

The Impact of the Right Heart Cavities Echocardiographic Features on Atrial-High Rate Episodes

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Abstract

Objectives

Atrial high-rate episodes (AHRE) defined as atrial tachy-arrhythmias, detected through continuous monitoring with a cardiac implantable electronic device (CIED). AHRE's have been associated with increased risks of developing clinically manifested atrial fibrillation (AF), thromboembolism, cardiovascular events, and mortality. Several variables have been researched and identified to predict AHRE existence. The present study evaluated the association between right-heart structural and functional echocardiographic parameters and AHRE in patients with CIEDs.

Materials and Methods

This prospective design study included 194 patients with CIED's. The study population was divided into two groups according to presence of AHRE and analyzed the echocardiographic variables which may able to be a predictor of AHRE.

Results

Patients was divided into two groups: patients with AHRE (+) and without AHRE (-). The distribution of patients' characteristics according to presence of AHRE was analyzed. The multivariate analysis revealed Age, LAVI, E/Em tricuspid (HR: 1,106, 1,015 – 1,205%95 CI, p = 0,022) and RAVI (HR: 1,035, 1,003 – 1,069 95% CI; p = 0,033) as independent predictors of AHREs. ROC curve analysis indicated that an E/Em tricuspid (AUC: 0,611, 95% CI: 0,538-0,680 p: 0.009) and RAVI (AUC = AUC: 0,707, 95% CI 0,637-0,770 p < 0.001) predicted AHREs with a cut-off value of 6.28 and a sensitivity of 53,2% and specificity of 66,7% and a cut-off value of 29,5 mL/m² with a sensitivity of 72,7% and a specificity of 65,9%, respectively.

Conclusion

The main finding of this study was "RAVI" and "E/Emtricuspid ratio" is associated with AHRE. Additionally, "RAVI" and "E/Emtricuspid ratio" is an independent predictor of AHRE existence.

INTRODUCTION

Atrial high-rate episodes (AHREs), also termed, subclinical atrial tachyarrhythmias, are frequently observed in patients with cardiovascular implantable electronic devices (CIEDs) [1]. AHREs are reportedly associated with increased risks of thromboembolic events, major adverse cardiovascular outcomes, and cardiovascular death [2–5]. Given these undesired consequences, current clinical practice guidelines strongly recommend closely monitoring patients with AHRE [6].

Recent studies have demonstrated that the presence of heart failure, the New York Heart Association (NYHA) classification class, presence of sick sinus syndrome (SSS) and large left-atrial volume index (LAVI) were independent predictors of new-onset AHREs in patients with CIEDs [7–8]. Additionally, presence of AHREs in patients with CIEDs has been associated with increased risks of stroke, systemic embolism, and heart failure [9–10]. Therefore, it is crucial to predict the existence of AHREs in patients without a history of atrial fibrillation (AF) in order to achieve better outcomes.

Left atrial dilatation and increased LAVI are established predictors of the pathogenesis and perpetuation of AHRE. Nevertheless, the status of right heart cavities and structural and functional remodeling in patients with AHREs have yet to be elucidated. In this context, the objective of this study is to investigate the relationship between right sided structural and functional remodeling determined by echocardiographic assessment and AHREs in patients with CIEDs.

MATERIAL and METHOD

Population and Sample

The population of this prospective consecutive study consisted of patients over 18 with a CIED ((pacemaker (PM), implantable cardioverter defibrillator (ICD), cardiac resynchronization therapy-pacemaker (CRT-P) and cardiac resynchronization therapy-defibrillator (CRT-D)) who were presented to the Cardiology Outpatient Clinic of Kafkas University Hospital between January 2022 and January 2023. Patients with CIEDs who were admitted to the outpatient clinic for in office follow-up were enrolled in the study. At the admission date, patients' baseline demographic variables, ECG records and echocardiographic measurements were performed and saved. Thereafter, these patients were examined retrospectively. Clinicians who evaluated ECG or ECHO recordings completed their assessments regardless of the presence or absence of AHRE. Patients with a single-chamber PM or an ICD, had a history of AF/AFL (atrial flutter) and moderate-to-severe valvular disease or valve prosthesis were excluded from the study. The study protocol was approved by Kafkas University Medicine Faculty Local Ethics Committee prior to the conduct of the study. The study was carried out in accordance with the ethical principles set forth in the Declaration of Helsinki and the ethical standards set by the authorized ethics committee on human experimentation.

Definition of Atrial High Rates Episodes

AHREs refer to atrial arrhythmias that feature atrial rates > 200 beats per minute (≥ 36 or 48 atrial beats and cycle lengths of ≤ 300 ms) and last at least 30 seconds recorded via telemetry. Electrocardiomatrix (ECM) images pertaining to AHREs were reviewed by at least one experienced electrophysiologist, who excluded lead noise or artifacts and paroxysmal supraventricular tachycardia, and visually confirmed the AF that had been recorded as AHRE [11].

Data Collection

Patients' medical history including comorbidities were obtained from patients' charts. The blood samples for the hemogram test and the measurements of biochemical markers were collected from all patients at the time of their admission to the outpatient clinic. An automated hematology and biochemical analyzer (Roche Diagnostics Cobas 8000 c502, Indianapolis, USA) was used to carry out the hemogram test and perform the measure the measurements of biochemical markers.

Echocardiography was performed using the General Electric Vivid-7 ultrasonographic machine (General Electric, Milwaukee, WI). All echocardiographic images were reviewed offline and analyzed by 2 independent investigators who were blinded to the research data using a proprietary software (EchoPACTM, version 202, GE Healthcare, Milwaukee, WI). All measurements were performed in accordance with the American Society of Echocardiography guidelines [12–13]. Left ventricular ejection fraction (LVEF) was measured by the biplane method of discs. Maximum anteroposterior left atrial diameter was measured from the parasternal long axis view. Maximum left atrial (LA) volume was measured by the biplane method of discs from the apical 2- and 4- chamber view. The calculated LA volumes were indexed to body surface area for LAVI. Pulsed-wave Doppler echocardiography was used to record transmitral inflow in the apical 4-chamber view and mitral inflow parameters ((peak early (E) and peak late (A) velocities and E/A ratio)) were calculated. The diastolic velocities were measured by tissue Doppler (e', a') at the septal and lateral sites and the E/e' ratios (for septal and lateral walls) were obtained.

Right ventricular (RV) functions were assessed using either conventional bidimensional echocardiography or tissue Doppler echocardiography. Most measurements, namely RV diastolic and systolic areas, tricuspid annular plane systolic excursion (TAPSE), tricuspid flow analysis (for E and A waves) and tricuspid regurgitation velocity (TRV) were performed from the apical 4-chamber view. Tissue Doppler ECHO of myocardial velocities were measured from the same view at the level of the tricuspid annular plane and E', A' and S' waves were calculated. Right atrial volume index (RAVI) was measured by based on modified Simpson's rule and was indexed to the body surface area. RV fractional area change (RVFAC), tricuspid E/A and E/Em ratios were determined according to measured values. The pulmonary artery systolic pressure (PASP) could not be determined due to the absence of inferior vena cava (IVC) the measurements. Hence, TAPSE/TRV [14] was calculated instead of TAPSE/PASP.

Statistical Analysis

SPSS 22.0 (Statistical Product and Service Solutions for Windows, Version 22.0, IBM Corp., Armonk, NY, U.S., 2013) software package was used to carry out the statistical analyses of the collected data. The descriptive statistics obtained from the research data were expressed as mean and standard deviation values in the case of continuous variables determined to conform to the normal distribution, as median and interquartile ranges in the case of continuous variables determined not to conform to the normal distribution, and as percentage values in the case of categorical variables. The normal distribution characteristics of continuous variables were analyzed using the Kolmogorov–Smirnov test. The two-sample student's t-test or the Mann–Whitney U-test was used to analyze the differences between the groups in terms of continuous variables. Additionally, Pearson's chi-squared test or Fisher's exact test was

used to analyze the differences between the groups in terms of baseline values of categorical variables. The impact of the variables on the AHREs was assessed based on the hazard ratios (HR) calculated within the scope of the univariate analysis. The parameters found to be significant in the univariate analysis were further analyzed using the multivariate analysis. In addition, forward conditional logistic regression analysis was used to determine the independent predictors of the development of AHRE. HR and 95% confidence interval (CI) values were calculated for each independent variable. Receiver operating characteristic (ROC) curve and their corresponding area under the curve (AUC) values were calculated in order to determine the optimal cut-off values of the variables found to be significant in the multivariate analysis in predicting the development of AHREs in patients with CIEDs. A probability (p) value of < 0.05 was considered significant.

RESULTS

The study population consisted of 264 patients with CIEDs who were admitted to the Kafkas University Hospital Cardiology Outpatient Clinic between January 2021 and January 2023. Patients with a history of AF ($n = 39$), with a single chamber ventricular (VVI) PM ($n = 6$) or ICD ($n = 9$), with moderate-to-severe valve disease ($n = 8$) and/or prosthesis heart valve ($n = 5$) and atrial lead dysfunction ($n = 3$) were excluded from the study. After exclusion, the research sample consisted of 194 patients with CIEDs.

The study population was divided into two groups: patients with AHREs ($n:77$), i.e., the AHRE (+) group and patients without AHRE ($n:117$), i.e., the AHRE (-) group. The mean age of the sample, of which 133 (58%) was male, was $68 (\pm 12)$ years. Patients with the AHRE (+) group was older than the AHRE (-) group. There was no significant difference between the groups in comorbidities. The distribution of the baseline demographic characteristics and laboratory findings by the groups is shown in Table 1.

Table 1

The baseline demographic characteristics and the laboratory of the study population (**Abbreviations:** DM: Diabetes Mellites, HT: hypertension, CAD: Coronary Artery Disease, BSA: Body Surface Area, WBC: White Blood Cell, Hgb: Hemoglobin, Na: Sodium, K: Potassium, CPR: C-reactive Protein, TSH: Thyroid Stimulating Hormone, PM: Pace-Maker, ICD: Implantable Cardioverter-Defibrillator, CRT: Cardiac Resynchronization Therapy)

Variables	AHRE			
	AHRE (-), n:117	AHRE (+), n:77	Total, n:194	P value
Age, years	67 ± 13	71 ± 12	68 ± 13	0.019
Male, n (%)	72 (61.5%)	41 (53.2%)	113 (58.2%)	0.253
DM, n (%)	32 (27.4%)	29 (37.7%)	61 (31.4%)	0.131
HT, n (%)	73 (62.4%)	58 (75.3%)	131 (67.5%)	0.610
CAD, n (%)	83 (70.9%)	62 (80.5%)	145 (74.7%)	0.134
Smoking, n (%)	19 (16.2%)	17 (22.1%)	36 (18.6%)	0.307
BSA, m ²	1.846 ± 0.148	1.807 ± 0.145	1.831 ± 0.149	0.101
WBC Count, 10 ³ /μL	7.41 ± 2.4	7.64 ± 1.76	7.5 ± 2.17	0.228
Neutrophil, 10 ³ /μL	4.9 ± 2	5 ± 1.46	4.9 ± 1.8	0.441
Hgb, g/dL	13 ± 1.8	13.35 ± 1.59	13.15 ± 1.73	0.235
Platelet, 10 ³ /μL	218 ± 57	233 ± 66	224 ± 61	0.229
Na, mmol/L	140 ± 2.7	140 ± 2.9	139 ± 2.8	0.250
K, mmol/L	4.43 ± 0.48	4.5 ± 0.43	4.4 ± 0.45	0.320
Creatinine, mg/dL	0.77 ± 0.39	0.84 ± 0.34	0.8 ± 0.37	0.108
Glucose, mg/dL	111 (96–125)	112 (98–144)	111 (97–129)	0.306
CRP, mg/dL	4.14 (0.52–8.67)	2.02 (0.84–5.54)	3.18 (0.6–6.94)	0.098
TSH, mIU/L	1.45 (0.99–2.14)	1.23 (0.75–1.89)	1.33 (0.91–2.07)	0.095
Device Type, n (%)	PM	56 (47.9%)	37 (48.1%)	0.606
	ICD	37 (31.6%)	18 (23.4%)	
	CRT	24 (20.5%)	22 (28.6%)	

The distribution of echocardiographic findings by the groups is shown in Table 2. Accordingly, in terms of left-sided parameters, the E/Emseptal ($13,6 \pm 7,4$ vs $15,7 \pm 7,1$; $p = 0,005$), E/Emlateral ($9,8 \pm 6$ vs $11,5 \pm 5$; $p = 0,005$) and LAVI ($37,32 \pm 11$ mL/m² vs $45,21 \pm 12,1$ mL/m²; $p < 0,001$) values were significantly higher

in the AHRE (+) group than in the AHRE (-) group. There was no significant difference between the groups in LVEF. Additionally, in terms of right-sided parameters, the RVS' ($10,4 \pm 3,2$ cm/s vs $12,3 \pm 4,2$ cm/s; $p = 0,011$), TAPSE (19 ± 6 mm vs 21 ± 5 mm; $p = 0,028$) and TAPSE/TRV ($10,8 \pm 7,8$ vs $11,9 \pm 5,3$; $p = 0,003$) values were significantly lower whereas the E/A tricuspid inflow ($1,14 \pm 0,49$ vs $0,99 \pm 0,47$; $p = 0,021$), E/Em tricuspid ratio ($7,5 \pm 4,1$ vs $6,3 \pm 3,5$; $p = 0,009$) and RAVI ($35,78 \pm 11,58$ mL/m² vs $29,38 \pm 11,51$ mL/m²; $p < 0,001$) values were significantly higher in the AHRE (+) group than in the AHRE (-) group.

Table 2

Echocardiographic variables for patients with and without AHRE (**Abbreviations**; E: Peak Early Inflow Velocity; A: Peak Late Inflow Velocity; Em: Early Diastolic Tissue Doppler Velocity; LAVI: Left Atrial Volume Index; LVEDD: Left Ventricle End Diastolic Diameter; LVEF: Left Ventricle Ejection Fraction; RV E', RV A' and RV S': Right Ventricle peak Early (E'), Late (A') and systolic (S') tissue doppler velocities; TAPSE: Tricuspid Annular Plane Systolic Excursion; TR vel: Tricuspid Regurgitation Velocity, RAVI: Right Atrial Volume Index; RVFAC: Right Ventricle fractional area change)

Variables	AHRE			
	AHRE (-), n:117	AHRE (+), n:77	Total, n:194	p value
E, mitral (cm/s)	69.2 ± 25.3	74.8 ± 24.4	71.4 ± 25.1	0.077
A, mitral (cm/s)	71.2 ± 25.3	79.2 ± 31.9	74.4 ± 28.3	0.102
E/A, mitral	1.19 ± 0.89	1.19 ± 0.89	1.18 ± 0.87	0.941
Emseptal, mitral (cm/s)	5.7 ± 1.9	5.2 ± 1.7	5.5 ± 1.8	0.087
Emlateral, mitral (cm/s)	8.1 ± 3	7.3 ± 2.3	7.8 ± 2.7	0.128
E/Emseptal, mitral	13.6 ± 7.4	15.7 ± 7.1	14.4 ± 7.3	0.005
E/Emlateral, mitral	9.8 ± 6	11 ± 5	10.3 ± 5.7	0.005
LAVI, (mL/m ²)	37.32 ± 11	45.21 ± 12.1	40.45 ± 12.06	<0.001
LVEDD, (cm)	50 ± 9	52 ± 8	51 ± 9	0.101
LVEF, (%)	36 ± 6	35 ± 8	38,5 ± 7,3	0.119
E, tricuspid (cm/s)	51.1 ± 16.3	55.3 ± 17.5	52.8 ± 16.9	0.088
A, tricuspid (cm/s)	57.3 ± 21.9	52.9 ± 16.3	55.6 ± 19.9	0.118
E/A, tricuspid	0.99 ± 0.47	1.14 ± 0.49	1.05 ± 0.48	0.021
RV E', (cm/s)	9.7 ± 4	8.4 ± 3	9.2 ± 3.7	0.055
RV A', (cm/s)	14.1 ± 4.2	13.6 ± 8.4	13.9 ± 6.2	0.102
RV S', (cm/s)	12.3 ± 4.2	10.4 ± 3.2	11.5 ± 4	0.011
E/Em, tricuspid	6.3 ± 3.5	7.5 ± 4.1	6.76 ± 3.79	0.009
TAPSE, mm	21 ± 5	19 ± 6	21 ± 5	0.028
TR Vel, m/s	2.05 ± 0.74	2.21 ± 0.78	2.11 ± 0.76	0.072
TAPSE/TRV, mmx(m/s) ⁻¹	11.9 ± 5.3	10.8 ± 7.8	11.47 ± 6.44	0.003
RAVI, mL/m ²	29.38 ± 11.51	35.78 ± 11.58	32 ± 11.95	<0,001
RVFAC, (%)	45 ± 11	43 ± 13	44 ± 12	0.083

The multivariate analysis revealed age, LAVI, E/Em tricuspid (HR: 1,106, 1,015 – 1,205%95 CI, p = 0,022) and RAVI (HR: 1,035, 1,003 – 1,069 95% CI; p = 0,033) as independent predictors of AHREs (Table 3). ROC curve analysis indicated that an E/Em tricuspid cut-off value of 6.28 predicted AHREs with a sensitivity of 53,2% and a specificity of 66,7% (AUC: 0,611, 95% CI: 0,538-0,680 p:0.009) and a RAVI cut-off value of 29,5 mL/m² predicted AHREs with a sensitivity of 72,7% and a specificity of 65,9% (AUC = AUC: 0,707, 95% CI 0,637-0,770 p < 0.001) (Fig. 1).

Table 3

Univariate and multivariate analyses of risk factors for AHRE (**Abbreviations**; E: Peak Early Inflow Velocity, A: Peak Late Inflow Velocity; Em: Early Diastolic Tissue Doppler Velocity; LAVI: Left Atrial Volume Index; RV S': Right Ventricle Peak Systolic Tissue Doppler Velocity, TAPSE: Tricuspid Annular Plane Systolic Excursion; TR vel: Tricuspid Regurgitation Velocity, RAVI: Right Atrial Volume Index) (HR: Hazard Ratio, CI: Confidence Interval)

Variable	Univariate			Multivariate		
	HR	95% CI	p value	HR	%95 CI	p value
Age, years	1.027	(1.002–1.052)	0.031	1.027	(1.001–1.055)	0.044
E/Emseptal mitral, cm/s	1.041	(0.999–1.082)	0.055	-		
E/Emlateral mitral, cm/s	1.041	(0.987–1.095)	0.140	-		
LAVI, mL/m ²	1.062	(1.032–1.092)	< 0.001	1.049	(1.019–1.079)	0.001
E/A ratio, tricuspid	1.932	(1.048–3.563)	0.035	-		
RV S', cm/s	0.866	(0.787–0.953)	0.003	-		
E/Em ratio, tricuspid	1.092	(1.009–1.182)	0.028	1.106	(1.015–1.205)	0.022
TAPSE, mm	0.935	(0.884–0.989)	0.019	-		
TAPSE/TRvel, mmx(m/s) -1	0.968	(0.921–1.017)	0.197	-		
RAVI, mL/m ²	1.057	(1.025–1.091)	< 0.001	1.035	(1.003–1.069)	0.033

DISCUSSION

The findings of this study, which aimed to assess the association between right-heart structural and functional echocardiographic parameters with AHREs in patients with CIEDs, revealed that RAVI and

E/Emtricuspid ratio were independent predictor of AHRE.

The CIEDs can detect and identify atrial arrhythmias, including AHREs. AHREs, which are commonly asymptomatic and only determined through long-term continuous rhythm monitoring are considered precursors of AF [11]. Previous studies have demonstrated the relationship between AHREs and increased incidence of clinical AF, stroke, systemic thromboembolism, and poor cardiovascular and cerebrovascular outcomes [1–3]. In this context, early identification of patients at high risk for AHREs may prevent undesirable outcomes. Several demographic, electrocardiographic, and echocardiographic risk factors have been investigated and found to be associated with AHREs in the literature. *Miyazawa et al.* reported that age and a history of AF/AFL were risk factors for AHRE [15]. Similarly, *Pastori et al.* reported that advanced age, a history of AF, and elevated white blood cell (WBC) counts were associated with AHRE [16]. In line with literature data, the mean age of the patients with AHREs included in this study was significantly higher than that of the patients without AHRE. Aging can cause abnormal atrial substrates leading to atrial cardiomyopathy characterized by atrial dilatation, atrial fibrosis, mechanical dysfunction, and/or endothelial dysfunction, thereby play a key role in the development of AHRE.

Recent studies have also demonstrated that LA volumes and left ventricular (LV) systolic and diastolic functions were associated with the presence of AHREs in patients with CIEDs. *Kim BS et al.* has shown that LA diameter > 41 mm and presence of SSS prior to CIED implantation was associated with the risk of developing AHREs [7]. Similarly, *Khoo CW et al.* reported that increased LA volumes was associated with the development of AHREs and atrial arrhythmia burden was independently associated with changes in LA and LV diastolic functions [17]. Additionally, *a recent clinical trial* revealed that the LV stiffness assessed by diastolic wall strain predicted asymptomatic AHREs in patients with CIEDs, and that increased LAVI was associated with AHREs [18]. In line with the literature data, the findings of this study revealed that LAVI and mitral E/Emseptal and E/Emlateral ratios were associated with the presence of AHREs. LV diastolic functions were associated with LV compliance and stiffness. In parallel, impaired LV compliance and increased LV stiffness were associated with increased LV filling pressure. Elevated LV filling pressure raises the LA wall stress and leads to LA remodeling. LA remodeling which is characterized by alterations in atrial conduction, interstitial fibrosis, and dilatation, may then lead to AHREs.

Right heart ECHO measurements conducted within the scope of this study demonstrated that patients with AHREs had impaired RV systolic and diastolic functions and increased RAVI. Additionally, E/Emtricuspid and RAVI were found to be independent predictors of AHRE. *Aziz EF et al.* investigated the incidence of new-onset AF in patients with acute decompensated heart failure and showed that RV dysfunction was a strong predictor of AF [19]. *Ting PC et al.* evaluated the relationship between RV function and AF after cardiac surgery and showed that RV dysfunction was significantly associated with AF [20]. *An animal study* reported that increased RV pressure along with right atrial (RA) enlargement was related with AF, and that right heart disease produced a substrate for AF maintenance due to RA re-entry activity and an underlying substrate that prominently included RA fibrosis and conduction abnormalities [21]. RV dysfunction due to pressure/volume overload could cause RA pressure/volume loading,

hypertrophy, and dilation. In response to chronic RA mechanical loading, tissue fibrosis and electrical abnormalities could be observed. RA stress is also related with increased expression of genes involved in hypertrophy, inflammation, apoptosis, and fibrosis. Taken Together, these abnormalities could constitute a proarrhythmic substrate that may lead to AHREs.

Given the very limited data in the literature on the relationship between echocardiographic findings of right heart functions and AHREs, the findings of this study may provide guidance for future studies to be conducted on this subject. Furthermore, the present study is the first that evaluate AHREs and right heart structures echocardiographic features.

CONCLUSION

AHREs are asymptomatic atrial tachy-arrhythmias detected in patients with a CIED. Most studies reported a relationship between AHREs and cardiovascular and cerebrovascular events and mortality. In this context, several demographic, electrocardiographic and echocardiographic parameters have been used to predict presence of AHRE in patients with a CIED. This study's findings, the first time in the literature, revealed that RAVI and E/Emtricuspid ratio were associated with the presence of AHREs and were independent predictors of AHRE existence in patients with a CIED.

Limitations of the study

The primary limitations of this study relate to its research design. Accordingly, the single-center, retrospective, observational design of the study and the relatively low number of patients with a CIED in a hospital setting may be deemed this study's limitations. The fact that all patients were from a single small region may not allow this study's findings to be generalized to other populations. Hence, prospective, large-scale, multicenter studies that also address other models not addressed in this study are needed to corroborate the findings of this study.

Declarations

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The authors have no conflicts of interest to declare.

The authors have done respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2013, as well as the national law

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Contributions

IA and IR contributed to the study conception and design. Echocardiographic analysis were performed by IA, MK and AA. IA, TO, MHS and DI enrolled patients and performed follow-up in the main studies and assisted in interpretation of results. IR assisted in interpretation of results and YK supervised the statistics. The first draft of the manuscript was written by IA and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figures

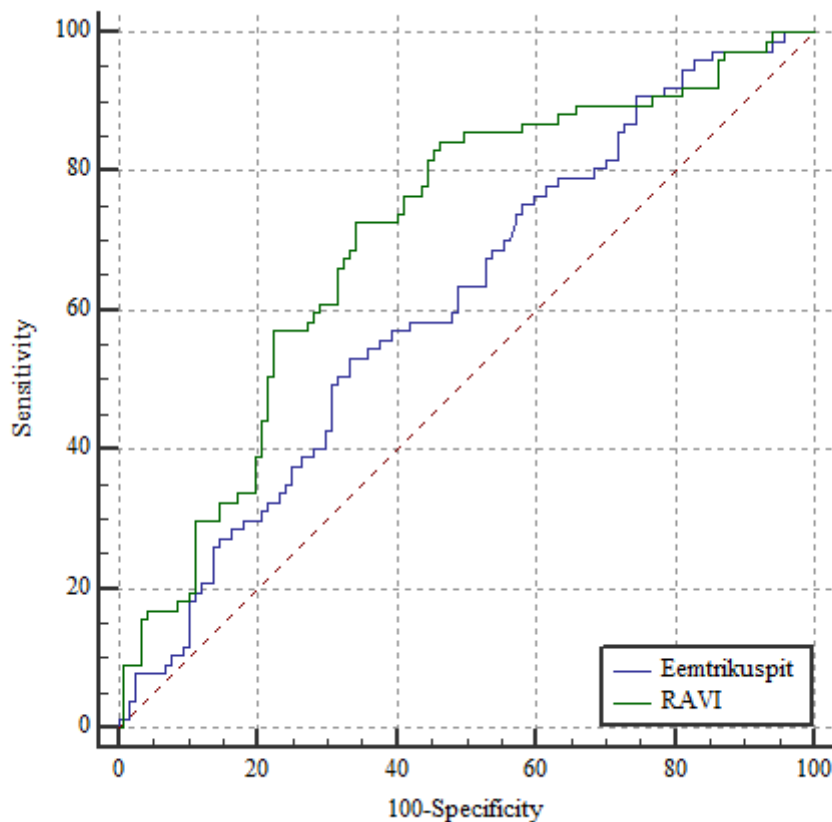


Figure 1

Receiver operating characteristic (ROC) curve analysis for RAVI and E/Em tricuspid ratio for AHRE existence (***Abbreviations***, RAVI: Right atrium volume index)