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Blunted rate-dependent left atrial pressure response during isoproterenol infusion in atrial fibrillation patients with impaired left ventricular diastolic function: a comparison to pacing

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Aims A heart rate (HR)-dependent haemodynamic linkage between peak left atrial (LA) pressure during sinus rhythm (LAP_{peak}) and estimated left ventricular (LV) filling pressure (E/Em) has not yet been explored. We hypothesized that rate-dependent LAP_{peak} response differs depending on E/Em in patients with atrial fibrillation (AF).

Methods and results A total of 331 patients (68.0% male, 59.8 ± 10.8 years old) undergoing radiofrequency catheter ablation (RFCA) for AF were included, and their LAP_{peak} in sinus rhythm was recorded at the beginning of the procedure and at the HRs of 90, 100, 110, and 120 b.p.m. during right atrial pacing and isoproterenol (ISO-stress) infusion. We compared LAP_{peak} changes between patients with E/Em ≥ 15 ($n = 58$) and those with <15 ($n = 273$). (i) The patterns of pacing rate-dependent LAP_{peak} increase were similar in both the E/Em < 15 ($P < 0.001$) and E/Em ≥ 15 groups ($P = 0.002$). (ii) The ISO-stress reduced LAP_{peak} in patients with E/Em < 15 ($P = 0.015$), but not in those with E/Em ≥ 15 ($P = 0.582$). (iii) Paradoxical ISO-stress LAP elevation in patients with E/Em ≥ 15 was independently associated with 1-year follow-up E/Em reduction ($B = -4.07$, 95% CI −5.41 to −2.72, $P < 0.001$). Coexistence of E/Em ≥ 15 and ISO-stress LAP elevation increased specificity in predicting 1-year follow-up E/Em reduction after AF ablation than E/Em alone.

Conclusion Isoproterenol LAP_{peak} reduction was blunted in patients with impaired LV diastolic function estimated by E/Em ≥ 15. The improvement of LV diastolic dysfunction 1 year after AF ablation was independently associated with both paradoxical ISO-stress LAP elevation and E/Em ≥ 15 at the time of procedure.

Clinicaltrials.gov NCT02138695.

Keywords Atrial fibrillation • Left atrial pressure • Heart rate • Diastolic function • Isoproterenol

Introduction

Left atrium (LA) and left ventricle (LV) are intricately coupled. During diastole, LA is under the direct influence of pressure in the LV through the open mitral valve.[1] In the presence of LV diastolic dysfunction, the high LV end-diastolic pressure (LVEDP) appears to alter LA in both structure and function.[1] In fact, many studies to date have demonstrated the associations of LV diastolic dysfunction with LA size,[1–3] LA mechanical function,[3–5] and increased risk of atrial fibrillation (AF),[6] all of which are also known risk factors of adverse cardiovascular outcome in general population as well as in selected clinical conditions.[5,7–10] The mechanism of electroanatomical remodelling of LA in this setting is thought to involve elevated LA pressure (LAP).[11] High LAP, by inducing stretch-associated atrial remodelling, is believed to contribute to both the initiation and maintenance of AF.[12] Despite the importance of the interaction between

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the two chambers, real-time haemodynamic changes in LA in relation to LV diastolic dysfunction have not yet been thoroughly explored. Currently, beta-adrenergic stimulation with isoproterenol (ISO-stress) is known to enhance diastolic function of LV.[13] In light of this view, we hypothesized that ISO-stress might have a favourable effect on LAP by facilitating LV diastolic function, but that the effect will be less in patients with LV diastolic dysfunction. In addition, we sought to evaluate the pattern of LAP response to heart rate (HR) changes induced by ISO-stress and compared it with LAP response to other methods, namely right atrial pacing. The purposes of this study were (i) to compare LAP between patients with LV diastolic dysfunction and those without; (ii) to evaluate and compare the patterns of HR-dependent LAP changes between right atrial pacing and ISO-stress; and (iii) to determine whether the patterns of HR-dependent LAP changes affect the reversal of LV diastolic dysfunction among patients undergoing AF catheter ablation.

Methods

Study population

The study protocol adhered to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Yonsei University Health System. All patients provided a written informed consent for inclusion in the Yonsei AF Ablation Cohort Database. We included 331 consecutive patients who underwent rate-dependent LAP change (90–120 b.p.m.) recordings under both ISO-stress and right atrial pacing in sinus rhythm during a radiofrequency catheter ablation (RFCA) procedure (68.0% male, 59.8 ± 10.8 years old, 74.6% paroxysmal AF). Exclusion criteria were as follows: (i) any mitral valve disease, including mild degree disease, (ii) associated structural heart disease other than left ventricular hypertrophy, (iii) prior AF ablation, (iv) uncontrolled hypertension (blood pressure above goal in spite of prescription of three agents including diuretics)[14] at LAP measurement, and (v) patients in whom LAP during both SR and AF, as well as HR changes, could not be measured. The presence of LV diastolic dysfunction was determined by using the ratio of mitral inflow E wave velocity to early diastolic mitral annulus velocity (E/Em) ≥15. Among 331 patients, 58 patients had LV diastolic dysfunction while the remaining 273 patients did not (Control). Before ablation, all antiarrhythmic drugs were discontinued for a minimum period of five half-lives, and amiodarone was stopped at least 4 weeks before the procedure.

Echocardiographic measurement

Transthoracic echocardiography (Sonos 5500, Philips Medical System, Andover, MA, or Vivid 7, GE Vingmed Ultrasound, Horten, Norway) was conducted on all patients before RFCA. Among the included 331 patients, 197 were in sinus rhythm, while 134 were in AF rhythm during pre-procedural echocardiogram. One-year follow-up echocardiogram was conducted on 283 of 331 patients because 48 patients had follow-up duration <1 year. The chamber size [LA volume index (LAVI), LA dimension, LV wall thickness, LV mass index (LVMI)], transmitral flow velocities (E wave, A wave), and tissue Doppler images of mitral annular septal area [peak diastolic velocity (Em) and peak systolic velocity (S′)] were acquired as described in the American Society of Echocardiography guidelines.[15,16]

Left atrial pressure measurement

Details of the LAP measurement technique are described in our previous study.[11] In brief, the Prucka Cardio Lab electrophysiology system (General Electric Medical Systems Inc., Milwaukee, WI, USA) was used to record intracardiac electrograms and haemodynamic measurements. A double transseptal puncture approach was taken for catheter access to the LA. Left atrial pressure was measured in the beginning of the procedure immediately after transseptal puncture using a 6-F pigtail catheter (A&A Medical Devices Inc., Gyeonggido, Republic of Korea) inserted into the LA via a long sheath (Schwartz left 1, St. Jude Medical Inc., Minnetonka, MN, USA). Depending on the baseline rhythm, the initial LAP measurement was followed either by internal cardioversion (2-10J biphasic shocks; Physio-Control Lifepack 12, Physio-Control Corp, Redmond, WA, USA) to restore sinus rhythm and measure LAP in SR [LAP(SR)] or by rapid atrial pacing (120–150 ms high right atrial pacing with 10 mA current for 10 s) to induce AF and measure LAP in AF [LAP(AF)]. We waited for LAP stabilization at least for 3 min after internal cardioversion. During AF, LAP responses were measured for at least 10 beats of rhythm, and the average value was taken as LAP(AF). During sinus rhythm, right atrial pacing and ISO-stress were carried out to induce HR changes, and LAP responses at HR of 120, 110, 100, and 90 b.p.m. were recorded. We excluded 18 patients because HR-dependent LAP could not be measured due to high baseline HR >90 b.p.m. ($n = 9$) or the patient could not tolerate ISO-stress infusion until HR reach to 120 b.p.m. ($n = 9$). We analysed LAP_{peak} (LAP at v wave), LAP_{nadir} (LAP at y descent), and LA pulse pressure (LApp; $LAP_{peak} - LAP_{nadir}$) (*Figure 1*).

Statistical analysis

Statistical analyses were performed using SPSS (Statistical Package for Social Sciences, Chicago, IL, USA) software for Windows (version 20.0). Continuous variables are expressed as means ± SD and were compared by Student's *t*-test, Mann–Whitney *U*-test, and ANOVAs followed by *post hoc* analyses using Bonferroni's method. Categorical variables are reported as frequencies (percentage) and were compared by χ^2 test or Fisher's exact test. The differences of LAP_{peak} measured under different conditions were assessed by paired *t*-test, and the presence of HR-dependent LAP changes was determined by repeated measures ANOVA. All correlations were performed using Spearman's rank

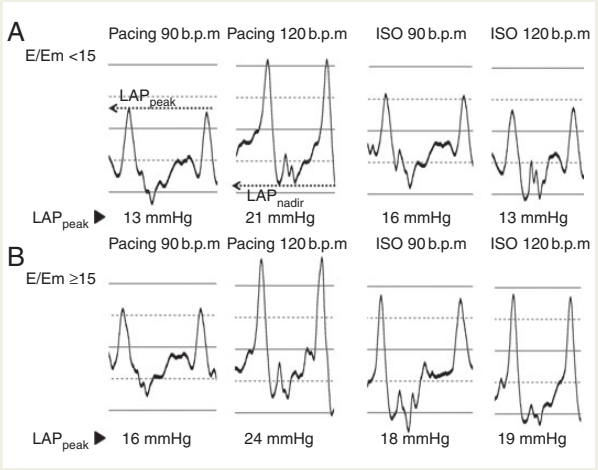

Figure 1 Representative figure for measurement of HR-dependent LAP changes during ISO-stress stress and atrial pacing in the control group (*A*) and the LV diastolic dysfunction group (*B*). LAP, left atrial pressure; LAP_{peak}, LAP at v wave.

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correlation test. A *P*-value of <0.05 (two-sided) was considered to be statistically significant.

Results

Baseline characteristics of the study population

Comparisons of baseline characteristics between patients with and without LV diastolic dysfunction assessed by E/Em are presented in *Table 1*. Patients in the E/Em $\geq$ 15 group were older ($P < 0.001$), more likely to be female ($P < 0.001$). These patients had smaller body surface area (BSA) ($P = 0.001$) and higher CHA_2DS_2-VASc scores ($P < 0.001$), and were more likely to have hypertension ($P < 0.001$) than the E/Em $<$ 15 group. The LA diameter ($P < 0.001$), LAVI ($P < 0.001$), and LVMI ($P < 0.001$) were all greater in patients with the E/Em $\geq$ 15 group than those with the E/Em $<$ 15 group. At baseline, patients in the E/Em $\geq$ 15 group tended to have higher LAP_{peak} (AF) ($P = 0.008$), LAP_{peak} (SR) ($P = 0.030$), and LApp (AF) ($P = 0.046$). The two groups did not demonstrate significant differences from one another in baseline HRs measured in AF ($P = 0.550$) and in SR ($P = 0.654$). At 1-year follow-up echocardiography, patients in the E/Em $\geq$ 15 group showed significant E/Em reduction ($P = 0.002$) and reverse LA remodelling ($P = 0.013$), as shown by ΔE/Em (post-RFCA 1 year E/Em – pre-RFCA E/Em) and ΔLAVI (post-RFCA 1 year LAVI – pre-RFCA LAVI).

Table 1 Comparison of study population according to LV diastolic function (E/Em)

	Overall ($n = 331$)	E/Em $<$ 15 ($n = 273$)	E/Em $\geq$ 15 ($n = 58$)	*P*-value
Male (%)	225 (68.0%)	197 (72.2%)	28 (48.3%)	**<0.001**
Age (years)	59.77 ± 10.75	58.74 ± 10.15	65.72 ± 9.73	**<0.001**
PAF (%)	247 (74.6%)	208 (76.2%)	39 (67.2%)	0.155
BSA (m^2)	1.78 ± 0.18	1.80 ± 0.17	1.71 ± 0.19	**0.001**
BMI (kg/m^2)	24.60 ± 2.86	24.55 ± 2.80	24.90 ± 2.87	0.396
CHA_2DS_2-VASc score	2.01 ± 1.62	1.81 ± 1.56	3.02 ± 1.67	**<0.001**
Heart failure (%)	39 (11.8%)	26 (9.5%)	13 (22.4%)	0.006
Hypertension (%)	171 (51.7%)	127 (46.5%)	44 (75.9%)	**<0.001**
Age >75 years (%)	34 (10.3%)	22 (8.1%0	12 (20.7%)	**0.004**
Diabetes (%)	43 (13.0%)	32 (11.7%)	11 (19.0%)	0.136
Stroke/TIA (%)	39 (14.5%)	33 (14.5%)	6 (14.6%)	0.979
Vascular disease (%)	36 (13.4%)	30 (13.2%)	6 (14.6%)	0.798
Echo parameters				
LA diameter (mm)	41.06 ± 5.93	40.38 ± 5.48	43.41 ± 6.25	**<0.001**
LAVI (mL/m^2)	36.02 ± 12.99	33.94 ± 11.30	42.45 ± 12.54	**<0.001**
LVEDD (mm)	49.80 ± 4.51	49.68 ± 4.42	50.60 ± 5.05	0.159
LVEF (%)	63.12 ± 8.42	63.19 ± 8.27	63.17 ± 9.26	0.988
LVMI (g/m^2)	94.92 ± 22.75	92.77 ± 21.25	105.36 ± 26.52	**<0.001**
E/Em	10.75 ± 4.44	9.14 ± 2.48	18.31 ± 3.77	**<0.001**
LAP measurement				
LAP_{peak} (AF)	23.49 ± 8.91	22.73 ± 8.63	26.66 ± 9.71	**0.008**
LAP_{nadir} (AF)	6.68 ± 5.52	6.39 ± 5.08	7.89 ± 7.31	0.095
LApp (AF)	16.80 ± 8.06	16.35 ± 8.06	18.77 ± 7.82	**0.046**
Heart rate (AF)	100.74 ± 30.03	101.03 ± 30.69	98.30 ± 27.27	0.550
LAP_{peak} (SR)	22.86 ± 10.57	22.14 ± 10.22	25.47 ± 11.54	**0.030**
LAP_{nadir} (SR)	6.28 ± 5.72	6.13 ± 5.28	6.82 ± 6.83	0.474
LApp (SR)	16.58 ± 8.96	16.01 ± 8.71	18.65 ± 9.69	0.062
Heart rate (SR)	71.65 ± 15.93	71.48 ± 16.72	72.54 ± 13.36	0.654
ΔISO-stress LAP_{peak} (120–90 b.p.m.)	−0.74 ± 7.45	−1.08 ± 6.71	0.58 ± 7.41	0.121
Comparison with 1-year follow-up echo ($n = 283$)				
ΔE/Em	0.09 ± 3.14	0.44 ± 2.75	−1.55 ± 4.26	**0.002**
ΔLAVI	−5.66 ± 10.58	−4.84 ± 9.77	−9.78 ± 13.29	**0.013**

Values are expressed as *n* (%) or means ± SDs.
AF, atrial fibrillation; BMI, body mass index; BSA, body surface area; Em, mitral annular septal area peak diastolic velocity; LA, left atrium; LAP_{peak}, LA pressure at v wave; LAP_{nadir}, LA pressure at y descent; LApp = LAP_{peak} – LAP_{nadir}; LAVI, LA volume index; LV, left ventricle; LVEDD, LV end-diastolic dimension; LVEF, LV ejection fraction; LVMI, LV mass index; PAF, paroxysmal atrial fibrillation; SR, sinus rhythm; TIA, transient ischaemic attack; ΔE/Em = post-RFCA 1 year E/Em – pre-RFCA E/Em; ΔLAVI = post-RFCA 1 year LAVI – pre-RFCA LAVI; ΔISO-stress LAP_{peak} (120–90 b.p.m.) = LAP_{peak} at 120 b.p.m. – ISO-stress LAP_{peak} at 90 b.p.m.
P-values <0.05 were marked as bold.

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Opposite patterns of heart rate-dependent left atrial pressure response to isoproterenol and right atrial pacing

Two different methods, right atrial pacing and ISO-stress, were used to induce HR changes. At 90 b.p.m., LAP_{peak} responses to the two methods were not statistically different (20.00 ± 10.84 vs. 20.25 ± 10.69 mmHg, $P = 0.606$ by paired *t*-test). However, as the HR was increased up to 120 b.p.m., LAP_{peak} response to the two methods significantly differed from one another. Peak left atrial pressure gradually increased when the HR change was induced by right atrial pacing ($P < 0.001$ by repeated measures ANOVA), but did not increase when the HR was altered under the ISO-stress ($P = 0.119$ by repeated measures ANOVA) (*Figure 2A*). Finally, at 120 b.p.m., LAP_{peak} response to pacing was statistically different from that to ISO-stress (22.81 ± 9.61 vs. 19.24 ± 11.01 mmHg, $P < 0.001$ by paired *t*-test).

Heart rate-dependent left atrial pressure response according to left ventricular diastolic dysfunction

We compared HR-dependent LAP changes at pacing HRs of 120, 110, 100, and 90 b.p.m. between patients in the E/Em ≥ 15 group and those in the E/Em < 15 group (*Figure 2*). Under right atrial pacing, both the E/Em < 15 group ($P < 0.001$ by repeated measures ANOVA) and E/Em ≥ 15 group ($P = 0.002$ by repeated measures ANOVA) showed gradual increase in LAP_{peak}. However, when ISO-stress HR-dependent LAP responses were compared between the two groups, we found that in patients in E/Em < 15, LAP_{peak} decreased gradually with HR increase from 90 to 120 b.p.m. ($P = 0.046$ by repeated measures ANOVA, *Figure 2B*) whereas in the E/Em ≥ 15 group, HR-dependent LAP_{peak} change was blunted ($P = 0.936$ by repeated measures ANOVA, *Figure 2C*).

Paradoxical left atrial pressure elevation under isoproterenol and reversal of left ventricular diastolic dysfunction

Isoproterenol LAP elevation was defined as the absence of LAP_{peak} reduction during HR increase from 90 to 120 b.p.m. under ISO-stress (ISO-stress LAP_{peak} at 120 b.p.m. – ISO-stress LAP_{peak} at 90 b.p.m. ≥ 0). In the E/Em ≥ 15 group, patients who showed ISO-stress LAP elevation demonstrated more significant E/Em reduction and LA reverse remodelling than all of other groups at 1-year follow-up, as shown by ΔE/Em (*Figure 3A*) and ΔLAVI (*Figure 3B*). There were no differences in E/Em reduction (−0.02 ± 2.90 vs. 0.01 ± 3.11, $P = 0.940$) and LA reverse remodelling (−5.56 ± 9.97 vs. −5.96 ± 10.41, $P = 0.769$) between patients with AF recurrence (107/283) and those without (176/283).

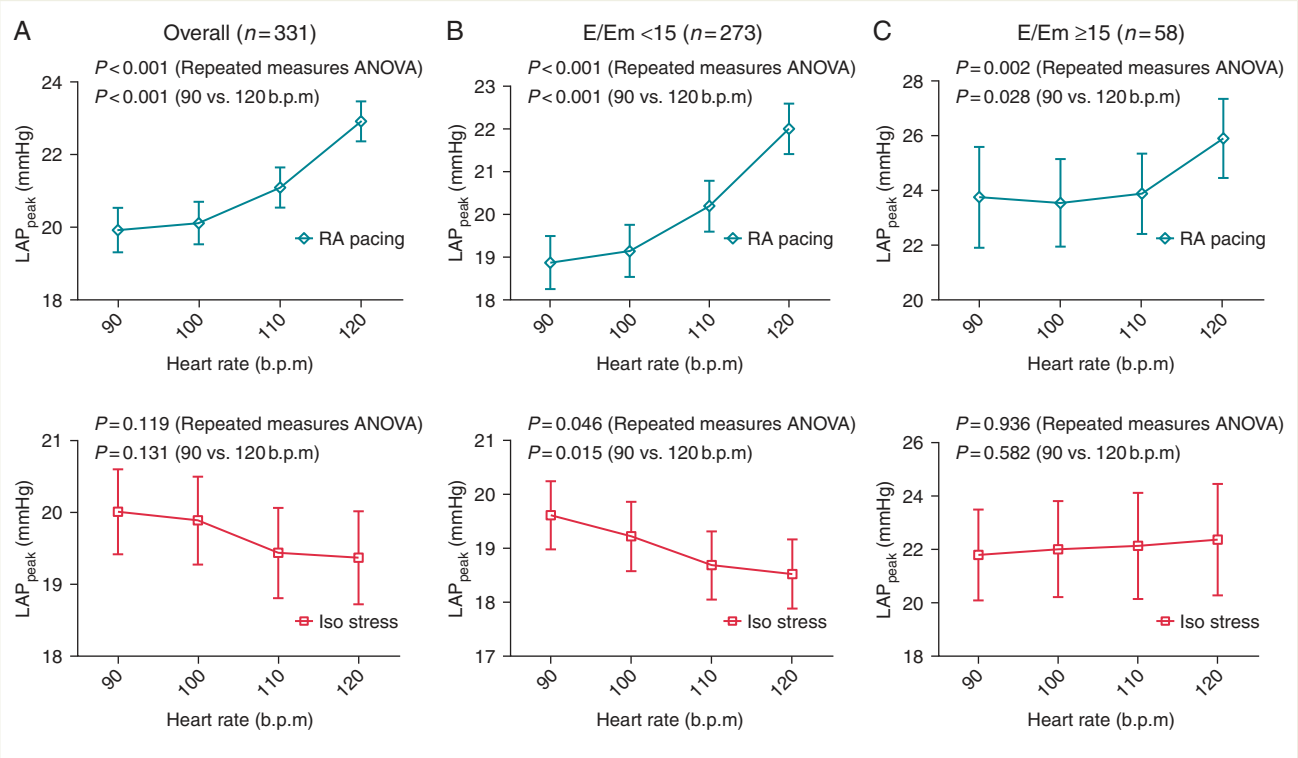

Figure 2 Opposite patterns of HR-dependent LAP changes in ISO-stress stimulation and right atrial pacing (*A*). In the E/Em < 15 group, changes in the HR from 90 to 120 b.p.m. by right atrial pacing induced gradual increase in LAP_{peak} while the HR changes induced by ISO-stress led to gradual decrease in LAP_{peak} (*B*). In the E/Em ≥ 15 group, LAP_{peak} also significantly increased as the paced HR increased from 90 to 120 b.p.m. However, LAP_{peak} showed no significant changes as the HR was increased with ISO-stress (*C*). LAP, left atrial pressure; LAP_{peak}, LAP at v wave.

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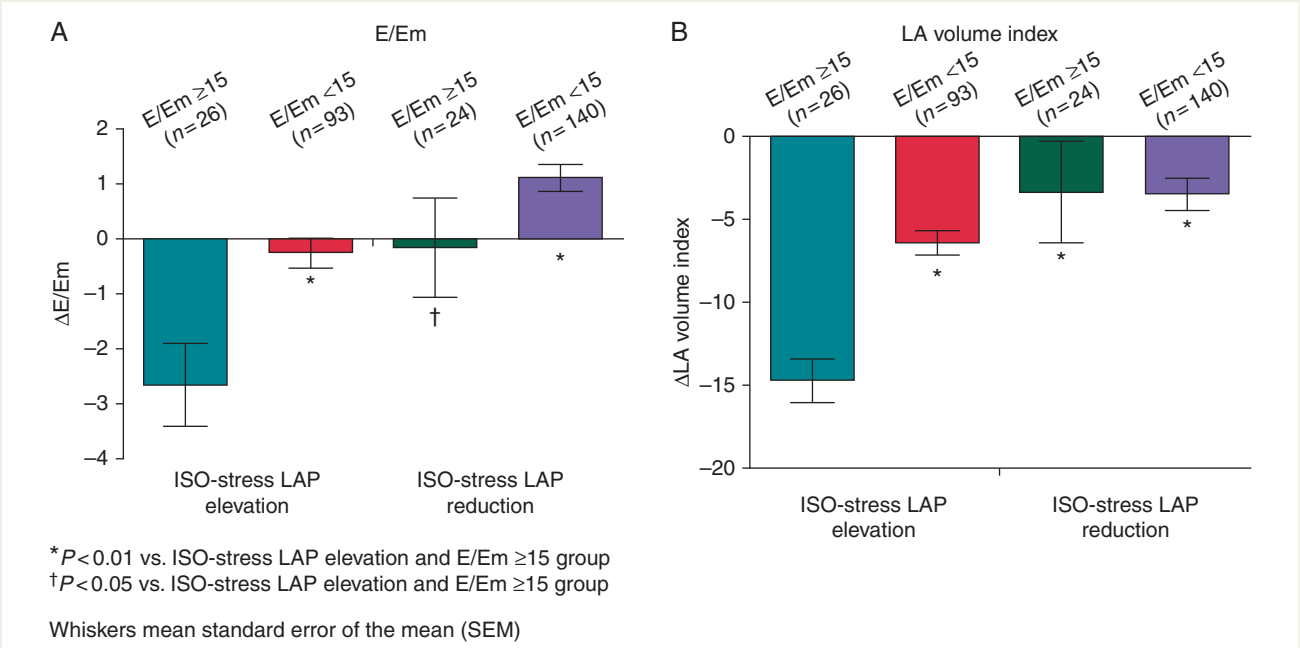

Figure 3 Comparisons of E/Em reduction (*A*) and LA reverse remodelling (*B*) at 1 year after the catheter ablation according to the presence of ISO-stress LAP elevation and E/Em > 15. LAP, left atrial pressure; ΔE/Em = post-RFCA 1 year E/Em – pre-RFCA E/Em; ΔLAVI = post-RFCA 1 year LAVI – pre-RFCA LAVI.

Table 2 Linear regression analysis to determine clinical variables predictive of decreased E/Em 1 year after RFCA

ΔE/Em	Univariate analysis		Multivariate analysis[a]	
	B (95% CI)	*P*-value	*B* (95% CI)	*P*-value
ΔISO-stress LAP (120–90 b.p.m.)[b]	−0.09 (−0.14 to −0.03)	**0.002**	−0.10 (−0.15 to −0.04)	**0.001**
ISO-stress LAP elevation	−1.69 (−2.42 to −0.95)	**<0.001**	−1.85 (−2.63 to −1.07)	**<0.001**
E/Em ≥ 15	−1.99 (−2.89 to −1.09)	**<0.001**	−2.83 (−3.82 to −1.84)	**<0.001**
ISO-stress LAP elevation + E/Em ≥ 15	−3.15 (−4.40 to −1.90)	**<0.001**	−4.07 (−5.41 to −2.72)	**<0.001**
LVEF	0.01 (−0.04 to 0.04)	0.964		
LAVI	0.03 (0.01 to 0.07)	**0.016**		
LVMI	0.01 (−0.01 to 0.02)	0.348		
Hypertension	0.03 (−0.67 to 0.73)	0.928		
Diabetes	−0.53 (−1.58 to 0.51)	0.317		

ISO-stress LAP elevation = ISO-stress LAP_{peak} at 120 b.p.m. – ISO-stress LAP_{peak} at 90 b.p.m. ≥ 0; CI, confidence interval; LA, left atrium; LAVI, LA volume index; LV, left ventricle; LVEF, LV ejection fraction; LVMI, LV mass index; ΔE/Em = post-RFCA 1 year E/Em – pre-RFCA E/Em.
[a]Adjusted by age, sex, BSA, BMI, AF type (PeAF), hypertension, LVMI, and pre-RFCA LAVI.
[b]Continuous variable (ISO-stress LAP_{peak} at 120 b.p.m. – ISO-stress LAP_{peak} at 90 b.p.m.).
P-values <0.05 were marked as bold.

In the multivariate linear regression analyses, both ISO-stress LAP elevation (*B* −1.85, 95% CI −2.63 to −1.07, $P < 0.001$) and baseline E/Em ≥ 15 (*B* −2.83, 95% CI −3.82 to −1.84, $P < 0.001$) were independently associated with E/Em reduction 1 year after the catheter ablation (*Table 2*). The co-existence of ISO-stress LAP elevation and baseline E/Em ≥ 15 before RFCA was also significantly associated with E/Em reduction (*B* −4.07, 95% CI −5.41 to −2.72, $P < 0.001$, *Table 2*) 1 year after the catheter ablation. Moreover, ISO-stress LAP elevation had additional predictive value (*Figure 4*), and increased specificity and positive predictive value (*Table 3*) than E/Em alone in determining those patients likely to see improvement in diastolic dysfunction 1 year after AF ablation. *Figure 5* shows the distribution of E/Em level and ΔISO-stress LAP (120–90 b.p.m.) of study population depending on the reduction of E/Em at 1 year after the catheter ablation. In the baseline E/Em ≥ 15 group, most of patients with ISO-stress LAP elevation had E/Em reduction 1 year after AF ablation (right upper part of *Figure 5*), which explains high specificity of the co-existence of

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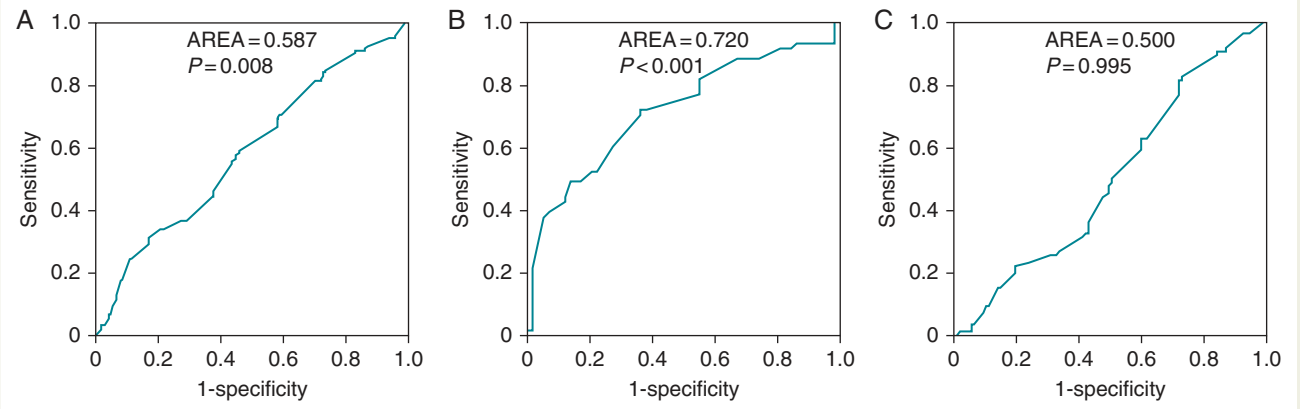

Figure 4 Receiver operating characteristic curves for the prediction of post-ablation 1-year improvement of E/Em by baseline E/Em in (*A*) total population, (*B*) patients with ISO-stress LAP elevation, and (*C*) patients with ISO-stress LAP reduction.

Table 3 Sensitivity, specificity, and predictive values of E/Em and ISO-stress LAP elevation for E/Em reduction 1 year after RFCA

Reduction of post-procedural 1 year E/Em (ΔE/Em < 0)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Baseline E/Em ≥ 15	24.5	89.1	66.7	57.0
ISO-stress LAP elevation	47.7	63.1	51.3	59.6
ISO-stress LAP elevation and baseline E/Em ≥ 15	18.1	98.1	88.5	59.5

ISO-stress LAP elevation = ISO-stress LAP_{peak} at 120 b.p.m. – ISO-stress LAP_{peak} at 90 b.p.m. ≥ 0; CI, confidence interval; ΔE/Em = post-RFCA 1 year E/Em – pre-RFCA E/Em.

ISO-stress LAP elevation and E/Em ≥ 15 for predicting the improvement of LV diastolic dysfunction after AF ablation (*Table 3*).

Discussion

In this retrospective observational cohort study with *post hoc* analysis, we found that the pattern of LAP_{peak} changes in response to paced tachycardia was opposite to response to ISO-stress-induced tachycardia in patients without LV diastolic dysfunction (E/Em < 15). Peak left atrial pressure increased gradually as paced HR increased, whereas LAP_{peak} gradually decreased with ISO-stress-induced HR change from 90 to 120 b.p.m. However, LAP_{peak} reduction during ISO-stress was blunted in patients with E/Em ≥ 15. Both ISO-stress LAP elevation and E/Em ≥ 15 were independently associated with E/Em reduction 1 year after the catheter ablation.

Left atrial pressure, left atrial remodelling, and left ventricular diastolic dysfunction

Left atrial pressure is influenced by many factors, such as LA relaxation, LV systolic and diastolic function, LA chamber stiffness, and volume status with right ventricular systole through pulmonary venous inflow.[17–20] Physiologically, LA is directly exposed to LV pressure during diastole; as a consequence, worsening LV diastolic dysfunction with increasing LVEDP elevates LAP in order to maintain adequate LV filling. Ultimately, LA wall tension and LA remodelling ensue. When the non-compliant LA is passively filled during LV systole, a high LAP_{peak} (v wave) is generated and is found

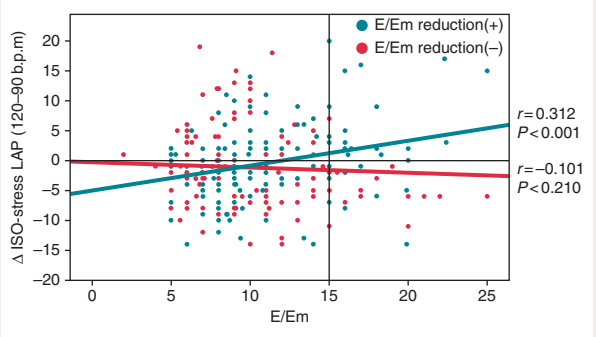

Figure 5 Correlations between baseline E/Em and ΔISO-stress LAP (120–90 b.p.m.) according to the presence of E/Em reduction at 1 year after the catheter ablation. ΔE/Em = post-RFCA 1 year E/Em – pre-RFCA E/Em; ΔISO-stress LAP (120–90 b.p.m.) = LAP_{peak} at 120 b.p.m. – ISO-stress LAP_{peak} at 90 b.p.m; E/Em reduction (+) = ΔE/Em < 0.

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to be associated with advanced LA remodelling and fibrosis.[21,22] Therefore, LAP_{peak} may reflect both pressure load through mitral valve and advanced LA remodelling from chronic exposure to high LVEDP.

Impaired left atrial pressure reduction under isoproterenol

Heart rate can affect LAP by modifying the LV diastolic filling period and LA relaxation period. In this study, LAP_{peak} increased as paced HR increased from 90 to 120 b.p.m. However, the pattern of LAP_{peak} changes in response to ISO-stress-induced tachycardia was the opposite, especially in the E/Em $<$ 15 group. Although tachycardia itself may shorten the LV diastolic filling period and thus increase LVEDP and LAP, LAP reduction in ISO-stress-induced tachycardia may be a physiological phenomenon because ISO-stress is known to enhance LV diastolic function.[13] The impaired ISO-stress LAP reduction, on the other hand, may be a reflection of LV diastolic dysfunction along with elevated E/Em. It is important to note that ISO-stress LAP elevation can induce as well as aggravate the severity of diastolic heart failure symptoms, especially during exertion, because elevated LAP can in turn elevate post-capillary pulmonary venous pressure.[23,24]

Blunted isoproterenol left atrial pressure reduction and the reversal of left ventricular diastolic dysfunction

Several studies have previously demonstrated that AF and diastolic dysfunction can induce one another, and that RFCA for AF improved LV diastolic function in 30% of study population.[25,26] For this reason, LV diastolic dysfunction with elevated E/Em and abnormal HR-dependent LAP response may be clinically valuable for predicting improvement in LV diastolic function and LA reverse remodelling after AF catheter ablation. Furthermore, our group recently reported that AF patients with higher E/Em had more significant improvement in LV diastolic function 1 year after catheter ablation than those with lower E/Em.[27] In the current study, we found that patients who had both ISO-stress LAP elevation and E/Em $\geq$ 15 at the time of ablation were more likely to have undergone E/Em reduction at 1 year after the catheter ablation, a finding that is consistent with our previous study. We also observed significant LA reverse remodelling in both patients with E/Em $\geq$ 15 and those with E/Em $<$ 15. However, the reduction of E/Em was shown only in the E/Em $\geq$ 15 group, and the reduction was mostly associated with decrease in E velocity.[27] It is possible that AF rhythm control may have brought more significant recovery of atrial dyssynchrony and improved coronary perfusion in patients with underlying LV diastolic dysfunction. It is also possible that patients with E/Em $<$ 15 showed no significant improvement because they were already within or near the normal range. Overall, these findings highlight that AF is a significant aggravating factor in heart failure with preserved ejection fraction. To date, only few studies have investigated the impact of HR on LAP and LV diastolic dysfunction, especially in patients with AF,[20] and further investigations are warranted to assess the association among LAP response, LV diastolic function, and LA reverse remodelling.

Study limitations

This study should be interpreted in the context of the following limitations. This was a single-centre retrospective observational cohort study that included a selected group of patients referred for AF catheter ablation; therefore, our findings cannot be generalized. Because of the small number of patients with LV diastolic dysfunction, small differences in LAP_{peak} would not be detected, potentially resulting in a type II error. In single ANOVA of all the patients and the between-group *P* values, ISO-stress LAP changes did not reach to significant different between the patients with E/Em $\geq$ 15 and those with $<$15. It might be due to small number of the patients with E/Em $\geq$ 15. Although we found significant linear correlation between ΔE/Em and ΔISO-stress LAP_{peak} (120−90 b.p.m.), there is no proven physiologic cut-off value for ISO-stress LAP_{peak} changes. Moreover, our study did not take into account the effect of aging, LV systolic function, and hypertension on LAP.[28,29] Although E/Em may be partially influenced by HR, HR-dependent E/Em changes were not assessed during the procedure. We used only E/Em as the non-invasive marker of elevated LV filling pressures and LV diastolic dysfunction. E/Em $\geq$ 15 may reflect only severe LV diastolic dysfunction, and omit mild to moderate degrees of LV diastolic dysfunction. As LAP is influenced by LA size and stiffness, mitral valvular function, LV systolic and diastolic function, and volume status, it is unclear whether LAP response to ISO-stress has a cause-and-effect relationship with LV diastolic dysfunction, or whether the two are simply associated even though LAP was measured at the beginning of the procedure in an overnight fasting state, and all valvular diseases were excluded. Although we waited for LAP stabilization at least for 3 min after internal cardioversion and there was no significant difference between LAP_{peak} with and without cardioversion (23.31 $\pm$ 9.99 vs. 22.32 $\pm$ 10.91 mmHg, $P = 0.410$), the mechanical stunning of the LA after cardioversion may affect LAP measurements.[30] However, it was not possible to exclude potential stunning even in patients with PAF who showed initial sinus rhythm at the beginning of the procedure. Although there were studies of LV diastolic function, comparing HR responses with or without sympathetic stimulation, our study represents the largest clinical study to date that examined the relationship between LAP and reversal of diastolic dysfunction 1 year after AF rhythm control.

Conclusions

The rate-dependent LAP_{peak} changes under ISO-stress were opposite in pattern to LAP changes in right atrial pacing, and LAP_{peak} reduction under ISO-stress was blunted in patients with impaired LV diastolic function estimated by E/Em $\geq$ 15. The improvement of LV diastolic dysfunction 1 year after AF ablation was independently associated with both LAP elevation under ISO-stress and baseline E/Em $\geq$ 15 at the time of procedure. Isoproterenol LAP elevation had additional predictive value with better specificity and positive predictive value than E/Em alone for the improvement in diastolic dysfunction 1 year after AF ablation.

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