A new clinical risk score for predicting the prevalence of low-voltage areas in patients undergoing atrial fibrillation ablation

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Abstract

Introduction: Although the presence of left atrial low-voltage areas (LVAs) is strongly associated with the recurrence of atrial fibrillation (AF) after ablation, few methods are available to classify the prevalence of LVAs. The purpose of this study was to establish a risk score for predicting the prevalence of LVAs in patients undergoing ablation for AF. Methods: We enrolled 1004 consecutive patients who underwent initial ablation for AF (age, 68 ± 10 years old; female, 346 (34%); persistent atrial fibrillation, 513 (51%)). LVAs were deemed present when the voltage map after pulmonary vein isolation demonstrated low-voltage areas with a peak-to-peak bipolar voltage of <0.5 mV covering [?]5 cm2 of the left atrium. Results: LVAs were present in 206 (21%) patients. The SPEED score was obtained as the total number of independent predictors as identified on multivariate analysis, namely female sex (odds ratio (OR) 3.4 [95% confidence interval (CI) 2.2-5.2], p <0.01), persistent AF (OR 1.8 [95% CI 1.1-3.0], p=0.02), age [?]70 years (OR 2.3 [95% CI 1.5-3.4], p <0.01), elevated brain natriuretic peptide [?]100 pg/ml or N-terminal pro-brain natriuretic peptide [?]400 pg/ml (OR 1.7 [95% CI 1.02-2.8], p=0.04), and diabetes mellitus (OR 1.8 [95% CI 1.1-2.8], p=0.02). LVAs were more frequent in patients with a higher SPEED score, and prevalence increased with each additional SPEED score point (OR 2.4 [95% CI 2.0-2.8], p <0.01). Conclusion: The SPEED score accurately predicts the prevalence of LVAs in patients undergoing ablation for AF.

Introduction

Catheter ablation has been established as an important therapy for atrial fibrillation (AF). The prevalence of left atrial low-voltage areas (LVAs) is strongly associated with the recurrence of atrial tachyarrhythmias following catheter ablation, and the addition of guided ablation of LVAs improves procedural outcomes compared to pulmonary vein (PV) isolation alone. [1,2,3,4]The ability to predict the presence of LVAs in advance of ablation would be useful in considering ablation indications and planning ablation methods. A preliminary study investigated a risk score named DR-FLASH,[5] which is composed of several clinical risk factors, including age >65 years and renal dysfunction (estimated glomerular filtration rate <90 mL/min/1.73m^2). In countries with an aging society, however, these cut-off values for elderly age (>65 years) and renal dysfunction (estimated glomerular filtration rate <90 mL/min/1.73m^2) appear so lenient that the score does not appropriately represent the risk of LVA presence. Hence, we sought a new risk score which allows the prediction of LVAs in elderly patients and contemporary clinical settings. The objective of this study was to explore predictors of LVA prevalence and establish a new clinical risk score for predicting the prevalence of LVAs in patients undergoing atrial fibrillation ablation.

Methods

Patients From October 2014 to December 2018, 1004 consecutive patients undergoing initial ablation for AF using Carto 3 (Biosense Webster, Inc., Diamond Bar CA, USA), Ensite NavX (St. Jude Medical, Inc., St. Paul

MN, USA) or Rhythmia (Boston Scientific, Boston MA, USA) were retrospectively enrolled at our hospital. Patients who could not undergo voltage mapping were excluded. Other exclusion criteria were age <20 years, left atrial thrombus, and prior catheter ablation of AF. This study complied with the Declaration of Helsinki. Written informed consent for ablation and the use of data in this study was obtained from all patients, and the protocol was approved by our institutional review board. *Catheter ablation procedure*Electrophysiological studies and catheter ablation were performed under intravenous sedation with dexmedetomidine or propofol, with the latter performed by four experienced operators (M.M, T.K, A.S, Y.M). From October 2014 to March 2016, radiofrequency catheter ablation was performed for all patients. From March 2016 to December 2018, in general, cryoballoon ablation was performed for paroxysmal AF and for persistent AF of short standing. Patients with common PVs or a large PV diameter underwent radiofrequency catheter ablation. In cryoballoon ablation, an Arctic Front Advance cryoballoon catheter with a 28-mm balloon size (Medtronic, Inc., Minneapolis MN, USA) was passed into each PV under guidance by fluoroscopy and the 3-D mapping system. After confirming PV occlusion by pulmonary venography, cryoablation commenced and continued for 180 s, during which individual PVs were isolated. If LA–PV conduction persisted after cryoballoon ablation, an additional touch-up ablation was performed using an open-irrigated Thermocool SmartTouch (Biosense Webster) or FlexAbility (St. Jude Medical) linear ablation catheter with a 3.5-mm tip. In radiofrequency catheter ablation, circumferential ablation around both ipsilateral PVs was performed using an open-irrigated Thermocool SmartTouch (Biosense Webster) or FlexAbility (St. Jude Medical) linear ablation catheter via an Agilis or Swartz Braided SL0 Transseptal Guiding Introducer Sheath (St. Jude Medical). Radiofrequency energy was applied for 30 s at each site using a maximum temperature of 42°C, maximum power of 35 W, and flow rate of 17 mL/min. PV isolation was considered complete when the 20-pole circular catheter no longer recorded any PV potentials. Additional ablation was also performed for spontaneous atrial flutter or flutter induced by atrial burst stimuli, and for any AF triggers originating from non-PV foci induced by isoproterenol infusion.

Voltage mapping Following PV isolation, detailed voltage mapping was performed using a bipolar 3.5-mm tip catheter or multi-electrode mapping catheter during sinus rhythm or with pacing from the right atrium. Mapping points were acquired to fill all color gaps on the voltage map using the electroanatomical mapping system. Respective fill and color interpolation thresholds were 15 mm and 23 mm using Carto 3 (Biosense Webster) and 20 mm and 7 mm using Ensite NavX (St. Jude Medical). Using Rhythmia (Boston Scientific), interpolation threshold was 5 mm and confidence mask was 0.03 mV. Sites at which LVAs were recorded were then evaluated by high-density mapping to precisely delineate their extent, using the confidence module with the Carto 3 system and Ensite Automap with Ensite NavX. Adequate endocardial contact was confirmed by distance to the geometry surface and stable electrograms. Each acquired point was classified according to the peak-to-peak electrogram as follows: >0.5 mV, healthy; <0.5 mV, LVAs, with the band pass filter was set at 30 to 500 Hz. LVAs were defined as regions with [?]5 cm^2 low-voltage points across the total surface area of the left atrium. The target number of mapping points was [?]100 with the 3.5-mm tip catheter and [?]1000 with the multi-electrode mapping catheter throughout the left atrium.

Patient followup Rhythm outcomes were followed for 24 months. Followup was performed as a part of routine visits, usually conducted every 3 months. Each routine visit included 12-lead electrocardiogram, while Holter electrocardiography was performed 6 months after the procedure. AF recurrence was defined as atrial tachyarrhythmias lasting >30 s at [?]90 d after the procedure.

Statistical methods Continuous data are expressed as mean +- standard deviation. Categorical data are presented as absolute values and percentages. Tests for significance were conducted using the unpaired or paired *t*-test for continuous variables and the chi-squared test for categorical variables. Receiver operating characteristic curve analysis was conducted between the clinical factors and prevalence of LVAs. Kaplan-Meier analysis and the log-rank test were used to investigate the association between the recurrence of atrial tachyarrhythmia and prevalence of LVAs. Univariate and multivariate logistic regression analyses were used to determine clinical factors associated with the prevalence of LVAs, wherein variables with a P value [?]0.05 in the univariate models were included in the multivariate analysis. A new risk score was obtained as the total number of independent predictors identified by multivariate analysis. All analyses were performed

using commercial software (SPSS , SPSS, Inc., Chicago IL, USA).

Results

Patient characteristics One thousand and four patients undergoing atrial fibrillation ablation were enrolled. PVI was successfully completed in all patients, using Carto 3 in 822 (82%), Ensite NavX in 159 (16%) and Rhythmia in 23 (2%). Patient characteristics are shown in Table 1.

Voltage mapping Left atrial voltage mapping was completed in all cases, with a median of 681 (119-1222) acquired mapping points. LVAs were identified in 206 (21%) cases. Procedural characteristics between the presence and absence of LVAs are compared in Table 2.

Predictors of LVAs prevalence Patients with LVAs were significantly older, more frequently female, and had a higher prevalence of persistent AF, diabetes mellitus, thromboembolism, and vascular disease than those without. In addition, patients with LVAs had lower hemoglobin, lower body mass index, lower estimated glomerular filtration rate, higher brain natriuretic peptide, higher N-terminal pro-brain natriuretic peptide, higher left ventricular mass index, higher left atrial diameter, higher E/e', and longer deceleration time than those without. On multivariate analysis, independent predictors of LVA prevalence were female sex, persistent AF, age [?]70 years, elevated brain natriuretic peptide [?]100 pg/ml or N-terminal pro-brain natriuretic peptide [?]400 pg/ml, and diabetes mellitus (Table 3).

New clinical risk score for LVAs prevalence The total number of independent predictors identified by multivariate analyses above - female sex, persistent AF, age [?]70 years, elevated brain natriuretic peptide [?]100 pg/ml or N-terminal pro-brain natriuretic peptide [?]400 pg/ml, and diabetes mellitus - was then used to devise a new clinical risk score, which we termed the SPEED score. LVAs were more frequent in patients who had a higher SPEED score (Figure 1, Figure 2), and the prevalence of LVAs increased with each additional SPEED score point (odds ratio 2.4 [95% confidence interval 2.0-2.8], $p < 0.01$). In patients with LVAs, the median total area of LVAs classified by SPEED score were 2.6 (1.7-3.1) cm^2 (0 point), 4.8 (2.4-15.3) cm^2 (1 point), 5.4 (2.9-9.7) cm^2 (2 points), 7.3 (3.6-14.8) cm^2(3 points), 11.7 (6.0-21.9) cm^2 (4 points) and 10.2 (6.9-25.6) cm^2 (5 points). Receiver operating characteristic curve analysis revealed that the SPEED score was a good predictor of LVAs (Figure 3, area under the curve, 0.742).

AF recurrence in LVAs prevalence During the 24-month study period, 277 (28%) patients developed AF recurrence. Freedom from recurrence was significantly lower in patients with LVAs than in those without (Figure 4), and was significantly lower in patients with a high SPEED score than in those with a low score (Figure 5).

Discussion

In this study of 1004 patients undergoing initial AF ablation, we found that LVAs were present in 21% of the total study population. Independent predictors of LVAs were female sex, persistent AF, age [?]70 years, elevated brain natriuretic peptide [?]100 pg/ml or N-terminal pro-brain natriuretic peptide [?]400 pg/ml, and diabetes mellitus. Using the SPEED score, calculated as the total number of independent predictors in each patient, LVAs were more frequent in patients with a higher SPEED score. These findings suggest that the SPEED score accurately predicts the prevalence of LVAs in patients undergoing ablation for AF.

Predictors of LVAs prevalence We identified the following as independent predictors of LVAs: female sex, persistent AF, age [?]70 years old, elevated brain natriuretic peptide [?]100 pg/ml or N-terminal pro-brain natriuretic peptide [?]400 pg/ml, and diabetes mellitus. The association between these predictors and the prevalence of LVAs might be explained by atrial fibrosis and decreased endocardial voltage. Mechanisms underlying the sex differences in atrial fibrosis have been identified.[6] On histological analysis of atrial tissue obtained during cardiac surgery, females showed stronger expression of CX 40 than males, which indicates remodeling–induced change in connexins.[7] In addition, fibrosis-related genes were upregulated in post-menopausal woman with AF.[8]A number of studies have shown that AF itself induces atrial fibrosis.[9,10] Conversely, atrial fibrosis is required to sustain AF, and the structural changes induced by AF in the atrium hinder termination of the arrhythmia.[11,12] Although the mechanisms of atrial fibrosis are not precisely known,

assessment of left atrial fibrosis by cardiac magnetic resonance imaging showed that patients with persistent AF had more late gadolinium-enhanced segments than those with paroxysmal AF.[13]Aging is another well-known factor associated with the promotion of myocardial fibrosis and atrial remodeling.[14] Senescence is associated with interstitial fibrosis, which reduces the capacity to cope with cardiac stress.[15] In addition, deposition of collagen in the ventricles of the heart with aging has been shown in animal models. [16,17] We set an age cut-off value of 70 years, which was previously defined as the lower limit of middle age.[18]A previous study showed that atrial fibrosis also occurred as a result of cardiac dysfunction, such as that which occurs in dilated cardiomyopathy.[19] Brain natriuretic peptide levels are correlated with left ventricular end-diastolic pressure and left atrial wall stress. [20,21] Left atrial wall stress is caused by elevated left atrial pressure, which reflects volume or pressure overload in the left ventricle and atrium. Left atrial wall stress can lead to left atrial fibrosis. [21] We set a cut-off value of brain natriuretic peptide and N-terminal pro-brain natriuretic peptide of 100 pg/ml and 400 pg/ml, respectively, based on Japanese guidelines for the diagnosis and treatment of acute and chronic heart failure.[22]Diabetes mellitus is a cause of electrical remodeling and changes in ionic currents, and additionally a cause of atrial structural remodeling.[23] Diabetes-related cardiac fibrosis is associated with the accumulation of collagen,[24] and hyperglycemia may promote a fibrogenic phenotype in cardiomyocytes and induce the synthesis and release of growth factors and cytokines that induce fibroblast proliferation and activation.[25]*New clinical risk score in LVA prevalence*Based on our findings, we established a new clinical risk score for predicting the prevalence of LVAs, which we named the SPEED score. A previous clinical risk score named DR-FLASH was based on diabetes mellitus, renal dysfunction (estimated glomerular filtration rate <90 mL/min/1.73m^2), persistent form of AF, left atrial diameter >45 mm, age >65 years, female sex, and hypertension.[5] Although this score was shown to be valuable, several limitations were noted. First, the score consists of seven items, and scoring was complex. Second, two of these seven items include the majority of patients, namely estimated glomerular filtration rate <90 mL/min/1.73m^2 and age >65 years. Indeed, among our 1004 subjects, 958 (96%) had an estimated glomerular filtration rate <90 mL/min/1.73m^2, and 670 (67%) were older than 65 years. Having many items which most patients come under can hinder risk stratification. Third, the only energy source of ablation used in the DR-FLASH study cohort was radio frequency, and mapping catheter use was limited. Finally, the cohort was relatively small, at about 240 patients. The SPEED score improves these limitations: it has only five items and is simple to score; the criterion that included the most patients - elevated brain natriuretic peptide [?]100 pg/ml or N-terminal pro-brain natriuretic peptide [?]400 pg/ml - accounted for fewer of our subjects than did an estimated glomerular filtration rate <90 mL/min/1.73m^2 and age >65 years; the study cohort included more than 1000 patients; and the score can be adapted for ablation with various energy sources, types of 3-D mapping, and mapping catheters. Additionally, receiver operating characteristic curve analysis revealed that the SPEED score had a tendency to be better predictor of LVAs (area under the curve, 0.742) than the DR-FLASH score (area under the curve, 0.694) in our subjects.

Clinical implications Previous studies showed that LVAs increase the risk of AF recurrence following catheter ablation.[4] Pre-procedural prediction of LVAs using the SPEED score is simple and noninvasive. Precise prediction of LVAs may influence indications for catheter ablation and allow the operator to prepare for atrial ablation in addition to PV isolation.

Limitations Several limitations of this study warrant mention. First, since we performed voltage mapping using either bipolar 3.5-mm tip catheters or multi-electrode mapping catheters, the distribution of LVAs might have changed, given that multielectrode catheters produce smaller LVA measurements than ablation catheters.[26] Second, our conduct of voltage mapping after the completion of PV isolation and in the left atrium only might have influenced the prevalence of LVAs. Third, LVA ablation was performed for only some patients, so the association between SPEED score and AF recurrence could not be assessed precisely. Finally, as this study was single center study, the statistical analyses might have been influenced by the study population.

Conclusions

The SPEED score, based on the total number of the independent predictors of female sex, persistent AF, age

[?]70 years, elevated brain natriuretic peptide [?]100 pg/ml or N-terminal pro-brain natriuretic peptide [?]400 pg/ml, and diabetes mellitus, accurately predicts the prevalence of LVAs in patients undergoing ablation for AF.

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Conflicts of Interest None declared

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Figure legends

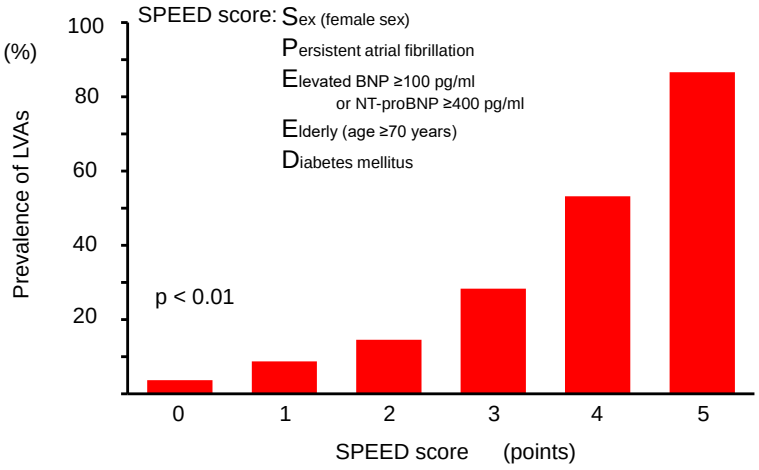
Figure 1. SPEED score and prevalence of LVAs LVA prevalence increased with increasing SPEED score. LVAs: low voltage areas, BNP: brain natriuretic peptide, NT-proBNP: N-terminal pro-brain natriuretic peptide

Figure 2. Likelihood of the prevalence of LVAs at each point of the SPEED score Odds ratio shows the likelihood for the prevalence of LVAs in each point of the SPEED score. The prevalence of LVAs increased for each additional point of the SPEED score. LVAs: low voltage areas, AF: atrial fibrillation, BNP: brain natriuretic peptide, NT-proBNP: N-terminal pro-brain natriuretic peptide, OR: odds ratio, CI: confidence interval

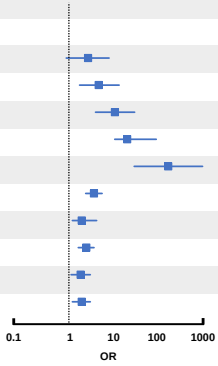
Figure 3. Receiver operating characteristics curve analysis of the association between SPEED score and LVA prevalence Receiver operating characteristics curve analysis revealed that the SPEED score was a good predictor of LVAs. LVAs: low voltage areas, AUC: area under the curve

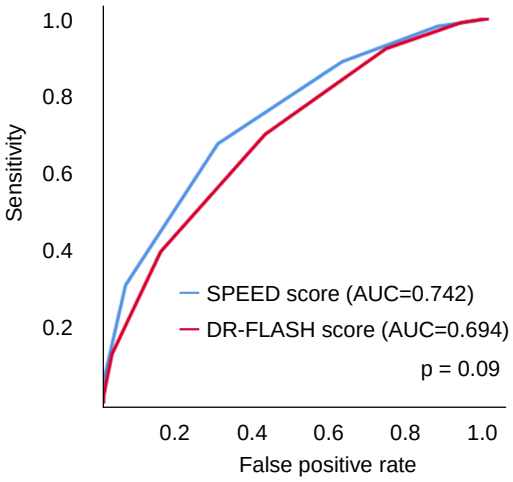
Figure 4. Freedom from AF recurrence in patients with and without LVAs Freedom from AF recurrence was significantly lower in patients with LVAs than in those without LVAs. AF: atrial fibrillation, LVAs: low voltage areas

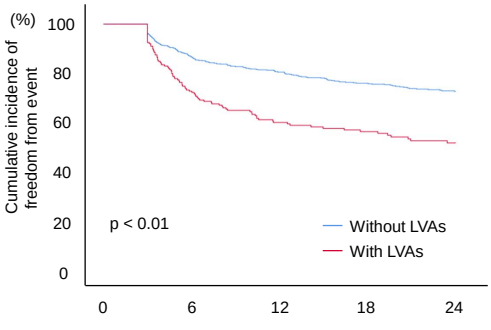
Figure 5. Freedom from AF recurrence in patients stratified by SPEED score Freedom from AF recurrence was also significantly lower in patients with a high SPEED score than in those with a low SPEED score. AF: atrial fibrillation, LVAs: low voltage areas



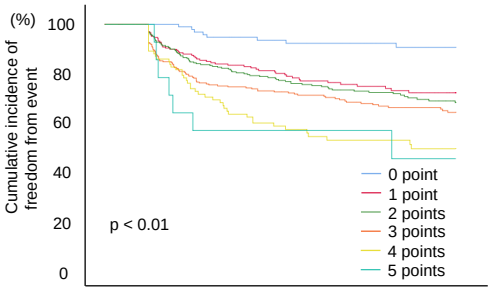
	No. of patients		OR (95% CI)	p
	With LVAs (n = 206)	Without LVAs (n = 798)		
SPEED score				< 0.01
0 point	4	104	1 (Reference)	
1 point	19	198	2.5 (0.8 – 7.5)	
2 points	44	258	4.4 (1.6 – 12.7)	
3 points	76	192	10.3 (3.7 – 28.9)	
4 points	50	44	19.5 (10.1 – 86.8)	
5 points	13	2	169 (28.1 – 1015)	
Female	116	230	3.4 (2.2 – 5.2)	< 0.01
Persistent AF	130	383	1.8 (1.1 – 3.0)	0.02
Age ≥70 years	144	340	2.3 (1.5 – 3.4)	< 0.01
BNP ≥100 pg/ml or NT-proBNP ≥400 pg/ml	157	409	1.7 (1.02 – 2.8)	0.04
Diabetes mellitus	53	114	1.8 (1.1 – 2.8)	0.02







No. at risk					
With LVAs	206	144	108	83	55
Without LVAs	798	647	530	400	261



No. at risk						
SPEED score	0 point	108	96	76	64	46
	1 point	217	177	140	95	60
	2 points	302	239	195	151	94
	3 points	268	203	174	133	89
	4 points	94	67	45	35	24
	5 points	15	9	8	5	3

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LVA_SPEED_tables JCE.docx available at https://authorea.com/users/311170/articles/469547-a-new-clinical-risk-score-for-predicting-the-prevalence-of-low-voltage-areas-in-patients-undergoing-atrial-fibrillation-ablation