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Original Article

Effect of Rheumatoid Factor on Vascular Stiffness in General Population without Joint Symptoms

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Objectives: The role of rheumatoid factor (RF) in vascular stiffness and cardiovascular risk in subjects without joint symptoms remains unclear. We investigated vascular stiffness in subjects without joint symptoms using pulse wave velocity (PWV), calculated Framingham risk scores (FRS), an estimator of cardiovascular risk, and analyzed whether vascular stiffness and FRS were affected by RF.
Methods: Two hundred forty-two subjects were included in this population-based study. RF was quantified with turbid immunometry using a cut-off of RF 〉 15 IU/ml to denote RF positivity. Information was then obtained on joint symptoms. Brachial-ankle PWV (baPWV) was measured using an automated device.
Results: Of the 242 subjects, 15 were RF-positive. RF-positive subjects without joint symptoms had a higher baPWV and FRS than RF-negative subjects without joint symptoms, but the difference did not reach statistical significance. However, when we stratified the subjects into two groups (group A – high RF: RF ≥ 40 IU/ml; group B – low RF: RF 〈 40 IU/ml), group A showed significantly higher baPWV (1640.7 ± 179.6 ㎝/s vs. 1405.7 ± 225.7 ㎝/s, P = 0.008) and FRS (25.7 ± 4.87 vs. 11.8 ± 9.6, P 〈 0.001). Multiple regression analysis was used to examine potential confounders, and RF exhibited significant but modest effects on baPWV (adjusted R-squared = 0.038, P = 0.030).
Conclusions: In a sample of the general population without joint symptoms, higher levels of RF were associated with increased vascular stiffness, suggesting a pathophysiologic link between RF and endothelial dysfunction.

Key Words: Pulse wave analysis, Rheumatoid factor, Vascular stiffness,

In patients with rheumatoid arthritis (RA), life expectancy is reduced by 3 to 10 years compared to that of the normal population, and this increased mortality is largely due to cardiovascular disease (CVD) caused by accelerated atherosclerosis found in RA.[1] A recent meta-analysis indicated that the risk of CVD-associated death and cerebrovascular disease could be as much as 50% higher in patients with RA compared with controls.[2] Enhanced vascular risk is not limited to individuals with diagnosed RA, because increased mortality in non-RA patients who have early inflammatory polyarthritis or elevated levels of rheumatoid factor (RF) has been reported.[3]

RA activity has been associated with CVD, and it is not clear whether the increased car-

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diovascular risk seen in RA patients is dependent on traditional cardiovascular risk factors. Del Rincon ID et al. suggested that the incidence of cardiovascular events in RA patients might actually be independent of traditional cardiovascular risk factors.[4] In his study, the incidence rate ratio of cardiovascular events in RA patients was meaningful after adjusting for traditional cardiovascular risk factors. Furthermore, a study in people without chronic arthritis described an association between high RF titers and increased cardiovascular and all-cause mortality after adjusting for traditional risk factors.[5] Also, RA patients who are positive for anti-cyclic citrullinated peptide antibodies (anti-CCP Abs) have greater subclinical atherosclerosis than those who are not.[6] A recent study revealed that ischemic heart disease in RA is independently associated with positive anti-CCP Abs.[7]

Although RF has been shown to be associated with increased cardiovascular mortality in RA, whether RF directly influences CVD remains unclear. RF is associated with smoking, which is a known cardiovascular risk factor.[8] RF is present in up to 15% of elderly subjects. RF may arise through polyclonal B cell activation caused by an infection or antigen-driven proliferation of B cells associated with autoimmune diseases, suggesting that immunological factors may have a role.[9] There is also the possibility that the effect of RF is mediated by inflammation, which has been found to predict CVD and mortality.

In this study, we investigated whether the presence of RF is associated with endothelial dysfunction in subjects without joint symptoms or inflammation. We evaluated the effect of RF on endothelial function using pulse wave velocity (PWV), which assesses arterial stiffness by measuring the status of large and small arteries in the lower extremities. We also calculated the Framingham Risk Score (FRS) to estimate cardiovascular risk.[10] To isolate the effect of RF, we restricted the analysis to RF-positive subjects without joint symptoms and with C-reactive protein (CRP) levels within normal range.

MATERIALS AND METHODS

1. Study Population

We performed cross-sectional analysis using 242 consecutive subjects without joint symptoms who underwent brachial-ankle (ba) PWV assessment from January 2010 to December 2012 in our hospital for health screening (Fig. 1). At enrollment, musculoskeletal symptoms during the preceding 12 months, including joint pain, joint swelling, and morning stiffness, were probed. Those who answered 'no' to all three questions were included in this study. We excluded subjects who were being treated for arthritis or had a history of rheumatoid arthritis. Subjects with CRP levels outside of the normal range were also excluded from the study. Subjects with autoimmune rheumatic diseases, ANA titers above 1:160, history of thyroid diseases, palpable goiter, or abnormal

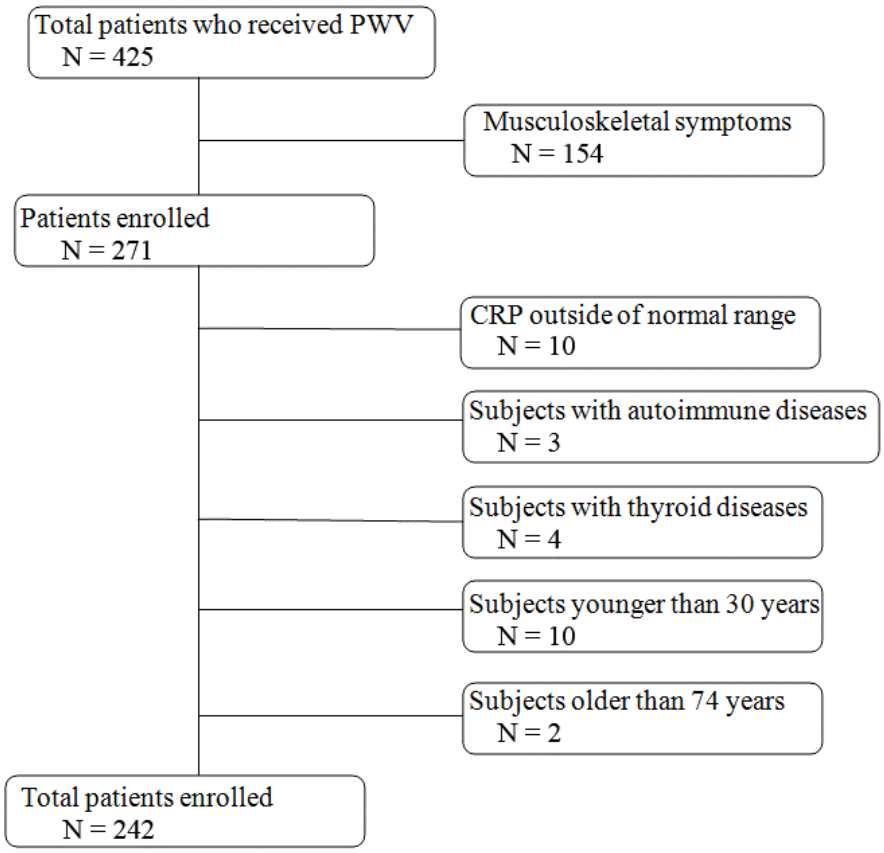

Fig. 1. Study population flowchart.

free T4 (FT4) or thyroid stimulating hormone (TSH) levels were additionally excluded. Subjects younger than 30 years or older than 74 years were excluded because of the limits on the age range in the FRS.[11] Informed consent from the patients was not required because we examined the data retrospectively from medical records and de-identified it after collection to ensure patient confidentiality. This study protocol was approved by the ethics review boards (MMC/2013/09/24-1[174]).

2. Baseline Data

Information on smoking (never, former, or current), alcohol, and medication use was obtained from a questionnaire. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. Blood pressure (BP) was measured with a standard mercury manometer. Hypertension was denoted by persistent blood pressures at or above 140/90 mmHg, as recommended by the Joint National Committee VII, or if the subject was being treated for hypertension.

3. Laboratory Evaluation

All subjects fasted for at least 12 hours at the beginning of the study before blood tests. Plasma glucose, total cholesterol, triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were determined by standard lab-

oratory procedures. The American Diabetes Association criteria were used to define Diabetes Mellitus (DM) and we considered a subject to have DM when fasting plasma glucose levels were ≥ 126 ㎎/dL on two consecutive assessments or if the subject was being treated for DM. Rheumatoid factor was quantified with turbid immunometry (Advia 1800, Siemens) using a cut-off of RF 〉 15 IU/ml to designate RF-positivity. The plasma concentration of high-sensitivity CRP (hsCRP) was measured by performing fully automated turbid immunometry (Advia 1800, Siemens). The study participants were also subdivided into two groups based on RF (group A: RF ≥ 40 IU/ml; group B: RF 〈 40 IU/ml).

4. FRS Measurement

The FRS was determined by summing the Framingham points assigned to each risk factor, such as age, LDL, HDL, BP (regardless of using antihypertensive medications), cigarette smoking, and DM.

5. Measurement of Arterial Stiffness

Arterial stiffness was assessed by measuring the baPWV using an automatic waveform analyzer (VP-1000; Colin Co., Komaki, Japan). The VP-1000 simultaneously records pulse waves, blood pressure (BP; both arms and ankles), ankle-brachial pressure index (ABI), ECG, and heart sounds, as described elsewhere.[12] ABI was calculated as the ratio of ankle systolic BP to arm systolic BP, with the lowest measured values of the ankle systolic BP used for the calculation. For the measurement of baPWV, pulse waves obtained from the brachial and tibial arteries were recorded simultaneously and the transmission time was defined by the time interval between the initial rise in brachial and tibial waveforms. The transmission distance from the arm to each ankle was calculated using body height. The baPWV was automatically computed as the transmission distance divided by the transmission time. All participants included in the present study had a normal ABI (〉 0.9). High baPWV values were defined as those in the gender-specific highest quartile among the study subjects [baPWV (the mean of the right and left values) ≥ 1,490 ㎝/s in females].

6. Statistical Analysis

Statistical analysis was performed using SPSS for Windows version 21.0 (Chicago, IL). Results are presented as the mean ± standard deviation (SD) or percentage. Because the number of RF-positive subjects and subjects with RF ≥ 40 IU/ml was relatively small and the assumption of the general-linear models was not met, comparisons between those groups were performed using the Mann-Whitney U test. Correlation coefficients were calculated using the Spearman correlation tests. Statistical significance was defined as a *P*-value 〈 0.05.

RESULTS

Table 1. Subjects' characteristics

	Men (n = 164)	Women (n = 78)	*P*
Age (years)	51.85±7.18	50.76±9.20	0.31
Smoking (n, %)	51 (31.1%)	3 (3.8%)	〈 0.001
Diabetes mellitus (n, %)	13 (7.9%)	3 (3.8%)	0.28
Hypertension (n, %)	24 (14.6%)	11 (14.1%)	0.99
SBP (mmHg)	126.7±15.07	124.8±14.61	0.35
DBP (mmHg)	80.3±11.89	76.1±10.56	0.008
Total cholesterol (mmol/l)	198.1±33.42	196.8±34.18	0.78
HDL (mmol/l)	49.2±11.58	61.6±17.52	〈 0.001
LDL (mmol/l)	123.2±30.8	116.3±28.43	0.09
Triglyceride (mmol/l)	155.3±104.86	101.6±54.03	〈 0.001
BMI (kg/㎡)	24.5±2.67	23.2±2.78	〈 0.001
ABI	1.1±0.06	1.09±.062	0.25
BaPWV (㎝/s)	1424.4±225.21	1387.6±232.29	0.24
Uric acid	6.04±1.25	4.2±1.12	〈 0.001
FRS	15.5±10.07	5.2±3.95	〈 0.001
RF (IU/mL)	8.7±14.09	7.0±3.84	0.14

Data are presented as number (%) or mean SD unless otherwise indicated. *P* 〈 0.05 was considered statistically significant. *SBP*, Systolic blood pressure; *DBP*, Diastolic blood pressure; *HDL*, high density lipoprotein; *LDL*, low density lipoprotein; *BMI*, body mass index; ABI,ankle brachial index; *baPWV*, brachial ankle pulse wave velocity; *FRS*, Framingham risk score; *RF*, rheumatoid factor

1. Clinical Characteristics of Subjects

Two hundred forty-two subjects (164 men, 78 women, 51.2 ± 8.9 years) were included in this population-based study. Of the 242 subjects, 15 were RF-positive (11 men and 4 women). Traditional risk factors, including smoking, elevated diastolic BP, TG, and BMI, were significantly more frequent in men than in women. Furthermore, HDL was significantly lower and FRS was significantly higher in men than in women. The baseline characteristics of participants are shown in (Table 1).

2. Association between RF and Arterial Stiffness

Systolic and diastolic BP, BMI, HDL, LDL, total cholesterol, and triglycerides showed no correlation with the presence of elevated RF levels. RF-positive subjects without joint symptoms had a higher baPWV and FRS than RF-negative subjects, but neither comparison reached statistical significance (Table 2). The study participants were further subdivided into two groups based on the RF value (group A, RF ≥ 40 IU/ml; group B, RF 〈 40 IU/ml). Group A was significantly older. There were no significant differences in SBP, DBP, total cholesterol, HDL, LDL, TG, uric acid, BMI, or ABI

Table 2. Baseline characteristics of RF-negative and RF-positive subjects. RF-positive subjects without joint symptoms had higher baPWV and FRS than RF-negative subjects, but neither comparison reached statistical significance

	RF-negative (n = 227)	RF-positive (n = 15)	*P*
Mean (SD) age (years)	53.40±7.20	51.38±7.94	0.123
Female sex (n, %)	74 (32.6%)	4 (26.7%)	0.780
Smoking (n, %)	2 (13.3%)	52 (22.9%)	0.532
Diabetes mellitus (n, %)	0 (0.0%)	16 (7.0%)	0.607
HBP (n, %)	3 (20.0%)	32 (14.1%)	0.461
Systolic blood pressure (mmHg)	124.73±14.94	126.20±14.95	0.560
Diastolic blood pressure (mmHg)	78.73±8.75	79.01±11.81	0.499
Total cholesterol (mmol/l)	187.93±21.11	198.37±34.21	0.144
HDL (mmol/l)	52.47±23.62	53.32±14.22	0.299
LDL (mmol/l)	121.60±24.20	120.94±30.62	0.843
Triglyceride (mmol/l)	137.20±57.93	138.11±96.93	0.379
BMI (㎏/㎡)	24.11±2.74	24.13±2.78	0.927
ABI	1.10±0.07	1.10±0.06	0.533
Mean baPWV (㎝/s)	1408.60±226.10	1472.60±251.03	0.312
Uric acid	5.50±1.42	5.47±1.48	0.742
Framingham	11.99±9.78	16.23±10.25	0.097

Data are presented as number (%) or mean SD unless otherwise indicated. $P < 0.05$ was considered statistically significant. *SBP*, Systolic blood pressure; *DBP*, Diastolic blood pressure; *HDL*, high density lipoprotein; *LDL*, low density lipoprotein; *BMI*, body mass index; *ABI*, ankle brachial index; *baPWV*, brachial ankle pulse wave velocity; *FRS*, Framingham risk score

between the two groups. However, significantly higher baPWV and FRS values were noted in group A when compared with those of group B (Table 3).

3. Correlation of Brachial Artery Pulse Wave Velocity Values with Clinical Features of Participants

Age (Spearman coefficient 0.355, $P < 0.001$), SBP (coefficient 0.631, $P < 0.001$), DBP (coefficient 0.455, $P < 0.001$), RF (coefficient 0.135, $P = 0.035$), and TG (coefficient 0.133, $P = 0.038$) showed significant correlations with baPWV. However, baPWV did not correlate with total cholesterol, HDL, LDL, uric acid, or BMI. In multiple regression analysis, age, SBP, and RF were significant contributors to increased baPWV (Table 4).

DISCUSSION

In this study, we analyzed the association of RF with arterial stiffness and endothelial function in subjects without joint symptoms or inflammation

Table 3. Comparison between high (≥ 40 IU/mL) and low (〈 40 IU/mL) RF group. Significantly higher baPWV and FRS values were noted in group A when compared with those of group B

	Group A (n = 7)	Group B (n = 235)	*P*
Mean (SD) age (years)	58.00±3.00	51.31±7.91	0.003
Female sex (n, %)	0 (0.0%)	78 (33.2%)	0.100
Smoking (n, %)	1 (14.3%)	53 (22.6%)	〉 0.99
Diabetes mellitus (n, %)	0 (0.0%)	16 (6.8%)	〉 0.99
HBP (n, %)	1 (14.3%)	34 (14.5%)	〉 0.99
Systolic blood pressure (mmHg)	133.14±15.96	125.90±14.88	0.238
Diastolic blood pressure (mmHg)	83.29±9.48	78.86±11.68	0.466
Total cholesterol (mmol/l)	186.86±14.95	198.05±33.97	0.315
HDL (mmol/l)	45.86±7.71	53.49±15.02	0.204
LDL (mmol/l)	123.43±18.36	120.91±30.53	0.765
Triglyceride (mmol/l)	136.14±23.03	138.11±96.231	0.270
BMI (㎏/㎡)	23.87±1.52	24.13±2.80	0.822
ABI	1.13±0.09	1.10±0.06	0.622
Mean baPWV (㎝/s)	1640.71±179.64	1405.77±225.75	0.008
Uric acid	6.26±0.77	5.44±1.48	0.086
Framingham	25.77±4.87	11.85±9.67	〈 0.001

Data are presented as number (%) or mean SD unless otherwise indicated. *P* 〈 0.05 was considered statistically significant. *SBP*, Systolic blood pressure; *DBP*, Diastolic blood pressure; *HDL*, high density lipoprotein; *LDL*, low density lipoprotein; *BMI*, body mass index; *ABI*, ankle brachial index; *baPWV*, brachial ankle pulse wave velocity; *FRS*, Framingham risk score.

using baPWV. The main findings are as follows: 1) subjects with high levels of RF had significantly higher baPWV and FRS, reflecting 10-year cardiovascular risk, and 2) RF was identified using multiple regression analysis as a contributing factor to increased baPWV.

RF is a family of autoantibodies that recognize epitopes on the Fc portion of IgG. The Fc portion of IgG is essential for complement fixation and interaction with the Fc receptor, and thus for uptake of immune complexes. A transient increase of RF is part of the normal immunoregulatory process that occurs during bacterial and viral infections, probably in response to immune complexes containing microbial antigens. A low titer of RF can be found in 10 to 15% of healthy individuals, whereas chronic persistence of high-affinity IgM-type RF at elevated titers and the presence of IgG and IgA subtypes are characteristic features of RA. RF can be found in lower titers in many other rheumatic autoimmune diseases as well.[13] At the commonly used cut-off value of 15 to 20 IU/mL, RF shows only moderate specificity for RA; specificity is considerably increased at higher titers, and several studies have found RF levels above 40 to 50 IU/mL to be quite

Table 4. Multiple regression analysis between baPWV and clinical parameters. Age, SBP, and RF were identified as significant contributors to increased baPWV in multiple regression analysis

	Univariate analysis			Multivariate analysis		
	Coefficient (β)	95% CI	*P*	R^2	Coefficient (β)	*P*
Age	11.897	8.555-15.238	< 0.001	0.170	8.367	< 0.001
SBP (mmHg)	9.516	8.000-11.031	< 0.001	0.389	7.720	< 0.001
DBP (mmHg)	8.066	5.797-10.335	< 0.001	0.170	1.771	0.122
Total cholesterol (mmol/L)	0.442	-0.417-1.302	0.312	0.004	-0.593	0.421
HDL (mmol/L)	-1.061	-2.999-0.877	0.282	0.005	-0.859	0.338
LDL (mmol/L)	0.287	-0.670-1.245	0.555	0.001	1.106	0.148
Triglyceride (mmol/L)	0.262	-0.042-0.565	0.091	0.012	-0.096	0.518
BMI (㎏/㎡)	4.100	-6.322-14.522	0.775	0.002	-7.128	0.081
RF (IU/mL)	3.743	1.341-6.145	0.002	0.038	1.194	0.030
baPWV(R^2 = 0.497, adjusted R^2 = 0.477 in multivariate analysis)						

Data are presented as number (%) or mean SD unless otherwise indicated. *P* < 0.05 was considered statistically significant. *SBP*, Systolic blood pressure; *DBP*, Diastolic blood pressure; *HDL*, high density lipoprotein; *LDL*, low density lipoprotein; *BMI*, body mass index; *RF*, rheumatoid factor.

specific for RA.[14,15] High titers of RF have considerable prognostic value because they are associated with severe RA, more rapid disease progression, worse outcome, extra-articular manifestations, and an increased likelihood of developing CVD. We found that RF-positive subjects had a higher baPWV than RF-negative subjects, but the association was not statistically significant. However, subjects with higher levels of RF showed significantly higher baPWV and FRS, suggesting that higher levels of RF are associated with arterial stiffness and cardiovascular mortality.

We previously reported that endothelial dysfunction, as measured by decreased elastic properties of the carotid artery wall, was more prevalent in the patients with RA.[16] Several studies suggested that RF has been associated with increased cardiovascular mortality in subjects with RA.[3,17,18] In addition, studies in people without arthritis showed an association between RF and cardiovascular mortality.[5,19] Our findings add to the previous findings on effects of RF on arterial stiffness. We used baPWV to quantify the severity of arterial stiffness; baPWV is defined as the time delay between the rapid upstroke of the feet and the simultaneously recorded pulse waves in the brachial artery and tibial artery, and has been reported to be a good marker for arterial stiffness.[20] Though the value of baPWV in predicting cardiovascular events has been suggested to be limited, there are some studies showing baPWV as an independent predictor of cardiovascular death

and cardiac events in elderly persons in the community and in patients with CVD.[21,22] BaPWV measurement is noninvasive and cost effective when conducted using simple techniques, and thus has significant potential for screening applications.

Exactly how RF leads to arterial stiffness remains unclear. However, there are several hypotheses concerning the vascular effect of RF. First, RF titer levels are positively associated with age (a known cardiovascular risk factor).[23] This association is found in this study, and similarly reported in other population cohorts and patients with RA. However, adjusting for age did not remove the effect of RF on baPWV, so the effect of RF cannot be explained by age alone. There were some studies suggesting that RF is associated with other cardiovascular risk factors, including smoking, DM, and serum cholesterol levels,[5,24] but we could not find any association between RF and these other cardiovascular risk factors. Second, inflammation has been reported to predict cardiovascular events. Previous studies in patients without RA pointed out the importance of inflammation in the atherosclerotic process.[25-27] The effect of RF might be explained by inflammation, so we recruited subjects with normal levels of C-reactive protein (CRP) and without joint symptoms to reduce the possible confounding influence of inflammation. Finally, it is possible that either immunologic factors play a role in atherosclerosis or RF has direct pathological effects on the endothelium. One study that immunohistochemically evaluated the role of RF in rheumatoid vascular injury suggested that vascular injury involves the production of RF on the endothelial cell surface in rheumatoid nodules.[28]

There are several limitations to this study. The first is the small number of subjects. Future studies with larger sample sizes should be undertaken to overcome this limitation. Another limitation is the cross-sectional study design, which cannot demonstrate causal associations. Also, it is possible that some subjects included in this study developed RA after the study was completed, so some results might be driven by RA itself. We evaluated hsCRP levels only once, which did not reflect the effects of changes in the inflammatory marker over time. Finally, we did not account for all of the medications that may have some effect on endothelial function.

In conclusion, higher levels of RF were associated with increased arterial stiffness in a sample of the general population without joint symptoms, suggesting a pathophysiologic link between RF and endothelial dysfunction. Longitudinal studies employing larger samples are needed to determine the prognostic implication of increased arterial stiffness in RF-positive subjects.

Higher levels of RF were associated with increased vascular stiffness in the general population, suggesting a pathophysiologic link between RF and endothelial dysfunction.

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