Left Ventricular Posterior Wall Thickness is an Independent Risk Factor for Paroxysmal Atrial Fibrillation

HF Xu, YM He, YX Qian, X Zhao, X Li, XJ Yang

ABSTRACT

Background: *Atrial fibrillation is the most common significant cardiac arrhythmia in clinical practice, but its risk factors remain to be clarified. We have hypothesized that left ventricular posterior wall thickness is an independent risk factor for paroxysmal atrial fibrillation (PAF).*

Methods: *A total of 166 consecutive patients with paroxysmal atrial fibrillation were included in this study. Another 166 healthy check-up people, strictly age and sex-matched, were enrolled as controls in the same period. Univariable analysis and multivariable conditional logistic stepwise regression analysis were conducted. Receiver operating characteristic (ROC) curve analysis was performed on those significant indices obtained from the multivariable logistic regression analysis.*

Results: *The multivariable stepwise analysis identified left ventricular posterior wall thickness, left atrial diameter, tricuspid insufficiency and residence (countryside) as independent predictors for paroxysmal atrial fibrillation. Receiver operating characteristic curve analysis demonstrated the cut-off values of those risk factors aforementioned.*

Conclusions: *In this strictly age and sex-matched population-based sample, left ventricular posterior wall thickness, left atrial diameter, tricuspid insufficiency and residence were predictive risks for paroxysmal atrial fibrillation. This study offers novel information therapeutically beyond that provided by traditional clinical atrial fibrillation risk factors.*

Keywords: Left atrial diameter, left ventricular posterior wall thickness, paroxysmal atrial fibrillation, tricuspid insufficiency

El Grosor de la Pared Posterior Ventricular Izquierda es un Factor de Riesgo Independiente para la Fibrilación Atrial Paroxística

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RESUMEN

Antecedentes: *La fibrilación atrial o auricular, es la arritmia cardíaca significativa más común en la práctica clínica, pero sigue siendo aún necesario poner en claro sus factores de riesgo. El presente trabajo asume la hipótesis de que el grosor de la pared posterior ventricular izquierda constituye un factor de riesgo independiente para la fibrilación atrial paroxística (FAP).*

Métodos: *El estudio abarca un total de 166 pacientes consecutivos con fibrilación atrial paroxística. Otras 166 personas saludables según el reconocimiento médico, pareadas estrictamente por edad y sexo, fueron registradas como controles en el mismo periodo. Se llevó a cabo un análisis de regresión logística condicional multivariante paso a paso y un análisis univariante. El análisis de la curva característica de la operación del receptor (ROC) se realizó sobre los índices significativos obtenidos a partir del análisis de regresión logística multivariante.*

Resultados: *El análisis multivariante paso a paso identificó el grosor de la pared posterior ventricular izquierda, el diámetro atrial izquierdo, la insuficiencia tricúspide y la residencia (el campo) como predictores independientes de la fibrilación atrial paroxística. El análisis de la curva característica de la operación del receptor demostró los valores límites de los factores de riesgo mencionados arriba.*

Conclusiones: *En esta muestra basada estrictamente en una población pareada por edad y género, el grosor de la pared posterior ventricular izquierda, el diámetro atrial izquierdo, la insuficiencia tricús-*

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pide y la residencia, fueron riesgos predictivos de la fibrilación atrial paroxística. Este estudio ofrece información novedosa, terapéuticamente más allá de la proporcionada por los factores de riesgo clínicos tradicionales de la fibrilación atrial.

Palabras claves: diámetro atrial izquierdo, grosor de la pared posterior ventricular izquierda, fibrilación atrial paroxística, insuficiencia tricúspide

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INTRODUCTION

Atrial fibrillation (AF) is the most common clinical arrhythmia, accounting for about one-third of arrhythmia in inpatients. From 1996 to 2001, hospitalizations with AF as the first-listed diagnosis increased by 34% (1). The results of epidemiological studies about China's *status quo* of atrial fibrillation showed that the total incidence of atrial fibrillation was 0.77% (2) and it increased with age (2, 3). The elderly who are > 80 years may have a higher incidence, up to 7.5% (2). Atrial fibrillation, which has been shown to be associated with increased risk of morbidity and mortality for cardiovascular diseases (3), can cause haemodynamic disturbances and thrombotic events. Left ventricular posterior wall thickness (LVPWT) is associated with varying heart diseases. However, the influence of the LVPWT *per se* on paroxysmal atrial fibrillation (PAF) has not been elucidated, so we evaluated those routine indices of PAF patients and healthy population, and attempted to determine the relationship between LVPWT and PAF.

SUBJECTS AND METHODS

A total of 236 PAF patients were obtained from the archives of the First Affiliated Hospital of Soochow University, China, from January 1, 2006 to December 31, 2008, and asymptomatic persons who came for routine health checks were recruited as controls in the same period. Those PAF patients with liver, kidney and thyroid diseases were excluded from this study. Some subjects were also excluded because of incomplete data. Thus, 166 PAF patients in total entered this study and all had routine assessment of medical history, physical examination, blood tests, 12-lead electrocardiograms (ECGs) and echocardiograms. The control group consisted of 166 strictly age- and sex-matched healthy controls. The age fluctuation was within two years.

Definition of PAF: If recurrent atrial fibrillation terminates by itself, it is designated paroxysmal; termination by pharmacological therapy or electrical cardioversion before expected spontaneous termination does not change the designation paroxysmal. The sustained duration is less than 7 days (4).

Clinical variables

Information on patient demographic characteristics, medical history, clinical characteristics, and in-hospital outcomes were collected through completion of a standardized case report form. Patients with right atrial enlargement were scored as 1, otherwise as 0. Aortic regurgitation (AR), mitral regurgitation (MR), tricuspid insufficiency (TI), aortic stenosis (AS) and mitral stenosis (MS) were graded as mild, moderate and severe depending on disease's degree and were scored as 1, 2 and 3, respectively. An extremely mild disease was scored as 0.5. If the disease degree was described as mild to moderate abnormality, it was scored as (1 +2) / 2 = 1.5.

Statistical analyses

Univariate analysis of continuous variables and categorical/ranking variables was first conducted. Those variables that were statistically significant by univariate analysis were analysed using conditional stepwise logistic regression analysis. The criteria for entry into the model and removal from the model for *sle* and *sls* were all at 0.05 level. Finally, the clinical relevant variables screened were analysed with receiver operating characteristic (ROC) curve analysis to get the cut-off values. A value of $p < 0.05$ was considered to be statistically significant. SAS statistical software version 8.0 (SAS Institute Inc, Cary, NC, USA) was used for all analyses.

RESULTS

Clinical baseline characteristics

Table 1 shows the baseline characteristics in patients with and without PAF. In the clinical baseline characteristics, there are five variables which have significant differences between the PAF group and control group ($p < 0.05$). Coronary heart disease (CHD), hypertension (HT) and pulmonary disease (PUD) occurred more frequently in PAF patients. Cardiac function classification IV occurred more frequently in PAF patients, whereas cardiac function classification I occurred less frequently in PAF patients. Interestingly, rural patients showed a significant trend toward not having PAF.

Univariate analysis results

Table 2 shows that echocardiography parameter abnormalities, such as LVPWT, interventricular septal thickness, left atrial diameter, left ventricular end-diastolic, end-systolic diameters, pulmonary artery pressure, right atrial enlargement, aortic regurgitation, mitral regurgitation and tricuspid insufficiency occurred more frequently in PAF patients. Paroxysmal atrial fibrillation increased four-fold in patients

Table 1: Baseline characteristics of 166 PAF patients and 166 non-PAF patients by the univariate analysis

Index	PAF	Non-PAF	wald χ^2	p	OR	95% CI (OR)
Sex (female)	75	75	0.0000	1.0000	1.000	0.649−1.541
Age (year)	65.5 (59, 72)	64 (59, 70)	1.5340	0.2155	1.013	0.992−1.035
Residence (countryside)	46	80	14.998	0.0001	0.412	0.261−0.650
Cardiac function (NYHA)	IV (7) III (116) II (4) I (11)	IV (1) III (100) I (63)	9.4708	0.0021	1.437	1.141−1.811
CHD	16	3	7.5544	0.0060	5.794	1.655−20.280
DCM	0	0	0.0000	1.0000	1.000	—
RHD	6	0	0.0003	0.9851	—	—
DM	0 (0, 0)	0 (0, 0)	2.4006	0.1213	1.156	0.962−1.390
HT	1 (0, 10)	0 (0, 3)	12.9440	0.0003	1.068	1.031−1.108
PUD	22	8	8.8032	0.0030	3.502	1.530−8.014
Cataptosis	8	3	3.4924	0.0617	3.483	0.941−12.892

PAF − paroxysmal atrial fibrillation; NYHA − New York Heart Association; CHD − coronary heart disease; DCM − dilated cardiomyopathy; RHD − rheumatic heart disease; DM − diabetes mellitus; HT – hypertension; PUD − pulmonary disease.

Age, DM and HT were numerical variables, but did not follow normal distribution, so they were shown as "median (No. 25−75 percentile)"; others are the number of cases of patients. —: OR (odds ratio) or 95% confidence interval of OR was unavailable in classified variables of univariate analysis.

Table 2: Univariate analysis

Index	PAF	Non-PAF	wald χ^2	p	OR	95% CI (OR)
AOD, mm	33 (31, 34)	32 (29, 35)	2.0364	0.1536	1.049	0.982−1.120
LVDD, mm	49 (46, 51)	48 (45, 50)	10.2142	0.0014	1.081	1.031−1.134
LVSD, mm	30 (28, 33)	29 (27, 32)	9.0410	0.0026	1.079	1.027−1.133
LAD, mm	40 (37, 44)	36 (33, 38)	43.7625	< 0.0001	1.182	1.125−1.242
IVST, mm	10 (9, 11)	9 (8, 10)	16.5680	< 0.0001	1.370	1.177−1.595
LVPWT, mm	10 (8, 10)	9 (8, 10)	18.2128	< 0.0001	1.440	1.218−1.702
LVEF, %	0.69 (0.64, 0.73)	0.70 (0.64, 0.73)	0.4234	0.5152	1.309	0.581−2.949
AR	2 (5) 1.5 (4) 1 (18) 0.5 (25) 0 (114) 2 (3) 1.5 (6)	1.5 (2) 1 (9) 0.5 (26) 0 (127) 2 (2)	7.5224	0.0061	2.209	1.254−3.892
MR	1 (19) 0.5 (33) 0 (105) 2.5 (1) 2(6) 1.5 (6)	1 (6) 0.5 (41) 0 (137) 1.5 (2)	6.9102	0.0086	2.123	1.211−3.723
TI	1 (16) 0.5 (92) 0 (45)	1 (18) 0.5 (53) 0 (93)	19.9159	< 0.0001	3.805	2.116−6.844
MS	1 (3) 0 (163)	0 (166)	0.0004	0.9838	—	—
PAP, mm	25 (25, 33)	25 (25, 31)	5.2520	0.0219	1.047	1.007−1.088
RAE	1 (12) 0 (154)	1 (3) 0 (163)	4.8509	0.0276	4.234	1.172−15.291
AS	1 (5) 0 (161)	0 (166)	0.0003	0.9864	—	—
T-BIL, μmol/L	11.9 (8.7, 16.0)	10.5 (8.4, 13.9)	3.5932	0.0580	1.037	0.999−1.076
D-BIL, μmol/L	6.0 (4.4, 8.5)	5.5 (4.2, 7.1)	5.9470	0.0147	1.107	1.020−1.201
ALT, U/L	21 (17, 31)	22.0 (16.0, 31.0)	0.4370	0.5086	1.001	0.997−1.005
AST, U/L	23 (19, 29)	25 (20, 31)	0.4168	0.5185	1.001	0.999−1.003
ALB, g/L	42.00 ± 4.29	42.32 ± 4.31	0.4492	0.5027	0.983	0.935−1.034
A/G	1.7 (1.5, 1.8)	1.6 (1.4, 1.8)	1.2565	0.2623	1.537	0.725−3.261
Cr-S, μmol/L	85 (69, 103)	80 (68, 94)	5.9535	0.0147	1.011	1.002−1.020
GLU, mmol/L	5.19 (4.69, 5.84)	4.99 (4.62, 5.51)	2.9528	0.0857	1.185	0.976−1.437
TC, mmol/L	3.93 (3.35, 4.54)	4.14 (3.69, 4.72)	5.9824	0.0144	0.722	0.556−0.937
TG, mmol/L	1.23 (0.87, 1.83)	1.17 (0.94, 1.82)	0.6283	0.4280	1.104	0.864−1.411
LDH, U/L	181 (158, 215)	169 (146, 202)	3.0649	0.0800	1.003	1.000−1.007

Table 2 (contd): Univariate analysis

Index	PAF	Non-PAF	wald χ^2	*p*	OR	95%CI (OR)
CK, U/L	69 (53, 93)	78 (61, 95)	1.3938	0.2378	1.001	0.999−1.003
HBDH, U/L	137 (120, 164)	130 (117, 159)	1.8623	0.1724	1.003	0.999−1.007
ADA, U/L	9.2 (7.7, 12.4)	9.2 (8.1, 11.2)	1.8335	0.1757	1.033	0.986−1.083
WBC, 10E9/L	5.8 (5.00, 6.88)	5.35 (4.37, 6.50)	7.2731	0.0070	1.183	1.047−1.337
HCT, L/L	0.38 (0.35, 0.42)	0.375 (0.350, 0.410)	0.0428	0.8360	1.238	0.164−9.330
BPC, 10E9/L	166.5 (142.0, 192.0)	162.5 (129.0, 201.0)	0.1972	0.6570	1.001	0.997−1.005
PCT, L/L	0.14 (0.19, 0.11)	0.14 (0.10, 0.18)	1.9868	0.1587	11.010	0.392−309.553
MPV, fl	8.9 (7.4, 10.4)	8.80 (6.60, 10.80)	0.0518	0.8199	1.008	0.938−1.084
PVDW, %	17.2 (16.3, 18.4)	17.9 (16.8, 18.6)	0.1655	0.6842	0.994	0.968−1.022

AOD − aortic dimension; LVDD/LVSD − left ventricular end-diastolic/ end-systolic diameters; LAD − left atrial diameter; IVST − interventricular septal thickness; LVPWT − left ventricular posterior wall thickness; LVEF − left ventricular ejection fraction; AR − aortic regurgitation; MR − mitral regurgitation; TI − tricuspid insufficiency; MS − mitral stenosis; PAP − pulmonary arterial pressure; RAE − right atrial enlargement; AS − aortic stenosis; T-BIL − total bilirubin; D-BIL − direct bilirubin; ALT − alanine aminotransferase; AST − aspartate aminotransferase; ALB − albumin; A/G − albumin/globulin; Cr-S − serum creatinine; GLU − blood glucose; TC − total cholesterol; TG − triglycerides; LDH − lactate dehydrogenase; CK − creatine kinase; HBDH − hydroxybutyrate dehydrogenase; ADA − adenosine deaminase; WBC − white blood count; HCT − haematocrit; BPC − blood platelet count; PCT − plateletcrit; MPV − mean platelet volume; PVDW − platelet volume distribution width.

All the numerical variables, except albumin which followed normal distribution and shown as "Mean ± SD", did not follow normal distribution and are shown as "median (No. 25−75 percentile)".
—: this means that we did not get OR or 95% confidence interval of OR in classified variables of univariate analysis. AR, MR and TI were researched by semi-quantitative scoring statistics, such as 2 (5) in AR. This means that there were five patients at the moderate degree of severity in 166 patients. AS, RAE and MS were to have or not counted as 1 or 0.

with right atrial enlargement compared to those without (OR = 4.234, 95% CI 1.172 − 15.291), but right atrial enlargement was removed from the logistical model in adjusted analysis. In addition, blood examination revealed that direct bilirubin, serum creatinine, total cholesterol and white blood cell count were significantly higher in patients with PAF than in those without.

Conditional logistic regression analysis results

In the clinical baseline characteristics, there were five significant clinical variables between PAF and non-PAF patients. In univariate analysis, there were 14 significant clinical variables, so 19 significant clinical variables in total were analysed by 1:1 paired conditional logistic regression analysis. We found that residence, LVPWT, left atrial diameter (LAD) and tricuspid insufficiency (TI) were independent risk factors for PAF. Living in the countryside (OR = 0.437, 95% [CI] 0.263, 0.725) appeared to be a protective factor for PAF. Left ventricular posterior wall thickness (OR = 1.348, 95% [CI] 1.111, 1.635), LAD (OR = 1.130, 95% [CI] 1.072, 1.191) and tricuspid valve regurgitation (TR) [OR = 2.876, 95% [CI] 1.483, 5.576] were risk factors for PAF (Table 3).

Receiver operating characteristic curve analysis (Figure)

In Table 4, the area under the curve of LAD was 0.743, showing that it occupied the maximum weight in PAF diagnostic power. Left ventricular posterior wall thickness and TI's weights were 0.644 and 0.643. Living in the countryside was a protective factor.

DISCUSSION

Previous studies have related LVPWT to the incidence of heart diseases. Left ventricular posterior wall thickness in patients with non-dipper hypertension was significantly higher than those with dipper hypertension (5). Increased

Table 3: The result of 1:1 matched conditional regression analysis

Index	AF group	non-AF	wald χ^2	*p*	OR	95% CI (OR)	stb
LAD	40 (37, 44)	36 (33, 38)	20.8354	< 0.0001	1.130	1.072−1.191	0.3995
LVPWT	10 (8, 10)	9 (8, 10)	9.1858	0.0024	1.348	1.111−1.635	0.2295
TI	0.52	0.29	9.7773	0.0018	2.876	1.483−5.576	0.2585
Residence (countryside)	46	80	10.2595	0.0014	0.437	0.263−0.725	-0.2219

stb − standardized partial regression coefficient; LAD − left atrial diameter; LVPWT − left ventricular posterior wall thickness; TI − tricuspid insufficiency.

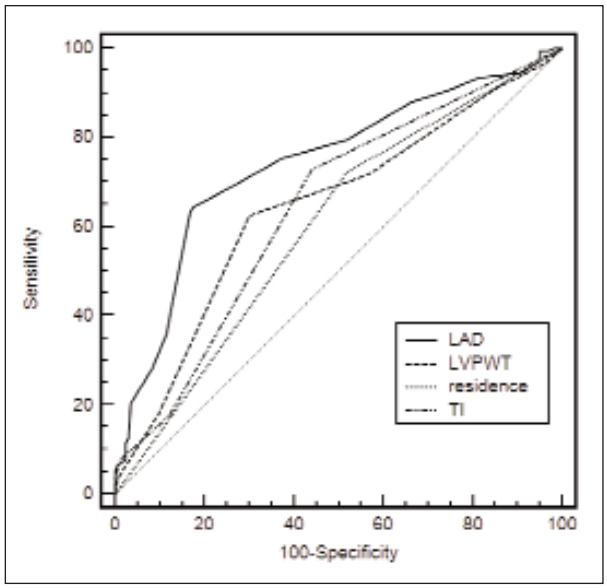

Figure: Receiver operating characteristic (ROC) curve analysis of LAD, LVPWT, residence and TI. LAD − left atrial diameter; LVPWT − left ventricular posterior wall thickness; TI − tricuspid insufficiency.

atrial arrhythmia was easy to be triggered, especially PAF. Ventricular hypertrophy was mainly seen in the hypertension patients. It showed that anti-hypertensive treatment could reduce left atrial diameter and the occurrence of atrial fibrillation, while poor blood pressure control could increase the occurrence of atrial fibrillation. Increased left atrial diameter is a recognized risk factor for atrial fibrillation (7).

In the present study, the PAF group had significantly different left atrial diameter compared with the non-PAF group, which was consistent with other researchers' investigations (7−9). Statistical analysis also showed that the weight of the left atrial diameter was largest amid the four risk factors, its standard partial regression coefficient and odds ratio being 0.3995 and 1.130, respectively. This also confirmed the reliability of this study.

Tricuspid insufficiency is an independent risk factor for PAF. The incidence of atrial fibrillation is about three-folds higher than in control groups. Tricuspid insufficiency is mostly secondary to right ventricular and tricuspid valve annulus enlargement. When it happens, some blood is pumped back from the right ventricle into the right atrium in

Table 4: The result of receiver operating characteristic

Index	AUC	95% CI	z statistic	Significance level	Cut-off value
LAD	0.743	0.692−0.789	9.006	0.0001	38
LVPWT	0.644	0.590−0.695	4.778	0.0001	9
TI	0.643	0.589−0.695	4.746	0.0001	0
Residence	0.602	0.548−0.655	3.312	0.009	countryside

AUC − area under curve, LAD − left atrial diameter, LVPWT − left ventricular posterior wall thickness, TI − tricuspid insufficiency.

LVPWT prolonged *p*-wave duration and dispersion in obese patients (6). The sum of left ventricular wall thickness (defined as septal wall thickness plus posterior wall thickness) was an independent risk factor for heart failure and atrial fibrillation (7). To our knowledge, this is the first report on the relationship of LVPWT to PAF.

In this study, both the interventricular septal thickness and the LVPWT in PAF patients had a statistically significant difference compared to the control group ($p < 0.001$), which confirmed the association of atrial fibrillation with left ventricular wall thickening. Thickened left ventricular wall with decreased compliance of the left ventricle led to diastolic dysfunction. In the presence of diastolic dysfunction, left ventricular end-diastolic pressure was increased in order that the left atrium would overcome the higher left ventricular pressure so as to contract (4). Persistent overcoming of the left ventricle's higher pressure caused the left atrial diameter to increase gradually (8). The left atrial pathological changes inevitably led to abnormal electrical activities, like atrial conduction delay, depolarization heterogeneity and the shortened refractory period of atrial myocytes. On this occasion, systole, leading to increased right atrial pressure and an enlarged right atrium, finally inducing atrial fibrillation. Enlargement of the right atrium was significant in the univariate analysis, but it was removed from the model in multivariate regression analysis. This may well be that the enlargement of the right atrium was recorded as classified variables, not as numerical variable, with some statistical information being missing.

We also found that residence was a protective factor for PAF (OR = 0.412). In other words, patients who lived in the countryside were not susceptible to PAF. Cardio-cerebrovascular diseases have become the lead-ing causes of death worldwide. This has been closely associated with population ageing, urbanization, stress *etc*. This result also reminds us that we should pay attention to the influence of mental health on the development of heart diseases in China, where unprecedented socio-economic changes have taken place.

Study limitations

As an observational study, the current study is subject to certain inherent limitations and potential biases, including

collection of nonrandomized data, missing or incomplete information and potential confounding by drug indication or other unmeasured covariates that must be considered when interpreting the results. The primary limitation of this study may be a relatively small sample size, which may affect the reliability of the results. Age and sex were strictly matched between two groups, thus improving the reliability of the present study. In addition, new biomarkers possibly related to a predisposition to PAF – pro-natriuretic peptides (10) – may provide further information related to the risk of PAF and may modify the relative value of other clinical risk factors.

CONCLUSIONS

In this strictly age, sex-matched, population-based sample, LVPWT, left atrial diameter and tricuspid insufficiency were independently related to PAF. Living in the countryside was associated with a lower incidence.

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