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Arterial stiffness, the hidden face of cardiovascular risk in autoimmune and chronic inflammatory rheumatic diseases

Marie Berger^a, Pierre Fesler^{a,b}, Camille Roubille^{a,b,*}

^a Department of Internal Medicine, CHU Montpellier, Montpellier University, Montpellier, France

^b PhyMedExp, University of Montpellier, INSERM U1046, CNRS UMR 9214, Montpellier Cedex 5, France

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ABSTRACT

Background and objective: Cardiovascular diseases (CVD) are the leading causes of death in chronic inflammatory rheumatic diseases and are not solely explained by the increased prevalence of cardiovascular (CV) risk factors in this population. Arterial stiffness, assessed primarily by pulse wave velocity (PWV) and more indirectly by augmentation index (AIx), is a surrogate marker of CVD that should be considered. The objective of this review was to investigate the relationship between arterial stiffness and chronic inflammatory and/or autoimmune diseases.

Methods: We performed a systemic literature review of articles published in Medline from January 2012 to April 2020 restricted to English languages and to human adults. We selected relevant articles about the relationship between arterial stiffness and rheumatoid arthritis, systemic lupus erythematosus, psoriasis, Sjogren's syndrome and ankylosing spondylitis. For each selected article, data on PWV and AIx were extracted and factors that may have an impact on arterial stiffness were identified.

Results: A total of 214 references were identified through database searching and 82 of them were retained for analysis. Arterial stiffness is increased in chronic inflammatory and autoimmune diseases. Traditional CV risk factors such as hypertension and dyslipidemia accentuate this relationship. Current data are insufficient to determine whether disease activity significantly influences arterial stiffness, whereas disease duration seems rather critical. TNF-alpha inhibitors and cardiorespiratory fitness tend to decrease arterial stiffness. Finally, increased arterial stiffness leads to diastolic dysfunction, which is the main mechanism of heart failure in chronic inflammatory rheumatic diseases.

Conclusion: CV risk assessment in chronic inflammatory and autoimmune diseases should also rely on PWV and AIx.

1. Introduction

Cardiovascular diseases (CVD) are the leading cause of death in chronic inflammatory and autoimmune rheumatic diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and spondyloarthritis [1]. This excess mortality cannot be explained solely by the increased prevalence of cardiovascular (CV) risk factors [2] and the underlying mechanisms leading to such an increased CV risk are not yet clearly understood.

Increasing arterial stiffness is one of the first steps in the atherosclerotic process [3]. Pulse wave velocity (PWV) and augmentation index (AIx) are currently considered independent predictors of major CV events and all-cause mortality [4]. These surrogate markers of

subclinical atherosclerosis provide some important prognostic information in addition to traditional CV risk factors [5].

PWV is widely accepted as an accurate and non-invasive method for assessing arterial stiffness in humans [6]. A higher velocity indicates increased arterial stiffness. Currently, the measurement of PWV between the carotid and femoral arteries, which is defined as the aortic PWV, appears to be the most clinically relevant. To date, some studies have supported the prognostic value of aortic PWV measurement as a surrogate marker for subclinical organ damage, in the general population and in patients at increased CV risk [7]. Applanation tonometry is the most useful tool for assessing PWV.

Pulse wave analysis allows us to establish another indirect arterial stiffness parameter: the AIx. While pulse wave spreads in vessels, it

* Corresponding author at: Département de Médecine Interne, Hôpital Lapeyronie, 371 avenue du doyen Gaston Giraud, Montpellier cedex 34295, France.

E-mail address: c-roubille@chu-montpellier.fr (C. Roubille).

encounters several caliber disparities. Part of the wave is transmitted, and another part is reflected and returns to the heart. The summation of the “reflected” waves adds to the pulse wave produced by the heart and is responsible for an increase in pressure, normally in the early diastole. The AIx is the ratio of the increased pressure due to the reflected wave and the pulse pressure (that is, the difference between systolic blood pressure and diastolic blood pressure). The greater the arterial stiffness, the faster the reflected wave returns to the heart in systole and the more AIx increases. Thus, systolic blood pressure, ventricular afterload and myocardial oxygen consumption increase, and cardiac coronary perfusion is impaired [8,9].

In recent years, there has been growing interest in the relationship between arterial stiffness, a marker of CV risk, and rheumatic diseases, mainly RA and SLE. Our objective was to conduct a systematic literature research on arterial stiffness in a wide range of chronic inflammatory and autoimmune diseases.

2. Methods

2.1. Data sources and study selection

We performed a systemic review of articles published from January 2012 to April 2020, restricted to English languages and to human adults, in Medline (via PubMed). We used the MeSH term “Arthritis, Rheumatoid”, “Lupus Erythematosus, Systemic” “Psoriasis”, “Arthritis, Psoriatic”, “Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis”, “Sjogren's Syndrome”, combined with the Boolean operator “AND” with “Vascular Stiffness” or “Pulse Wave Analysis”. This last two terms included the concept of arterial stiffness, aortic stiffness, carotid stiffness, wave reflection and augmentation index which were not registered as MeSH term.

We reviewed the abstracts of all the articles we found in the systematic research for relevance. We selected the original articles focusing on the relationship between arterial stiffness and the inflammatory and/or autoimmune disease of interest. Irrelevant references and reviews were excluded.

2.2. Data extraction

The following data were extracted for each article using a predefined

data collection form: the study design, sample size, mean age, gender and treatment received by the patients when available. Next, we focused on comparing patients and controls in terms of PWV and AIx. The main findings of each study were collected and factors that had an impact on this association were highlighted.

3. Results of search

A total of 214 references were identified through database searching. After reading the abstract, 82 articles were selected for qualitative analysis (Fig. 1). We obtained respectively 42 results for RA (Table 1), 12 for SLE (Table 2), 14 for psoriasis or psoriatic arthritis (Table 3),

9 for spondyloarthritis (Table 4), and 5 for Sjögren's syndrome (Table 5).

4. Discussion

4.1. Rheumatoid arthritis (RA) and arterial stiffness

4.1.1. Increased arterial stiffness in RA

Among all the studies investigating the relationship between arterial stiffness and RA compared with controls, only two [10,11] found no increase in PWV or AIx. For instance, Anyfanti et al. reported higher levels of PWV among 104 patients with RA, compared to 52 controls (8.2 ± 2.1 vs 7.4 ± 1.4 m/s, $p = 0.016$) [12]. RA patients also showed significantly

greater values of AIx compared to healthy controls (32.2 ± 8.6 vs. $28.4 \pm 8.9\%$, $P = 0.02$) [13]. In addition, there appears to be an increase in arterial stiffness in early RA [14].

4.1.2. Influence of disease characteristics and CV risk factors on arterial stiffness

Some authors have sought to determine which characteristics may influence arterial stiffness in RA patients. However, evidence is scarce, due to studies with small samples.

First, it has been reported that the duration of the disease may influence arterial stiffness. In a study of 106 RA patients, without CV risk factors, patients with a duration of RA greater than 10 years had a significant increase in PWV compared to those with a recent diagnosis (duration of disease duration <2 years) [15]. Interestingly, the authors

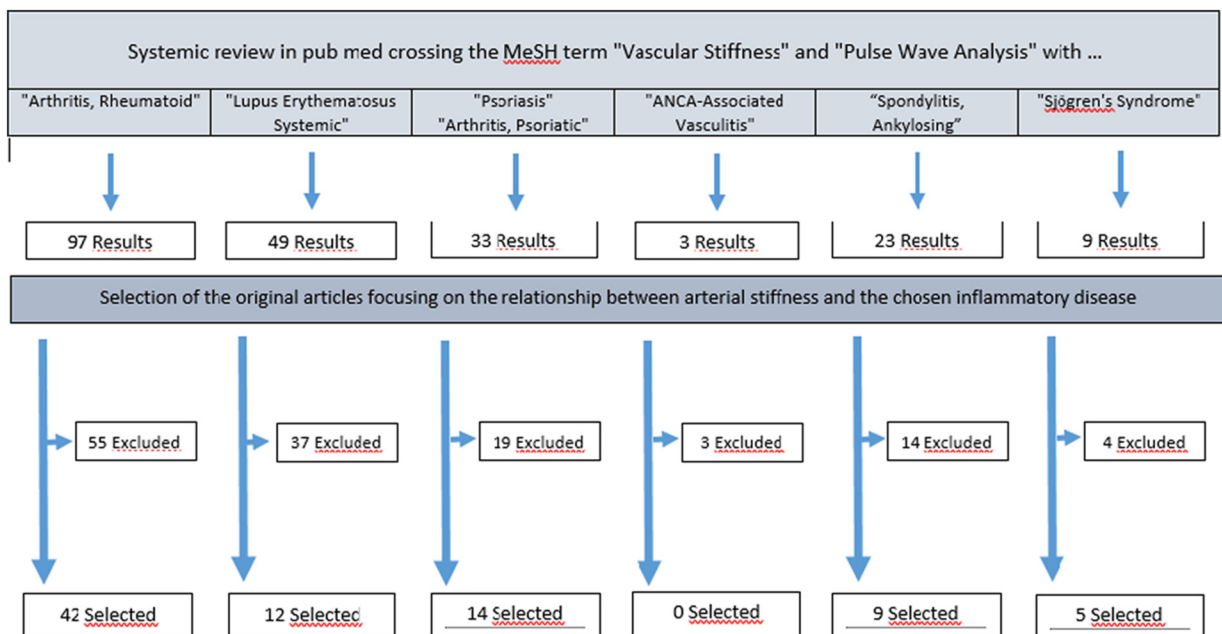


Fig. 1. Flowchart of the selected studies.

Table 1
Rheumatoid arthritis and arterial stiffness.

Reference	Design	Population	Treatment	Outcome
Anyfanti et al. 2018 [12]	Cross-sectional study	Patients $n = 104$ Age: 60 ± 11.4 years Female: 78.8% Controls $n = 52$ Age: 57.2 ± 8.2 years Female: 78.8%	75% sDMARD 43% bDMARD 27.9% CTC	\nearrow PWV in RA (8.2 ± 2.1 vs 7.4 ± 1.4 m/s, $p = 0.016$).
Maloberti et al. 2018 [13]	Cross-sectional study	Patients $n = 55$ Age: 62.8 ± 8.9 years Female: 73.4% Controls $n = 55$ Age: 62.8 ± 8.9 years Female: 73.4%	52.7% CTC 66.6% MTX 54.5% bDMARD	\nearrow AIX in RA (32.2 ± 8.6 vs. $28.4 \pm 8.9\%$, $p = 0.02$).
Gunter et al. 2018 [37]	Cross sectional study	Patients $n = 163$ Age: 58.4 ± 11.7 years Female: 79.1%	92.6% sDMARD or bDMARD	PWV is not associated with plaque (OR 1.03 [0.66–1.62], $p = 0.9$). AIX is not associated with plaque (OR 1.56 CI95% [0.94–2.70], $p = 0.08$).
Şirin Özcan et al. 2017 [16]	Cross sectional study	Patients $n = 70$ Age: 52.2 ± 10.8 years Female: 90% Controls $n = 35$ Age: 53.5 ± 6.7 years Female: 88%	44% SLZ 68% HCQ 54% CTC 68% MTX 8% LEF 3% bDMARD	\nearrow PWV in RA (7.76 vs 6.41 m/s, $p = 0.009$). \nearrow CMT in RA ($p = 0.0015$).
Vazquez-Del Mercado et al. 2017 [15]	Cohort study	Patients $n = 106$ Age: 46 ± 12 years Female: 95.3%	MD	In multivariate regression, PWV was positively correlated with age ($r = 0.450$, $p < 0.001$) and RA disease duration ($r = 0.340$, $p < 0.001$).
Aslan et al. 2017 [19]	Cross sectional study	Patients $n = 140$ Age: 52.2 ± 10.7 years Female: 90% Controls $n = 140$ Age: 52.7 ± 8.0 years Female: 90%	42.8% SLZ 68.5% HCQ 54.2% CTC 68.6% MTX	\nearrow PWV in RA (7.37 ± 1.70 vs 6.49 ± 0.92 m/s, $p < 0.001$). Seronegative patients had significantly elevated PWV than seropositive (7.68 ± 2.24 vs 7.12 ± 1.34 m/s, $p = 0.031$).
Gunter et al. 2017 [83]	Cohort study	Patients $n = 177$ Age: 58.0 ± 12.1 years Female: 100%	90.3% sDMARD 11.3% bDMARD	Factors associated with PP: - RA duration ($p = 0.04$) - RF status ($p = 0.001$ to 0.003) - Leukocytes counts ($p = 0.02$ to 0.05) - Cholesterol ($p < 0.01$ to 0.03) TNF- α inhibition was related to reduced PWV ($p < 0.01$).
Robustillo-Villarino et al. 2017 [39]	Cohort study	Patients $n = 194$ Age: 60.4 ± 13.2 years Female: 75.4%	100% sDMARD 32% bDMARD	After adjustment, PWV was no longer related to either IMT or plaque.
Cypiene et al. 2017 [22]	Cross sectional study	Patients $n = 149$ Age: 48.8 ± 13.5 years Female: 89.6% Controls $n = 156$ Age: 42.8 ± 11.0 years Female: 73.1%	48.3% SLZ 10.3% HCQ 17.4% CTC 20.1% MTX 12.8% LEF 26.6% bDMARD	\nearrow PWV in RA (8.53 m/s CI95% [8.28–8.77] and 8.01 m/s CI95% [7.77–8.24], $p = 0.008$). \nearrow AIX in RA (24.81% CI95% [23.1–26.45] vs 17.55% CI95% [15.97–19.12], $p < 0.0001$).
Scanlon et al. 2017 [17]	Correlative study	Patients $n = 50$ Age: 57.5 years Female: 76%	32% CTC 62% MTX 42% other sDMARD 66% bDMARD	AIX correlated with time-averaged tender joint count ($r = 0.37$, $p = 0.008$), CDAI ($r = 0.36$, $p = 0.01$), HAQ-II ($r = 0.36$, $p = 0.01$), swollen joint count ($r = 0.36$, $p = 0.10$).
Cioffi et al. 2016 [20]	Cross sectional study	Patients $n = 226$ Age: 60 ± 12 years Female: 72% Controls $n = 226$ Age: 60 ± 12 years Female: 69%	35% NSAID 11% HCQ 45% CTC 47% MTX 65% bDMARD	AoSI was significantly higher in RA patients (6.3 ± 4.5 vs. $4.6 \pm 3.5\%$, $p < 0.001$).
Dzieża- Grudnik et al. 2017 [10]	Cross sectional study	Patients $n = 26$ Age: 40 ± 9.7 years Female: 80.7% Controls $n = 29$ Age: 40 ± 7.6 years Female: 44.8%	38% NSAID 62% CTC	No differences in PWV between RA and controls (10 CI95% [8.8–10.9] vs 9.2 CI95% [8.3–11.4] m/s, $p = 0.14$). No differences in AIX between RA and controls (24.3 ± 11.5 vs $10 \pm 12.8\%$, $p = 0.22$).
Ikdahl et al. 2016 [84]	Longitudinal study	Patients $n = 138$ Age: 59.0 [51–66.9] years Female: 76%	21.7% bDMARD 65.2% sDMARD 30.4% CTC 31.2 NSAID	Patients with CVD events had significantly higher PWV at baseline compared with those who did not experience CVD events during follow-up ($p < 0.001$).
Karp et al. 2016 [51]	Cross sectional study	Patients $n = 31$ Age: 54.7 ± 14.7 years Female: 100% Controls $n = 53$ Age: 53.5 ± 13.9 years Female: 100%	6.5% AZA 16% HCQ 48% CTC 71% MTX 6% LEF 42% bDMARD	\nearrow PWV in RA (9.2 ± 4.4 vs 7.6 ± 3.0 m/s, $p = 0.04$). \searrow aortic distensibility in RA (4.4 ± 4.6 vs. 5.8 ± 4.9 kPa, $p = 0.04$).
Mitrović et al. 2017 [23]	Cross sectional study	Patients $n = 52$ Age: 60.1 ± 11.1 years Female: 70.9% Controls $n = 42$	MD	\nearrow AoSI in hypertensive RA compared to hypertensive-non RA controls (0.47 ± 0.16 vs 0.38 ± 0.17 , $p = 0.016$). \nearrow cIMT in Hypertensive RA compared to hypertensive-non RA controls (0.9 ± 0.26 vs 0.74 ± 0.23 mm, $p < 0.001$).

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Table 1 (continued)

Reference	Design	Population	Treatment	Outcome
Karakulak et al. 2015 [85]	Cross sectional study	Age: 56.7 ± 11.7 years Female: 71.4% Patients n = 33 Age: 54.2 ± 12.3 years Female: 27.3% Controls n = 33 Age: 52.6 ± 9.4 years Female: 36.4%	84.8% MTX + LEF 9% MTX + HCQ + SLZ 6% MTX + ADA	↗ AoSI in RA compared to controls (0.45 ± 0.12 vs 0.38 ± 0.10, p = 0.019). Nondipper status (β = 0.316, P = 0.007) was an independent predictor affecting AoSI.
Arida et al. 2015 [11]	Cross sectional study	Patients n = 41 Age: 49 ± 13 years Female: 88% Controls n = 41 Age: 49 ± 13 years Female: 88%	75.6% CTC 75.6% MTX 7.3% LEF 41.5% bDMARD	No difference in arterial stiffness between RA and control. ↗ carotid and/or femoral plaques in RA compared to healthy controls (29 vs 12%, p = 0.039).
Li et al. 2013 [24]	Cross sectional study	Patients n = 138 Age: 50.2 ± 12.5 years Female: 80.4% Controls n = 150 Age: 49.6 ± 8.7 years Female: 79.3%	6.5% sDMARD 53.2% NSAID	↗PWV in RA (1705.44 ± 429.20 vs 1386.23 ± 411.09 cm/s, p < 0.001). baPWV was independently associated with age and serum triglycerides level.
Santos et al. 2012 [53]	Cross sectional study	RA Patients n = 107 Age: 50.2 ± 14.1 years Female: 100% SLE Patients n = 127 Age: 43.9 ± 13.9 years Female: 100% Controls n = 124 Age: 46.9 ± 13.7 years Female: 100%	RA patients: 19% HCQ 100% CTC 82% MTX SLE patients: 74% HCQ 10.9% CTC 10% MTX	↗Aix in SLE as compared to RA (16% vs 11%, p = 0.04).
Pieringer et al. 2012 [86]	Cross sectional study	Patients n = 203 Age: 56.3 ± 12.2 years Female: 83.7% Controls n = 208 Age: 49.6 ± 12.7 years Female: 81.7%	5.9% SLZ 31.5% CTC 71.4% MTX 11.4% LEF 42% bDMARD	↗Aix in RA (30.5 ± 9.0% vs 24.0 ± 11.0%, P < 0.001).
Tam et al. 2013 [87]	Cohort study	Patients n = 95 Age: 52 ± 11 years Female: 87%	32% SLZ 27% HCQ 48% MTX 9% LEF	56.4% achieved disease remission at 12 months. Significant reductions in Aix (30.7 ± 10.5 at baseline vs 26.3 ± 11.1% p = 0.001) and PWV (for the right side 14.94 ± 3.37 at baseline vs 14.47 ± 3.27 m/s, p = 0.017).
Kim et al. 2012 [88]	Cohort study	Patients n = 262 Age: 56.7 years Female: 82%	56.9% CTC 84% MTX	baPWV was significantly correlated with systolic blood pressure (r = 0.739, p < 0.001), age (r = 0.661, p < 0.001) but not with swollen joint count, evaluator's global assessment, CRP, and ESR.
Ilter et al. 2016 [89]	Cross sectional study	Patients n = 35 Age: 47.1 ± 6.3 years Female: 85.7% Controls n = 25 Age: 46.8 ± 6.9 years Female: 68%	31.4% NSAID 62.8% CTC 42.8% anti-TNF α 91% sDMARD	↗ PWV in RA (28.3 ± 10.3 vs. 21.8 ± 9.3 m/s, p = 0.03). ↗Aix in RA (10.2 ± 2.3 vs. 9.2 ± 1%, p = 0.01).
Ntusi et al. 2019 [36]	Cross sectional study	Patients n = 69 Age: 53 ± 12 years Female: 71% Controls n = 63 Age: 50 ± 11 years Female: 62%	90% MTX 60% HCQ 25% SLZ 16% LEF 4% RTX 12% CTC	↗PWV in RA with CVRFs compared with RA without CVRFs, controls with CVRFs and controls without CVRFs (8.2 ± 3.3 vs 6.8 ± 2.7 vs 6.0 ± 1.7 vs 4.6 ± 2.2 respectively, p < 0.001).
Dregan 2018 [18]	Cross sectional study	Patients n = 1672 Age: 59 ± 7 years Female: 70% Controls n = 165,149 Age: 57 ± 8 years Female: 55%	36% NSAID 13% CTC 42% sDMARD	↗ AoSI in RA (9.47, CI95% [9.33–9.62] vs 9.32 CI95% [9.31–9.34]).
Pieringer et al. 2017 [21]	Cross sectional study	Patients n = 287 Age: 58.4 ± 12.6 years Female: 80.8% Controls n = 232 Age: 49.9 ± 13.4 years Female: 80.2%	70.7% MTX 8% HCQ 6.6% SLZ 11.2% LEF 2.4% RTX 1.7% TCZ 30% anti-TNFα 3.1% ABT	↗ Aix in RA patients (31.1 ± 9.3 vs 23.6 ± 11.3%, p < 0.0001). In RA patients Aix and central PP, are correlated with SCORE and QRISK2.
Yang et al. 2019 [14]	Cross sectional study	Patients n = 72 Age: 47.4 ± 6.88 years Female: 81.9% Controls n = 55 Age: 46.2 ± 6.72 years Female: 81.8%	Patients had not used any CTC, IS or NSAID before the study.	In RA patients, the hfPWV (5.49 ± 1.19 m/s) and cfPWV (6.70 ± 1.23 m/s) were significantly higher than that in controls (=0.0006, p = 0.0001, respectively). hfPWV, brPWV and faPWV only showed an increase trend without significance.
Byram et al. 2018 [90]	Cross sectional study	Patients with RA n = 165 Females: 69% - RA exercisers n = 63 Age: 54 years [44–66] - RA non exercisers n = 102 Age: 54 years [46–61]	MD	↘ PWV in exercisers compared to non- exercisers (8.48 CI95% [7.15–9.70] vs. 9.07 [8.15–10.03] m/s, p = 0.005). Non-significant decrease in Aix in exercisers (28% [21–35] vs. 32% [25–37], p = 0.10).

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Table 1 (continued)

Reference	Design	Population	Treatment	Outcome
Woodman et al. 2019 [91]	Longitudinal study	Patients $n = 86$ Age: 64 [56–69] years Female: 73%	8.1% NSAID 34.9% CTC 65.1% MTX	Comparing 5 patterns of fatty acid intake: higher reported intake of n-3 fatty acids, palmitoleic acid and arachidonic acid is associated with a lower A1x ($p = 0.023$).
Novikova et al. 2016 [31]	Longitudinal study	Patients $n = 55$ Age: 50.4 ± 1.7 years Female: 100%	100% RTX 98% NSAID 80% CTC 86% sDMARD: - 55% MTX - 38% LEF - 7% Others sDMARD	\ PWV in RTX responders ($n = 41$), after 6 months of treatment (9.9 ± 0.9 m/s vs 14.7 ± 0.9 m/s, $p < 0.05$). No significant decrease after 6 months in non- responders ($n = 14$).
Provan et al. 2015 [33]	Prospective study	Patients $n = 36$ - RTX $n = 24$ Age: 56.9 [25–72] years Female: 71% - ABT $n = 5$ Age: 53.9 [41–67] years Female: 100% - TCZ $n = 7$ Age: 52.3 [36–59] years Female: 86%		\ PWV at 3 months only in the TCZ group (-0.9 ± 1.0 m/s, $p = 0.03$). \ PWV at 12 months in the RTX group (7.3 [6.8–7.9] vs 7.7 [7.2–8.2] m/s, $p = 0.04$).
Mäki-Petäjä et al. 2012 [26]	Prospective study	Patients $n = 17$ Age: 58 ± 5 years Female: 65% Controls $n = 34$ Age: 58 ± 5 years Female: MD	100% anti-TNF α : -70% ADA -30% ETN 47% HCQ 53% MTX 47% LEF 35% CTC 12% SLZ	\ PWV after 8 weeks of Anti-TNF α (from 9.09 ± 1.77 to 8.63 ± 1.42 m/s, $p = 0.04$). \ Disease activity score after 8 weeks of Anti-TNF α (from 6.52 ± 0.78 to 4.38 ± 1.61 , $p < 0.0001$).
Tam et al. 2012 [27]	Randomized open-label study	Patients $n = 40$ - MTX + IFX $n = 20$ Age: 53 [47–61] years Female: 95% - MTX $n = 20$ Age: 53 [43–59] years Female: 75%	Among all patients: 93% NSAID 3% LEF 5% HCQ 23% CTC	Greater reduction in PWV in the MTX-IFX group compared with the MTX alone group at 6 months (-0.78 ± 1.13 m/s vs 0.18 ± 1.59 m/s, $p = 0.044$). No differences between the two groups in the changes in A1x after 6 months.
Angel et al. 2012 [28]	Prospective study	Patients $n = 55$ (25 RA, 19 AnS and 11 PsA) - Anti-TNF- α Age: 47.2 ± 11.6 years Female: 39% - Controls: Age: 51.9 ± 14.5 years Female: 42%	Among all patients: 40% CTC 44% NSAID 42% MTX 13% SLZ	PWV was improved in the Anti-TNF α group, but not in the control group (-0.54 ± 0.79 m/s vs. 0.06 ± 0.61 m/s, $p = 0.004$).
Mathieu et al. 2012 [92]	Prospective study	Patients $n = 33$ Age: 60.9 ± 12 years Female: 88%	100% RTX 60.6% MTX 3% LEF 9.1% HCQ 6.1% Several sDMARD	No change in PWV, at 6 or 12 months of RTX (8.1 ± 3.1 at baseline, vs 8.1 ± 2.8 and 8.0 ± 2.7 m/s, $p = 0.924$) No change in A1x, at 6 or 12 months of RTX (30.4 ± 8.2 at baseline, vs 28.6 ± 7.6 and $29.4 \pm 6.7\%$, $p = 0.216$)
Kume et al. 2011 [32]	Open-label randomized controlled trial	Patients $n = 64$ - TCZ $n = 22$ Age: 62 ± 16 years Female: 86% - ETN $n = 21$ Age: 61 ± 15 years Female: 86% - ADA $n = 21$ Age: 63 ± 17 years Female: 86%	No prior treatment with MTX, CTC, or bDMARD.	\ CAVI at 24 weeks of treatment for all the groups (TCZ: 0.85 ± 0.15 m/s, $p = 0.02$; ETN: 0.81 ± 0.18 m/s, $p = 0.03$; ADA: 0.90 ± 0.21 m/s, $p = 0.02$). \ A1x at 24 weeks of treatment for all the groups (TCZ $3.59 \pm 0.33\%$, $p = 0.03$; ETN $1.03 \pm 0.44\%$, $p = 0.03$; ADA $3.54 \pm 0.52\%$, $p = 0.02$) Δ CAVI and Δ A1 was not significantly different among groups.
Mäki-Petäjä et al. 2006 [25]	Cross sectional study	Patients $n = 77$ Age: 57 ± 13 years Female: 84% Controls $n = 142$ Age: 57 ± 11 years Female: 73%	17% anti-TNF α 58% MTX 36% Other sDMARD 74% NSAID 39% CTC	\nearrow PWV in RA patients (8.35 [7.14–10.24] vs 7.52 [6.56–9.18] m/s, $p = 0.005$). No difference in A1x.
	Prospective study	Patients $n = 9$ Age: 54 ± 19 years Female: MD	100% ETN 67% CTC	

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Table 1 (continued)

Reference	Design	Population	Treatment	Outcome
		Controls <i>n</i> = 24 Age: MD Female: MD%	33% MTX 11% SLZ 56% NSAID	√PWV by ETN (from 8.82 ± 2 0.04 m/s at baseline to 7.94 ± 1.86 and 7.68 ± 1.56 m/s at 4 and 12 weeks, <i>p</i> = 0.0003). No change in AIx.
Gkaliagkousi et al. 2018 [93]	Cross sectional study	Patients <i>n</i> = 91 Age: 61.4 ± 11.9 years Female: 79.1% Controls <i>n</i> = 50 Age: 58.5 ± 7.2 years Female: 78%	73.6% sDMARD 38.5% bDMARD 28.6% CTC	∇PWV in RA (8.3 ± 2.2 vs 7.5 ± 1.3 m/s, <i>p</i> = 0.01). Dipping levels (%) were inversely associated with PWV (<i>r</i> = -0.218, <i>p</i> = 0.045).
Botta et al. 2016 [94]	Cross sectional study	Active RA <i>n</i> = 27 Age: 56 ± 9 years Female: 93% Inactive RA <i>n</i> = 17 Age: 56 ± 12 years Female: 82% Controls <i>n</i> = 33 Age: 49 ± 11 years Female: 79%	84% MTX 18% Anti-TNFα 30% HCQ 9% LEF 2% RTX	∇PWV in active RA compared with inactive RA and controls (<i>p</i> = 0.030).
Vassilopoulos et al. 2015 [29]	Prospective study	RA sDMARD + ADA <i>n</i> = 18 Age: 59 ± 13 years Female: 89% RA with MTX only <i>n</i> = 18 Age: 61 ± 10 years Female: 83%	ADA group: 39% ADA only 33% MTX 24% LEF 6% HCQ 61% CTC	At 12 weeks: - ∇PWV in the ADA group (from 8.18 ± 2.03 to 7.01 ± 1.78 m/s, <i>p</i> = 0.00006). - No significant change in PWV in the MTX group. - No significant change in AIx in both groups.
Daïen et al. 2013 [95]	Prospective study	RA with ETN <i>n</i> = 28 Age: 57 ± 13 years Female: 100% RA with sDMARD <i>n</i> = 20 Age: 51 ± 17 years Female: 100%	sDMARD group: 30% CTC ETN group: 72% 89% sDMARD	With 6 months of treatment, no significant change in PWV or AIx in both groups.
Angel et al. 2011 [96]	Prospective study	Patients <i>n</i> = 17 (RA <i>n</i> = 8 / AS <i>n</i> = 6 / PsA <i>n</i> = 3) Age: 54 ± 12.1 years Female: 52.9%	100% IFX 29.4% CTC 29.4% NSAID 58.8% MTX	No changes in AIx or PWV during the period between the two IFX infusions (weeks 4–8).

ADA: Adalimumab; AIx: Augmentation Index; Anti-TNFα: TNF-α Inhibitors; AoSI: Aortic Stiffness Index; AS: Ankylosing Spondylitis; AZA: Azathioprine; CAVI: Cardio-Ankle Vascular Index; CDAI: Clinical Disease Activity Index; CRP: C-Reactive Protein; CTC: Corticoids; CVD: Cardio-Vascular Disease; sDMARD: synthetic Disease Modifying Anti-Rheumatic Drug; bDMARD: biologic Disease Modifying Anti-Rheumatic Drug; ESR: Erythrocyte Sedimentation Rate; ETN: Etanercept; HAQ-II: Health Assessment Questionnaire; HCQ: Hydroxychloroquine; HT: Hypertension; (c)IMT: (carotid) Intima-Media Thickness; IFX: Infliximab; IS: Immunosuppressive drug; IM: Immunomodulatory drug; LEF: Leflunomide; MD: Missing Data; MTX: Methotrexate; NSAID: Nonsteroidal Anti-Inflammatory Drug; PP: Pulse Pressure; PsA: Psoriatic Arthritis; PWV: Pulse Wave Velocity (hf: heart-femoral, cf.: carotid-femoral, hc: heart-carotid, br: brachial-radial, fa: femoral-ankle); QRISK2: Cardiovascular Risk Score; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; RTX: Rituximab; SCORE: Systematic Coronary Risk Estimation; SLE: Systemic Lupus Erythematosus; SLZ: Sulfasalazine; TCZ: Tocilizumab.

showed that each year of disease duration had a greater impact on the carotid to femoral PWV than age.

Second, arterial stiffness has been associated with disease activity and inflammatory markers [1]. Comparing 70 RA patients (36 with active disease and 34 with inactive disease) to 35 controls, carotid PWV was significantly higher in patients with active RA (defined as a Disease Activity Score (DAS28) score ≥ 3.2) [16]. In another study of 50 RA patients, corrected aortic AIx was correlated with Clinical Disease Activity Index (CDAI) and Health Assessment Questionnaire (HAQ-II) [17]. In a very large sample (the UK Biobank study), the association appeared to increase progressively with the severity of chronic inflammation, as assessed by a composite measure of inflammatory biomarkers [18]. We found only one study specifically exploring the correlation between the presence of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP), and arterial stiffness. Seronegative patients had significantly higher PWV than seropositive patients (7.68 ± 2.24 vs 7.12 ± 1.34 m/s, respectively, *p* = 0.031) [19]. However, seronegative patients had slightly higher Body Mass Index (BMI), systolic blood pressure and C-reactive protein (CRP) level. Further studies are needed.

In addition, Cioffi et al. reported that Aortic Stiffness Index (AoSI) was significantly higher (almost twice as high) in RA patients than in controls matched for CV risk factors (6.3 ± 4.5 vs. 4.6 ± 3.5%, *p* < 0.001) [20], highlighting that increased aortic stiffening exists beyond CV risk factors, probably related to the inflammation itself. It also suggests that CV risk cannot be assessed solely by scores that take into account CV risk factors alone [21].

However, the influence of traditional CV risk factors must not be overlooked. Most published evidence supports that arterial stiffness in RA is also associated with age and hypertension. For example, in 149 RA

patients, mean blood pressure accounted for 28.9% of the variance in PWV [22]. Besides, arterial stiffness index and common carotid intima-media thickness have been reported to be higher in hypertensive RA patients than in hypertensive patients without RA. [23]. Brachial-ankle PWV has also been independently associated with serum triglycerides levels in RA [24]. These results emphasize that CV risk factors must be strictly controlled in RA patients as they increase the risk associated with RA itself.

4.1.3. Influence of RA treatment on arterial stiffness

Exploring the impact of RA treatments on arterial stiffness seems challenging given the indications selection bias and potential confounding factors. For example, in a group of 104 RA patients, 27% of whom received glucocorticoids (GC), GC use was independently associated with PWV [12]. However, patients with more severe arthritis are more likely to receive GC, which may artificially lead to increased vascular dysfunction while also reducing disease activity, which could reduce arterial stiffness.

TNF-α inhibitors (TNFi) seem to have a beneficial impact on arterial stiffness [25–29], as reported in a meta-analysis [30]. Improvement in carotid-femoral PWV was found independently of the reduction in DAS28. It may be assumed that RA patients with increased aortic stiffness may benefit from early prescription of TNFi [30]. A preferential effect of etanercept and adalimumab was evidenced over infliximab. Although data are more scarce, rituximab [31] and tocilizumab [32,33] have also shown a beneficial effect on arterial stiffness [34]. Thus, the reduction of AIx and PWV by biological therapy supports the role of inflammation in increasing arterial stiffness in RA.

Table 2
Systemic Lupus Erythematosus and arterial stiffness.

Reference	Design	Population	Treatment	Outcome
Montalbán-Méndez et al. 2018 [42]	Cohort study	Patients <i>n</i> = 49 Age: 41.3 ± 13.8 years Female: 100%	No bDMARD or CTC > 10 mg/j in the past 6 months	CRF was significantly associated with PWV - Siconolfi (<i>b</i> = 0.773, <i>p</i> < 0.001) - 6MWT (<i>b</i> = 0.590, <i>p</i> < 0.001)
Cypiene et al. 2017 [22]	Cross sectional study	Patients <i>n</i> = 63 Age: 53.3 ± 15.3 years Female: 87.3% Controls <i>n</i> = 156 Age: 42.8 ± 11.0 years Female: 73.1%	47.3% HCQ 2.2% CTC 39.8% MTX 58.1% AZA	No difference in PWV between SLE and controls. ∠Aix in SLE (25.49 CI95% [23.43–27.54] vs 17.55 CI95% [15.97–19.12], <i>p</i> < 0.0001). MBP was the only significant variable in the model and accounted for 14.3% of the variance of PWV.
Tziomalos et al. 2017 [46]	Cross sectional study	Patients <i>n</i> = 55 Age: 53.3 ± 15.3 years Female: 87.3% Controls <i>n</i> = 61 Age: 55.4 ± 8.1 years Female: 91.8%	MD	After adjustment for confounders, PWV and Aix did not differ between SLE and controls (<i>B</i> = 0.542, <i>p</i> = 0.107 and <i>B</i> = 0.446, <i>p</i> = 0.319, respectively).
Karp et al. 2016 [51]	Cross sectional study	Patients <i>n</i> = 30 Age: 41.2 ± 13.3 years Female: 100% Controls <i>n</i> = 53 Age: 53.5 ± 13.9 years Female: 100%	87% HCQ 67% CTC 20% AZA 3% Belimumab 7% MMF	∠PWV in SLE (6.2 ± 2.3 vs. 5.4 ± 1.7 m/s, <i>p</i> = 0.04). PWV was associated with SLE (<i>B</i> = 0.24, <i>p</i> = 0.02), age (<i>B</i> = 0.53, <i>p</i> < 0.001), triglycerides level (<i>B</i> = 0.31, <i>p</i> = 0.01), HDL (<i>B</i> = 0.24, <i>p</i> = 0.04) and duration of SLE (<i>B</i> = 0.55, <i>p</i> = 0.01).
Jurcut et al. 2012 [55]	Cross sectional study	SLE + SAPL <i>n</i> = 12 Age: 44.7 ± 10.6 years Female: 75% SLE non-SAPL <i>n</i> = 20 Age: 44.2 ± 16.7 years Female: 85%	In SLE + SAPL: -CTC: 12.29 ± 10.8/day -HCQ: 333.3 ± 98.4 mg/day In SLE: -CTC: 18.7 ± 12.9 mg/day -HCQ: 290 ± 120.9 mg/day	∠PWV in SLE + SAPL patients (6.42 ± 0.92 vs 5.35 ± 0.74 m/s, <i>p</i> < 0.01). No difference concerning Aix.
Valero-Gonzalez et al. 2014 [45]	Cohort study	Patients <i>n</i> = 46 Age: 48 years Female: 100%	30.4% HCQ only 47.8% HCQ + IS 4.3% IS only	PWV was strongly associated with metabolic syndrome (OR 6.6 CI95% [1.2–38], <i>p</i> < 0.03) and SLICC/ACR score (OR 1.5 CI95% [1–2.32, <i>p</i> < 0.05).
Sacre et al. 2014 [52]	Cross sectional controlled study	Patients <i>n</i> = 41 Age: 39 ± 10 years Female: 83% Controls <i>n</i> = 36 Age: 37 ± 8 years Female: 80%	100% HCQ 65.9% CTC 68.3% IS or IM drugs	∠PWV in SLE patients (7.16 ± 1.6 vs 6.36 ± 0.8 m/s, <i>p</i> = 0.01 after Framingham score adjustment). ∠ICWT in SLE patients (1.3160.67 vs 0.9360.25 mm, <i>p</i> = 0.003 after Framingham score adjustment)
Morreale et al. 2016 [97]	Cross sectional study	Patients <i>n</i> = 50 Age: 38 ± 11.8 years Female: 90% Controls with hypertension <i>n</i> = 50 Age: 38.9 ± 10.6 years Female: 90%	54% CTC 40% AZA or MMF	PWV was not significantly different in patients with SLE compared with patients having hypertension (8.8 ± 2 vs 9.2 ± 2 m/s, <i>p</i> = 0.31).
Ding et al. 2016 [49]	Cross sectional study	Patients <i>n</i> = 161 Age: 33 years Female: 100% Controls <i>n</i> = 135 Age: 32 years Female: 100%	79.7% HCQ 25.8% MMF Cumulative dose of prednisone on 24 months 4.6 g. 49.7% CYC	The correlation coefficients between age and arterial stiffness significantly differed among the SLE patients relative to controls (0.46478 and 0.52612, respectively; <i>t</i> = 2.05; <i>p</i> = 0.0409).
Mercurio et al. 2019 [54]	Cross sectional study	Patients <i>n</i> = 43 Age: 41 ± 11 years Female: 9.7% Controls <i>n</i> = 43 Age: 39 ± 12 years Female: 90.7%	90.7% CTC	∠Aix in SLE patient compared to controls (21.0 IQR [17] vs. 9.0 IQR [16], <i>p</i> < 0.001).
Parra et al. 2019 [50]		Patients <i>n</i> = 69 Age: 49 ± 16.8 years Female: 100% Controls <i>n</i> = 34 Age: 48.7 ± 13.2 years Female: 100%	32% HCQ	∠Aix in SLE patients (20.30 ± 21.54% versus 10.84 ± 11.51%, <i>p</i> = 0.0021). ∠IMT in SLE (0.702 ± 0.147 mm versus 0.633 ± 0.891 mm, <i>p</i> = 0.012).
Stortz et al. 2020 [47]	Cross sectional study	Patients <i>n</i> = 125 Age: 46 ± (35–54) years Female: 88% Controls <i>n</i> = 104 Age: 49 (37–56) years Female: 88.7%	60.8% HCQ 68% CTC 50.4% IS 28% Belimumab	No difference in PWV between SLE and controls.

6MWT: 6 Minute Walking Test; Aix: Augmentation Index; AZA: Azathioprine; CRF: Cardio-Respiratory Stiffness; CTC: Corticoids; CYC: Cyclophosphamide bDMARD: biologic Disease Modifying Anti-Rheumatic Drug; HCQ: Hydroxychloroquine; (c)IMT: (carotid) Intima-Media Thickness; ICWT: internal carotid wall thickness; IS: Immunosuppressive drug; IM: Immunomodulatory drug; IQR: Interquartile Range; MBP: Mean Blood Pressure; MD: Missing Data; MTX: Methotrexate; PWV: Pulse Wave Velocity (hf: heart-femoral, cf.: carotid-femoral, hc: heart-carotid, br: brachial-radial, fa: femoral-ankle); SAPL: Antiphospholipid Syndrome; SLE: Systemic Lupus Erythematosus; SLICC/ACR: systemic lupus international collaborating clinics American College of Rheumatology Damage index.

Table 3
Psoriasis and Psoriatic arthritis and arterial stiffness.

Reference	Design	Population	Treatment	Outcome
Costa et al. 2012 [62]	Case control study	Patients n = 20 Age: 38.6 [22–53] years Female: 30% Controls n = 20 Age: 38.7 [22–53] years Female: 30%	70% sDMARD	↗ PWV in PsA (8.2 ± 0.8 vs 6.8 ± 1.0 m/s, $p < 0.0001$). PWV was associated with the duration of the arthritis ($\beta = 0.011$; $p = 0.013$).
Shang et al. 2012 [72]	Cross sectional study	Patients n = 73 Age: 47.1 ± 12 years Female: 49% Controls n = 50 Age: 44 ± 14 years Female: 44%	64.4% NSAID 56.2% sDMARD 8.2% CTC	AIx was higher in PsA patients with HT or LVH than PsA patients without HT or LVH than controls (29.1 ± 15.3 vs 22.0 ± 15.5 vs $14.7 \pm 8.8\%$, $p = 0.001$). Positive correlation with the duration of the arthritis ($r = 0.259$, $p = 0.036$).
Shen et al. 2015 [71]	Case control study.	Patients n = 72 Age: 49.6 ± 1.7 years Female: 50% Controls n = 47 Age: 43.1 ± 10.2 years Female: 72.3%	45.8% NSAID 50% sDMARD 6.5% CTC	↗PWV in PSA (14.6 ± 2.9 vs 13.23 ± 3.8 , $p = 0.008$). Cumulative averages of repeated measures of ESR were associated with high PWV.
Kim et al. 2015 [98]	Cross sectional study	Patients n = 45 PsO + 9 PSA Age: 41.8 ± 12.9 years Female: 52% Controls n = 60 Age: 39.3 ± 11.5 years Female: 53%	9.3% topical only 59.3% MTX 50% CIC 59.3% Phototherapy 15.5% bDMARD	↗BSI in PsO (8.15 ± 3.72 vs 5.85 ± 2.05 , $p < 0.001$). No statistical difference in cIMT.
Dattilo et al. 2018 [67]	Cross sectional study	Patients n = 33 Age: 35.6 ± 5.7 years Female: 43% Controls n = 33 Age: 36.3 ± 5.9 years Female: 45%	No systemic treatment	↗ PWV in PsO (9.23 ± 1.53 vs 8.06 ± 1.68 m/s, $p < 0.004$).
Balta et al. 2014 [64]	Cross sectional study	Patients n = 32 Age: 34.6 ± 10.3 years Female: 100% Controls n = 35 Age: 36.8 ± 10.1 years Female: 100%	No treatment	↗ PWV in PsO (7.63 vs 6.96 m/s, $p = 0.01$) PWV correlated positively with age, sex, BMI, diastolic blood pressure, and CRP level ($p < 0.05$).
Altekin et al. 2012 [66]	Cross sectional study	Patients n = 57 Age: 41 ± 10.8 years Female: 45.6% Controls n = 60 Age: 40 ± 9.4 years Female: 46.7%	No treatment	↗PWV in PsO (7.04 ± 1.1 vs 6.03 ± 0.61 m/s, $p < 0.001$). ↗cIMT in PsO (0.73 ± 0.09 vs 0.66 ± 0.06 mm, $p < 0.001$).
Sunbul et al. 2015 [65]	Cross sectional study	Patients n = 50 Age: 43.3 ± 13.2 years Female: 48% Controls n = 50 Age: 45.0 ± 6.1 years Female: 34%	34% topical 26% oral retinoid 10% phototherapy 36% MTX 12% CIC 12% ETN 10% IFX 100% CIC	↗PWV in PsO (6.78 ± 1.42 vs 6.18 ± 0.80 m/s, $p = 0.011$). ↗AIx in PsO (25.8 ± 13.1 vs $17.4 \pm 12.3\%$, $p = 0.001$).
Ikonomidis et al. 2015 [68]	Cross sectional study	Patients n = 59 Age: 51 ± 12.2 years Female: 37% Controls with CAD n = 59 Age: 53 ± 9 years Female: 30% Controls n = 40 Age: 49 ± 9 years Female: 45%		PsO patients had higher PWV than healthy controls ($p < 0.05$) but similar PWV than CAD patient ($p > 0.05$) (0.4 ± 1.8 vs 8.6 ± 1.5 vs 10.3 ± 2 m/s). PsO patients had higher AIx than healthy controls ($p < 0.05$) but similar AIx than CAD patient ($p > 0.05$).
Oliveira et al. 2019 [69]	Cross sectional study	Patients n = 11 Age: 64 ± 12.5 years Female: 0% Controls n = 33 Age: 60 ± 9 years Female: 0%	18% MTX 9% Topical CTC	↗PWV in PsO (9.1 ± 1.8 and 8 ± 2 m/s, $p = 0.033$). No difference on AIx between PsO and controls.
Patschan et al. 2018 [63]	Cross sectional study	Patients with PsO n = 30 Age: 49 ± 2.8 years Female: 43% Patients with PsA n = 31 Age: 47.7 ± 2.2 years Female: 48% Controls n = 26 Age: MD Female: MD	PsO: 33.3% bDMARD PsA: 45.1% bDMARD	No differences in AIx and PWV between PsO, PSA and controls.
Hansen et al. 2018 [70]	Cross sectional study	Patients n = 254 Age: 53.9 ± 11.9 years Female: 42.5% Controls n = 4431 Age: 52.4 ± 12.8 years Female: 47.6%	MD	↗ PWV in PsO (8.62 ± 2.34 vs. 8.31 ± 2.31 m/s, $p = 0.04$).
Di Vito et al. 2018 [99]	Cross sectional study	Low CV risk patients n = 34 Age: 42.5 ± 10.3 years Female: 47% Low CV risk controls n = 39 Age: 46.2 ± 6.7 years Female: 54% High CV risk patients n = 23 Age: 55.7 ± 11.3 years Female: 43% High CV risk controls n = 15 Age: 57.9 ± 6.5 years Female: 57%	MD	<u>In the High CV risk group:</u> ↗ PWV in patients with PsO (8.7 ± 1.6 vs. 7.5 ± 0.9 m/s, $p = 0.024$). <u>In the Low CV risk group:</u> No difference in PWV between groups.

(continued on next page)

Table 3 (continued)

Reference	Design	Population	Treatment	Outcome
Dregan 2018 [18]	Cross sectional study	Patients $n = 2091$ Age: 57 ± 8 years Female: 48% Controls $n = 165,149$ Age: 57 ± 8 years Female: 55%	15% NSAID 12% sDMARD 8% CTC	\nearrow SI in Pso (9.49 IC95%[9.36–9.61] vs 9.32 CI95%[9.31–9.34])

AIx: Augmentation Index; BSI: Beta Stiffness Index; CAD: Coronary Artery Disease; CIC: Ciclosporine; CRP: C-Reactive Protein; CTC: Corticoids; CV: Cardio- Vascular; sDMARD: synthetic Disease Modifying Anti-Rheumatic Drug; bDMARD: biologic Disease Modifying Anti-Rheumatic Drug; ESR: Erythrocyte Sedimentation Rate; ETN: Etanercept; HT: Hypertension; (c)IMT: (carotid) Intima-Media Thickness; IFX: Infliximab; LVH: Left Ventricular Hypertrophy MD: Missing Data; MTX: Methotrexate; NSAID: Nonsteroidal Anti-Inflammatory Drug; PsA: Psoriatic Arthritis; PsO: Psoriasis; SI: Stiffness Index PWV: Pulse Wave Velocity (hf: heart-femoral, cf.: carotid-femoral, hc: heart-carotid, br: brachial-radial, fa: femoral-ankle).

4.1.4. Influence of arterial stiffness on cardiac function and atherosclerosis

By increasing systolic blood pressure, ventricular afterload and myocardial oxygen consumption increase, and by reducing coronary perfusion, arterial stiffness lead to heart failure [8]. In this regard, RA patients have an almost two-fold higher incidence of heart failure and this is primarily associated with diastolic dysfunction [35].

In a setting of 104 RA patients (DAS28-ESR 3.5 ± 1.2), the thoracic fluid content index, which reflects diastolic dysfunction, was significantly elevated compared to controls [12]. In another study, there was no difference in overall LV systolic function size and mass between RA patients and matched controls, whereas regional function as assessed by magnetic resonance strain imaging was impaired in RA [36].

Besides, whether arterial rigidity may be a surrogate marker for atherosclerosis in RA patients is still under debate. For example, in 163 patients, PWV was not associated with carotid plaque [37]. In a smaller cohort of 96 individuals, without clinical CVD and classical CV risk factors, the 48 patients with RA had more than twice the prevalence of carotid and/or femoral atheromatous plaques compared with healthy controls, whereas all indices assessing arterial stiffness were similar between the two groups [11]. Authors raised the fact that arterial stiffness may also induce functional changes that may contribute to CV risk beyond morphological changes [38]. These results suggest that arterial stiffness may contribute to CV event through adverse hemodynamic effects rather than through increased atherogenesis. Diastolic dysfunction has been documented in RA patients without CVD, suggesting that increased PWV or/and AIx may contribute to CV events in RA, also via their adverse hemodynamic effects [39].

4.2. Lupus and arterial stiffness

4.2.1. Increased arterial stiffness in SLE

The prognosis for SLE has improved considerably in recent decades, leading to new comorbidities, such as CVD, which is now the main cause of death in this population [1,40]. Some studies have suggested that SLE is an independent CV risk factor [41]. It has also been shown that traditional CV risk factors, such as hypertension, dyslipidemia and diabetes, do not fully explain the excess CV morbidity and mortality [42–44]. Surrogate markers, such as PWV and AIx, should be evaluated to help identify atherosclerosis at the earliest stage [45]. With the exception of two [46] [47], all studies, including a meta-analysis [48], reported an increase in arterial stiffness in SLE compared with controls. This difference is noticeable even in younger age groups [49].

4.2.2. Influence of disease characteristics and CV risk factors on arterial stiffness

The increase in arterial stiffness is not solely explained by CV risk factors [47,50,51], which may mean that the assessment of arterial stiffness may also be useful for CV risk stratification. However, as for RA, traditional CV risk factors should not be overlooked and should be managed as early as possible. For example, in a group of 93 SLE patients, mean blood pressure accounted for 14.3% of the variance of PWV. The differences in AIx and carotid-radial PWV were greater in younger patients, when inflammation played the main role, but less significant in

older patients, as age added to other influencing factors [22]. Similarly, physical activity should be enhanced. Improved cardiorespiratory fitness may reduce age-related arterial stiffness in women with SLE [42].

Regarding the characteristics of SLE affecting arterial stiffness, in several studies, there was no association between Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and arterial stiffness [22,45,52,53]. This could be explained by the fact that SLEDAI echoes severity at a specific point in time but does not correlate with disease burden. However, a significant association between PWV and a damage score, the Systemic Lupus Erythematosus International Collaborating Clinics (SLICC/ACR score), was reported [45,54]. In addition, intima media thickness and PWV values were significantly higher in patients having both SLE and anti-phospholipid syndrome (APLS) than in patients with SLE or APLS alone [55]. An increase in arterial stiffness was also reported to be associated with the presence of β 2-glycoprotein1 antibodies [50].

4.3. Sjogren's syndrome and arterial stiffness

4.3.1. Increased arterial stiffness in Sjogren's syndrome

Five articles were found to explore the relationship between Sjogren's syndrome and arterial stiffness. The largest study involved 75 women with primary Sjogren's syndrome who had higher mean PWV than controls (8.2 ± 1.5 m/s vs. 7.5 ± 1.4 m/s; $p = 0.01$) [56].

4.3.2. Influence of disease characteristics and CV risk factors on arterial stiffness

Arterial stiffness was associated with age, blood pressure and LDL levels [56], again highlighting the importance of controlling CV risk factors. Currently, there is insufficient data to conclude whether there is an association between disease activity and arterial stiffness, particularly because of small cohorts sizes and low activity levels [57]. The influence of Sjogren's characteristics on arterial stiffness needs to be studied in more detail.

4.3.3. Influence of arterial stiffness on cardiac function

Although cardiac involvement in patients with primary Sjogren's syndrome is less frequent than in patients with other rheumatic diseases such as RA and SLE, left ventricular diastolic dysfunction has been described [58]. This cardiac dysfunction could be linked to the increased arterial stiffness in this population. For instance, one study involving 22 patients with primary Sjogren's syndrome reported that LV radial and longitudinal strain was impaired, compared with controls and that PWV was increased [59].

4.4. Psoriasis, psoriatic arthritis and arterial stiffness

4.4.1. Increased arterial stiffness in psoriasis and psoriatic arthritis

Increased CV morbidity in patients with psoriasis (Pso) and psoriatic arthritis (PsA) is well established [60]. Although CV risk factors play a major role [61] and should be controlled as early as possible, again, they do not fully explain excess mortality, and other factors, such as arterial stiffness, should be considered in management. For example, when

Table 4
Spondyloarthritis and arterial stiffness.

Reference	Design	Population	Treatment	Outcome
Berg et al. 2018 [80]	Cohort study	Patients <i>n</i> = 118 Age: 48.9 ± 11.2 years Female: 36%	65% NSAID 20% Anti-TNF α	Inverse relations between VO2peak and both AIx (<i>p</i> < 0.001) and PWV (<i>p</i> < 0.001).
Berg et al. 2015 [78]	Cohort study	Patients <i>n</i> = 85 Age: 47.3 ± 12.6 years Female: 41.2%	83.5% NSAID 16.5% sDMARD 1.2% Anti-TNF α 3.5% CTC	AIx increased stepwise with increasing CRP (<i>p</i> = 0.01), ESR (<i>p</i> = 0.05) and ASDAS (<i>p</i> = 0.04).
Dzieża-Grudnik et al. 2017 [10]	Cross sectional study	Patients <i>n</i> = 45 Age: 33 ± 6.6 years Female: 13.3% Controls <i>n</i> = 29 Age: 32 ± 7.6 years Female: 44.8%	92% NSAID 5% CTC	No differences between AS patients and controls: - PWV (10.7 CI95% [9.1–11.8] vs 9.2 CI95% [8.3–11.4] m/s, <i>p</i> = 0.14) - AIx (5.7 ± 12.4 vs 10 ± 12.8%; <i>p</i> = 0.22)
Avram et al. 2016 [76]	Cross sectional study	Patients <i>n</i> = 24 Age: 45.8 ± 11.7 years Female: 17% Controls <i>n</i> = 24 Age: 44.9 ± 12.2 years Female: 17%	83% NSAID 29% SLZ 50% anti-TNF α	∠PWV in AS (8.7 CI95% [7.3–10] vs 6.7 CI95% [6.2–7.2], <i>p</i> = 0.047). ∠ AIx (25.5 CI95% [20.6–30.5] vs 17.7 CI95% [12–23.5] %, <i>p</i> = 0.038). PWV and AIx were significantly associated with BASFI score (<i>p</i> = 0.012, <i>r</i> = 0.504; and <i>p</i> = 0.041, <i>r</i> = 0.421 respectively).
Berg et al. 2015 [74]	Cross sectional study	Patients <i>n</i> = 151 Age: 49.2 ± 11.1 years Female: 39.1% Controls <i>n</i> = 134 Age: 52.7 ± 11.4 years Female: 41.8%	65.6% NSAID 16% sDMARD 19.3% anti-TNF α 7.9% CTC	∠ AIx in AS (19.4 ± 0.7 vs 16.9 ± 0.7, <i>p</i> = 0.01). No difference in PWV between groups.
Ozkaramandli Gur et al. 2018 [82]	Cross sectional study	Patients <i>n</i> = 75 Age: 41.7 ± 10.1 years Female: 37.3% Controls <i>n</i> = 30 Age: 38.5 ± 9.9 years Female: 43.3%	52% NSAID 25% sDMARD 52% Anti-TNF α	∠ PWV in AS (5.9 ± 1.46 vs 5.2 ± 0.85 m/s, <i>p</i> = 0.011).
Ozen et al. 2018 [79]	Cross sectional study	Patients <i>n</i> = 55 Age: 43.33 ± 7.87 years Female: 41.8% Controls <i>n</i> = 20	27% NSAID 14.7% sDMARD 47% Anti-TNF α	∠ AoSI in AS (3.32 ± 1.58 vs 2.3 ± 0.96, <i>p</i> = 0.009).

Table 4 (continued)

Reference	Design	Population	Treatment	Outcome
Kaplanoglu et al. 2019 [77]	Cross sectional study	Age: 44.60 ± 8.06 years Female: 65% Patients <i>n</i> = 38 Age: 39.6 ± 11.4 years Female: 42.1% Controls <i>n</i> = 49 Age: 35.5 ± 8.4 years Female: 59.2%	28.9% NSAID 71.1% sDMARD+ NSAID 10.5% Anti-TNF α	No difference between AS and controls in term of arterial stiffness.
Biesbroek et al. 2018 [100]	Cross sectional study	Patients <i>n</i> = 14 Age: 62 ± 7 years Female: 7% Controls <i>n</i> = 20 Age: 55 ± 6 years Female: 10%	79% NSAID 14% sDMARD 43% Anti-TNF α	∠PWV in AS (9.7 CI95% [7.1–11.8] vs 6.1 CI95% [4.6–7.6], <i>p</i> < 0.001). PWV was associated with BASFI (<i>r</i> = 0.62, <i>p</i> = 0.018).

AIx: Augmentation Index; Anti-TNF α : TNF- α Inhibitors; AoSI: Aortic Stiffness Index; AS: Ankylosing Spondylitis; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASFI: Bath Ankylosing Spondylitis Function Index; CRP: C-Reactive Protein; CTC: Corticoids; sDMARD: synthetic Disease Modifying Anti-Rheumatic Drug; ESR: Erythrocyte Sedimentation Rate; NSAID: Nonsteroidal Anti-Inflammatory Drug; PWV: Pulse Wave Velocity (hf: heart-femoral, cf: carotid-femoral, hc: heart-carotid, br: brachial-radial, fa: femoral-ankle); SLZ: Sulfasalazine; VO2peak: Oxygen uptake peak.

comparing 20 PsA patients to 20 controls, all free of CV risk factors, PWV was significantly higher in the PsA group [62].

With the exception of one study [63], arterial stiffness was greater in PsO and PsA patients than in controls in all the studies [64–70]. One study showed that the level of PWV in psoriatic patients was as high as that observed in patients with coronary artery disease (CAD) [68].

4.4.2. Influence of disease characteristics and CV risk factors on arterial stiffness

Costa and al. showed that in PsA patients, increased arterial stiffness was directly associated with the duration of joint involvement rather than the duration of psoriasis itself [62].

The differing results on whether arterial stiffness in PsO and PsA is associated with disease activity and severity [71] [64] [68] [66] may be explained by the lack of reproducibility of studies.

in terms of patient age, duration, severity of the disease and treatment. Further studies are needed.

4.4.3. Influence of arterial stiffness on cardiac function

In a cohort of 73 PsA patients, compared to controls, PsA patients had increased ventricular and arterial stiffness and early impairment of LV longitudinal systolic and diastolic function. These results were also reported in PsO [67]. Cardiac involvement was associated with disease duration [72] [67]. LV longitudinal strain and strain rate in PsO patients were similar to those in patients with CAD [68].

4.5. Ankylosing spondylitis and arterial stiffness

4.5.1. Increased arterial stiffness in ankylosing spondylitis

Mortality in patients with ankylosing spondylitis (AnS) is 1.5 times higher than in the general population and 20%–40% of these deaths are thought to be due to CV events [73]. Increased arterial stiffness in this population may be detected even though the European Heart Score and

Table 5
Sjögren's syndrome and arterial stiffness.

Reference	Design	Population	Treatment	Outcome
Sabio et al. 2015 [57]	Cross sectional study	Patients n = 44 Age: 52 [44–56] years Female: 100% Controls n = 78 Age: 50 [43–55] years Female: 100%	19% NSAID 34% HCQ 21% CTC 16% AZA 5% MTX 2% MMF	✓PWV in SS patients (8.2 [IQR 7.1–9.5] vs 7.7 [IQR 7.0–8.5] m/s p = 0.03). Parameter associated with elevated PWV: metabolic syndrome, age, SSDI and the absence of SSA and SSB
Sezis Demirci et al. 2016 [56]	Cross sectional study	Patients n = 75 Age: 54.0 ± 9.3 years Female: 100% Controls n = 68 Age: 51.9 ± 9.9 years Female: 100%	13.7% CTC 9.6% IS	✓PWV in SS patients (8.2 ± 1.5 vs. 7.5 ± 1.4 m/s, p = 0.01).
Zardi et al. 2014 [101]	Cross sectional study	Patients n = 18 Age: 70 years Female: 100% Controls (OA) n = 18 Age: 69 years Female: 100%	No specific treatment.	No difference in vascular stiffness. No difference in carotid plaque.
Atzeni et al. 2014 [59]	Cross sectional study	Patients n = 22 Age: 60.1 ± 7.8 years Female: 72% Controls n = 22 Age: 60.1 ± 7.8 years Female: 72%	The majority of the patients were being treated with HCQ, AZA and MTX. 32% CTC	✓PWV in SS patients (8.90 [8.00–10.00] vs 6.89 [6.30–7.10] m/s, p < 0.0001). No difference in CIMT.
Ozisler et al. 2019 [102]	Cross sectional study	Patients n = 30 Age: 41.4 ± 9.4 years Female: MD Controls n = 30 Age: 38.7 ± 8.3 years Female: MD	100% HCQ 3.3% AZA 3.3% MTX	✓PWV in SS patients (7.6 ± 2.5 vs 6.5 ± 2.5, p = 0.003).

AIx: Augmentation Index; AZA: Azathioprine; CTC: Corticoids; HCQ: Hydroxychloroquine; (c)IMT: (carotid) Intima-Media Thickness; IS: Immunosuppressive drug; IQR: Interquartile Range; MD: Missing Data; MTX: Methotrexate; NSAID: Nonsteroidal Anti-Inflammatory Drug; OA: Osteoarthritis; PWV: Pulse Wave Velocity (hf: heart-femoral, cf: carotid-femoral, hc: heart-carotid, br: brachial-radial, fa: femoral-ankle); SS: Sjögren's Syndrome; SSDI: Sjögren's Syndrome Damage Index.

the Framingham Risk Score showed no difference between AnS patients and controls [74]. This illustrates that, again, traditional CV risk factors may not fully explain the increase in CVD in AnS, and, as with other inflammatory diseases, early detection of vascular dysfunction appears to be crucial.

Out of a total of 35 articles, involving 1535 patients with AnS and 1347 controls, a meta-analysis reported a significant increase in PWV in patients with AnS compared to controls [75]. In this meta-analysis, AIx was not documented. However, the results of several studies showed an

increase in AIx in AnS patients compared with controls [76] [74]. Two studies found no association between arterial stiffness and AnS [10,77] but suffer from numerous biases such as a small sample size, a young population, a short duration of the disease and a high percentage of patients taking Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) that may induce a low disease activity [77].

4.5.2. Influence of disease characteristics and CV risk factors on arterial stiffness

Disease activity appears to be associated with arterial stiffness. In a study of 85 AnS patients, AIx increased progressively with increasing CRP, erythrocyte sedimentation rate (ESR) and Ankylosing Spondylitis Disease Activity Score (ASDAS) [78]. In this study, baseline Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) has not been associated with increased arterial stiffness, suggesting that objective assessment of disease activity such as ASDAS appears to be more relevant than disease activity measured only by BASDAI to evaluate CV risk. Finally, in a smaller cohort of 24 AnS patients, PWV and AIx were significantly associated with Bath Ankylosing Spondylitis Functional Index (BASFI) score [76].

4.5.3. Influence of treatment on arterial stiffness

A few studies focused on the effect of AnS treatment on arterial stiffness. When echocardiographic parameters were evaluated according to the different drug treatment groups, in 55 AnS patient, the aortic stiffness index was highest in those taking conventional synthetic Disease Modifying Anti-Rheumatic Drugs (csDMARDs) and was significantly higher in this group than in the control group and the TNFi group [79]. However, these results should be treated with caution. Indeed, AnS patients taking DMARDs had higher ESR and CRP levels, which may be a potential bias. Moreover, physical activity is a cornerstone in AnS treatment, and reduced cardiorespiratory fitness may induce an increased risk of CVD in AnS. Among 118 participating patients, a significant inverse association between VO₂ peak and arterial stiffness was reported, independently of traditional CV risk factors and disease activity measures [80].

4.5.4. Influence of arterial stiffness on cardiac function

Myocardial involvement in AnS is usually manifested by diastolic dysfunction [81]. In a study of 75 patients with a mean disease duration of 5 years, AnS was associated with reduced LV strain in all myocardial layers [82].

5. Conclusion

Arterial stiffness is increased in chronic inflammatory and autoimmune diseases. This association is not solely related to the presence of the presence of CV risk factors. Therefore, CV risk assessment in these patients should not be based solely on the traditional CV risk scores but may also consider PWV and AIx.

However, CV risk factors, especially arterial hypertension, play a major role in arterial stiffness and should be controlled as early and as strictly as possible. Arterial stiffness is also clearly implicated in LV diastolic dysfunction, which is known to be the main mechanism of heart failure in chronic inflammatory condition. The link between arterial stiffness and atherosclerosis remains unclear in systemic inflammatory diseases. The lack of data and the high prevalence of CV risk factors make interpretation of the results difficult.

It remains unclear which characteristics of the disease may influence the presence or severity of the arterial aging and further studies or meta-analyses need to be conducted. To this end, indices which consider the burden of inflammatory disease rather than a measure of activity at a specific point in time would be useful.

TNFi appear to reduce arterial stiffness. One could therefore imagine that in the future, prescribing TNFi would be based not only on disease control but also on CV risk level.

To summarize, this review highlights the relationship between arterial stiffness and chronic inflammatory and autoimmune diseases, supporting that CV risk assessment in inflammatory patients should also rely on PWV and AIx.

Author contributions

Conceptualization: Berger, Fesler, Roubille.

Data curation: Berger.

Formal analysis: Berger, Fesler, Roubille.

Funding acquisition: NA.

Investigation: Berger.

Methodology: Berger, Fesler, Roubille.

Project administration: Fesler, Roubille.

Resources; Software; Supervision; Validation: Fesler, Roubille.

Writing - original draft: Berger, Roubille.

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MB has no conflict of interest to declare.

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