Can Echocardiographic Parameters Predict the Missing Link between Subclinical Atrial Fibrillation and Permanent Pacemakers? (Echocardiography and subclinical AF in permanent pacemaker)

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Abstract

Background and Objectives: Patients on implanted permanent pacemakers frequently develop atrial fibrillation (AF). We aimed to determine the Echocardiographic and clinical parameters predicting AF in patients with a dual-chamber (DDD) pacemaker.

Methods: This retrospective study included 208 patients with permanent pacemaker, classified according to development of AF during follow up into 2 groups: AF (77, 37%) and non AF (131, 63%), baseline: clinical, ECG(P-wave dispersion) and echo {diastolic wall strain (DWS),left arial volume index (LAVI), left ventricular stiffness index(LVSI)} data were assessed.

Results: AF group were older with more P wave dispersion, lesser DWS, greater LVSI& LAVI, LVSI at a cut off >0.13 and DWS at a cut off <0.34 were predictors of AF in patients with DDD pacemakers.

Conclusion: LVSI and DWS could be used as simple good predictors for AF in patients with DDD pacemakers, for timely initiation of anticoagulants according to CHA_2DS_2VASc score to decrease ischemic stroke burden.

Introduction

Atrial fibrillation (AF) is the commonest sustained cardiac arrhythmia that increases with aging, associated with increased risk of morbidity and mortality. It may be associated with all types of cardiovascular disorders; no single mechanism is concerned with the development of AF. Its pathophysiology may involve a complex interplay of electrophysiologic factors and structural changes. Clinical entities, such as hypertension, heart failure, and coronary disease, through mechanisms such as myocardial stretch, fibrosis, disruption in cell-to-cell coupling, and autonomic dysfunction all may promote development of AF (1). Up to a third of AF patients are asymptomatic and ischemic stroke is still often the first presentation of AF (2,3). This is numerically smaller than patients with clinical AF and the role of oral anticoagulants (OAC) is not yet established (4). The AF burden and episode duration that merits anticoagulation is also unknown (5).

Patients on implanted permanent pacemakers frequently develop atrial high-rate events (AHREs); defined as events with an atrial frequency of ≥180 bpm and a duration of ≥5 min (6 minutes exclude most episodes of over sensing), which is considered as clinically relevant according to current guidelines (6).AHREs are associated with an increased risk of clinical atrial fibrillation (AF) (7), ischemic stroke or systemic embolism (8), and cardiovascular death (9). AF frequently observed with progressively increased burden over time after implantation (10). So it is of an interest to explore AF- pacemakers' relationship (7).

Atrial-based pacing is as close as possible to a physiological pacing method; ventricular pacing is more non-physiological and causes cardiac mechanical dysynchrony. Higher atrial pacing rate by virtue of pacing alone may maintain uniform atrial rate and suppress premature atrial contractions, prevent short-

long-short sequences and may prevent bradycardia-induced dispersion of atrial repolarization. Therefore it is conceivable to prevent AF virtually by pacing atria at high rates (11, 12).

Aim of the study: The present study aimed to determine the echocardiographic and clinical parameters predicting the occurrence of AF in patients with a dual-chamber (DDD) pacemaker, without previously documented AF and to detect the high risk groups vulnerable for AF.

Methods

This retrospective study (record of the last 5 years data base in the electrophysiology unit) was performed in Cardiology department, Faculty of Medicine, Zagazig University Hospitals, included 208 consecutive patients who had dual-chamber (DDD) pacemaker for sinus node dysfunction (SND) or atrioventricular block (AVB), according to the indication guidelines. Patients were excluded from the study if they had: <18 years old, no follow-up data / Echocardiographic findings, undergone cardiac surgery, prior clinical atrial tachyarrhythmia (AF or atrial flutter rhythm), significant valvular disease, decompensate renal or liver diseases, uncontrolled thyroid disorders, COPD or pulmonary diseases. All patients provided written informed consents, after approval by the local ethics committee.

They were classified according to development of AF during follow up into 2 groups:

Group (A): patients who developed AF episodes on follow up (77 patients; 37%).

Group (B): patients without AF (131 patients; 63%).

All patients subjected (at base line before pacemaker implantation) to the following:

Complete history taking: concerning the basic demographic information including age, gender and risk factors to assess the CHA_2DS_2VASc score.

Physical examination: Full general and local examination.

Diagnostic tools:

A-Laboratory Tests: serum creatinine, creatinine clearance, HbA1C and Hb level.

B- Electrocardiography:12-lead electrocardiography (ECG) analysis for; heart rate, PR interval, P wave dispersion (in patients with sinus rhythm, defined as the difference between the shortest and the longest P-wave duration in any of the 12 ECG leads), QRS, QT and corrected QT durations (QTc , using Bazett's method).

C- Echocardiography: Transthoracic echocardiography (TTE) for; left atrial volume (LAV) indexed to the BSA for the LAVI, left ventricular ejection fraction (LV EF) and LV mass index (LVMI; using modified

Simpson's method) by 2D- echo. The LV diameters were assessed using M-mode. Mitral E and A wave velocities and E wave deceleration time were measured using pulsed wave Doppler. Tissue Doppler study for mitral (e') wave velocities (lateral, septal and average) and E/e' ratio was calculated.

LV stroke volume (SV) was measured; (LV end diastolic volume - LV end systolic volume) and indexed to BSA for SV index (SVI).

Diastolic wall strain (DWS) estimated from the following equation: DWS= (PWs-PWd) / PWs; reported as a non-invasive direct measure of the LV compliance **(13**).

LV stiffness index was measured using the following equation:

$$LV\ Stiffness\ index = \frac{\text{Transmitral E: lateral mitral annular e'}}{\text{End} - \text{diastolic volume}}$$

This parameter provides an estimate of the pressure to volume relationship **(14).**

Results

The main demographic data of the study groups are in table 1, with the mean age of the studied cases 61.67±8.13 years and 53.4% of them were female, 87 with SND and 121 with AVB, AF group was older (p=0.02), hypertension (HTN) was the most common risk factor found among the studied cases (42.3%) with no significant difference between the studied groups regarding presence of HTN.

Anticoagulants, BBs and diuretics were more used in AF group, the mean CHA_2DS_2VASc score among the studied cases was 1.59, AF group had higher score but not reach statistical significance (p=0.09).

P wave dispersion was higher in AF group compared to non AF (45.51±3.33 vs. 20.91±5.77 msec, respectively, p<0.001), table 2.

AF group compared to non AF group; had a highly significant increase in LAVI (40.65±11.24 vs. 28.34±6.07 ml/m^2), E/é (12.19±0.83 vs. 6.3±0.98) and LVSI (0.14±0.01vs. 0.06±0.01 ml^{-1}), p<0.001, and a highly significant decrease in posterior wall thickness in systole (PWs); (1.2±0.17 vs. 1.36±0.12 mm), DWS (0.28±0.08 vs. 0.38±0.10), EDV(128.64± 5.59 vs. 154.81±11.99 ml), SVI (43.43±3.88 vs. 59.61±9.12 ml/m^2) and EF (57.78±3.39 vs. 65.56±6.1%) , p<0.001, table 2.

LVSI had significant +ve correlation with older age (r=0.643, p=0.03) , LAVI (r = 0.928 , p<0.001) and P wave dispersion(r =0.946, p<0.001) and had significant -ve correlation with end diastolic volume (EDV) , r = -0.937 , p<0.001) , SVI (r = -0.741 , p<0.001), EF (r = -0.429 , p<0.001) and DWS (r = -0.92 , p<0.001) among AF cases.

DWS had significant –ve correlation with LAVI (r = -0.888 , p<0.001), P wave dispersion(r = -0.94 , p<0.001), and LVSI (r = -0.600 , p<0.001) and significant +ve correlation with age (r=0.3, p<0.001) , EDV(r=0.6, p= 0.001), SVI (r=0.95, p<0.001) and EF(r=0.65, p<0.001) among AF group.

Univariate analysis indicated that reduced DWS, EDV and SVI, older age, larger LAVI, higher P wave dispersion and increased LVSI were significant variables. On multivariable analysis, only the LVSI (B=-0.159, HR=1.5, 95% CI=2.301-0.637, p<0.001) and DWS (B=0.165, HR=0.8 , 95% CI=0.323-1.194, p<0.001) were independent predictors of AF occurrence in patients with dual chamber (DDD)pacemakers, table (3).

ROC analysis showed that: DWS at a cut off value <0.34 had a sensitivity of 80.5%, a specificity of 75.6%, NPV of 86.8%, PPV of 66% and an accuracy of 77.4% (AU=0.79, p<0.001) in prediction of AF among the studied cases, fig 1, and LV stiffness at a cut off value >0.13 had a sensitivity of 61.1%, a specificity of 78.6% ,NPV of 77.4%, PPV of 62.7% and an accuracy of 69.95% (AU=0.78, p<0.001) in prediction of AF among the studied cases, fig 2.

Discussion

AF is the most common arrhythmia encountered in clinical practice and is associated with high morbidity and mortality **(15)**. Some patients suffering from AF may have no or mild symptoms (subclinical episodes), which results in a significant underestimation of the incidence of AF. In an aging patient population, it is frequently necessary to implant a permanent pacemaker. Current dual-chamber permanent pacemakers (PPMs) that incorporate atrial leads are able to detect and store AHREs occurrence which have been shown to be a reliable surrogate of atrial tachyarrhythmia, especially for AF (16). It has been suggested that AHREs lasting 5 minutes or more identify patients who are 2 times as likely to die or have strokes. The increased risk associated with developing AHREs may be similar to that for AF, reinforcing the concept that AHREs and AF are likely to represent a clinical continuum in the spectrum of atrial tachyarrhythmia (17)

The Silent AF Detection With Stored EGMs (SAFE) registry was the first prospective registry to evaluate the incidence, duration, and predictors of newly diagnosed AF in a general population of patients with no history of AF after dual chamber pacemaker implantation, its main findings were: 10% of its patients experienced ≥1 AHREs, most of these episodes were asymptomatic (18).

Left ventricular (LV) diastolic dysfunction is potentially linked to AF (19)**.** LV diastolic wall strain (DWS) can identify a subgroup of subtle LV diastolic dysfunction, as it measures LV compliance (20). Increased LV stiffness estimated by DWS has been reported to be a strong determinant of AF prevalence in structurally normal patients**(21).** So, the link between echocardiographic parameters, clinical data of patients on permanent pacemakers and occurrence of AF need more extensive studies.

Current study showed that; AF group was older in age, in agreement with **Lopes RD et al (22), Pastori et al.,** (23) and **Skanes et al**. (24) who reported that older age, could predict the development of chronic AF in

patients with a pacemaker.

We found that hypertension was the most common risk factor found among the studied groups, more in AF group but it did not reach statistical significance difference in concordance with **Healey, Connolly** (25), **Pioger** (26) and **H. Kishima et al.(** 27) but they found significance, this may be due differences between the study populations. **Rovaris et al.** (28) indicated that the incidence of AF increased with increasing CHA_2DS_2-VASc score, in agreement with these findings, we found that patients in AF group had higher CHA_2DS_2-VASc score but not reached significance.

Current study showed that anticoagulants, beta blockers and diuretics were used more in AF group compared to non AF group and this is in agreement with **H. Kishima et al**. (27) but different results were observed by **Uetake et al.** (21) who found no significant difference between studied groups in medications.

We detected that P wave dispersion was more in AF group, in agreement with **Dilaveris and Gialafos** (29).

We found that LAVI was higher among AF group, in agreement with **Antoni et al**. (30) and **Lopes RD, et al**(22), PWs was lesser among AF group compared to non-AF group , in agreement with **Takeda et al.** (13) and **H. Kishima et al.**(27).

We found that the AF group had higher E/é ratio, in agreement with **H. Kishima et al** (27).

We found that DWS was lesser in AF group ,in agreement with **Takeda et al.**(13), **Uetake et al.**(21) and **H. Kishima et al**(27). And we found that DWS at a cut off value <0.34 had a sensitivity of 80.5%, a specificity of 75.6%, NPV of 86.8%, PPV of 66% and an accuracy of 77.4% (AU=0.79, p<0.001) in prediction of AF among the studied cases, this is near to the results of **Uetake et al**.(21) who found that DWS<0.38 was the strongest indicator of AF.

The following mechanism correlated low DWS and AF; as Low DWS -which indicates increased LV stiffness and decreased compliance- augments LV filling pressure which in turn raises the LA wall stress, leading to LA remodeling, interstitial fibrosis, with alterations in atrial conduction, and dilatation, that may then lead to AF, so early stage of diastolic dysfunction could start with a decreased DWS even in patients with normal LV diastolic function **Kang et al.** (20).

We detected that the AF group had higher degree of LV stiffness index, in agreement with **Ryu et al.** (31) and we found that LV stiffness index at a cut off value >0.13 had a sensitivity of 61.1%, a specificity of 78.6%, NPV of 77.4%, PPV of 62.7% and an accuracy of 69.95% (AUC=0.78, p**<**0.001) in prediction of AF among the studied cases; this new echocardiographic index estimating LV stiffness was compared to the gold standard of cardiac catheterization using pressure-volume loop analysis and was found to be accurate as a surrogate measure of LV stiffness, as it correlates the diastolic function assed by tissue Doppler against the measured end-diastolic volume (14).

Also we found that EDV were lower among AF group, in agreement with **Ngiam et al.** (32) who stated that the higher the LV stiffness, the lower EDV and SVI.

We detected that the LV stiffness index had significant +ve correlation with older age, LAVI and P wave dispersion and had significant -ve correlation with EDV, SVI, EF and DWS in AF group. DWs had significant-ve correlation with LAVI, P wave dispersion and LV stiffness, also DWS had significant +ve correlation with age, EDV, SVI and EF among AF group.

On multivariable analysis we found that AF was only associated with reduced DWS and increased LV stiffness index, which are contributing factors in subtle diastolic dysfunction, patients with reduced DWS (<0.33) and high LV stiffness index (>0.13 ml^{-1}) had a higher risk to develop AF.

Asymptomatic AF delays clinical diagnosis, which can result in ischemic stroke or other embolic complications, early detection (which is difficult by conventional methods) of asymptomatic AF and timely initiation of anticoagulants according to CHA_2DS_2-VASc score are essential for management of this group of patients.

On the other hand, our study went with other many studies (18,21,33) that evaluated development of AHREs and they showed that it is very common during follow-up of pacemaker-equipped patients.

Conclusion

High LV stiffness index at a cut off value >0.13 and Low DWS at a cut off value <0.34 could be used as simple good predictors for development of AF in patients with dual chamber (DDD) pacemaker implantations, for timely initiation of anticoagulant therapy according to CHA_2DS_2-VASc score, for patients who develop asymptomatic AF to prevent thromboembolic events and decrease ischemic stroke burden.

Limitations Of The Study

This is a retrospective study only from the same geographic area and from a single medical center (Zagazig University Hospitals) with a small number of patient subgroups, cases of cardiac resynchronization therapy (CRT) or ICD implantation were excluded and, thus, the AF detection rate may be underestimated, with lake of information about the incidence of stroke, systemic embolism, heart failure, acute myocardial infarction, and other cardiovascular and cerebrovascular events within the period of pacemaker implantation.

Recommendations

LV stiffness index and DWS are simple useful predictors of AF in patients with DDD pacemaker. Our findings may provide additional diagnostic information for the other diagnostic parameters. In our opinions patients with pacemakers detected AHREs, low DWS, high LV stiffness index and high CHA_2DS_2-

VASc score need oral anticoagulation to prevent thromboembolic events and decrease burden of ischemic stroke as the incidence of subclinical AF is high in this patient population. On follow up of pacemaker, once AHRE occurs, 24-h Holter should be carried out for early AF detection and treatment.

Declarations

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Conflict of interest:

No conflict of interest to declare.

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Tables

Table (1): Demographic, clinical, medical and laboratory data of the studied groups:

Variable		Total (n=208)		AF (n=77)		Non AF (n=131)		P
Age: (years)		61.67±8.13		63.34±7.91		60.69±8.13		**0.02**
Serum creatinine(mg/dl)		1.18±0.26		1.21±0.25		1.17±0.27		0.37
Creatinine clearance(ml/min)		67.14±7.84		66.87±7.9		67.29±7.83		0.71
HBA1C (%)		5.99±0.33		6.03±0.32		5.96±0.32		0.18
Hb(g/dl)		12.63±1.11		12.56±1.14		12.67±1.09		0.49
CHA_2DS_2-VASc Score:		1.59±1		1.74±0.97		1.5±1.01		0.09
Variable		**No**	**%**	**No**	**%**	**No**	**%**	**P**
gender	Female	111	53.4	42	54.5	69	52.7	0.79
	Male	97	46.6	35	45.5	62	47.3	
Risk factors	CHF	0	0	0	0	0	0	
	HTN	88	42.3	34	44.2	54	41.2	0.98
	DM	37	17.8	14	18.2	23	17.6	
	Vascular insult							
	MI	5	2.5	3	3.9	2	1.5	
	PVD	8	3.85	2	2.6	6	4.6	
	Stroke/TIAs	13	6.3	7	9	6	4.6	
Drugs	Antiplatelet	63	30.3	23	29.9	40	30.6	**0.02**
	Anticoagulant	8	3.9	5	6.5	3	2.3	
	ACEI/ARBS	77	37.1	28	36.4	49	37.5	
	BBs	33	15.9	20	26	13	10	
	Statins	47	22.6	18	23.4	29	22.2	
	Diuretics	21	10.1	10	13	11	8.4	

SD: Standard deviation: Independent t test χ^2: Chi square test NS: Non-significant (P>0.05)

SBP; Systolic Blood pressure, DPB ;Diastolic blood pressure, HbA1C;glycosylated hemoglobin, CHF; congestive heart failure, HTN; Hypertension, DM; diabetes mellitus, MI; myocardial infarction, PVD;

peripheral vascular disease, TIAs; transient ischemic attacks, BB; beta blockers, ACEI; angiotensine converting enzyme inhibitor, ARBS; angiotensin receptor blockers.

Table (2): ECG and Echo results among the studied groups:

Variable	AF (n=77)	Non AF (n=131)	P
Rate: (beat/min)	64.61±4.04	65.38±3.9	0.18
PR interval:(msec.)	143.91±36.86	145.65±38.77	0.52
P wave dispersion (msec.)	45.51±3.33	20.91±5.77	<0.001
QRS: (msec.)	150.91±17.33	148.7±18.58	0.40
QTc: (msec.)	469.35±34.58	465.04±36.82	0.41
LA VI(ml/m^2)	40.65±11.24	28.34±6.07	<0.001
EDD(mm):	42.96±5.45	43.5±5.89	0.52
ESD(mm):	42.96±3.3	42.59±3.06	0.43
PWs(mm):	1.2±0.17	1.36±0.12	<0.001
PWd(mm):	0.87±0.15	0.84±0.12	0.11
DWS:	0.28±0.08	0.38±0.10	<0.001
EDV(ml):	128.64± 5.59	154.81±11.99	<0.001
ESV(ml):	54.8±3.74	53.52±7.59	0.11
SV I: (ml/m^2)	43.43±3.88	59.61±9.12	<0.001
EF: (%)	57.78±3.39	65.56±6.1	<0.001
E/A ratio	1.13±0.12	1.20±0.16	0.2
E/é	12.19±0.83	6.3±0.98	<0.001
LV mass index (g/$m^{2)}$	63.87±7.47	64.34±12.08	0.73
LV stiffness(ml^{-1})	0.14±0.01	0.06±0.01	<0.001

QTc; corrected QT interval, msec; millisecond, DWS; diastolic wall strain assessed by PWs-PWd/PWs, E/é; ratio between early mitral inflow velocity and mitral annular early diastolic velocity(tissue Doppler), EDD; end diastolic diameter, ESD; end systolic diameter, EDV; end diastolic volume, ESV; end systolic volume,

EF; ejection fraction, LA; left atrium, LV; left ventricle, PWd; Post wall diameter at end-diastole , PWs; Post wall diameter at end-systole, SV; stroke volume.

Table (3): Multivariate regression analysis for independent predictors of AF, after the implantation of dual-chamber (DDD) pacemaker.

Variable	Univariate		Multivariate				
	t	P value	ß	t	HR	95%CI	P value
Age(years)	2.29	**0.02**	-0.128	-2.809	0.1	0.013-0.002	0.7
P- wave dispersion(msec)	39.1	**<0.001**	-0.245	-7.664	0.1	0.012-0.007	0.08
CHA_2DS_2-VASc Score:	1.66	0.09	0.030	0.652	0.1	0.029 - 0.058	0.515
EDD(mm)	0.65	0.52	0.034	2.237	0.1	0.020 - 0.045	0.3
EDV(ml)	-21.34	**<0.001**	-0.059	-0.659	0.1	0.007 - 0.004	0.5
SVI (ml/m^2)	-17.72	**<0.001**	0.456	9.600	0.1	0.009 - 0.014	0.1
LAVI(ml/m^2)	10.26	**<0.001**	-0.173	-3.286	0.1	0.013-0.003	0.04
LV stiffness(ml^{-1}):	50.97	**<0.001**	-0.159	-3.482	1.5	2.301-0.637	**<0.001***
DWS	7.86	**<0.001**	0.165	3.436	0.8	0.323 - 1.194	**<0.001***
Serum creatinine(mg/dl)	0.9	0.37	-0.004	-0.092	0.2	0.153 - 0.140	0.927
HbA_1C(%)	1.35	0.18	0.00	-0.009	0.2	0.124 - 0.123	0.993
CRP(mg/L)	0.013	1	0.025	0.607	0.1	0.015 - 0.028	0.544

t: Independent t test ,HR: hazard ratio , CI: Confidence interval.

Figures

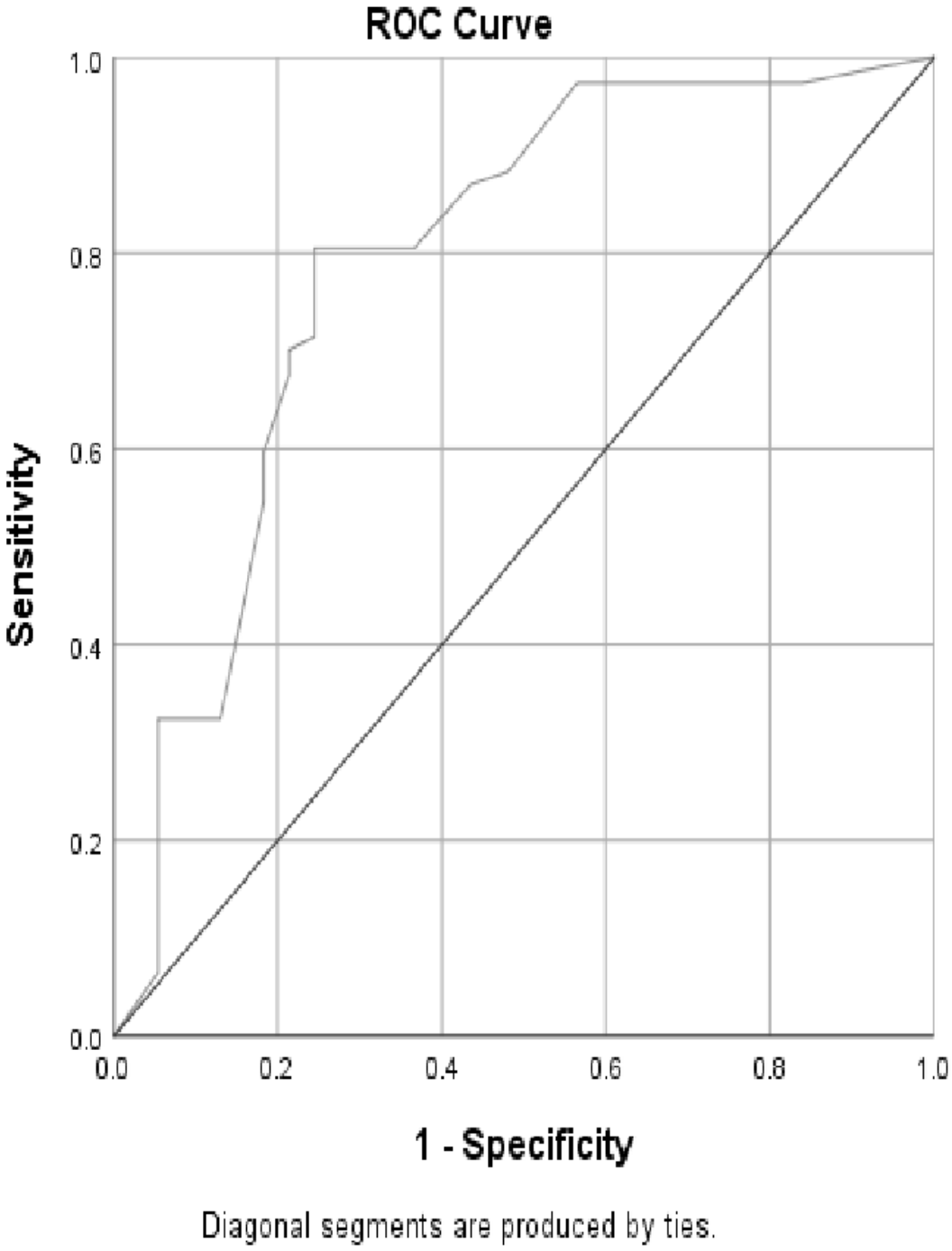

Figure 1

Roc curve of validity of DWS in prediction of AF among the studied cases.

Figure 2

Roc curve of validity of LVSI in prediction of AF among the studied cases.