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Resting and Exercise-Induced Left Atrial Hypertension in Patients With Atrial Fibrillation

The Causes and Implications for Catheter Ablation

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ABSTRACT

OBJECTIVES The aim of this paper was to investigate the prevalence of resting and exercise-induced left atrial hypertension (LAH) in patients with nonvalvular atrial fibrillation (AF), association of the LAH with other cardiac abnormalities, and its implications for AF catheter ablation.

BACKGROUND The clinical role of LAH in patients with established AF is largely unknown.

METHODS Patients scheduled for catheter ablation of AF (n = 240, age 60 ± 10 years, 67% men, 62% paroxysmal AF) underwent detailed echocardiography, assessment of quality of life (QoL), left atrial (LA) voltage mapping, and measurement of the LA pressure at rest and during isometric handgrip exercise. After ablation they were followed for AF recurrence for 16 ± 6 months.

RESULTS Resting and exercise-induced LAH (mean LA pressure >15 mm Hg) occurred in 15% and 34% of the patients, respectively. Both the patients with resting and exercise-induced LAH had typical features of latent heart failure with preserved ejection fraction associated with advanced LA structural and functional remodeling. AF recurred after ablation in 45% of the patients. LAH was an independent risk factor for arrhythmia recurrence (hazard ratio 1.7, 95% confidence interval 1.2 to 2.2). The patients with LAH had worse baseline QoL, but they benefited significantly more from a successful ablation than the patients without LAH.

CONCLUSIONS Presence of either resting or exercise-induced LAH identified AF patients with a distinct clinical profile, extensive LA substrate, and different clinical response to catheter ablation. Stratification of AF patients based on the LA exercise hemodynamics could help in the future to tailor the ablation strategy. (J Am Coll Cardiol EP 2017;■:■–■)

Catheter ablation has become a standard therapy for atrial fibrillation (AF) (1). However, to be effective, the ablation strategy must reflect the patient-specific left atrial (LA) pathology. Patients with less diseased LA may benefit from a simple isolation of the pulmonary veins, whereas patients with more diseased LA may have a better outcome after extensive substrate-targeting ablation (2).

Whether a patient has diseased LA is currently estimated based on the AF duration, presence of comorbidities, cardiac imaging, or LA voltage mapping. This approach is inaccurate and reflects only a few aspects of the LA disease (1). Direct assessment of the LA pressure could provide a more complex and self-contained information on the LA condition. It is based on the key role of LA hypertension (LAH) in the

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

HFpEF = heart failure with preserved ejection

LA = left atrium/atrial

LAH = left atrial hypertension

LV = left ventricle/ventricular

QoL = quality of life

SR = sinus rhythm

LA remodeling, where it acts as a unifying pathway and a major force through which diverse clinical factors realize their detrimental effects (3). Assessment of the LA pressure during an exercise stress test could even more realistically reflect the LA hemodynamics and it could uncover conditions that do not manifest at rest.

In this study we hypothesized that the presence of either resting or exercise-induced LAH in patients with nonvalvular AF and preserved left ventricular (LV) ejection fraction would identify a distinct subgroup of patients who would have more diseased LA, different clinical responses to AF ablation, and who could benefit from a different strategy of the ablation. We also investigated factors causing LAH and its association with other cardiac abnormalities.

METHODS

STUDY PROTOCOL. The study enrolled 240 patients who underwent catheter ablation for AF at our institution. Excluded were patients with a cardiomyopathy, congenital heart disease, valvular heart disease, or LV ejection fraction <40%. The study was approved by institutional ethical committee and all patients provided written consent with the investigation.

On the day before ablation, patients underwent clinical evaluation, echocardiography, blood sampling for analysis of cardiac biomarkers, and assessment of quality of life (QoL) by the short form 36-item (SF-36) questionnaire. Catheter ablation was performed under conscious sedation using 3-dimensional navigation (CARTO, Biosense Webster, Diamond Bar, California) and point-by-point radiofrequency ablation (3.5-mm Navistar Thermocool catheter, Biosense Webster). All patients underwent circumferential pulmonary vein isolation. Additional LA linear lesions (n = 83), coronary sinus ablations (n = 42), and electrogram-guided ablations (n = 33) were performed stepwise if the AF sustained and the LA mapping revealed low-voltage areas or complex fractionated atrial electrograms. The LA pressure was not considered while planning the ablation strategy.

After ablation, the patients were followed during regular visits for a minimum of 1 year. The details of our follow-up examinations of patients after AF ablation have been described elsewhere (4). The involved physicians were blinded to the baseline study data. Antiarrhythmic drugs were discontinued in 86% of the patients within the first 3 months after the ablation. Arrhythmia recurrence was defined as any documented symptomatic or asymptomatic episode of AF or atrial tachycardia lasting >30 s, after excluding a blanking period of 3 months (5). QoL was re-assessed at 6 months after ablation.

ASSESSMENTS OF CARDIAC STRUCTURE AND FUNCTION. Echocardiography (Vivid 7, GE Healthcare, Chalfont St Giles, United Kingdom) was performed by experienced operators according to the guidelines (6,7). LA phasic function, wall stress, and diastolic stiffness were estimated as previously described (8). The phasic LA volumes and maximal right atrial volume were obtained by the area-length method in the apical 4-chamber view. Right atrial pressure was estimated based on the inferior vena cava diameter and collapsibility (7). Systolic pulmonary artery pressure was determined from the right atrial pressure and tricuspid regurgitant jet peak velocity. In case of present AF, all measurements were obtained by averaging of at least 5 consecutive beats.

LA tissue pathology was assessed by endocardial bipolar voltage mapping during spontaneous rhythm, using the ablation catheter. Adequate catheter contact was verified real-time by checking the appearance of the atrial electrograms, intracardiac echocardiography, and tactile feedback. The voltage maps (>100 points in 94% of the patients) were carefully edited, contiguous regions with low voltage were manually delineated, and the surface area of the low-voltage regions was related the total LA surface area (9). For definition of the low voltage we used 3 different cut-offs: <0.5 mV, <0.15 mV, and a combined cut-off of <0.5 mV for patients in sinus rhythm (SR) and <0.15 mV for patients in AF.

LA loading was estimated by midregional pro-atrial natriuretic peptide (MR-proANP assay, BRAHMS, Henningsdorf, Germany), LV loading was assessed by B-type natriuretic peptide (BNP), and galectin-3 served as a biomarker of fibrosis (BNP and Galectin-3 Architect assays, Abbott Diagnostics, Lake Forrest, Illinois).

MEASUREMENT OF LA PRESSURE. LA pressure was measured at the beginning of the ablation procedure through an 8 F transseptal sheath placed in the LA cavity. The pressure transducer was zeroed at the midthoracic level. LA pressure, heart rate, and right-arm blood pressure were recorded at rest and subsequently during 3 min of isometric handgrip exercise. The handgrip was performed with a constant force of 40% of maximum voluntary contraction using a dynamometer (Kern & Sohn, Balingen, Germany) placed in the patient's left hand (10). The patients were encouraged to breathe regularly to avoid Valsalva maneuver. LA mean pressure was calculated over several breath cycles. LAH was defined as the LA

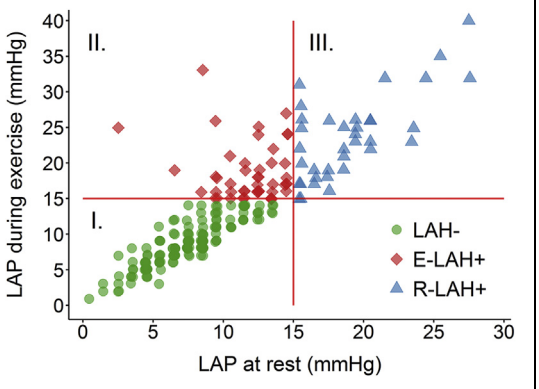
TABLE 1 Patient Characteristics (N = 240)

Age (yrs)	60 ± 10
Male	160 (67)
Body mass index (kg/m^2)	29 ± 4
Persistent AF	90 (38)
Arterial hypertension	152 (63)
Coronary artery disease	26 (11)
Diabetes mellitus	25 (10)
Antiarrhythmic drugs	147 (61)
Beta-blockers	156 (65)
ACEI/ARBs	108 (45)
LV ejection fraction (%)	57 ± 5
LA volume index (ml/m^2)	39 ± 11
AF present at the assessment*	67 (28)

Values are n (%) or mean ± SD. *AF present during measurement of the LA pressure and electroanatomic mapping.

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blockers; LA = left atrial; LV = left ventricular.

FIGURE 1 Relationship Between Mean Left Atrial Pressure at Rest and During Isometric Handgrip Exercise



Three hemodynamic profiles can be identified: **(I)** No left atrial hypertension (LAH) both at rest and during exercise (LAH–), **(II)** LAH absent at rest but induced by exercise (E-LAH+), and **(III)** LAH present already at rest (R-LAH+). It is apparent that the handgrip exercise was most useful for unmasking LAH in the patients with resting mean left atrial pressure (LAP) between 8 mm Hg and 15 mm Hg.

mean pressure >15 mm Hg, either at rest or during the exercise (11).

STATISTICAL ANALYSIS. Group comparisons were performed by the Student *t* test, Mann-Whitney U test, chi-square test, or Fisher's test, as appropriate. Serial changes were evaluated using the Wilcoxon paired test. Between-groups differences in various sub-group analyses were expressed by standardized mean difference. Factors associated with LAH were identified by stepwise multivariable logistic regression analysis. Candidate variables for the regression models were selected based on the absence of cross-correlation, completeness of the data, and significant association in univariable regression analysis. Predictive value of LAH for arrhythmia recurrence after ablation was assessed using Cox's regression analysis by adjusting for all significant univariable predictors. The analyses were conducted in R (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

PREVALENCE OF LAH. The study comprised 240 patients with preserved LV ejection fraction and nonvalvular AF, most of them being overweight hypertensive men with paroxysmal AF (Table 1). At rest, the mean LA pressure was 9 ± 2 mm Hg; LAH occurred in 36 (15%) patients. During the isometric handgrip exercise, the mean LA pressure increased by up to 19 mm Hg (median: 2 mm Hg, interquartile range: 1 to 4 mm Hg, $p < 0.001$); this unmasked LAH in an additional 46 (19%) patients (23% of those who did not have LAH at rest) (Figure 1). In total, 82 (34%) patients had either resting or exercise-induced LAH.

COMPARISON BETWEEN RESTING LAH AND EXERCISE-INDUCED LAH. Tables 2 and 3 show comparisons between the patients who had LAH already at rest and the patients who developed LAH only during exercise. The patients with resting LAH did not differ significantly from the patients with only exercise-induced LAH, except in having higher resting and exercise-induced LA pressure, higher resting systolic blood pressure, higher resting LA wall stress, and higher pulmonary artery pressure which was assessed only at rest. Therefore, in the further analyses we considered both the patients with resting LAH and the patients with exercise-induced LAH as a single group.

CLINICAL, STRUCTURAL, AND HEMODYNAMIC CHARACTERISTICS ASSOCIATED WITH LAH. The patients with LAH were significantly older, more obese, more often women, and they had more frequently arterial hypertension and diabetes mellitus (Table 2, Figure 2). Although systolic blood pressure was one of the strongest factors associated with LAH, no significant correlation was found between increase in the blood pressure and increase in the LA pressure in response to exercise.

Compared to patients without LAH, patients with LAH had worse LV diastolic dysfunction (as reflected by the increased E wave velocity, E/E' ratio, BNP, and galectin-3), a higher grade of mitral valve regurgitation, and signs of right heart pressure overload. Importantly, the presence of LAH could not be

TABLE 2 Comparison of Baseline Clinical Characteristics

	LAH- (n = 158)	LAH+ (n = 82)	SMD All Patients/ Patients in SR*	R-LAH+ (n = 36)	E-LAH+ (n = 46)	SMD E-LAH+ vs. R-LAH+
Age (yrs)	58 ± 10	64 ± 7	0.61†/0.50†	65 ± 7	63 ± 7	0.31
Males	119 (75)	41 (50)	0.54†/0.43†	14 (39)	27 (59)	0.39
Body mass index (kg/m^2)	28 ± 4	31 ± 5	0.69†/0.85†	32 ± 5	31 ± 5	0.22
Arterial hypertension	90 (57)	62 (76)	0.40†/0.44†	29 (81)	33 (72)	0.21
Diabetes mellitus	10 (6.3)	15 (18)	0.37†/0.30†	10 (28)	5 (11)	0.40
Coronary artery disease	14 (9)	12 (15)	0.18/0.20	2 (6)	10 (22)	0.48
CHA2DS2-VASc score	1.5 ± 1.1	2.4 ± 1.4	0.71†/0.69†	2.8 ± 1.5	2.2 ± 1.3	0.42
Persistent AF	51 (32)	39 (48)	0.32†/0.08	17 (47)	22 (48)	0.12
AF present‡	42 (27)	42 (51)	0.51/–	20 (56)	22 (48)	0.16
AF persistence (months)§	1 (0-5)	4 (2-6)	0.22/–	4 (2-5)	4 (1-7)	0.19
Antiarrhythmic drugs	100 (63)	47 (57)	0.15/0.14	21 (58)	26 (57)	0.04
Beta blockers	95 (60)	61 (74)	0.91†/0.38†	29 (81)	32 (70)	0.25
ACEI/ARBs	67 (42)	41 (50)	0.15/0.12	17 (47)	24 (52)	0.10

Values are mean ± SD, n (%), or median (interquartile range). Differences between the various subgroups are expressed by SMD. *Subanalysis of patients who were in SR during the hemodynamic assessment (LAH+/-, n = 40 of 116). †Significant association by univariate logistic regression analysis. ‡Patients who were in AF during the hemodynamic assessment. §Duration of uninterrupted AF before ablation in patients with persistent.

E-LAH+ = exercise-induced LAH only; IQR = interquartile ratio; LAH+/- = resting or exercise-induced left atrial hypertension present/absent; Pts = patients; R-LAH+ = resting LAH only; SMD = standardized difference mean; SR = sinus rhythm; other abbreviations as in Table 1.

explained by fluid overload, as the estimated right atrial pressure was equally low in in both groups (Table 3).

Presence of LAH was strongly associated with the LA structural and functional remodeling, which was reflected by the LA enlargement, increased LA stiffness, decreased LA contractility, and decreased LA distensibility. The LA enlargement along with the increased LA pressure generated greater LA wall stress, which was also reflected by increased MR-proANP (Table 3).

Moreover, LAH was strongly associated with greater LA surface area of low (<0.5 mV) bipolar voltage (Table 3). This association was significant also when only patients in SR were considered (Table 3), when the low voltage was defined by the stricter 0.15 mV cut-off (unadjusted odds ratio [95% confidence interval]: 1.06 [1.03 to 1.1] per percentage of the LA surface, 1.03 [1.02 to 1.07] when considering only patients in SR), or when the low voltage was defined by the combined cut-off of 0.5 mV for patients in SR and 0.15 mV for patients in AF (unadjusted odds ratio = 1.04 [1.02 to 1.05] per percentage of the LA surface). Confluent areas with voltage <0.5 mV occurred in 76% of the patients with LAH versus 39% of the patients without LAH (59% vs. 19% if considering only patients in SR; $p < 0.001$ for both).

LAH was also associated with the presence of AF during the hemodynamic assessment, although this relationship could not be explained by an excessive heart rate (Table 3). Compared to patients with SR, the patients with AF had mean LA pressure increased on average by 2 mm Hg at rest and by 4 mm Hg during the exercise ($p < 0.001$ for both). Nevertheless, the main differences found between the patients with and without LAH remained consistent even when only patients in SR were included in the analyzes (see the footnotes to Tables 2 and 3).

Table 4 shows the factors that were independently associated with the LAH. Table 4 also emphasizes that the presence of LAH could be reliably estimated based on a few clinical and echocardiographic characteristics. In addition to the factors listed in the Table 4, there was an independent association of LAH with the greater extent of low LA voltage (significant odds ratio 1.02 to 1.04 per percentage of the LA surface when added to any of the models).

CATHETER ABLATION, LAH, AND RISK OF ARRHYTHMIA RECURRENCE. A minimum follow-up of 12 months after ablation (mean 16 ± 6 months, identically for both groups) was available in 77 patients with LAH and in 138 patients without LAH. Arrhythmia recurred during the follow-up in 45% of the patients: 58% with LAH versus 38% without LAH ($p = 0.003$) (Figure 3).

Interestingly, the patients without LAH had less arrhythmia recurrence when they underwent only pulmonary vein isolation as compared to an extensive LA ablation (i.e., linear lesions, coronary sinus ablation, and electrogram-guided ablations in addition to the pulmonary vein isolation). In the patients with LAH, the ablation procedure was usually lengthier and more complex (radiofrequency time: 58 ± 22 min vs. 48 ± 21 min; cumulative radiofrequency energy: 1,344 ± 540 W/min vs. 1,080 ± 505 W/min; $p < 0.001$ for both); however, their outcome of the ablation did not differ with regard to the ablation strategy (Figure 3).

TABLE 3 Comparison of Cardiac Structure, Function, and Systemic Hemodynamics

	LAH- (n = 158)	LAH+ (n = 82)	SMD All Patients/ Patients in SR*	R-LAH+ (n = 36)	E-LAH+ (n = 46)	SMD E-LAH+ vs. R-LAH+
Left atrium						
LA volume (ml)	71 ± 26	92 ± 30	0.56†/0.59†	93 ± 34	91 ± 25	0.02
LA volume index (ml/m^2)	37 ± 10	43 ± 11	0.61†/0.56†	43 ± 10	43 ± 13	0.02
LA total ejection fraction (%)	46 ± 13	38 ± 11	0.64†/0.92†	38 ± 10	38 ± 11	0.09
LA passive filling (%)‡	30 ± 12	24 ± 9	0.63†/0.65†	24 ± 10	24 ± 8	0.01
LA active emptying (%)‡	26 ± 12	20 ± 10	0.54†/0.54†	20 ± 12	20 ± 10	0.08
LAA outflow velocity (cm/s)§	55 (40-72)	38 (28-49)	0.84†/0.68†	33 (28-48)	39 (34-49)	0.23
LA stiffness (mm Hg/ml)	0.56 ± 0.35	0.93 ± 0.62	1.92†/0.84†	1.01 ± 0.54	0.87 ± 0.67	0.23
LA voltage <0.5 mV (%)	0 (0, 20)	59 (19, 79)	1.41†/0.94†	56 (22, 85)	62 (17, 74)	0.15
LAP at rest (mm Hg)	7 ± 3	14 ± 5	1.98†/1.82†	18 ± 3	11 ± 2	2.40†
LAP at exercise (mm Hg)	9 ± 3	21 ± 5	2.71†/2.46†	24 ± 6	19 ± 4	0.99†
LA wall stress (kdynes/cm^2)	99 ± 33	190 ± 64	1.92†/1.70†	226 ± 55	162 ± 56	2.39†
MR-proANP (μmol/m)‖	93 (62-158)	132 (85-191)	0.42†/0.38	127 (87-187)	132 (84-187)	0.18
Left ventricle						
LV end diastolic diameter (mm)	53 ± 5	53 ± 5	0.07/0.16	52 ± 4	54 ± 5	0.19
LV ejection fraction (%)	57 ± 5	56 ± 5	0.09/0.20	57 ± 4	56 ± 5	0.20
LV mass (g)	184 ± 46	189 ± 52	0.11/0.26	183 ± 51	194 ± 53	0.22
E wave velocity (cm/s)	70 ± 20	86 ± 20	0.81†/0.63†	89 ± 17	85 ± 22	0.22
E/E' ratio	8 ± 3	9 ± 3	0.51†/0.63†	10 ± 3	9 ± 3	0.22
E deceleration time (ms)	202 ± 71	185 ± 62	0.81†/0.44	170 ± 39	196 ± 74	0.34
Mitral regurgitation (1-4)	1.0 ± 0.2	1.2 ± 0.4	0.50†/0.49†	1.2 ± 0.4	1.2 ± 0.4	0.12
BNP (pg/ml)‖	38 (18-78)	84 (31-103)	0.44†/0.41†	88 (28-125)	84 (46-101)	0.13
Galectin-3 (ng/ml)‖	12 ± 3	14 ± 4	0.54†/0.80†	13 ± 4	14 ± 5	0.16
Right heart						
PA systolic pressure (mm Hg)¶	27 ± 5	34 ± 10	0.83†/1.04†	37 ± 11	31 ± 7	0.61†
RV diameter at base (mm)	37 ± 5	38 ± 5	0.22/0.24	37 ± 5	39 ± 5	0.27†
TAPSE (mm)	22 ± 5	20 ± 4	0.39†/0.29†	19 ± 4	21 ± 5	0.38†
Tricuspid regurgitation (1-4)	1.0 ± 0.2	1.2 ± 0.4	0.39†/0.34†	1.3 ± 0.6	1.1 ± 0.3	0.38
RA volume (ml)	51 ± 19	63 ± 27	0.50†/0.42†	59 ± 22	66 ± 31	0.23
Mean RA pressure (mm Hg)¶	4 ± 3	4 ± 2	0.10/0.02	4 ± 3	4 ± 2	0.05
Systemic hemodynamics						
Heart rate at rest (min^{-1})	70 ± 18	71 ± 20	0.05/0.71	72 ± 21	70 ± 20	0.10
Heart rate at exercise (min^{-1})	83 ± 22	85 ± 25	0.07/0.17	84 ± 26	85 ± 25	0.02
Systolic BP at rest (mm Hg)	129 ± 18	141 ± 22	0.61†/0.71†	147 ± 20	136 ± 22	0.53†
Systolic BP at exercise (mm Hg)	145 ± 22	161 ± 24	0.72†/0.78†	164 ± 23	159 ± 25	0.22

Values are mean ± SD, %, or median (interquartile range). Data reported as in Table 2. *Subanalysis of patients who were in SR during the hemodynamic assessment (LAH+/-, n = 39 and 116). †Significant association by univariate logistic regression analysis. ‡Measurable only in patients with SR (LAH+/-, n = 39 and 116). §Measured by transesophageal echocardiography (LAH+/-, n = 51 and 59 [18 and 25 for SR]). ‖Available in a subset of patients (LAH+/-, n = 26 and 80 [n = 16 and 60 for SR]). ¶Available in patients with measurable tricuspid regurgitation jet (LAH+/-, n = 50 and 90, [24 and 64 for SR]).

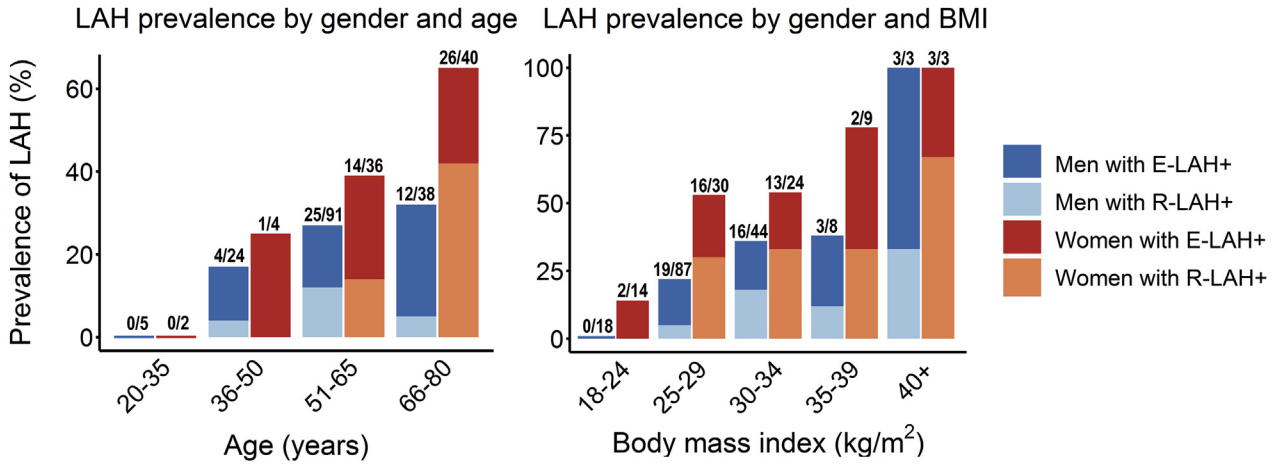
BP = blood pressure; BNP = B-type natriuretic peptide; LAA = LA appendage; LAP = mean left atrial pressure; MR-proANP = mid-regional pro-atrial natriuretic peptide; PA = pulmonary artery; RA = right atrium; TAPSE = tricuspid annular plane systolic excursion; other abbreviations as in Tables 1 and 2.

In Cox regression analysis—after adjusting for age, LA volume, AF persistence, LA low-voltage, and extent of the procedure—the presence of either resting or exercise-induced LAH was independently associated with arrhythmia recurrence (significant hazard ratios 1.6 to 1.7) (Table 5). On the other hand, LAH did not predict the arrhythmia recurrence when only resting LA pressure had been considered.

LAH AND QoL. Serial assessment of QoL was available in 34 patients with LAH and in 77 patients without LAH. Before ablation, the patients with LAH had lower QoL than the patients without LAH by 36% in the physical component and by 24% in the mental component (both had $p < 0.01$). After ablation, both groups improved significantly ($p < 0.01$) their physical component of QoL (patients with LAH by 14%; patients without LAH by 5%, $p = 0.20$ for between-group comparison of the relative change). Neither of the groups improved in the mental component.

In a subanalysis of the patients who remained arrhythmia-free until the re-assessment of QoL at 6 months (29 patients with LAH and 68 patients without LAH), both groups improved significantly in both of the components (all $p < 0.01$). However, in relative numbers, the improvement in the QoL was

FIGURE 2 Gender-Specific Prevalence of Resting and Exercise-Induced Left Atrial Hypertension in the Respective Age and Body Mass Index Categories



The fractions represent absolute numbers of the patients with either R-LAH+ or E-LAH+ in each respective category. BMI = body mass index; other abbreviations as in Figure 1.

greater in the patients with LAH versus those without LAH (31% vs. 6% in the physical component, p = 0.005; and 11% vs. 4% in the mental component, p = 0.043) (Figure 4).

DISCUSSION

This was the first study to investigate the prevalence, associated factors, and clinical implications of both resting and exercise-induced LAH in patients undergoing ablation of AF. LAH occurred either at rest or during the isometric handgrip exercise in one-third of the patients, even though they did not have LV systolic dysfunction or significant mitral valve disease. The patients who had LAH already at rest did not differ from the patients who developed LAH only during the exercise, but all the patients with LAH differed fundamentally from the remaining AF population in terms of worse clinical profile, advanced cardiac remodeling, extensive LA substrate, and a higher rate of arrhythmia recurrence after ablation. These findings indicate that assessment of the LA pressure during isometric handgrip exercise could be used clinically to stratify patients undergoing AF ablation.

TABLE 4 Noninvasive Predictors of Left Atrial Hypertension

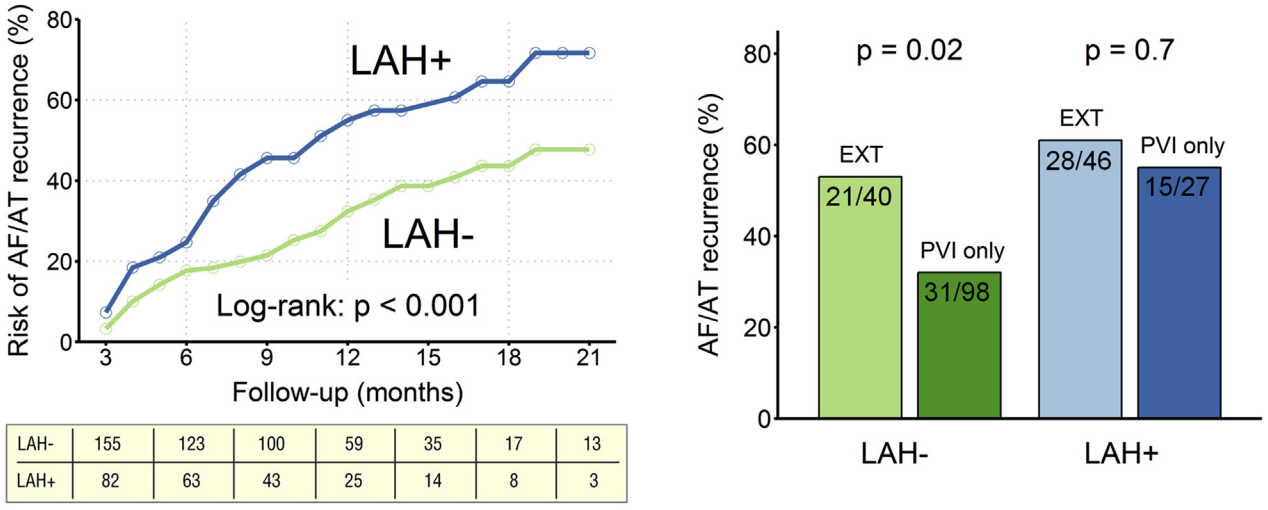
	Model 1: Baseline Clinical Variables	Model 2: Baseline Clinical Variables + TTE	Model 3: Baseline Clinical Variables + TTE + TEE
Age (yrs)	1.06 (1.01-1.11)*	1.04 (0.90-1.09)	–
Female	1.85 (1.14-3.70)†	1.70 (0.82-3.60)	–
BMI (kg/m^2)	1.16 (1.06-1.26)‡	1.15 (1.06-1.27)*	1.40 (0.99-1.30)
AF present	3.80 (1.77-8.01)‡	2.50 (1.17-5.40)†	1.60 (0.51-4.90)
Systolic BP at rest (mm Hg)	1.03 (1.01-1.05)*	1.02 (1.01-1.05)*	1.05 (1.02-1.10)*
LAVI (ml/m^2)	–	1.04 (1.00-1.08)†	1.04 (1.00-1.08)†
E wave velocity (cm/s)	–	1.02 (1.00-1.04)†	1.02 (0.99-1.05)
LAA outflow velocity (cm/s)	–	–	0.96 (0.93-0.99)†
Model C-statistics	0.81 (0.75-0.87)	0.84 (0.78-0.89)	0.86 (0.78-0.94)

Values are odds ratio (95% confidence interval). The table presents final multivariable logistic regression models for non-invasive prediction of resting/exercise induced LAH. The following variables were also tested stepwise but none of them improved the models' performance: history of arterial hypertension, history of diabetes, persistent form of AF, BNP, MR-proANP, Galectin-3, E/E', mitral regurgitation grade, LA total ejection fraction, tricuspid regurgitation grade, pulmonary artery systolic pressure, TAPSE, and RA volume. Of note, discrimination of all the 3 models slightly improved when the systolic BP at rest was substituted by the maximal systolic BP during exercise (C statistics: 0.82, 0.85 and 0.88, respectively). *Adjusted p value <0.01. †Adjusted p value <0.05. ‡Adjusted p value <0.001.

BMI = body mass index; CI = confidence interval; LAVI = left atrial volume index; MR grade = mitral regurgitation grade; TEE = transesophageal echocardiography; TR grade = tricuspid regurgitation grade; other abbreviations as in Tables 1-3.

ETIOLOGY OF LAH. Our data suggest that most of the patients with LAH had in fact an early stage of heart failure with preserved LV ejection fraction (HFpEF). Besides the characteristic clinical profile (older age, female, arterial hypertension, obesity, and diabetes) and evidence of LV diastolic dysfunction, they had limiting exertional symptoms which were reflected by the decreased physical component of QoL (12). In addition, the often dramatic improvement in the physical component of the QoL after a successful ablation was clearly related to the fact that these patients were more dependent on the atrial contribution to the LV filling. The high prevalence of HFpEF found in our patients corresponds to the recent data from the Framingham Heart Study, which observed HFpEF in up to one-third of the patients with AF (13), thus emphasizing the close relationship between HFpEF and AF.

FIGURE 3 Arrhythmia Recurrence After Ablation With Regard to the Left Atrial Hypertension



(Left) Cumulative risk of arrhythmia recurrence after ablation according to the absence/presence of LAH–/+. **(Right)** Arrhythmia recurrence after ablation with regard to the LAH and extent of the ablation. The **numbers in the bars** represent the fraction of the patients with arrhythmia recurrence. AF = atrial fibrillation; AT = atrial tachycardia; EXT = PVI + extensive substrate modification with linear lesions and/or coronary sinus ablation and/or electrogram-guided ablations; PVI = pulmonary vein isolation only; other abbreviation as in Figure 1.

LAH AND LA REMODELING. LAH is the final hemodynamic pathway of diverse risk factors and left heart conditions. At the same time, it is a major force that induces the LA remodeling (3,14). In this respect, this study confirmed the central role of LAH as a mechanistic link between some of the notorious risk factors of AF, LA remodeling, AF persistence, and consequently worse outcome of the AF ablation. An important finding was that in many of the patients the LA remodeling had developed rather by accumulation of brief but repetitive episodes of exercise-induced LAH occurring in everyday life than by permanent pressure overload. From a clinical perspective, these findings imply that the assessment of the LA exercise hemodynamics could be used as a complex and self-contained test of the overall LA condition.

LAH AND IMPLICATIONS FOR AF ABLATION. The association between LAH detected at rest and worse outcome of AF ablation has been previously reported (14–16). Our study showed that the presence of either resting or exercise-induced LAH had an additive predictive value for the AF recurrence that was independent from other known risk factors. However, we found that only the integration of the resting and exercise LA pressure data predicted the outcome of ablation. This was related to the fact that the resting hemodynamic assessment missed many patients with significant burden of intermittent exercise-induced LAH, which we have shown importantly contributed to the LA disease. These findings emphasize the importance of a stress test when evaluating the LA hemodynamics.

Importantly, we believe that the presence of LAH should not alone defer these patients from the ablation. The hemodynamic stratification of the patients should rather help in choosing an appropriate strategy of the ablation procedure. We showed that the patients without LAH, who had overall healthy LA, had lower AF recurrence when the ablation procedure was limited to a simple isolation of the pulmonary veins. Whether this was related to the reduction of arrhythmias ensuing from the post-ablation scarring remains

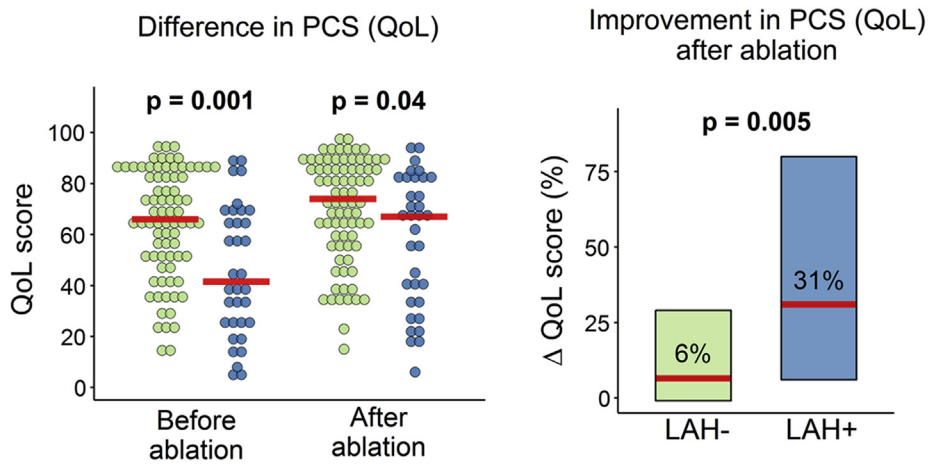
TABLE 5 Predictors of Arrhythmia Recurrence After Ablation

	Model 1	Model 2
Age (yrs)	0.99 (0.97–1.03)	1.01 (0.97–1.05)
Persistent AF	1.01 (0.98–1.06)	1.30 (0.80–2.10)
LA volume (ml)	1.01 (1.01–1.02)*	1.01 (1.00–1.02)†
LAH at rest or during exercise	1.70 (1.10–2.6)†	1.60 (1.02–2.60)†
Radiofrequency ablation time (min)	–	1.02 (1.00–1.03)‡
Extent of LA voltage <0.5 mV (%)	–	1.00 (0.99–1.01)

Values are adjusted hazard ratios (95% confidence intervals) calculated by the multivariable Cox's regression analysis. Model 1 was based on clinical variables, echocardiography and hemodynamic data. Model 2 included additional LA endocardial bipolar voltage mapping and duration of ablation, as a surrogate of the procedural complexity. *Adjusted p value <0.001. †Adjusted p value <0.05. ‡Adjusted p value <0.01.

Abbreviations as in Tables 1 and 2.

FIGURE 4 Comparison of the Physical Component Summary of Quality of Life Between the Patients Without LAH and With LAH



The **right panel** shows greater relative improvement in the QoL after a successful ablation (i.e., no arrhythmia recurrence until the re-assessment of the QoL at 6 months) in the LAH+ versus LAH– patients (n = 29/68, respectively). The **red horizontal lines** and the **boxplots** represent median and interquartile range. LAH–/+ = **green/blue color**, respectively; PCS = physical component summary; QoL = quality of life; other abbreviation as in Figure 1.

unclear. Conversely, it is conceivable that the patients with LAH, in whom the AF had developed in the setting of extensive LA substrate, might benefit from a more aggressive LA ablation which would target the LA substrate (2). However, the latter may be confirmed only by a future randomized study.

STUDY LIMITATIONS. The design of our study prevents firm conclusions on the causality between LAH, the LA remodeling, and AF persistence. Because the echocardiography was performed only at rest, we cannot estimate the contribution of dynamic mitral regurgitation to the LAH. Although all the patients were able to complete the handgrip exercise during the catheterization, it is possible that the given mild sedation could have influenced the grip force. Moreover, some centers prefer to ablate AF under general anesthesia. But in such cases the handgrip might be replaced by a fluid challenge or leg elevation (10). Lastly, the LA voltage maps were obtained during the patient's spontaneous rhythm without the use of contact-force technology and the maps were relatively sparse.

CONCLUSIONS

Presence of either resting or exercise-induced LAH identified a subpopulation of AF patients who had a distinct clinical profile, more extensive LA substrate, and different clinical response to the ablation. Future studies must confirm whether such hemodynamic stratification of the patients can help to guide the ablation strategy and thereby improve its clinical efficacy.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: LAH is common in patients undergoing AF ablation and its presence usually indicates an early phase of HFpEF.

COMPETENCY IN PATIENT CARE: Resting or exercise-induced LAH in patients with AF can be regarded as a complementary index of present LA disease. Elimination of AF substrate in these patients may be more challenging; however, successful ablation results in substantial improvement in the QoL.

TRANSLATIONAL OUTLOOK: Future clinical trial should confirm whether the efficacy of AF ablation would improve if the strategy of the procedure was guided by the LA exercise hemodynamics.

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KEY WORDS **atrial pressure, atrial remodeling, atrial substrate, exercise hemodynamics, heart failure with preserved ejection fraction, substrate ablation**