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Arterial Distensibility in Systemic Lupus Erythematosus

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Abstract - **Systemic lupus erythematosus (SLE) is a prototypical autoimmune disease that is atherogenic. Decreased arterial distensibility (AD) is a risk factor for cardiovascular disease, and this precursor may be associated with SLE. Accordingly, we tested the hypothesis that patients with SLE will have significantly ($p < 0.05$) decreased AD when compared to normal, healthy age, and gender matched controls. Noninvasive, high resolution ultrasound was performed on 30 patients with chronic SLE and 16 age and gender matched controls. All were female. Maximum systolic and minimum diastolic diameters (mm) and intima-media thickness (IMT, mm) in the right common carotid artery were measured from M-mode images. In vitro arterial models were used for quality control. With a single, blinded observer, the 95% confidence levels for accuracy and precision for noninvasive systolic and diastolic tonometric arm blood pressures (SBP, DBP) and carotid sonographic diameters were ~5 mmHg and ~0.10 mm, respectively. Derived measurements for strain (%), stiffness (units), and AD (units) were determined by published arterial mechanical models and algorithms. Results (mean/standard deviation) were as follows: (patients/controls; # =$p<0.05$) Age 39/11, 35/11 years; SBP 130/20, 117/8# mmHg; DBP 82/11, 74/9# mmHg; strain 11/4, 11/4 %); stiffness 19/10, 17/11 units; IMT 0.44/0.08, 0.41/0.06 mm; AD 3.10/1.49, 3.30/1.63 units. There were no statistically significant differences ($p<0.05$) in measurements of AD and IMT in the common carotid artery between relatively young SLE patients and well matched controls.**

Keywords: **arterial distensibility, systemic lupus erythematosus, intima-media thickness, noninvasive ultrasound, carotid artery**

I. INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem disease characterized by disturbances in the immune system [1]. The etiology of SLE is multifactor and includes an atherosclerotic component. Importantly, SLE predominately affects women of child bearing age. It is estimated that approximately one of every 700 white women and one of every 245 black women will develop SLE [2]. Young women with SLE experience substantially higher incidence of cardiovascular disease, ischemia, hypertension, and stroke [3]. This may be due to a non-atherosclerotic component (inflammation mediated) or an immune-mediated, systemic vasculitis [4]. A recent study has found an association between arterial stiffness, intima-media thickness, and early atherosclerosis in SLE [5]. Data also have shown that endothelial dysfunction, due to chronic vascular inflammation, may contribute to vascular stiffness and reduction in the elasticity of central arteries [6]. This increase in stiffness may act as a marker of early changes that predispose the artery to the development of major vascular disease. These changes include an increase in vascular wall stiffness or reduced arterial distensibility (AD) and an increase in arterial wall thickness as indexed by intima-media thickness (IMT). Although studies have focused on arterial stiffness, AD has only recently been described in SLE [5]. It is increasingly recognized that patients with SLE have high cardiovascular morbidity and mortality that cannot be entirely predicted by traditional risk factors [7].

Recent technical developments in high temporal and spatial resolution ultrasound have allowed noninvasive investigations of vascular structure and function by accurate and portable measurements of the arterial wall and lumen dimensions. Real time imaging is also relatively inexpensive and can be a hand carried noninvasive technique that can be widely used to determine AD and IMT. Nevertheless, reliable measurements of AD and IMT depend heavily on measurement variability, instrumentation, operator proficiency, appropriate and standard physical models, and careful interpretation. Improved axial spatial resolution (<0.10mm) is possible with a transmission frequency of 10MHz or greater. Accordingly, we applied this noninvasive, high resolution tool to determine AD and IMT values in SLE patients. Our purpose was to further investigate AD and IMT in SLE with an in vitro validated method and appropriate statistical power.

II.METHODS

A Sonosite 180Plus portable imaging system (Bothell, WA) equipped with L38/10-MHz linear array transducer was used to image (Figure 1) the right common carotid artery (CCA) ~1cm proximal to its bifurcation in 30 SLE patients (age, 39/11 years) and 16 age and gender matched controls (age, 35/11 years).

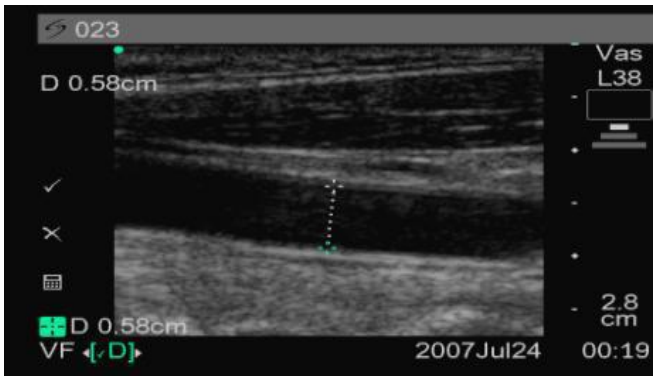

Figure 1. Frozen frame, two dimensional, long axis image of CCA used to locate subsequent M-mode measurements of arterial dimensions

As shown in Figure 2, we used high axial and temporal resolution M-mode imaging (~6ms) for accurate and precise measurements of the cyclic CCA diameters. Importantly, pre-requisite in vitro arterial phantom and interoperator variability studies documented the ~0.10 mm axial resolution and < 5% coefficient of variability of the technique. During the in vivo studies, the near and far walls of the interfaces defining the blood-intima-media boundaries were imaged [8]. For optimal quality control, images were printed and dimensions were measured with hand calipers by a single, blinded observer. Systolic (SD) and diastolic (DD) diameters of the carotid artery were measured from the proximal interface of the lumen and intima to the distal interface of the lumen intima during systole and diastole. All arterial measurements and concurrent tonometric radial artery blood pressures (SBP, DBP) were averaged over 3 cardiac cycles. Strain, stress, and AD were calculated using standard mathematical models [8]-[9]. Standard unpaired t tests were used to determine p values.

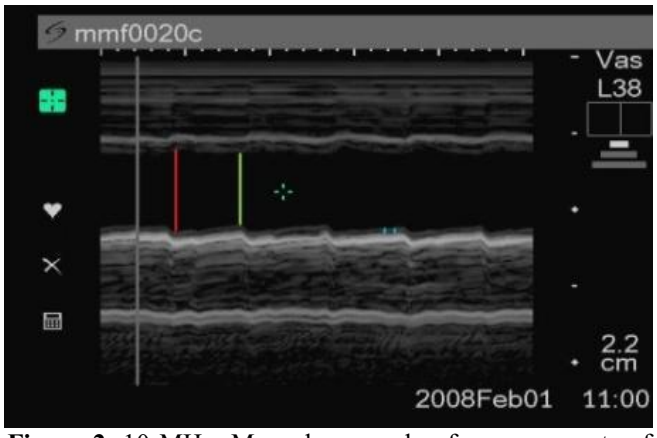

Figure 2. 10 MHz, M mode example of measurements of CCA systolic and diastolic diameters used for AD values

III.RESULTS

Technically adequate noninvasive measurements were made during supine rest in all 30 SLE patients and 16 controls. Results were given as means and standard deviations in Table. Importantly, there were no statistically significant differences in AD and IMT between SLE patients and age and gender matched controls. The possibility of a type 2 error (false negative) was <10%.

Variable	SLE	Controls	P
Age (years)	39 ± 11	35 ± 11	0.196
SBP (mmHg)	130 ± 20	117 ± 8	0.001
DBP(mmHg)	82 ± 11	74 ± 9	0.003
SD (mm)	6.01 ± 0.76	6.02 ± 0.60	0.949
DD (mm)	5.41 ± 0.68	5.45 ± 0.59	0.842
IMT (mm)	0.44 ± 0.08	0.41 ± 0.06	0.206
Strain (%)	11 ± 4	11 ± 4	0.976
AD (units)	3.10 ± 1.49	3.30 ± 1.63	0.692
Stiff (units)	19 ± 10	17± 11	0.569

Table. Means and standard deviations of measured and calculated variables with p values

V. DISCUSSION

Because SLE is a systemic disorder, subclinical cardiovascular disease may be manifested throughout the vascular system. By distinguishing the arterial distensibility of SLE compared to controls, we attempted to identify AD as either an accelerated risk factor for premature atherosclerosis and cardiovascular/cerebrovascular disease or as a manifestation of endothelial function induced by cytokines resulting from inflammation. Surprisingly, we found that AD is not significantly decreased in patients with SLE. A decrease in AD in the CCA has been associated with stroke and cardiovascular risk factors in other diseases such as hypertension, diabetes mellitus, hyperlipidemia, atherosclerosis, and myocardial infarction. Published values for AD in studies of atherosclerosis and angina patients and those at risk for stroke ranged from 4.72 ± 0.59 to 1.64 ± 1.03. Unfortunately, published values of AD vary considerably due to different algorithms for the AD calculations. Furthermore, most studies are without in vitro validation, limits of measurements, or statistical power analysis. Therefore, it is difficult to compare our data with the literature values for AD.

AD is a derived variable. There are numerous algorithms used to calculate this metric. One AD algorithm is represented as the inverse of stiffness (1/stiffness), and does not include IMT. In other clinical studies, AD is derived from changes in pulse pressure and systolic-diastolic diameter changes. These metrics do not include the percent

change associated with vessel deformation (strain) or IMT measurements. In describing the importance of deciding which algorithm to use, it is useful to explain the difference between the measurement of stiffness and arterial distensibility. Stiffness is a measurement of vessel tension and force between two points. Stiffness is directly related to the amount of force required to distend the vessel walls. AD may be a better in vivo measurement for assessing overall arterial mechanical dysfunction in living organisms. It is a function of the blood pressure and arterial wall thickness in relationship to the changes in vessel wall diameter. We chose the algorithm:

$$(AD) = (DD/IMT)/[\ln(SBP/DBP)/strain]$$

This model is adjusted for IMT and includes both systolic and diastolic diameters as well as blood pressure. All are statistically important risk factors in SLE.

AD reflects mechanical properties of the arterial wall and decreases with age. A reduction in arterial distensibility increases arterial impedance and leads to increases in cardiac afterload. Thus, a decrease in AD may result in alteration in cardiac structure, function, and cause increases in pulse pressure. The summation of these factors further complicates the overall cardiovascular risk profile in SLE. Our relatively young cohort of SLE patients may have yet to be impacted by this possible pathological mechanism.

Furthermore, we also did not find a statistically significant increase in intima-media thickness in SLE patients when compared to controls. Literature values for IMT (mm) in premenopausal women with SLE are reported in the range of 0.60-0.70mm. Our values were smaller. This difference may be due to variance in spatial resolutions or to the relative young age of our subjects. Previous studies often used 5MHz transducers and older patients. We used a 10 MHz transducer with double the spatial resolution (~0.10 mm). Clearly, this approach reduces the blurring of the acoustic interfaces.

Endothelial dysfunction has also been reported to correlate negatively with IMT. It is thought that reduced elasticity of the arterial walls (sclerosis) may be one of the earliest changes in the development of major cardiovascular disease in SLE. The rate of myocardial infarction in women with SLE (35 to 44 years of age) is ~50 times that of a comparative population. Our findings in relatively young SLE patients do not suggest that mechanisms related to inflammation have a significant association with vessel wall thickening (IMT) and elasticity (AD).

Both cohorts were premenopausal. It is known that development of cardiovascular disease is confounded by hormonal status and menopause. Literature values of IMT were also increased in postmenopausal women when compared to premenopausal women with SLE. It is for this reason that many studies stratify menopause in their major analysis.

A major advantage of this method of measuring human arterial mechanics is its convenience. The instrument is hand held, portable, and requires low power (<100 W). It also has an extended battery life and can be used anywhere from the bed side to fields studies. Operator training is required, but not extensive. The method is also relatively inexpensive and the noninvasive exams can be done in < 20 minutes. With proper transducer selection and technique, the instrument can be used for all standard, dynamic ultrasound medical imaging. If data on arterial mechanics were shown to be clinically useful and cost effective, this robustness and availability of equipment would allow easy and inexpensive measurements.

Our data does not rule out the possibility that with additional aging, a statistically significant and independent association between AD and SLE could occur. We also strongly suggest that because of the variability of sonographic measurements found in the literature, investigators should develop methods to reduce variance by improving scanning protocols, measurement technique, and quality control. Appropriate interoperator reproducibility and measurement precision can be achieved. Standardization of measurement technique and mechanical modeling are required. Our results suggest that larger, well powered studies are needed to accept AD and IMT as independent risk factors for cardiovascular disease that are associated with inflammatory processes in SLE.

IV. CONCLUSIONS

After careful validation with in vitro models, our data suggests that AD and IMT are not significantly different in relatively young patients with SLE and well matched controls. Larger, statistically powered, prospective studies on AD and IMT in SLE may find significant associations, but their prognostic and clinical implications may be limited.

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