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ORIGINAL ARTICLE

Atrial Electro-Mechanical Asynchrony as A Predictor of Cerebrovascular Stroke in Patients with Sinus Rhythm And Normal Left Ventricular Systolic Function

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ABSTRACT

Background: Stroke is the second leading cause of death worldwide. Recently, atrial cardiopathy has become recognized as a substantial risk factor for cerebrovascular stroke. Greater LA size is linked to stroke in AF patients, but few data linking LA size to stroke in population with sinus rhythm.

Aim: To investigate the value of total atrial conduction time (TACT) measured non-invasively by assessing PA-TDI duration as a predictor of stroke in patients who initially presented with sinus rhythm and have normal LV systolic function.

Patients and methods: In our case-control study, we studied patients were admitted to Zagazig university hospital with acute ischemic stroke. It included 156 patients with acute ischemic stroke and 50 control subjects all presented in sinus rhythm and normal LV systolic function. All participants underwent echocardiography. The bi-plane modified Simpson's approach was used to determine the left ventricular ejection fraction. The left atrial (LA) diameter was measured also left atrial volume index (LAVI) was assessed and indexed for body surface area using. The PA-TDI interval was used to estimate the TACT. The average of the measurements made at the septal and lateral annuli was taken into account.

Results: There was no statistically significant difference between both groups regarding LA diameter (p: 0.3), LA volume index was larger in the stroke group (39.24±4 versus 33.6±2.8, p: 0.01), PA-TDI duration showed statistical highly significant difference between both groups (165.94±21.695 versus 99.4±22.960, p: <0.001). ROC curve showed the best cutoff point for LA volume index is >42.2 ml/m^2 for prediction of stroke with area under the curve: 0.7, 52.8 % sensitivity, 80.8% specificity, p value is 0.005. ROC curve showed the best cutoff point for PA-TDI is >155.5 ms for prediction of stroke with area under the curve: 0.9, 70 % sensitivity, 78% specificity, p value: <0.001. Using multivariate logistic regression analysis showed that hypertension, LA volume index and PA-TDI duration are independent predictors of stroke (p: < 0.05, < 0.05, and < 0.001 respectively).

Conclusion: The assessment of electromechanical asynchrony by measuring the PA-TDI duration on echocardiography in population with sinus rhythm and normal systolic function may help to predict patients at risk for stroke. We also advise patients who exceed the cutoff points of LA volume index and PA-TDI duration to receive antithrombotic therapy for better stroke prevention.

Keywords: Atrial asynchrony, Cerebrovascular stroke, Sinus rhythm.

INTRODUCTION

The second most common cause of death worldwide is stroke [1]. Additionally, stroke survivors frequently have significant impairment, which leads to an increased demand on medical and social services [2]. Finding out more reliable methods for stroke risk stratification will decrease the stroke burden on patients and economy. Recent research has shown that atrial cardiopathy is a substantial risk factor for stroke [3].

Especially in the elderly, an enlarged left atrium (LA) increases the risk of cardiovascular

problems like heart failure, atrial fibrillation (AF), and stroke [4]. There is strong evidence connecting ischemic stroke and AF; most of those patients develop strokes have been seen in people who at first glance looked to be in sinus rhythm. Therefore, it has been hypothesized that larger LAs are related to stroke in older persons with sinus rhythm [5].

Atrial electromechanical asynchrony or delay can be measured using the total atrial conduction time (TACT) obtained from echocardiography, a marker of atrial remodeling that reflects both morphological (atrial size) and electrical (conduction velocity) features [6].

Total atrial conduction time (TACT) is measured during sinus rhythm as the time interval from the beginning of the P-wave on the surface electrocardiogram (ECG) to the peak A' -wave on the Tissue-Doppler Imaging (TDI) tracing of the lateral left atrial (LA) wall on echocardiography (PA-TDI duration) [7]. The length of time required for the atrial depolarization to travel from the sinus node via the atrial tissue to the LA lateral wall and cause an active contraction is known as the PA-TDI duration. Measuring the PA-TDI length provides a more detailed assessment of the degree of atrial remodeling than other measurements [8]. TACT is a well-researched echocardiographic measure in AF patients, but not in populations with sinus rhythm.

In order to improve the accuracy of stroke prediction, we hypothesized that the TACT, a metric for atrial cardiopathy, would be useful. This study's goal was to determine whether TACT could be used to predict stroke in patients who originally displayed sinus rhythm and normal LV systolic function.

PATIENTS AND METHODS.

In our case-control study, we studied patients were admitted to Zagazig university hospital with acute ischemic stroke. It included 156 patients with acute ischemic stroke and 50 control subjects.

Informed consent and ethics committee/IRB approval:

The study was approved by the research ethics council of the faculty of medicine at Zagazig University under "ZU-IRB #9215" and all participants supplied written informed permission (stroke patients with significant handicap were excluded from the study). This study adhered to the Declaration of Helsinki, a guideline of ethics for medical research involving human subjects.

Inclusion criteria:

Acute ischemic stroke was defined according to the diagnostic criteria set by the World Health Organization as a sudden onset of clinical symptoms and signs (focal or global) of changes in cerebral function that continue longer than 24 hours and have no obvious explanation other than vascular origin. Also patients with early or recent imaging signals of cerebral infarction on computed tomography (CT) or magnetic resonance imaging (MRI) [9]. All of the included patients and control subjects had sinus rhythm and normal systolic function.

Exclusion criteria:

Patients with CT scan findings of intracerebral hemorrhage, subarachnoid hemorrhage, head injury or surgery, with brain tumors or other systemic malignancies, with CNS infections or systemic sepsis, with metabolic disorders or systems failure, with LV ejection fraction <50%, Known AF, History of previous MI or CABG or PCI or coronary artery disease or pathological Q wave on ECG, also patients with severe disability from stroke were not included in the study.

All patients were subjected to the following:

History taking with special interest on age, smoking, hypertension and diabetes mellitus. Clinical examination was performed including measurements of vital signs and local cardiac examination. Blood samples for complete blood count and lipid profile were collected on admission. Twelve lead surface ECG confirming sinus rhythm was done on admission. All patients had trans-thoracic echocardiography using the Vivid 9 machine from GE Healthcare in Chicago, Illinois, the United States. Under the supervision of experienced cardiologists who were certified by the European Association of Cardiovascular Imaging in adult transthoracic echocardiography, all patients underwent two-dimensional transthoracic echocardiography, and echocardiographic parameters were assessed in agreement with the American Society of Echocardiography's guidelines [10]. The bi-plane modified Simpson's approach was used to determine the left ventricular ejection fraction. The left atrial (LA) diameter was measured in the parasternal long axis view at the end of systole. The biplane area-length method was utilized to determine the left atrial volume index (LAVI) using apical 4- and 2-chamber images. Before the mitral valve opened at the end of systole, measurements were made in the frame and indexed for body surface area [11]. The PA-TDI interval

was used to estimate the TACT. Every patient had this measured twice, and the mean value was computed. In the apical four-chamber view, the pulsed-wave tissue Doppler sample was positioned on the lateral and septal walls of the LA above the mitral annulus. The time between the onset of the P wave (lead II) and the peak of the A' wave was called the PA-TDI interval [12]. The average of the measurements made at the septal and lateral annuli was taken into account (Figure 1).

Statistical Analysis

Data was analyzed using SPSS 20 (Statistical Package for the Social Services) (SPSS). The findings were displayed using both tabular and graphical formats. Results were displayed using standard statistical measures such as means, medians, standard deviations, and confidence intervals. The accuracy of the data was demonstrated with the help of statistics. When assessing data involving quantitative independent variables, the student's t test (T) is utilized. Pearson Chi-Square test was used to analyze the qualitative data (X2). Receiver- operating characteristics (ROC) curve was performed to assess the cut-off point of PA-TDI duration. P value of 0.05 or less was judged statistically significant.

RESULTS

Except for hypertension, there was no statistically significant difference between the studied groups regarding demographic and clinical characteristics (Table 1). In stroke group, 104 (66.7) patients had hypertension but in the control group, 12 (24%) patients had hypertension (p: 0.03). There was no significant difference between both groups regarding LA diameter (39.82±4.773 versus 38.10±2.717, p: 0.3), but LA volume index was statistically higher in the stroke group (39.24±4 versus 33.6±2.8, p: 0.01), PA-TDI duration showed statistically highly significant difference between both groups (165.94±21.695 versus 99.4±22.960, p: <0.001). (Table 2). There was significant positive correlation between PA-TDI duration and LA volume index (r: 0.5, p: 0.001) (Figure 2). ROC curve showed the best cutoff point for LA volume index is >42.2 ml/m^2 for prediction of stroke with area under the curve: 0.7, 52.8 % sensitivity, 80.8% specificity, p value is 0.005 (Figure 3). ROC curve showed the best cutoff point for PA-TDI is >155.5 ms for prediction of stroke with area under the curve: 0.9, 70 % sensitivity, 78% specificity, p value: <0.001 (Figure 4). Using multivariate logistic regression analysis, table (4) demonstrates that among all variables, hypertension, LA volume index and PA-TDI duration are independent predictors of stroke (p: < 0.05, < 0.05, and < 0.001 respectively).

Table 1: Table (1): Demographic and clinical characteristics of the studied groups.

	Stroke group (N.: 156)	Control group (N.: 50)	p-value
Age	62.79± 8.525	63.16±8.457	0.25
Male sex	96 (61.5%)	25 (50%)	0.12
Hypertension	104 (66.7%)	12 (24%)	0.03*
Diabetes mellitus	72 (46.2%)	25 (50%)	0.142
Platelet count (x103)	267.90±67.882	251.72±96.735	0.155
Serum total cholesterol (mg/dl)	206.12±32.136	212.20±46.786	0.302
Serum triglycerides (mg/dl)	128.51±30.691	130.40±36.149	0.42

Table (2): Description of the echocardiographic characteristics in the studied groups.

	Stroke group (N.: 156)	Control group (N.: 50)	p-value
LA diameter (mm)	39.82±4.773	38.10±2.717	0.3
LA volume index (mL/m2)	39.24±4	33.6±2.8	0.01*
PA-TDI duration (ms)	165.94±21.695	99.4±22.960	<0.001*

Table (3): Multivariate logistic regression analysis for factors predictive of stroke.

Variable	B	SE	p-value	Odds	95% CL	
Age	0.01	0.022	> 0.05	1.01	0.96	1.05
Sex	- 0.17	0.38	> 0.05	0.84	0.39	1.7
HTN	-1.08	0.39	< 0.05	0.33	0.15	0.73
DM	- 0.23	0.38	> 0.05	0.78	0.37	1.6
Smoking	- 0.13	0.38	> 0.05	0.87	0.41	1.85
Dyslipidemia	- 0.55	0.38	> 0.05	0.57	0.26	1.23
LA diameter	0.028	0.04	> 0.05	1.02	0.95	1.11
LA volume index	-1.1	0.42	< 0.05	0.35	0.21	0.8
PA-TDI duration	0.14	0.045	< 0.001	1.16	1.06	1.26

B: Regression coefficient, SE: Standard error, CL: Confidence interval.

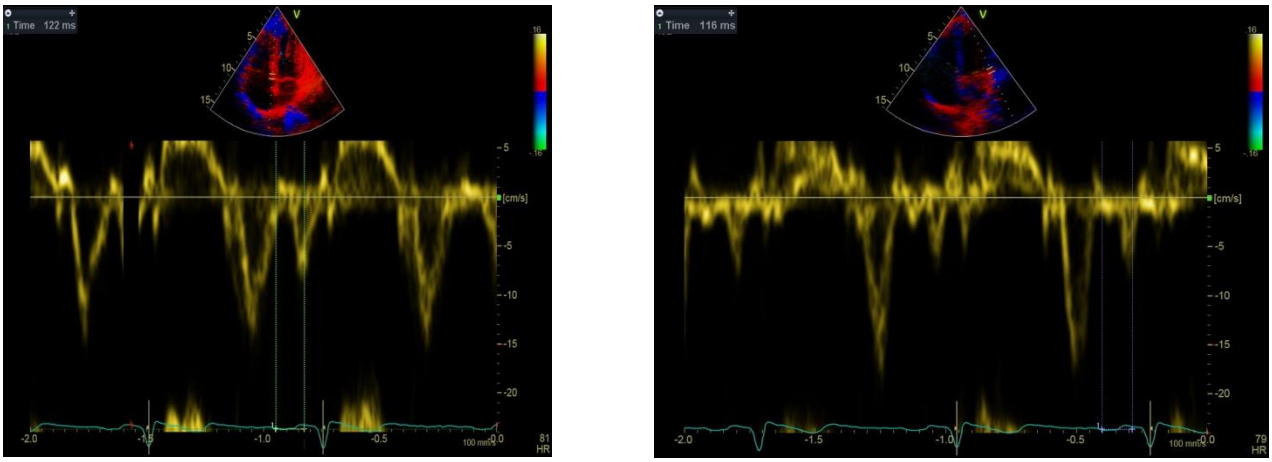

Figure (1): Example of measuring PA-TDI duration on tissue Doppler imaging, the time between the onset of the P wave (lead II) and the peak of the A' wave was measured at the septal and lateral annuli. The average of the two measurements was taken into account.

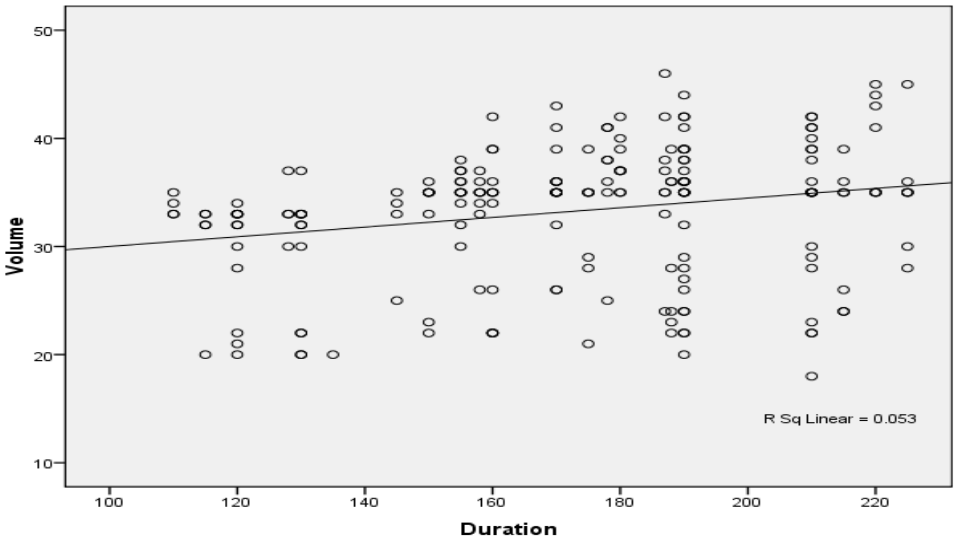

Figure (2): Correlation between PA-TDI duration and LA volume index.

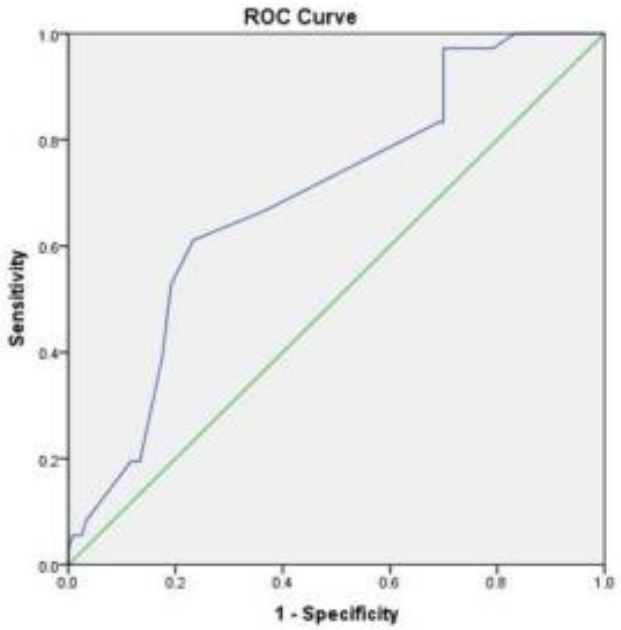

Figure (3): ROC curve to determine the predictive value of LA volume index. ROC curve showed the best cutoff point for LA volume index is >42.2 ml/m2 for prediction of stroke with area under the curve: 0.7, 52.8 % sensitivity, 80.8% specificity, p value is 0.005.

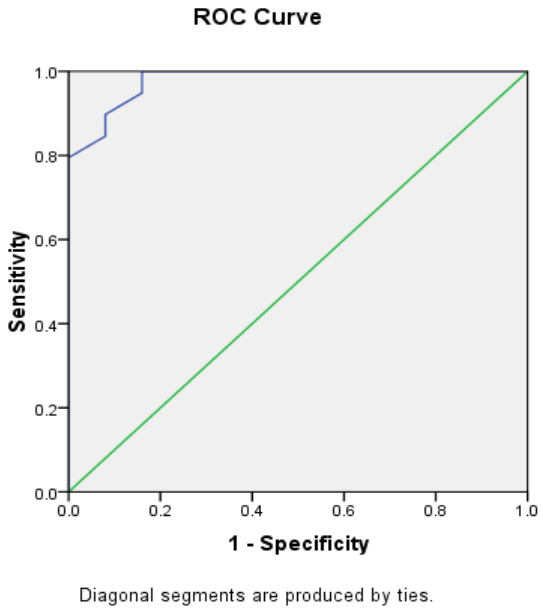

Figure (4): ROC curve to determine the predictive value of PA-TDI duration. ROC curve showed the best cutoff point for PA-TDI is >155.5 ms for prediction of stroke with area under the curve: 0.9, 70 % sensitivity, 78% specificity, p value: <0.001.

DISCUSSION

Ischemic stroke has been linked to several indications of aberrant atrial structure and function outside of AF. The relationship between increased left atrial volume and embolic stroke of unknown source (ESUS), despite a hallmark of atrial cardiopathy, is still up for debate because of conflicting findings from earlier research [13]. The CHA2DS2-VASc score and other stroke risk stratification models for people with atrial fibrillation (AF) are designed to be simple and helpful, but they do not take into account echocardiographic, biochemical, or coagulation parameters that may be related to blood stasis in the left atrium and LA appendage resulting in thromboembolization [14]. Instead, they rely on upstream clinical factors like age, sex, and diabetes mellitus. Few people, particularly those with sinus rhythm, who are classified by these criteria as being at low risk and who are not given anticoagulation may still get a stroke, indicating that we need for enhanced risk classification that goes beyond clinical characteristics alone.

The aim of the current study was to find new echocardiographic indicators of LA electromechanical remodeling that may improve risk assessment, particularly in sinus rhythm and normal LV systolic function, for the identification of stroke risk factors who might benefit from systemic anticoagulation.

But why LA enlargement is linked to stroke in patients presented in sinus rhythm? Firstly, higher LA volume may be associated with bouts of subclinical AF. The other explanation is that bigger LA could also be an adaption to endothelial dysfunction that is affecting the vascular bed. Abnormal reactivity to certain cytokines, including nitric oxide, angiotensin II, plasminogen inhibitor I, thrombomodulin, and endothelin can lead to endothelial dysfunction [15]. Abnormal regulation of angiotensin II and its receptor promote thrombogenicity, fibrosis, atrial dilatation and thromboembolism by interfering with the electrical coupling of the atria [16].

By measuring the size and function of the LA, atrial remodeling is frequently quantified using echocardiography [17]. However, compared to three-dimensional imaging techniques like MRI or CT, traditional 2D echocardiography is less accurate at measuring LA size because LA frequently has an asymmetrical geometry [18]. This limits the clinical relevance of volumetric measurements acquired from echocardiography, such as LA size and function, to forecast the outcome of AF. As a result, LA size and function have not consistently shown to predict AF- outcomes than PA-TDI interval [19].

Total atrial conduction time (TACT), measured as the PA-TDI interval (the time between the beginning of the P wave and the peak of the A' wave), correlates with the degree of atrial fibrosis and predict the emergence of postoperative AF following cardiac surgery [20] as well as shows better predictive value for stroke in AF patients, independent of the CHA2DS2-VASc score [21]. Because it incorporates both the electrical and morphological aspects of atrial remodeling, PA-TDI duration has an advantage over other metrics in that it offers a more thorough assessment of atrial remodeling [22].

In comparison to 2D echocardiography and strain analyses, the TDI-tracings feature a high temporal resolution and angle-independent measurement of PA-TDI duration. Additionally, the PA-TDI interval has a low intra- and inter-observer variability and may be assessed directly on the echo machine without the need for time-consuming offline post-processing.

Our study found no statistically significant difference in LA diameter between the two groups (39.82±4.773 versus 38.10±2.717, p: 0.3), but that the LA volume index was statistically significantly higher in the stroke group (39.24±4 versus 33.6±2.8, p: 0.01), which was in agreement with Walter P et al.'s [23] findings that LA volume is preferable to LA diameter and should be used regularly in clinical assessment of LA size. The stroke group's PA-TDI duration was noticeably longer (165.94±21.695 versus 99.4±22.960, p: <0.001). This was in line with the findings of den Uijl et al 2011 [7], who demonstrated that PA-TDI, a measure of atrial remodeling, more accurately predicted AF recurrence following catheter ablation. In a prospective analysis of 279 anticoagulant-naive individuals who had no recurrences of AF after catheter ablation, atrial electromechanical delay as determined by the PA-TDI has been linked to higher stroke risks. In this investigation, the PA-TDI duration also improved the CHA2DS2-VASc score's ability to predict outcomes [24].

Our research indicates that PA-TDI >155.5 ms and LA volume index >42.2 ml/m2 can both serve as accurate predictors of stroke (p values: 0.005, < 0.001 respectively). This is consistent with the findings of Sieweke et al., 2020, who discovered that even in the absence of a prior history of AF or

stroke, patients with a PA-TDI greater than 161.43 ms had significantly higher stroke risk on 2 years' follow-up [25].

Our multivariate logistic regression model revealed that hypertension, LA volume index, and length of PA-TDI are independent predictors of stroke (p: 0.05, 0.05, and 0.001 respectively). This was in agreement with Fatema et al., 2008, who noted that 75% of people experiencing their first ischemic stroke have higher LAVI levels [26].

Our study's key finding, which concurs with Nattel et al. (2008), was that patients with stroke had longer PA-TDI while having normal LV function in a sinus rhythm population. This discovery can be explained by the fact that atrial fibrosis reduces the atrial compliance during the LA reservoir phase, which leads to blood stagnation in the LA and its appendage and resulting stroke [27].

According to Srivastava et al. (2005), the PA-TDI obtained at the septal mitral valve ring was even more effective at predicting AF than the lateral derived PA-TDI. Technically speaking, it is simpler and less impacted [28]. The mean PA-TDI duration recorded at the lateral and septal annuli was employed in the current study.

Study limitations

Although the study was limited by the inter- and intra-observer variability of the measured parameter, measurements were made twice for each patient, and the mean value was then computed and monitored by skilled cardiologists who were certified by the European Association of Cardiovascular Imaging. Lack of continuous holter ECG monitoring to identify concealed subclinical AF was another drawback. The study's single centre design and small sample size were further drawbacks. This thesis should be further investigated in larger prospective trials with continuous rhythm monitoring and including LA reservoir strain parameter in the research approach in order to evaluate the utility of TACT as a potential risk index.

CONCLUSION

In populations with sinus rhythm and normal systolic function, the assessment of electromechanical asynchrony by measuring the PA-TDI duration on echocardiography may aid to detect patients at risk for stroke and so may benefit from anticoagulant medication. For better stroke risk classification in populations with sinus rhythm, we advise including this measure in the CHA2DS2-VASc risk score. We also advise patients who exceed the cutoff points of LA volume index and PA-TDI duration to receive antithrombotic therapy for better stroke prevention.

The authors report no conflicts of interest.

All authors have approved the final article should be true and included in the disclosure.

(5) Conflict of Interest: No conflict of interest to disclose.

(6) Financial Disclosures: No financial interests to disclose.

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