded Methods section, table, and figure, please see the online version of this article.