Assessment of Vascular Stiffness and Relation to Cardiovascular Risk Factors in Patients with Systemic Lupus Erythematosus

Thesis
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ABSTRACT

Background:

Cardiovascular disease is a major cause of morbidity and mortality in systemic lupus erythematosus (SLE) patients. Interestingly, SLE was suggested to be a coronary artery disease equivalent. Accurate risk stratification would require a simple, non-invasive index integrating all traditional and emerging risk factors. Vascular stiffness – proven to have better predictive value for cardiovascular events than traditional risk factors in hypertensives and patients with coronary artery disease – fulfills these requirements.

Aim of the study:

We investigate whether arterial stiffness is increased in SLE patients compared to healthy controls and to correlate the arterial stiffness in SLE patients with cardiovascular risk factors .

Subjects and Methods:

This study included 100 subjects divided into 50 SLE patients and 50 age- and gender-matched healthy individuals. All individuals underwent standard clinical evaluation. Assessment of aortic stiffness was performed by calculation of aortic elastic indices using M-mode transthoracic echocardiography (TTE) .Endothelial function was assessed using brachial flow mediated dilation (FMD). Carotid duplex ultrasound was performed to measure quality arterial stiffness (QAS) parameters using Esaote MyLab 60 (Linear array transducer LA523). We calculated carotid-femoral pulse wave velocity (cf-PWV) as the carotid-femoral travel distance divided by the transit time ($\Delta L/\Delta t$).

Results:

Our study included 50 SLE individuals (47 females, median age 29, range 17 – 45 years) and 50 age- and gender-matched healthy individuals. SLE patients had higher median aortic stiffness index (SI) and lower strain and distensibility, compared to controls (*p* value for all <0.001). SLE patients had significantly impaired FMD compared to controls: the median (range) in SLE patients was 8.82 (2.5 - 21.87), compared to 19 (12 - 37.5) in controls (z = -7.695, p <0.001). Regarding QAS parameters, SLE patients had significantly lower median carotid distension, distensibility coefficient, and compliance coefficient, with higher median carotid SI, carotid pulse wave velocity (PWV), and augmentation index (AI), compared to controls (*p* value for all $\leq$0.001).

SLE patients had a higher median cf-PWV 6.5 m/sec (4.8 – 11.8), compared to a median of 4.6 m/sec (3.8 – 6.9) in controls ($z = -8.193$, $p < 0.001$).

Linear regression analysis to adjust for hypertension and diabetes mellitus yielded a statistically significant difference between both groups for all of the above parameters ($p = 0.014$ for maximum carotid IMT and <0.001 for remaining parameters), with the exception of the maximum carotid augmentation index ($p = 0.184$).

Carotid AI and FMD were significantly associated with hypertension, with hypertensive patients having higher median AI compared to non-hypertensives ($z = -2.749$ & -2.298, $p= 0.006$ & 0.022, respectively). There was a positive association between SLE duration and each of carotid PWV, carotid SI, and cf-PWV ($r = 0.363$, 0.361, and 0.302, respectively; $p = 0.01$, 0.011, and 0.033, respectively).

Conclusion:

In this study, SLE patients have significantly impaired FMD and increased arterial stiffness compared to healthy controls. This was documented after adjusting for hypertension and diabetes mellitus, highlighting the fact that SLE is an independent cardiovascular risk factor. SLE duration is an important predictor of arterial stiffness. These findings emphasize the need for early diagnosis of SLE and aggressive risk factor modification.

Key words: Systemic lupus erythematosus, arterial stiffness, flow-mediated dilatation

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List of Abbreviations

Abb.	Full Term
Ab PWV	Ankle brachial pulse wave velocity
ACL	Anticardiolipin antibodies
ACR	American Colleague of Rhuematology
AGEs	Advanced glycation end products
A II	Angiotensin II
AI	Augmentation index
AoA	Aortic Atherosclerosis
AoS	Aortic stiffness
APS	Antiphospholipid syndrome
BMI	Body mass index
C3	Complement 3
Carotid AI	Carotid Augmentation index
CAS	Carotid arterial stiffness
CBC	Complete blood count
CC	Compliance coefficient
CCP	Central pulse pressure
CFPWV	Carotid-femoral pulse wave velocity
CHD	Coronary heart disease
CIMT	Carotid intima-media thickness
CKD	Chronic kidney disease
CT	Computed tomography.
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DC	Distensibility coefficient
ECG	Electrocardiogram
ESC	European Society of Cardiology
ESH	European Society of Hypertension
ESKD	End stage kidney disease
FMD	Flow Mediated Dilation
HDL	High-Density Lipoprotein
HMG CoA	Hydroxy _methyl_ glutryle CoA
HTN	Hypertension
LAP antibodies	Lupus anticoagulant antibodies
ICAM-1	Intercellular adhesion molecule 1.
IL-1	Interleukin -1
INF	Interferone
IMT	Intima-media thickness
ISH	International Society of Hypertension
LDL	Low-density lipoprotein
LocPsys	Local systolic pressure

LVSD .....: Left ventricular systolic diameter.
MAP.....:Mean arterial pressure
MCSF.....: Monocyte Colony Stimulating Factor
MI.....: Myocardial Infarction
M-mode.....: Motion mode.
MMP .....: Matrix metalloprotinase
MRI.....: Magnetic resonance imaging
NO.....: Nitric Oxide
Ox LDL.....:Oxidized Low-density lipoprotein
PP .....: Pulse pressure
PWV.....: Pulse wave velocity
QAS.....:Quality arterial stiffness
RA .....:Rheumatoid artheritis
RAAS .....:Renin_Angiotensin_Aldosterone System
RF.....: Radiofrequency
ROI.....: Region of interest
ROS .....:Reactive oxygen Species
SBP .....: Systolic blood pressure
SD .....: Systolic diameter
SD .....: Standard deviation
SI.....: Stiffness index
SLE .....:Systemic Lupus Erythematosus
SLEDAI .....: Systemic Lupus Erythematosus Disease Activity Index
SLICC .....: Systemic Lupus International Collaborative Clinics
SV .....: Stroke Volume
TC .....:Total cholesterol
TEE .....:Transesophegeal echocardiography
TGF.....: Transforming growth factor
TLR .....:Toll_like_Receptor
TTE .....:Transthoracic echocardiography
TLC.....:Total leucocytic count
TNF.....: Tumour necrosis factor
VCAM-1 .....: Vascular cell adhesion molecule 1
VSMC .....: Vascular smooth muscle cell
WBCs.....: White blood cells
WHR .....: Waist_Hip ratio
ΔT.....: Transit time
ΔL.....: Travel distance

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Introduction

Cardiovascular disease is a major cause of morbidity and mortality in systemic lupus erythematosus (SLE) patients. These patients have a higher incidence and an earlier age of onset of ischemic heart disease, carotid atherosclerosis, cerebrovascular stroke, and peripheral vascular disease, despite being mostly pre-menopausal females.[1-3] Interestingly, SLE was suggested to be a coronary artery disease equivalent.[4] SLE activity and disease duration increased the risk of vascular events in some studies.[5]

Traditional cardiovascular risk factors, including hypertension, diabetes mellitus, dyslipidemia, and physical inactivity, only account partially for the elevated vascular risk in SLE patients.[6,7] Other emerging vascular risk factors include elevated plasma homocysteine, lipoprotein (a), leptin, and markers of oxidative stress such as asymmetric dimethyl arginine are emerging.[8, 9] Accurate risk stratification would require a simple, non-invasive and practical indices integrating all these risk factors. Vascular stiffness-proven to have better predictive value for fatal and non-fatal cardiovascular events than traditional risk factors in hypertensives and patients with end-stage renal disease and coronary artery disease(CAD). [10]

Arterial stiffness is defined as the arteries' capacity to expand and contract during the cardiac cycle. Arterial compliance, distensibility and elasticity are all different aspects of arterial stiffness. Stiffness can be determined by measuring pulse wave velocity (PWV) in the aorta using a mechanotransducer, tonometer, echotracking, or Doppler probes; or the superficial arteries (common carotid, common femoral, brachial and radial arteries) using video-image analysis or echotracking devices. The latter use a radiofrequency signal to directly determine the local arterial stiffness from the change in pressure driving the change in volume, with a higher spatial resolution than the former. Echotracking devices are currently the only non-invasive means to derive the elastic properties of the arterial wall-Young's elastic modulus by measuring the intima-media thickness. Finally, arterial stiffness can be assessed by measuring the augmentation index, which represents the augmentation of central pulse pressure during late systole by the earlier return of wave reflection due to arterial stiffening. [11,12]

Most of the published studies have shown increased vascular stiffness in SLE patients as compared to healthy controls.[13-14] These studies either included a small number of patients or used dedicated instruments other than the standard ultrasound machines used to perform the echocardiographic / peripheral vascular studies in ordinary cardiology services. Few studies could not identify differences between SLE patients and healthy controls regarding some indices of stiffness of some arteries.[15-16]

A healthy endothelium maintains arterial elasticity, mainly through the production of nitric oxide. Endothelial dysfunction represents the initial step of atherosclerosis and correlates with arterial stiffness. Patients with SLE demonstrated reduced flow-mediated dilatation (an index of endothelial function) compared with healthy individuals. This difference persisted after adjustment for established vascular risk factors.[17]

The identification of elevated vascular risk in SLE patients may warrant aggressive use of antihypertensives, statins, and immunomodulating agents despite the lack of prospective studies that prove the value of this approach. Therefore, assessment of arterial stiffness can be useful to guide therapeutic decisions in these patients in the future.

Aim of the work

1. Determine whether arterial stiffness is increased in SLE patients compared to healthy controls.

2. Correlate the arterial stiffness in SLE patients with cardiovascular risk factors.

Arterial stiffness

The arterial system consists of the large elastic arteries (thoracic aorta, carotid arteries), the more muscular conduit peripheral arteries (i.e. iliac, brachial, radial and femoral arteries) and the arterioles.

The arterial wall consists of three concentric layers: the tunica adventitia, tunica media, and tunica intima (**figure 1**). There is a single layer of endothelial cells between the blood and the vessel wall.[18] The wall of large arteries is rich in elastin and collagen while that of small muscular arteries is rich in vascular smooth muscle. Elastin fibres play an important part in determining the mechanical strength of the vessels at lower pressures and collagen fibres bear most of the strength at the higher pressures.

Large elastic arteries such as the aorta buffer flow and pressure variations generated by the intermittent LV contraction and convert pulsatile variations into steady values to the periphery. This cushioning function provides continuous oxygenation to the tissues and cardiac work. Elastic recoil of the central arteries in diastole is important for coronary perfusion and for diastolic blood flow to other organs as well.

Loss of elasticity impairs coronary flow and may contribute to coronary artery disease and also leads to pulsatile stress to peripheral organs such as the brain and the kidneys.

Epidemiological studies have drawn attention to the relationship of systolic pressure and pulse pressure (PP) to morbid and fatal cardiovascular (CV) events and have thus emphasized that blood pressure abnormalities characterizing hypertension and determining its CV complications originate not only from an increase in vascular resistance but also from an increase in central arterial stiffness. Because of its elastic properties, the aorta can dilate by increasing blood pressure in systole and can recoil to its initial shape by decreasing pressure in diastole. Aortic stiffness characterizes the elastic resistance against the distension, whereas aortic compliance describes the readiness for systolic aortic expansion. Aortic stiffness is evaluated by the change in volume because of blood injection in the aorta as well as by the pressure change induced by this volume change.

Arterial stiffness is a generic term that simply describes the rigidity of the arterial wall. Increased central arterial stiffening is a hallmark of the aging process and the consequence of many disease states such as diabetes, atherosclerosis, chronic kidney disease (CKD), also a marker for increased CV risk, including myocardial infarction, heart failure, and total mortality, as well as stroke, dementia and worsening of kidney function.

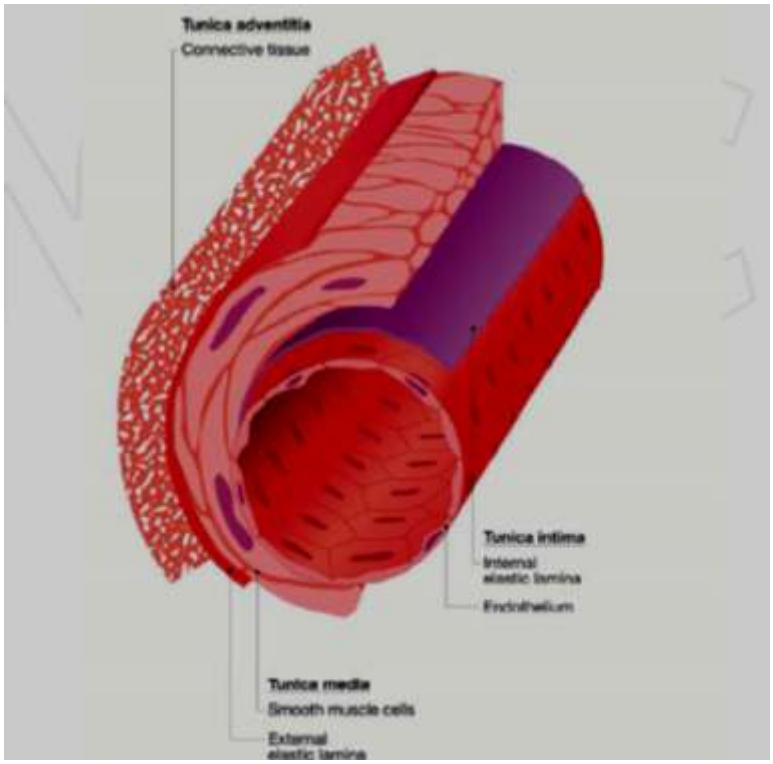

Figure 1.Arterial wall structure [18]

Stiffness is not uniformly disseminated throughout the vascular tree but is often patched occurring in central and conduit vessels while sparing peripheral arteries. Diseases, such as hypertension and diabetes mellitus, or simply aging itself, amplify the vascular changes that induce artery stiffening and can do so in different, yet synergistic, ways. Aging, as one of the major determinants of arterial stiffness, has different effects on arteries. While elastic arteries (aortic, carotid) stiffen progressively with age, the stiffness of muscular arteries (radial, femoral) changes little.[19] In the media of elastic arteries, the degeneration of elastic fibers is associated with an increase in collagenous material and is accompanied by calcium (Ca^{+2}) deposition in ground substance. [20]

Pathophysiology of arterial stiffness

Arterial stiffening develops from complex changes involving structural and cellular elements of the arterial wall (**Figure 2**). These vascular changes, occurring mainly in large arteries, are highly influenced by hemodynamic forces, as well as by several factors such as salt, hormones, uremia, and glucose.

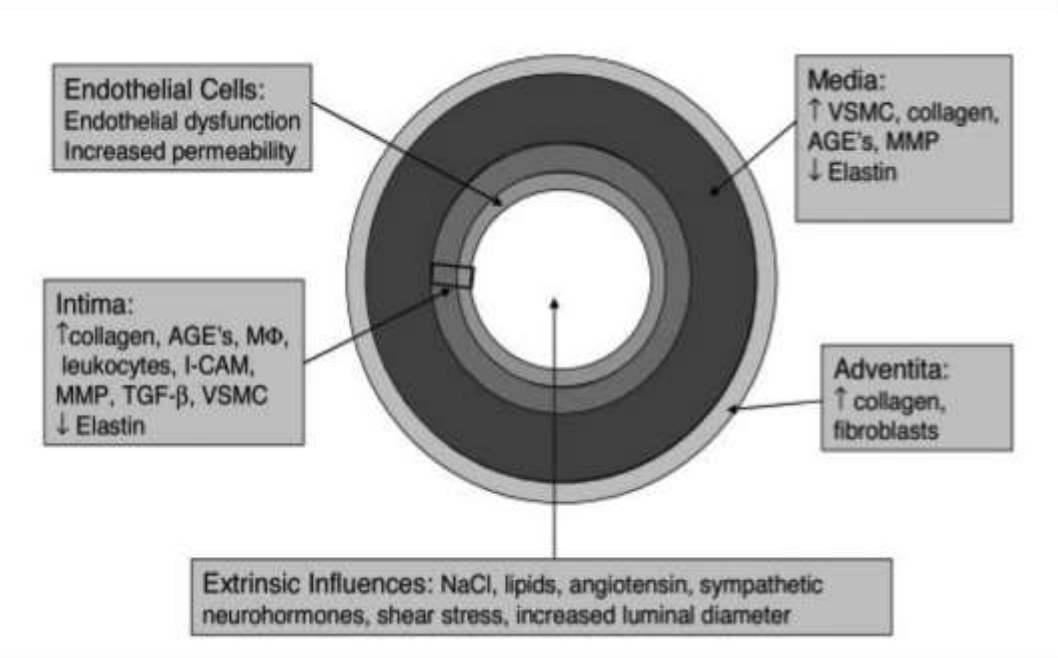

Figure 2. Summary of the multiple causes of arterial stiffness [21]

VSMC:vascular smooth muscle cell,AGE: advanced glycation end product, MMP: matrix metalloproteinase, TGF-β: transforming growth factor.

Structural Components of Arterial Stiffening

The functional characteristics of the vascular wall are dependent on the balance of relative amount of ***collagen and elastin,*** which is regulated by a slow, but dynamic process of production and degradation. Dysregulation of this balance, mainly by inflammation, leads to overproduction of abnormal collagen and less production of normal elastin, which contribute to vascular stiffness.[22] This leads to an impressive increase of intima-media thickness and development of a hypertrophied smooth muscle stratum. Histology of the intima of stiff arteries reveals abnormal endothelial cells, increased collagen, broken elastin, infiltration of smooth muscle cells, macrophages and mononuclear cells, and increased matrix metalloproteinases (MMPs), transforming growth factor (TGF)-β, intracellular cell adhesion molecules and cytokines. [23]

Collagen molecules provide the tensile strength of the vessel wall and are enzymatically cross-linked soon after their formation to render them insoluble to hydrolytic enzymes.[24] Breaks in the integrity of these intermolecular bonds cause unraveling of the collagen matrix. Elastin is also stabilized by cross-links; disruption of which results in the weakening of the elastin array. Collagen and elastin are regulated by the catabolic effect of ***MMPs*** that degrade the extracellular matrix, resulting in structurally abnormal collagen and elastin molecules. Vascular cells and inflammatory cells produce various types of MMPs.[25]