Relationship between common carotid distensibility/aortic stiffness and cardiac left ventricular morphology and function in a group of patients affected by chronic rheumatic diseases: an observational study

A. Dalbeni[1], A. Giollo[2], F. Cattazzo[1], M. Bevilacqua[1], A. Mantovani[1], A. Tagetti[1], G. Orsolini[2], G. Cioffi[2], F. Ognibeni[2], P. Minuz[1], M. Rossini[2], O. Viapiana[2], C. Fava[1]

[1]Department of Medicine, General Medicine and Hypertension Unit, [2]Department of Medicine, Division of Rheumatology, University of Verona & Azienda Ospedaliera Universitaria Integrata di Verona, Italy.

Abstract

Objective

Chronic inflammatory arthritis (CIAs), including rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) are characterised by high cardiovascular disease (CVD) risk, partly due to endothelial dysfunction and increased arterial stiffness of the carotid artery and aorta. The aim of the present study is to determine whether ultrasonography measures of carotid and aortic stiffness are correlated with left ventricular mass and function in patients affected by CIAs.

Methods

In this cross-sectional study, we consecutively enrolled outpatients diagnosed with CIAs with no overt CVD. For each participant we assessed disease characteristics, CVD risk factors, medications, including disease-modifying anti-rheumatic drugs (DMARDs), blood pressure, lipids and glucose levels. Carotid ultrasonography was performed in all patients using carotid distensibility (CD) and aortic stiffness index (AoSI) as measures of arterial stiffness. Participants underwent the same day a full echocardiographic study including assessment of left ventricular function and mass (LVM).

Results

The study population comprised 208 CIAs patients (mean age 57.4±11.4 y; females 63.9%), including 137 (65.9%) RA, 42 (20.2%) PsA and 29 (13.9%) AS patients. In multiple regression analysis, CD correlated with age (β=-0.198, p<0.0001), mean arterial pressure (β=-0.281, p<0.0001) and treatment with DMARDs (β=-1.976, p=0.021), while AoSI was not associated with any anthropometric, haemodynamic or clinical covariates. CD was inversely related to LVM (r=-0.20, p=0.005), whereas AoSI was directly correlated with diastolic function of the left ventricle (E/E'; r=0.191, p=0.007).

Conclusion

Our results underline the strict correlation between arterial stiffness and left ventricular mass and function in patients with CIAs.

Key words

arterial stiffness, carotid distensibility, aortic stiffness index, echocardiography

Andrea Dalbeni, PhD
Alessandro Giollo, MD
Filippo Cattazzo, MD
Michele Bevilacqua, MD
Anna Mantovani, MD
Angela Tagetti, MD
Giovanni Orsolini, MD
Giovanni Cioffi, MD
Federica Ognibeni, Sonographer
Pietro Minuz, MD
Maurizio Rossini, PhD
Ombretta Viapiana, PhD
Cristiano Fava, PhD

Please address corresponding to:
Filippo Cattazzo,
AOUI Verona - Policlinico G.B. Rossi,
Piazzale L.A. Scuro 10,
37132 Verona, Italy.
E-mail: cattazzo.f@gmail.com

Received on February 6, 2020; accepted in revised form on April 20, 2020.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2021.

Competing interests: none declared.

Introduction

Arterial stiffening that specifically affects central arteries, such as aorta and common carotids, is a progressive pathological process whose major determinant is increasing age (1). In fact, the elastin layer of the arterial wall, that is normally responsible for the compliance of the vascular tree, progressively deteriorates because of chronic mechanical stress (2). However, atherosclerosis, diabetes, hypertension, dyslipidaemia, renal failure, and connective tissue diseases have been associated with increased arterial stiffness, mainly because of vessel fibrosis, smooth muscle necrosis and wall calcification (3). Furthermore, there are some clinical evidence regarding an association between subclinical atherosclerosis and conduit arteries stiffening in the context of chronic inflammatory arthritis (CIAs); in particular, in patients affected by rheumatoid arthritis (RA) (4). Intriguingly, chronic or subclinical inflammation is now recognised as an important co-factor in determining arterial stiffening through multiple mechanisms involving leucocyte degranulation, oxidative stress and pro-inflammatory cytokines (5). Previous studies showed that patients suffering from chronic rheumatic diseases are more prone to develop accelerated clinical and subclinical atherosclerosis (6, 7) and conduit arteries stiffening (8) as compared to subjects with comparable traditional cardiovascular risk factors; moreover, disease activity of patients diagnosed with RA was related to higher carotid-pulse wave velocity (PWV) compared to both subjects with inactive disease and controls (9). These results are consistent with those of a previous meta-analysis in which indices of vascular stiffness were higher in RA patients compared to controls; interestingly, even considering only the study conducted on early RA, a significant difference in aortic PWV between RA patients and controls was observed. Furthermore, meta-regression analysis demonstrated a linkage among the inflammation severity and arterial stiffness (10). Nevertheless, some uncertainties remain on the hypothesised relationship between the disease aggressiveness and vascular stiffening. In a recent study conducted in patients with RA, Taverner and colleagues found that the only determinants of several indices of arterial stiffness, such as carotid distensibility (CD), PWV and augmentation index, were gender, anthropometric variables and blood pressure (BP). No association with markers of disease activity or duration was observed (11).
Stiffening of conduit arteries, such as aorta and carotid arteries, is considered a target organ damage in hypertensive patients (12-14) being associated with cardiovascular risk (15) and future events (16), especially coronary artery diseases (17), myocardial infarction, unstable angina and stroke (18). In this context, the interaction between vascular properties and cardiac morphology and function plays a key role in determining cardiovascular morbidity of arterial stiffening as witnessed by the linkage existing between this pathological process and left ventricular remodelling, diastolic dysfunction and impaired coronary perfusion pressure (19).
Therefore, the purpose of the present study was to investigate, in a sample of patients affected by CIAs, the determinants of carotid and aortic stiffness indices and the existing relationship between these and echocardiographic morpho-functional parameters, searching for possible clinical implications about cardiovascular prevention.

Methods

Study design

In this single-centre observational study, from 2014 to 2016, 208 patients affected by different types of chronic arthropathies, referred to the rheumatologic outpatient clinic, were enrolled. The study population comprised non-institutionalised subjects with RA diagnosed according to the 2010 ACR/EULAR classification criteria (20), psoriatic arthritis (PsA) and ankylosing spondylitis (AS), respectively diagnosed by the CASPAR (21) and the ASAS criteria (22). The inclusion criteria comprised an age between 18 and 75 years and no history of previous cardiovascular events. Anthropometric measurements (height, weight), medical history, cardiovascular risk factors (previous diagnosis of hy-

pertension, dyslipidaemia or diabetes, smoke), use of drugs (including antihypertensive agents and statins) and previous disease, were also recorded. An accurate assessment of rheumatologic therapy was performed, focusing on corticosteroids and disease-modifying anti-rheumatic drugs (DMARDs) which includes antimalarials (chloroquine, hydroxychloroquine), methotrexate and biologic drugs (anti-TNFs, tocilizumab, abatacept, rituximab). Hypertension was defined as office systolic BP values at least 140 mmHg and/or diastolic BP values at least 90 mmHg, or use of antihypertensive medications as indicated in the last ESH/ESC guidelines (23). Dyslipidaemia was defined as total cholesterol >190 mg/dL or LDL cholesterol >115 mg/dL or HDL cholesterol <45 mg/dL or triglycerides >150 mg/dL, or the use of anti-lipemic drugs (24). Diagnostic criteria for diabetes were fasting plasma glucose ≥126 mg/dL and/or random plasma glucose/2h plasma glucose after an oral glucose tolerance test ≥200 mg/dL and/or glycated haemoglobin ≥48 mmol/mol (25). Values of C-reactive protein (CPR), glycaemia, LDL cholesterol, uric acid leves and triglycerides were performed for clinical use by the laboratory analysis of the Azienda Ospedaliera Universitaria Integrata of Verona. A single rheumatologist evaluated each participant in order to define disease activity (Disease Activity Score 28 [DAS28] for RA and PsA; Ankylosing Spondylitis Disease Activity Score [ASDAS] for AS). BP was measured with an oscillometric device (TM-2501, A&D Instruments Ltd., Abingdon Oxford, UK), in clinostatic position, at rest, by averaging 3 BP measurements performed 5 minutes apart. Each subject underwent carotid ultrasound and echocardiography by a single expert sonographer who was not blinded to the patient's clinical information.

Ethical approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of University of Verona and with the Helsinki Declaration of 1975, as revised in 2000. No animal studies were carried out by the authors for this article. Informed consent was obtained from all individual participants included in the study.

Carotid ultrasonography

All the measurements were performed by the same expert operator using high-resolution ultrasound (LOGIQ P5 pro, GE, Indianapolis, USA) and a linear probe (5–13 MHz, axial resolution of 0.01 mm). Carotid Intima-Media Thickness (cIMT) (right and left cIMT mean) was measured during the evaluation on the far wall of the distal common carotid artery 1 cm from the bifurcation using dedicated hardware (Hardware multimedia Video Engine II, MVE2) DSP Lab). The right and the left common CD were determined in conjunction with brachial BP measurements and were calculated using the following formula: $CD = (\Delta A/A) / PPa$, where ΔA is the stroke change (*i.e.* distension) in carotid artery cross-sectional area, which was normalised to the total diastolic carotid artery cross-sectional luminal area (A), and PPa is the differential pressure, assuming that the cross-section of the artery is circular (26). Changes in diameters were detected using ultrasound B-mode image sequences of the right and left common carotid arteries, which were acquired at different steps and analysed by the above mentioned automatic system (27). Arterial plaques were defined for cIMT higher than 1.5 mm or thicker than 0.5 mm or >50% of the surrounding values (28).

Echocardiography

A transthoracic echocardiography was performed in all participants by a single expert sonographer, focusing on both the left and right section of the heart. Doppler echocardiographic studies were performed using an Alpha Esaote Biomedica machine (Esaote SpA, Genova, Italy) equipped with a 2.5 to 3.5-MHz annular-array transducer following a standardised protocol and forwarded for final interpretation to the Echo-Lab of Villa Bianca Hospital of Trento, Italy. In the parasternal long-axis view, M-mode method was used to measure diastolic interventricular septum thickness (IVS) and posterior wall thickness (PWT). Aortic diameters were measured at the level of pulmonary artery bifurcation (2–3 cm above the aortic valve). M-mode diameter measurements were performed in systole (point of maximal anterior motion of the ascending aorta) and at end-diastole. Aortic stiffness index (AoSI) was obtained as follows $AoSI = ln(Ps/Pd)/[(As - Ad)/Ad]$, where *ln* is the natural logarithm, *As* is the aortic diameter at end-systole, *Ad* is the aortic diameter at end-diastole, *Ps* is the systolic BP and *Pd* is the diastolic BP (3). Left ventricular diameters and volumes were calculated by B-mode echocardiography. Ejection Fraction was calculated through the formula (tele-diastolic volume – tele-systolic volume)/tele-diastolic volume. Pulsed Doppler on the mitral annular plane from the apical four-chamber view revealed early (E) and late (A) trans-mitral flow velocity and its deceleration time. The early (e´) median mitral annular diastolic velocity was determined by spectral tissue Doppler imaging at the medial corner of the mitral annulus from the apical four-chamber (29). E/A and E/e' were obtained subsequently and were used to identify left ventricular diastolic dysfunction (30). Relative wall thickness (RWT) was calculated through the following formula: (PWT*2)/tele-diastolic diameter and indicated concentric left ventricular geometry if ≥0.43 (31). Devereux equation was used to obtain left ventricular mass (LVM) ($LVM=0.80*1.04$ [(tele-diastolic diameter + PWT + IVS)^3 - tele-diastolic diameter^3] + 0.6 gr) (32), then indexed per body surface area (obtained with the Mosteller formula). Mitral annular calcification (33) and aortic valve sclerosis were searched for all patients and considered in the statistical analyses.

Statistical analysis

Continuous variables are presented as the mean ± standard deviation whereas categorical variables are expressed as a percentage. Anthropometric, anamnestic and clinical variables of patients grouped according to rheumatic disease were compared using one-way ANOVA. Pearson's correlation was used to identify univariate associations between

Table I. Baseline anthropometric, anamnestic, laboratory, vascular and echocardiographic parameters in total population and in subgroups defined according to rheumatic disease.

	Whole sample (n=208)	RA (n=137)	PsA (n=42)	AS (n=29)	ANOVA *p*-value
Age (years)	57.4 ± 11.4	59.5 ± 11.3§	54.6 ± 8.9§	51.3 ± 12.3§	**<0.001**
Males (%)	36.1	21.1*	54.2	69.0	**<0.001**
BMI (kg/m^2)	25.8 ± 4.4	25.5 ± 4.3	26.2 ± 3.6	26.5 ± 4.9	0.422
Hypertension (%)	48.1	48.2	47.6	48.3	0.998
Dyslipidaemia (%)	63.0	65.0	64.2	51.7	0.403
Smoke (%)	42.2	44.1	42.9	32.1	0.507
Diabetes (%)	9.1	8.8	9.5	10.3	0.960
Anti-hypertensive drugs (%)	43.4	45.2	36.6	44.8	0.720
Statins (%)	24,5	27,0	26,2	10,3	0.132
DMARDs	71.2	73.7	71.4	58.6	0.312
CRP (mg/dL)	4.23 ± 7.44	4.24 ± 7.74	2.84 ± 3.32	6.18 ± 9.8	0.178
Glucose (mg/dL)	93.0 ± 23.0	91.2 ± 23.0	96.4 ± 23.1	96.7 ± 22.2	0.351
Triglycerides (mg/dL)	108.9 ± 55.1	114.3 ± 60.0	104.6 ± 43.6	92.3 ± 37.5	0.168
LDL-cholesterol (mg/dL)	119.8 ± 33.7	121.2 ± 33.3	113.8 ± 36.8	121.2±30.9	0.510
DAS28	2.65 ± 1.13	2.66 ± 1.08	2.60 ± 1.26	---	---
ASDAS	---	---	---	1.40 ± 0.77	---
cIMT (mm)	0.70 ± 0.14	0.71 ± 0.15 ʃ	0.71 ± 0.13	0.64 ± 0.14 ʃ	**0.042**
Carotid distensibility (kPa^{-1} 10^{-3})	19.7 ± 7.4	18.7 ± 6.6 ʃ	20.6 ± 8.1	22.7 ± 8.4 ʃ	**0.019**
Carotid plaques (%)	32.7	37.2 ʃ	31.0	13.8 ʃ	**0.049**
SBP (mmHg)	137.1 ± 17.8	138.4 ± 18.3	134.4 ± 16.5	135.3 ± 16.8	0.368
DBP (mmHg)	83.6 ± 9.7	83.1 ± 9.6	84.0 ± 10.2	85.0 ± 8.4	0.610
MAP (mmHg)	53.6 ± 13.5	55.5 ± 13.5*	50.4 ± 12.5	50.3 ± 12.8	**0.043**
IVS (mm)	1.05 ± 0.15	1.04 ± 0.16	1.07 ± 0.12	1.08 ± 0.15	0.368
EF (%)	65.9 ± 6.0	65.6 ± 6.1	67.7 ± 5.9	64.8 ± 4.7	0.078
LVM (g/m^2)	98.0 ± 21.7	97.6 ± 22.9	100.4 ± 20.8	96.3 ± 16.7	0.709
RWT	0.45 ± 0.07	0.45 ± 0.07	0.46 ± 0.05	0.47 ± 0.07	0.139
E/A	0.92 ± 0.31	0.92 ± 0.32	0.91 ± 0.31	0.94 ± 0.39	0.903
E Deceleration tme (ms)	201 ± 56	196 ± 50	210 ± 65	212 ± 67	0.191
E/E'	6.25 ± 1.67	6.16 ± 1.41	6.40 ± 1.79	6.46 ± 2.49	0.572
Aortic stiffness index (%)	5.8 ± 3.6	5.6 ± 3.8	5.9 ± 3.1	5.8 ± 3.4	0.980

RA: rheumatoid arthritis; PsA: psoriatic arthritis; AS: ankylosing spondylitis; BMI: body mass index; CRP: C-reactive protein; LDL: low-density lipoproteins; DAS28; Disease Activity score 28; DMARDs: disease-modifying anti-rheumatic drugs; ASDAS: Ankylosing Spondylitis Disease Activity Score; cIMT: carotid intima-media thickness; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; IVS: inter ventricular septum; EF: ejection fraction; LVM: left ventricular mass indexed per body surface area; RWT: relative wall thickness.
Tuckey *post-hoc* test at one-way ANOVA.
§significant differences between all groups; *RA significantly different compared to both PsA and AS; ʃRA significantly different compared to AS.

carotid and aortic stiffness and echocardiographic parameters, particularly left heart structure and functionality. Setting the α level at 0.05, the statistical power of the present study to detect a correlation (ϱ) >0.2 was estimated to be >80%. A multivariate linear regression analysis was performed in order to determine if any anthropometric, anamnestic and clinical variables (age, sex, body mass index [BMI], mean arterial pressure [MAP]), presence of carotid plaques, anti-hypertensive drugs and/or statins, prior diagnosis of hypertension, diabetes, dyslipidemia, smoking habit, type of arthritis, disease duration and activity estimated by CPR levels, use of corticosteroids and various DMARDs (such as methotrexate, antimalarials and biologic drugs) could be independently associated with markers of arterial stiffness (CD and AoSI) and of heart hypertrophy or dysfunction (LVM and E/e'). The variable selection was done through a stepwise method (or sequential replacement) using a combination of forward and backward techniques. If the *p*-value was less than 0.05 or above 0.1 the aforementioned covariates were respectively included and excluded from the regression model (34). No fixed variables were considered. In all cases, a statistically significant result was considered if the *p*-value was <0.05. SPSS Statistics 22 and GraphPad Prism 7 were used for all data analysis.

Results

Characteristics of the study population

Two-hundred and eight consecutive subjects (age=57.4±11.4 years, males 36.1%) participated. RA was the diagnosis in 65.8% (137/208), PsA in 20.1% (42/208) and AS in 13.9% (29/208) of the patients. Baseline characteristics of total population and subgroups defined according to the different rheumatologic diseases are shown in Table I.

Determinants of CD and AoSI and correlations between arterial stiffness indices and echocardiographic parameters

CD was not correlated with AoSI in the whole sample (r=0.136, *p*=0.052). CD was independently associated with age, MAP and assumption of any DMARDs; these variables along with others explained 50.3% of the total variance (Table II). The same results were found in the RA subgroup, but not in PsA and AS sub-groups. When specific anti-rheumatic drugs (methotrexate, antimalarials and biologic drugs) en-

Table II. Determinants of carotid distensibility in stepwise multivariate linear regression analysis.

		beta	SEM	*p*-value	R^2
Age (years)	Carotid distensibility (kPa^{-1} 10^{-3})	-0.198	0.036	<0.0001	0.503
MAP (mmHg)		-0.281	0.030	<0.0001	
DMARDs		-1.976	0.851	0.021	

MAP: mean arterial pressure; DMARDs: disease modifying anti-rheumatic drugs.
Model: R=0.709, R^2=0.503
Excluded from the final model: sex, body mass index, presence of carotid plaques, hypertension, dyslipidaemia, diabetes, assumption of anti-hypertensive drugs, statins and corticosteroids, arthritis type, disease duration, C-reactive protein.

tered the regression analysis instead of any DMARDs, age and MAP were the only parameters independently associated with CD. AoSI was not associated with any anthropometric, anamnestic or clinical parameters (including cardiovascular and rheumatologic drugs) in the whole sample and in RA, PsA and AS sub-groups.

Regarding echocardiographic parameters, an hypertrophic and concentric cardiac remodelling was found in females and males respectively, in both the whole sample and the RA subgroup, since LVM was found to be above the normal reference range in women (98.8±23.5 g/m^2 *vs*. $95g/m^2$ as cut-off value in women according to European Society of Cardiology guidelines (35)) but normal in men (96.6±18.2 g/m^2 *vs*. $115g/m^2$ as cut-off value in men according to European Society of Cardiology guidelines (35)) and RWT was higher than the validated cut-off for cardiac structural remodelling (males = 0.44±0.06, females = 0.45±0.05 *vs*. 0.42 as reference value for both sexes (31)). AoSI was significantly associated to E/e' in the whole sample (r=0.191, *p*=0.007) and in RA group (r=0.166, *p*=0.05), but not in PsA and AS subgroups. Considering the whole sample, an inverse correlation was found between CD and LVM (r=-0.201, 0.004); similar results were found in the RA (r=-0.214, *p*=0.014) and PsA subgroups (r=-0.294, *p*=0.05), but not in the AS subgroup (r=-0.065, *p*=0.721). Interestingly, LVM remained independently associated with CD in stepwise multivariate linear regression analysis rather than the above mentioned clinical and anamnestic variables (beta±SEM=-0.663±0.206; *p*=0.001). Similarly, the only independent factor associated with E/e' was found to be AoSI (beta±SEM=0.097±0.033, *p*=0.004).

Discussion

In the present study, we analysed two markers of arterial stiffening measured in central arteries and standard echocardiographic parameters trying to identify the possible determinants of vascular stiffness and searching for a link between this pathological process and cardiac remodelling in subjects affected by different types of chronic arthropathies. In the last decades, the pathogenetic mechanisms of cardiovascular disease have been progressively dissected (36); in particular, arterial stiffness was found to be strictly associated with the atherosclerotic process, which has a pivotal role in determining cardiovascular events (37). In addition to depending on classical cardiovascular risk factors, arterial compliance and elasticity were seen to be influenced by chronic inflammation, as shown in rheumatic disorders (38). In our population and in line with a previous study of our group (39), CD was significantly associated with traditional clinical variables and cardiovascular risk factors such as age and MAP whereas AoSI was not. Therefore these parameters might be the readout of something in some way different, a hypothesis that could be supported not only by the aforementioned data but also from the absence of any correlation between these two markers of arterial stiffness. Regarding the supposed role of inflammation severity as a determinant of vascular stiffening, in our population, the indices of acute inflammation or disease activity seemed to significantly affect neither carotid nor aortic elasticity. However, disease activity was clinically low in this population (normal CPR, DAS28 values in AR and PsA and ASDAS values in AS significant for disease remission in almost all participants) and this could probably explain the apparent independency of cardiovascular properties and indices of acute inflammation or disease activity. Nonetheless, DMARDs assumption (regardless of the drug), rather than the type of arthritis and disease duration, was shown to negatively associate with CD; that is, the more aggressive the disease (requiring DMARDs), the stiffer are central arteries probably because of the subclinical and continuous inflammatory background of chronic arthropathies.

Few studies reported a close association between ventricular remodelling/left ventricular diastolic function and vascular stiffness (40-42) and mostly in samples of healthy or hypertensive subjects. In fact, an earlier pulse wave reflection due to stiffer arteries causes increased central BP which is known to be associated with higher left ventricular afterload, concentric remodelling, hypertrophy and myocardial fibrosis (3). Furthermore, the mismatch between oxygen demand and supply can determine myocardial ischaemia and impaired ventricular relaxation during diastole, leading to higher filling pressures (43). In this study, when split according to sex, female patients showed an increase in both LVM and RWT while males had normal LVM and abnormal RWT, defining a hypertrophic and concentric remodelling, respectively. Furthermore, LVM was negatively associated with CD, and this relationship was kept after adjustment for traditional cardiovascular risk factors and rheumatologic parameters. CD was not related to left ventricular diastolic or systolic dysfunction, unlike a recent study were carotid β stiffness and β-PWV (measured as one-point PWV) was correlated not only with LVM, RWT and left atrial volume, but even with E/A and E/e'(44), markers of left ventricular diastolic function (45). Conversely, AoSI was shown to be related to E/e', suggesting a closer association between ascending aorta and left ventricular diastolic properties compared

to classical indices of cardiac remodelling. As for CD, AoSI was associated with E/e' independently by traditional cardiovascular risk factors and rheumatologic history. However, E/e' was within the normal range in almost all patients while E/A, although not correlated with AoSI, resulted on average lower than 1, defining a grade 1 diastolic dysfunction. That is, the stiffening of ascending aorta could be more aligned with the progressive impairment of left ventricular relaxation in diastole than other more peripheral arteries, such as common carotids.

These data suggest, firstly, a possible pathophysiological link for cardiac abnormalities when central arteries are progressively stiffer and, moreover, a possible predictive role of carotid ultrasound for the early detection of possible cardiac remodelling in the context of CIAs, a result consistent with the findings of another study in which the authors stated that carotid ultrasonography could be useful to detect high cardiovascular risk in axial spondyloarthritis patients (46).

Our study evaluated a relatively large population of patients affected by several types of chronic arthropathies but has some limitations: in particular, i. the absence of a control group; ii. the lack of follow-up; iii. the relative heterogeneity of participants in terms of rheumatic diagnosis; iv. the recruitment of subjects in a single center may affect the representativeness of the sample exposing to potential selection biases and precluding the generalisability of the study results to the entire population. Nonetheless, stiffness of carotid artery and ascending aorta were evaluated with validated ultrasound techniques; CD was obtained through a dedicated high definition ultrasound method that showed reproducibility and agreement with standard radio-frequency based techniques and echo-tracking systems used to identify interfaces in the arterial wall (26, 27). AoSI was assessed with a simple, non-invasive, quantitative and validated ultrasound method based on BP and vascular systo-diastolic diameters to produce an index suitable also for clinical medicine (3, 47).

In conclusion, in a sample of patients suffering from different types of chronic arthritis, CD was related to LVM and ventricular remodelling, while AoSI showed an association with left ventricular diastolic function. These associations show once again the strict interdependence between arterial stiffness and cardiac remodelling and function. Indeed, carotid ultrasound may be considered in the future as a relatively simple test to predict which arthritic patients could be at greater risk of cardiac remodelling. These hypotheses should be further pursued along with the estimate of a possible predictive role of CD in the assessment of cardiac impairment in chronic inflammatory conditions.

Acknowledgments

We thank our colleagues of the Azienda Opsedaliera Universitaria Integrata of Verona for the great support they gave us in conducting this study.

References

1. BENETOS A, WAEBER B, IZZO J *et al.*: Influence of age, risk factors, and cardiovascular and renal disease on arterial stiffness: clinical applications. *Am J Hypertens* 2002; 15: 1101-8.
2. MIKOLA H, PAHKALA K, RÖNNEMAA T *et al.*: Distensibility of the aorta and carotid artery and left ventricular mass from childhood to early adulthood. *Hypertension* 2015; 65: 146-52
3. NEMES A, GELEIJNSE ML, FORSTER T, SOLIMAN OI, TEN CATE FJ, CSANÁDY M: Echocardiographic evaluation and clinical implications of aortic stiffness and coronary flow reserve and their relation. *Clin Cardiol* 2008; 31: 304-9.
4. GUNTER S, ROBINSON C, WOODIWISS AJ *et al.*: Arterial wave reflection and subclinical atherosclerosis in rheumatoid arthritis. *Clin Exp Rheumatol* 2018; 36: 412-20.
5. JAIN S, KHERA R, CORRALES-MEDINA VF, TOWNSEND RR, CHIRINOS JA: Inflammation and arterial stiffness in humans. *Atherosclerosis* 2014; 237: 381-90.
6. SALMON JE, ROMAN MJ: Subclinical atherosclerosis in rheumatoid arthritis and systemic lupus erythematosus. *Am J Med* 2008; 121: S3-8.
7. GIOLLO A, DALBENI A, CIOFFI G *et al.*: Factors associated with accelerated subclinical atherosclerosis in patients with spondyloarthritis without overt cardiovascular disease. *Clin Rheumatol* 2017; 36: 2487-95.
8. ROMAN MJ, DEVEREUX RB, SCHWARTZ JE *et al.*: arterial stiffness in chronic inflammatory diseases. hypertension. 2005; 46: 194-9.
9. ŞIRIN ÖZCAN AN, ASLAN AN, ÜNAL Ö, ERCAN K, KÜÇÜKŞAHIN O: A novel ultrasound-based technique to establish a correlation between disease activity and local carotid stiffness parameters in rheumatoid arthritis. *Med Ultrason* 2017; 19: 288-94.
10. AMBROSINO P, TASSO M, LUPOLI R *et al.*: Non-invasive assessment of arterial stiffness in patients with rheumatoid arthritis: A systematic review and meta-analysis of literature studies. *Ann Med* 2015; 47: 457-67.
11. TAVERNER D, PAREDES S, FERRÉ R, MASANA L, CASTRO A, VALLVÉ JC: Assessment of arterial stiffness variables in patients with rheumatoid arthritis: A mediation analysis. *Sci Rep* 2019; 9: 1-8.
12. LAURENT S: Arterial stiffness in arterial hypertension. *Curr Hypertens Rep* 2006; 8: 179-80.
13. MANCIA G, DE BACKER G, DOMINICZAK A *et al.*: 2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension. *J Hypertens* 2007; 25: 1751-62.
14. MULÈ G, NARDI E, MORREALE M *et al.*: The relationship between aortic root size and hypertension: an unsolved conundrum. In: *Advances in Experimental Medicine and Biology*. 2016. p. 427-45.
15. BLACHER J, SAFAR ME: Large-artery stiffness, hypertension and cardiovascular risk in older patients. *Nat Clin Pract Cardiovasc Med* 2005; 2: 450-5.
16. SAID MA, EPPINGA RN, LIPSIC E, VERWEIJ N, VAN DER HARST P: Relationship of arterial stiffness index and pulse pressure with cardiovascular disease and mortality. *J Am Heart Assoc* 2018; 7: e007621.
17. BONARJEE VVS: Arterial stiffness: a prognostic marker in coronary heart disease. available methods and clinical application. *Front Cardiovasc Med* 2018; 5: 64.
18. MITCHELL GF, HWANG S-J, VASAN RS *et al.*: Arterial stiffness and cardiovascular events. circulation. 2010; 121: 505-11.
19. CHIRINOS JA, SEGERS P, HUGHES T, TOWNSEND R: Large-artery stiffness in health and disease. *J Am Coll Cardiol* 2019; 74: 1237-63.
20. ALETAHA D, NEOGI T, SILMAN AJ *et al.*: 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010; 69: 1580-8.
21. TAYLOR W, GLADMAN D, HELLIWELL P, MARCHESONI A, MEASE P, MIELANTS H: Classification criteria for psoriatic arthritis: Development of new criteria from a large international study. *Arthritis Rheum* 2006; 54: 2665-73.
22. RUDWALEIT M, VAN DER HEIJDE D, LANDEWÉ R *et al.*: The development of Assessment of SpondyloArthritis International Society Classification Criteria For Axial Spondyloarthritis (part II): Validation and final selection. *Ann Rheum Dis* 2009; 68: 777-83.
23. WILLIAMS B, MANCIA G, SPIERING W *et al.*: 2018 ESC/ESH Guidelines for the management of arterial hypertension. *J Hypertens* 2018; 36: 1953-2041.
24. CATAPANO AL, GRAHAM I, DE BACKER G *et al.*: 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *Eur Heart J* 2016; 37: 2999-3058.
25. AMERICAN DIABETES ASSOCIATION: 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2019;

Diabetes Care 2019; 42 (Suppl. 1): S13-S28.
26. BIANCHINI E, BOZEC E, GEMIGNANI V *et al*.:assessment of carotid stiffness and intima-media thickness from ultrasound data. *J Ultrasound Med* 2010; 29: 1169-75.
27. GIANNARELLI C, BIANCHINI E, BRUNO RM *et al*.: Local carotid stiffness and intima-media thickness assessment by a novel ultrasound-based system in essential hypertension. *Atherosclerosis* 2012; 223: 372-7.
28. TOUBOUL PJ, HENNERICI MG, MEAIRS S *et al*.: Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). *Cerebrovasc Dis* 2012; 34: 290-6.
29. NAGUEH SF, SMISETH OA, APPLETON CP *et al*.: Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Hear J Cardiovasc Imaging* 2016; 17: 1321-60.
30. REDFIELD MM, JACOBSEN SJ, BURNETT JC, MAHONEY DW, BAILEY KR, RODEHEFFER RJ: Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA* 2003; 289: 194-202.
31. DE SIMONE G, DANIELS SR, KIMBALL TR *et al*.: Evaluation of concentric left ventricular geometry in humans: evidence for age-related systematic underestimation. *Hypertens* 2005; 45: 64-8.
32. DEVEREUX RB, ALONSO DR, LUTAS EM *et al*.: Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986; 57: 450-8.
33. FOX CS, VASAN RS, PARISE H *et al*.: Mitral annular calcification predicts cardiovascular morbidity and mortality: the Framingham Heart Study. *Circulation* 2003; 107: 1492-6.
34. LEWIS-BECK M, BRYMAN A, FUTING LIAO T: Stepwise regression. *SAGE Encycl Soc Sci Res Methods* 2012; 1-9.
35. LANG RM, BADANO LP, MOR-AVI V *et al*.: Recommendations for cardiac chamber quantification by echocardiography in adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; 28: 1-39.e14.
36. PATEL AK, SURI HS, SINGH J *et al*.: A review on atherosclerotic biology, wall stiffness, physics of elasticity, and its ultrasound-based measurement. *Curr Atheroscler Rep* 2016; 18: 83.
37. BOESEN ME, SINGH D, MENON BK, FRAYNE R: A systematic literature review of the effect of carotid atherosclerosis on local vessel stiffness and elasticity. *Atherosclerosis* 2015; 243: 211-22.
38. YILDIZ M: Arterial distensibility in chronic inflammatory rheumatic disorders. *Open Cardiovasc Med J* 2010; 4: 83-8.
39. DALBENI A, GIOLLO A, TAGETTI A *et al*.: Traditional cardiovascular risk factors or inflammation: Which factors accelerate atherosclerosis in arthritis patients*? Int J Cardiol* 2017; 236: 488-92.
40. RUSSO C, JIN Z, PALMIERI V *et al*.: Arterial stiffness and wave reflection. *Hypertension* 2012; 60: 362-8.
41. JAROCH J, ŁOBOZ GRUDZIEŃ K, BOCIĄGA Z *et al*.: The relationship of carotid arterial stiffness to left ventricular diastolic dysfunction in untreated hypertension. *Kardiol Pol* 2012; 70: 223-31.
42. HIGASHI H, OKAYAMA H, SAITO M *et al*.: Relationship between augmentation index and left ventricular diastolic function in healthy women and men. *Am J Hypertens* 2013; 26: 1280-6.
43. LÜERS C, TRIPPEL TD, SEELÄNDER S *et al*.: Arterial stiffness and elevated left ventricular filling pressure in patients at risk for the development or a previous diagnosis of HF – A subgroup analysis from the DIAST-CHF study. *J Am Soc Hypertens* 2017; 11: 303-13.
44. VRIZ O, MAGNE J, DRIUSSI C *et al*.: Comparison of arterial stiffness/compliance in the ascending aorta and common carotid artery in healthy subjects and its impact on left ventricular structure and function. *Int J Cardiovasc Imaging* 2017; 33: 521-31.
45. MITTER SS, SHAH SJ, THOMAS JD: A test in context. *J Am Coll Cardiol* 2017; 69: 1451-64.
46. RUEDA-GOTOR J, LLORCA J, CORRALES A *et al*.: Cardiovascular risk stratification in axial spondyloarthritis: Carotid ultrasound is more sensitive than coronary artery calcification score to detect high-cardiovascular risk axial spondyloarthritis patients. *Clin Exp Rheumatol* 2018; 36: 73-80.
47. HAYASHI K, YAMAMOTO T, TAKAHARA A, SHIRAI K: Clinical assessment of arterial stiffness with cardio-ankle vascular index: theory and applications. J *Hypertens* 2015; 33: 1742-57.