Are left atrial abnormalities a risk for stroke?

Amanj J. Khidhir, *DM, FICMS (Neuro),* ***Ehsan K. Al-Shimmery,*** *FICMS (Neuro), DCN,*
Mohammed H. Alwan, *FICMS (Gen Med), FICMS (Cardiol).*

ABSTRACT

الأهداف: تقييم دور مخطط القلب الصدوي (Echo–LAE) و مخطط القلب الكهربائي للأذين (ECG–LAA) الأيسر المتضخم كعامل خطورة للجلطة الإحتشائية الحادة أو النزف الدماغي الحاد.

الطريقة: اشتملت هذه الدراسة الوصفية المستقبلية 140 حالة طارئة دماغية مثبتة بفحص التصوير المقطعي CT أو الرنين المغناطيسي للدماغ MRI – مستشفى رزكاري التعليمي – اربيل – العراق خلال الفترة من يناير 2008 حتى يناير 2009م. تم إجراء تخطيط القلب الصدري للأذين ECG و وتخطيط القلب الصدوي Echo لكل المرضى. حددت اختلال الأذين الأيسر إذا كان شدفة موجة p القوة النهائية في القطب ($PTFV_1$) V_1 أكثر من 40mm.ms<. تم تشخيص تضخم الأذين الأيسر بالتخطيط الصدري إذا كان معامل الأذين الأيسر أكثر من $2.3cm/m^2$.

النتائج: اختلال الأذين الأيسر LAA بتخطيط القلب الكهربائي كان أعلى لدى المرضى المصابين بالجلطات الإحتشائية مقارنة بحالات الطارئة النزفية. أسباب تضخم الأذين الأيسر ECG–LAA على تخطيط القلب الكهربائي بينت كالآتي حسب الترتيب؛ ارتفاع ضغط الدم (56%)، تقدم العمر (47%)، مرض الشريان التاجي (27%)، السكري (26%)، البدانة (21%)، اعتلال صمامات القلب (21%)، و عدم وجود سبب في 2.6% من الحالات. بين تضخم الأذين الأيسر بالتخطيط القلب الصدري LAE في 34% من الجلطات الإحتشائية و 30% من الطارئات النزفية دون وجود اختلاف مهم.

خاتمة: على الرغم من علاقة اختلال الأذين الأيسر (ECG–LAA) بتخطيط القلب الكهربائي والجلطة الإحتشائية هناك شك بأن زيادة معيار ($PTFV_1$>40 mm.ms) في مخطط القلب الكهربائي LAA عامل خطورة غير معتمد، لأن نسبة حدوث العامل دون حدوث العوامل الأخرى المؤكدة للجلطات الإحتشائية كان نادراً.

Objectives: To show that echocardiographic left atrial enlargement (Echo-LAE) and electrocardiographic left atrial abnormalities (ECG-LAA) may be probable new risk factors for ischemic and hemorrhagic stroke.

Methods: This descriptive prospective case study included 140 CT or MRI-confirmed hemorrhagic and ischemic stroke patients, who were admitted to Rizgary Teaching Hospital, Erbil, Iraq from January 2008 to January 2009. Twelve lead ECG and 2-dimensional transthoracic Echo were performed for all patients. Electrocardiographic LAA were identified when the P terminal force in lead V_1 ($PTFV_1$) was >40 mm.ms. Echocardiographic LAE was identified when the left atrial index was more than $2.3 cm/m^2$.

Results: Electrocardiographic LAA were significantly higher in ischemic stroke patients in comparison with the hemorrhagic strokes. Causes of ECG-LAA were found to be as follows in order of frequency; hypertension (56%), advanced age (47%), coronary artery disease (27%), diabetes mellitus (26%), obesity (21%), valvular heart disease (21%), and 2.6% of patients had no identifiable cause. Echocardiographic-LAE was seen in 34% of ischemic strokes, and 30% of hemorrhagic strokes with no significant difference.

Conclusion: Although ECG-LAA ($PTFV_1$>40 mm.ms) is significantly associated with ischemic stroke, it may not be an independent risk factor for stroke as it rarely occurred without other risk factors. Echocardiographic LAE is associated with both ischemic and hemorrhagic strokes equally.

Neurosciences 2010; Vol. 15 (1): 21-26

From the Department of Medicine (Khidhir), Rizgary Teaching Hospital, and the Neurology Unit (Al-Shimmery), Department of Medicine (Alwan), Hawler College of Medicine, Erbil, Iraq.

Received 7th July 2009. Accepted 17th November 2009.

Address correspondence and reprint request to: Dr. Ehsan K. Al-Shimmery, Neurology Unit, Department of Medicine, Hawler College of Medicine, Erbil, Iraq. Tel. +964 (750) 4946459. E-mail: eshimmery@yahoo.com

Stroke is defined as the sudden occurrence of a non-convulsive, focal neurologic deficit lasting more than 24 hours.[1,2] Pathologically, stroke falls into 3 subtypes, ischemic stroke (approximately 80%), primary intracerebral hemorrhage (approximately 15%), and

subarachnoid hemorrhage (around 5%). Cerebral ischemia is usually caused by a reduction in blood flow that lasts for several seconds to a few minutes.[3-5] Definite risk factors for stroke[5] include hypertension, dyslipidemia, carotid stenosis, atrial fibrillation, cigarette smoking, diabetes mellitus, ischemic heart disease, valvular heart disease, and obesity. These factors form around 60-80% of the causal risk factors, other factors are less common.[5-7] Increased atrial size as a potential risk factor for ischemic and hemorrhagic stroke has been discussed in many studies. Some of these studies agreed that this risk factor should be considered,[8-14] and other studies disagreed.[15-18] However, the patient sample in most of these studies included patients with mitral valve diseases or atrial fibrillation, and atrial size was not an independent risk factor, because of an already present cardiac disorder that leads to atrial enlargement. The Framingham study[19] highlighted that left atrial enlargement (LAE) can be considered as a potential independent risk factor for ischemic stroke only in men, with the consideration of left ventricular (LV) mass as a possible partner in this issue. The role of echocardiographic left atrial size in hemorrhagic stroke has been negated by the Framingham study, but the sample size of the cases of hemorrhagic stroke was small and the study did not deal with electrocardiographic left atrial abnormalities (ECG-LAA). Left atrial abnormality may be caused by[20] hypertension (HTN), diabetes mellitus (DM), and obesity (the mechanism by which overweight leads to LAE is unclear), but a relation to hemodynamic changes seen in obese patients, including increased intravascular volume and larger stroke volume and cardiac output, has been suggested,[21,22] advanced age, and valvular heart disease. Echocardiographic left atrial enlargement (Echo-LAE) is commonly used for evaluating left atrial size (in which the normal atrial size ranges from 1.9-4 cm) but has limitations related to left atrial irregular geometry and physical constraints imposed by the spine and sternum.[23,24] We observed that available clinical studies of Echo-LAE in ischemic stroke showed a controversial outlook, and were of no value for predicting thromboembolism in patients with chronic atrial fibrillation,[17] while atrial size was a strong predictor for ischemic stroke in another study.[25] The ECG-LAA estimation is a noninvasive and universally available method. It is known to reflect increases in LV filling pressure and the consequent remodeling process in hypertensive heart disease.[26,27] This fact can be utilized in investigating every stroke patient received at the emergency room in order to identify each particular patient's risk factors.[24] The aim of this study is to assess the role of ECG-LAA and Echo-LAE as risk factors in acute stroke, and to investigate whether there is any relation between different risk factors in ischemic and hemorrhagic stroke and LAE, in addition to study the effect of patients gender on these variables.

Methods. This descriptive prospective case study was carried out at Rizgary Teaching Hospital at Erbil, Iraq from January 2008 to January 2009. One hundred and fifty-seven patients, aged over 39 years with CT or MRI-confirmed hemorrhagic and ischemic stroke comprised the study population. Most of those patients were admitted under the supervision of specialist neurologists or under the supervision of a general physician. Informed consent was received from all patients, and the Research Committee at the College of Medicine, Hawler Medical University approved the study protocol. Seventeen stroke patients were excluded from the study because of absence of native P-waves on ECG examination (for example, atrial fibrillation, pacemaker rhythm) or because they did not complete the investigations, and 140 stroke patients were included in the study. Stroke risk factors were collected by direct interview with the patients. Routine laboratory tests including complete blood counts, coagulation studies, serum electrolytes, liver function tests, glucose, and lipid profile. Arterial blood pressure was examined in all patients. Arterial hypertension was defined as the presence of a positive history or history of antihypertensive treatment, or blood pressure values >160 mm Hg (systolic) or >95 mm Hg (diastolic) during the interview. Hypercholesterolemia was defined as a total serum cholesterol >200 mg/dl or the presence of appropriate drug treatment. Diabetes mellitus was defined on the basis of abnormal fasting blood sugar, or positive history, or history of oral hypoglycemic treatment or insulin treatment. Coronary artery disease included history of myocardial infarction or typical angina, the presence of a positive diagnostic test (stress test or coronary angiography), or drug treatment.[24] Evaluation of cardiac function, atrial diameter or abnormalities was carried out on a 12-lead ECG machine and 2-dimensional color-Doppler transthoracic echocardiography. The left atrial size was defined as an area represented by the terminal negative component of a biphasic P-wave in precordial lead V_1 ($PTFV_1$), if it was >40 ms mm it was considered enlarged.[23,28-32] The left atrial diameter is usually measured by 2D transthoracic echocardiography at the level of the aortic valve and normalized by the subject's body surface area (BSA). The results of the normalized left atrial diameter should be divided into quartiles, patients results falling into the highest 2 quartiles were considered to have LAE. Quartile cutoffs were 2.05 (first), 2.29 (second), 2.48 (third) and >2.48 cm/m^2 (fourth). Left ventricle mass index was also calculated using the same echocardiography machine. The LV was visualized with the patient lying in a modified left lateral decubitus position, with the ultrasound probe at the left parasternal window angled to visualize the heart in the long axis view. The LV measurements for the study included interventricular septal thickness (IVST) at end diastole (IVSd), LV internal diameter at

end diastole (LVIDd) and left ventricular posterior wall thickness at end diastole (LVPWd) with M-mode. The left ventricular mass (LVM) was subsequently calculated using the validated formula:

LVM (g) = 0.8 x 1.04 ((IVSd + LVIDd + LVPWd)^3 – (LVIDd)^3) + 0.6 g

were the LVPW, IVS, and LVIDd were measured in centimeters. The following formula was used to calculate the BSA:

BSA (m^2) = the root of (Ht x Wt/3600) = √Ht x Wt/3600.

were Ht is height in cm and Wt is weight in kilograms. Then the LVM was indexed (LVMI) to BSA to minimize the influence of Ht and Wt using the following formula; LVMI = LVM/BSA. However, this formula does not justify male and female differences. The indexed LVM limits used to establish LV hypertrophy (LVH) were 116g/m^2 for males and 104 g/m^2 for females.[30,31]

Statistical analyses were carried out using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL). Chi square and Fisher's exact test were used to test the association between ECG and Echo-LAA and stroke. A *p*-value <0.05 was considered statistically significant.

Results. Demographic analysis of our studied sample showed that 110 patients had ischemic stroke (54 male and 56 female patients) and 30 had hemorrhagic strokes (18 male and 12 female patients). The mean age of patients with ischemic stroke was 62.1 years, while the mean age for hemorrhagic patients was 53.3 years; the patients' age range was between 39-82 years. The association among the potential risk factors in ischemic and hemorrhagic subtypes was analyzed in our studied sample showing that P terminal force in lead V_1 ($PTFV_1$) was increased in a greater number of ischemic stroke patients than hemorrhagic stroke patients. The *p*-value was significant in patients with ischemic stroke only, even when the LVMI is excluded from the calculations, the *p*-value remained significant. Echocardiographic examination showed increased left atrial index (LAI) in 34% of patients having ischemic stroke and 30% of hemorrhagic stroke patients, while LVMI increased in 42% of ischemic and 30% of hemorrhagic stroke patients (**Table 1**). Hypertension was a risk factor in 54% of ischemic patients, and 90% of the hemorrhagic stroke patients, chi-square showed a highly significant difference between ischemic and hemorrhagic strokes. Smoking was a risk factor in both ischemic and hemorrhagic stroke patients. Coronary artery diseases (CAD) were significantly higher in ischemic patients in comparison with hemorrhagic stroke patients. Diabetes mellitus was a risk factor in 24% of ischemic patients and 20% of hemorrhagic strokes. Congestive heart failure was present in 8% of ischemic, and 10% of hemorrhagic stroke patients. Hypercholesterolemia was present in 6% of ischemic, and 13% of hemorrhagic stroke patients, while previous stroke or transient ischemic attack was seen in 15% of ischemic and 20% of hemorrhagic strokes. **Table 2** shows the effect of gender on increased LAI and LVMI and other risk factors for ischemic stroke. The risk factors were relatively distributed equally between both genders, chi-square showed no significant differences. **Table 3** shows the relation between the estimated echocardiographic LAI to patient's age in patients with

Table 1 - Association among the potential risk factors. N=140 (110 ischemic and 30 hemorrhagic strokes). Percentage is according to subtypes of stroke.

Risk factor	Ischemic stroke	Hemorrhagic stroke	X^2	*P*-value	Total
	n (%)				
$PTFV_1$> 40 ms.mm	76 (69)	12 (40)	7.87	0.005	**88**
↑LAI	38 (34)	9 (30)	0.10	0.7518	**47**
↑LVMI	47 (42)	9 (30)	0.66	0.4165	**56**
HTN	60 (54)	27 (90)	13.88	0.0001	**87**
Smoking	36 (32)	9 (30)	0.20	0.6547	**45**
CAD	26 (23)	3 (10)	4.78	0.0287	**29**
DM	27 (24)	6 (20)	0.21	0.6467	**33**
Congestive heart failure	9 (8)	3 (10)	0.31	0.5776	**12**
↑Cholesterol	7 (6)	4 (13)	3.01	0.872	**11**
Previous stroke or TIA	17 (15)	6 (20)	1.02	0.3125	**23**
Total	**343 (307)**	**89 (243)**			**432**

PTFV - P terminal force at lead V_1, LAI - left atrial index, LVMI - Left ventricular mass index, HTN - hypertension, CAD - coronary artery disease, DM - diabetes mellitus, ns - non significant.
When the ↑LVMI is excluded from the equation, chi square test remained significant for increased $PTFV_1$, X^2=9.45, *p*=0.0021

Table 2 - The effect of gender on risk factors for ischemic stroke (N=110).

Risk factor	Ischemic		Total	X^2	*P*-value
	M	F			
$PTFV_1$> 40 ms mm	35	41	**76**	0.029	0.8647
↑LAI	13	25	**38**	2.02	0.1552
↑LVMI	22	25	**47**	0.059	0.8080
HTN	24	36	**60**	0.749	0.3867
Smoking	16	10	**26**	3.08	0.0792
CHF	6	3	**9**	1.727	0.1887
CAD	11	15	**26**	0.084	0.7719
DM	12	15	**27**	0.003	0.9563
↑Cholesterol	3	4	**7**	0.240	0.6242
Previous stroke or TIA	8	9	**17**	0.029	0.8647
Total	**150**	**183**	**333**		

$PTFV_1$ - P terminal force at lead V_1, LAI - left atrial index, LVMI - left ventricular mass index, HTN - hypertension, CAD - coronary artery disease, DM - diabetes mellitus, CHF - congestive heart failure, TIA - transient ischemic attack. After omitting the effect of LVMI from the equation, X^2 for LAI *p*-value remains insignificant (X^2=1.28, *p*=0.258)

Table 3 - Left atrial index abnormality in relation to age in ischemic stroke patients.

LAI cm/m^2	Age groups		Total
	40-59 years	≥60 years	
≤2.3	24	48	**72**
>2.3	26	12	**38**
Total	**50**	**60**	**110**

Chi-square = 12.4, *p*=0.0001 (highly significant).

ischemic stroke. It revealed that patients younger than 60 years had significantly more LAE than patients equal or above the age of 60 years. The percentage of patients with ischemic stroke falling in different quartiles is shown in **Figure 1**. Forty-one percent of patients having PTFV1>40 mm.ms fall in the lower 2 quartiles of the LAI, and 27.4% of patients fall in the higher quartiles of LAI. The sensitivity and specificity of $PTFV_1$ were 78% and 56%. The positive and negative predictive values were 41% and 76%. The percentage of patients with $PTFV_1$>40 mm.ms in quartiles of the echocardiographic LAI in patients with hemorrhagic stroke are shown in **Figure 2**. Ten percent of patients with $PTFV_1$>40 mm.ms fall in the lower 2 quartiles of the LAI, and 30% of patients having $PTFV_1$>40 mm.ms fall in the higher quartiles of LAI. Sensitivity and specificity were 81% and 84%, while the predictive values for positives and negatives were 75% and 60%. The frequency of the

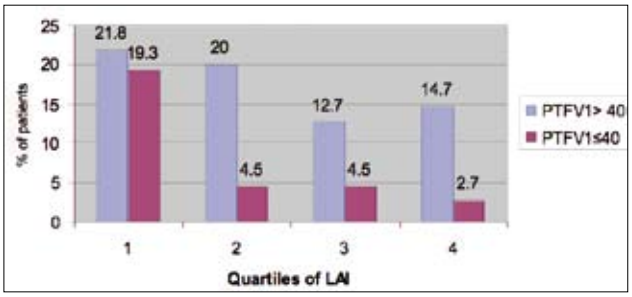

Figure 1 - Quartiles of LAI in relation to $PTFV_1$ in patients with ischemic stroke. LAI - left atrial index, $PTFV_1$ - P terminal force at lead V_1.

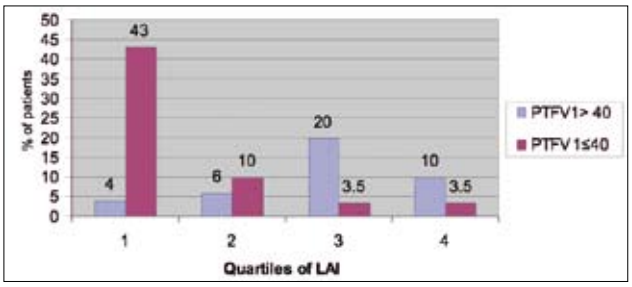

Figure 2 - Quartiles of LAI in relation to $PTFV_1$ in patients with hemorrhagic stroke. LAI - left atrial index, $PTFV_1$ - P terminal force at lead V_1.

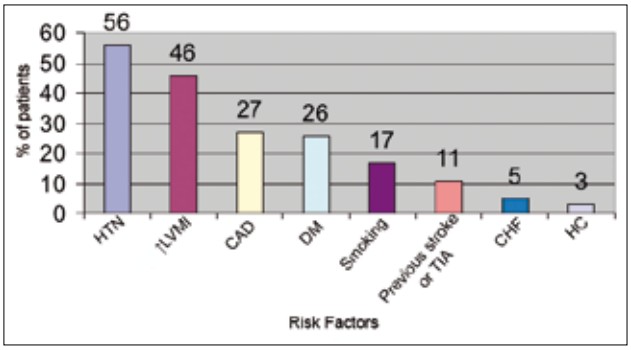

Figure 3 - Frequency of risk factors of stroke in patients with $PFTV_1$ >40 mm.ms. $PTFV_1$ - P terminal force at lead V_1, HTN - hypertension, LVMI - left ventricular mass index, CAD - coronary artery disease, DM - diabetes mellitus, CHF - congestive heart failure, HC = hypercholesterolemia

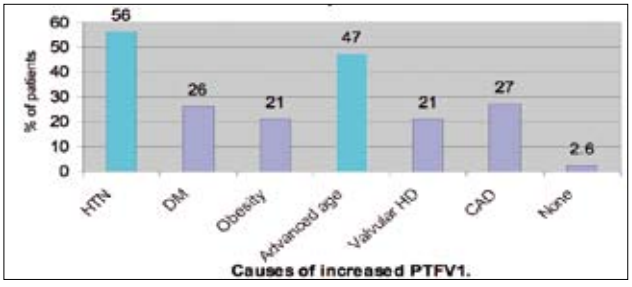

Figure 4 - Frequency of causes of $PFTV_1$ >40 mm.ms in ischemic stroke patients. $PTFV_1$ - P terminal force at lead V_1, HTN - hypertension, CAD - coronary artery disease, DM - diabetes mellitus, HD - heart disease

stroke risk factors in patients with ischemic stroke and a $PTFV_1$>40 mm.ms is shown in **Figure 3**. The frequency of causes of increased $PTFV_1$ in ischemic stroke patients is shown in **Figure 4**.

Discussion. In this study we tried to analyze the effect of left atrial diameter as a possible risk factor in both ischemic and hemorrhagic stroke, and tried to find out whether this variable was associated with other modifiable and non-modifiable risk factors such as gender and age. We found that there is a significant association between increase in the $PTFV_1$ and ischemic stroke in 69% of our studied sample, similar to previous studies.[8,10,19,24] Hypertension found to be the most common cause of increase in $PTFV_1$ in most patients (90%), and although it is the leading cause of hemorrhagic stroke, still the association of hypertension with $PTFV_1$ was higher with ischemic rather than hemorrhagic stroke. This significant difference did not seem to be dependent on the echocardiographic LVH, as it remained significant even when patients with LVH were excluded from the statistical calculation. This finding may suggest a different and independent relationship between ischemic stroke and ECG LAA, as also suggested by Kohsaka et al.[24] There was no significant difference in echocardiographic LAE or LVH between ischemic and hemorrhagic stroke patients, because such enlargement would be expected in most patients with different stroke pathological types, since most of those patients are hypertensive.[1,3,9,22,26,27] In our studied sample, hypertension was more significantly associated with hemorrhagic stroke, but it also remains a potential risk factor for ischemic stroke as 54% of our ischemic stroke patients are hypertensives. The Framingham Heart study showed no relation between LAE and hemorrhagic stroke, but it did show a significant relationship between LAE and overall stroke in men, and this association was attenuated by adjustment for echocardiographic LVM.[19] These results may be attenuated by the inclusion of only a few patients with hemorrhagic stroke in both the Framingham study and this study, and a higher number, or a specific study that includes only hemorrhagic stroke patients should be planned in the future to investigate whether left atrial size may also be a risk factor for hemorrhagic stroke.

Smoking as a risk factor was not significantly different in ischemic or hemorrhagic stroke in our case series. These findings may be attributed to both the increase in smoking habits in men and women, and due also to a small sample size of the hemorrhagic stroke group. Coronary artery disease was significantly higher among the ischemic stroke patients, and could be due to its relation to cardioembolic stroke, especially after subendocardial or all layers infarction, or because both ischemic stroke and coronary artery diseases have common atherosclerotic etiological processes. We found no significant difference between males and females regarding all risk factors of ischemic stroke including ECG and echocardiographic parameters of LAE and LVH, similar to the findings described by Kohsaka et al,[24] in which they did not observe a significant difference in gender regarding $PTFV_1$. However, the Framingham study showed gender differences in relation to LAE and in another study by Di Tullio et al,[8] they showed that echo-LAE is associated with an increased risk of ischemic stroke in men only of all ages, whereas in women this effect was attenuated by other factors, especially LVH.

Table 3 shows that echo-LAE was significantly associated with ischemic stroke in patients less than 60 years of age. This was in concordance with other studies.[8] The weaker role played by LAE in the older subgroup may be a reflection of the relatively greater contribution of other conventional stroke risk factors. **Figure 1** shows that ECG LAA ($PTFV_1$>40 mm.ms) has a sensitivity of 78% and a specificity of 56% in identifying an echocardiographic LAE. This figure differs from previous studies by Hazan[28] (95% sensitivity) and Palani[23] (sensitivity 51%, 81% specificity). These differences can be attributed to 2 causes; first in the study by Hazan, the number 40 in the identification had been included, so the sensitivity was higher, and another difference is that in both studies, the echocardiographic LA size was not indexed for BSA. The figure also revealed that 41.8% of patients with ECG LAA were in the lower quartiles of the echocardiographic LA size. This indicates that ECG LAA is sensitive for detecting stress on the LA and appears sooner than echo-LAE (pressure phenomena), but it is less specific,[29,32] so it may be partially explained by the electrophysiological effect of acute stroke itself. **Figure 2** shows that patients with ECG LAA mostly fall into higher quartiles of the echo-LAI. Regarding sensitivity and specificity, positive and negative predictive values are refined in comparison with ischemic stroke patients. This study was unable to define the cause of this difference, whether it is due to a stronger association between these patients and uncontrolled and long duration of hypertension or due to a smaller sample size. **Figures 3 & 4** are designed to explain the cause of significant association between ischemic stroke and ECG LAA as shown in **Table 2**. It revealed that most of the risk factors for ischemic stroke are causes for ECG LAA and only 2.6% of them had no identifiable cause, or may be due to the electrophysiological effects of stroke itself.[24]

A few study limitations emerged as we collected our data for this study, some of them related to the difficulties we faced in transferring our stroke patients from our neurology ward to the echocardiography department, since the responsible echocardiographer or the cardiologist that shared this study was practicing in another general hospital in Erbil city, and the difficulty in recruiting normal controls because the echocardiography

department is fully booked and crowded with everyday long lists of patients.

In conclusion, although ECG-LAA ($PTFV_1$>40 mm.ms) is significantly associated with ischemic stroke, it may not be an independent risk factor for stroke as it rarely occurred without potential risk factors of stroke, such as hypertension. A P terminal force in V_1 above 40 mm.ms has a sensitivity of detecting LAA in 78% of stroke patients, but it is not a specific tool for identification of LA enlargement and so cannot replace the role of 2 Dimensional echocardiography. Echocardiographic LAE is significantly associated with both ischemic and hemorrhagic stroke, but mainly in men.

References

1. Ropper AH, Robert HB, editors. Major categories of neurologic disease: Cerebrovascular diseases. In: Adams and Victor's Principles of Neurology. 8th ed. New York (NY): McGraw Hill; 2005. p. 660-740.
2. Warlow C, Sudlow C, Dennis M, Wardlaw J, Sandercock P. Stroke. ***Lancet*** 2003; 362: 1211-1124. Review.
3. Smith WS, Claiborne JS, Easton JD. Neurologic disorders: Cerebrovascular Diseases. In: Kasper DL, Fauci AS, Longo DL, Braunwald E, Hauser SL, Jameson JL, editors. Harrison's Principle's of Internal Medicine. 16th ed. New York (NY): McGraw-Hill; 2005. p. 2372-2393.
4. Ralph L. Vascular disease: Pathogenesis Classification and Epidemiology of Cerebrovascular Disease. In: Rowland LP, Merritt HH, editors. Merrit's Neurology. 11th ed. Philadelphia (PA): Lippincott Williams & Wilkins; 2005. p. 275-291.
5. Hankey GJ. Potential new risk factors for ischemic stroke: what is their potential? ***Stroke*** 2006; 37: 2181-2188.
6. Ridker PM. Inflammatory biomarkers, statins, and the risk of stroke: cracking a clinical conundrum. ***Circulation*** 2002; 105: 2583-2585.
7. Greenberg DA, Aminoff MJ, Simon RP, editors. Stroke. In: Clinical Neurology. 5th ed. New York (NY): McGraw Hill; 2002. p. 282-316.
8. Di Tullio MR, Sacco RL, Sciacca RR, Homma S. Left atrial size and the risk of ischemic stroke in an ethnically mixed population. ***Stroke*** 1999; 30: 2019-2024.
9. Dewar HA, Weightman D. A study of embolism in mitral valve disease and atrial fibrillation. ***Br Heart J*** 1983; 49: 133-140.
10. Caplan LR, D'Cruz I, Hier DB, Reddy H, Shah S. Atrial size, atrial fibrillation, and stroke. ***Ann Neurol*** 1986; 19: 158-161.
11. Cabin HS, Clubb KS, Hall C, Perimutter RA, Feinstein AR. Risk for systemic embolization of atrial fibrillation without mitral stenosis. ***Am J Cardiol*** 1990; 65: 1112-1116.
12. Aronow WS, Gutstein H, Hsieh FY. Risk factors for thromboembolic stroke in elderly patients with chronic atrial fibrillation. ***Am J Cardiol*** 1989; 63: 366-367.
13. Corbalán R, Arriagada D, Braun S, Tapia J, Huete I, Kramer A, et al. Risk factors for systemic embolism in patients with paroxysmal atrial fibrillation. ***Am Heart J*** 1992; 124: 149-153.
14. Predictors of thromboembolism in atrial fibrillation: II. Echocardiographic features of patients at risk. The Stroke Prevention in Atrial Fibrillation Investigators. ***Ann Intern Med*** 1992; 116: 6-12.
15. Burchfiel CM, Hammermeister KE, Krause-Steinrauf H, Sethi GK, Henderson WG, Crawford MH, et al. Left atrial dimension and risk of systemic embolism in patients with a prosthetic heart valve. Department of Veterans Affairs Cooperative Study on Valvular Heart Disease. ***J Am Coll Cardiol*** 1990; 15: 32-41.
16. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. ***N Engl J Med*** 1990; 323: 1505-1511.
17. Petersen P, Kastrup J, Helweg-Larsen S, Boysen G, Godtfredsen J. Risk factors for thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK Study. ***Arch Intern Med*** 1990; 150: 819-821.
18. Moulton AW, Singer DE, Haas JS. Risk factors for stroke in patients with nonrheumatic atrial fibrillation: a case-control study. ***Am J Med*** 1991; 91: 156-161.
19. Benjamin EJ, D'Agostino RB, Belanger AJ, Wolf PA, Levy D. Left atrial size and the risk of stroke and death. The Framingham Heart study. ***Circulation*** 1995; 92: 835-841.
20. Laukkanen JA, Kurl S, Eränen J, Huttunen M, Salonen JT. Left atrium size and the risk of cardiovascular death in middle-aged men. ***Arch Intern Med*** 2005; 165: 1788-1793.
21. Rutter MK, Parise H, Benjamin EJ, Levy D, Larson MG, Meigs JB, et al. Impact of glucose intolerance and insulin resistance on cardiac structure and function: sex-related differences in the Framingham Heart Study. ***Circulation*** 2003; 107: 448-454.
22. Gerdts E, Oikarinen L, Palmieri V, Otterstad JE, Wachtell K, Boman K, et al. Correlates of left atrial size in hypertensive patients with left ventricular hypertrophy: the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) Study. ***Hypertension*** 2002; 39: 739-743.
23. Palani JA. Sensitivity, specificity, predictive value and diagnostic reliability of the electrocardiogram for the diagnosis of left atrial enlargement. ***Zanko Journal of Medical Sciences*** 1997; 3: 9-14.
24. Kohsaka S, Sciacca RR, Sugioka K, Sacco RL, Homma S, Di Tullio MR. Electrocardiographic left atrial abnormalities and risk of ischemic stroke. ***Stroke*** 2005; 36: 2481-2483.
25. Stroke Prevention in Atrial Fibrillation Study. Final results. ***Circulation*** 1991; 84: 527-539.
26. Tezcan H, Bihorac A, Akoglu E, Oktay A. Association between left atrial enlargement and target organ damage in essential hypertension. ***Am J Hypertens*** 1998; 11: 732-733.
27. Genovesi-Ebert A, Marabotti C, Palombo C, Ghione S. Electrocardiographic signs of atrial overload in hypertensive patients: indexes of abnormality of atrial morphology or function? ***Am Heart J*** 1991; 121: 1113-1118.
28. Hazan MS, Marwick TH, Underwood DA. Diagnostic accuracy of the resting electrocardiogram in detection and estimation of left atrial enlargement: an echocardiographic correlation in 551 patients. ***Am Heart J*** 1991; 122: 823-828.
29. David MM, Ary LG. Electrocardiography. In: Peter L, Robert OB, Douglas PZ, Douglas LM, editors. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine,. 8th ed. Philadelphia (PA): WB Saunders; 2007. p. 162.
30. Crow RS, Hannan P, Grandits G, Leibsong P. Is the echocardiogram an appropriate ECG validity standard for the detection and change in left ventricular size? ***J Electrocardiol*** 1996; 29: 248-256.
31. Devereux RB, Dahlof B, Levy D, Pfeffer MA. Comparison of enalapril versus nifedipine to decrease left ventricular hypertrophy in systemic hypertension (the PRESERVE trial). ***Am J Cardiol*** 1996; 78: 61-65.
32. Mishra A, Mishra C, Mohanty RR, Behera M. Study on the diagnostic accuracy of left atrial enlargement by resting electrocardiography and its echocardiographic correlation. ***Indian J Physiol Pharmacol*** 2008; 52: 31-42.