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Stiffening of aorta is more preferentially associated with rheumatoid arthritis than peripheral arteries

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Abstract

The objective of this study is to investigate the relative impact of rheumatoid arthritis (RA) and other factors on arterial stiffness of different regions assessed by regional pulse wave velocity (PWV). Seventy-two patients with RA and 55 strictly matched healthy controls were included. Doppler ultrasound was used to measure the PWV of heart–carotid (hcPWV), heart–femoral (hfPWV), brachial–radial (brPWV), femoral–ankle (faPWV) and carotid–femoral segments (cfPWV) in all subjects. The reproducibility of regional PWV measurement was evaluated in 30 random RA patients. In RA patients, the hfPWV and cfPWV were significantly higher than that in controls ($P=0.0006$, $P=0.0001$, respectively), and the hcPWV, brPWV and faPWV only showed an increase trend without significance. The mean increase magnitude of hfPWV (17.5%) and cfPWV (18.5%) were greater than brPWV (7.2%) and faPWV (1.7%) in RA patients. The association between RA and both hfPWV, cfPWV remained significant after adjustments for other confounders ($P<0.001$). However, the association between RA and brPWV ($P=0.199$), faPWV ($P=0.599$) was not significant. In addition, age and systolic blood pressure were also significant independent factors associated with hfPWV and cfPWV. The reproducibility analysis showed that hfPWV and cfPWV measurements had lower coefficient of variation than others. The stiffness of different arterial regions is not equally affected by RA. The stiffening of aorta is more preferentially associated with RA than that of the peripheral arteries in extremities. The discrepant stiffening between aorta and peripheral arteries may provide a new insight into the pathogenesis of cardiovascular and microvascular dysfunction frequently occurred in RA.

Keywords Rheumatoid arthritis · Vascular stiffness · Aorta · Doppler · Ultrasonography

Introduction

Rheumatoid arthritis (RA) is associated with higher risk of cardiovascular disease than the general population. The accelerated atherosclerosis which is mainly caused by the

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systemic autoimmune disorder and chronic inflammatory lesions mostly contributes to the increased morbidity and mortality in RA [1]. Early detection of subclinical atherosclerosis grows in importance and could help clinicians to take appropriate prevention strategies for cardiovascular outcomes in patients with RA [2, 3]. Arterial stiffness (AS) is one of the earliest detectable manifestations within the atherosclerotic vessel wall [4], and now acts as a strong independent predictor of cardiovascular adverse events and all-cause mortality in various populations [5, 6]. Aortic pulse wave velocity (PWV) has been confirmed to be the most validated and "gold standard" method to noninvasively quantify AS [5].

In recent years, there has been a growing interest in the relationship between AS and RA. Many previous studies have demonstrated that aortic PWV, usually measured by carotid–femoral PWV (cfPWV) which mainly covers the descending and abdominal aorta, was significantly increased in RA patients [7–9]. The brachial–ankle PWV (covering the lower limb arteries and a distal part of aorta) in RA patients was also observed to be increased by some studies [10, 11]. Furthermore, another study showed that RA patients had an increased prevalence of lower limb peripheral arterial disease [12]. However, interestingly, a recent meta-analysis indicated that the carotid–radial PWV (upper limb arteries) did not increase significantly but show a trend towards rising [13], even though in which some results remained discrepant. Thus, AS of different regions seems to be unequally impaired by RA and supposed to have different roles in the cardiovascular pathologies in RA.

There is currently very limited information regarding risk factors involved in AS of different arterial regions in patients with RA. To date, there is no single study that examined the relative impact of RA and other factors on AS of different arterial regions. Roles of AS of different regions in the pathogenesis of cardiovascular dysfunction in RA are largely unknown. The objective of this study was to investigate the impact of RA and other factors on AS of different arterial regions assessed by PWV.

Methods

Subjects

Seventy-two patients with early RA and 55 strictly matched healthy controls were included in this study. They were comparable in age, gender, body weight and height. The patients were enrolled from the newly diagnosed patients attending to the Rheumatology Department of Tangdu Hospital, Fourth Military Medical University from Mar. 2016 to Dec. 2018. The controls were enrolled from participants of the health checking center in the hospital during the same time period, based on a careful medical assessment. RA was diagnosed according to the 2010 American College of Rheumatology criteria [14]. The early RA refers to the disease duration ≤ 2 years. The disease duration which refers to the particular time interval from the initial onset of the symptom to the RA diagnosis was established. All patients with early RA had not used any corticosteroids, immunosuppressive medication or nonsteroidal anti-inflammatory drugs before the study. The age of the subjects ranged from 35 to 55 years old. The exclusion criteria were: hypertension, hyperlipidemia (total cholesterol levels ≥ 200 mg/dL), diabetes mellitus, arrhythmia, reduced left ventricular ejection fraction ($< 50\%$), renal dysfunction (plasma creatinine > 1.5 mg/dL), current pregnancy, fever or any other known established cardiovascular disease.

This study was approved by Ethics Committee of Tangdu Hospital of Fourth Military Medical University (approval number: TDLL-2016234, approval date: Feb. 26, 2016) and conformed to the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant after study explanation.

Regional PWV measurement

In this study, five regional PWVs including heart–carotid PWV (hcPWV), heart–femoral PWV (hfPWV), brachial–radial PWV (brPWV), femoral–ankle PWV (faPWV) and cfPWV, were measured by a trained sonographer (Y.Y.) using Doppler ultrasound which was previously validated to be a reliable and accurate method [15, 16]. A PHILIPS IU22 ultrasonography system (Philips, Netherlands) with a 3–9-MHz linear array transducer (L9-3) and a 1–5-MHz sector scanning transducer (S5-1) were used. Before the study, each participant adopted a supine position at least 10 min rest in a quiet, temperature-controlled (22 ± 1 °C) room to achieve hemodynamic stability. Each regional PWV was calculated as the pulse wave transit distance between two sampling sites divided by the corresponding pulse wave transit time (T).

In this study, T was calculated by subtracting the time delay from peak R wave of ECG to the foot of the Doppler flow waveform at the proximal sampling site from that of the distal site. The specific algorithm for determining T of each regional PWV is illustrated in Fig. 1. Intersecting tangent method was used for wave foot detection on the spectra [17]. The time interval between peak R wave of ECG and wave foot of the Doppler flow spectra at the aortic valve (T_{heart}), right common carotid artery ($T_{carotid}$), right common femoral artery ($T_{femoral}$), right brachial artery ($T_{brachial}$), right radial artery (T_{radial}), right posterior tibial artery (T_{ankle}) were carefully measured, respectively, as shown in Fig. 1. Measurements from ten consecutive heart beats under a stable heart rate (variation ≤ 3 bpm) were taken and then averaged as one result. Thus, the

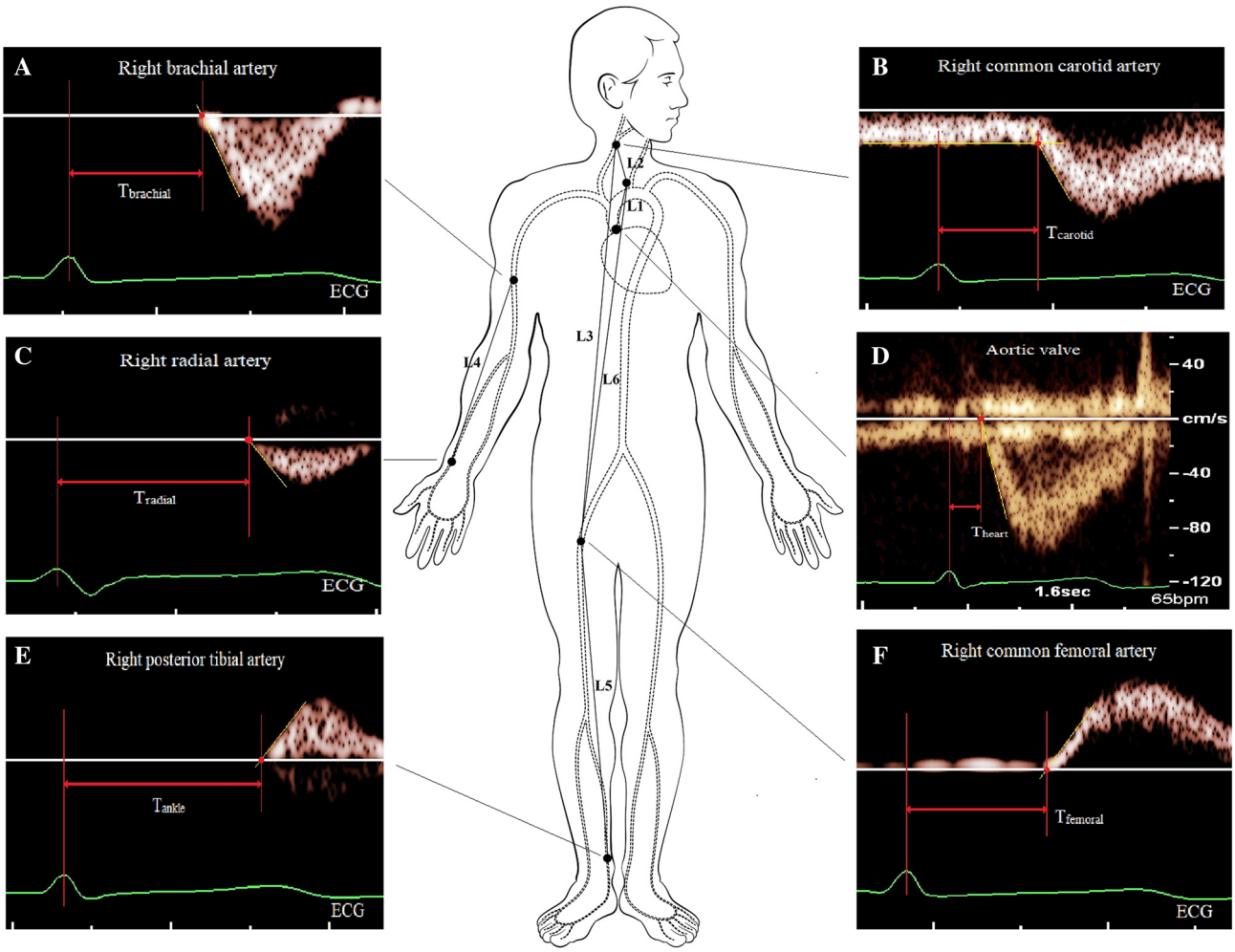

Fig. 1 Methodology of measuring regional PWV by Doppler ultrasound. The Doppler flow velocity spectra were recorded at the right brachial artery (**a**), common carotid artery (**b**), radial artery (**c**), aortic valve (**d**), right posterior tibial artery (**e**) and common femoral artery (**f**) with maximal sweep speed. The time interval between peak R wave of ECG (at bottom) and the wave foot of each spectrum was measured. Then the transit time of each arterial segment could be calculated (see text). On the body surface, six direct straight distances (L1–L6) between the sampling points or anatomic mark were measured. The transit distances were, thus, determined based on these distances (see text)

heart–carotid transit time can be calculated as $T_{\text{carotid}} - T_{\text{heart}}$, similarly, heart–femoral transit time $= T_{\text{femoral}} - T_{\text{heart}}$, brachial–radial transit time $= T_{\text{brachial}} - T_{\text{radial}}$, femoral–ankle transit time $= T_{\text{femoral}} - T_{\text{ankle}}$, carotid–femoral transit time $= T_{\text{femoral}} - T_{\text{carotid}}$.

The transit distances were determined based on the tape measured direct straight distances between body surface points (Fig. 1), where L1 represented the straight distance between the projective point of aortic valve on the body surface (determined by 2D echocardiography) and the suprasternal notch; L2 was the distance between the suprasternal notch and the sampling point of right common femoral artery; L3 was the distance between the sampling points of right common carotid artery and the right common femoral artery; L4 was the straight distance between the sampling points of right brachial artery and the radial artery; L5 was the straight distance between the sampling points of right common femoral artery and the right posterior tibial artery; L6 was the straight distance from suprasternal notch to the right common femoral artery. Thus, the heart–carotid transit distance was calculated as L1 + L2, the carotid–femoral transit distance = L3 × 80% [18], the brachial–radial transit distance = L4, the femoral–ankle transit distance = L5 and the heart–femoral transit distance = L6. Each regional transit distance was averaged from three measurements. Based on the above measurements, each regional PWV was then calculated as each transit distance divided by the corresponding transit time.

Laboratory profiles and other parameters

Laboratory profiles including lipid profiles, blood glucose, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and rheumatoid factor (RF) were collected from the hospital administrative database. The above laboratory data of the RA patients were collected before the onset of clinical treatment. Blood pressure (BP) was measured in the supine position at the brachial artery using a sphygmomanometer before the study and three measurements were averaged. The left ventricular ejection fraction (LVEF) was obtained from the routine echocardiographic examination by standard method.

Reproducibility of PWV measurements

Intra- and inter-observer variability of each Doppler ultrasound measured regional PWV was performed randomly in 30 RA patients. The measurements were performed in the same condition by two independent observers.

Statistics

Data are expressed as the mean ± SD for continuous variables unless noted otherwise. Normal distribution of data was analyzed by Kolmogorov–Smirnov normality test. If the normality of the parameters (e.g., ESR or CRP) was not achieved, log-transformed values were used for analysis. The sample size in this study was calculated to provide a power > 0.8. Difference in mean values between groups was assessed using one-way analysis of variance (ANOVA), followed by unpaired *t* test, as appropriate. The difference in prevalence was assessed by Chi-square test. The coefficient of variation (CV) of the measurements was calculated as the SD of the differences between paired measurements divided by the mean of all measurements. Multiple regression analysis was applied in this study to assess independent associations between regional PWVs and more independent variables which may affect AS. The results were analyzed using the statistical software SPSS 15.0 (SPSS, Chicago, IL, USA). A P value < 0.05 was regarded as statistically significant.

Results

Clinical characteristics of participants

Table 1 summarizes the clinical characteristics of the subjects. RA patients and the healthy controls were comparable in age, gender, body mass index (BMI), diastolic BP, pulse pressure, heart rate (HR), blood glucose, lipid profiles except triglycerides, smoking proportion and LVEF. The mean duration of the RA patients was 9.8 months, ranging from 1 to 24 months. A significant difference was found in the systolic BP ($P = 0.0448$), triglycerides ($P < 0.0001$) between two groups.

Table 1 Clinical characteristics of the participants in this study

	Controls	RA patients ($n = 72$)	P value
Age (years)	46.2 ± 6.72	47.4 ± 6.88	0.3097
Female (n, %)	45 (81.8%)	59 (81.9%)	0.9854[a]
Height (cm)	162.2 ± 5.96	160.8 ± 6.24	0.2023
Weight (kg)	58.71 ± 7.71	58.90 ± 9.04	0.9097
BMI (kg/m^2)	22.35 ± 2.93	22.70 ± 3.03	0.4584
Systolic BP (mmHg)	119 ± 11	124 ± 14	0.0448
Diastolic BP (mmHg)	75 ± 7	78 ± 7	0.0509
PP (mmHg)	44 ± 7	46 ± 10	0.1816
HR (bpm)	74 ± 11	76 ± 11	0.1459
FBG (mmol/L)	5.11 ± 0.67	5.15 ± 0.78	0.3435
Total cholesterol (mmol/L)	4.56 ± 0.63	4.68 ± 1.14	0.4758
HDL cholesterol (mmol/L)	1.41 ± 0.40	1.46 ± 0.51	0.5102
LDL cholesterol (mmol/L)	2.23 ± 0.63	2.26 ± 0.68	0.7523
Triglycerides (mmol/L)	1.09 ± 0.31	1.49 ± 0.60	< 0.0001
RF (positive, %)	–	79.2%	–
CRP (mg/L)	–	41.59 ± 35.26	–
ESR (mm/h)	–	35.24 ± 24.59	–
DAS-28$_{ESR}$ (median, range)	–	3.79, 2.7–6.1	–
Smoking (n, %)	4 (7.3%)	5 (6.9%)	0.9430[a]
Disease duration (months)	–	9.8 ± 7.49	–
LVEF (%)	70 ± 4.21	69 ± 4.12	0.8060

Values are mean ± SD

RA rheumatoid arthritis, *BMI* body mass index, *BP* blood pressure, *PP* pulse pressure, *HR* heart rate, *FBG* fasting blood glucose, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *RF* rheumatoid factor, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *DAS-28$_{ESR}$* disease activity score on 28 joints based on erythrocyte sedimentation rate, *LVEF* left ventricular ejection fraction

[a]Chi-square test

Changes in PWV of different regions in RA patients

The measurements of the five regional PWVs by Doppler ultrasound are shown in Table 2, and the comparison of each regional PWV between patients with RA and the controls is displayed in Fig. 2. In RA patients, the measurements of hfPWV and cfPWV were significantly higher than heathy controls (6.45 ± 1.70 vs 5.49 ± 1.19 m/s, $P = 0.0006$; 7.94 ± 2.07 vs 6.70 ± 1.23 m/s, $P = 0.0001$, respectively). An increase trend was found in hcPWV,

Table 2 The measurements of the regional PWV in RA patients and controls

Regional PWV	Controls ($n=55$)	RA patients ($n=72$)	P value
hcPWV (m/s)	9.24 ± 1.93	10.21 ± 4.18	0.1116
hfPWV (m/s)	5.49 ± 1.19	6.45 ± 1.70	0.0006
brPWV (m/s)	11.87 ± 2.28	12.72 ± 3.54	0.1197
faPWV (m/s)	11.10 ± 1.65	11.29 ± 2.36	0.6207
cfPWV (m/s)	6.70 ± 1.23	7.94 ± 2.07	0.0001

Values are mean ± SD

RA rheumatoid arthritis, *hcPWV* heart–carotid pulse wave velocity, *hfPWV* heart–femoral pulse wave velocity, *brPWV* brachial–radial pulse wave velocity, *faPWV* femoral–ankle pulse wave velocity, *cfPWV* carotid–femoral pulse wave velocity

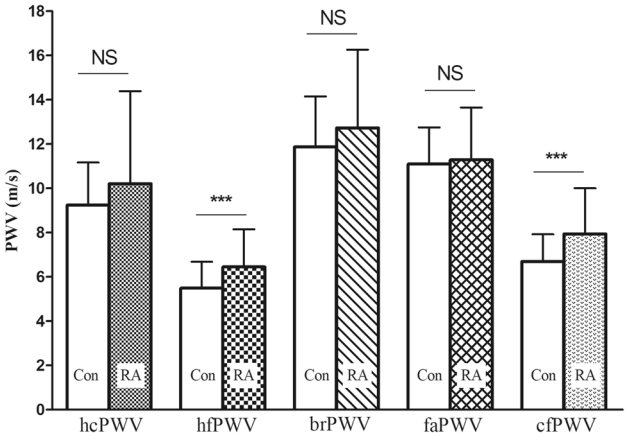

Fig. 2 Measurements of regional PWV in RA patients and controls. *RA* rheumatoid arthritis, *Con* control group, *hcPWV* heart–carotid pulse wave velocity, *hfPWV* heart–femoral pulse wave velocity, *brPWV* brachial–radial pulse wave velocity, *faPWV* femoral–ankle pulse wave velocity, *cfPWV* carotid–femoral pulse wave velocity, *NS* non-significant, ***$P<0.001$

brPWV and faPWV in RA patients, but no statistical significant difference was shown when compared with the control group.

To compare the relative influence of RA and other factors on AS of different arterial regions, the increase magnitude of each regional PWV in RA patients was expressed as percentages relative to the corresponding mean value of the 55 age–gender-matched healthy controls in this study. As shown in Fig. 3, the increase magnitudes of regional PWV of RA patients were significantly unequal among the five arterial regions ($P=0.0098$, by one-way ANOVA). The mean increase magnitude of hfPWV (17.5%) and cfPWV (18.5%) was greater than that in faPWV (1.7%) and brPWV (7.2%) in patients with RA.

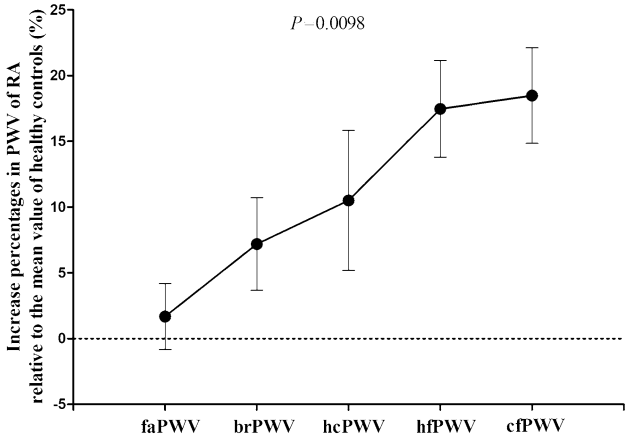

Fig. 3 Magnitude of influence of RA on stiffness of different arterial regions. The relative influences of RA on different regional PWVs were expressed as their increase percentages relative to the corresponding mean value of the age–gender-matched healthy controls. The results showed that the increase magnitudes of regional PWV of RA patients were significantly unequal among the five arterial regions ($P=0.0098$, by one-way ANOVA). Mean ± SE, abbreviations as in Fig. 2

Table 3 Multiple regression analysis of factors that affect regional PWV in total subjects ($n=127$)

	hcPWV	brPWV	faPWV	hfPWV	cfPWV
Age	0.235*	0.139	0.069	0.406***	0.388***
Female gender	0.027	−0.042	−0.178*	0.035	0.104
Smoking	0.074	0.041	−0.123	−0.107	0.028
Systolic BP	−0.096	−0.164	0.226	0.245*	0.418***
Diastolic BP	0.099	0.004	0.109	−0.057	−0.120
Total cholesterol	0.076	0.106	0.066	0.133	0.173*
Triglycerides	−0.246*	0.067	0.029	−0.037	−0.003
HDL cholesterol	−0.081	−0.096	0.099	−0.049	−0.057
LDL cholesterol	0.199*	−0.069	0.225*	0.008	−0.014
HR	0.017	0.094	0.006	−0.086	−0.117
Presence of RA	0.208*	0.128	−0.049	0.268***	0.264***
R^2	0.156*	0.094	0.206**	0.393***	0.499***

This table gives each variable's standard regression coefficients (β) and the corresponding level of significance. Dummy variables were used for female gender (female = 1, male = 0), smoking (smoker = 1, non-smoker = 0), presence of RA (yes = 1, no = 0). R^2, the coefficient of determination. Abbreviations as in Table 1

*$P<0.05$; **$P<0.01$; ***$P<0.001$

Independent factors that affect regional PWV

Table 3 demonstrates the multiple regression analysis used for assessing the independent association between each

regional PWV and the possible confounders which may affect AS. The association between the presence of RA and both hfPWV, cfPWV remained strongly significant ($P < 0.001$) even after adjustments for age, gender, smoking, BP, HR and lipids profiles. The association between the presence of RA and hcPWV showed moderate significant ($P = 0.032$) after adjustments for above factors. However, the association between RA and brPWV ($P = 0.199$), faPWV ($P = 0.599$) was not significant in this multivariate model.

After adjusting for other confounding factors, age and systolic BP were significant factors associated with both hfPWV and cfPWV, but for other arterial segments, such association had almost no significance, especially for faPWV and brPWV. In addition, the female sex was not a significant factor associated with hfPWV, cfPWV, hcPWV or brPWV, but its association with faPWV showed a moderate significance ($P = 0.041$).

Reproducibility of regional PWV measurements

Intra-observer and inter-observer variability of each regional PWV measurement was assessed randomly in 30 RA patients, as shown in Table S1 (Online supplement data). Among the five regional PWV measurements, hfPWV and cfPWV had lower variability (lower CV values) between repeated measurements than that of other regional PWVs included in this study.

Discussion

In the present study, we measured five regional PWVs in different arterial regions by Doppler ultrasound in patients with RA and healthy subjects to investigate the relative impact of RA and other factors on AS of different arterial segments. The results showed that the stiffness of different arterial regions was not equally affected by RA and other factors. In RA, the stiffening of aorta, measured by aortic PWV parameters (hfPWV and cfPWV), was significantly greater than that of the peripheral arteries in the extremities. Furthermore, among the risk factors, the presence of RA, age and systolic BP, were the independent factors associated with the stiffening of aorta. Our findings also suggested that reproducible aortic stiffness parameters, such as hfPWV and cfPWV, are more suitable for early detecting the subclinical atherosclerosis in RA patients.

To our knowledge, this is the first study to assess the impact of RA on the AS of different arterial regions non-invasively measured from the same individual under strict inclusion criteria. In recent years, some case–control studies have observed and documented the increased stiffness in different arteries, such as aorta [8, 19–23] (measured mainly by cfPWV), upper limb [24, 25] (mainly by carotid–radial PWV) and lower limb arteries [11, 26] (mainly by brachial–ankle PWV) in patients with RA. However, based on the previous studies, it should be very prudent to draw the conclusion about the influence and the magnitude of the influence of RA on stiffness of different arterial regions in human. As the different inclusion and exclusion criteria, different disease activity status, various concomitant risk factors, differences among assessment techniques and devices in those studies almost make it impossible to conclusively ascertain about the above issue which may be currently available in this study.

The results of this study indicated that the hfPWV and cfPWV were more preferentially affected by RA and other factors. In contrast, the measurements of hcPWV, brPWV and faPWV did not show significant difference compared with controls even though an increase trend could be found (Fig. 2). Ambrosino P et al. analyzed a total of 25 studies in their meta-analysis and showed that RA patients had a significantly higher aortic PWV ($P < 0.00001$) and brachial–ankle PWV ($P = 0.01$) compared with controls, and the carotid–radial PWV only showed a trend toward increasing ($P = 0.07$) [13]. Their results of aortic PWV and carotid–radial PWV (similar to brPWV included in this study, they both reflected the stiffness of the upper limb arteries) are in good agreement with our data. It is notable that the faPWV used in our study is different from brachial–ankle PWV. Thus, the discrepant results between our data and previous studies could be interpreted as that the faPWV covers the arterial regions of the lower limb arteries; however, the brachial–ankle PWV covers not only the lower limb arteries but also a distal part of aorta because the PWV propagates along the aorta with a lower speed than at other regions. The significantly increased aortic PWV may contribute to the increase of brachial–ankle PWV in RA patients. However, the measurement of faPWV in our study indicated that the stiffness of lower limb arteries did not significantly increase in patients with RA. Another study by Turesson et al. found that the stiffness of the abdominal aorta was increased in women with RA, but the stiffness of the common carotid artery was less markedly increased [27]. This result also agreed well with our data even though a local stiffness parameter was used. In addition, our study showed the presence of RA was not a significant factor associated with brPWV and faPWV after adjustment for other confounders, indicating that the effect of RA on stiffness of peripheral limb arteries was only modest. Overall, our data in this study demonstrated for the first time that RA was more preferentially associated with increased aortic stiffness than that of the peripheral arteries in the upper and lower extremities.

Importantly, the discrepant impacts of RA and other factors on the stiffness of aorta and peripheral arteries found in this study may shed a fresh light on our understanding

of the increased cardiovascular complications and impaired peripheral microcirculation in RA patients. In physiological condition, the aortic PWV is markedly lower than peripheral PWV [28], this stiffness mismatch will generate greater wave reflections with low propagating speed and return to the aortic root mainly during diastole. Therefore, this kind of reflection will not increase the left ventricular afterload and systolic BP, meanwhile, it will help to the coronary perfusion [5]. The distensible aorta and the greater wave reflections also limit the transmission of pulsatile pressure energy to peripheral part and protect the microcirculation. However, in patients with RA, if the aortic PWV significantly increased over peripheral PWV, the stiffness gradient was reduced that means impedance mismatch losing or inversion; so less pressure waves are reflected, but they will propagate at a high velocity and return to the aortic root mainly in systole. Thus, the systolic BP, ventricular afterload and myocardial oxygen consumption will increase, cardiac coronary perfusion is damaged. Even worse, the pulsatile pressure is inadequately dampened as it transmits down to smaller arteries and triggers the microcirculation damage [29]. This mechanism caused by the discrepant changes in stiffness between aorta and peripheral arteries may provide new insights into understanding the cardiovascular complications [1, 30] and microvascular dysfunction frequently occurred in RA [31–33].

The chronic inflammatory state exerts increased cardiovascular risk leading to higher morbidity and mortality in diabetes, hypertension, RA and some other autoimmune diseases. Therefore, some systemic markers of inflammation or biomarkers of atherosclerosis are established to help to detect and clinically prevent the cardiovascular risk. For this purpose, AS (measured by PWV), carotid intima-medial thickness (cIMT) and flow-mediated dilatation (FMD) were found and accepted as the markers of cardiovascular risk.

As one of the standard indicators of subclinical atherosclerosis and vascular aging, cIMT is usually measured at the common carotid arteries using B-mode ultrasonography with relative high-frequency transducers. Numerous cross-sectional studies have demonstrated increased IMT in patients with RA, which indicates accelerated atherosclerosis [34]. FMD, a noninvasive technique, has frequently been used to assess endothelial function. Endothelial function is a key aspect of the disturbed vascular biology throughout the natural history of atherosclerosis. Impaired endothelial function was reported in diabetes, hypertension as well as rheumatic diseases in numerous studies. Soltész et al assessed AS, FMD and cIMT in patients with systemic autoimmune diseases in a comparative study [35], where they showed that AS indicated by PWV may be strongly associated with endothelial dysfunction and overt atherosclerosis in those patients. It suggested that assessment of AS, FMD, and cIMT could be used for the complex assessment of vascular abnormalities. However, compared with cIMT and FMD, to our knowledge, AS has the following advantages: (1) AS has shown a stronger predictive value. A number of studies examined the ability of arterial stiffness to predict the risk of future fatal and nonfatal CV events (myocardial infarction, stroke, revascularization, stroke, end-stage renal failure, aortic syndromes) and total mortality [36–43]. The clinical prognostic role of AS in various populations as an independent predictor of cardiovascular events has been well discussed in two excellent reviews [4, 6]. In addition, a number of clinical studies have shown that AS of patients with RA could be reversed and improved by anti-TNF therapy or anti-inflammatory therapies [44–50]. By contrast, the ability of cIMT and FMD in predicting the risk of cardiovascular events is less impressive. For example, a comparative study showed that cIMT had only moderate sensitivity in predicting future cardiovascular events [51]. Less information is available for the prediction of future cardiovascular outcomes by FMD. A meta-analysis [52] and a review [53] have mentioned the relationship between FMD and future cardiovascular events in populations with higher CV risk levels. Furthermore, FMD was reported did not correlate with carotid atherosclerosis and seemed not reliably predict further major cardiovascular events in elderly population [54]. As stated mentioned by Kerekes et al. in their review [55] that "The long term predictive value of FMD might only be useful in patients with stable disease, those in remission or by performing sequential measurements. Although these patients at high cardiovascular risk need to be identified early, routine or repeated assessments of FMD are not recommended in daily practice owing to increased cost without a better patient outcome". It seems that the prognostic role of FMD for cardiovascular risk is somehow limited. (2) The methodology of AS is of simplicity and accuracy. Although the evaluation of cIMT and FMD are suitable and reliable techniques to assess carotid atherosclerosis and endothelial dysfunction, both methods are relatively expensive and require special expertise. In contrast, measuring PWV is a simple and relatively cheap technique. As we know that cIMT and FMD measurement are both operator-dependent and affected by many non-disease-related factors. On the contrary, aortic PWV obtained by non-invasive automatic devices based on the expert consensus [5] would make the measurement accurate and reliable. Of course, AS, measured by PWV, still has some shortcomings, one is the lack of comparable, age-adjusted normal values or standardized cut-off value for specific patients (also the case in FMD), the second is the inaccuracy of pulse wave transit distance estimation. The autoimmune disease such as RA per se is the baseline CV risk. Crowson et al. reported an excellent work in 2012 on prediction of risk scores for CV risk in patients with RA employing a population-based cohort [56]. They concluded that the Framingham and Reynolds risk scores

substantially underestimated CV risk in patients with RA of both genders, especially in older ages and in patients with positive rheumatoid factor. There are increasing studies reminding us that traditional CV disease risk factors and risk algorithms developed for the general population cannot completely account for the high CV diseases morbidity and mortality observed in patients with RA. The traditional risk factors such as hypertension, hyperlipidemia, diabetes mellitus, smoking, etc. are included in CV risk scoring system such as the Framingham score. However, autoimmune conditions presently are not included in any CV risk calculator [57].

On this basis, AS measured by aortic PWV, is expected to detect the excess atherosclerotic cardiovascular disease risk in autoimmune diseases. In the current study, as shown in Table 3, the aortic PWV measurements were independently associated with the presence of RA, after adjustments for age, gender, smoking, blood pressure, heart rate and lipids profiles. We also previously reported that the aortic PWV was independently associated with Takayasu's arteritis [16], another kind of autoimmune disease. In addition to our study, other studies [8, 35] also showed that the AS was independently associated with RA, after adjusting for traditional risk factors. Furthermore, a recent meta-analysis showed that aortic PWV enables to improve prediction of CV events beyond conventional risk factors [36]. Thus, we believe that aortic PWV assessment in patients of RA may provide incremental value for better identification of CV risk in these patients and may help them to benefit from CV risk factor management.

As mentioned before, the cfPWV has been shown to have a robust, independent predicting value for cardiovascular events in various patients as well as the general population. It is now considered as the "gold standard" method to noninvasively measure the aortic stiffness. However, as we know, cfPWV actually does not cover the whole aorta, as it excludes the important segment of the proximal part of aorta, which anatomically and haemodynamically couples the heart and the systemic arterial tree. The exclusion of this segment may lose some biomechanical information. So, in this study, we included the parameter hfPWV, which covered all part of the aorta, and described its measurement in RA patients and healthy controls for the first time. The results of this study showed that the hfPWV had the similar close association with RA as the cfPWV did. Regarding to the reproducibility, the hfPWV measurement had the lowest variability, seems a little better than the cfPWV. Therefore, our findings may suggest that the hfPWV could also be used as a reliable parameter like cfPWV for assessing aortic stiffness in clinical settings. Even though hfPWV theoretically may provide more information about the overall elastic properties of the aorta, however, its scientific or clinical significance still needs to be further studied.

The major strength of this study is a design that allowed the simultaneous measurements of regional PWV in different arterial regions in the same individual by a simple, noninvasive and objective way. However, some potential limitations of our study need to be discussed. The first was that the pulse wave transit distance was somehow cannot be accurately measured [58]. The approximatively tape measured direct straight distances on body surface may under- or overestimated the true values. However, this limited inaccuracy may partly be balanced by including strictly matched controls and would not influence the conclusion of this study. Previous studies have shown that PWV measured based on Doppler ultrasound is a reliable method of aortic PWV measurement [15]. The regional PWVs in our study were measured by Doppler ultrasound, using the same theory and methodology with the above study. Thus, based on our expertise, we think that the methodology in this study was reliable. Secondly, we just only included Chinese patients aged from 35 to 55 years old in this study. As age is a strong determinant of AS, additional studies with larger simple size including wider age range, if better in other ethnic groups, are needed to further confirm the findings in this study. Finally, this study was a cross-sectional design, which only observationally showed an association between stiffness of different regions with RA and other cardiovascular risk factors based on a relative small sample size. Thus, the causal relationship was not able to be affirmed in the current study. In our study, the sample size was determined before the investigation. To get a power > 0.8, two-tailed, a sample size of 76 (38:38) was needed, calculated by the software Empower Stats (X&Y Solutions Inc., USA). In this study, we included 72 patients and 55 controls which were sufficient to draw the conclusion. Of course, further careful longitudinal studies based on a large sample size are needed to explore a clear causal conclusion.

Conclusions

Taken together, this study demonstrates that the stiffness of different arterial regions is not equally affected by RA and other factors. The stiffening of aorta is more preferentially associated with RA than that of the peripheral arteries in the extremities. The discrepant stiffening between aorta and peripheral arteries may provide a new insight into the pathogenesis of cardiovascular and microvascular dysfunction frequently occurred in RA.

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the work: WZ, YY; all authors revised the manuscript for important intellectual content and final approved the version to be published; all authors agreed to be accountable for all aspects of this work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All co-authors take full responsibility for all parts of the final manuscript and reassure that no part of it has been copied or published elsewhere.

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Availability of data and material The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethics approval and consent to participate This study was approved by Ethics Committee of Tangdu Hospital of Fourth Military Medical University (Approval number: TDLL-2016234, Approval date: Feb. 26, 2016) and conformed to the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant after study explanation.

Consent for publication Not applicable.

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