Full Length Research Paper

Left Atrial Enlargement as a Predictor of Silent Paroxysmal Atrial Fibrillation

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Atrial fibrillation (AF) is the most common cardiac arrhythmia and it may be symptomatic (manifest), or asymptomatic (silent). Silent AF is much more common than manifest AF. Both paroxysmal (PAF) and persistent AF confer a risk of embolic stroke. Increased left atrial (LA) size is associated with an increased prevalence of non-valvular AF and could be a predictor of stroke. Relationship between LA size and asymptomatic attacks of PAF in hypertensive patients. Sixty hypertensive patients following at the cardiac outpatient clinic having controlled hypertension (HTN) underwent ambulatory Holter monitoring (HM) for detection of silent PAF and measurement of left atrium antero-posterior diameter (LAAPd) using M-mode echocardiogram. Patients were classified into two groups according the LAAPd: group I; twenty-six patients and having increased LAAPd and group II; thiry-four having normal LAAPd. Patients in both groups have comparable demographic variables, cardiovascular (CV) risk factors, controlled BP; antihypertensive drugs used to control BP, and left ventricular size and function. Upon HM, 11 (18%) patients found to silent PAF, 8 (30.7%) in group I and 3 in group II (8.8%). Thus hypertensive patients with normal LAAPd (P = 0.043). Increased LAAPd can be used in selecting hypertensive patients for HM to identify patients having silent PAF and thus at risk for embolic stroke.

Keywords: Atrial fibrillation, Left atrium, Hypertension, Holter monitoring.

INTRODUCTION

Atrial fibrillation is the most common sustained form of arrhythmia, affecting approximately 3 % of the adult population (Friberg and Bergfeldt, 2013). The true number, however, will never be fully grasped as there are likely a large number of people with undiagnosed silent PAF.

In 1987 Framingham data introduced AF as a potential source of embolic stroke (Wolf et al., 1978). It was also proposed that persistent AF was a possible source of embolic stroke and the duration of AF was correlated to the risk of stroke.² Subsequent studies have further proven that PAF confers a risk of stroke as great as that of permanent AF(Friberg et al., 2010).

LA size and function have been found to exhibit a linear relationship with adverse CV outcomes such as: AF, stroke, congestive heart failure and death (Vaziri et

al., 1994; Tsang et al., 2001; Barnes et al., 2004; Benjamin et al., 1995; Tsang et al., 2002). Electrocardiographic features of left atrial enlargement have been observed in the setting of hypertensive heart disease (Frohlich et al., 1971; Tarazi et al., 1966).

Relationship between LA size and asymptomatic attacks of PAF in hypertensive patients.

PATIENTS AND METHODS

Sixty hypertensive patients following at the OPD in the period between October 2015 and March 2016 underwent:

- I- Informed consent taking.
- II- Full history taking including history of CV risk factors

(hypertension, diabetes mellitus, smoking, and dyslipidemia) and current anti-hypertensive medications. III-BP measurement:

BP was measured according to the American Heart Association recommendations using mercury sphygmomanometer with the Korotkoff 's sound technique and the following guidelines: (Pickering et al., 2005)

- Patient seated comfortably, with back supported, legs uncrossed, and upper arm bared.

- Patient's arm supported at heart level.

- Cuff bladder encircles 80 percent or more of the patient's arm circumference.

- Mercury column deflated at 2 to 3 mm per second.

Two readings were taken at intervals of at least 1 minute, and the average of those readings was used to represent the patient's blood pressure. If there was > 5 mmHg difference between the first and second readings, additional one reading was obtained, and then the average of these multiple readings was used.

BP is considered controlled according to the JNC8 (James et al., 2014) if:

- BP is < 140/90 mmHg in patients < 60 years

- BP is < 150/90 mmHg in patients \geq 60 years

IV-Twenty-four hour HM:

Ambulatory 24 hour HM was recorded using Schiller Microvit MT-101 two channel recorder and the data analyzed using Schiller MT-200 Holter-ECG V 2.54 software. AF on HM was defined as irregular ventricular response in the absence of P-waves or with fibrillatory waves for > 30 seconds (Fuster et al., 2006; Tagawa et al., 2007).

V- Trans-thoracic echocardiogram:

All echocardiographic data were obtained from performed examination at the outpatient echocardiographic laboratory. Trans-thoracic Doppler echocardiographic examination was performed in sinus rhythm with the patient in the left lateral position using Phillips iE 33 station equipped with S 1 - 5 MHz transducer. Two-dimensional guided M-mode images were obtained from parasternal long-axis and short-axis views, according to the standers of American Society of Echocardiography (Sahn et al., 1978). LAAPd was measured at left ventricular end-systole as its greatest diameter and the exact location of the posterior wall was confirmed by two-dimensional echocardiography (Suarez et al., 1991). All the measures were calculated by considering the average of three cardiac cycles.

Inclusion criteria

- 1- Age > 18 years
- 2- Hypertensive for at least one year

- 3- Controlled HTN
- 4- Normal left ventricular dimensions and function

Exclusion criteria

1- Valvular and congenital heart diseases

2- Ischemic heart disease(IHD) (history suggesting of IHD, previous percutaneous coronary intervention (PCI), previous CABG (coronary artery bypass grafting), ECG findings suggesting IHD, or echocardiographic findings suggesting IHD).

- 3- Dilated left ventricular
- 4- Low ejection fraction (EF)
- 5- History of PAF
- 6- Chronic AF patients
- 7- Bronchial asthma
- 8- Hyporthyroidism
- 9- Hyperthyroidism
- 10- Uncontrolled HTN

Statistical methods

SPSS 11.0 statistical software program was used for statistical analysis. Continuous variables are expressed as mean \pm standard deviation, and categorical variables expressed as percentage. Student's t test was used for the comparison of continuous variables in both groups. Fisher's exact test was used for the comparison of categorical values. A value of P < 0.05 was considered statistically significant.

RESULTS

Study population

Sixty hypertensive patients, forty men (67%) and twenty women (33%) were enrolled in the study. Their age ranged from 31 to 70 years, with a mean \pm SD of 51.35 \pm 9.2 and a median of 51.5 years.

Fourteen of these patients (23%) were smokers, twenty-four (40%) were diabetics, fifteen (25%) were dyslipidemic (table 1).

Regarding the anti-hypertensive medications, fortytwo patients (70%) were taking ARBs, forty-one (68%) were taking CCBs, twenty-two (37%) were taking diuretics, thirteen (22%) were taking ACEI, and ten patients (17%) were taking BB, figure 1.

All the patients had controlled hypertension with their systolic BP raging form 110 to 145 with a mean ± SD of 128.08±8.88 mmHg and their diastolic BP ranging

Risk factors		No	%	
Gender	Male	40	67%	
	Female	20	33%	
Smoking	Yes	14	23%	
	No	46	77%	
Diabetes Mellitus	Yes	24	40%	
	No	36	60%	
Dyslipidemia	Yes	15	25%	
	No	45	75%	

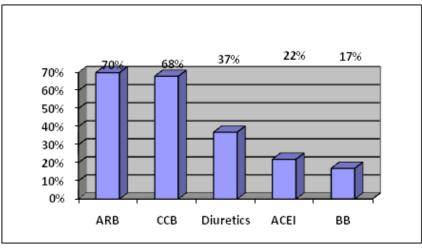


Figure 1. anti-hypertensive drugs. ARB = angiotensin receptor blocker, CCB = calcium channel bocker, <math>ACRI = angiotensinogen converting enzyme inhibitor, BB = beta blocker

form 70 to 85 with a mean \pm SD of 76.83 \pm 5.20 mmHg.

Echocardiographic findings

All the patients had normal LV dimensions with their left ventricular end diastolic dimensions (LVEDD) raging from 4.0 to 5.5 with a mean \pm SD of 4.91 \pm 0.34 cm and left ventricular end systolic dimensions (LVESD) raging from 2.8 to 3.6 with a mean \pm SD of 3.17 \pm 0.23 cm and normal LV ejection fraction (EF) ranging from 58% to 71% and a mean \pm SD of 64.43 \pm 3.2.

According the LA size, the patient had classified into two groups:

1- **Group I**: Included twenty-six (43%) patients and had dilated LA with the LAAPd ranging from 4.0 to 5.2 cm with a mean \pm SD of 4.4 \pm 0.29.

2- Group II: Included thirty-four (57%) patients and had normal LA size with the LAAPd ranging from 2.8 to

3.7 cm and a mean±SD 3.2±0.27.

Holter findings

The sixty patients had HM completed for a mean±SD of 23.43±0.65 hours. Eleven patients of the sixty (18%) had silent PAF.

Comparison between the two groups

1. Demographic variables

Group I patients age ranged from 32 to 69 years, with a mean \pm SD of 50.77 \pm 9.75 and in group II it ranged from 31 to 70 years, with a mean \pm SD of 51.76 \pm 8.8. Thus the two groups were comparable regarding the age (P = 0.68). In group I seventeen patients were male (65%) and nine (35%) patients were female, while in group II

twenty-three (68%) patients were male and eleven (32%) patients were female without any statistically significant difference between the two groups (P = 1.00), table 2.

2. Cardiovascular risk factors

Ten patients (38%) were diabetics, six (23%) were smokers, and seven (27%) were dyslipidemic in group I and in group II fourteen (41%) were diabetics, eight (24%) were smokers, and eight (24%) were dyslipidemic. There was no statistically significant difference between the two groups regarding the CV risk factors (P = 1.00, 1.00, 0.77 respectively), table 2.

3. Blood pressure and anti-hypertensive drugs

The BP was controlled in both groups $(127.88\pm8.39 / 76.54\pm5.05 \text{ in group I Vs } 128.24\pm9.36 / 76.91\pm5.22 \text{ mmHg in group II})$ without any statistically significant difference (P = 0.88 and 0.79 respectively), table 3.

Eighteen patients (69%) were taking ARBs, fifteen (58%) were taking CCB, nine (35%) were taking diuretics, five (19%) were taking ACEI, and four (15%) were taking BB in group I and in group II twenty-four (71%) were taking ARBs, twenty-six (76%) were taking CCB, thirteen (38%) were taking diuretics, eight (24%) were taking ACEI, and six (18%) were taking BB. There was any statistically significant difference between the two groups regarding the anti-hypertensive medications (P = 1.00, 0.16, 0.79, 0.76, and 1.00 respectively), table 3.

4. Echocardiographic data

All the patients in the two groups have normal LV dimensions and EF without statistically significant difference between the two groups (LVEDD = 4.94 ± 0.33 vs. 4.90 ± 0.36 ; P = 0.68, LVESD = 3.18 ± 0.22 vs. 3.08 ± 0.54 ; P = 0.39, EF = $64.58\pm3.14\%$ vs. $64.32\pm3.29\%$; P = 0.76), table 4.

The LA was enlarged in group I patient with the LAAPd ranging from 4.0 to 5.2 cm and mean \pm SD is 4.4 \pm 0.29 cm while group II patients have normal LA size with the LAAPd ranging from 2.8 to 3.6 cm and mean \pm SD is 3.2 \pm 0.27 cm (P = 0.0001), table 4.

5. Holter monitoring

Patients in both groups were monitored for a comparable period $(23.39\pm0.67 \text{ vs. } 23.46\pm0.63, P = 0.355)$, table 5. The Holter monitoring was positive for PAF in eight patients (30.7%) in group I and three patients (8.8%) in group II. Thus hypertensive patients having dilated LA (group I) have significantly more attacks of silent PAF than hypertensive patients with normal LA size (P = 0.043), table 5 and figure 2.

DISCUSSION

This study included 60 patients having controlled HTN.

All the patients have normal LV dimensions and function assessed by M-mode and 2D echocardiogram. All the patient underwent Holter monitoring for 23.43±0.65 hours for detection of silent PAF.

Twenty-six (43%) patients (group I) have increased LAAPd, while the remaining thirty-four (57%) patients (group II) had normal LAAPd measured by M-mode echocardiogram.

Although M-mode LAAPd, routinely used and accepted as a surrogate of LA size, may underestimate the actual LA dimension compared with the determination of LA area or volume (Khankirawatana et al., 2004). However, this measure was shown to strongly correlate with two-dimensional values in both parasternal and apical views in a population free from valvular heart disease (Lemire et al., 1976). This observation may lead to the assumption that M-mode LAAPd also provides a good level of accuracy in the estimation of LA size in LPAF patients.

Although electrocardiographic features of left atrial enlargement have been observed in the setting of hypertensive heart disease (Frohlich et al., 1971; Tarazi et al., 1966),data conflict regarding the effect of blood BP on echocardiographically determined left atrial size (Dunn et al., 1977; Miller et al., 1988; Pearson et al., 1991; Savage et al., 1979).

In a study of 31 hypertensive subjects without clinically evident coronary heart disease, Dunn et al. 1977 found that hypertensive subjects with evidence of left atrial abnormality by electrocardiogram or LV hypertrophy by either electrocardiogram or chest roentgenogram had significantly greater left atrial indexes (left atrial size/body surface area) than 14 agematched normotensive subjects. Miller et al. 1988 in an evaluation of 14 hypertensive and 10 normotensive subjects with normal coronary angiography, demonstrated significantly increased left atrial dimension and left atrial index among the hypertensive subjects. A recent study by *Pearson et al. 1991* of 144 participants of the Systolic Hypertension in the Elderly Program (SHEP) trial and 55 age-matched normotensive control subjects found significantly increased left atrial index in the hypertensive group. However, among 234 subjects with mild to moderate hypertension in a study by Savage et al. 1979 only 5% of hypertensive subjects were found to have abnormal left atrial dimensions (defined as values above the 95% prediction interval derived from 124 normotensive control subjects).

The association between HTN (blood pressure >140/90) and AF is well established(Gardin et al., 1979; Krahn et al., 1995; Conen et al., 2009; Kannel et al., 1998). Although the increase in risk is relatively modest (relative risk, 1.2–1.5), the high prevalence of

		Group I (N = 26)	Group II (N = 34)	P value
Gender	Male	17 (65%)	23 (68%)	1.00
	Female	9 (35%)	11 (32%)	
Diabetes Mellitus	5	10 (38%)	14 (41%)	1.00
Smoking		6 (23%)	8 (24%)	1.00
Dyslipidemia		7 (27%)	8 (24%)	0.77

Table 2. Comparison between the two groups regarding the demographic variables and CV risk factors. *N* = number of patients.

Table 3. Comparison between the two groups regarding the BP and anti-hypertensive drugs. N = number of patients, SBP = systolic blood pressure, DBP = diastolic blood pressure, ARB = angiotensin receptor blocker, CBB = calcium channel blocker, ACEI = angiotensinogen converting enzyme inhibitor, BB = beta blocker

	Group I (N = 26)	Group II (N = 34)	P value
SBP	127.88±8.39	128.24±9.36	0.88
DBP	76.54±5.05	76.91±5.22	0.79
ARB	18 (69%)	24 (71%)	1.00
ССВ	15 (58%)	26 (76%)	0.16
Diuretics	9 (35%)	13 (38%)	0.79
ACEI	5 (19%)	8 (24%)	0.76
BB	4 (15%)	6 (18%)	1.00

Table 4. comparison between the two groups regarding the echocardiographic data. N = number of patients, LA = left atrium, EDD = left ventricular end diastolic dimension, LVESD = left ventricular end systolic dimensions, EF = ejection fraction

	Group I	Group II (N = 34)	Duchus
	(N = 26)		P value
LA size	4.4±0.29	3.2±0.27	0.0001
LVEDD	4.94±0.33	4.90±0.36	0.68
LVESD	3.18±0.22	3.08±0.54	0.39
EF	64.58±3.14	64.32±3.29	0.76

Table 5. Comparison between the two groups regarding the HM data. N = number of patients, AF = atrial fibrillation

	Group I (N = 26)	Group II (N = 34)	P value
Duration	23.39±0.67	23.46±0.63	0.355
Positive for AF	8 (30.7%)	3 (8.8%)	0.043

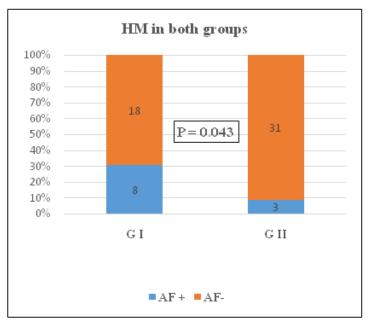


Figure 2. Patients with and without silent PAF in the two groups. G I = group I, G II = group II

hypertension in the general population renders it the most significant population-attributable risk factor for AF beyond age and sex. It is estimated that hypertension is responsible for 14% of all cases of AF. In agreement with these findings, our study demonstrated that 18% of hypertensive patients had silent PAF.

Increased left atrial size is associated with an increased prevalence of non-rheumatic AF, (Henry et al., 1976; Takahashi et al., 1982; Keren et al., 1987), and in addition, it is a predictor of stroke, once AF is manifest (Cabin et al., 1990).

In our study we evaluated the ability to prospectively predict the occurrence of AF within a short time span by echocardiography. Our results showed that patients with increased LAAPd (group I) have significantly more frequent attacks of silent PAF than those having normal LAAPd (30.7% vs. 8.8%, P = 0.043).

Our findings are in consistent with those found by *Sobocinski et al. 2012* who studied 249 patients with ischemic strokes / TIAs without known cardiopulmonary source. They found that LA was enlarged in 13% of the whole population in contrast to 24% of those having silent PAF.

The potential clinical value of our observation is that LAAPd can be used as a guide for screening for silent PAF which will help in identifying patients at embolic CVA risk and will benefit from receiving long-life oral anticoagulants.

CONCLUSION

This study confirms the association between increased LA size silent PAF, and provides an evidence for the role of the LA size in selecting patients in need for screening for silent PAF.

Study Limitation

It has several potential limitations; the major ones are:

- Small No. of population
- The usage of M-mode LAAPd as a measure of the LA szie
- Short duration of Holter monitoring

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