

# Brachial - ankle pulse wave velocity in patients with rheumatoid arthritis

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### ABSTRACT

**Objective.** To evaluate 7 brachial-ankle pulse wave velocity (baPWV) in patients with 33 rheumatoid arthritis (RA); and find out the relationship between baPWV and risk factors, disease-related factors, some echocardiographic indicators.

41 **Methods.** A cross-sectional study was conducted on 47 patients with RA who were 5 admitted to the Hue University Hospital Department of Cardiology. A control group that included 34 patients without RA who agreed to participate in the investigation was enrolled.

**Results.** The average baPWV of the RA group was  $1736.6 \pm 436.8$  cm/s and was higher 23 than that of the control group ( $1275.8 \pm 224.2$  cm/s),  $p < 0.001$ . There were moderate 54 correlations between baPWV and the SCORE index ( $r = 0.583$ ,  $p < 0.001$ ). With the same 25 risk factors such as age, gender, obesity, hypertension, and smoking, the baPWV of the 42 RA group was higher than the control group. There were moderate correlations between 11 baPWV and velocity A ( $r = 0.562$ ,  $p < 0.001$ ), E/e' ratio ( $r = 0.394$ ,  $p = 0.006$ ), E/A ratio ( $r = -0.449$ ,  $p = 0.002$ ), septal e' ( $r = -0.488$ ,  $p < 0.001$ ), lateral e' ( $r = -0.397$ ,  $p = 0.006$ ).

49 **Conclusion.** RA is associated with increased arterial stiffness compared to subjects without RA.

**Keywords:** Pulse wave velocity, rheumatoid arthritis.

### INTRODUCTION

51 In 2020, estimated 17.6 million people worldwide have rheumatoid arthritis, with a forecast of 31.7 million by 2050. The global prevalence of rheumatoid arthritis was 0.21% in 2020 [1]. Mortality rates in patients with rheumatoid arthritis are higher than those expected in the general population. The cause with the highest mortality rate is 38 cardiovascular disease, accounting for 39.6% of deaths [2]. One of the cardiac 8

manifestations of rheumatoid arthritis is early atherosclerosis. Many studies have documented the direct relationship of rheumatoid arthritis with atherosclerosis and its independence from other traditional factors risk. Arterial stiffness, as a preclinical marker of atherosclerosis, is a predictor of cardiovascular disease [3]. Ankle-brachial pulse wave velocity reflects the stiffness of large to medium-sized arteries, which is simple to measure in clinical practice. An increase in ankle-brachial pulse wave velocity of 1 m/s corresponds to a 12%, 13%, and 6% increase in the total number of cardiovascular events, cardiovascular mortality, and all-cause mortality, respectively cause [4]. To better understand the relationship between factors associated with rheumatoid arthritis, as well as traditional cardiovascular risk factors, and arterial stiffness measured by ankle-brachial pulse wave velocity, we conducted the present study to explore pulse wave velocity in patients with rheumatoid arthritis and evaluate the relationship between pulse wave velocity and factors related to rheumatoid arthritis, cardiovascular risk factors and some Doppler echocardiographic indices.

## MATERIALS AND METHODS

A cross-sectional descriptive study was conducted on 81 patients  $\geq 18$  years old. These patients were divided into 2 groups, with 47 patients diagnosed with RA according to ACR/EULAR 2010 standards in the disease group and 34 people without RA in the control group at the University hospital. Hue Medicine and Pharmacy from June 2022 to August 2023.

Exclusion criteria were: Patients with contraindications to the measurement of baPWV: deep vein thrombosis, calcified vessels, hardness that cannot be compressed, severe pain in the leg and foot, amputation; Infection, inflammation due to other causes, edema; Patients with other connective tissue diseases: systemic lupus erythematosus, scleroderma, dermatomyositis-polymyositis, mixed connective tissue disease; Poor cardiac Doppler ultrasound image quality.

The disease group records variables: age, gender, smoking, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), duration of RA, speed Erythrocyte sedimentation rate (ESR), serum CRP concentration, RF, Anti-CCP, DAS28, SDAI, CDAI, anemia, blood lipid profiles, cardiovascular risk assessment using the SCORE scale (in Vietnam, use the chart for the group of low-risk countries. Very high, high, medium and low risk correspond to  $\geq 10\%$ ,  $\geq 5\%$ - $<10\%$ ,  $\geq 1\%$ - $<5\%$ ,  $<1\%$ ), indicators Doppler echocardiography (relative wall thickness (RWT), left ventricular mass index (LVMI), ejection fraction (EF), diastolic function indices such as E wave

velocity, A wave velocity, E/A ratio, septal e' wave velocity, lateral e' wave velocity, E/e' ratio and left atrial volume (LAVI)) were measured using a Philips Anffiniti 70G and baPWV was measured using a VP- 1000 plus.

The control group recorded the following variables: age, gender, BMI, SBP, DBP, Doppler echocardiography indices measured with a Philips Affiniti 70G machine and baPWV measured with a VP-1000 plus machine similar to the patient group.

Data were analyzed using SPSS 26.0 software, Excel 2016.

## RESULTS

Among 47 patients with rheumatoid arthritis, disease activity indexes, average DAS28ESR was  $14.1 \pm 7.0$ . There were 26 patients (55.3%) diagnosed for the first time and not yet treated; 17 patients (36.2%) had regular treatment and 4 patients (8.5%) had irregular treatment. Regarding the SCORE scale: The average was  $4.77 \pm 4.55$  points, of which 1 patient (2.1%) had a low-risk SCORE score, 32 medium-risk patients (68.1%), high-risk had 6 patients (12.8%), very high-risk had 8 patients (17%). From the results of Table 1, RA patients had higher baPWV than the control group ( $p < 0.001$ ), Doppler echocardiography indices (LVMI, E, A wave velocity, septal e', lateral e', ratio E/A ratio, E/e') of the disease group and control group had a statistically significant difference ( $p < 0.05$ ).

**Table 1.** Characteristics of study subjects

Characteristics	Case group (n=47)	Control group (n=34)	p
Age (year), $\bar{x} \pm SD$	$58.3 \pm 12.0$	$55.0 \pm 12.0$	0.233
Female, n (%)	36 (76.6%)	16 (47.1%)	0.006
BMI ( $\text{kg}/\text{m}^2$ ), $\bar{x} \pm SD$	$21.6 \pm 3.8$	$21.1 \pm 2.5$	0.541
HATT (mmHg), $\bar{x} \pm SD$	$118.8 \pm 10.6$	$118.5 \pm 12.9$	0.909
HATTr (mmHg), $\bar{x} \pm SD$	$72.2 \pm 7.7$	$70.4 \pm 8.7$	0.332
RWT	$0.41 \pm 0.07$	$0.40 \pm 0.06$	0.258
LVMI ( $\text{g}/\text{m}^2$ )	$102.9 \pm 26.8$	$92.5 \pm 10.6$	<b>0.018</b>
EF (%)	$69.5 \pm 6.9$	$69.6 \pm 3.8$	0.885
E (cm/s)	$79.3 \pm 21.4$	$92.4 \pm 15.0$	<b>0.003</b>

A (cm/s)	87.8 ± 20.6	75.6 ± 12.5	<b>0.001</b>
E/A	0.95 ± 0.39	1.25 ± 0.28	<b>&lt;0.001</b>
e' septal (cm/s)	7.7 ± 2.1	9.9 ± 1.9	<b>&lt;0.001</b>
e' lateral (cm/s)	10.0 ± 2.7	15.4 ± 3.4	<b>&lt;0.001</b>
E/e'	9.1 ± 2.2	7.6 ± 2.2	<b>0.003</b>
LAVI (mL/m <sup>2</sup> )	20.8 ± 11.5	21.1 ± 6.3	0.863
baPWV (cm/s), $\bar{x} \pm SD$	1736.6 ± 436.8	1275.8 ± 224.2	<b>&lt;0.001</b>

When analyzing the same risk factors such as age, gender, obesity, hypertension, and smoking, the baPWV of the case group was higher than the control group. This difference was statistically significant with  $p < 0.05$  (Table 2).

**Table 2.** Comparison of pulse wave velocity in the case group and control group according to cardiovascular risk factors

Characteristics		baPWV (cm/s)		p
		Case group (n=47)	Control group (n=34)	
Age (year)	<50	1462.5 ± 246.8	1259.3 ± 200.4	<b>0.041</b>
	50 - 59	1543.2 ± 282.6	1242.5 ± 192.3	<b>0.003</b>
	≥60	2038.0 ± 444.1	1310.2 ± 267.8	<b>&lt;0.001</b>
Sex	Male	1969.4 ± 494.1	1258.0 ± 145.4	<b>0.001</b>
	Female	1665.5 ± 398.5	1295.9 ± 293.0	<b>0.002</b>
Fat		1533.3 ± 339.4	1136.5 ± 3.0	<b>0.021</b>
Hypertension		2104.1 ± 444.3	1260.3 ± 74.6	<b>0.044</b>
Smoke		2122.7 ± 484.7	1231.0 ± 147.3	<b>0.001</b>

Most untreated and treated patients had baPWV >1400 cm/s, accounting for 76.9% and 71.4%, respectively. These two rates were not statistically significant ( $p > 0.05$ ). The average baPWV value in the untreated group was higher than in the treated group, but it was not statistically significant ( $p > 0.05$ ) (Table 3).

**Table 3.** Rate of increase in baPWV in treated and untreated groups (n=47)

Characteristics		Not treated	Treated	p
baPWV	>1400 cm/s (n. %)	20 (76.9%)	15 (71.4%)	0.668
	≤1400 cm/s (n. %)	6 (23.1%)	6 (28.6%)	
	$\bar{x} \pm SD$ (cm/s)	1817.9 ± 463.3	1635.9 ± 389.0	0.158
<b>Total</b>		26 (100.0%)	21 (100.0%)	

According to Table 4, in people with comorbidities such as hypertension, diabetes, smoking, and dyslipidemia, baPWV was higher than those without it and the difference was statistically significant,  $p < 0.05$ . Similar to older age or different genders, there was also a difference in baPWV,  $p < 0.05$ .

**Table 4.** Comparison of baPWV between 2 RA groups with or without cardiovascular risk factors

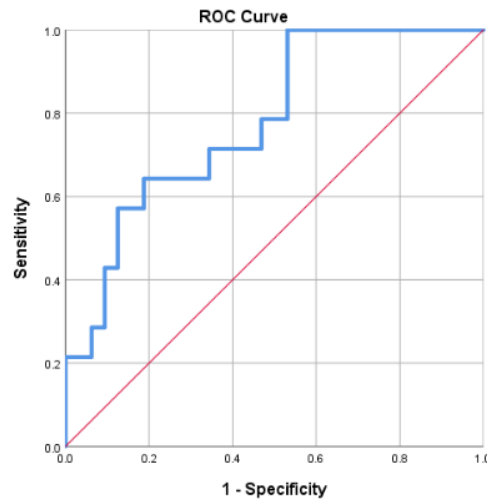
Risk factors		n (%)	baPWV (cm/s)	p
Hypertension	Yes	6 (12.8)	2104 ± 444	0.026
	No	41 (87.2)	1683 ± 414	
Diabetes	Yes	9 (19.1)	2199 ± 500	<0.001
	No	38 (80.9)	1626 ± 344	
Smoke	Yes	8 (17.0)	2123 ± 485	0.005
	No	39 (83.0)	1657 ± 387	
Lipid disorders	Yes	33 (70.2)	1817 ± 442	0.050
	No	14 (29.8)	1546 ± 372	
Overweight. obese (BMI ≥ 23 kg/m <sup>2</sup> )	Yes	15 (31.9)	1678 ± 432	0.533
	No	32 (68.1)	1764 ± 443	
Sex	Male	11 (23.4)	1969 ± 494	0.042
	Female	36 (76.6)	1665 ± 398	

Age (year)	≥ 60	20 (42.6)	2038 ± 444	<0.001
	< 60	27 (57.4)	1513 ± 268	

The results of our study show a strong positive correlation between baPWV and age ( $r=0.512$ ,  $p < 0.001$ ) and the SCORE score ( $r=0.583$ ,  $p < 0.001$ ). However, no significant correlation was found between baPWV and RA-related factors, such as DAS28, RF, and AntiCCP (Table 5). With the cutoff point baPWV>1509 cm/s, pulse wave velocity was meaningful in diagnosing high-risk factors according to the SCORE scale with sensitivity: 100%, specificity: 46.9% (95%CI: 0.640-0.918). Area under the ROC curve: AUC = 0.779 with  $p=0.003$  (Figure 1).

**Table 5.** Correlation between baPWV and cardiovascular risk factors, some Doppler echocardiographic indices.

Variable	baPWV (cm/s)	
	$r$	$p$
Age (year)	0.512	<0.001
BMI (kg/m <sup>2</sup> )	-0.126	0.398
SBP (mmHg)	-0.108	0.471
DBP (mmHg)	0.076	0.610
Duration (year)	-0.146	0.328
Cholesterol total (mmol/L)	-0.017	0.912
Triglyceride (mmol/L)	0.074	0.619
HDL-C (mmol/L)	-0.194	0.192
LDL-C (mmol/L)	-0.003	0.987
RF (IU/mL)	0.005	0.972
Anti-CCP (IU/mL)	0.008	0.956
ESR (mm/h)	0.080	0.592
CRP (mg/L)	0.235	0.112
DAS28ESR	-0.195	0.190
SCORE	0.583	<0.001



**Figure 1.** ROC curve of baPWV according to SCORE

From Table 6, we see a strong positive correlation between baPWV and A-wave velocity ( $r = 0.562$ ,  $p < 0.001$ ), an average positive correlation between baPWV and E/e' ratio ( $r = 0.394$ ,  $p = 0.006$ ). There is a moderate negative correlation between baPWV and E/A ratio ( $r = -0.449$ ,  $p = 0.002$ ), e' septal ( $r = -0.488$ ,  $p < 0.001$ ), e' lateral ( $r = -0.397$ ,  $p = 0.006$ ).

**Table 6.** Correlation between baPWV and some echocardiographic indices

Variable	baPWV			
	Case group (n=47)		Control group (n=34)	
	r	p	r	p
RWT	0.091	0.544	0.185	0.295
LVMi	-0.027	0.856	-0.106	0.551
EF	-0.112	0.453	-0.132	0.458
E	-0.091	0.542	-0.396	<b>0.021</b>
A	0.562	<b>&lt;0.001</b>	0.484	<b>0.004</b>
E/A	-0.449	<b>0.002</b>	-0.578	<b>&lt;0.001</b>
e' septal	-0.488	<b>&lt;0.001</b>	-0.422	<b>0.013</b>
e' lateral	-0.397	<b>0.006</b>	-0.477	<b>0.004</b>
E/e'	0.394	<b>0.006</b>	0.362	<b>0.036</b>
LAVI	0.135	0.365	-0.199	0.260



## DISCUSSION

Rheumatoid arthritis is a common disease, especially in women, with many potentially dangerous risks. Therefore, early detection through assessment of risk factors and characteristics of rheumatoid arthritis helps develop appropriate and timely monitoring and treatment intervention strategies.

Diastolic dysfunction is when there is a relaxation dysfunction; the ventricles become stiff during diastole. Many studies evaluate arterial stiffness or pulse wave velocity to diastolic dysfunction. For example, according to the study of Takayuki Namba and colleagues [5], arterial stiffness contributes to the development of left ventricular diastolic dysfunction. According to Chen Gailing et al [6], elevated baPWV is significantly related to diastolic function in essential hypertension patients with left ventricular hypertrophy. Therefore, our study also sought the relationship between baPWV and some Doppler echocardiographic indices of diastolic function.

According to the research results of Hoang Trung Dung, on 122 RA patients, the A-wave of the disease group was statistically significantly higher than the control group with  $p < 0.01$ . The E/A ratio of the disease group was statistically significantly lower than the control group with  $p < 0.05$  [7]. According to Erdem Fatma, Koc Bunyamin, research on 76 RA patients and 50 healthy control subjects, E waves and E/A ratio in RA patients were lower than healthy patients (E:  $74 \pm 10$  and  $86 \pm 12$ ,  $p = 0.01$  compared with E/A:  $1.1 \pm 0.8$  and  $1.24 \pm 0.1$ ,  $p = 0.001$ ), also, E/e' ratio in RA patients higher than patients with non-rheumatoid arthritis (E/e':  $8.7 \pm 1.6$  and  $8.0 \pm 1.4$ ,  $p = 0.020$ ) [8]. However, according to research by Davis et al. (2015), 160 RA patients and 1391 healthy people were studied as a control group. The results of Doppler ultrasound through the mitral valve showed that the E/A ratio in RA patients was lower than in the control group with  $r = -0.096$ ,  $p < 0.0001$ . There was an increase in A wave velocity over time between RA patients compared to the control group with  $r = 0.030$ ,  $p < 0.0001$ . The e' velocity decreased and the E/e' ratio increased over time in both groups, but these changes did not differ between the two groups [9]. Thus, our research results are similar to domestic and foreign research.

From Table 1, we also present research results showing that the pulse wave velocity in the disease group is higher than the control group and is statistically significant. The results of our study are similar to the study of Ping Li, Cheng-Xun-Han et al., baPWV was significantly higher in the rheumatoid arthritis group ( $1705.44 \pm 429.20$  cm/s) compared to the healthy control group ( $1386.23 \pm 411.09$  cm/s) ( $P < 0.001$ ) [10].

According to Young-Sam Kim, Yoon-Kyoung Sung et al., the study included 262 patients with RA treated in a tertiary clinic with a mean baPWV of  $1559 \pm 354$  cm/s [11]. So, our research results are higher. The difference in study sample size may explain this.

We also refer to some studies on PWV in disease groups other than rheumatoid arthritis such as the study by author Ho Thi Kim Ngan on patients with ischemic heart disease, baPWV in disease groups and control groups respectively:  $15.75 \pm 1.99$  and  $13.8 \pm 1.83$  m/s; in diabetic patients:  $15.89 \pm 2.07$  and  $14.06 \pm 1.29$  m/s; smokers:  $15.76 \pm 1.97$  and  $13.82 \pm 1.45$  m/s; overweight people:  $15.69 \pm 1.79$  and  $13.59 \pm 2.12$  m/s. From here, the author concludes that the average baPWV and the rate of increased baPWV ( $\geq 14$  m/s) in the disease group are higher than the control group. In people with hypertension, diabetes, smoking, and overweight, the baPWV of the disease group was statistically significantly higher than that of the control group with  $p < 0.05$  [12]. Thus, good control of risk factors not only reduces cardiovascular events but can also reduce arterial stiffness in RA patients.

Research by Diana S. Novikova and colleagues also shows that rituximab therapy can suppress systemic inflammation, improve lipid composition and atherosclerosis index, reduce carotid artery IMT, and improve cardiovascular characteristics. elasticity of the arterial wall in patients with rheumatoid arthritis without cardiovascular disease [13].

The results of our study show a strong positive correlation between baPWV and age ( $r=0.512$ ,  $p < 0.001$ ) and the SCORE score ( $r=0.583$ ,  $p < 0.001$ ). However, no significant correlation was found between baPWV and RA-related factors, such as DAS28, RF, and AntiCCP. The results of this study are different from the results of Ping Li, Cheng-Xun Han et al., baPWV of patients with RA has a positive correlation with age, TC, TG, and LDL-C, there is no relationship between baPWV and disease duration, DAS28, RF, Anti-CCP, ESR, CRP [10]. In the study by Jiahui Liu et al., TG, TC, LDL-C, and non-HDL-C were all positively and independently correlated with baPWV in multivariable logistic regression analysis. HDL-C concentration is negatively correlated with baPWV [14]. However, our results are similar to the study of Taquet et al. on 429 healthy middle-aged women; no association was observed between baPWV and HDL-C, TC and TG [15], as well as the study by Jianghua Wen et al. also found no significant association between high baPWV and TC, LDL-C, HDL-C and non-HDL-C after adjustment for other variables in men—Chinese age [16].

Our study's differences or similarities to the above studies show that participants' medical history, race, gender, age, and sample size may affect the results.

According to Lebogang Mokotedi, studying 173 RA patients, PWV is related to E/e' [17]. According to Minkwan Kim, Hack-Lyoung Kim, research on 7,013 participants, the results showed a significant correlation of baPWV with wall e' velocity ( $r = -0.408$ ;  $p < 0.001$ ), E/e' ( $r = 0.349$ ,  $p < 0.001$ ), LAVI ( $r = 0.122$ ,  $p < 0.001$ ) [18].

E/A and E/e' have been used repeatedly to predict all-cause mortality, cardiovascular mortality, and heart failure hospitalizations in several conditions, including acute myocardial infarction, cardiomyopathy, and heart failure. In asymptomatic individuals with risk factors for heart failure (age, hypertension, diabetes, and obesity), worsening stages of ED based on E/A and E/e' are also weak. Predictor of adverse cardiovascular outcomes [19].

## CONCLUSION

Rheumatoid arthritis is associated with increased arterial stiffness compared to control subjects who do not have rheumatoid arthritis. More research is needed using pulse wave velocity measurement on a larger scale, with prospective monitoring and other invasive and non-invasive scientific means to compare and strengthen the relationship between pulse wave velocity - arterial stiffness - rheumatoid arthritis, thereby facilitating application in clinical practice.

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