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Progression of atherosclerosis versus arterial stiffness with age within and between arteries in systemic lupus erythematosus

Paola C. Roldan[1] · Ernest R. Greene[1] · Clifford R. Qualls[1] · Wilmer L. Sibbitt Jr.[1] · Carlos A. Roldan[1]

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Abstract

The progression of atherosclerosis versus arterial stiffness with age within and between arteries has not been defined. Systemic lupus erythematosus (SLE) is a human model of accelerated arterial disease that may permit this determination. 76 SLE patients (69 women, age 37 ± 12 years) and 26 age-and-sex-matched controls (22 women, age 34 ± 11 years) underwent transesophageal echocardiography and carotid ultrasonography for assessment of atherosclerosis [plaques and intima–media thickening (IMT)] and arterial stiffness [increased pressure-strain elastic modulus (PSEM)] of the descending thoracic aorta and carotid arteries. Since IMT is highly associated with plaques, IMT was used as a marker of atherosclerosis to assess its progression in relation with age and PSEM. Aortic and carotid plaques, IMT, and PSEM were greater in patients than in controls (all $p \leq 0.05$). Within the aorta and within the carotid arteries, the average percent increases per decade of age for IMT versus PSEM were similar in patients (8.55% versus 9.33% and 3.39% versus 2.46%, respectively) and controls (5.53% versus 6.60% and 4.75% versus 3.49%, respectively) (all $p \geq 0.58$). However, in SLE patients, the average percent increases per decade of age for IMT and PSEM were higher in the aorta than in the carotid arteries (8.55% and 9.33% versus 3.39% and 2.46%, respectively, both $p \leq 0.03$). In patients with SLE, atherosclerosis and arterial stiffness progress with age parallel to each other within arteries, but divergently between arteries with different anatomy and hemodynamics.

Keywords Aorta · Carotid arteries · Atherosclerosis · Arterial stiffness · Systemic lupus erythematosus

Introduction

Atherosclerosis and arterial stiffness occur and progress at two–five fold higher rates in patients with systemic lupus erythematosus (SLE) than in age-and-sex-matched controls [1–15] and are associated with increased cardiovascular and cerebrovascular morbidity and mortality [16–20]. However, atherosclerosis and arterial stiffness have been reported separately in different arterial beds in diverse populations using diverse imaging modalities. To our knowledge, no previous controlled study has simultaneously assessed both atherosclerosis and arterial stiffness in the central (aorta) and peripheral (carotid arteries) conduit vessels in the same population using the same imaging modality. Therefore, it is unknown whether atherosclerosis and arterial stiffness progress in relation with age within and between arteries in parallel or divergent manner. SLE, a human model of accelerated arterial disease may permit this determination.

Transesophageal echocardiography (TEE) [2, 4, 21, 22] and carotid ultrasonography [1, 3, 6, 12, 15, 23] allow adequate spatial, temporal, and dynamic resolution for accurate assessment of plaques and intima–media thickness (IMT) as well as of change in diameter during the cardiac cycle of the thoracic aorta and carotid arteries, respectively.

This cross-sectional and controlled study was designed to simultaneously assess atherosclerosis and arterial stiffness in the thoracic aorta and carotid arteries using TEE and carotid ultrasonography, respectively, in patients with SLE and age- and sex-matched controls without SLE.

We hypothesized that in SLE and in relation with age, atherosclerosis and arterial stiffness would progress parallel

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✉ Carlos A. Roldan
croldan@salud.unm.edu

[1] Divisions of Cardiology and Rheumatology, Department of Medicine, University of New Mexico School of Medicine, Cardiology 5-ACC, MSC 10-5550, University of New Mexico, Albuquerque, NM 87131-0001, USA

to each other within an artery, but divergently between arteries with different anatomy and hemodynamics.

Methods

Study populations

This study was approved by the Institutional Review Board for the study of the association of cardiovascular and cerebrovascular disease in patients with SLE and was consistent with the Declaration of Helsinki. All participants signed an informed consent form prior to participation in the experimental protocol.

Inclusion criteria for patients included: (1) diagnosis of SLE [24] and (2) patients were regularly followed at the Rheumatology Clinics of the University Health Sciences Center, and (3) age $\geq$ 18 and $\leq$ 60 years.

Inclusion criteria for controls enrolled with a one control to three patients' ratio as approved and limited by the Institutional Review Board due to the semi-invasive nature of TEE included: (1) age $\geq$ 18 and $\leq$ 60 years (2) a negative medical history and (3) a normal cardiovascular physical examination.

Exclusion criteria included pregnancy, atrial fibrillation/flutter, cardiomyopathy with an ejection fraction < 50%, renal dysfunction with a serum creatinine level of > 0.11 mmol/L, or drug abuse.

Therefore, 76 SLE patients (69 women, age 37 ± 12 years, range 18–60 years) recruited from 266 well-characterized SLE patients and 26 age-and-sex-matched controls without SLE (22 women, age 34 ± 11 years, range 18–57 years) participated in the study.

Each participant underwent clinical and laboratory evaluations, TEE, and carotid ultrasonography on the same day. All studies were coded, de-identified, and interpreted by independent experienced observers blinded to subjects' clinical and imaging data and each other's measurements.

Clinical and laboratory evaluations

Patients and controls underwent assessment of demographics, traditional atherogenic risk factors, and basic laboratory tests. Patients were also characterized with regard to SLE duration, activity, damage, standard serology, autoantibodies, and therapy.

TEE

All subjects underwent a standardized imaging protocol with multiplane TEE by an experienced cardiologist using Philips I-E33 imaging systems (Andover Massachusetts, USA) using a 7 MHz transducer with an axial resolution of ~ 0.1 mm. At a depth of 3–4 cm and using a narrow sector scan to optimize spatial resolution, two-dimensional images were used to assess the presence of plaques of the posterior, medial, and lateral walls of the descending thoracic aorta. Two-dimensional guided M-mode images were used to assess (1) the intima–media thickness (IMT) outside plaques of the posterior wall and (2) end-systolic and end-diastolic diameters of the proximal (25–30 cm from the incisors), mid (30–35 cm), and distal (35–40 cm) descending thoracic aorta [2, 4, 21, 22]. At each aortic location and from short- or long-axis views, assessment of the presence of plaques, 3 end-diastolic measurements of IMT, and 3 end-systolic and end-diastolic diameters were performed off-line by one experienced observer using electronic calipers and then averaged. In 10 randomly selected studies (7 patients, 3 controls), inter-observer variability for measurement of aortic IMT showed a mean difference of 5%. In 26 randomly selected TEE studies (16 patients, 10 controls), inter-observer variability for measurement of aortic diameters showed mean differences of 2–6%.

Carotid ultrasonography

All subjects underwent standardized bilateral carotid B-mode ultrasonography by an experienced ultrasonographer using Philips IU-22 systems with a 9 MHz transducer with an axial resolution of < 0.1 mm. From longitudinal B-mode images (a preferred approach over monoplane M-mode imaging), the presence of plaques at the common, internal, and external carotid arteries was determined. From similar B-mode images and at ~ 1 cm apart, 3 near and far wall IMT measurements of the right and left common carotid arteries were performed off-line using electronic calipers [1, 23]. To assess carotid stiffness, the last 44 of 76 patients and 17 of 26 controls underwent standardized carotid M-mode ultrasonography using a Sonosite system (Bothel Washington, USA) with a 10 MHz transducer with axial resolution of < 0.1 mm [25, 26]. Using longitudinal M-mode images, 3 end-systolic and end-diastolic diameters (~ 1 cm apart) of the right common carotid artery were measured off-line using electronic calipers and then averaged. Assessment of the presence of plaques, measurements of IMT, and measurement of diameters of the carotid arteries were performed by a second experienced observer. In 10 randomly selected studies (6 patients, 4 controls), inter-observer variability for measurement of carotid IMT showed a mean difference of 4%. In another 10 randomly selected studies (6 patients, 4 controls), inter-observer variability for measurement of carotid artery diameters showed mean differences of 2–4%.

Blood pressure measurements

During imaging of the aorta and carotid arteries, 3–6 standard automated brachial blood pressures were obtained and matched in time with measurement of arterial diameters.

Assessment of aortic and carotid atherosclerosis

Atherosclerosis was determined by the presence of plaques. However, IMT outside plaques has been associated with plaques [1–3, 12, 21, 23]. In this study, for each increase of a standard deviation in aortic IMT (0.32 mm) and carotid IMT (0.09 mm) in SLE patients, the odds of having aortic and carotid plaques increased by a factor of 3.95 (95% CI 1.70–9.16, $p=0.001$) and 2.5 (95% CI 1.35–4.66, $p=0.004$), respectively. Therefore, in this study, IMT as a continuous variable was used as a surrogate marker of aortic and carotid atherosclerosis to assess their progression in relation with age, arterial stiffness, and to each other.

Assessment of aortic and carotid artery stiffness

Arterial stiffness was assessed at the proximal, mid, and distal thoracic aorta and at the right common carotid artery using the Pressure-Strain Elastic Modulus (PSEM) defined as $= [k\ (\mathrm{sBP}-\mathrm{dBP})/[(\mathrm{sD}-\mathrm{dD})/\mathrm{dD}]$, where $k=133.3$ is the conversion factor from mmHg to Nm^{-2} (Pascal Units, PaU), sBP and dBP = systolic and diastolic blood pressures, and sD and dD = end-systolic and end-diastolic diameters. PSEM is a well-validated parameter for assessing static arterial stiffness independently of IMT or plaques [3–6, 25, 26]. Aortic and carotid stiffness are presented as continuous values of PSEM to assess their relationships to age, IMT, and to each other.

Statistical analysis

Student's t test (for continuous variables) and Fisher's exact test (for categorical variables) were used to compare groups. In SLE patients, paired t test was used for paired comparison of continuous variables. Analysis of covariance (ANCOVA) with multivariable adjustment was used to compare aortic and carotid atherosclerosis and stiffness between SLE patients and controls. Logistic regression was used to show that IMT is closely related to plaques. To determine whether the increase in IMT versus PSEM within arteries (aorta and carotid arteries) and between arteries (aorta versus carotid arteries) progress in a parallel or divergent fashion, IMT and PSEM were modeled as a function of age using repeated measures (RM) ANCOVA, where IMT versus PSEM or aorta versus carotid arteries was the repeated factor and age was the continuous fixed factor. Log-transformed IMT and PSEM values were used in the RM ANCOVA to reduce influence of outliers, to adjust for unequal variances, to compute percent change per decade of age (slopes), and to compute valid p values for comparison of slopes (see Supplemental Material for details). A 2-tailed p value <0.05 was considered significant.

Results

Clinical and laboratory characteristics of patients and controls

Patients and controls had similar age, sex, ethnicity, body mass index, and overall prevalence of traditional atherogenic risk factors (all $p\geq0.21$) (Table 1). Patients as compared to controls had higher non-hypertensive range of systolic, diastolic, and mean arterial blood pressures (all $p\leq0.02$), but similar pulse pressures ($p=0.56$) and a trend toward higher prevalence of hypertension ($p=0.06$). Patients had lower hemoglobin, platelets and albumin levels and had higher fasting glucose and creatinine levels than controls (all $p\leq0.03$). SLE patients had a mean age of 29 years at diagnosis and disease duration of 8 years, 72% of patients had active disease, 53–93% had elevated inflammatory markers, and 60% had positive antiphospholipid antibodies. With regard to standard therapy, 44% were on corticosteroids, 36% on cyclophosphamide, 28% on antimetabolite immunosuppressive (mycophenolate mofetil, azathioprine, mercaptopurine, or methotrexate), 67% on hydroxychloroquine or chloroquine, and 42% on antithrombotic therapy (Supplemental Table 1).

Atherosclerosis and arterial stiffness in patients and controls

Patients had higher frequency of plaques and greater IMT of the aortic and carotid arteries than controls (all $p\leq0.05$) after simultaneously adjusting for clinical and laboratory differences between both groups (systolic and diastolic blood pressures, hypertension, fasting glucose, hemoglobin, platelet count, creatinine level, and albumin level) (Table 2). Patients also had higher aortic and carotid PSEM than controls (all $p\leq0.06$) after simultaneously adjusting for hypertension, fasting glucose, hemoglobin, platelet count, creatinine level, and albumin level. No adjustment for systolic and diastolic blood pressures was made, since these values are part of the formula of PSEM.

Progression of atherosclerosis versus arterial stiffness within arteries in relation with age

The average percent increases per decade of age for aortic IMT versus PSEM were similar in patients (8.55%

Table 1 Clinical and laboratory data in patients with SLE and controls

Parameter	Patients with SLE ($N=76$)	Controls ($N=26$)	p value
Age (years)	37 ± 12	34 ± 11	0.21
Women	69 (91%)	22 (85%)	0.46
Ethnicity/race (hispanic/non-hispanic white)	48 (63%)/19 (25%)	13 (50%)/8 (31%)	0.45
Body mass index (kg/m^2)	27 ± 6	27 ± 5	0.77
Systolic blood pressure (mmHg)	123 ± 15	116 ± 8	0.004
Diastolic blood pressure (mmHg)	76 ± 10	71 ± 9	0.02
Mean arterial blood pressure (mmHg)	92 ± 11	86 ± 7	0.004
Pulse pressure (mmHg)	46 ± 10	44 ± 9	0.56
Hypertension*	10 (13%)	0	0.06
Dyslipidemia or statin therapy	34/74 (46%)	9/25 (36%)	0.49
Cholesterol (mmol/L)	4.66 ± 1.19	4.99 ± 1.11	0.19
LDL cholesterol (mmol/L)	2.79 ± 1.03	2.87 ± 0.83	0.75
HDL cholesterol (mmol/L)	1.29 ± 0.41	1.29 ± 0.47	0.91
Triglycerides (mmol/L)	1.74 ± 0.90	1.81 ± 1.08	0.76
Diabetes mellitus	3/74 (4%)	0	0.56
Fasting glucose (mmol/L)	5.0 ± 1.44	4.61 ± 0.5	0.03
Current Smoking	24/75 (32%)	6 (23%)	0.46
Atherogenic risk factors	50/75 (67%)	14 (54%)	0.25
Postmenopausal	5 (7%)	0	0.30
Hemoglobin (g/dL)	13 ± 2	14 ± 2	0.004
White blood cell count (× 10^3/mm^3)	6 ± 3	7 ± 2	0.43
Platelets (× 10^3/mm^3)	242 ± 87	273 ± 44	0.02
Creatinine (mmol/L)	0.08 ± 0.04	0.06 ± 0.01	0.01
Albumin (g/dL)	3.8 ± 0.6	4.2 ± 0.4	0.002

Cell formats are mean ± SD and (n) or frequency/n (%)

HDL high-density lipoprotein, *LDL* low-density lipoprotein, *SLE* systemic lupus erythematosus

*Hypertension = SBP > 140 or DBP > 90 mmHg

Table 2 Aortic and carotid atherosclerosis and stiffness in patients with SLE versus controls

Variable	Patients with SLE ($N=76$)	Controls ($N=26$)	P value
Aortic atherosclerosis			
Plaques	19 (25%)	0	0.003/0.05†
Overall IMT (mm)*	0.84 ± 0.32 (range 0.42–2.21)	0.67 ± 0.17 (range 0.49–1.2)	0.001/0.009†
Aortic PSEM			
Overall PSEM (PaU)*	8.19 ± 4.11 (range 3.1–21.5)	5.97 ± 2.31 (3.32–8.8)	0.001/0.047‡
Carotid atherosclerosis			
Plaques	14 (18%)	0	0.02/0.04†
Overall IMT (mm)*	0.52 ± 0.09 (range 0.36–0.80)	0.48 ± 0.08 (range 0.36–0.71)	0.06/0.01†
Carotid artery PSEM			
Overall PSEM (PaU)*	6.27 ± 2.90 ($n=44$) (range 2.63–17.6)	5.55 ± 2.68 ($n=17$) (range 2.84–13.4)	0.06/0.06‡

SLE systemic lupus erythematosus, *IMT* intima–media thickness, *PSEM* pressure-strain elastic modulus, *PaU* Pascal Units

*Overall = average mean across the proximal, mid, and distal descending thoracic aorta

†p value after simultaneously adjusting for systolic and diastolic blood pressures, hypertension, fasting glucose, hemoglobin level, platelet count, creatinine level, and albumin level by stepwise regression analysis (for continuous variables) or logistic regression analysis (for binary variables)

‡p value after simultaneously adjusting for hypertension, fasting glucose, hemoglobin level, platelet count, creatinine level, and albumin level by stepwise regression analysis (for continuous variables) or logistic regression analysis (for binary variables)

versus 9.33%, $p = 0.69$) and controls (5.53% versus 6.6%, $p = 0.62$, respectively) (Fig. 1). In addition, the average percent increases per decade of age for carotid IMT versus PSEM were similar in patients (3.39% versus 2.46%, $p = 0.62$) and controls (4.75% versus 3.49%, $p = 0.71$, respectively) (Fig. 2).

Progression of atherosclerosis and stiffness between arteries in relation with age

In patients, the average percent increases per decade of age for IMT and PSEM were greater in the aorta than in the common carotid arteries (8.55% and 9.33% versus 3.39% and 2.46%, respectively, both $p \leq 0.02$) (Fig. 3). In controls, the average percent increases per decade of age in IMT and PSEM were similar in the aorta and carotid arteries ($p = 0.66$ and $p = 0.74$, respectively) (Fig. 4).

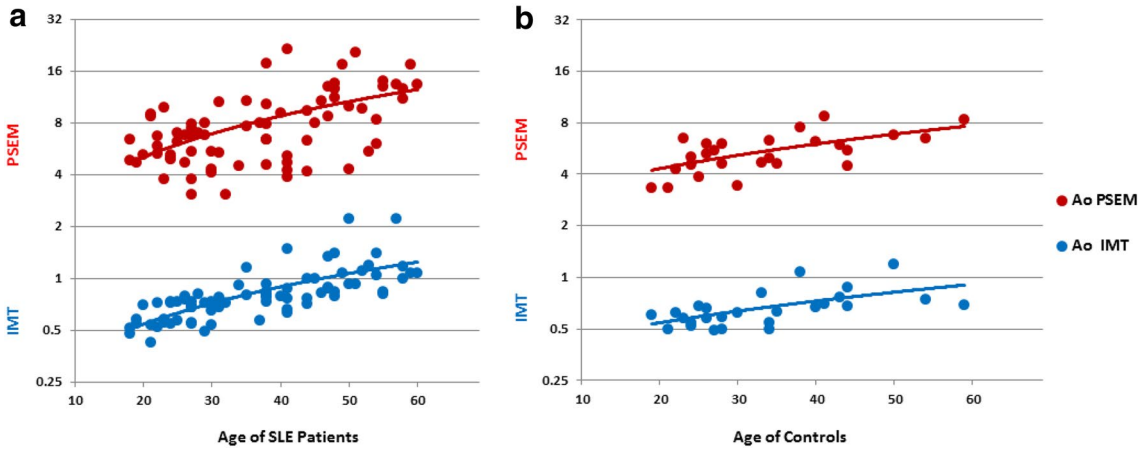

Fig. 1 Progression of aortic IMT versus PSEM in relation with age in SLE patients and controls. **a** In SLE patients, the scatterplot and fitted regression lines for aortic (Ao) IMT (blue circles and line, values ranging from 0.4 to 2.2 mm) and for Ao PSEM (red circles and line, range 3.1–21.5 PaU) demonstrate that the average percent increases per decade of age for IMT versus PSEM were similar (8.6% and 9.0%, respectively, $p = 0.83$). **b** In controls, Ao IMT (range 0.5–1.2 mm) and Ao PSEM (range 3.3 to 8.8 PaU) also demonstrates similar average percent increases per decade of age (5.5% and 7.2%, respectively, $p = 0.58$)

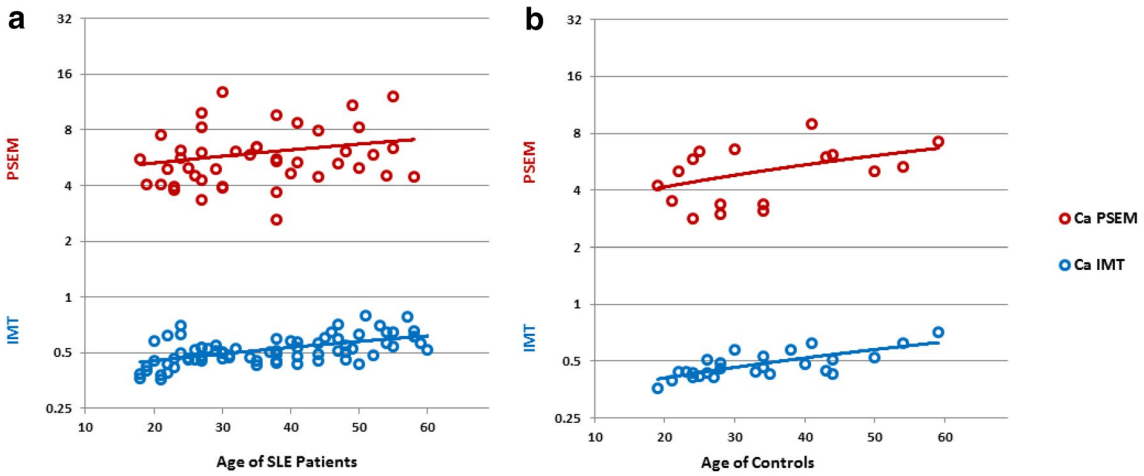

Fig. 2 Progression of carotid artery IMT versus PSEM in relation with age in SLE patients and controls. **a** In SLE patients, the scatterplot and fitted regression lines for carotid (Ca) IMT (blue circles and line, values ranging from 0.36 to 0.80 mm) and for Ca PSEM (red circles and line, range 2.6–12.8 PaU) demonstrate that the average percent increases per decade of age for IMT versus PSEM were similar (3.4% and 2.5%, respectively, $p = 0.62$). **b** In controls, Ca IMT (range 0.36–0.7 mm) versus Ca PSEM (range 2.8–9.0 PaU) demonstrates also similar percent increases per decade of age (4.8% and 3.5%, respectively, $p = 0.72$)

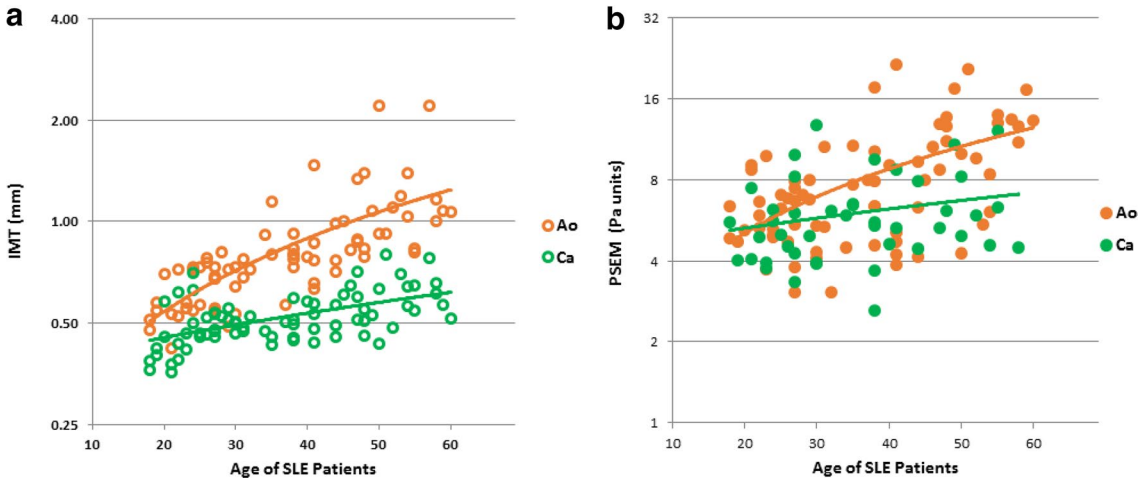

Fig. 3 Progression of aortic versus carotid IMT and PSEM in relation with age in SLE. **a** Scatterplot and fitted regression lines demonstrate that in SLE the rates of increase per decade of age for aortic (Ao) IMT (orange circles and line) are greater (8.6%) than for the carotid (Ca) arteries (3.4%, green circles and line) ($p<0.001$). **b** Scatterplot and fitted regression lines demonstrate that in SLE the rates of increase per decade of age for aortic (Ao) PSEM (orange circles and line) are greater (9.0%) than for the carotid (Ca) arteries (2.5%, green circles and line) ($p=0.03$)

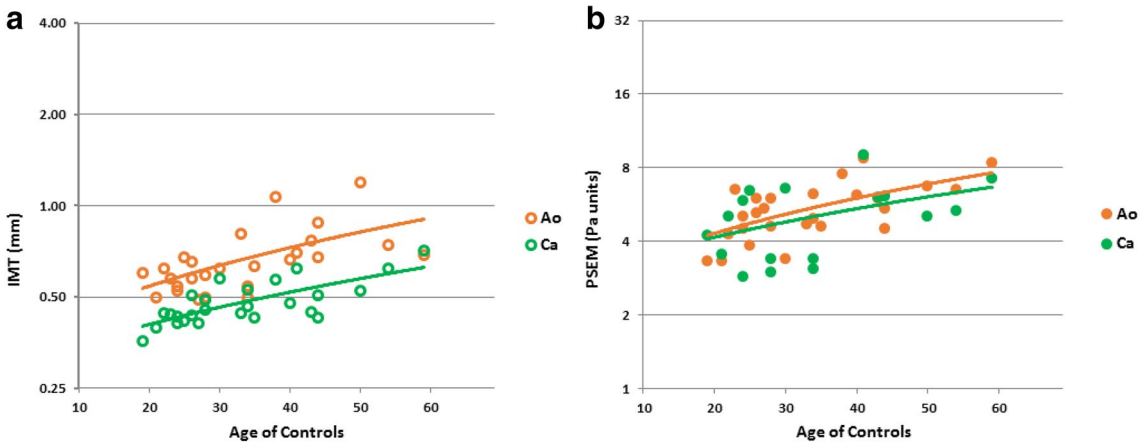

Fig. 4 Progression of aortic versus carotid IMT and PSEM in relation with age in controls. This scatterplot and regression lines demonstrate that in controls, the rates of increase per decade of age for the aortic IMT (Ao, orange circles and lines) in **a** (5.5%) and PSEM in **b** (7.2%) are similar to those for the carotid arteries (Ca, green circles and lines) (4.8% and 3.5%, $p=0.66$ and $p=0.41$, respectively)

Discussion

Major findings

To our knowledge, this is the first controlled study to demonstrate in both SLE patients and controls that (1) within the aorta and within the carotid arteries, atherosclerosis versus arterial stiffness progress with age in a parallel manner and (2) in SLE patients, atherosclerosis and arterial stiffness progress with age to a greater extent in the aorta than in the common carotid arteries. These findings support that pathogenic factors of arterial disease including aging and inflammation lead to (1) a parallel progression of atherosclerosis and stiffness within a specific artery and (2) a divergent rate of progression of atherosclerosis and stiffness between the aorta and carotid arteries likely due to the superimposed effect of aging and inflammation on the divergent anatomy, histology, and hemodynamics of these arteries.

Pathophysiologic implications

The known effect of aging on arterial disease compounded by SLE-related systemic and vascular inflammation [1–9] may lead to simultaneously occurring endothelial

denudation, apoptosis, and dysfunction; subendothelial smooth muscle cell proliferation; increased collagen-to-elastin ratio in the media; plaque formation with associated intima–media thickening and fibrosis; microvascular disease of the adventitial vasa vasorum with resultant adventitial thickening and fibrosis [10–15]; vessel stiffening with increased impedance; and a progressive and self-perpetuating cycle of atherosclerosis and stiffness [27–29].

The divergent progression of thoracic aortic versus carotid atherosclerosis and stiffness in SLE patients may be explained by an enhanced effect of aging and SLE-related inflammation on the complex physical characteristics of the thoracic aorta, including the 180° turning, proximal to distal narrowing (in this study, 2.72 ± 0.30 cm at the sinuses level, 2.03 ± 0.56 cm at the distal arch, and 1.59 ± 0.28 cm at the mid descending thoracic aorta, $p \leq 0.003$ for all), and high impedance of the thoracic aorta with dissimilar blood flow and pressure waveforms and velocity profiles exhibiting both antegrade and retrograde, and highly oscillatory blood flow patterns during the cardiac cycle [2, 4, 7, 21, 30, 31]. In contrast, in the relatively straight non-tapering common carotid arteries exhibiting predominantly resistive impedances (less reactance), the antegrade-directed blood flow and pressure waveforms are similar both in magnitude and direction [1, 10, 12, 23, 31]. Therefore, pulse pressure, velocity profiles, and radial–circumferential-and longitudinal shear wall stresses are higher on the thoracic aorta than in the carotid arteries. These effects may be compounded in the thoracic aorta by a greater degree of inflammatory microvascular disease of the adventitia and outer media due to a richer plexus of vasa vasorum than in the carotid arteries [21, 32, 33].

Potential clinical implications

This study suggests that the progression of atherosclerosis in relation with age within a specific artery implies a similar parallel progression of arterial stiffness and vice versa. Thus, detection of either atherosclerosis or arterial stiffness may indicate the presence of more advanced arterial disease and the need for aggressive anti-inflammatory therapy to prevent further inflammation-driven progression of both atherosclerosis and stiffness and the associated risk of cardiovascular and cerebrovascular morbidity and mortality in SLE patients [2, 4, 6, 22, 29, 34–38]. However, the effect of anti-inflammatory therapy and non-pharmacologic interventions including physical activity [34, 39–43] in the rate of progression with age of atherosclerosis and arterial stiffness within and between arteries in SLE needs to be defined in a cross-sectional and longitudinal study.

The divergent and predominant thoracic aortic atherosclerosis and stiffness result in the loss of the aortic cushioning to ventricular emptying and loss of the dampening effect to reflected waves from peripheral vessels leading to higher systolic blood pressures, an increase in pulse pressure, higher pressure fluctuations, and higher shear stresses on the aorta, which are then transmitted to the coronary, carotid, and cerebral arteries [29–32, 44]. These aortic hemodynamic abnormalities in combination with plaque formation and intima–media thickening may contribute to plaque ulceration and thrombosis, aneurysmal formation, atherothrombosis, atheroembolism, myocardial infarction, stroke, and death [16, 17, 22, 44–46]. Finally, the resultant systolic hypertension from aortic stiffness increases left ventricular afterload resulting in left ventricular hypertrophy-and-fibrosis, diastolic dysfunction, and ultimately heart failure [4, 6, 29–31, 44, 47].

While our findings apply explicitly to SLE, they may also apply to other immune-mediated inflammatory conditions characterized by accelerated arterial disease such as rheumatoid arthritis, systemic sclerosis, psoriasis, and ankylosing spondylitis [29, 48–53].

Finally, TEE is semi-invasive and poses potential risks, and, therefore, should not be used as a routine screening technique for detecting the presence and progression of aortic atherosclerosis and stiffness. However, as the present study indicates, in patients who undergo TEE for appropriate clinical indications, assessment of aortic atherosclerosis and stiffness is feasible and clinically relevant [2, 4, 22]. Carotid M-mode ultrasonography and carotid to femoral arterial tonometry are appropriate diagnostic modalities [1, 5, 7, 25, 54, 55].

Comparison with previous studies

To our knowledge, no previous study has determined a parallel progression of atherosclerosis and arterial stiffness. However, there are supportive data regarding divergent arterial disease in SLE and non-SLE populations. Jiu et al. [56], in a study including 52 SLE patients and 60 age-and-sex-matched controls who underwent multi-detector computed tomography demonstrated that SLE patients in comparison with controls had significantly higher rates of calcification (calcium score > 0) predominantly in the descending thoracic aorta (40.4% versus 6.7%) and coronary arteries (38.5% versus 1.7%) and much lower rates in the carotid arteries (7.7% versus 1.7%) (all $p \leq 0.02$). Wang et al. [57] in a study of 85 patients with rheumatoid arthritis and 85 matched controls, demonstrated significantly higher rates of aortic followed by coronary and then carotid arteries calcifications in patients than in controls (64%, 41%, and 19% versus 12%, 18%, and 6%, respectively, all $p < 0.02$). These studies showed 3–5 times higher rates of calcifications in the descending thoracic aorta than in the carotid arteries. Finally, Redheuil et al. [58], in a study of 111 healthy adults (54 men, age range

20–84 years) who underwent assessment of aortic and carotid stiffness by aortic MRI and carotid ultrasonography, respectively, demonstrated that aortic stiffness progressed at significantly higher rates than carotid stiffness with each decade of life.

Study limitations

(1) This was a cross-sectional study. The timing of progression of atherosclerosis versus arterial stiffness within and between arteries needs confirmation in a larger cross-sectional and longitudinal study. However, this type of study requires the inclusion of patients and controls before they develop arterial disease, multiple serial imaging studies over a long period of time, and adaptation to the inevitable changes in imaging technology and movement of study populations. (2) A small control group limited in size by the IRB due to the semi-invasive nature of TEE and mainly intended to assist blinded interpretation of all studies and validate the study findings. (3) The TEE near-field limited resolution precluded assessment of the aortic anterior wall and, therefore, may have led to underestimation of the extent of aortic atherosclerosis. (4) Assessment of IMT of the common carotid arteries and of PSEM of the right common carotid artery may have led to underestimation of the extent of carotid atherosclerosis and stiffness, respectively. However, limited visualization and misalignment of the ultrasound beam with the walls of the carotid bulb and of the internal and external carotid arteries preclude accurate quantification of IMT and PSEM in these segments. In addition, differences in stiffness between the right and left common carotid arteries have not been established.

Conclusion

In SLE patients and controls, atherosclerosis versus arterial stiffness progress in relation with age parallel to each other within the aorta and within the common carotid arteries. However, in SLE patients, the higher rate of progression of aortic versus carotid atherosclerosis and stiffness may be due to aging and superimposed inflammation on the different anatomy and hemodynamics of these arteries.

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Compliance with ethical standards

Conflict of interest None of the authors have financial or non-financial conflicts of interest to disclose.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

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