

Significance of Left Atrial Electromechanical Function for Atrial Fibrillation Prediction after Cardiac Surgery

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ABSTRACT

Background: Postoperative atrial fibrillation (POAF) is the most important type of secondary AF. POAF is a complication in approximately one-third of patients undergoing cardiac surgery. The duration from P-wave onset on ECG to the peak of the A' lateral wave on tissue Doppler imaging (PA-TDI) provides a reliable estimation of total atrial conduction time.

Objective: To evaluate the efficacy of the PA-TDI duration for predicting post-operative atrial fibrillation in patients undergoing cardiac surgery.

Patients and methods: This prospective study was conducted at national heart institute for 70 patients who were eligible and planned for undergoing cardiac surgery. Patients were divided into 2 groups according to the presence of post-operative AF. Accordingly, patients in the study were divided into group (I) that included patients who developed POAF and group (II), which included patients who remained in sinus rhythm and did not develop POAF.

Results: PA-TDI duration in group I was longer than in group II with highly significant difference between the two groups with P-value < 0.001. It was found that PA-TDI duration (≥ 171.5 ms) has sensitivity equal to 91 and specificity 95%.

Conclusion: PA interval measured by TDI preoperatively seems to be a simple method to predict incidence of POAF in patients undergoing cardiac surgery and it may be part of preoperative cardiovascular examination. The current study suggests that longer PA-TDI duration to be additive to conventional risk factors and biomarkers in predicting POAF and that PA-TDI duration is a predictor of POAF, and the best cut off value of PA-TDI duration for POAF is 171.5 ms.

Keywords: Left atrial electromechanical function, Atrial fibrillation prediction, Cardiac surgery.

INTRODUCTION

An important type of secondary atrial fibrillation, known as new-onset atrial fibrillation (AF), is postoperative atrial fibrillation (POAF), which is defined as the emergence of AF shortly after surgery. Patients who experience POAF, which increases hospital costs, time in the intensive care unit (ICU), and length of stay all as a result of their cardiac surgery, are in the minority. The research has covered a wide range of mechanisms. In addition, numerous therapy options for prevention have been floated. Despite this, POAF is still common, and it's a problem⁽¹⁾. There is a lack of knowledge about the exact causes, predictors, and risk factors for POAF, however old age and various heart disorders that alter structural alterations and promote inflammation have been related to POAF repeatedly⁽²⁾.

Patient's with POAF require an average hospital stay and additional treatment costs of between ten thousand to twenty thousand dollars, roughly a day of longer ICU time, and an extra two to five days as inpatient. POAF has been linked to a higher risk of stroke, bleeding, cardiac death, renal or respiratory failure, infection, and a variety of neurological complications including the need for a permanent pacemaker. It has also been linked to an increased risk of death from any cause within the first month and six months, according to several studies⁽³⁾.

After mitral valve surgery (MVS), the probability of POAF was greater than after coronary artery bypass

grafting (CABG) or surgery. Clearly, postoperative POAF should be avoided and managed⁽⁴⁾. In order to identify high-risk patients before surgery and provide them with appropriate preventive regimens, several approaches have been evaluated for calculating the risk of developing POAF⁽⁵⁾. Several studies have found that measuring LA characteristics such the left atrium volume index (LAVI), total atrial conduction time (TACT), left atrial strain, and total atrial conduction time improves prediction of POAF significantly. Even while electrocardiography (ECG) theoretically has the ability to measure TACT, there are various other methods for doing so. TACT can be accurately estimated using the time elapsed between the start of the P-wave on the ECG and the peak of the A' lateral wave on tissue Doppler imaging (TDI; PA-TDI duration). The length of the PA-TDI has been linked to several types of AF and the frequency with which they reoccur⁽⁴⁾.

PATIENTS AND METHODS

This prospective cohort study was conducted at Cardiology Department, National Heart Institute for 70 patients who underwent open heart surgery. Patients were divided into 2 groups according to the presence of POAF. Accordingly, patients in the study were divided into: Group I that included patients who developed POAF and group II, which included patients who remained in sinus rhythm and did not develop POAF.



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Ethical approval:

Every participant signed an informed consent form and submitted them to Zagazig University' Research Ethics Committee, which approved the study (ZU-IRB#6214/29-1-2021). This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria: Patients aged group > 18 years. Patients undergoing elective cardiac surgery e.g. CABG, valve replacement or repair and ASD closure, and patients with sinus rhythm.

Exclusion criteria: Patients with chronic kidney disease (estimated glomerular filtration rate < 60 mL/min per 1.73 m²)⁽⁵⁾. Patients who developed myocardial infarction within two months prior to operation. Patients who underwent Previous cardiac surgery. Patients with overt heart failure, atrial fibrillation, frequent extra systoles or any uncontrolled arrhythmias, hypertension, Electrolyte's imbalance, and Patients with Pre-excitation syndromes.

All participants in this study were subjected to the following:

I. General examination: History of hypertension, smoking, dyslipidemia or COPD. The term paroxysmal AF refers to AF that ends within seven days of start, either spontaneously or with medical intervention, and which may recur with varying frequency and treatment history.

II. Cardiologic examination: By inspection, palpation, percussion and auscultation to detect signs of heart failure, arrhythmias and shock.

III. Routine laboratory investigations including: Complete blood count, glyated hemoglobin test (HbA1c), renal function tests, liver function tests, bleeding profile, arterial blood gases and serum electrolytes.

Electrocardiography:

Standard 12-lead ECG recordings were performed to all patients pre-operative to document sinus rhythm. Electrocardiograms were recorded using 12-channel equipment, at paper speed of 25mm/s and with 10 mm/mV standardization.

In the intensive care unit, patients were monitored continuously with electrocardiography (ECG) after surgery. Whenever tachycardia or an irregular pulse was detected, or patients complained of palpitations, further ECG recordings were made as a precautionary measure. There were no discernible P waves, and the heart's rhythm was described as abnormally irregular. After the

operation, POAF episodes lasting less than 30 seconds necessitated pharmacologic or electrical treatment.

Echocardiographic examination:

Evaluation of transthoracic echocardiography was performed to all patients on admission. A 2.5 MHz transducer on a commercially available echocardiographic system was used to record the echocardiograms. Just below the mitral valve leaflets, at the chordal level, two-dimensional guided M-Mode echocardiograms were recorded. The thicknesses of the septal and posterior walls, as well as the dimensions of the left ventricular chamber were evaluated in accordance with American Society of Echocardiography (ASE) recommendations.

LA parameters

LA diameter: LA diameters were measured at the end of systole in the para-sternal long axis view (antero-posterior).

LA Volume and LA Volume index: LA volume was estimated using the biplane area-length method where LA volume = (0.85 x Area4ch x Area2ch)/(Longest atrial length). The LA long axis dimension and area were measured in standard apical 2-chamber and apical 4-chamber views. Measured values were indexed to body surface area (BSA)⁽⁶⁾.

PWD was used to evaluate diastolic LV function. Two- and three-millimeter-sized sample volumes were placed in the inflow part of the LV, halfway between the mitral valve leaflet tips and Doppler investigations were recorded from the apical four-chamber view. Mitral velocity profiles were digitized from the modal velocity of the Doppler tracings. The peak E (early rapid ventricular filling) and peak A (atrial-assisted filling) wave velocities were computed to calculate the E/A velocity ratio. There are four basic Echocardiographic patterns of diastolic heart failure, which are graded I to IV⁽⁷⁾.

In order to obtain the Nyquist limit of 15–20 cm/s and use the least optimal gain, tissue Doppler imaging (TDI) was carried out at transducer frequencies of 3.5–4.0MHz. We used spectral pulsed Doppler for the apical 4-chamber view to quantify the early and late diastolic velocity of myocardium in the left ventricle. To establish the PA-TDI interval, researchers took three cardiac cycles to measure and average the time between the initiation of the P-wave (lead II) and a' wave's peak on the LA lateral wall tissue Doppler tracing as shown in figure (1)⁽⁸⁾.

Postoperative follow up included hemodynamics, fluid balance, laboratory results and ECG rhythm during ICU stay.



Figure (1): PA-TDI measurement ⁽⁹⁾.

Statistical analysis

Microsoft Excel was used to code, enter, and analyse data gathered from historical sources, basic clinical examinations, laboratory investigations, and outcome measurements. To conduct the study, the data were imported into SPSS version 20.0 (Statistical Package for the Social Sciences). The following tests were employed to determine whether differences were statistically significant based on the type of data, which was either qualitative or quantitative. The Chi-square test was used to compare the differences in frequencies (qualitative variables) and percentages among groups. While, t test and Kappa agreement to test agreement between parametric quantitative independent groups. Logistic regression was used to account for multiple independent variables. P value ≤ 0.05 was considered significant.

RESULTS

Table (1) showed that as regards age, there was statistical difference between both groups where mean age in POAF group was 51.00 ± 11.67 compared to 42.64 ± 13.04 in -ve POAF group ($p = 0.015$). Regarding BMI, there was no statistical difference between both groups where mean BMI in POAF group was 21.90 ± 2.80 compared to 21.02 ± 2.38 in -ve POAF group ($p = 0.190$). As regards gender, there was no statistical difference between both groups ($p = 0.22$) where the number of males in POAF group was 14 patients (70 %) compared to 27 patients (54%) in -ve POAF group and the number of females in POAF group was (6 patients 30 %) compared to 23 patients (46%) in -ve POAF group. As regards smoking, there was no statistical difference between both groups ($p = 0.26$) where number of smokers in POAF group was 6 patients (30 %) compared to 18 patients (36 %) in -ve POAF group. As regards to DM, there was no statistical difference between both groups ($p = 0.67$) where number of diabetic patients in POAF group was 5 patients (25%) compared to 15 patients (30 %) in -ve POAF group. As regards to COPD, there was no

statistical difference between both groups ($p = 0.78$) where number of COPD patients in POAF group was 2 patients (10%) compared 4 patients (8%) in -ve POAF group. As regards hyperlipidemia, there was no statistical difference between both groups ($p = 0.76$) where number of patients in POAF group was 12 patients (60%) compared to 28 patients (56%) in -ve POAF group.

Table (2) showed that regarding operation type, there was no statistical difference between both groups ($p = 0.44$).

Table (3) showed that regarding post-operative complications, there was statistical difference between both groups ($p = 0.01$) where number of patients with complications in POAF group was 17 patients (85%) compared to 6 patients (12%).

Table (4) showed that concerning P wave duration, there was no statistical difference between both groups ($p = 0.131$) where P wave duration in POAF was 113.98 ± 14.36 ms compared to 112.76 ± 13.62 ms in -ve POAF group. As regards p wave dispersion, there was no statistical difference between both groups ($p = 0.213$) where P wave dispersion in POAF was 63.6 ± 15.23 ms compared to 61.51 ± 12.66 ms in -ve POAF group. As regards LAV, there was statistical difference between both groups ($p = 0.001$) where LAV in POAF group was 65.21 ± 18.73 compared to 51.23 ± 7.56 in -ve POAF group. Regarding LAVI, there was statistical difference between both groups ($p = 0.004$) where LAVI in POAF group was 43.25 ± 12.36 compared to 31.63 ± 10.36 in -ve POAF group.

Table (5) showed that regarding PA_TDI duration, there was high statistical difference between both groups ($p < 0.001$) where PA_TDI duration in POAF group was 204.85 ± 26.88 compared to 149.44 ± 24.06 in -ve POAF group.

(Table 6 & figure 2) showed that PA_TDI duration at cut off value >171.5 ms can predict occurrence of POAF after cardiac surgery with sensitivity of 91% and specificity of 95% (AUC = 0.964, P value < 0.001 , 95% CI between 0.918 to 1.000).

Table (1): Demographic data distribution between studied groups

			-VE PO AF (n = 50)	+VE PO AF (n = 20)	t/ X ²	P
Age (years)			42.64 ± 13.04	51.00 ± 11.67	2.493	0.015*
BMI (kg/m²)			21.02 ± 2.38	21.90 ± 2.80	1.325	0.190
Sex	Female	N	23	6		
		%	46.0%	30.0%		
	Male	N	27	14	1.50	0.22
		%	54.0%	70.0%		
Smoking	No	N	32	14		
		%	64.0%	70.0%		
	Yes	N	18	6	2.65	0.26
		%	36.0%	30.0%		
DM	No	N	35	15		
		%	70.0%	75.0%		
	Yes	N	15	5	0.17	0.67
		%	30.0%	25.0%		
COPD	No	N	46	18		
		%	92.0%	90.0%	0.07	0.78
	Yes	N	4	2		
		%	8.0%	10.0%		
Hyperlipidemia	No	N	22	8		
		%	44.0%	40.0%	0.09	0.76
	Yes	N	28	12		
		%	56.0%	60.0%		
Total			N	50	20	
			%	100.0%	100.0%	

Table (2): Operation type distribution between studied groups

			PO_AF		X ²	P	
			-VE	+VE			
Type of operation	ASD closure	N	4	1			
		%	8.0%	5.0%			
	AVR	N	8	4			
		%	16.0%	20.0%			
	CABG	N	16	6			
		%	32.0%	30.0%			
	DVR	N	5	0			
		%	10.0%	0.0%			
	DVR & T repair	N	1	3	7.84	0.44	
		%	2.0%	15.0%			
	MV Repair	N	13	5			
		%	26.0%	25.0%			
	MVR&T repair	N	2	1			
		%	4.0%	5.0%			
	OZAKI AVR	N	1	0			
		%	2.0%	0.0%			
	Total			N	50	20	
				%	100.0%	100.0%	

ASD: atrial septal defect, AVR: aortic valve replacement, CABG: coronary artery bypass graft, DVR: double valve replacement, T repair: tricuspid repair, MV: mitral valve, MVR: mitral valve replacement

Table (3): Complication distribution between studied groups

			PO_AF		X ²	P
			-VE	+VE		
Complication	No	N	44	3		
		%	88.05%	15.0%		
	Bleeding	N	1	2		
		%	8.0%	10.0%		
	Cardiogenic shock	N	2	4		
		%	4.0%	20.0%		
	Respiratory failure	N	0	2	16.79	0.01*
		%	32.0%	10.0%		
	Stroke	N	0	3		
		%	10.0%	15.0%		
	Acute kidney injury	N	2	5		
		%	26.0%	25.0%		
	Pneumothorax	N	1	1		
		%	2.0%	5.0%		
Total		N	50	20		
		%	100.0%	100.0%		

Table (4): ECG and ECHO data distribution between studied groups

	-VE PO AF	+VE PO AF	t	P
P wave duration (ms)	112.76±13.62	113.98±14.36	1.524	0.131
P wave dispersion (ms)	61.51±12.66	63.6±15.23	1.325	0.213
EF (%)	61.22±8.25	62.60±6.62	0.665	0.508
LVIDd (cm)	5.26±0.80	5.19±0.55	0.355	0.723
LVIDs (cm)	3.45±0.66	3.32±0.57	0.818	0.416
EDV (ml)	136.24±36.52	135.05±32.27	0.127	0.899
ESV (ml)	52.78±18.88	50.70±17.97	0.406	0.686
LA Diameter (cm)	4.12±0.56	4.38±0.73	1.547	0.127
LAV (ml)	51.23±7.56	65.21±18.73	3.421	0.001**
LAVI	31.63±10.36	43.25±12.36	3.255	0.004*
E/e'	12.36±4.23	11.58±3.66	1.258	0.213
Mitral E velocity (cm/s)	0.93±0.36	1.10±0.39	1.313	0.194
Mitral A velocity (cm/s)	0.97±0.31	1.07±0.34	0.810	0.421
E/A	1.04±0.29	1.13±0.33	0.800	0.427
DT (ms)	296.64±97.63	357.95±115.9	1.493	0.140

EF: ejection fraction, LVIDd: left ventricular internal dimension(diastole), LVIDs: left ventricular internal dimension(systole) ,EDV : end diastolic volume, ESV : end systolic volume, LA: left atrium , LAV: left atrial volume, LAVI: left atrial volume index, DT: deceleration time

Table (5): PA_TDI distribution between studied groups

	-VE	+VE	t	P
PA_TDI (ms)	149.44 ± 24.06	204.85 ± 26.88	8.416	0.00**

PA_TDI duration: time interval from P-wave onset on ECG to the peak of the A' lateral wave on tissue Doppler imaging

Table (6): AUC cutoff and validity

Area	Cutoff	P	95% Confidence Interval		Sensitivity	Specificity
			Lower Bound	Upper Bound		
0.964	> 171.5	0.00**	0.918	1.000	91.0%	95.0%

AUC: area under the curve, CI: confidence interval

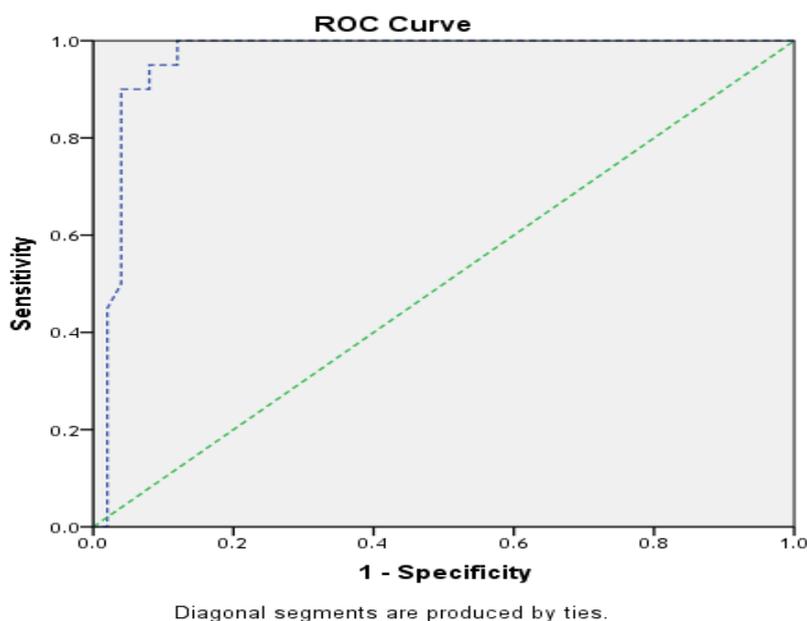


Figure (2): ROC Curve of PA_TDI cutoff and validity

DISCUSSION

Despite POAF was thought to be transient and self-limiting, it is appreciated as a risk factor for stroke and mortality⁽¹⁰⁾. POAF is the most common postoperative complication following cardiac surgical procedures and occurs in 25% after isolated CABG, 30% after isolated valvular procedures and 40–50% following combination CABG/valvular operations. Notably, the incidence of POAF has remained largely unchanged despite contemporaneous improvements in cardiac surgery-associated morbidity and mortality⁽¹¹⁾.

By evaluating left atrium-related variables such as the left atrial volume index (LAVI) and total atrial conduction time (TACT), echocardiographic examinations have recently achieved significantly better prediction of POAF. Although, there are numerous ways to evaluate TACT, the time gap between the onset of the P-wave on the electrocardiogram (ECG) and the peak of the A' lateral wave on TDI (PA-TDI duration) gives a valid estimate of TACT, and the PA-TDI duration has been linked to new-onset AF. A previous study revealed that the PA-TDI duration was predictive of AF in patients undergoing off- pump CABG⁽¹²⁾.

Regarding age, there was statistical difference between both groups where mean age in POAF group was 51.00 ± 11.67 compared to 42.64 ± 13.04 years in non-POAF group (p = 0.015). This can be explained by loss of myocardial fibers, increased fibrosis and collagen deposition in the atria related to ageing process, which change the electrical properties of the atrium. Our finding

is in agreement with **Takahashi et al.**⁽¹³⁾ study, which enrolled patients undergoing mitral valve surgery and monitored them for POAF and divided patients into two groups; NO-POAF group and POAF group, there was significant difference between the mean age in the two groups (59.4 ± 16.6 in NO-POAF group vs 65.8 ± 11.3 years in the POAF group with P-value=0.05)⁽²¹⁾.

As regards BMI, sex, smoking, diabetes mellitus, COPD and hyperlipidemia, there was no statistical difference between both groups. This agrees with **Takahashi et al.**⁽¹³⁾, and **Haffajee et al.**⁽¹⁴⁾ studies, and disagrees with **Mariscalco et al.**⁽¹⁵⁾ study, which included 17622 patient who were planned for cardiac surgery (CABG or valve surgery), 8.4% of patients in the POAF group had chronic pulmonary disease and 5.2% of patients in the sinus group with (p- value <0.001)⁽¹⁵⁾. This difference may be due to small sample size in our study.

Regarding operation type, there was no statistical difference between both groups. Our finding agrees with **Haffajee et al.**⁽¹⁴⁾ study.

Regarding post-operative complications, there was statistical difference between both groups (p=0.01). Post-operative bleeding was risk factor for POAF. This can be explained by that bleeding is associated with anemia and need for blood transfusion both can trigger POAF. Post-operative cardiogenic shock was risk factor for POAF. This can be explained by hemodynamic instability, activation of neuro-hormonal mechanisms and need for inotropic support that can trigger POAF.

Post-operative respiratory failure was risk factor for POAF. This can be explained by hypoxia and high inflammatory mediators due to chest infection that can trigger POAF. Post-operative acute kidney injury was risk factor for POAF, which may be due to electrolyte disturbances that increase incidence of POAF. This agrees with **Mariscalco et al.** ⁽¹⁵⁾ and **Gorczyca et al.** ⁽¹⁶⁾.

Regarding P-wave duration, there was no significant difference between both groups (113.98 ± 14.36 ms in POAF group vs 112.76 ± 13.62 ms in sinus group with p-value =0.131). Abnormal P wave duration could be predictor for POAF as it reflects abnormality of LA size, interatrial conduction defect and LA structural abnormalities. These findings agree with **Takahashi et al.** ⁽¹³⁾ study where P-wave duration on surface ECG was not statistically different between the POAF and NO-POAF groups (118.8 ± 12.6 & 115.6 ± 15.1 with P-value=0.3295), and also agree with **Fujiwara et al.** ⁽¹⁷⁾ study where p wave duration was not statistically different between POAF group and sinus group (114.9 ± 13.3 & 112.2 ± 11.0 ms with p value=0.29). While, our results disagree with **Takahashi et al.** ⁽¹⁸⁾ study which reported that there was statistical difference between both groups regarding p-wave duration where POAF group has a mean p-wave duration 119.6 ± 13.8 and patients with no-POAF 108.7 ± 11.8 with p-value 0.0027. This difference may be due to inclusion of patients undergoing aortic valve surgery only. Regarding p wave dispersion, there is no significant difference between both groups (63.6 ± 15.23 ms in POAF group vs 61.51 ± 12.66 ms in sinus group with p-value = 0.213). Additionally, our findings disagree with **Lazzeroni et al.** ⁽¹⁹⁾ study, which enrolled 200 patients undergoing cardiac surgery and follow up post-operative to examine the role of p wave dispersion to predict occurrence of POAF, this study reported that there was statistical difference between POAF group and sinus group regarding p wave dispersion (79 ± 20 ms in POAF group vs 57 ± 20 ms in sinus group with p value < 0.001) ⁽¹⁸⁾. This difference may be due to small sample size of our study.

Regarding ECHO data, there was no statistical difference between both groups, except for left atrial volume (LAV) and left atrial volume index (LAVI) where there was statistical difference between both groups (p = 0.001) and (p = 0.004) respectively. This can be explained by elevated left atrial volume and pressure that may lead to fibrosis and electrical remodeling in the atrium, providing a substrate for the development of AF. Our finding agrees with **Fujiwara et al.** ⁽¹⁷⁾ study where LA volume and LAVI were greater in patients with POAF than in those without POAF (64.6 ± 26.1 vs. 51.2 ± 17.6 ml, P=0.006 and 41.1 ± 16.4 vs. 31.8 ± 10.6 ml/m², P=0.005). Also, agrees with **Takahashi et al.** ⁽¹⁸⁾ study, which reported that there was statistical difference between POAF group and sinus group regarding LAV (74.9 ± 21.8 ml vs 63.6 ± 19.5 ml, p- value = 0.047) and LAVI (51.0 ± 16.8 ml/m² VS 42.6 ± 12.3 ml/m², p-value = 0.043).

Regarding PA_TDI duration, there was high statistical difference between both groups where mean PA-TDI in POAF group was 204.85 ± 26.88 ms vs 149.44 ± 24.06 ms in sinus group (p < 0.001). This can be explained by increase PA-TDI duration reflects structural atrial changes that retard transmission of intra- and interatrial electrical impulse and might be due to diastolic dysfunction ⁽²⁰⁾. Our finding agrees with **Fujiwara et al.** ⁽¹⁷⁾ study, which reported that there was statistical difference between both groups regarding PA-TDI duration (156.3 ± 19.5 ms in POAF group vs. 128.2 ± 15.0 ms in sinus group, P < 0.0001). In addition, our finding is in agreement with **Müller et al.** ⁽²¹⁾ study, which revealed that patients with POAF after cardiac surgery during the first 10 days had a significantly longer PA-TDI interval at pre-operative assessment compared to patients who remained in sinus rhythm (152.1 ± 3.0 & 120.8 ± 1.8 milliseconds respectively with P < 0.001). The difference in optimal PA-TDI cut-off may be explained by changes in the size of the LA. Therefore, the optimal cut-off should be evaluated separately ⁽²¹⁾.

According to our study with the guidance of the receiver-operator characteristic (ROC) curve, it was found that PA-TDI duration >171.5 ms can predict occurrence of POAF after cardiac surgery with sensitivity of 91% and specificity of 95%. This result was relatively concordant with **Takahashi et al.** ⁽¹³⁾ study where the optimal P-A' interval duration was 159.4 ms with sensitivity of 55.8% and specificity of 84.6%. Also, according to **Müller et al.** ⁽²¹⁾ study at the cut-off value of P-ATDI duration was 133 ms with sensitivity and specificity related to POAF were 100% and 86%, respectively.

CONCLUSION

In conclusion, PA interval measured by TDI preoperatively seems to be a simple method to predict incidence of POAF in patients undergoing cardiac surgery and it may be part of preoperative cardiovascular examination. The current study suggests that longer PA-TDI duration to be additive to conventional risk factors and biomarkers in predicting POAF and that PA-TDI duration is a predictor of POAF and the best cut off value of PA-TDI duration for POAF is 171.5 ms. PA interval is a parameter, which could be measured during routine echocardiographic study using tissue Doppler that does not require any additional expense and it is readily available and easily done marker. Consequently, it can help to simply identify individuals at high risk for PAOF who might need a more aggressive prophylactic and therapeutic approach and closer clinical follow up.

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