

Research Paper

# Heart Rate Significantly Influences the Relationship between Atrial Fibrillation and Arterial Stiffness

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## Abstract

**Background.** Atrial fibrillation (AF) and vascular disease share several risk factors and the two diseases often coexist. Heart rate (HR) is reported to be a major determinant of arterial stiffness. AF patients often have a transiently or persistently rapid HR. Hence, this study was to assess whether AF was significantly associated with arterial stiffness and HR could significantly influence the relationship between AF and arterial stiffness. Besides, we also determine the main correlates of arterial stiffness in AF patients and see whether HR was correlated with arterial stiffness in these patients.

**Methods.** We included 166 AF and 1336 non-AF patients from subjects arranged for echocardiographic examinations. Arterial stiffness was assessed by brachial-ankle pulse wave velocity (baPWV).

**Results.** Compared to non-AF patients, AF patients had a higher baPWV ( $p < 0.001$ ). In a multivariate model, including covariates of age, sex, blood pressures and so on, the presence of AF was significantly associated with baPWV ( $\beta = 0.079$ ,  $P = 0.001$ ). However, further adjustment for HR made this association disappear ( $\beta = 0.005$ ,  $P = 0.832$ ). In addition to age and systolic blood pressure, increased HR ( $\beta = 0.309$ ,  $p < 0.001$ ) was a major determinant of increased baPWV in our AF patients.

**Conclusions.** This study demonstrated the presence of AF was associated with increased baPWV, but this association became insignificant after further adjustment for HR, which suggested HR could significantly influence the relationship between AF and baPWV. Besides, HR was positively correlated with arterial stiffness in our AF patients.

Key words: atrial fibrillation; arterial stiffness; pulse wave velocity; heart rate

## Introduction

Vascular disease has been found to increase the risk of atrial fibrillation (AF) [1, 2] and AF has similarly been shown to be a major risk factor of vascular disease [1, 3, 4]. AF and vascular disease share several risk factors, including old age, obesity, diabetes, heart failure and hypertension, and the two diseases often

coexist [2, 5, 6]. Therefore, the presence of AF may have an influence on the vascular function.

Pulse wave velocity (PWV) reflects arterial stiffness and is a useful indicator of both the severity of vascular damage and the prognosis of cardiovascular and renal diseases [7-13]. To assess arterial stiffness,

many noninvasive methods have been developed, and they usually require expertise techniques [14]. A clinical device, ABI-form (VP1000; Colin Co. Ltd., Komaki, Japan), has been developed to automatically and simultaneously record pulse waves of the brachial and posterior tibial arteries, using an automated oscillometric method. Using this device, we can easily and automatically calculate the brachial-ankle PWV (baPWV) [15, 16]. The baPWV has been reported as a good marker for arterial stiffness [16].

Several studies have demonstrated that heart rate (HR) is positively associated with arterial stiffness [17-19]. AF patients often have a transiently or persistently rapid HR, so AF patients may have an increased arterial stiffness and HR may significantly influence the relationship between AF and arterial stiffness. Besides, although tachycardia-induced cardiomyopathy is a well-known reason of cardiac dysfunction in patients with AF [20], there is no study to evaluate whether tachycardia is also correlated with vascular dysfunction in these patients.

Hence, the first aim of this study was to compare baPWV between patients with and without AF and see whether AF patients had an increased arterial stiffness. The second aim of this study was to assess whether AF per se was a major determinant of increased arterial stiffness and whether HR could significantly influence the relationship between AF and arterial stiffness. The third aim of this study was to determine the main correlates of baPWV in AF patients and see whether HR was a major determinant of arterial stiffness in these patients.

## Methods

### Study patients

This was a cross-sectional study. Study subjects were prospectively included from a group of patients who arranged for echocardiographic examinations at Kaohsiung Municipal Hsiao-Kang Hospital. Patients with inadequate image visualization were excluded. AF patients were consecutively included. However, non-AF patients were not consecutively included because baPWV measurement must be performed within 10 minutes after the completion of echocardiographic examination. Finally, 166 patients with persistent or permanent AF and 1336 non-AF patients were included in this study.

### Ethics Statement

The study protocol was approved by the institutional review board of the Kaohsiung Medical University Hospital (KMUH-IRB-20130014). Informed consents have been obtained in written form from patients and all clinical investigation was conducted according to the principles expressed in the Declara-

tion of Helsinki. The patients gave consent for the publication of the clinical details.

### Assessment of baPWV

After at least 10 minutes of rest from the beginning of echocardiographic examination, baPWV was assessed using an ABI-form device, which automatically and simultaneously measures blood pressure in both arms and ankles using an oscillometric method [15]. For measuring baPWV, pulse waves that were obtained from the brachial and tibial arteries were recorded simultaneously and the transmission time, which was defined as the time interval between the initial increase in brachial and tibial waveforms, was determined. The transmission distance from the arm to each ankle was calculated according to body height. The value of baPWV was automatically computed as the transmission distance divided by the transmission time. HR, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by the same device. In non-AF patients, the examination of ABI-form device was performed once. The average of bilateral baPWV values and the averages of SBP and DBP of bilateral arms were used for later analysis. In AF patients, the examination of ABI-form device was performed thrice and the average of 6 baPWV values, the average of 3 values of HR and the averages of 6 values of SBP and DBP obtained from the repeated examinations were used for later analysis.

### Collection of demographic, medical and laboratory data

Demographic and medical data including age, gender, history of diabetes mellitus, hypertension, cerebrovascular accident, smoking and chronic heart failure and body mass index were obtained from medical records or interviews with patients. Body mass index was calculated as the ratio of weight in kilograms divided by the square of height in meters. Laboratory data including total cholesterol and triglyceride were also collected. The value of estimated glomerular filtration rate (eGFR) was calculated using the 4-variable equation in the Modification of Diet in Renal Disease study [21]. In addition, information regarding patient medications including angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs),  $\beta$ -blockers, calcium channel blockers (CCBs) and diuretics during the study period was obtained from medical records.

### Statistical analysis

SPSS 18.0 software (SPSS, Chicago, IL, USA) was used for statistical analysis. Data were expressed as mean  $\pm$  standard deviation or percentage. Continuous and categorical variables between groups were compared by independent samples t-test and Chi-square

test, respectively. The multiple linear regression analysis was employed to identify the determinants of baPWV. The impact of HR on the relationship between AF and baPWV was assessed by a modified stepwise procedure in 4 modeling steps. The first model consisted of age and SBP. The second model consisted of the significant variables in the univariate analysis except HR. The third step was adding HR. To avoid over-adjustment of HR, we further performed an interaction-analysis in the final model by adding a variable of AF  $\times$  HR. All tests were 2-sided and the level of significance was established as  $P < 0.05$ .

## Results

Table 1 showed the comparison of baseline characteristics between patients with and without AF. Compared to patients without AF, patients with AF had a higher baPWV, older age, lower prevalence of female gender, higher HR, lower SBP and DBP, lower prevalence of hypertension, higher prevalence of cerebrovascular accident and chronic heart failure, lower total cholesterol and triglyceride and higher percentage of ACEI and/or ARB and diuretic uses.

In a univariate analysis, baPWV had a positively correlation with the presence of AF, age, female gender, HR, SBP and DBP, diabetes, hypertension, cerebrovascular accident and using of ACEIs and/or ARBs, CCBs and diuretics and negatively correlation with body mass index, smoking, triglyceride and eGFR ( $P \leq 0.024$ ). After a multivariate analysis, increased baPWV was associated positively with age, HR, SBP, DBP, and cerebrovascular accident and

negatively with body mass index ( $P \leq 0.019$ ). A multiple linear regression equation showed that  $\text{baPWV} = -777.106 + 14.155 \times (\text{age}) + 7.036 \times (\text{HR}) + 9.266 \times (\text{SBP}) + 1.698 \times (\text{DBP}) + 104.167 \times (\text{cerebrovascular accident}) - 9.526 \times (\text{body mass index})$ . Table 2 displays the non-standardized coefficient, standardized coefficient  $\beta$  and coefficient of determination ( $R^2$ ) estimates for baPWV by the presence of AF with and without adjustment for demographic, clinical and biochemical parameters, HR and AF  $\times$  HR. The presence of AF was associated with baPWV in the age- and SBP-adjusted model (standardized coefficient  $\beta = 0.106$ ; 95% confidence interval [CI], 98 to 209;  $P < 0.001$ ) and in the multivariate model adjusting for the significant variables in the univariate analysis except HR (standardized coefficient  $\beta = 0.079$ ; 95% CI, 40 to 163;  $P = 0.001$ ). This relation between AF and baPWV was disappeared after adjustment for HR (standardized coefficient  $\beta = 0.005$ ; 95% CI, -58 to 72;  $P = 0.832$ ). The association between AF and baPWV was still insignificant after further adjustment for AF  $\times$  HR (standardized coefficient  $\beta = 0.232$ ; 95% CI, -12 to 615;  $P = 0.059$ ).

Table 3 shows the correlates of baPWV in patients with AF. In the univariate analysis, increased age, female gender, increased HR, high SBP and DBP, low body mass index, non-smoking and decreased eGFR were independently associated with increased baPWV. After the multivariate analysis, old age, high SBP and increased HR were still the major determinants of increased baPWV in our AF patients.

**Table 1.** Comparison of baPWV and baseline characteristics between patients with and without AF

Characteristics	Patients with AF (n = 166)	Patients without AF (n = 1336)	P
baPWV (cm/s)	1940 $\pm$ 526	1731 $\pm$ 438	<0.001
Age (yr)	69 $\pm$ 10	61 $\pm$ 14	<0.001
Female gender (%)	33	44	0.008
HR (min <sup>-1</sup> )	85 $\pm$ 18	70 $\pm$ 13	<0.001
SBP (mmHg)	132 $\pm$ 17	136 $\pm$ 21	0.031
DBP (mmHg)	75 $\pm$ 11	77 $\pm$ 12	0.010
BMI (kg/m <sup>2</sup> )	26.2 $\pm$ 4.2	26.1 $\pm$ 4.0	0.706
Diabetes mellitus (%)	30	29	0.681
Hypertension (%)	60	69	0.025
CVA (%)	17	6	<0.001
CHF (%)	30	9	<0.001
Smoking (%)	15	15	1.000
Total cholesterol (mg/dL)	177 $\pm$ 37	191 $\pm$ 44	<0.001
Triglyceride (mg/dL)	122 $\pm$ 72	155 $\pm$ 150	0.016
eGFR (mL/min/1.73 m <sup>2</sup> )	58 $\pm$ 18	57 $\pm$ 21	0.544
Medications			
ACEIs and/or ARBs (%)	61	54	0.039
$\beta$ blockers (%)	47	40	0.075
CCBs (%)	33	35	0.569
Diuretics (%)	42	28	<0.001

baPWV: brachial-ankle pulse wave velocity; AF: atrial fibrillation; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; CVA: cerebrovascular accident; CHF: chronic heart failure; eGFR: estimated glomerular filtration rate; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB: calcium channel blocker

**Table 2.** Relation of AF to baPWV

AF	baPWV				
	Non-standardized Coefficient	Standardized Coefficient $\beta$	95% CI	P	R <sup>2</sup>
Unadjusted	208.437	0.143	135 - 282	< 0.001	0.020
Age and SBP adjusted	153.647	0.106	98 - 209	< 0.001	0.469
Multivariate adjusted (1)	101.785	0.079	40 - 163	0.001	0.520
Multivariate adjusted (2)	7.068	0.005	-58 - 72	0.832	0.549
Multivariate adjusted (3)	301.537	0.232	-12 - 615	0.059	0.551

CI: confidence interval; R<sup>2</sup>: coefficient of determination. The other abbreviations are the same as in Table 1.

Multivariate model (1): adjusted for age, sex, SBP, DBP, BMI, diabetes mellitus, hypertension, CVA, smoking, eGFR, triglyceride, ACEI/ARB use, CCB use, diuretic use.

Multivariate model (2): model (1) + HR.

Multivariate model (3): model (2) + AF  $\times$  HR.

**Table 3.** Univariate and multivariate correlates of baPWV in patients with AF

	Univariate analysis		Multivariate analysis	
	Standardized coefficient $\beta$	p	Standardized coefficient $\beta$	P
Age (yr)	0.505	<0.001	0.422	<0.001
Female gender	0.213	0.007	0.017	0.811
HR (min <sup>-1</sup> )	0.166	0.038	0.309	<0.001
SBP (mmHg)	0.457	<0.001	0.479	<0.001
DBP (mmHg)	0.262	0.001	-0.119	0.240
BMI (kg/m <sup>2</sup> )	-0.18	0.026	-0.085	0.210
Diabetes mellitus	0.047	0.556		
Hypertension	0.015	0.852		
CVA	0.045	0.571		
CHF	-0.004	0.957		
Smoking	-0.167	0.037	-0.063	0.379
Total cholesterol (mg/dL)	0.134	0.150		
Triglyceride (mg/dL)	-0.093	0.318		
eGFR (mL/min/1.73 m <sup>2</sup> )	-0.198	0.014	-0.025	0.725
Medications				
ACEIs and/or ARBs	-0.076	0.343		
$\beta$ blockers	-0.058	0.469		
CCBs	0.123	0.124		
Diuretics	0.022	0.783		

Abbreviations are the same as in Table 1.

## Discussion

In the present study, we compared baPWV between patients with and without AF and evaluated the determinants of baPWV in all patients and in patients with AF. We found that compared to non-AF patients, AF patients had a higher baPWV. AF was significantly associated with increased baPWV even after adjusting for demographic, clinical and biochemical risk factors. However, additional adjustment for HR made the association between AF and baPWV disappear. In order to avoid over-adjustment of HR, we further adjusted AF  $\times$  HR, but AF was still not associated with baPWV in the final model of Table 2. Hence, HR had an important impact on the relationship between AF and baPWV. Furthermore, in addi-

tion to old age and high SBP, increased HR was also an important determinant of baPWV in our AF patients.

AF is the most common cardiac arrhythmia in clinical practice. AF shares several risk factors and pathophysiological features with atherosclerosis. In fact, peripheral vascular disease is highly prevalent in AF patients and associates with increased mortality [1, 2, 5, 6]. Lee et al. evaluated the effects of AF on arterial stiffness in patients with hypertension and found the presence of AF was significantly correlated with a higher PWV, independently of age or blood pressure in their patients [22]. In this study, we also demonstrated patients with AF had a higher baPWV than those without AF. After adjustment for many

confounding factors, including age and SBP, this association remained significant. However, after additional adjustment for HR, such association disappeared. This association was still insignificant even after further adjustment for AF  $\times$  HR. Hence, HR could significantly influence the relationship between AF and baPWV in our present study. Several studies showed HR was significantly associated with arterial stiffness [17-19]. Some mechanisms might explain the significant association between increased HR and arterial stiffness. First, a higher HR might suggest a higher sympathetic tone [23], which might result in increased vascular tone and resistance. Increased sympathetic tone was positively correlated with a higher rate of oxygen consumption and increased production of proinflammatory cytokines [24]. These cytokines might cause endothelial dysfunction and alter arterial elastic properties, leading to structural stiffness. Second, an increased HR might also reflect an increased metabolic rate, leading to increased oxidative stress and chronic low-grade inflammation [19]. Therefore, increased HR and arterial stiffness might be linked by a chronic low-grade inflammation in the vessel walls. Third, HR might impact directly on the status of the arterial wall, probably because of mechanical pulsatile stress, and also possibly involving the proinflammatory actions of oscillatory fluid shear stresses acting on the vascular endothelium [25]. High HR was reported to be strongly and directly associated with increased arterial rigidity in hypertensive patients, independent of age and blood pressure [26]. In fact, further adjustment for HR substantially attenuated the association between AF and arterial stiffness in the present study. Hence, AF per se might be not a major determinant of arterial stiffness in this study. The higher baPWV in our AF patients was probably resulted from the higher HR in these patients.

In this study, age, SBP and HR were the major determinants of baPWV in our AF patients. Old age and high SBP were well-established parameters of increased arterial stiffness in non-AF patients [27-30]. Our study in AF patients was consistent with these well-established findings. However, whether HR also influences PWV remains controversial. Several cross-sectional population studies in non-AF patients have found either no correlation [31, 32] or a positive correlation between PWV and resting HR [19, 33]. Lee et al. evaluated the determinants of PWV in 68 patients combined non-AF and AF and found HR had no correlation with PWV [22]. Discrepancies in results from these studies might be explained, in part, by different study populations and methodologies in measuring PWV. In the present study, we found HR was a major determinate of baPWV in AF patients.

Hence, rapid ventricular response in AF may be a risk factor of increased arterial stiffness. Good rate control in AF patients may be beneficial in reducing the arterial stiffness.

Obesity might be associated with early vascular changes. Some studies had demonstrated an association between obesity and increased aortic stiffness [34-36]. However, Rodrigues et al. found carotid-femoral PWV was negatively correlated with body mass index and concluded that the previously reported finding of an association between obesity and aortic stiffness was probably confounded by the progressive increase in blood pressure observed in obesity [37]. In this study, we similarly found body mass index had a negative correlation with baPWV in our AF patients in the univariate analysis. After the multivariate analysis, the association between body mass index and baPWV disappeared. Hence, obesity was not a major determinant of baPWV in our AF patients. Because the effect of smoking discontinuation on arterial stiffness remained uncertain, previous studies showed no difference in arterial stiffness between nonsmokers and long-term smokers [38, 39]. In our study, after the multivariate analysis, we similarly found smoking was not associated with baPWV both in all study patients and in AF patients.

Impairment of renal function might increase arterial stiffness. Several studies had shown decreased eGFR had a significant association with increased arterial stiffness in non-AF patients [13, 40, 41]. In our AF patients, we consistently found eGFR had a negative correlation with baPWV in the univariate analysis. However, after the multivariate analysis, this correlation disappeared. Hence, the association between eGFR and baPWV in our AF patients was probably confounded by age, SBP and HR.

### Study limitations

The majority of our patients were treated chronically with antihypertensive medications. For ethical reasons, we did not withdraw these medications. Hence, we could not exclude the influence of antihypertensive agents on our findings. However, in order to minimize the influence of drugs, we had added different classes of antihypertensive drugs in the multivariate analysis. Although we averaged the values of blood pressures, HR and baPWV from 3 time examination in AF patients, the beat-to-beat variation of these values during AF might make the measurement technically difficult and inaccurate. In addition, only resting HR was measured in this study. The evaluation of HR by 24-hour Holter monitoring should be more accurate and reliable than only evaluation of resting HR.

## Conclusions

This study demonstrated the presence of AF was associated with increased baPWV in a multivariate model, but this association became insignificant after further adjustment for HR, which suggested HR could significantly influence the relationship between AF and baPWV. Hence, an association between AF and arterial stiffness was probably confounded by the increased HR in AF patients. Besides, HR was positively correlated with arterial stiffness in our AF patients.

## Competing Interests

The authors have declared that no competing interest exists.

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