Isoproterenol Loading Transesophageal Echocardiography in Atrial Fibrillation

Brief title: TEE with isoproterenol in AF

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Abstract

Purpose: In patients with sludge or severe spontaneous echo contrast (SEC) in the left atrial appendage (LAA), cases with isoproterenol loading transesophageal echocardiography (ISP-TEE) have been reported to identify the presence of thrombus in the LAA. This study aimed to assess the validity and hemodynamic changes of ISP-TEE in the LAA.

Methods: We prospectively enrolled patients with atrial fibrillation (AF) who underwent ISP-TEE. The degree of sludge/SEC was categorized as being either absent (grade 0), mild SEC (grade 1), moderate SEC (grade 2), severe SEC or sludge (grade 3). The hemodynamic evaluation was performed by measuring LAA flow velocity, LAA tissue Doppler imaging (LAA-TDI) velocity, and pulmonary vein systolic forward flow velocity (PVS).

Results: In total, 35 patients (mean age 71 ± 7 years; 71% male) underwent ISP-TEE. Among 35 patients, 30 patients had grade 3 or 2 SEC, 5 patients had grade 1 SEC. After ISP loading, 23 patients (66% of all patients) showed improved sludge/SEC and one patient was diagnosed with thrombus in the LAA. There were 25 patients with grade 1 SEC, or no SEC (classified as Group1), 10 patients had residual sludge or grade 2 to 3 SEC (classified as Group2) after ISP administration. LAA flow, LAA-TDI, and PVS velocities were significantly higher in group 1 than in group 2 after ISP administration. There was no complication during the examination and after 24 hours and 3 months.

Conclusion: ISP infusion may be a potential tool to recognize LAA thrombus under the sludge/SEC during TEE in AF.

Key Words: echocardiography; transesophageal echocardiography; atrial fibrillation, spontaneous echo contrast.

Introduction

Atrial fibrillation (AF) is the most encountered arrhythmia in daily practice. In patients with AF, thrombus formation in the left atrium is known to occur due to multiple causes, such as endothelial damage, abnormal blood stasis, and fibrosis.[1] Thrombus formation within the left atrium, especially in the left atrial appendage (LAA)[2] is a direct cause of cardiogenic embolism, and is a contraindication to procedures such as electrical cardioversion,[3] catheter ablation,[4] and catheter-based LAA occlusion.[5] Therefore, accurate diagnosis of LAA thrombus before these procedures is essential. Transesophageal echocardiography (TEE) is the most widely used imaging modality for diagnosing LAA thrombi, and occasionally shows smoky appearances called spontaneous echo contrast (SEC) or sludge. These findings are associated with future thrombus formation, subsequent thromboembolic events[6] and reduced visibility in LAA. Thus, the indications for electrical cardioversion, catheter ablation, and LAA occlusion in patients with these findings are controversial. Recently, a case was reported in which isoproterenol (ISP) administration during TEE could distinguish SEC from thrombus.[7] This method has been suggested to be useful in situations where it is necessary to differentiate between SEC and thrombus in the LAA. However, the validity and physiological effects of this method are unclear. This study aimed to assess the validity of isoproterenol loading transesophageal echocardiography (ISP-TEE) to identify LAA thrombus and the hemodynamic changes caused by ISP loading.

Methods

Study population. We prospectively enrolled 47 patients with AF and confirmed sludge/SEC by TEE before electrical cardioversion or catheter ablation at our institution from April 2020 to January 2022. **Figure 1** shows a selection of eligible patients and the enrollment process. AF was based on an electrocardiogram or 24-hour Holter electrocardiogram. The exclusion criteria were as follows: (1) More than moderate mitral regurgitation, because of a possibility that the quantitative evaluation of LAA function could not be accurately assessed due to the regurgitation jet. (2) Hemodynamic instability, such as on other inotropic agents or unstable angina. (3) No subject consent for ISP administration. (4) Contraindications to ISP, such as patients with idiopathic hypertrophic subaortic stenosis or digitalis poisoning. Subjects were also excluded if they had poor echocardiographic images. Thirty-five patients fulfilled all criteria for the final analysis. After ISP loading, we divided into two groups according to grades: Group 1 was defined as grade 1 or grade 0 SEC and Group 2 was defined as grade 3 or 2 SEC (**Figure 2**). Transthoracic echocardiography was performed by experienced sonographers/doctors using a commercially-available ultrasound machine. Measurements and recordings were obtained according to the American Society of Echocardiography and European Association of Cardiovascular Imaging recommendations.[8],[9] The Ethics Committee approved all procedures used in this research of Tokushima University Hospital. Written informed consent was obtained from the patient to conduct and publish this study and accompanying images.

Transesophageal Echocardiographic assessment. 2D and 3D TEE were performed by experienced doctors with a commercially-available ultrasound machine (EPIQ7G, Philips Healthcare, Amsterdam, the Netherlands) using a matrix-array 3D TEE probe (X8-2t; Philips Medical Systems). TEE procedures were performed with the patients sedated with midazolam administration via IV. As an evaluation of LAA, multiplanar imaging was performed to continuously visualize the LAA in the mid-esophageal view, by rotating the imaging sector in steps from 0° to 135°. Referring to past studies,[10] we defined the visual grade of SEC into four levels as follows; grade 0: absence of echogenicity, grade 1: minimal echogenicity located in the LAA that may be detectable only transiently during the cardiac cycle, grade 2: dense swirling pattern in the LAA detectable constantly throughout the cardiac cycle, grade

3: intense echo density and very slow swirling patterns in the LAA. In this study, sludge was classified as grade 3 SEC. Hemodynamic evaluation in the LAA was performed using LAA blood flow velocity, LAA tissue Doppler imaging (LAA-TDI) velocity, pulmonary vein systolic forward flow (PVS) velocity. **Figures 3-A** and **3-B** show the measurement method of LAA blood flow velocity and LAA-TDI. PVS velocity was measured for the left upper pulmonary vein with pulsed wave (PW) Doppler echocardiography. These echocardiographic parameters were measured in three cardiac cycles with RR intervals as equal as possible in each case, and the mean values were calculated. The 3D images of the LAA were acquired using the 3D zoom mode to obtain with high frame, and 3D LAA volumes were quantified using the stacked-contour method, a method for measuring the volume of structures with irregular surfaces.[11] (**Figure 3-C**). 3D echocardiographic data were digitally stored and analyzed offline (QLAB 15.0 GI 3DQ; Philips Medical Systems). The various LAA forms were visually classified as chicken wings, or no-chicken wing, as previously reported.[12] LAA volume fraction (LAAVF) was calculated using the following equation: LAAVF (%) = (maximal LAA volume – minimal LAA volume) / maximal LAA volume × 100 (**Figure 3**).

Isoproterenol Loading Transesophageal Echocardiography. ISP was administered via the same venous route used for sedation. ISP, diluted to 1μg/ml concentration in saline, was administered via IV boluses by 1μg increments to maintain the target heart rate (HR) defined as follows: maximal HR [beats per minutes: bpm] = 220 – age (years), target HR [bpm] = maximal HR × 0.8. We evaluated patients' condition (changes in systolic blood pressure and HR) before and after ISP loading. To check complications, we assessed the presence or absence of worsening heart failure, new arrhythmias other than atrial fibrillation, cerebral infarction or transient ischemic attack, and other thromboembolic events during the examination and after 24 hours and 3 months. We evaluated the changes in sludge/SEC and the hemodynamic changes in LAA induced by ISP administration.

Statistical analysis. For continuous variables, the normality of the distribution was assessed using the Shapiro-Wilk test. Variables with normal distributions were presented as mean values ± standard deviation, otherwise as medians and the lower and upper quartile (Q1-Q3). The categorical data were presented as the percentage and number of patients. Statistical significance of differences between before and after ISP was assessed using the paired samples t-test for data with normal distribution. The Wilcoxon test was used for data that were not normally distributed. Statistical significance of differences between groups was assessed using the independent samples t-test for data with normal distribution, and the Mann-Whitney test was used for data that were not normally distributed. For categorical variables, Fisher's exact test was used. Statistical analysis was performed using standard statistical software packages (MedCalc Software 17; Mariakerke, Belgium). Statistical significance was defined as $p<0.05$.

Results

Baseline characteristics. A total of 35 patients with AF who underwent ISP-TEE were included in this study. Baseline characteristics of the study group are presented in **Table 1**. The mean age was 71±7 years. Most patients were male (71 %), and around 43 % of patients had long-standing persistent AF according to current guideline classifications. [3] The median CHA_2DS_2-VASc score was 4 (interquartile range [IQR], 2-4). Out of 35 patients, 18 patients had grade 3 SEC in the LAA, 12 patients had grade 2 SEC, and 5 patients had grade 1 SEC.

ISP-TEE. A median of 3.0 µg of ISP was administered to reach and maintain the target HR. With ISP administration, heart rate was significantly increased compared to baseline, but systolic blood pressure was not significantly different (**Table 2**). After ISP loading, 23 patients (66% of all patients) showed improved sludge/SEC, and 6 patients had grade 3 SEC or sludge in the LAA, 4 patients had grade 2, 14 patients had grade 1, and 11 patients had grade 0 (**Figure 4**). There were 25 patients in group 1 and 10 patients in group 2. In patients with improved sludge/SEC, we found one case that had a thrombus during ISP-loading (**Figure 5**). No complications were observed during and 24 hours and 3 months (median duration of 104 days, IQR: 96-111) after the examination in all cases. Two investigators (TT and SH) separately evaluated the visual grade of SEC at baseline and after ISP administration, respectively. The agreement for grading evaluation of SEC was assessed using the weighted Cohen's kappa coefficient. There were excellent agreements on SEC grade at baseline (κ=1.00) and after ISP administration (κ=0.92).

Comparison of characteristics between two groups. There was a significant difference between the two groups in E wave velocity and E/e'. There was no significant difference in ISP dosage between the two groups. Before and after ISP administration, blood pressure did not change significantly in either group. In both groups, heart rate increased with ISP, and the degree of increase (ΔHR) was not significantly different between the groups (ΔHR: 44 ± 15 bpm in Group 1 vs. 44 ± 18 bpm in Group 2, p=0.885).

Comparison of LAA parameters. **Table 2** showed TEE parameters in the LAA at baseline and after ISP loading. Both LAA velocity and LAA-TDI velocity were accelerated by ISP loading compared to baseline (**Figure 6**). PV S wave velocity was also accelerated by ISP administration compared to baseline. As for the volume of LAA, maximal LAA volume did not change significantly with ISP loading, but minimal LAA volume decreased significantly, resulting in a significant increase in LAAVF with ISP administering. These LAA hemodynamic parameters with LAA velocity and PVS wave velocity were significantly accelerated after ISP administration in Group 1. However, there was no significant difference before and after ISP administration in Group 2. LAA-TDI velocity and LAAVF increased significantly in both groups after ISP, but the difference before and after ISP tended to be greater in Group 1 (ΔLAA-TDI 1.45±0.99 vs. 0.68±0.57, p=0.03, ΔLAAVF 12.1±10.9 vs.

6.2±8.3, p=0.155).

Discussion

In this study, we made two crucial observations: 1) in patients with AF, ISP improved sludge/SEC in 66% of patients, 2) the associated improvement indicators were LAA blood flow velocity, LAA-TDI velocity, PVS velocity, and LAAVF, 3) one patient (3% of patients) was diagnosed with thrombus in the LAA during ISP loading.

The major strength of this study is that it appears to be the largest series of patients in whom this procedure was conducted in a standardized and well controlled setting. Our study brings the hypothesis that ISP infusion to recognize LAA thrombus under sludge/SEC during TEE can be a tool to manage cases with AF intervention cases. In addition, our findings related to improved LAA function in a subset of patients post ISP could form the basis of further investigation evaluating the predictive value of this response in assessing a variety of clinical outcomes such as procedural success, complication, rate of arrhythmia recurrence, long-term outcomes and complications.

ISP effects on sludge/SEC. In our results, ISP improved sludge/SEC in 66% of patients with AF. Sludge in the LAA, as a precursor to thrombus, is an independent risk factor for embolism and death, as is thrombus.[6] In general, the presence of sludge in the LAA is a relative contraindication to invasive therapies such as electrical cardioversion.[13] On the other hand, some reports show that ablation[14] and cardioversion[15] can be safely performed even in patients with sludge/SEC in the LAA. The strategy for patients with sludge/SEC is controversial. In the present study, among 35 patients, a hidden thrombus at the bottom of the LAA was identified in one patient after ISP administration (**Figure 5**). The patient decided to postpone the planned electrical cardioversion and to intensify anticoagulation. The rest of the patients, whose thrombus could be ruled out, underwent electrical cardioversion or catheter ablation as planned. These results suggested that patients, who have been concerned about the embolism related to invasive therapies, can choose invasive therapies with more confidence using ISP loading TEE.

The results of this study showed that there were no adverse events in patients who underwent ISP loading. Still, the concern with ISP infusion in patients with sludge/SEC, would be dislodgement of thrombus which is obscured by a sludge/SEC, causing embolic phenomena. Therefore, we believe that ISP is not recommended in cases where a thrombus is clearly present or where the presence of a thrombus is strongly suspected (e.g., patients without anticoagulation therapies). In addition, if the presence of a thrombus becomes apparent after administration of ISP, it is important that the administration should be discontinued immediately.

ISP effects on LAA function. In patients in Group 1, LAA functional parameters (LAA blood flow velocity, LAA-TDI velocity, PVS velocity, and LAAVF) were significantly improved after ISP administration. ISP increased heart rate in most patients of both groups, but ΔHR (changes between before and after ISP) did not differ between the two groups. In 3D analysis of the LAA, LAAVF increased more in Group 1 than in Group 2. Previous research has shown that ISP enhances left ventricular relaxation and improves diastolic pressure-volume relations compared with pacing tachycardia even at the same heart rate.[16] Another report showed that ISP administration improved atrial function after cardioversion of chronic atrial fibrillation and atrial flutter.[17] These previous reports and our present findings suggest that the mechanism of sludge/SEC improvement by ISP administration is due to the improvement of LAA function by a positive inotropic effect on the myocardium, rather than the contribution of increased heart rate alone.

Clinical implication. The diagnostic performance of TEE for thrombus in the LAA is good.[18] However, its diagnostic ability in patients with sludge/SEC has not been investigated in AF. Although the guidelines recommended TEE thrombus evaluation before invasive treatment,[3] there is no explicit policy for cases with sludge/SEC. It is essential to exclude thrombus in the LAA to determine the appropriate treatment strategy in cardioversion and cardiac ablation and LAA closure and transcatheter mitral valve intervention preoperatively.

Study limitation. Although this is the first study of ISP-TEE, there were several limitations. The first limitation is that this study had a small sample size. This study was a single-center trial in a selected patient population. Although there were no complications with ISP administration in this study, we cannot make definitive comments on safety due to the small sample size. The second is no gold standard for detecting sludge or SEC. The third is that each group's average left ventricular ejection fraction was within normal limits and the results may not be applicable to a population with various degrees of left ventricular dysfunction another important variable related to left atrial function. The fourth is that this study observed the dynamics of LAA with ISP loading, and the relationship between the diagnosis of sludge/SEC with ISP loading and clinical events is still unknown. The fifth is that we cannot compare the diagnostic performance of the ISP loading method with that of using echo contrast agents which have been reported in recent years,[19] because echo contrast agents are not approved in Japan. The sixth is that the peak LAA velocity and other LAA functional indicators may be affected by other variables besides ISP. Based on these limitations, this study should be considered for hypothesis generation, and we believe that a larger multicenter study is needed to validate our findings.

Conclusion

ISP infusion may be a potential tool in patients with AF to recognize LAA thrombus under the sludge/SEC during TEE. The results may provide insights into the mechanisms of ISP loading on sludge/SEC in the LAA.

Disclosures: None.

Contributorship: Design of the work: TT, KK, and SH. Conduct of the work and data acquisition: TT, SH, NY, SM, YH, SN, YS, TI, KY, SY, HY, TS, and TW. Data analysis and interpretation: TT and KK. Drafting the work: TT, KK, SH, and RZ. Reviewing the work and providing input: all authors. Final approval: all authors.

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Data availability statement: Data are available upon reasonable request.

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Figure legends

Figure 1: Flow diagram of the study population. AF, atrial fibrillation; SEC, spontaneous echo contrast; TEE, transesophageal echocardiography; CA, catheter ablation; ISP, isoproterenol.

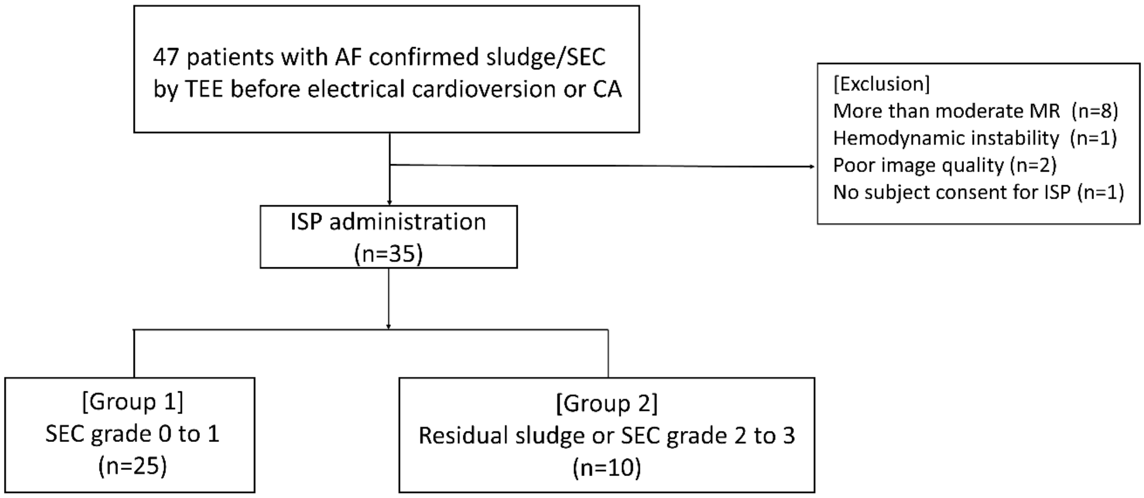


Figure 2: Representative cases of Group 1 and Group 2 in LAA baseline and after ISP loading. LAA, left atrial appendage; ISP, isoproterenol; HR, heart rate; SEC, spontaneous echo contrast

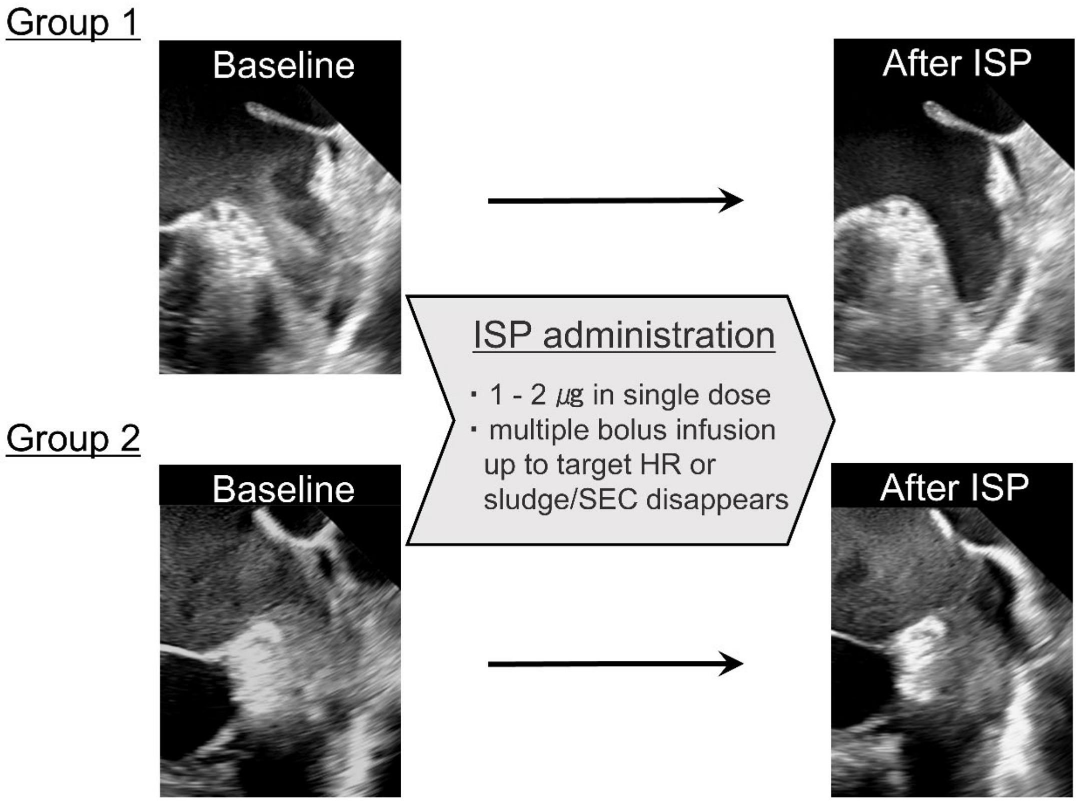


Figure 3: Panel A. Measurement procedure for pulse wave tissue Doppler imaging in LAA.

a) The sample volume was placed at the LLR (circle) and BMAS (square). b) Maximum LLR velocity in pulse wave Doppler imaging (yellow arrow).

Panel B. Measurement procedure for LAA blood flow velocities.

c) The sample volume was placed within the LAA cavity >1 cm away from LA cavity.

d) The peak emptying (yellow arrow) and filling (white arrow) velocities were analyzed and averaged for 3 cardiac cycles with pulsed wave Doppler echocardiography.

Panel C. Quantification of LAA volume from a 3D full-volume acquisition using the stacked-contour method.

e) A full LAA 3D pyramidal scan volume. f) and g) The analysis is performed by slicing 15 cross sections in the long-axis view from MPR and tracing the endocardial borders. h) After tracing in all cross sections, the volume is automatically calculated (QLAB 15.0 GI 3DQ; Philips Medical Systems).

LAA, left atrial appendage; LLR, left lateral ridge; BMAS, baso-medial appendage segment. 3D, 3-dimentional; MPR, multi-planar reconstruction

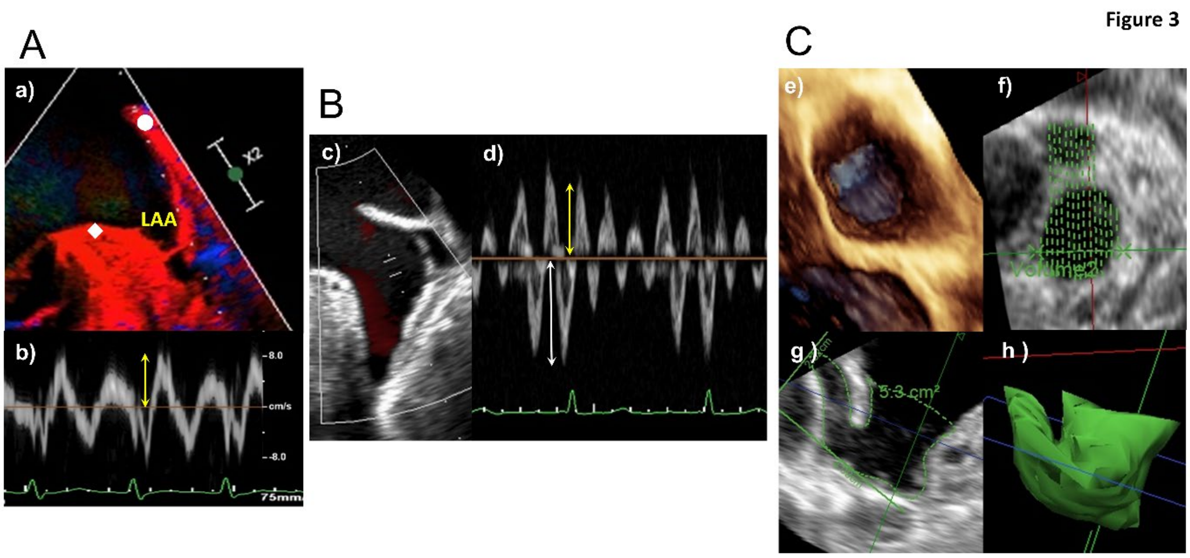


Figure 4: Change in SEC baseline and after ISP loading.

The numbers in the regular circles represent the number of patients. Group 1 (blue squares) was defined as the group with SEC of 0 or 1 after ISP administration, and Group 2 (red squares) as the group with SEC of 2 or 3.

SEC, spontaneous echo contrast; ISP, isoproterenol.

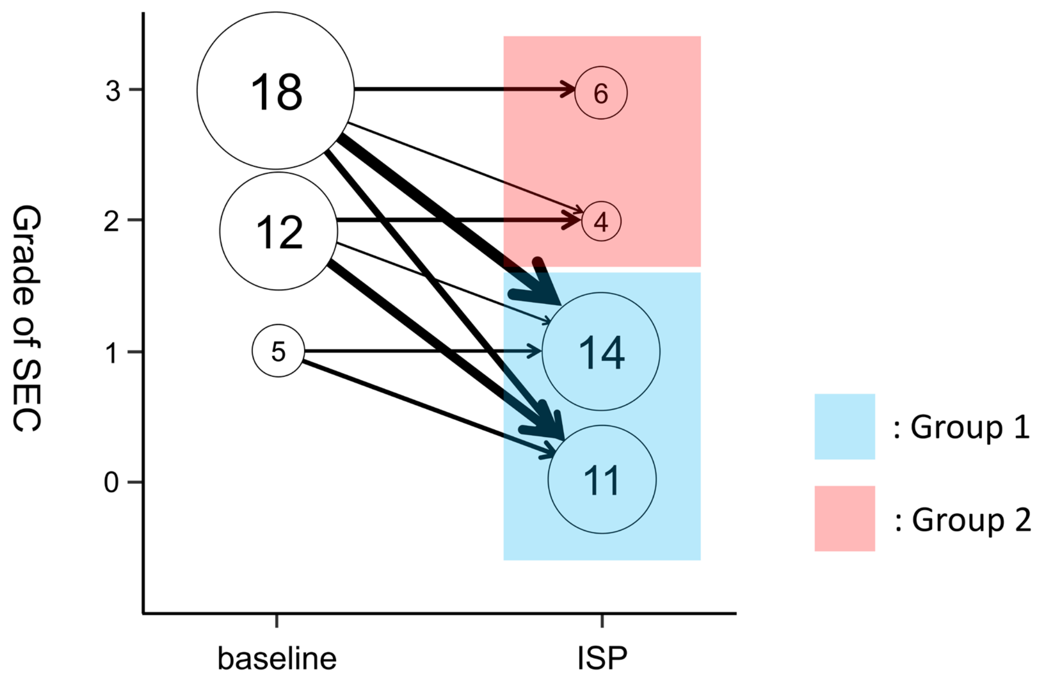


Figure 5: A case where ISP loading revealed the presence of a thrombus in the LAA.

Left: Before ISP loading; the presence of thrombus is not obvious due to sludge in the LAA (yellow arrow).

Right: After ISP loading; the sludge in the LAA has disappeared and a thrombus can be clearly seen at the bottom of the LAA (red arrow).

ISP, isoproterenol; LAA, left atrial appendage; LA, left atrium

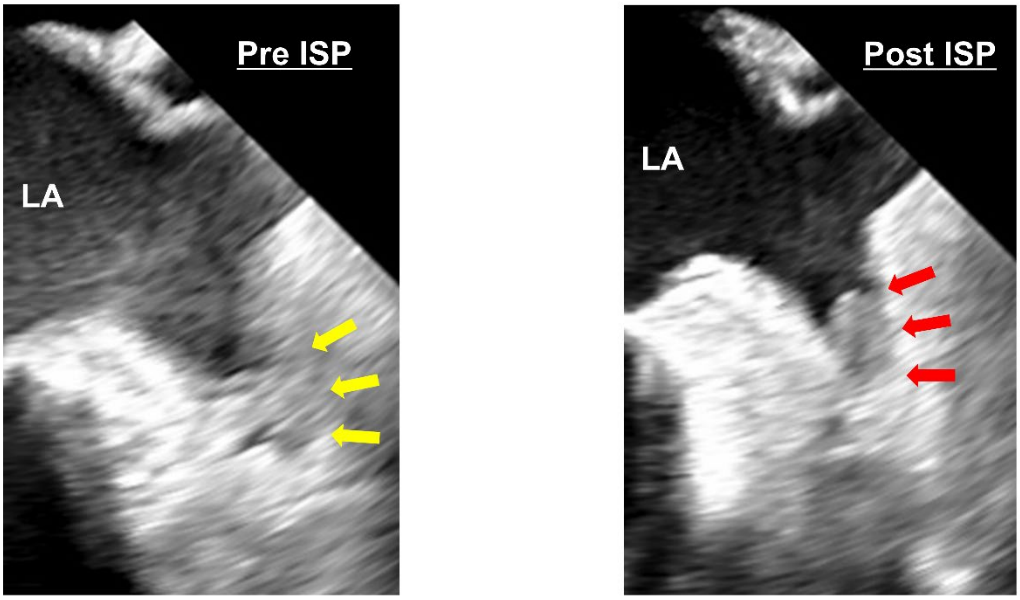
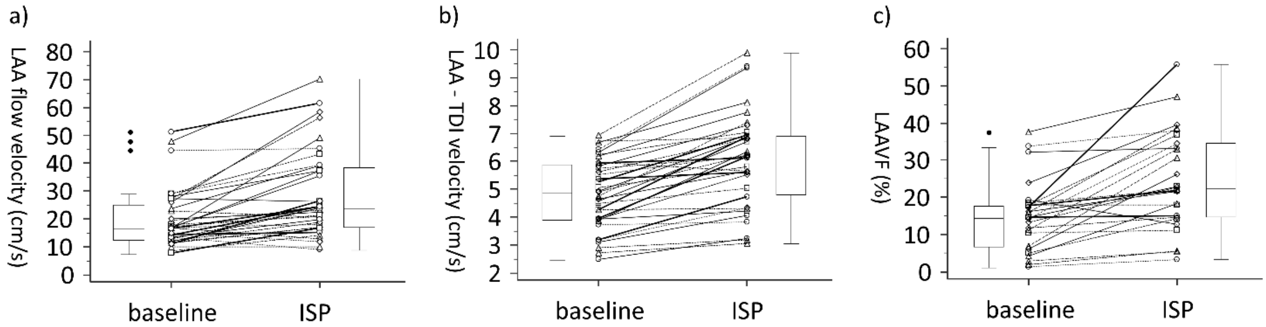


Figure 6: Changes in a) LAA blood flow velocity, b) LAA maximal velocity in pulse wave tissue Doppler and c) LAAVF imaging in patient baseline and after ISP loading test. In a total of 9 patients (all in Group 1), 3D image analysis was not possible due to poor image quality. LAA, left atrial appendage; LAAVF, left atrial appendage volume fraction; ISP, isoproterenol



Isoproterenol Loading Transesophageal Echocardiography in Atrial Fibrillation: a preliminary study

Highlights

- In patients with AF, ISP improved sludge or spontaneous echo contrast in 66% of patients.
- The improvement of sludge or spontaneous echo contrast were associated with improved LAA functional parameters.
- One patient (3% of patients) was diagnosed with thrombus in the LAA during ISP loading.
- ISP-TEE, a simple technique, is clinically feasible for the evaluation of LAA thrombus in AF patients with sludge or spontaneous echo contrast.

Table 1: Baseline characteristics of Group 1 and Group 2

	All (n=35)	Group1 (n=25)	Group2 (n=10)	*p* value
Clinical characteristics				
Age, y	71 ± 7	71 ± 7	70 ± 8	0.776
Male sex, n (%)	25 (71)	18 (72)	7 (70)	0.907
Body mass index	25.6 ± 5.5	25.4 ± 4.8	26.2 ± 7.2	0.697
AF duration				
Paroxysmal, n (%)	4 (11)	3 (12)	1 (10)	-
Persistent, n (%)	16 (46)	12 (48)	4 (40)	1.000
Long-standing persistent, n (%)	15 (43)	10 (40)	5 (50)	1.000
$CHADS_2$	2 (1-3)	2 (1-3)	2.5 (2-4)	0.228
CHA_2DS_2-VASc	4 (2-4)	3 (2-4)	4 (3-4)	0.373
OAC, n (%)	33 (94)	24 (96)	9 (90)	0.496
AAD, n (%)	27 (77)	17 (68)	10 (100)	0.073
Isoproterenol administration				
Dose, μg	3.0 (2.0-5.0)	3.0 (2.0-5.0)	3.5 (2.0-8.0)	0.442
Complication				
Under examination, n (%)	0 (0)	0 (0)	0 (0)	-
After 24 hours, n (%)	0 (0)	0 (0)	0 (0)	-
Laboratory data				
Hb, g/dL	13.9 ± 1.9	13.8 ± 1.9	14.3 ± 2.0	0.487
eGFR, ml/min/1.73	58.0 ± 17.6	56.5 ± 18.2	61.8 ± 16.2	0.429
BNP, pg/mL	162 (102-419)	127 (99-356)	287 (139-577)	0.089
Echocardiographic characteristics				
LVMi, g/m^2	84.8 ± 22.5	85.0 ± 24.9	84.3 ± 16.4	0.979
LVEDVi, ml/m^2	56.0 (46.8-72.0)	56.0 (46.0-68.5)	56.5 (48.0-82.0)	0.411
LVESVi, ml/m^2	24.0 (17.0-35.8)	24.0 (17.3-33.0)	24.0 (17.0-60.0)	0.638
LAVi, ml/m^2	55.1 ± 15.7	53.9 ± 16.1	58.1 ± 14.7	0.812
LVEF, %	57 (44-63)	57 (47-62)	60 (31-65)	0.927
E, cm/s	89.2 ± 22.0	84.5 ± 21.5	101 ± 19.5	0.043
E/e'	11.3 ± 3.6	10.4 ± 3.4	13.2 ± 3.5	0.004
TRV, m/s	2.4 ±0.3	2.4 ± 0.3	2.6 ± 0.3	0.133
LAA morphology*				
Chicken wing, n (%)	11 (42)	5 (31)	6 (60)	0.228

Values are mean ± SD or median and interquartile range or n (%).

AF = atrial fibrillation, OAC = oral anticoagulant, AAD = anti-arrhythmic drug, Hb = hemoglobin level, eGFR = estimated glomerular filtration rate, BNP = plasma B-type natriuretic peptide level, LVDd = left ventricular diameter (end-diastolic), LVDs = left ventricular diameter (end-systolic), LAD = left atrial diameter, LVMi = left ventricular mass index, LVEDVi = left ventricular end-diastolic volume index, LVESVi = left ventricular end-systolic volume index, LAVi = left atrial volume index, LVEF = left ventricular ejection fraction, E = early diastolic transmitral flow velocity, e' = early diastolic mitral annular velocity,

LAA = left atrial appendage. * In a total of 9 patients (all in Group 1), 3D image analysis was not possible due to poor image quality.

Table 2: Transesophageal echocardiographic parameters at baseline and after ISP loading

	All (n=35)			Group1 (n=25)			Group2 (n=10)		
	baseline	ISP	p value	baseline	ISP	p value	baseline	ISP	p value
Heart rate, beats/min	82.3±14.7	126.4±20.5	<0.001	84.2±15.0	128.6±19.1	<0.001	77.6±13.5	121.1±23.7	<0.001
Systolic BP, mmHg	129.3±17.0	124.3±21.8	0.153	133.3±16.8	128.7±22.7	0.325	119.4±13.4	113.2±15.6	0.176
SEC grade	3.0 (2.0-3.0)	1.0 (0-2.0)	<0.001	2.0 (2.0-3.0)	1.0 (0-1.0)	<0.001	3.0 (2.3-3.0)	3.0 (2.0-3.0)	-
LAA velocity, cm/s									
filling	20.0±10.6	29.8±15.1	<0.001	21.7±11.8	34.4±14.8	<0.001	15.6±5.0	18.4±8.4	0.120
emptying	20.0±11.1	28.0±17.5	<0.001	21.1±12.5	32.6±18.1	<0.001	17.1±5.7	16.6±8.6	0.649
average	20.0±10.6	28.9±15.8	<0.001	21.4±11.9	33.5±15.9	<0.001	16.4±5.1	17.5±8.3	0.442
TDI-PW, cm/s	4.85±1.25	6.08±1.71	<0.001	5.08±1.12	6.54±1.59	<0.001	4.25±1.43	4.93±1.49	0.005
PVS, cm/s	30.0±14.4	45.1±21.6	<0.001	31.3±14.9	49.7±23.1	<0.001	26.3±12.9	32.0±7.7	0.046
LAA volume, ml*									
LAAVmax	13.6±4.2	13.5±4.4	0.846	13.0±4.4	12.5±4.1	0.252	14.6±3.7	15.2±4.5	0.371
LAAVmin	11.6±4.0	10.2±4.0	0.009	11.1±4.4	9.2±3.7	0.009	12.3±3.3	12.0±4.0	0.536
LAAVF, %*	14.9±9.4	24.7±13.3	<0.001	15.2±10.1	27.3±13.8	<0.001	14.5±8.7	20.6±11.9	0.042

Values are mean ± SD or median and interquartile range

ISP = isoproterenol BP = blood pressure, SEC = spontaneous echo contrast, LAA = left atrial appendage, TDI-PW = tissue Doppler imaging-pulse wave, PVS = pulmonary venous systolic forward flow velocity, LAAVmax = maximal left atrial appendage volume, LAAVmin = minimal left atrial appendage volume, LAAVF = left atrial appendage volume fraction. * In a total of 9 patients (all in Group 1), 3D image analysis was not possible due to poor image quality.