

Right atrial contraction function measured by echocardiography predicting atrioventricular synchrony for Micra-AV leadless pacemaker

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Research Article

Keywords: leadless pacemaker, Micra-AV, atrioventricular synchrony, echocardiography, ultrasonic speckle tracking imaging, Doppler

Posted Date: August 13th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10530339/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background

Micra-AV leadless pacemaker could achieve atrioventricular synchrony (AVS) by sensing atrial mechanics. However, Micra-AV showed low atrial tracking capability and AVS percentage in some patients.

Objectives

Echocardiographic parameters were testified to predict AVS of Micra-AV, which could potentially facilitate to screen suitable patients for Micra-AV.

Methods

Patients with atrioventricular block and indicated for Micra-AV were included. Ultrasonic speckle tracking imaging was used to assess atrial contraction/conduit/reservoir strain. Early diastolic (E) and atrial systolic (A) peak flow velocities, early diastolic (E') and atrial systolic (A') tissue Doppler velocities at mitral or tricuspid annulus were measured. AVS was defined as AV interval ≤ 300 ms by Holter monitor.

Results

60 patients diagnosed with atrioventricular block were included. For AVS with 70% and above, tricuspid E/A ratio < 1.62 (OR = 3.237, 95% CI: 1.495 to 7.012, $p = 0.003$) and right atrial contraction strain $< -3.3\%$ (OR = 3.794, 95% CI: 1.718 to 7.765, $p = 0.001$) were verified as potent predictor. For AVS with 80% and above, tricuspid E/A ratio < 1.48 (OR = 6.571, 95% CI: 2.998 to 15.02, $p < 0.001$) and right atrial contraction strain $< -4.8\%$ (OR = 7.667, 95% CI: 3.441 to 16.81, $p < 0.001$) were verified as potent predictor. Nonetheless, left atrial parameters failed to attain statistical significance.

Conclusions

Right atrial echocardiographic parameters are predominant over left ones in relevancy of AVS. Tricuspid E/A and right atrial contraction strain showed great potency to predict AVS independently in Micra-AV.

Introduction

Leadless pacemaker (LPM) is a breakthrough in the implication of pacing therapy for treatment of cardiac bradycardia, and has been proved to be associated with significant reduction in procedural complications^{1,2}. The mainstream LPM, Micra VR, delivers only ventricular pacing (VVI/VVIR), which

could not meet the needs of patients with atrio-ventricular (AV) block^{3,4}. Since atrial output accounts for approximate 25% of total cardiac output^{5,6}, atrioventricular synchrony (AVS) is critical for the maintenance of normal cardiac function. Accordingly, the upgraded LPM, Micra AV, was developed to achieve atrial synchronous ventricular pacing (VDD)^{5,6}.

However, the performance of Micra AV in maintaining AVS is not satisfying. Previous studies failed to demonstrate a desirable AVS percentage compared with that of conventional transvenous pacemaker. The largest micraAV feasibility and efficacy MARVEL 2 and AccelAV studies showed an AVS percentage ranged from 31.9% to 99.1% in patients with AVB and normal sinus function^{6,7}. Briongos-Figuero et al⁸ reported general AVS percentage ranging from 31.2% to 89%, and, Arps et al⁹ reported AVS rate ranging from 49% to 98% in total patients and ranging from 0% to 74% in patients requiring $\geq 50\%$ pacing. Specifically, it was reported that 35% patients with Micra-AV might have inadequate atrial mechanical sensing and ventricular pacing (AM-VP)¹⁰. Therefore, better approaches to predict the AVS percentage after Micra AV implantation is needed to guide appropriate patient selection.

Since Micra AV is implanted in the right ventricle and works based on collected mechanic and hemodynamic data from the right atria and ventricle, we hypothesized that right-sided echocardiographic parameters which are associated with right atrial mechanical and hemodynamics activities could predict the AVS percentage to optimize patient selection for Micra AV.

Methods

Study design

This study was an investigator-initiated, prospective, observational, single-center cohort study. Patients with AV block indicated for pacemaker and scheduled for Micra-AV implantation were investigated. The primary objective of this study was to assess the value of echocardiographic parameters to predict AVS of Micra-AV. Moreover, this study aims to evaluate the AVS rate during VDD pacing mode induced by Micra-AV in natural state rather than experimental state.

Study population

Patients scheduled for Micra-AV implantation at Zhongshan Hospital were recruited from October 2022 to October 2023. The inclusion criteria were sinus rhythm and indications of pacemaker implantation for second-, high-, or third-degree AVB. The exclusion criteria were sinus bradycardia with possible demand for atrial pacing, and recorded paroxysmal atrial fibrillation.

The study was approved by the Ethics Committee of Zhongshan Hospital [No.B2022-530(2)], and informed consents were obtained from all patients. The study was carried out in accordance with the principles of the Declaration of Helsinki.

Echocardiography

Trans-thoracic echocardiographic echocardiograms (TTE) were performed in all patients on a GE LOGIQ E9 instrument with an analysis software (Echopac version: 204) following the American Society of Echocardiography instructions¹¹.

Firstly, both right and left early diastolic (E) and atrial systolic (A) peak flow velocities at mitral/tricuspid inflow were measured by Doppler flow imaging, and early diastolic (E') and atrial systolic (A') tissue Doppler velocities at mitral/tricuspid annulus were measured by pulsed-wave tissue Doppler, could reflect atrial hemodynamics and mechanical activity¹¹. In addition, the measurement of right atrial strain might be more predominant in predicting AVS for its sensitivity and specificity to reflect changes of atrial mechanical activity^{12, 13}. Right E, E', A, A' and atrial strain which could directly reflect right atrial mechanical activity would precisely predict the probability of AV synchronous pacing before the operation of LPM implantation. Accordingly, it might be possible to select more suitable patients for Micra-AV to increase the overall response rate of atrial sensing and atrioventricular synchronous pacing by an echocardiography based pre-operative assessment tool. Both sides of E, A, E' and A' were measured. Measurements of atrial longitudinal strain and radial longitudinal strain by two-dimensional (2D) speckle tracking echocardiography (STE) were following published technique instruction¹⁴. Furthermore, three strain values corresponding to the three different phases of the cardiac cycle of both atria were measured, including the reservoir strain in systole, the conduit strain in early diastole and the contraction strain in late diastole, standing for the storage function, conduit function and systolic function of the atrium, respectively^{12, 13, 15}. The echocardiographic parameter concerning on atrial contraction function was measured to screen candidate predictor, including E-wave, A-wave, E'-wave, A'-wave, E/A ratio, E'/A' ratio, atrial longitudinal strain rate (LSR), atrial radial strain rate (RSR), atrial conduit strain, atrial reservoir strain, and atrial contraction strain. Correlation between AVS percentage with each echocardiographic parameter was applied to find out the candidate predictor (with the absolute value of correlation coefficient $r > 0.5$).

All echocardiographic image acquisition and related data collection was done by the same echocardiography professional fellow to guarantee the consistency of each measurement.

LPM implantation, programming and optimization

The LPM implantation was performed by an experienced cardiology physician following the standard procedure practice. All LPM were placed to interventricular septum (IVS) including superior IVS, medium IVS, and inferior IVS. After the implantation procedure, the LPM was algorithmically optimized and programmed to VDD mode. As was recommended by Medtronic Inc., the LPM device could adjust atrial sensing parameters automatically via the "Atrial Sensing Setup" function. LPM of Micra-AV could provide presumed information of AVS by recording details of atrial mechanical sensing and ventricular sensing

(AM-VS); AM-VP; ventricular sensing (VS) only; and ventricular pacing (VP) only, and these data were also collected.

Ambulatory electrophysiology (ECG) monitor

An ambulatory Holter monitor (General Electric Company) was used to record continuous ECGs, and an electrophysiology professional fellow manually analyzed the interval between P wave initiation and QRS complex initiation. The AVS was evaluated by Holter monitor. The interval of P wave initiation to QRS complex initiation ≤ 300 ms was regarded as successful atrial tracking and AVS based on previously published articles^{4, 7, 8}. AVS adequacy was defined as a atrioventricular synchrony proportion $\geq 70\%$ and 80% respectively, to testify the efficacy of different echocardiographic parameters.

Statistical analysis

Continuous variables were expressed as mean $\pm$ SD or median (interquartile range). Categorical variables are presented as numbers (percentages). Continuous variables were analyzed by t-test, and the categorical variables were analyzed by Pearson's χ^2 test. Fisher's exact test was applied to calculate the odds ratio (OR). Pearson correlation analysis was conducted to test the correlation between echocardiographic parameters and AVS percentage in the continuous variable form. To investigate the influence of different echocardiographic parameters on AVS, univariate and multivariate regression models were fitted. Multivariate logistic regression models were used to evaluate the association between AVS and different parameters. The multivariate model included all variables from the univariate models with $p < 0.1$, and two-sided $p < 0.05$ was considered significant. After multivariate analysis, potential predictors with statistical significance were further processed by receiver operating characteristic curve (ROC) analysis to calculate the Youden's index (sensitivity + specificity - 1), namely the area under the ROC curve (AUROC), to identify the optimal cut-off points. Statistical analyses were performed using Pism9.5 (GraphPad Software, California USA).

Results

Patient characteristics

A total of sixty patients were included in this study. Patients were divided into two groups based on whether AVS attained 70% and above or 80% and above. Patients' demography and LPM electrical parameters were shown in Table 1. There was no difference in baseline or in-implant characteristics between the patients with adequate or inadequate AVS. of the frequency distribution of gender, comorbidity disease, tricuspid regurgitation, LPM location, and deployments. In addition, LVEF, LVEDD, LVESD, TAPSE, and plasma NTproBNP at baseline showed no significant difference between groups. LPM electrical parameters of threshold, R-wave sensing, and impedance, as well as procedure duration

and fluoroscopy exposure were comparable. Approximate 90,000 of total heart beats with about 65% pacing proportion was shown in each group without significant difference ($p > 0.05$).

Table 1
Demographic characteristics

	AVS $\geq$ 70% (N = 60)			AVS $\geq$ 80% (N = 60)		
	No	Yes	P	No	Yes	P
Gender male, %	61.5	62.8	> 0.05	65.9	68.6	> 0.05
Age, year	64.5 (8.5)	68.4 (9.9)	> 0.05	65.7 (9.1)	66.9 (10.5)	> 0.05
Previous AF	9	7	> 0.05	8	8	> 0.05
Ischemic heart disease	14	16	> 0.05	17	13	> 0.05
Non-ischemic heart disease	8	8	> 0.05	9	7	> 0.05
Pulmonary disease	4	5	> 0.05	5	4	> 0.05
HTN	12	15	> 0.05	10	17	> 0.05
DM	5	7	> 0.05	4	8	> 0.05
CKD	2	1	> 0.05	1	2	> 0.05
Hemoglobin	125.8 (21.6)	130.1 (30.2)	> 0.05	127.6 (25.8)	129.3 (29.5)	> 0.05
LVEF, %	63.2 (7.8)	65.8 (8.6)	> 0.05	62.9 (8.8)	66.8 (8.1)	> 0.05
LVEDD, mm	45.4 (7.7)	44.7 (6.8)	> 0.05	46.6 (8.1)	43.8 (9.5)	> 0.05
LVESD, mm	29.7 (8.5)	31.5 (6.9)	> 0.05	30.7 (7.3)	31.1 (8.7)	> 0.05
TAPSE, mm	17.5 (3.5)	17.2 (4.1)	> 0.05	17.8 (4.4)	17.1 (5.2)	> 0.05
Tricuspid regurgitation, %						
AF: atrial fibrillation; HTN: hypertension; DM: diabetes mellitus; CKD: chronic kidney disease; AVS: atrioventricular synchrony; NTproBNP: N terminal pro-B type natriuretic peptide; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; sPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion.						

	AVS $\geq$ 70% (N = 60)			AVS $\geq$ 80% (N = 60)		
	No	Yes	P	No	Yes	P
Slight	21.2	20.9	> 0.05	20.5	22.3	> 0.05
Mild	7.9	9.1	> 0.05	8.5	8.9	> 0.05
Moderate	3.5	3	> 0.05	3.2	4.1	> 0.05
sPAP, mmHg	26.5 (5.5)	27.1 (4.6)	> 0.05	26.9 (6.1)	26.8 (5.5)	> 0.05
LPM location, %						
High septum	8.3	9.5	> 0.05	8.9	9.1	> 0.05
Medium septum	65.6	70.2	> 0.05	66.9	69.6	> 0.05
Low septum	26.1	20.3	> 0.05	24.2	21.3	> 0.05
NTproBNP, pg/ml	585.9 (88.2)	611.4 (105.8)	> 0.05	590.4 (98.5)	610.2 (110.7)	> 0.05
Deployments, times	1.5 (1.4)	1.3 (1.7)	> 0.05	1.6 (1.5)	1.2 (1.5)	> 0.05
Thershold, v $\times$ 0.24ms	0.55 (0.18)	0.51 (0.29)	> 0.05	0.49 (0.21)	0.53 (0.33)	> 0.05
R-wave sensing, mv	12.5 (4.4)	13.1 (5.8)	> 0.05	11.9 (4.1)	12.9 (5.2)	> 0.05
Impedance, Ω	855.7 (112.6)	812.6 (170.8)	> 0.05			> 0.05
Procedure duration, min	45.9 (9.9)	52.5 (10.1)	> 0.05	48.2 (11.1)	51.5 (13.4)	> 0.05
Fluoroscopy exposure, mGy	40.2 (10.5)	41.9 (9.8)	> 0.05	40.9 (9.8)	41.5 (8.7)	> 0.05
Duration of Holter monitoring, hour	23.5 (2.1)	23.1 (3.2)	> 0.05	23.2 (2.8)	23.6 (3.7)	> 0.05
AF: atrial fibrillation; HTN: hypertension; DM: diabetes mellitus; CKD: chronic kidney disease; AVS: atrioventricular synchrony; NTproBNP: N terminal pro-B type natriuretic peptide; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; sPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion.						

	AVS $\geq$ 70% (N = 60)			AVS $\geq$ 80% (N = 60)		
	No	Yes	P	No	Yes	P
Total heart beats	89722.8 (4035.5)	92113.5 (5185.9)	> 0.05	90896.3 (4356.9)	91996.7 (55790.4)	> 0.05
Pacing proportion, %	76.2 (12.8)	80.1 (20.2)	> 0.05	77.5 (13.5)	79.5 (19.9)	> 0.05
AF: atrial fibrillation; HTN: hypertension; DM: diabetes mellitus; CKD: chronic kidney disease; AVS: atrioventricular synchrony; NTproBNP: N terminal pro-B type natriuretic peptide; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; sPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion.						

Correlation between echocardiographic parameter with AVS percentage

Tricuspid E-wave showed negative correlation with AVS percentage ($r = -0.471$, 95% CI: -0.647 to -0.246, $p < 0.001$) (Supplemental Fig. 1A), and tricuspid A-wave showed positive correlation with AVS percentage ($r = 0.510$, 95% CI: 0.294 to 0.676, $p < 0.001$) (Supplemental Fig. 1B), while tricuspid E/A ratio showed better correlation ($r = -0.753$, 95% CI: -0.845 to -0.616, $p < 0.001$) (Fig. 1A). Tricuspid E'-wave showed negative correlation with AVS percentage ($r = -0.412$, 95% CI: -0.603 to -0.176, $p = 0.001$) (Supplemental Fig. 1C), and tricuspid A'-wave showed positive correlation with AVS percentage ($r = 0.347$, 95% CI: 0.103 to 0.553, $p = 0.007$) (Supplemental Fig. 1D). Similarly, tricuspid E'/A' ratio showed better correlation ($r = -0.455$, 95% CI: -0.635 to -0.227, $p < 0.001$) (Fig. 1B). Mitral E-wave showed no correlation with AVS percentage ($r = 0.004$, 95% CI: -0.250 to 0.258, $p = 0.973$) (Supplemental Fig. 1E), and mitral A-wave showed positive correlation with AVS percentage ($r = 0.313$, 95% CI: 0.065 to 0.526, $p = 0.015$) (Supplemental Fig. 1F). Mitral E/A ratio showed slightly better correlation ($r = -0.360$, 95% CI: -0.562 to -0.116, $p = 0.005$) (Fig. 1C). Mitral E'-wave showed no correlation with AVS percentage ($r = -0.039$, 95% CI: -0.290 to 0.217, $p = 0.767$) (Supplemental Fig. 1G), and mitral A'-wave showed no correlation with AVS percentage ($r = 0.140$, 95% CI: -0.119 to 0.380, $p = 0.287$) (Supplemental Fig. 1H). Mitral E'/A' ratio showed no correlation ($r = -0.105$, 95% CI: -0.350 to 0.153, $p = 0.424$) (Fig. 1D).

Right atrial conduit strain ($r = -0.257$, 95% CI: -0.480 to 0.003, $p = 0.047$) (Fig. 2A), left atrial conduit strain ($r = 0.206$, 95% CI: -0.051 to 0.437, $p = 0.115$) (Fig. 2B), and left atrial reservoir strain ($r = -0.064$, 95% CI: -0.312 to 0.194, $p = 0.630$) (Fig. 2C) showed no correlation with AVS. Right atrial reservoir strain ($r = 0.568$, 95% CI: 0.367 to 0.718, $p < 0.001$) (Fig. 2D), right atrial contraction strain ($r = -0.625$, 95% CI: -0.759 to -0.441, $p < 0.001$) (Fig. 2E), and left atrial contraction strain ($r = -0.510$, 95% CI: -0.676 to -0.294, $p < 0.001$) (Fig. 2F) showed relatively strong correlation with AVS. Right atrial LSR ($r = -0.112$, 95% CI: -0.356 to 0.146, $p = 0.393$) (Supplemental Fig. 2A) and RSR ($r = 0.154$, 95% CI: -0.104 to 0.146, $p = 0.393$) (Supplemental Fig. 2B) showed no correlation with AVS. Likewise, left atrial LSR ($r = -0.244$, 95% CI:

-0.469 to 0.010, $p = 0.060$) (Supplemental Fig. 2C) and RSR ($r = -0.214$, 95% CI: -0.443 to 0.043, $p = 0.101$) (Supplemental Fig. 2D) showed no correlation with AVS, either.

Finally, after the initial filtration by correlation analysis, tricuspid A-wave, tricuspid E/A ratio, right atrial contraction strain, right atrial reservoir strain, and left atrial contraction strain were qualified for further analysis.

Echocardiographic parameters to predict AVS adequacy

Tricuspid A-wave, tricuspid E/A ratio, right atrial contraction strain, right atrial reservoir strain, and left atrial contraction strain, as well as other clinical parameters, for instance LVEF, LPM location, age, and gender were gathered together to collectively find out the independent predictor of AVS.

For comparison of patients with or without 70% and above AVS, tricuspid A-wave (49.75 ± 28.70 cm/s vs. 66.38 ± 21.03 cm/s, $p = 0.018$) (Fig. 3A), tricuspid E/A ratio (1.832 ± 1.103 vs. 0.819 ± 0.381 , $p < 0.001$) (Fig. 3B), right atrial contraction strain ($-10.11\% \pm 10.10\%$ vs. $-20.61\% \pm 10.84\%$, $p < 0.001$) (Fig. 3C), right atrial reservoir strain ($15.01\% \pm 7.839\%$ vs. $23.98\% \pm 8.071\%$, $p < 0.001$) (Fig. 3D), and left atrial contraction strain ($-4.873\% \pm 5.696\%$ vs. $-11.56\% \pm 8.871\%$, $p < 0.001$) (Fig. 3E) showed significant difference. Additionally, for patients with or without 80% and above AVS, tricuspid A-wave (53.64 ± 28.04 cm/s vs. 66.38 ± 20.75 cm/s, $p = 0.010$) (Fig. 4A), tricuspid E/A ratio (1.582 ± 1.083 vs. 0.867 ± 0.353 , $p = 0.023$) (Fig. 4B), right atrial contraction strain ($-13.09\% \pm 11.69\%$ vs. $-18.74\% \pm 10.21\%$, $p = 0.01$) (Fig. 4C), and right atrial reservoir strain ($16.55\% \pm 8.126\%$ vs. $25.99\% \pm 8.478\%$, $p < 0.001$) (Fig. 4D), and left atrial contraction strain ($-6.466\% \pm 6.728\%$ vs. $-11.46\% \pm 10.22\%$, $p = 0.040$) (Fig. 4E) showed significant difference.

Based on the above analysis, we build the binary logistic regression model to identify the candidate predictor (Table 2). In multivariate analysis, tricuspid E/A ratio, right atrial reservoir strain, and right atrial contraction strain showed predictive value for both 70% and 80% AVS (Table 2).

Table 2
Univariate analysis by binary logistic regression

Parameters	OR	95% CI	p
70% and above AVS			
E3/A3	0.1649	0.04220 to 0.4310	< 0.0001
RA cont ϵ	0.1652	0.05136 to 0.4393	0.0003
RA res ϵ	0.03699	0.004481 to 0.1936	< 0.0001
LA cont ϵ	0.2494	0.09911 to 0.5581	0.0008
tricuspid A wave (cm/s)	1.028	1.005 to 1.056	0.015
80% and above AVS			
E3/A3	0.3235	0.08773 to 0.7951	0.0098
RA cont	0.1424	0.04140 to 0.3970	0.1197
RA res ϵ	0.03699	0.004481 to 0.1936	< 0.0001
LA cont ϵ	0.1404	0.04681 to 0.3491	0.0462
tricuspid A wave (cm/s)	1.016	0.9942 to 1.041	0.1484
AVS: atrioventricular synchrony; OR: odds ratio; CI: confidential interval; E3/A3: early diastolic (E) and atrial systolic (A) peak flow velocities ratio at tricuspid inflow; RA cont ϵ : right atrial contraction strain; RA res ϵ : right atrial conduit strain; LA cont ϵ : left atrial contraction strain.			

Table 3
Multivariate analysis to screen echocardiographic parameters correlating with AVS.

Included echocardiographic parameters	Odds ratios	95% CI	P value
70% and above AVS			
tricuspid A wave (cm/s)	1.023	0.9895 to 1.067	0.2409
tricuspid E/A ratio	0.132	0.01044 to 0.6054	0.0407
right atrial reservoir strain (%)	1.275	1.139 to 1.491	0.0003
right atrial contraction strain (%)	0.8695	0.7743 to 0.9556	0.0078
left atrial contraction strain (%)	1.049	0.9706 to 1.144	0.2395
80% and above AVS			
tricuspid A wave (cm/s)	1.024	0.9966 to 1.058	0.1172
tricuspid E/A ratio	0.8945	0.8223 to 0.9625	0.0049
right atrial contraction strain (%)	1.091	1.017 to 1.185	0.0238
right atrial reservoir strain (%)	1.26	1.141 to 1.443	< 0.0001
left atrial contraction strain (%)	0.1456	0.01230 to 0.6899	0.0653
AVS: atrioventricular synchrony; OR: odds ratio; CI: confidential interval; E3/A3: early diastolic (E) and atrial systolic (A) peak flow velocities ratio at tricuspid inflow.			

ROC analysis to identify the optimal cut-off points of included echocardiographic parameters

In terms of 70% AVS, tricuspid A-wave (AUROC = 0.756, 95% CI: 0.634 to 0.877, $p < 0.001$) (Fig. 5A), tricuspid E/A ratio (AUROC = 0.776, 95% CI: 0.660 to 0.891, $p < 0.001$) (Fig. 5A), right atrial contraction strain (AUROC = 0.755, 95% CI: 0.636 to 0.875, $p < 0.001$) (Fig. 5A), right atrial reservoir strain (AUROC = 0.766, 95% CI: 0.645 to 0.886, $p < 0.001$) (Fig. 5A), and left atrial contraction strain (AUROC = 0.723, 95% CI: 0.585 to 0.861, $p = 0.004$) (Fig. 5A) all verified by the ROC analysis. The cut-off points of tricuspid A-wave, tricuspid E/A ratio, right atrial contraction strain, right atrial reservoir strain, and left atrial contraction strain to potentially predict AVS with 70% and above were > 49.5 cm/s, < 1.62 , $< -3.3\%$, $> 18.93\%$, and $< -5.1\%$, respectively.

In terms of 80% AVS, tricuspid A-wave (AUROC = 0.695, 95% CI: 0.550 to 0.840, $p = 0.033$) (Fig. 5B), tricuspid E/A ratio (AUROC = 0.702, 95% CI: 0.564 to 0.839, $p = 0.030$) (Fig. 5B), right atrial contraction strain (AUROC = 0.686, 95% CI: 0.537 to 0.836, $p = 0.043$) (Fig. 5B), and right atrial reservoir strain (AUROC = 0.784, 95% CI: 0.645 to 0.923, $p = 0.002$) (Fig. 5B) all passed the ROC analysis, except for left atrial contraction strain (AUROC = 0.642, 95% CI: 0.461 to 0.822, $p = 0.121$) (Fig. 5B). The cut-off points of tricuspid A-wave, tricuspid E/A ratio, right atrial contraction strain, right atrial reservoir strain, and left

atrial contraction strain to potentially predict AVS with 80% and above were > 61 cm/s, < 1.48 , $< -4.8\%$, and $> 20.92\%$, respectively.

Validating the cut-off point of the candidate echocardiographic parameter

Tricuspid A-wave, tricuspid E/A ratio, right atrial contraction strain, right atrial reservoir strain, and left atrial contraction strain were analyzed by Pearson's χ^2 test. On condition of AVS with 70% and above, tricuspid E/A ratio < 1.62 (OR = 3.237, 95% CI: 1.495 to 7.012, $p = 0.003$) and right atrial contraction strain $< -3.3\%$ (OR = 3.794, 95% CI: 1.718 to 7.765, $p = 0.001$) were verified as potent predictor. However, tricuspid A-wave > 49.5 cm/s (OR = 1.714, 95% CI: 0.8188 to 3.441, $p = 0.200$), right atrial reservoir strain $> 18.93\%$ (OR = 1.403, 95% CI: 0.6671 to 2.802, $p = 0.462$), and left atrial contraction strain $< -5.1\%$ (OR = 1.5, 95% CI: 0.7148 to 2.998, $p = 0.359$) were excluded for failing to attain statistical significance (Fig. 5C). On condition of AVS with 80% and above, tricuspid E/A ratio < 1.48 (OR = 6.571, 95% CI: 2.998 to 15.02, $p < 0.001$) and right atrial contraction strain $< -4.8\%$ (OR = 7.667, 95% CI: 3.441 to 16.81, $p < 0.001$) were verified as potent predictor. However, tricuspid A-wave > 61 cm/s (OR = 1.947, 95% CI: 0.8489 to 4.472, $p = 0.156$) and right atrial reservoir strain $> 20.92\%$ (OR = 2.042, 95% CI: 0.8489 to 4.472, $p = 0.156$) were excluded for failing to attain statistical significance (Fig. 5D). Considering the tricuspid E/A ratio being calculated dependent on A-wave, the absolute value of A-wave should be regarded as the prerequisite.

Discussion

The main finding of the present study was that tricuspid E/A ratio < 1.62 (OR = 3.237, 95% CI: 1.495 to 7.012, $p = 0.003$) and right atrial contraction strain < -3.3 (OR = 3.794, 95% CI: 1.718 to 7.765, $p = 0.001$) were significantly associated with AVS after micra-AV implantation and independent predictors of adequacy of AVS. These echocardiographic parameters could help to optimize patient selection for Micra AV.

This study was designed based on the hypothesis that atrial echocardiographic parameters could objectively reflect the intensity of A4 signal of Micra-AV. Our study demonstrated that right atrial echocardiographic parameters are more predominant over left ones in relevancy of AVS. Tricuspid E/A ratio and right atrial contraction strain showed great potency to predict AVS independently in Micra-AV. To some extent, our study suggested right atria contributed more to atrial mechanical activity sensing than left atria did, and measurements of contraction function by echocardiography could reliably predict AVS for LPM of Micra-AV. The novelty of this study which gained deeper interpretation to us were that tricuspid E/A and right atrial contraction strain (pre-operative) correlated with AVS, and they could be regarded as a reliable and readily available parameter effectively predicting AVS. However, considering the tricuspid E/A ratio being calculated dependent on A-wave, the absolute value of A-wave > 49.5 cm/s and A-wave > 61 cm/s should be the prerequisite of tricuspid E/A ratio < 1.62 for AVS with 70% and above and tricuspid E/A ratio < 1.48 for AVS with 80% and above, respectively to predict AVS.

Although LPM could radically solve complications from the lead and pocket of conventional pacemaker, the characteristics of single chamber pacing limited its clinical application^{1,2}. During the initial experience of LPM implantation practice, the first generation of LPM could not satisfy the need of atrioventricular synchronous pacing until the Micra-AV coming out⁴. However, a certain proportion of patients showed low percentage of AVS as mentioned before, and the specific mechanism remained unclear. Finding out related predictors would facilitate the patient selection for Micra-AV. The rationale for atrial sensing by Micra-AV is primarily depending on its innately incorporated electronic component of a three-axis accelerometer sensor⁴. Accordingly, relatively regular and normal atrial electro-mechanical activity should be the prerequisite of correct atrial sensing and AVS. In fact, it was reported that P wave indices on surface ECG didn't correlate with atrial strain or structural remodeling¹⁶. Similarly, the present study found that amplitude, area, and duration of P-wave didn't correlate with right atrial contraction strain, A4 signal, or AVS. It seemed that P-wave indices of surface ECG could not reflect atrial mechanical activity¹⁶. Consequently, the sick sinus syndrome which is characterized of sinus arrest sinus or bradycardia might not be suitable for Micra-AV for apparent incompetence of atrial mechanical sensing. Moreover, atrial electromechanical uncoupling, for instance the atrial standstill, could take place¹⁷. In the case of atrial standstill, atrial mechanical activity could be very weak or even absent regardless of presenting relatively normal P-waves, which making it almost impossible for Micra-AV to track atria and keep AVS. This might, to some extent, explain why there existed patients who had low AVS percentage. As a result, preoperative evaluation of atrial mechanical activity, especially the right atrial mechanics, should be recommended to all patients who are planning to receive Micra-AV. From this point of view, the AVS could be maintained in regular motion state of a day by Micra-AV in real world, if the right atrial mechanical activity was tested well.

Recently, Garweg et al¹⁸ reported the percentage of atrial mechanical sensing and ventricular pacing (AM-VP) was about 75%, however, the AM-VP merely correlates with AVS, it could not take the place of continuous Holter ECG to reflect the proportion of atrial tracked ventricular pacing. On the contrary, Neugebauer et al¹⁹ reported that AM-VP inversely correlate with AVS. Moreover, it was reported that 35% patients with Micra-AV might have inadequate AM-VP¹⁰. Therefore, low AVS percentage in Micra-AV should draw some attention. The indirect atrial sensing by Micra-AV located in right ventricle rather than directly located in right atrium might explain incompetent atrial sensing of Micra-AV. If the mechanical activity of right atrium is weak, the capability of atrial sensing in Micra-AV might be influenced. Right atrial echocardiographic parameters, especially the tricuspid E/A and right atrial contraction strain could predict AVS may be owing to precisely reflect right atrial mechanics. Weakened atrial mechanical activity could potentially influence the atrial sensing and further dampen the AVS in patients with Micra-AV. Echocardiographic predictors could screen more suitable patients for Micra-AV to improve its performance of AVS.

Echocardiography, as a noninvasive method, could accurately evaluate the atrial morphology, inner diameter, strain, and hemodynamics. Left-sided E, A, E' and A' could reflect left atrial hemodynamics and mechanical activity. In a post-hoc analysis based on data set from Marvel 2 study, echocardiographic

parameters, for instance E/A ratio < 0.94 , was assumed to be related to high atrio-ventricular synchrony rate²⁰. Besides, another study suggested that E/A ratio < 1.2 could independently predict atrial mechanical tracking²¹. Additionally, pulsed Doppler A-wave was regarded as an aid in patient selection for atrioventricular synchrony²². However, Briongos-Figuero et al²³ argued that measurements of pulsed wave Doppler mitral inflow failed to predict atrioventricular synchrony in Micra-AV implanted patients. Obviously, the value of Doppler echocardiographic parameters from left-side chamber to predict atrio-ventricular synchronous pacing is limited. Indeed, Micra-AV is localized in right cardiac chamber, and left atrial mechanical activity and hemodynamics seemed to be difficult to sense by right-sided Micra-AV. Logically, atrial sensing by Micra-AV should be primarily in basis of right atrial mechanical activity and hemodynamics signal. Accordingly, right-sided echocardiographic parameters might take more advantages of predicting the capability of atrioventricular synchrony maintenance in Micra-AV. In addition, the measurement of right atrial strain might be more predominant in predicting atrioventricular synchrony for its sensitivity and specificity to reflect changes of atrial mechanical activity. There are three strain values corresponding to the three different phases of the cardiac cycle of the atrium, which are the reservoir strain in systole, the conduit strain in early diastole and the contraction strain in late diastole, standing for the storage function, conduit function and systolic function of the atrium, respectively^{12, 13}. From this study, right atrial strain has been proved to be an optimal predictor. Considering reservoir strain was measured in the systolic phase, right atrial reservoir strain showed low grade correlation with AVS. Oppositely, the conduit strain and the contraction strain were measured in early diastolic phase and late diastolic phase, which should somehow explain the high grade correlation with AVS.

At last, we want to further discuss an alternative scheme about how to maintain AVS for single chamber LPM in patients with relatively normal atrial electric activity. Some wearable electronic device could provide continuous ambulatory ECG recording²⁴. Imagine a wireless communication between LPM and the wearable ECG device which could directly offer atrial electric activity information which is approximately equal to P-wave. As a consequence, single chamber LPM could receive and identify this ECG atrial electric signal, so that AVS could be achieved. Besides, P-wave of ECG signal recorded by the wearable device could be an internal reference of A4 signal, and the surface ECG could dynamically correct the A4 signal to improve the accuracy of atrial mechanical sensing. Simultaneously recording surface ECG and A4 signal might potentially guarantee AVS, especially on condition of sinus tachycardia.

Study limitations

Routine 24-hour Holter ECG monitor could only reflect the ECG variability in a certain day. In order to evaluate conditions experienced by patients with Micra-AV in longer term, perhaps, an extended Holter ECG monitoring could be used to get more information of AVS. This study failed to acquire echocardiographic parameters of premature atrial contraction, and therefore, the predictive value of atrial contraction strain could not be evaluated. Sample size is relatively small, and long term follow-up

data should be collected in future. Although postoperative optimization was given to each patient, the effect of repeated optimization and the impact of programming change on AVS could still lead to bias.

Conclusion

Echocardiography could potentially predict AVS of Micra-AV. Right atrial echocardiographic parameters are predominant over left ones in relevancy of AVS. For AVS with 70% and above, tricuspid E/A ratio < 1.62 (with prerequisite of tricuspid A-wave > 49.5 cm/s) and right atrial contraction strain $< -3.3\%$ were verified as potent predictor. For AVS with 80% and above, tricuspid E/A ratio < 1.48 (with prerequisite of tricuspid A-wave > 61 cm/s) and right atrial contraction strain $< -4.8\%$ were verified as potent predictor. Tricuspid E/A and right atrial contraction strain showed great potency to predict AVS independently in Micra-AV. Considering the tricuspid E/A ratio being calculated dependent on A-wave, the absolute value of A-wave (> 49.5 cm/s for 70% AVS and > 61 cm/s for 80% AVS) should be regarded as the prerequisite.

Abbreviations

A: atrial systolic peak flow velocities at mitral/tricuspid inflow measured by Doppler flow imaging

A': atrial systolic tissue Doppler velocities at mitral/tricuspid annulus measured by pulsed-wave tissue Doppler

AM-VS: atrial mechanical sensing and ventricular sensing

AM-VP: atrial mechanical sensing and ventricular pacing

AV: atrioventricular

AVB: atrioventricular block

AVS: atrioventricular synchrony

E: early diastolic peak flow velocities at mitral/tricuspid inflow measured by Doppler flow imaging

E': early diastolic tissue Doppler velocities at mitral/tricuspid annulus measured by pulsed-wave tissue Doppler

ECG: electrocardiogram

LPM: leadless pacemaker

IVS: interventricular septum

LSR: longitudinal strain rate

LVEF: left ventricular ejection fraction

LVEDD: left ventricular end-diastolic diameter

LVESD: left ventricular end-systolic diameter

NT-proBNP: N-terminal pro-B-type natriuretic peptide

OR: odds ratio

ROC: receiver operating characteristic curve

RSR: radial strain rate

STE: speckle tracking echocardiography

TAPSE: tricuspid annular plane systolic excursion

TTE: trans-thoracic echocardiography

VP: ventricular pacing

VS: ventricular sensing

VDD: atrial synchronous ventricular pacing

VVI/VVIR: ventricular inhibited pacing

AUROC: area under the receiver operating characteristic curve

Declarations

Conflicts of interest:

None.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Zhongshan Hospital [No.B2022-530(2)], and informed consents were obtained from all patients. The study was carried out in accordance with the principles of the Declaration of Helsinki.

Consent for publication

Not applicable

Competing Interests

The authors declare that they have no conflict of interest.

Funding

This study was supported by National Natural Science Foundation of China (Grant Number: 82100370 and Grant Number: 82170386).

Author Contribution

Y.Z. and F.Z. conceived and designed the research. Y.Z., F.Z., Z.L., C.X. collected clinical data and performed statistical analysis. C.H., W.Q., S.X. conducted electrophysiology procedures and acquired imaging data. L.Y. and S.Y. supervised the whole study. G.J. provided critical revision of the manuscript. Y.Z. and F.Z. drafted the original manuscript. All authors read, reviewed, and approved the final submitted version.

Acknowledgements

We especially appreciate Hongyang Lu on giving modification of this article to improve its structure and language.

Data Availability

The datasets generated and analysed during the current study are not publicly available due to local ethical restrictions protecting patient privacy, but are available from the corresponding author upon reasonable request following formal ethical approval.

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Figures

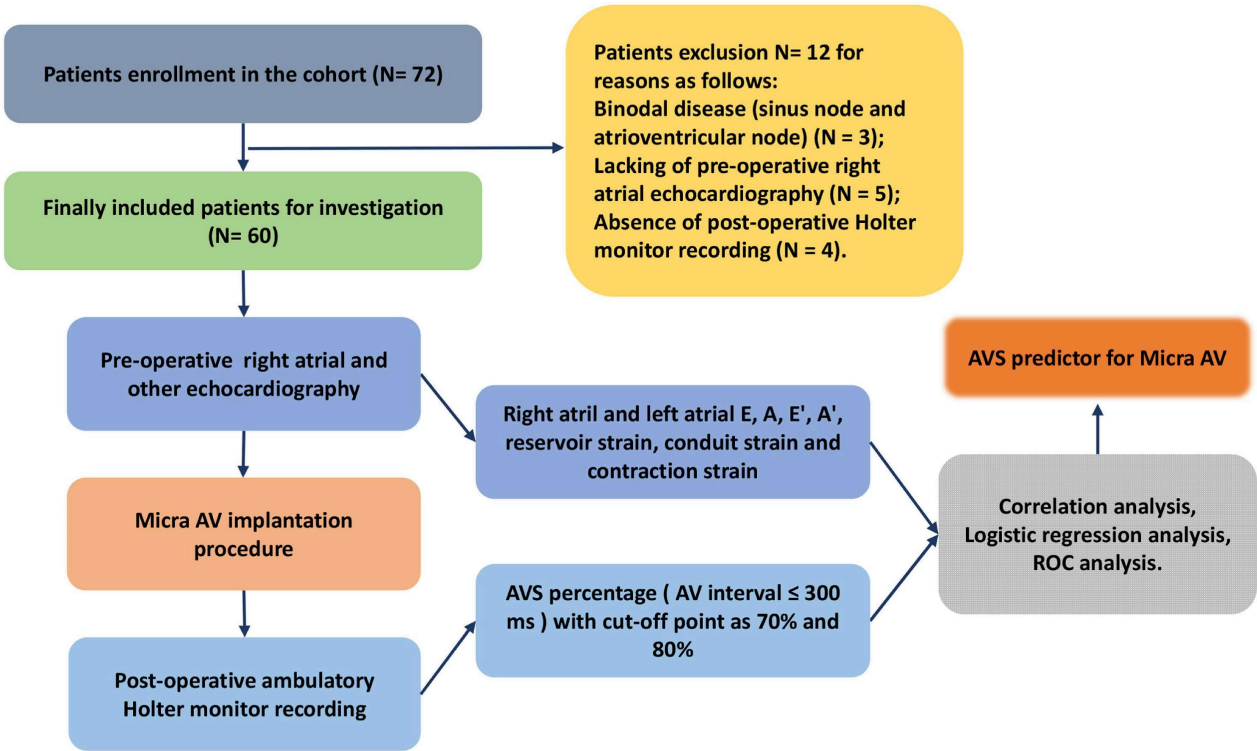


Figure 1

Study flow chart

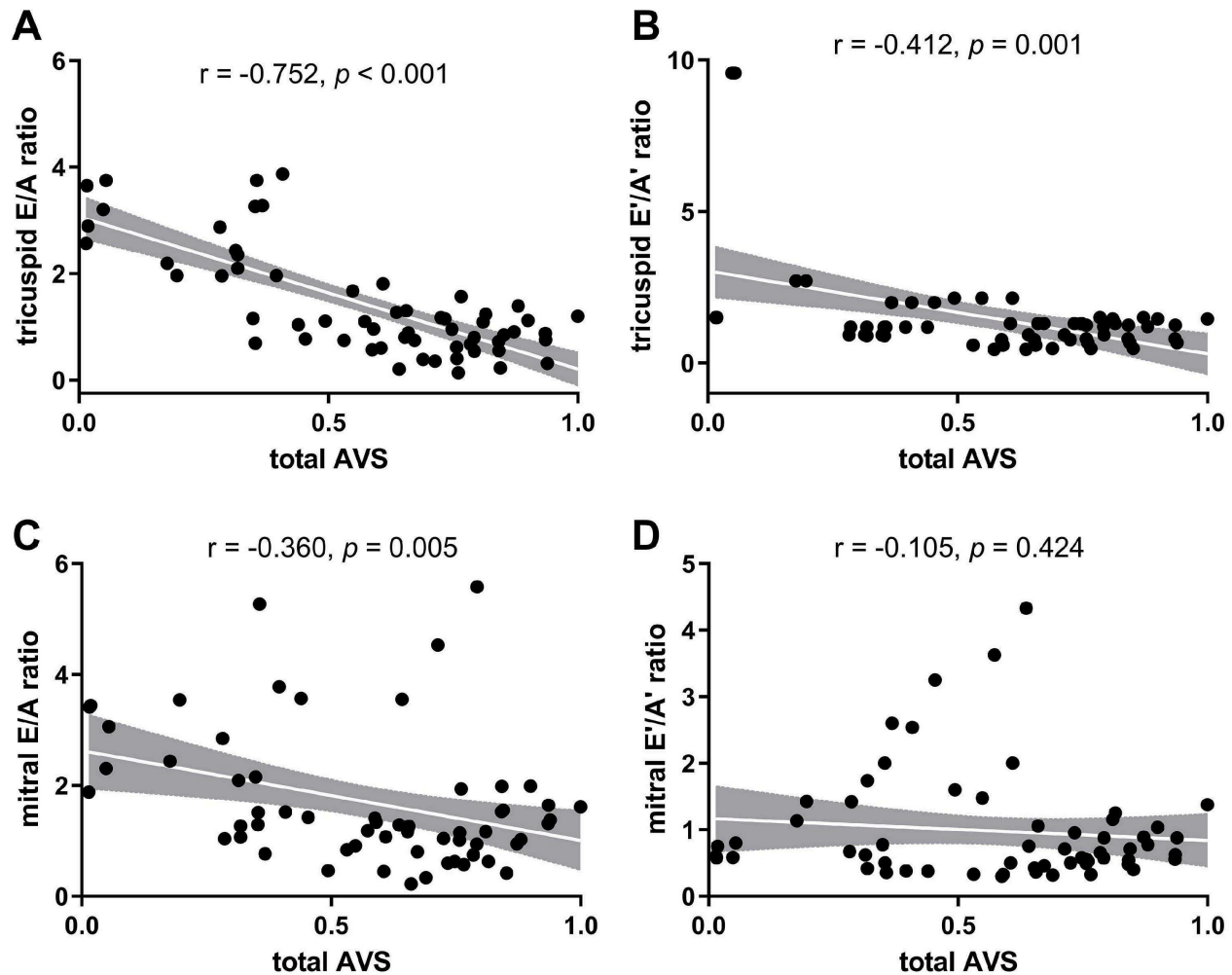


Figure 2

Correlation between right atrial tricuspid flow and tissue velocity measurement by Doppler and AVS percentage.

A: Correlation between tricuspid E/A ratio and AVS percentage; B: Correlation between tricuspid E'/A' ratio and AVS percentage; C: Correlation between mitral E/A ratio and AVS percentage; D: Correlation between mitral E'/A' ratio and AVS percentage

AVS: atrioventricular synchrony; E: early diastolic peak flow velocities at mitral/tricuspid inflow measured by Doppler flow imaging; E': early diastolic tissue Doppler velocities at mitral/tricuspid annulus measured by pulsed-wave tissue Doppler; A: atrial systolic peak flow velocities at mitral/tricuspid inflow measured by Doppler flow imaging; A': atrial systolic tissue Doppler velocities at mitral/tricuspid annulus measured by pulsed-wave tissue Doppler

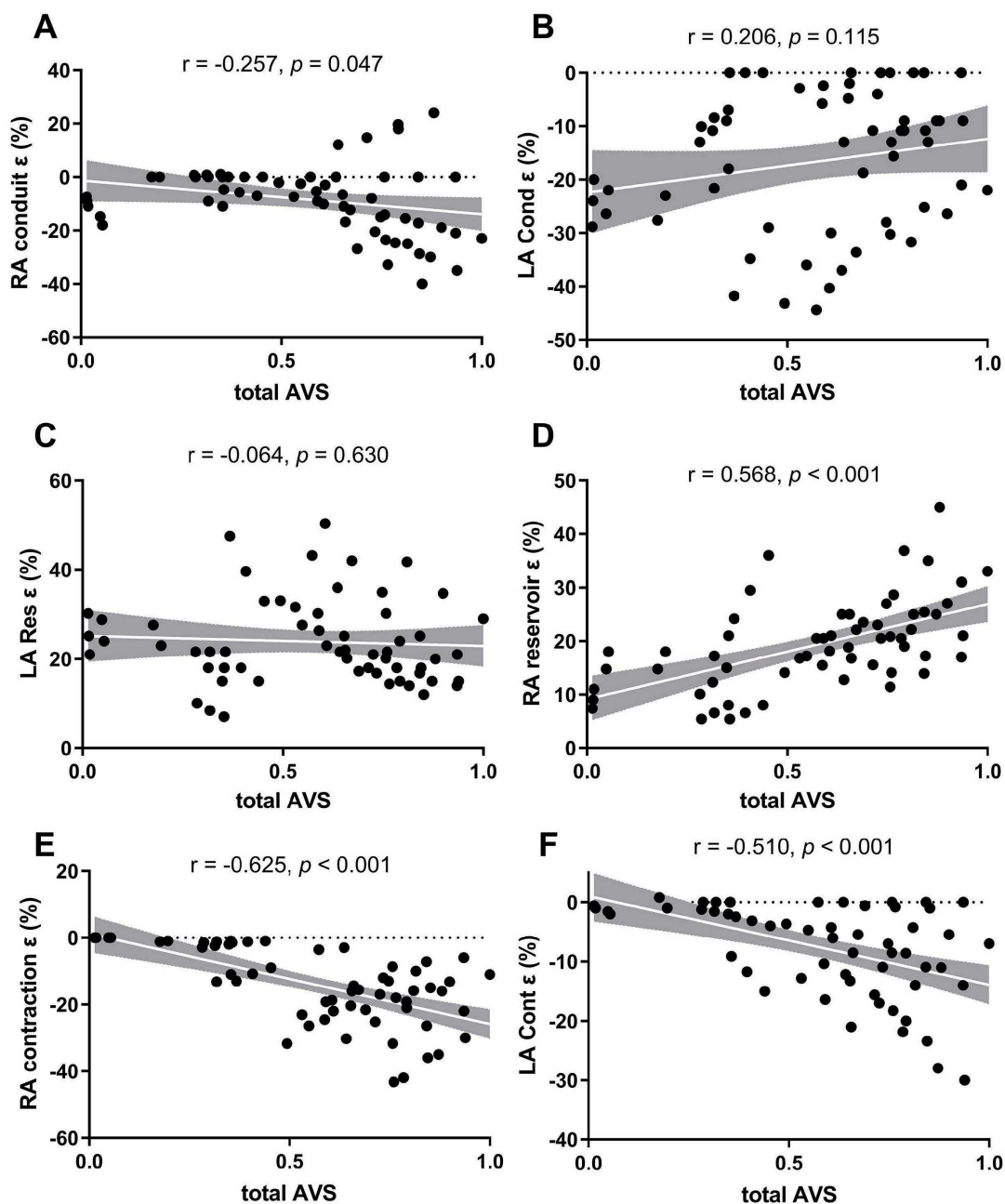


Figure 3

Correlation between right atrial conduit/reservoir/contraction strain measurement by two-dimensional speckle tracking echocardiography and AVS percentage.

A: Correlation between right atrial conduit strain and AVS percentage; B: Correlation between left atrial conduit strain and AVS percentage; C: Correlation between left atrial reservoir strain and AVS percentage;

D: Correlation between right atrial reservoir strain and AVS percentage; E: Correlation between right atrial contraction strain and AVS percentage; F: Correlation between left atrial contraction strain and AVS percentage

AVS: atrioventricular synchrony

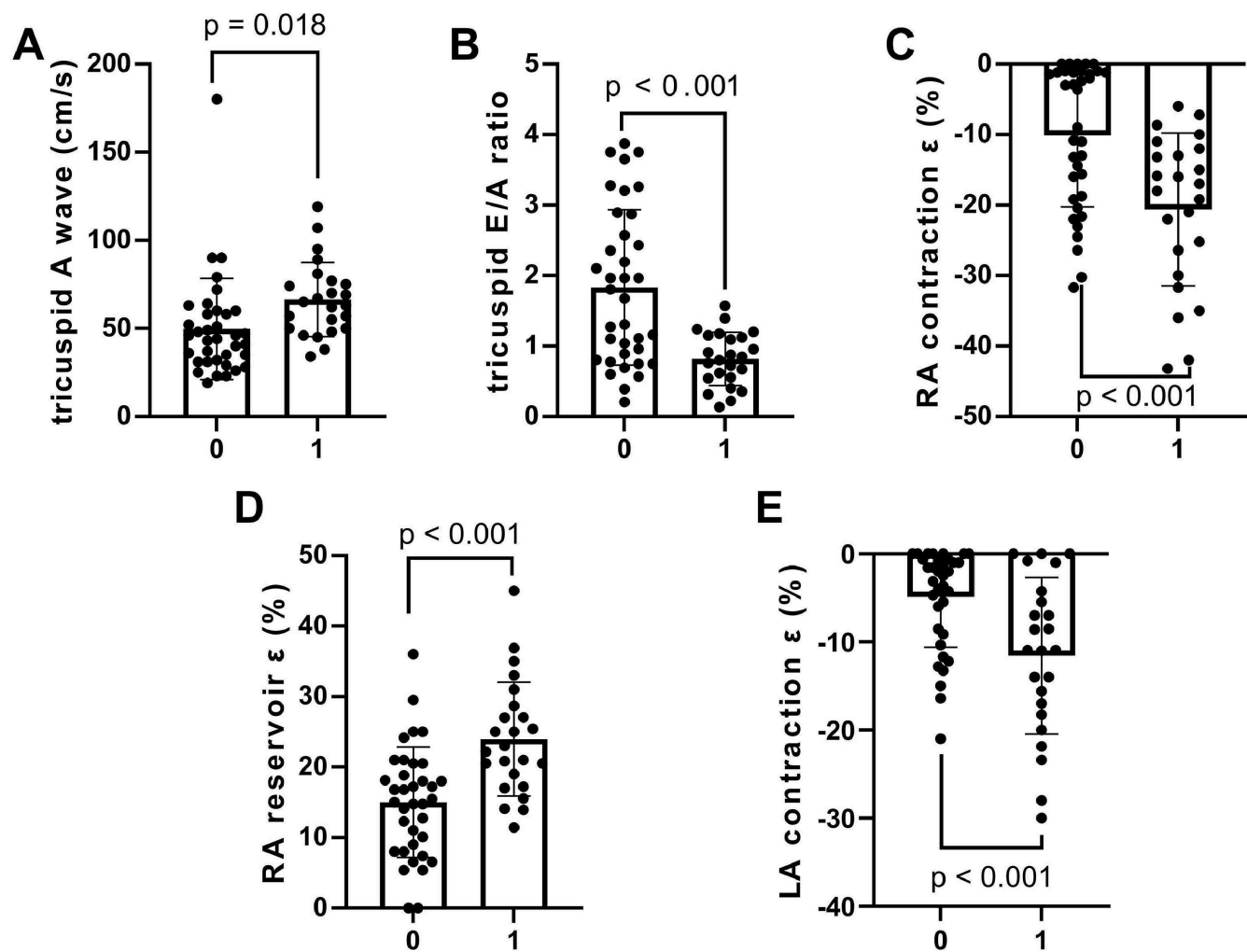


Figure 4

Comparison of patients with or without 70% and above AVS.

A: Difference of tricuspid A-wave value; B: Difference tricuspid E/A ratio value; C: Difference right atrial contraction strain value; D: Difference right atrial reservoir strain value; E: Difference left atrial contraction strain value

AVS: atrioventricular synchrony

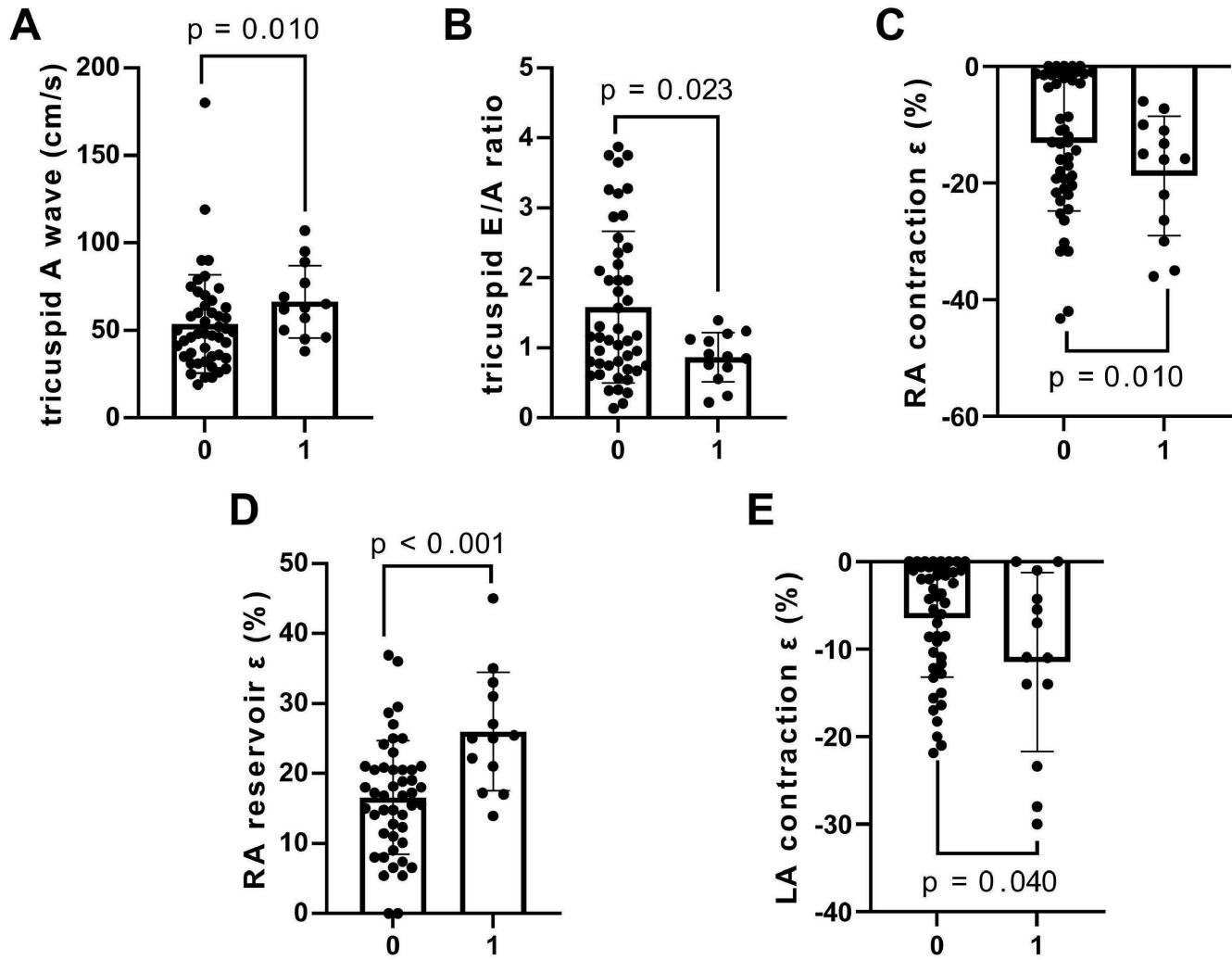


Figure 5

Comparison of patients with or without 80% and above AVS.

A: Difference of tricuspid A-wave value; B: Difference tricuspid E/A ratio value; C: Difference right atrial contraction strain value; D: Difference right atrial reservoir strain value; E: Difference left atrial contraction strain value

AVS: atrioventricular synchrony

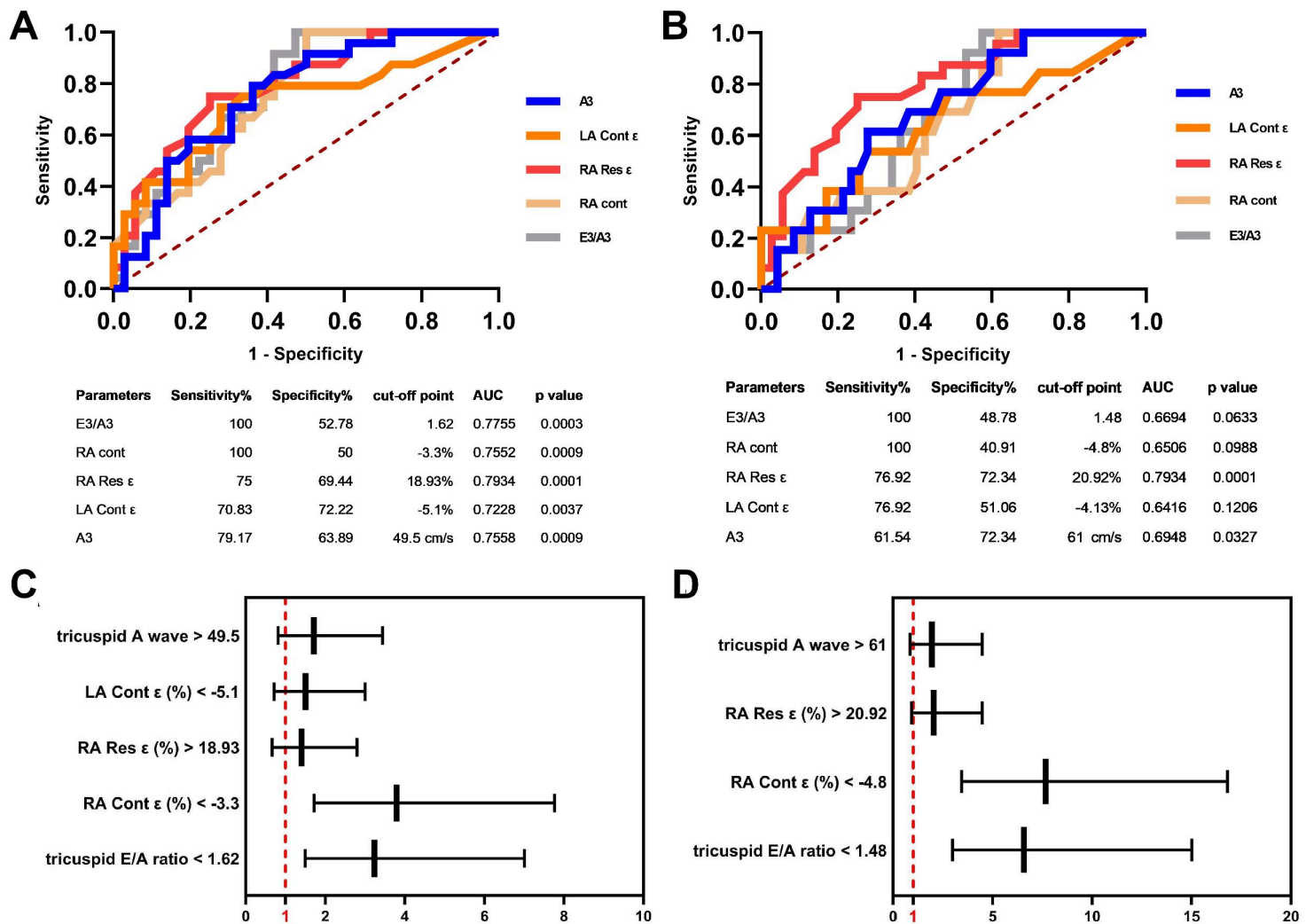


Figure 6

ROC analysis to identify the optimal cut-off points of included echocardiographic parameters and validation of the cut-off point of the candidate echocardiographic parameter.

A: Comparison of patients with or without 70% and above AVS of tricuspid A-wave, tricuspid E/A ratio, right atrial contraction strain, right atrial reservoir strain, and left atrial contraction strain in terms of AUROC, sensitivity, specificity, and cut-off point; B: Comparison of patients with or without 80% and above AVS of tricuspid A-wave, tricuspid E/A ratio, right atrial contraction strain, right atrial reservoir strain, and left atrial contraction strain in terms of AUROC, sensitivity, specificity, and cut-off point; C: Validation of the cut-off point of the candidate echocardiographic parameter for patients with or without 70% and above AVS; D: Validation of the cut-off point of the candidate echocardiographic parameter for patients with or without 80% and above.

ROC: receiver operating characteristic curve; AUROC: area under the ROC curve

AVS: atrioventricular synchrony

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