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Journal of Cardiovascular Translational Research (2019) 12:580–590
https://doi.org/10.1007/s12265-019-09892-3

ORIGINAL ARTICLE

# Early Wave Reflection and Pulse Wave Velocity Are Associated with Diastolic Dysfunction in Rheumatoid Arthritis

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Received: 5 March 2019 / Accepted: 6 May 2019 / Published online: 22 May 2019
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## Abstract

Rheumatoid arthritis (RA) impacts arterial and diastolic function. This study examined whether arterial properties can determine diastolic function in RA. In 173 RA patients, arterial function measures including carotid femoral pulse wave velocity (PWV), central systolic and pulse pressure, pulse pressure amplification, and the magnitude and timing of the forward and reflected waves were measured using applanation tonometry. Diastolic function parameters including the ratio of early-to-late transmitral velocity (E/A) and ratio of E to the mean of the lateral and septal wall myocardial tissue lengthening (e') were measured using echocardiography. The timing of the reflected wave was associated with E/A; PWV was related to E/e'. The timing of the reflected wave, forward wave magnitude, and pulse pressure amplification were associated with impaired relaxation; PWV was related to increased left ventricular (LV) filling pressure. Early wave reflection and PWV are associated with LV-impaired relaxation and increased filling pressure, respectively, in RA.

**Keywords** Large artery function · Diastolic function · Rheumatoid arthritis

## Abbreviations

| | |
|---|---|
| ACEI | Angiotensin converting enzyme inhibitors |
| Alx | Augmentation index |
| ARB | Angiotensin receptor blockers |
| BB | Beta blockers |
| CCB | Calcium channel blockers |
| cPP | Central pulse pressure |
| e' | The mean of the lateral and septal wall myocardial tissue lengthening |
| E | Trans-mitral velocity in the early period of left ventricular diastolic filling |
| E/A | Early-to-late transmitral velocity |
| LV | Left ventricle |
| LVMI | Left ventricular mass indexed to body surface area |
| Pb | Backward wave pressure |
| P b time | Time to wave reflection |
| Pf | Forward wave pressure |
| PPamp | Pulse pressure amplification |
| PWV | Pulse wave velocity |
| RA | Rheumatoid arthritis |
| RM | Reflection magnitude |

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Associate Editor Ana Barac oversaw the review of this article

**Electronic Supplementary Material** The online version of this article (https://doi.org/10.1007/s12265-019-09892-3) contains supplementary material, which is available to authorized users.

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## Introduction

Patients with rheumatoid arthritis (RA) are particularly prone to heart failure with a preserved ejection fraction (HFpEF) [1, 2]. This contributes substantially to the increased cardiovascular disease mortality risk in RA [2]. In non-RA subjects, impaired large artery function plays an important role in overt

heart failure [3–7] and has been associated with left ventricular (LV) diastolic dysfunction [8, 9], a pre-clinical measure that precedes HFpEF [10]. Altered aortic hemodynamics contributes to the development of cardiac dysfunction through changes in the steady-state and/or pulsatile components of blood pressure [11–16]. Whereas steady-state pressure influences cardiac remodeling, changes in aortic function mediate pulsatile hemodynamics that further increase the load on the heart. Indeed, pulsatile hemodynamics increase target organ damage and cardiovascular events independent of steady-state pressure [11–13, 15–19]. Arterial pulsatility estimation is often limited to pulse pressure measurements. However, the central pulse pressure waveform is determined by forward as well as backward wave components [20], both of which are affected by arterial stiffening [11, 20, 21] and enhance loading on the heart [22]. Besides affecting cardiac function by enlarging pulse pressure, aortic stiffening can impact the heart through impaired mechanical ventricular-arterial coupling [23, 24]. RA patients experience enhanced aortic pulse wave velocity (PWV), a reported marker for arterial stiffness [25] and an increased prevalence of diastolic dysfunction both of which are related to systemic inflammation and other disease characteristics [1, 26, 27]. Currently, no therapeutic intervention was shown to benefit HFpEF [28]. Systemic inflammation comprises an increasingly implicated mechanism in arterial function [29], diastolic dysfunction, and HFpEF [30]. To our knowledge, whether specific aortic functional changes are associated with cardiac function in RA and, if so, which factors mediate these relationships, has not been reported. The aim of the present study was to determine large artery functional characteristics that are associated with alterations in LV function, independent of traditional cardiovascular risk factors and disease features in patients with RA.

## Methods

### Patients

One hundred eighty-six patients who met the American College of Rheumatology/European League Against Rheumatism criteria for RA [31] were recruited at the Milpark hospital. Among these, 173 patients that did not have heart failure and in whom high-quality echocardiography and arterial function measures could be obtained were included in the study. This investigation obtained approval from the University of the Witwatersrand Human (Medical) Research Ethics Committee (approval number: M06-07-33; protocol number: M120562 renewed as M170592) and was conducted in line with the principles of the Helsinki declaration. All participants provided written, informed consent.

### Demographic Features, Cardiovascular Risk Factors, and RA Characteristics

Demographic parameters, cardiovascular disease risk factors, and RA characteristics were obtained using standard approaches, as previously reported [32, 33].

### Arterial Function

Arterial waveforms were assessed by applanation tonometry at the radial, carotid, and femoral artery pulses, each for 10 s using a high-fidelity SPC-301 micromanometer (Millar Instrument, Inc., Houston, Texas) interfaced with a computer employing SphygmoCor, version 9.0 software (AtCor Medical Pty. Ltd., West Ryde, New South Wales, Australia) as previously described [32]. When the systolic or diastolic variability on consecutive waveforms were > 5% or the amplitude of the pulse wave signal was < 80 mV, recordings were discarded. Brachial blood pressure measurements taken immediately before the recordings were used to calibrate the pulse wave. A validated transfer function in the SphygmoCor software was used to obtain the central (aortic) wave form, from which central (aortic) systolic blood pressure (cSP) was determined and central pulse pressure (cPP), augmentation index (AIx), and pulse pressure amplification (PPamp) were calculated. Using SphygmoCor software, the aortic waveform was separated into the aortic forward (Pf) and backward (Pb) waves assuming a triangular flow wave [34]. Reflection magnitude (RM), the time to wave reflection (Pb time), and time to the peak of the forward wave (Pf time) were determined from the separated forward and backward waves. Aortic pulse wave velocity was measured from sequential waveform measurements at carotid and femoral sites as previously described [32]. The time delay in the pulse waves between the carotid and femoral sites was determined using an electrocardiograph derived R wave as a fiducial point. Pulse transit time was calculated as the average of 10 sequential beats. The distance, which the pulse wave travels, was determined as the difference between the distance from the femoral sampling site to the suprasternal notch and from the carotid sampling site to the suprasternal notch. Aortic carotid-femoral PWV was calculated as distance in metres divided by transit time in seconds. All measurements were performed by a single experienced observer who was blinded to the cardiovascular risk factor profiles of the patients.

### Echocardiography

Echocardiography was performed according to the American Society of Echocardiography convention using a Sonosite M-Turbo ultrasound (SonoSite® Inc., Bothell, WA, USA) [35]. LV dimensions were determined using two-dimensional directed M-mode echocardiography in the parasternal long axis

view. LV end diastolic and systolic volumes were determined using the Teichholz method [36]. LV ejection fraction (EF) was calculated as previously reported [33] and was considered reduced when its value was < 50%. LV mass was determined using a standard formula [36] (LVM = 0.8 × (1.04 (LV end diastolic diameter + LV end diastolic septal wall thickness + LV end diastolic posterior wall thickness) 3 − (LV end diastolic diameter) 3) + 0.6 g) and indexed to body surface area (LVMI). LV relative wall thickness was calculated as previously described [35]. LV hypertrophy was identified when LV mass index was > 95 g $m^{-2}$ for women and > 115 g $m^{-2}$ for men, and concentric remodeling was diagnosed when relative wall thickness > 0.42 [35].

LV diastolic function was assessed using pulsed wave Doppler and Tissue Doppler indices (TDI) [33]. Briefly, using pulsed wave Doppler in the apical four-chamber view, mitral inflow patterns were measured during the early (E) and late (A) period of ventricular filling and expressed as E/A, which is an index of myocardial relaxation. Myocardial tissue lengthening velocity was measured during early (e') and late (a') diastole at the septal and lateral corners at the level of the mitral annulus using TDI. Data were expressed as the E/(mean of the septal and lateral e') ratio (an index of LV filling pressure). Patients were considered to have impaired LV relaxation when their E/A was < 0.8 [37], and an increased filling pressure when their E/e' was > 12; the latter cut-off value was previously reported as clinically relevant and predicts increased incidence of HFpEF [38]. Left atrial area was measured using planimetry in the apical two chamber view and left atrial volume was indexed to body surface area. Diastolic dysfunction was classified according to the previously reported criteria [39] and the recently published criteria [37]. Echocardiography was performed by two experienced observers that were blinded to the cardiovascular risk factor profiles of the patients. As previously reported, the intra- and interobserver variabilities are low in our setting [33].

### Statistical Analysis

Statistical analysis was performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC). Data are expressed as mean (SD), median (interquartile range (IQR)), or proportions. Non-normally distributed variables were logarithmically transformed. Multiple linear and backward logistic regression analyses were performed to determine the independent relations between aortic and diastolic function and diastolic dysfunction, respectively. Based on reported evidence, age, sex, race, height, weight, mean arterial pressure, and heart rate were included in the known confounder-adjusted multivariate models [11, 13, 16, 32]. In the fully adjusted multivariate models, additional potential confounders included those factors that were associated with aortic function or diastolic function measures in RA [32, 33]. As LV mass and concentric hypertrophy are strongly associated with diastolic function, the relationships of LV mass index and relative wall thickness with diastolic function parameters were determined. In the univariate analysis, LV mass index was more strongly and consistently associated with diastolic function parameters than relative wall thickness and, hence, was forced in additional regression models with diastolic dysfunction as dependent variable. As it was recently suggested that inflammation is strongly implicated in diastolic dysfunction [30], C-reactive protein (CRP) and interleukin-6 concentrations as well as the Disease Activity Score in 28 joints (DAS28) were forced additionally into separate models. Deformed joint count as a marker of cumulative inflammation was also forced into separate models. Sensitivity analysis was performed in women as 80% of participants were female. Significance was set at $p \leq 0.05$.

## Results

### Patient Characteristics

Table 1 gives the recorded characteristics. Mean (SD) age was 58.4 years (12.4) with a median (IQR) disease duration of 14.6 years (8.9–22.0); 39.9% of patients with hypertension were receiving anti-hypertensive treatment; 49.7 and 5.2% of the participants had dyslipidaemia and diabetes mellitus, respectively. The majority of patients (74.6%) tested rheumatoid factor (74.6%) or/and anti-citrullinated peptide antibody (70.4%) positive. Disease activity was well controlled with a mean DAS28 of 2.8 (1.7) and median (IQR) Clinical Disease Activity Index of 6 (1–13); 89.6% of patients were receiving conventional synthetic disease modifying agents and 11.0% used biologic disease-modifying agents.

Median (IQR) pulse wave velocity was 7.3 m $s^{-1}$ (6.2–9.4) and mean (SD) central systolic and pulse pressure were 126 mmHg (15) and 43 mmHg (14), respectively; 18.8% of the patients had LV hypertrophy, 55.9% had concentric remodeling, and 21.2% had a reduced ejection fraction. Of the participants, 22.9% had a reduced E/A (< 0.8), 42.1% had an increased E/e' (> 12), 57.8% had a decreased lateral e' (< 10 cm $s^{-1}$), and 2.9% had an increased left atrial volume index.

### Associations of Arterial Function Measures with LV Geometry

Pulse pressure amplification was related to relative wall thickness in a fully adjusted multivariable model (partial $r = -0.17$, $p = 0.04$). There were no other associations between arterial function markers and LV relative wall thickness of LV mass index (data not shown). In multivariable backward logistic regression analysis, no associations between arterial function parameters and LV hypertrophy were found (data not shown).

**Table 1** Recorded characteristics in 173 patients with RA

| | |
|---|---|
| Demographic characteristics | |
| Age at study time (years) | 58.4 (12.4) |
| Age at disease onset (years) | 42.2 (14.1) |
| Female sex (%) | 80.92 |
| Lifestyle factors | |
| Exercise (%) | 31.8 |
| Alcohol use (%) | 32.4 |
| Current smoking (%) | 10.4 |
| Anthropometry | |
| Body mass index (kg $m^{-2}$) | 26.7 (5.3) |
| Waist circumference (cm) | 92 (13) |
| Waist-hip ratio | 0.88 (0.09) |
| Cardiometabolic risk markers | |
| Systolic BP (mmHg) | 128 (15) |
| Diastolic BP (mmHg) | 81 (8) |
| Hypertension (%) | 39.9 |
| Total cholesterol (mmol $l^{-1}$) | 4.5 (1.0) |
| HDL cholesterol (mmol $l^{-1}$) | 1.64 (0.47) |
| LDL cholesterol (mmol $l^{-1}$) | 2.4 (0.9) |
| Triglycerides (mmol $l^{-1}$) | 1.0 (0.7–1.3) |
| Cholesterol-HDL ratio | 2.7 (2.3–3.2) |
| Dyslipidemia (%) | 49.7 |
| Glucose (mmol $l^{-1}$) | 4.8 (4.5–5.1) |
| Diabetes (%) | 5.2 |
| HOMA-IR | 1.4 (1.0–1.9) |
| Cardiovascular agents | |
| Antihypertensives (%) | 39.9 |
| Statins (%) | 42.8 |
| Ezetimibe (%) | 9.4 |
| Oral glucose lowering agents (%) | 1.7 |
| Insulin (%) | 1.7 |
| RA characteristics | |
| RA duration (years) | 14.6 (8.9–22.0) |
| Rheumatoid factor positive (%) | 74.6 |
| ACPA positive (%) | 70.4 |
| CDAI | 6 (1–13) |
| DAS 28 | 2.8 (1.7) |
| ESR (mm $h^{-1}$) | 12 (4–25) |
| CRP (mg $l^{-1}$) | 3.3 (1.3–8.0) |
| Interleukin 6 (pg $ml^{-1}$) | 7.5 (3.5–14.2) |
| Leukocytes (n $nl^{-1}$) | 5.5 (4.6–7.0) |
| Deformed joints (n) | 0 (0–11) |
| EA manifestations (%) | 23 |
| Stanford HAQ-DI | 0.4 (0.0–0.9) |
| Conventional synthetic DMARD | |
| Methotrexate (%) | 75.7 |
| Chloroquine (%) | 48.0 |
| Leflunomide (%) | 40.5 |
| Sulphasalazine (%) | 15.0 |
| Tetracycline (%) | 15.6 |
| Azathioprine (%) | 6.9 |
| Synthetic DMARD (*n*) | 2.0 (1.1) |
| Synthetic DMARD (%) | 89.6 |
| Biological DMARD | |
| TNF-α inhibitors (%) | 8.7 |
| Abatacept (%) | 2.3 |
| Biologic DMARD (%) | 11.0 |
| NSAID (%) | 33.0 |
| Prednisone use (%) | 2.3 |
| GFR (ml $min^{-1}$ 1.73 $m^{-2}$) | 91 (23) |
| Arterial function | |
| PWV (m $s^{-1}$) | 7.3 (6.2–9.4) |
| Augmentation index (%) | 31.4 (11.1) |
| Central systolic BP (mmHg) | 126 (15) |
| Central pulse pressure (mmHg) | 43 (14) |
| Brachial pulse pressure (mmHg) | 47 (13) |
| Pulse pressure amplification | 1.14 (0.27) |
| Forward wave pressure (mmHg) | 28 (9) |
| Backward wave pressure (mmHg) | 21 (8) |
| Reflection magnitude | 0.75 (0.23) |
| Time to peak forward wave (ms) | 138 (39) |
| Time to wave reflection (ms) | 255 (19) |
| Echocardiography | |
| LV mass index (g $m^{-2}$) | 78.8 (66.2–92.7) |
| LV relative wall thickness | 0.44 (0.08) |
| Stroke volume (ml) | 55.3 (24.2) |
| Ejection fraction (%) | 58.6 (13.4) |
| Lateral e' (cm $s^{-1}$) | 9.6 (7.7–12.1) |
| Septal e' (cm $s^{-1}$) | 7.8 (6.4–9.6) |
| E/A | 1.0 (0.8–1.3) |
| E/e' | 11.2 (7.9–13.5) |
| Left atrial volume index (ml $m^{-2}$) | 20.5 (6.0) |
| DD by previous criteria (%) | 59.4 |
| DD by new criteria (%) | 22.9 |

*BP*, blood pressure; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *HOMA-IR*, homeostatic model of insulin resistance; *ACPA*, anti-citrullinated peptide antibody; *CDAI*, clinical disease activity index; *DAS28*, disease activity score in 28 joints; *ESR*, erythrocyte sedimentation rate; *CRP*, C-reactive protein; *EA*, extra-articular; *HAQ-DI*, health assessment questionnaire disability index; *DMARD*, disease modifying anti-rheumatic drugs; *NSAID*, non-steroidal anti-inflammatory drugs; *GFR*, glomerular filtration rate; *PWV*, pulse wave velocity; *LV*, left ventricular; *DD*, diastolic dysfunction

## Associations of Arterial Function Measures with Diastolic Function

Table 2 gives the independent relationships of arterial function measures with those of diastolic function. The time to wave reflection was associated with E/A in the known confounder (partial $r = 0.19$, $p = 0.03$) and fully adjusted models (partial $r = 0.17$, $p = 0.03$). PWV was related to E/e' in the known confounder (partial r = 0.20, $p = 0.01$) and fully adjusted models (partial $r = 0.19$, $p = 0.02$); central systolic pressure was associated with E/e' in the known confounder (partial $r = 0.16$, $p = 0.04$) but not fully adjusted model. Arterial function was not related to left atrial volume index (data not shown).

**Table 2** Association of arterial stiffness properties with diastolic function markers

| | E/A[a] | | E/e'[a] | |
|---|---|---|---|---|
| | Partial *r* | *p* | Partial *r* | *p* |
| Known confounder-adjusted model[b] | | | | |
| PWV[a] | −0.07 | 0.41 | *0.20* | *0.01* |
| AIx | 0.008 | 0.92 | −0.02 | 0.80 |
| cSP | 0.07 | 0.36 | *0.16* | *0.04* |
| cPP | 0.07 | 0.35 | 0.12 | 0.11 |
| pPP | 0.05 | 0.55 | 0.14 | 0.08 |
| PPamp | −0.02 | 0.83 | 0.02 | 0.79 |
| Pf | 0.04 | 0.64 | 0.15 | 0.06 |
| Pb | 0.05 | 0.54 | 0.10 | 0.19 |
| RM | 0.002 | 0.98 | −0.05 | 0.49 |
| Pf time | 0.12 | 0.14 | 0.04 | 0.60 |
| Pb time | *0.19* | *0.01* | −0.07 | 0.35 |
| Fully adjusted model[c] | | | | |
| PWV[a] | −0.10 | 0.22 | *0.19* | *0.02* |
| AIx | −0.05 | 0.56 | −0.06 | 0.51 |
| cSP | 0.07 | 0.39 | 0.09 | 0.22 |
| cPP | 0.04 | 0.66 | 0.04 | 0.58 |
| pPP | 0.02 | 0.81 | 0.03 | 0.73 |
| PPamp | 0.04 | 0.64 | 0.03 | 0.74 |
| Pf | 0.03 | 0.73 | 0.08 | 0.29 |
| Pb | −0.003 | 0.97 | 0.06 | 0.43 |
| RM | −0.02 | 0.76 | −0.04 | 0.63 |
| Pf time | 0.09 | 0.26 | 0.04 | 0.62 |
| Pb time | *0.17* | *0.03* | −0.06 | 0.46 |

Significant associations are shown in italics

*PWV*, pulse wave velocity; *AIx*, augmentation index; *cSP*, central systolic pressure; *cPP*, central pulse pressure; *pPP*, peripheral pulse pressure; *PPamp*, pulse pressure amplification; *Pf*, forward wave pressure; *Pb*, backward wave pressure; *RM*, reflection magnitude; *Pf time*, time to the peak of the Pf; *Pb time*, time to wave reflection; *HDL*, high-density lipoprotein; *TNF-α*, tumor necrosis factor alpha; *DMARD*, disease modifying anti-rheumatic drugs; *ACPA*, anti-citrullinated peptide antibody

[a] Characteristics that were logarithmically transformed

[b] Known confounder-adjusted model: age, sex, race, height, weight, heart rate, and mean arterial pressure

[c] Fully adjusted model included: E/A—age at disease onset, sex, race, height, mean arterial pressure, heart rate, disease duration, waist-hip ratio, erythrocyte sedimentation rate, and glomerular filtration rate; E/e'—age, sex, race, height, diastolic blood pressure, and heart rate; PWV—waist-hip ratio, total cholesterol-HDL cholesterol ratio, extra-articular manifestations, statin therapy, TNF-α inhibitor therapy, and abatacept therapy; AIx—total cholesterol concentrations, HDL cholesterol concentrations, homeostatic model of insulin resistance, and TNF-α inhibitor therapy; cSP—total cholesterol-HDL cholesterol ratio, statin therapy, and chloroquine therapy; cPP—total cholesterol-HDL cholesterol ratio, statin therapy, and chloroquine therapy; pPP—total cholesterol-HDL cholesterol ratio, C-reactive protein concentrations, statin therapy, tetracycline therapy, and chloroquine therapy; PPamp—waist-hip ratio, total cholesterol concentrations, glucose concentrations, leflunomide therapy, and TNF-α inhibitor therapy; Pf—total cholesterol-HDL cholesterol ratio and statin therapy; Pb—number of DMARD; RM—HDL cholesterol concentrations, TNF-α inhibitor therapy, and leflunomide therapy; Pb time—waist-hip ratio, erythrocyte sedimentation rate, white cell count, and ACPA status

Figure 1 depicts the known confounder-adjusted means and SDs of arterial function variables stratified by tertiles of diastolic function. The time to wave reflection increased across tertiles of E/A. Pulse wave velocity increased across tertiles of E/e'.

## Independent Relations of Arterial Function Measures with Impaired LV Relaxation and Increased Filling Pressure

Table 3 gives the associations of arterial function measures (1 SD increase) with impaired LV relaxation and increased filling pressure. The time-to-wave reflection was associated with a decreased E/A in the known confounder-adjusted (OR (95%CI) = 0.48 (0.31–0.74)) and fully adjusted backward logistic regression models (OR (95%CI) = 0.53 (0.33–0.85)). Upon forcing PWV or central pulse pressure additionally into this model, the time-to-wave reflection remained associated with a reduced E/A (OR (95%CI) with PWV in the model = 0.57 (0.35–0.94); OR (95% CI) with central pulse pressure in the model = 0.53 (0.33–0.85)). Pulse pressure amplification (OR (95% CI) = 0.58; (0.39–0.89)) and time to the peak of the forward wave (OR (95% CI) = 1.71 (1.15–2.53)) were related to a reduced and increased E/A, respectively, in the fully adjusted model. In the known confounder-adjusted model, PWV (OR (95% CI) = 1.69 (1.14–2.49)), central systolic pressure (OR (95% CI) = 1.57 (1.04–2.37)), and peripheral pulse pressure (OR (95% CI) = 1.41 (1.00–1.99)) were related to an increased E/e'. PWV remained associated with an increased E/e' (OR (95% CI) = 1.64; (1.13–2.83)) in the fully adjusted model. When central pulse pressure was additionally forced into this model, PWV remained associated with an increased E/e' (OR (95% CI) = 1.65; (1.13–2.37)).

When sensitivity analysis was performed in patients with isolated diastolic dysfunction (ejection fraction ≥ 50%), the results were not materially altered (Table 3).

When LV mass index or CRP and interleukin-6 concentrations and DAS28 or deformed joint count were additionally forced into the models shown in Table 3, the results were also materially unaltered (data not shown).

In sensitivity analysis among women (Supplemental Table 1), PWV (OR (95% CI) = 1.80 (1.06–3.04)) and the time-to-wave reflection (OR (95% CI) = 0.38 (0.20–0.71)) were associated with an increased and reduced E/A, respectively. PWV was associated with an increased E/e' (OR (95% CI) = 1.58 (1.04–2.40)).

## Independent Relations of Arterial Function Measures with LV Diastolic Dysfunction According to Previous and Current Criteria Sets

Figure 2 shows arterial function measures (1 SD increase) that predicted the presence of diastolic dysfunction according to previous [39] and recent [37] classification criteria. Upon applying recently reported criteria [37], forward wave time was associated with the presence of diastolic dysfunction in the

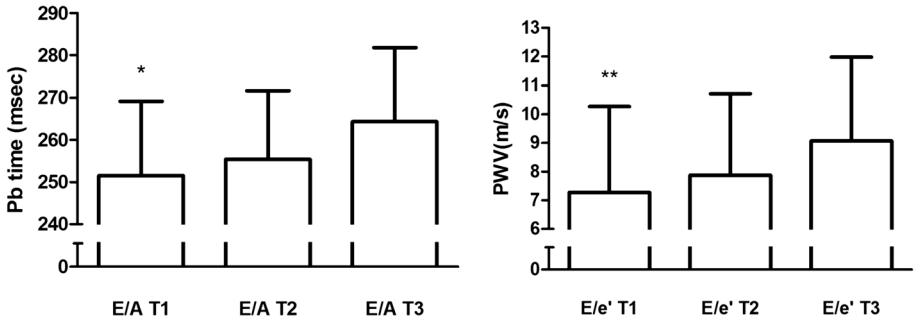



**Fig. 1** Adjusted means of arterial function properties across tertiles of diastolic function. Adjusted for known confounders: age, sex, race, height, weight, heart rate, and mean arterial pressure. *$p$ = 0.04 versus tertile 3; **$p$ = 0.004 versus tertile 3. Pb time, time to wave reflection; PWV, pulse wave velocity; T, tertile

known confounder- (OR (95% CI) = 1.43 (1.00–2.04)) and fully adjusted models (OR (95%CI) = 1.58 (1.05–2.36)). Upon applying previously reported criteria [39], in the known confounder-adjusted model, PWV (OR (95% CI) = 1.97 (1.25–3.12)) and central systolic pressure (OR (95% CI) = 2.03 (1.27–3.24)) were directly associated with diastolic dysfunction whereas the time-to-wave reflection was inversely (OR (95% CI) = 0.64 (0.45–0.90)) related to diastolic dysfunction. In the fully adjusted model, PWV (OR (95%CI) = 1.86 (1.20–2.90)) and the time-to-wave reflection (OR (95% CI) = 0.66 (0.47–0.92)) remained associated with diastolic dysfunction.

**Table 3** Association of arterial function properties (1 SD increase) with impaired relaxation and increased filling pressure

| | Decreased E/A (< 0.8) | | Increased E/e' (> 12) | |
|---|---|---|---|---|
| | OR (95% CI) | $p$ | OR (95% CI) | $p$ |
| Known confounder-adjusted model[a] | | | | |
| PWV | | | 1.69 (1.14–2.49) | 0.008 |
| cSP | | | 1.57 (1.04–2.37) | 0.03 |
| pPP | | | 1.41 (1.002–1.99) | 0.048 |
| Pb time | 0.48 (0.31–0.74) | 0.001 | | |
| Fully adjusted model[b] | | | | |
| PWV | | | 1.64 (1.13–2.38) | 0.009 |
| PPamp | 0.58 (0.39–0.89) | 0.01 | | |
| Pf | 1.71 (1.15–2.53) | 0.008 | | |
| Pb time | 0.53 (0.33–0.85) | 0.009 | | |
| Fully adjusted model[b] in those with isolated diastolic dysfunction | | | | |
| PWV | | | 1.59 (1.02–2.48) | 0.04 |
| PPamp | 0.43 (0.25–0.74) | 0.002 | | |
| Pf | 2.16 (1.31–3.56) | 0.003 | | |
| Pb time | 0.41 (0.23–0.71) | 0.002 | | |

*PWV*, pulse wave velocity; *cSP*, central systolic pressure; *cPP*, central pulse pressure; *pPP*, peripheral pulse pressure; *PPamp*, pulse pressure amplification; *Pf*, forward wave pressure; *Pb time*, time to wave reflection

[a] Known confounder-adjusted model: age, sex, race, height, weight, heart rate, and mean arterial pressure

[b] Fully adjusted model: age at disease onset, sex, race, heart rate, disease duration, waist-hip ratio, diastolic blood pressure, azathriopine therapy, and triglyceride concentrations

As also given in Fig. 2, among patients with isolated diastolic dysfunction (ejection fraction ≥ 50%), the relationships of PWV, the time-to-wave reflection, and time to the peak of the forward wave with diastolic dysfunction persisted. In addition, central systolic pressure predicted the presence of diastolic dysfunction according to both recent and previous recommended criteria.

Upon forcing LV mass index or markers of current or cumulative inflammation additionally into the models, the results were materially unaltered (data not shown).

As also shown in Supplemental Table 1, in sensitivity analysis among women, arterial function measures did not predict the presence of diastolic dysfunction according to recent criteria [37]. PWV (OR (95% CI) = 2.03 (1.20–3.44)), central systolic pressure (OR (95% CI) = 1.60 (1.06–2.40)), and the time-to-wave reflection (OR (95% CI) = 0.66 (0.46–0.95)) were associated with diastolic dysfunction according to previous criteria [39].

The core findings of the current study together with previously reported relations among systemic inflammation, traditional cardiovascular disease risk factors, arterial function, and diastolic function are reported in Fig. 3.

## Discussion

We report for the first time that an early return of the reflected wave is independently associated with impaired LV relaxation and PWV, a reported marker of arterial stiffness, is related to increased LV filling pressure in RA. These results were reproduced when the analysis was restricted to patients with a normal systolic function or isolated diastolic dysfunction as well as women with RA. Reflected wave timing and PWV predicted the presence of diastolic dysfunction according to the criteria proposed by Redfield and colleagues [39] but not those by Nagueh et al. [37].

Enhanced PWV and early return of the reflected wave increase LV load and reduce coronary perfusion. In contrast to majority of previously reported findings, we found that the associations of PWV and reflected wave timing with impaired diastolic function were not explained by central pulse pressure (Fig. 3). This indicates that patients with RA may experience

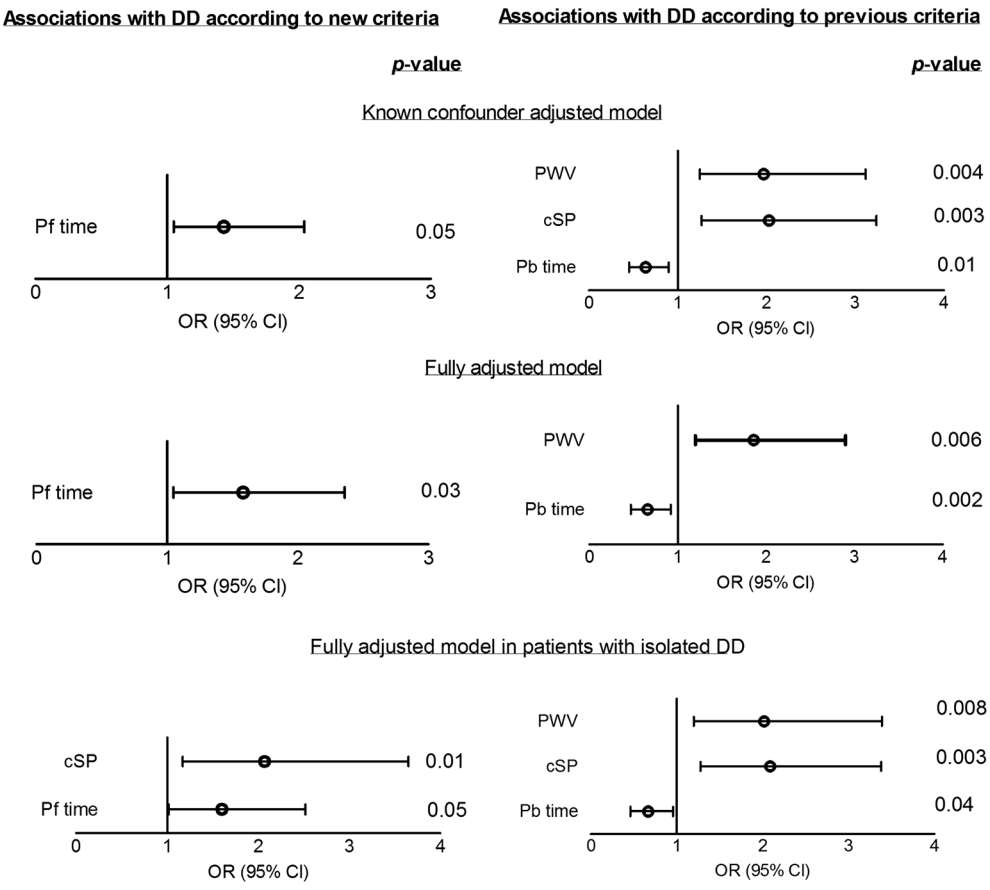



Fig. 2 Associations of arterial function properties (1 SD increase) with diastolic dysfunction according to new and previous criteria sets. Known confounder-adjusted model: age, sex, race, height, weight, heart rate, and mean arterial pressure. Fully adjusted model: age at disease onset, sex, race, heart rate, disease duration, waist-hip ratio, diastolic blood pressure, azathriopine therapy, and triglyceride concentrations. DD, diastolic dysfunction; Pf time, time to the peak of the forward wave; PWV, pulse wave velocity; cSP, central systolic pressure; Pb time, time to wave reflection

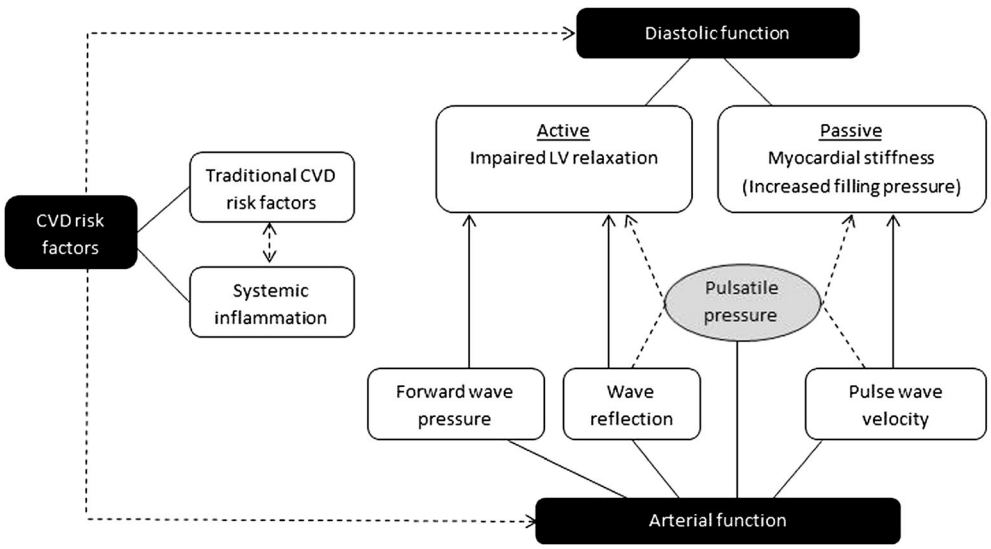



Fig. 3 Relationships among cardiovascular risk factors and aortic and diastolic function. Previous RA and non-RA studies revealed that traditional cardiovascular disease risk factors and systemic inflammation can impact aortic and diastolic function (dashed arrows). Non-RA investigations also documented that pulse wave velocity and wave reflection associate with diastolic function parameters but this relationship was mostly mediated by pulsatile pressure. In the present RA study (solid arrows), we found that pulse wave velocity is directly associated with increased left ventricular filling pressure, independent of pulsatile pressure as well as traditional cardiovascular risk factors and inflammatory markers. Additionally, early return of the reflected wave and forward wave pressure were related to impaired left ventricular relaxation independent of pulsatile pressure, pulse wave velocity, inflammation and traditional cardiovascular risk factors. Our results suggest that arterial dysfunction may exacerbate diastolic dysfunction directly through impaired ventricular-arterial coupling. CVD, cardiovascular disease; LV, left ventricular; RA, rheumatoid arthritis

impaired mechanical coupling of the left ventricle to the proximal aorta whereby large artery stiffness and wave reflection load the heart directly. In support of impaired mechanical ventricular-arterial coupling as an underlying mechanism of diastolic function, strategies aimed at reducing cardiac afterload are reportedly unsuccessful in patients with HFpEF [28]. Impaired myocardial-arterial coupling is more frequent in non-RA women than men [22]. This may explain the increased susceptibility to heart failure among women. Eighty-one percent of RA patients in the present study were women.

The relationships of PWV and reflected wave timing with diastolic function also persisted after adjusting for current and cumulative inflammation markers. We and others have previously reported evidence towards a role of inflammation in arterial function and/or diastolic function in patients with RA [25–27, 32]. Our current results suggest that arterial functional changes can impact diastolic function irrespective of the inflammatory burden in RA. However, as disease activity was overall well controlled in this cohort, our findings may not apply in patients with moderate or markedly active RA.

The associations of PWV and reflected wave timing with diastolic function were equally consistent in our analyses. Reflected wave timing was related to impaired LV relaxation and diastolic dysfunction independent of PWV. As arterial stiffness, as measured by PWV, predicts cardiovascular disease beyond brachial blood pressure in hypertensive persons [14, 16], current hypertension guidelines recommend consideration of PWV in refining cardiovascular risk stratification [40]. Recent studies, particularly those in which separation analysis was applied, have identified wave reflection as an additional and equally important independent contributor to cardiovascular outcomes [9, 13, 17]. Congruently, we recently documented that reflected wave pressure and reflection magnitude were strongly associated with subclinical atherosclerosis in hypertensive as well as normotensive RA patients [41]. Arterial stiffening was not related to atherosclerosis in RA [41]. Strikingly, the present study revealed that reflection wave timing rather than the absolute pressure was associated with LV relaxation in RA. In keeping with this finding, a previous investigation by Chirinos and colleagues disclosed that the loading sequence is more important than the actual pressure in determining myocardial wall stress among Asklepios Study participants [22].

Compared with early wave reflection and PWV, pressure pulsatility measures were less consistently related to diastolic function in patients with RA. Besides reflection wave timing, pulse pressure amplification and forward wave pressure but not PWV were independently associated with impaired LV relaxation ($E/A < 0.8$). This reinforces the importance of wave reflection in impaired diastolic function among patients with RA.

In all RA patients, central systolic blood pressure was not associated with diastolic dysfunction. By contrast, in a sensitivity analysis among patients without concurrent systolic dysfunction, central systolic blood pressure predicted the presence of diastolic dysfunction according to both the reported criteria by Nagueh and colleagues [37] and Redfield et al. [39]. In this regard, pressure pulsatility ultimately arises from the interaction between LV contractility and arterial properties [42]. Our current results therefore suggest that in RA patients with diastolic dysfunction and concurrent impaired systolic function, central systolic blood pressure does not impact diastolic function due to reduced LV ejection. As only 21.2% of our patients had a reduced ejection fraction, our finding on the central systolic blood pressure-diastolic dysfunction relation should be investigated further in future larger studies. This issue has clinical implications since low systolic blood pressure is reportedly associated with increased mortality in heart failure patients with and without preserved ejection fraction [43].

Whereas early wave reflection and PWV were consistently associated with core features of diastolic dysfunction in RA, these arterial properties predicted the presence of diastolic dysfunction as defined according to the criteria by Redfield and colleagues [39] but not Nagueh et al. [37]. Forward wave timing was not related to LV relaxation or filling pressure but was associated with diastolic dysfunction as defined by Nagueh and colleagues [37]. Both a recent population study [44] and an RA investigation [33] documented marked disparities in the estimated prevalence of diastolic dysfunction and its associated risk factors upon application of the different reported classification criteria sets. Previously reported findings together with our present results indicate that the identification of persons at risk of developing HFpEF by applying currently available definitions requires further study.

The findings of this study have treatment implications in patients with RA. We previously reported that markers of current and cumulative inflammation as well as traditional cardiovascular risk factors are associated with wave reflection in RA [32]. Taken together with our present findings, treatment of the respective risk factors may improve wave reflection and thereby LV relaxation and diastolic dysfunction in RA. Tumor necrosis factor-α treatment is associated with reduced PWV in RA [32, 45]. Therefore, tumor necrosis factor-α inhibitors and possibly other disease modifying agents may reduce arterial stiffness mediated LV filling pressure in RA. Further, considering that (1) increased wave reflection precedes arterial stiffening [8]; (2) wave reflection is reduced by angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and calcium channel blockers (CCB) independent of blood pressure control, unaltered by diuretics and increased by beta blockers (BB) [46]; and (3) the association of wave reflection with diastolic dysfunction was independent of blood pressure in the current study, ACEI, ARB, CCB, and diuretics may comprise first-line agents for hypertension in RA patients. This contrasts with the current European League Against Rheumatism recommendations on cardiovascular

disease risk management in RA [47]. The effects of disease activity control and different antihypertensive agents on diastolic function in patients with RA should be evaluated in future longitudinal and mechanistic studies.

Our study has strengths and further limitations. We investigated a relatively large group of RA patients. We accounted for a comprehensive range of carefully identified potential confounding characteristics. We evaluated different functional arterial properties that were each previously documented to predict cardiovascular events in non-RA persons [11–17, 20]. Our study design was cross-sectional and age- and sex-matched healthy controls were not investigated, which precludes the identification of cause-effect relationships. Future longitudinal and interventional studies should include healthy matched controls in order to determine whether these findings are unique to RA. As we assessed a comprehensive set of arterial function measures, multiple associations were evaluated. However, the results remained consistent when continuous and dichotomized outcomes were used in differently adjusted multivariable models. As all hypertensive patients were receiving antihypertensive agents and blood pressure control was adequate in the present cohort, our findings on enhanced PWV may not apply in RA patients with untreated or/and uncontrolled hypertension. We used the "triangulation method" of aortic wave separation to determine aortic forward and backward wave pressure. Although this method was validated, it may not be optimal [48]. Future studies should determine the impact of the forward and backward waves on LV function using simultaneous recording of actual aortic flow and pressure in RA. Although carotid femoral PWV is considered the gold standard, non-invasive measure of arterial stiffness [14], this method relies on body surface estimations and represents an average for the arterial tree [49]. Future studies should include aortic distensibility measurements (magnetic resonance imagining), in addition to PWV to assess local and regional assessments of the aorta and improve the accuracy of calculating PWV. Finally, we used the linear echocardiographic method to determine LV mass. Although this method is validated [35], it utilizes the Devereux "cube" formula, which assumes a prolate ellipsoid shape of the LV. Future studies should determine LV mass using real-time 3D echocardiography, which relies on the direct measurement of the LV without geometric assumptions regarding LV shape and wall thickness.

In conclusion, as highlighted in Fig. 3, this study demonstrates that aortic early wave reflection and PWV are associated with LV-impaired relaxation and increased filling pressure, respectively, in patients with RA. The relationships of arterial function with diastolic dysfunction were independent of steady state and pulsatile pressure. This suggests that impaired direct ventricular-arterial coupling mediates diastolic dysfunction in RA. Different classification criteria sets markedly impact the associations of arterial function measures with estimated diastolic dysfunction in RA. As there are currently no effective treatment strategies for HFpEF, our results indicate that aortic stiffness and wave reflection are potential therapeutic targets for the management of diastolic dysfunction in RA.

**Acknowledgments** The authors thank the voluntary contribution of the patients in this study.

**Funding** Funding for this work was provided by the National Research Foundation (Thuthuka programme) and the University of the Witwatersrand.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Ethical Approval** This investigation was approved by the University of the Witwatersrand Human (Medical) Research Ethics Committee (approval number: M06-07-33; protocol number: M120562 renewed as M170592) and was conducted in line with the principles of the Helsinki declaration. This article does not contain any studies with animals performed by any of the authors.

**Informed Consent** Informed consent was obtained from all participants included in the study.

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