Vascular stiffness: influencing factors on carotid-femoral pulse wave velocity in systemic lupus erythematosus

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Abstract

Objective

Patients with systemic lupus erythematosus (SLE) are under increased risk for cardiovascular events (CVE) and mortality. Aortic stiffness, as measured by carotid-femoral pulse wave velocity (cfPWV), has been shown to predict CVE and mortality in the general population. The aim of the present study was to examine the factors associated with cfPWV in patients with SLE and to determine differences of SLE patients in comparison to healthy controls.

Methods

125 patients with SLE and 104 controls were included. Demographic, medication and cardiovascular risk factor data were collected from all participants. Furthermore, clinical and laboratory SLE associated parameters were documented in the patients' group. All subjects underwent measurements of blood pressure and cfPWV.

Results

Interestingly, only age (β=0.55; p<0.001), mean arterial pressure (MAP) (β=0.29; p<0.001) and estimated glomerular filtration rate (eGFR) (β=-0.20; p=0.033) were associated independently with cfPWV in patients with SLE. Moreover, there was no difference of cfPWV between patients with SLE and controls before (p=0.301) and after adjustment for disparities between the groups (p=0.671).

Conclusion

Vascular stiffness in patients with SLE seems to be independent from SLE-related factors and from most traditional CVRF and is mainly associated with age, MAP and renal function defined as eGFR. There is an independent correlation between eGFR and cfPWV in a SLE population with a widely normally ranged eGFR. There is no difference of cfPWV between patients with SLE and controls.

Key words

systemic lupus erythematosus, carotid-femoral pulse wave velocity, vascular stiffness, pulse wave velocity, renal function, glomerular filtration rate

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Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease that affects predominantly women in childbearing age (1). Even if the all-cause mortality for SLE decreased over the last decades, partly due to improvements in therapy partly due to improvements in diagnostics, patients with SLE still show increased all-cause and cause-specific mortality rates compared to the general population (1-3). Main causes of death for patients with SLE are renal diseases, infections and cardiovascular diseases (CVD) (4). In SLE patients the risk of mortality from CVD is distinctly increased (1.5- to nearly 3-fold) compared to the general population (2-4). In contrast to the decreased SLE associated mortality over the last decades, mortality due to CVD has remained unaltered high (5). Moreover, the CVD mortality in the general population decreased during the last decades, but there was no improvement for patients with SLE (4). Furthermore the risk for a myocardial infarction is 2–10 times higher for patients with SLE compared to the general population, with a strikingly elevated relative risk especially for premenopausal women (6).

The increased cardiovascular risk (CVR) for patients with SLE seems to be caused by a premature and accelerated atherosclerosis, attributable to lupus-specific risk factors (*i.e.* increased systemic inflammation) and traditional cardiovascular risk factors (CVRF) (7, 8). CVR assessment tools which are based on traditional CVRF, such as Framingham risk score, failed to predict the CVR for patients with SLE adequately (9).

In many patient groups and in the general population the aortic stiffness, measured by carotid-femoral pulse wave velocity (cfPWV), predicted future cardiovascular events (CVE) and mortality independently from traditional CVRF(10). It is, however, still unclear whether cfPWV can also predict future CVE and mortality in patients with SLE. Although numerous studies have analysed cfPWV in patients with SLE, the associated factors with arterial stiffness remain somewhat unclear. Various studies showed uneven results (11-24). Additionally, it is not clear whether vascular stiffness in patients with SLE is increased compared to healthy controls. Regarding this question, some studies also showed inconsistent results (11-14, 16, 18, 19, 22-24).

Therefore, the aim of the present study was to identify associations of various risk factors, traditional CVRF as well as SLE related factors, with aortic stiffness in SLE. Furthermore, our purpose was to evaluate the cfPWV, as a determinant of aortic stiffness and possible CVR defining tool, in patients with SLE and healthy controls.

Materials and methods

Study participants

Patients with SLE were recruited from the Rheumatology Unit of the First Department of Medicine at the University Medical Center of the Johannes-Gutenberg University, Mainz, Germany during their regular follow-up visit and at the Acura Center of Rheumatology, Bad Kreuznach, Germany during an inpatient stay in clinic between November 2015 and January 2017. All patients fulfilled at least 4 of the American College of Rheumatology criteria for SLE (25). Controls were recruited from the employees of the University Medical Center and from the ACURA Center of Rheumatology as well as from social networks. Subjects with untreated hypertension, active infection, age <18 years, malignancy and pregnancy were excluded from the study as well as controls with chronic inflammatory diseases.

In all subjects, demographic data (age, sex), current medication and history of CVRF (diabetes mellitus, hypertension, dyslipidaemia, smoking) were collected. SLE related data were analysed for patients. Height and weight were measured as well as systolic blood pressure (SBP) and diastolic blood pressure (DBP). Body mass index (BMI) was calculated by dividing the weight by the square of the height and a BMI ≥30 kg/m^2 was considered as obesity. MAP was calculated by the formula $MAP=DBP+\frac{1}{3}(SBP-DBP)$. Hypertension was defined as SBP >140

Table I. Characteristics of patients with SLE and controls.

	Controls (n=104)	SLE patients (n=125)	*p*-value
Age (years)	50 (37-56)	46 (35-54)	0.221
MAP (mmHg)	93 ± 11	94 ± 10	0.701
BMI (kg/m²)	23.73 (21.12-27.04)	26.31 (22.18-29.31)	**0.020**
Female sex (%)	88.5	88	0.914
Hypertension (%)	19.2	36	**0.005**
Diabetes (%)	0	9	0.062
Dyslipidaemia (%)	11.5	27.2	**0.006**
Smoking (%)	21.2	20	0.830
Antihypertensive therapy (%)	17.3	39.,2	**<0.001**
Statin therapy (%)	0	10,4	**0.021**
Heart rate (1/min)	66 ± 9	71 ± 10	**0.003**
cfPWV (m/s)	6.71 (6.00-7.44)	6.40 (5.95-7.29)	0.301
eGFR (ml/min/1.73m²)	-	96.20 (79.15-107.18)	-
eGFR <90 ml/min/1.73m² (%)		36.6	
Disease duration (years)	-	10 (4-18)	-
Low complement (%)	-	52	-
C3 (g/l)	-	1.08 ± 0.27	-
C4 (g/l)	-	0.19 (0.13-0.26)	-
ESR 1h (mm)	-	14 (6-28)	-
Current dose of steroids (mg/d prednisolone)	-	3 (0-5)	-
Leukocyte count (1/nl)	-	6.2 (4.8-8.2)	-
Thrombocyte count (1/nl)	-	235 (201-295)	-
HDL (mg/dl)	-	56 (46-73)	-
LDL (mg/dl)	-	114 (92-133)	-
TAG (mg/dl)	-	96 (74-150)	-
Current ANA-positivity (%)	-	69.6	-
Positive ENA-Screen (%)	-	40.8	-
Anti-dsDNA-Ab-positivity (%)	-	66.4	-
Rheumafactor positivity (%)	-	8.8	-
Steroids (%)	-	68	-
HCQ (%)	-	60.8	-
Belimumab (%)	-	28.8	-
Immunosuppressives (%)	-	50.4	-
Skin involvement (%)	-	75.2	-
Renal involvement of SLE (%)	-	28.8	-
Neurological disorders (%)	-	8	-
Pleuritis or pericarditis (%)	-	21.6	-
Non-erosive arthritis (%)	-	39.2	-
Haematological disorders (%)	-	28.8	-
Immunological disorders (%)	-	82.3	-
ANA-positivity ever (%)	-	89.6	-
SLEDAI (points)	-	4 (2-6)	-
SDI (points)	-	0 (0-1)	-

All values are expressed as median (1st quartile-3rd quartile), mean ± SD or relative frequency in %. *p*-values are for the respective comparing test.
SLE: Systemic lupus erythematosus; MAP: mean arterial pressure; BMI: body mass index; cfPWV: carotid-femoral pulse wave velocity; eGFR: estimated glomerular filtration rate; ESR: erythrocyte sedimentation rate; HDL: high-density lipoproteine; LDL: low-density lipoproteine; TAG: tricyglycerides; ANA: antinuclear antibodies; anti-dsDNA-Ab: anti-double stranded DNA-antibodies; HCQ: hydroxychloroquine; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SDI: Systemic Lupus International Collaborating Clinics Damage Index.
Immunosupressives include azathioprine, calcineurin inhibitors, mycophenolate mofetile.

mmHg and/or DBP >90 mmHg and/or being on treatment with BP-lowering drugs for hypertension. Dyslipidaemia was defined as fulfilling one or more of the following criteria: HDL <40 mg/dl; LDL >160 mg/dl; LDL/HDL >4 despite a treatment with statins.

SLE disease activity was assessed by using the SLEDAI-2K score (26). A SLEDAI-2K score >4 points was defined as active disease. Cumulative organ damage was measured with the SLICC damage index (SDI) and a score ≥1 point was defined as organ damage (27).

All study participants gave their informed consent to participate in this study and the study was reviewed and approved by the Standing Committee for Clinical Studies by the local ethics commission of Medical Association of Rhineland-Palatine.

Laboratory measurements

Laboratory measurements were performed for the patients with SLE after a 12-hour fasting period and included complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TAG), complement C3, complement C4, antinuclear antibodies (ANA), Extractable nuclear antigens-

(ENA) screening, dsDNA-antibodies, creatinine and rheumatoid factor (RF). Estimated glomerular filtration rate (eGFR) was calculated by the CKD-EPI formula (28). An ANA-titre ≥1:160 was considered as ANA-positive. Low complement was defined as C3 <0.8 g/l and/or C4 <0.2 g/l.

Vascular assessment

CfPWV measurements were conducted by two experienced independent medical assistants who received examination training by SMT medical and one of the authors. Oscillometric cfPWV measurements were performed with the Vicorder® (Skidmore Medical Limited, Bristol, UK), which calculated the cfPWV by dividing the travelling-distance of the pulse wave by the transit time (29). The travelling-distance was measured as the distance from a cuff around the neck at the level of the right common carotid artery to the upper thigh at the level of the right femoral artery and was multiplied with 0.8, which seems to be the most accurate method to assess the travelling-distance and is therefore recommended by an expert consensus paper (30). All measurements were performed in supine position in a quiet room after 10 minutes of rest (30). Participants did not smoke, eat or consume caffeine within 3 hours before the measurement (30). Three measurements were performed and the median of this measurements was used. Heart rate was also counted by Vicorder®.

Statistical analysis

Normally distributed continuous variables are presented as mean ± standard deviation (SD) and were compared by using unpaired *t*-test. Non-normal distributed variables are presented as median with interquartile range (IQR) from 1st to 3rd quartile and were compared by using Mann-Whitney U-test. Categorical variables are presented as relative frequencies (%) and categorical differences were evaluated with the χ^2-test. Spearman's correlation coefficient (rho) was used to evaluate the association between cfPWV and continuous variables. To evaluate the association between cfPWV and categorical variables with two categories, the cfPWV of the two groups was compared. Multivariate linear regression models were used to evaluate independent associations of bivariate correlating variables with cfPWV and for performing adjustments for potential confounders. A two-tailed *p*-value <0.05 was defined as significant. Statistical analyses were made with SPSS 23.0 (IBM, Armonk, USA).

Table II. Analysis of bivariate correlations between potential influencing factors and cfPWV.

Factor	Spearman's rho	*p*-value
Age	0.59	**0.001**
MAP	0.35	**0.001**
Heart rate	0.04	0.684
eGFR	-0.41	**0.001**
BMI	0.11	0.243
SLEDAI-2K score	-0.05	0.613
SDI score	0.19	**0.036**
ESR	0.25	**0.006**
C3-concentration	0.19	**0.035**
C4-concentration	0.01	0.933
Leukocyte count	0.07	0.458
Thrombocyte count	0.02	0.810
HDL-concentration	0.20	**0.030**
LDL-concentration	0.31	**0.001**
TAG-concentration	0.14	0.132
Disease duration	0.24	**0.008**
Current dose of steroids	-0.01	**0.577**

SLE: Systemic lupus erythematosus; MAP: mean arterial pressure; BMI: body mass index; eGFR: estimated glomerular filtration rate; ESR: erythrocyte sedimentation rate; HDL: high-density lipoproteine; LDL: low-density lipoproteine; TAG: tricyglycerides; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SDI: Systemic Lupus International Colaborating Clinics Damage Index.

Results

Study population

125 patients with SLE (88% women, median age 46 years with IQR 35–54 years) and 104 controls (88.5% women, median age 50 years with IQR 37–56 years) were examined. Clinical characteristics of SLE patients and controls are shown in Table I. The median duration of SLE was 10 (4–18) years and prednisone was being taken by 68% of the patients with SLE. Hydroxychloroquine (HCQ) was being taken by 60.8% of the patients with SLE and immunosuppressants by 50.4%. A combination of prednisone, HCQ and immunosuppressants was taken by 23.2% of patients. The median SLEDAI-2K score was 4 (2–6) points and median SDI was 0 points with an IQR from 0 to 1 point. The BMI was higher in the group of SLE patients with 26.31 (22.18–29.31) kg/m² *vs*. 23.73 (21.12–27.04) kg/m² (*p*=0.020) as well as the heart rate (*p*=0.003). Moreover, hypertension (*p*=0.005), antihypertensive treatment (*p*<0.001), dyslipidaemia (*p*=0.006) and statin therapy (*p*=0.021) were more frequent in the group of patients.

Associations of arterial stiffness in SLE patients: bivariate correlations

In the group of SLE patients cfPWV was shown to correlate with age (rho=0.59, *p*<0.001), MAP (rho=0.35, *p*<0.001), eGFR (rho=-0.41, *p*<0.001), SDI-score (rho=0.19, *p*=0.036), ESR (rho=0.25, *p*=0.006), C3-concentration (rho=0.19, *p*=0.035), HDL-concentration (rho=0.20, *p*=0.030), LDL-concentration (rho=0.31, *p*=0.001) and disease duration (rho=0.24, *p*=0.008). No correlation with cfPWV was found for heart rate, BMI, SLEDAI-2K-score, C4-concentration, leukocyte-count, thrombocyte-count, TAG-concentration and current daily dose of corticosteroids (Table II).

Association of arterial stiffness in SLE patients: analysis of binomial variables

To analyse the relationship between binomial variables and cfPWV in patients with SLE, the cfPWV of the patients with and without the respective feature was compared (Table III). A difference between two groups was only found between patients with (n=45) and

without (n=80) hypertension and between patients with (n=61) and without (n=64) organ damage (defined as SDI ≥1), whereas the cfPWV was higher for patients with hypertension and patients with organ damage. But patients with hypertension were older (p<0.001), had higher MAP (p=036), and lower eGFR (p<0.001) than patients without. After an adjustment for these disparities there was no significant difference of cfPWV between patients with and without hypertension (p=0.175). Patients with organ damage were older (p<0.001) and had a lower eGFR (p<0.001) than patients without organ damage. After statistical adjustment for parameters which were statistically significantly different in the two groups and therefore could have a confounding effect on the results there was no significant difference of cfPWV between the two groups (p=0.459). No differences between two groups were found regarding the variables smoking, diabetes, gender, dyslipidaemia, statin therapy, antihypertensive therapy, ANA-positivity, anti-dsDNA-antibody positivity, RF positivity, renal involvement, low complement, ENA positivity, obesity and active disease. The group of patients under antihypertensive therapy included more patients than the group of patients with hypertension because of the use of antihypertensive drugs for patients with renal impairment.

Associations with arterial stiffness in SLE patients: multivariate analysis

All variables that showed a p-value <0.05 in the analyses of bivariate correlations and analyses of binomial variables were taken together into a multivariate linear regression model for analysing independent associations between them and cfPWV (Table IV). This model included age, MAP, eGFR, SDI, ESR, C3-concentration, HDL-concentration, LDL-concentration, disease duration and hypertension. The binomial variable organ damage was not included, because the SDI-score was already included. The multivariate regression model for cfPWV performed moderately (R^2=0.463). In multivariate analysis, only age (p<0.001), MAP (p<0.001) and eGFR (p=0.033) showed independently a significant influence on cfPWV in SLE patients. Age was the main influencing factor on cfPWV in patients with SLE (β=0.55). Standardised regression coefficients of MAP and eGFR were β=0.29 and β=-0.20, respectively.

Table III. Analysis of associations between binomial variables and cfPWV. CfPWV of patients fulfilling the respective criteria compared with cfPWV of patients not fulfilling the respective criteria.

Factor	Number of patients fulfilling the respective criteria	p-value
Female sex	110	0.284
Hypertension	45	**0.005**
Smoking	25	0.907
Diabetes	9	0.560
Dyslipidaemia	34	0.637
Statin therapy	13	0.515
Antihypertensive therapy	49	0.102
ANA-positivity	87	0.729
dsDNA-Ab-positivity	83	0.522
Rheumatoid factor-positivity	10	0.705
Renal involvement	36	0.541
Low complement	65	0.804
positive ENA-Ab-screening	51	0.612
ANA-titre > 1:160	69	0.968
Obesity	26	0.717
Organ damage (SDI >0)	61	**0.018**
Disease activity (SLEDAI >4)	41	0.577

ANA: antinuclear antibodies; anti-dsDNA-Ab: antis-double stranded DNA-antibodies; ENA-Ab: extractable nuclear antigens-antibodies; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SDI: Systemic Lupus International Colaborating Clinics Damage Index.

Table IV. Multivariate linear regression model for cfPWV in the group of 125 patients with SLE (R^2 = 0,463).

Factor	Standardised regression coefficient β	p-value
Age	0.55	**<0.001**
MAP	0.29	**<0.001**
eGFR	-0.20	**0.033**
SDI-score	-0.06	0.493
ESR	0.04	0.648
C3-concentration	-0.05	0.514
HDL-concentration	-0.02	0.776
LDL-concentration	0.02	0.800
Disease duration	-0.02	0.845
Hypertension	-0.11	0.226

MAP: mean arterial pressure; eGFR: estimated glomerular filtration rate; ESR: erythrocyte sedimentation rate; HDL: high-density lipoproteine; LDL: low-density lipoproteine; SDI: Systemic Lupus International Colaborating Clinics Damage Index.

Comparison of cfPWV between patients and controls

The median of cfPWV in the control group was 6.71 (6.00–7.44) m/s and 6.40 (5.95–7.29) m/s for the SLE group. The difference was not significant before (p=0.301) and after adjusting for the disparities between the two groups in BMI, heart rate, frequency of hypertension, frequency of statin therapy and dyslipidaemia (p=0.671). Figure 1 shows the distribution of cfPWV in both groups. A statistical adjustment for the disparity in frequency of antihypertensive treatment was not performed, because almost exclusively subjects with hypertension received antihypertensive agents.

Discussion

The main finding of the present study is that cfPWV, as a determinant of aortic stiffness, was independently associated with age, MAP and eGFR in lupus patients. SLE related factors like disease activity, laboratory parameters

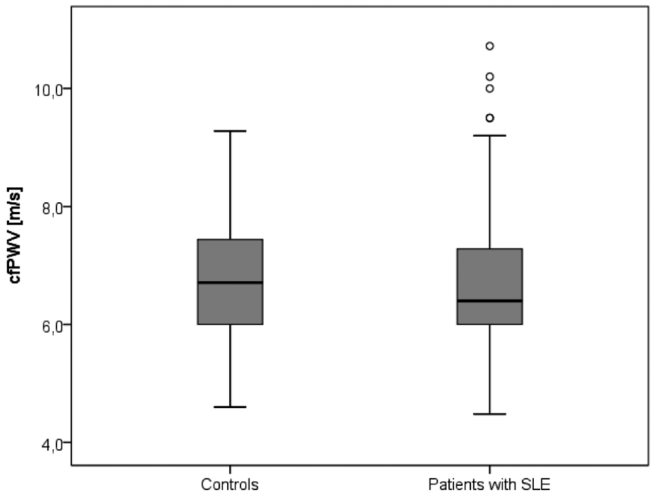

Fig. 1. CfPWV is not different in SLE patients compared to controls. Comparison of cfPWV on control subjects and SLE patients. The figure shows the distribution of cfPWV in controls and in SLE patients pictured as boxplots.

or cumulative organ damage as well as most of traditional CVRF were not correlated independently with cfPWV. Furthermore, there was no difference of the cfPWV between SLE patients and healthy controls.

To the best of our knowledge, the present study is the first, which describes a negative association between GFR and vascular stiffness in patients with SLE, independent from blood pressure, age and other CVRF. In the light of the fact that most patients (63.4%) in the present study had an eGFR in normal range (≥90 ml/min/1,73m^2) with a median eGFR of 96.20 (79.15–107.18) ml/min/1.73m^2 and only 28.8% of the patients had a renal involvement of SLE, this finding is remarkable. Only 4 patients had a severe proteinuria (protein-to-creatinine ratio >50 mg/mmol) and only 9 patients had a moderately increased protein urine excretion (protein-to-creatinine ratio 15–50 mg/mmol). An association of a decreased GFR with an increased vascular stiffness has been described by several studies with non-SLE populations before (31-34). Most studies included patients with chronic kidney disease (CKD) or older aged people (31-33). All populations had an impaired renal function according to GFR (31-33). Only one study on patients with essential hypertension found an independent association between a normal ranged GFR and cfPWV (34). A bidirectional relation between vascular stiffness and renal function is known: An impaired renal function is correlated with vascular calcification, even in early stages of renal disease (35). On the other hand, if aortal stiffness is increased the microvasculature of the kidney is exposed to higher pressure amplitudes (36). The exposition to higher pressure amplitudes results, because of the low vascular resistance of renal vessels, in renal vascular damage and thereby in an impaired renal function (36, 37). The observed independent correlation of decreasing GFR with increasing cfPWV in a SLE population with a widely normally ranged GFR and young age (median 46 years) in our study might indicate both: a beginning vascular stiffening in an early stage of impaired renal function or a beginning renal impairment caused by increasing vascular stiffness in SLE patients. Thus, in the future it would be interesting to examine whether assessment of vascular stiffness by cfPWV measurement might help to identify SLE patients, which are at risk for renal damage despite a GFR in normal range. Moreover, these results could then identify patients that are at increased risk for CVE, since an association between impaired renal function, increased vascular stiffness and increased CVR is known.

Interestingly, age and MAP were independently associated with cfPWV in our SLE patient cohort. This is consistent with results from the general population in which age and MAP are described as the main influencing factors on cfPWV in a large review including various patient populations and general population (38). The established independent statistical significant association between MAP and cfPWV is not surprising. The influence of blood pressure on aortic stiffness at the time of measurement is a very important factor. Because of the elasticity of the aorta, the vessel wall gets stretched if a force is applied to it (39). On the other hand, the applied force depends on blood pressure, so the higher the distending pressure is, the higher is the stretching of the vessel wall and by stretching, the vessel wall gets stiffer (39). The measured determinants of stiffness should be corrected for this part of stiffness which is caused by the distending pressure (39). To take the MAP into consideration for correcting stiffness measurements respectively to the distending pressure is therefore recommended (39, 40). In our study, some associations lost their statistical significance after bringing the MAP into the analysis.

Age has been found as the major factor correlated with cfPWV in the present study. The age dependence of aortic stiffness is due to structural changes in the media layer of the vessel wall over lifetime (41). Especially a loss of elastin fibres and an accumulation of collagen fibres over time change the mechanical properties of the arterial wall and lead to increasing vascular stiffness over lifetime (41). These changes are independent of other processes (41) and age has been repeatedly described as a major contributing factor to vascular stiffness and cfPWV (38, 42).

Most of other traditional CVRF showed no independent association with the cfPWV in the present study. The majority of them, for example an increased LDL-concentration or a decreased HDL-concentration, are associated with atherosclerosis whereas arterial stiffness is widely independent from atherosclerotic changes in the intima of the vessel wall and reflects changes in the mechanical properties of the vessel wall, especially in the media layer (38, 41). Because of this independence of risk factors for atherosclerosis, assessment of vascular stiffness can provide additional information about the CVR (38). This additional information might be crucial for patients with SLE, where

traditional CVRF do not fully account for the increased CVR.

SLE- and inflammation-related factors were not independent associated with cfPWV in the present study. Other studies found associations between cfPWV and C3 (20, 21), dsDNA-antibodies (20), disease duration (12), SDI-score (15, 20) or medication (19, 20). A recent meta-analysis did not describe exactly which SLE-related factors were examined (24). C3, SDI-score and disease duration were also correlated with cfPWV in the present study, but lost the significance in the multivariate model. However, there might be an association between SLE related factors and vascular stiffness, but SLE is a very heterogenous disease (1). Therefore, correlations between disease-related factors and vascular stiffness might differ from patient to patient due to different manifestations of SLE. Thus, further investigation should subdivide SLE patients by manifestation. Evaluation of these distinct SLE populations might result in an association of SLE related factors with vascular stiffness in a subpopulation of patients.

To the best of our knowledge, the present study is the largest study comparing cfPWV between adult SLE patients and healthy controls. Several smaller studies addressed this comparison of vascular stiffness between patients with SLE and controls (11-14, 16, 18, 19, 22, 23). Most of them found higher cfPWV values in patients with SLE compared to controls (11-14, 16, 18, 19, 23). Only in one recent study by Tziomalos *et al*. no difference in cfPWV between SLE patients and controls has been shown (22). In contrast to the present study many of the other studies examined a relatively small group of subjects, potentially missing statistical power (11-13, 19, 23). Furthermore, in most of the studies there were no adjustments for differences in potential confounding factors on cfPWV between patients and controls performed (13, 14, 16, 18, 23). There are also differences in patient medication between the present study and other studies. The frequency of patients under steroids and immunosuppressants was lower than in some comparable studies, showing a relatively mild affected collective in comparison (11, 19, 23).

A recent meta-analysis found higher cfPWV values in SLE patients compared to controls (24). The meta-analysis by Wang *et al*. included especially studies with a small sample size but found an effect of the sample size on the PWV levels (24). How potentially missing adjustments in the included studies were considered was not mentioned as well as the approach to heterogeneity of SLE-related factors and the CVRF between the single included studies (24). Therefore, the different results between the present work and other studies might be caused by differences in methodology, especially in adjusting for differences between the groups and/or differences in examined population.

Our study has several limitations. First, whereas the sample size was larger than in other comparative studies it was still relatively small to investigate that large number of potential influencing factors on vascular stiffness without a lack of statistical power. Second, the cross-sectional-design does not allow to draw conclusions about causalities. Vascular stiffness respectively stiffening is a dynamic process changing over time. Most of the analysed variables are changing over time, too. Because of these dynamics, time related correlations might not get captured by only one examination at a specific moment in time.

The findings of the present study should be confirmed by future research on larger populations of SLE patients. Prospective studies are needed to analyse correlations between cfPWV-values and CVE in subgroups of SLE patients. These studies are necessary to determine if the assessment of vascular stiffness is suitable to predict CVE and cardiovascular mortality in patients with SLE. Furthermore, prospective studies are required for additional information about the predictive value of cfPWV measurements for a future renal impairment of patients with SLE.

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