Turk Gogus Kalp Dama 2016;24(1):20-26
doi: 10.5606/tgkdc.dergisi.2016.11749

Original Article / Özgün Makale

Systemic lupus erythematosus disease activity index is related with increased aortic stiffness and decreased left ventricular longitudinal strain as shown by two-dimensional speckle tracking echocardiography

İki boyutlu ekokardiyografide benek takibi analiz yöntemi ile gösterildiği gibi, sistemik lupus eritematozus hastalık aktivite indeksi artmış aort sertliği ve azalmış sol ventrikül boylamsal gerginlik ile ilişkilidir

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ABSTRACT

Background: This study aims to investigate whether the degree of stiffness of the aorta is increased and if this has a relationship with left ventricular global peak systolic longitudinal strain and disease activity index in patients with systemic lupus erythematosus.

Methods: Forty-three consecutive patients with systemic lupus erythematosus (8 males, 35 females; mean age 42±12 years; range 29 to 67 years) and 30 control subjects (7 males, 23 females; mean age 42±15 years; range 20 to 60 years) who were treated in our clinic between February 2014 and April 2014 were enrolled in the study. Aortic pulse wave velocity was measured by the carotid to femoral method. Aortic augmentation index was calculated as the ratio between the augmented pressure and the central pulse pressure. Global peak systolic longitudinal strain was calculated by averaging the strain values of the six segments in the apical four-chamber view.

Results: Global peak systolic longitudinal strain value was statistically significantly lower in systemic lupus erythematosus patients than the control group (–19±3.1 vs. –21±3.3, p=0.009, respectively). Left ventricular diastolic function which was assessed by E/e' was higher in patients with systemic lupus erythematosus (13±4.3 vs. 11±3.6, p=0.025). Values of aortic pulse pressure, aortic augmentation, aortic augmentation index, and pulse wave velocity were statistically significantly different between systemic lupus erythematosus patients and control group. Pulse wave velocity was negatively associated with global peak systolic longitudinal strain (β= –0.35, p=0.033) and positively correlated with systemic lupus erythematosus disease activity index (r=0.40, p=0.006) and E/e' (r=0.431, p=0.001). Systemic lupus erythematosus disease activity index was negatively correlated with global peak systolic longitudinal strain (r= –0.45, p=0.002).

Conclusion: This study indicates that disease activity score is significantly associated with aortic stiffness, global peak systolic longitudinal strain, and left ventricular diastolic function in patients with systemic lupus erythematosus. Patients with lower disease activity had lower pulse wave velocity and aortic augmentation, and higher global peak systolic longitudinal strain and E/e'.

Keywords: Aortic stiffness; diastolic function; global peak systolic longitudinal strain; pulse wave velocity; systemic lupus erythematosus.

ÖZ

Amaç: Bu çalışmada, sistemik lupus eritematozus hastalarında aort sertlik derecesinin artıp artmadığı ve bunun sol ventrikül global pik sistolik boylamsal gerginlik ve hastalık aktivite indeksi ile ilişkisi olup olmadığı araştırıldı.

Çalışma planı: Şubat 2014 - Nisan 2014 tarihleri arasında kliniğimizde tedavi edilen 43 ardışık sistemik lupus eritematozus hastası (8 erkek, 35 kadın; ort. yaş 42±12 yıl; dağılım 29-67 yıl) ve 30 kontrol deneği (7 erkek, 23 kadın; ort. yaş 42±15 yıl; dağılım 20-60 yıl) çalışmaya dahil edildi. Aortik nabız dalga hızı karotis-femoral yöntemi ile ölçüldü. Aortik artış indeksi basınçtaki artış ve santral nabız basıncı arasındaki oran olarak hesaplandı. Global pik sistolik boylamsal gerginlik apikal dört boşluk görüntülemedeki altı segmentin gerginlik değerlerinin ortalaması alınarak hesaplandı.

Bulgular: Global pik sistolik boylamsal gerginlik değeri sistemik lupus eritematozus hastalarında kontrol grubundan istatistiksel olarak anlamlı şekilde düşük idi (sırasıyla –19±3.1'e karşı –21±3.3, p=0.009). E/e' ile değerlendirilen sol ventrikül diyastolik fonksiyon sistemik lupus eritematozus hastalarında daha yüksek idi (13±4.3'e karşı 11±3.6, p=0.025). Aortik nabız basıncı, aortik artış, aortik artış indeksi ve nabız dalga hızı değerleri sistemik lupus eritematozus hastaları ve kontrol grubu arasında istatistiksel olarak anlamlı şekilde farklı idi. Nabız dalga hızı global pik sistolik boylamsal gerginlik ile negatif (β= –0.35, p=0.033), sistemik lupus eritematozus hastalık aktivite indeksi (r=0.40, p=0.006) ve E/e' ile pozitif ilişkili idi (r=0.431, p=0.001). Sistemik lupus eritematozus hastalık aktivite indeksi global pik sistolik boylamsal gerginlik ile negatif ilişkili idi (r= –0.45, p=0.002).

Sonuç: Bu çalışma sistemik lupus eritematozus hastalarında hastalık aktivite skorunun aort sertliği, global pik sistolik boylamsal gerginlik ve sol ventrikül diyastolik disfonksiyonu ile anlamlı olarak ilişkili olduğuna işaret etmektedir. Daha düşük hastalık aktivitesi olan hastalar daha düşük nabız dalga hızı ve aortik artışa ve daha yüksek global pik sistolik boylamsal gerginlik ve E/e'ye sahipti.

Anahtar sözcükler: Aort sertliği; diyastolik fonksiyon; global pik sistolik boylamsal gerginlik; nabız dalga hızı; sistemik lupus eritematozus

Available online at
www.tgkdc.dergisi.org
doi: 10.5606/tgkdc.dergisi.2016.11749
QR (Quick Response) Code

Received: March 19, 2015 *Accepted:* July 29, 2015

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Cardiac involvement is one of the major concerns in patients suffering from systemic lupus erythematosus (SLE), a multisystem, autoimmune disease. Several autoantibodies such as anti-phospholipid antibodies, anti-SSA/Ro antibodies, and anti-endothelial cell antibodies can directly affect the heart tissue. Also, epidemiological studies and autoptic investigations showed that an accelerated atherosclerotic process which may be triggered by autoantibodies is largely responsible for the increased cardiovascular events in patients with SLE.[1-3] In post-mortem studies, significant atherosclerosis was observed in more than 50% of deceased SLE patients regardless of the actual cause of death.[4] Nevertheless, atherosclerotic diseases are more prevalent in SLE patients than in general population and cardiovascular diseases have been recognized as risk factors for mortality.[5,6] Some studies have shown that the three most common traditional cardiovascular risk factors such as older age at diagnosis, hypercholesterolemia, and hypertension are also more predictive in SLE patients than in age- and sex-matched healthy subjects.[7,8]

Because accelerated atherosclerosis is considered an important cause of morbidity and mortality in patients with SLE, one of the recently accepted ultrasound-derived markers of early, asymptomatic atherosclerosis is increased arterial stiffness, as evidenced by increased pulse wave velocity (PWV) in the proximal aorta.[9] Arterial stiffness is commonly assessed with aortic PWV measurement, while peripheral pulse pressure is computed as the difference between systolic and diastolic blood pressure.[10] A more compliant central artery means greater percentage of stroke volume, whereas stiffer artery declares more of stroke volume passes down the arterial system with a more rapid PWV.[11] However, PWV may be considered an indirect measure of the biophysical properties of the aorta that occur at early stages of vascular disease which may predispose to major cardiovascular diseases. Augmentation index (AIx) is the result of the arterial wave reflection which represents the amount of afterload, and is considered as a predictor of vascular disease and arterial stiffness.[12]

Echocardiographic strain imaging is an innovative approach developed to assess the left ventricular myocardial mechanics. This novel echocardiographic approach has improved the assessment of myocardial regional and global systolic and diastolic function.[13]

In this study, we aimed to investigate whether the degree of stiffness of the aorta is increased and if this has a relationship with left ventricular global peak systolic longitudinal strain (GPSLS) and disease activity index in patients with SLE.

PATIENTS AND METHODS

We planned a study with 43 experimental subjects and 30 control subjects by using the Power and Sample Size Program. In this study, 43 consecutive patients (8 males, 35 females; mean age 42±12 years; range 20 to 67 years) with SLE were enrolled. All individuals met at least four of the American College of Rheumatology criteria for SLE.[14] Extensive screening for coronary artery diseases was undertaken in all patients. Among patients included in the study, 38 had normal cardiac stress test, three had normal myocardial perfusion single-photon emission computed tomography, and two had normal coronary angiogram. Patients with known peripheral arterial disease, coronary artery disease, angina pectoris, left bundle branch block in electrocardiogram (ECG), pericarditis, pulmonary hypertension, congestive heart failure, arrhythmia, and stroke were excluded. We also excluded the patients with other forms of autoimmune diseases. The Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLE disease activity index (SLEDAI) score was used to assess the disease activity in patients with SLE.[15,16] The control group consisted of thirty individuals (7 males, 23 females; mean age 42±15 years; range 20 to 60 years) without significant differences in age, sex or body surface area from the patients with SLE. Also, none of the patients had a history of dissection, previous cardiac surgery or clinical disorders known to compromise myocardial function such as diabetes mellitus, renal impairment, anemia, thyroid or liver disorder. In addition, smoking and excessive alcohol consumption were considered as exclusion criteria.

Echocardiography (echo) was performed using a Vivid 7 ultrasonographic machine (Vivid 7, GE Vingmed, Horten, Norway). The left ventricular ejection fraction (EF) was calculated by Simpson's biplane method of discs according to the American Society of Echocardiography.[17] Mitral annular peak systolic velocities (Sm) were assessed from above the mitral annular regions (septal and lateral) using tissue Doppler imaging (TDI). All conventional and strain data were acquired with a 2.5 or 3.5 MHz multiphased array probe and the images were digitally stored for offline analysis by means of the Echo Pack system with GE brand software (Vivid 7, General Electric Healthcare, Milwaukee, WI, USA). Two-dimensional speckle tracking analyses were performed on three consecutive

end-expiratory cardiac cycles using the high frame rate (69.8-147.7 frames/s) harmonic imaging of the left ventricle obtained in the apical four-chamber views. Acquired data of two-dimensional longitudinal strain was subsequently transferred to the computer for off-line analysis. Global peak systolic longitudinal strain was calculated by averaging the six regional values in the apical four-chamber.

Blood pressure was measured in supine position after a brief rest period of at least 10 minutes and pulse wave analysis was performed using a commercially available device (Sphygmo Cor, Pulse Wave Analysis System, At Cor Medical, Sydney, Australia) by a single investigator. The studies with an acceptable quality score (operator index >80%) were included in the analysis. The variability for duplicate measurements was <5%.

Aortic pulse wave velocity was measured by the carotid to femoral method. The time difference (t) between ECG R wave and the Doppler flow onset at right common carotid artery and common femoral artery was measured and the delay was computed. The distance from the suprasternal notch to the carotid measurement point was referred as 'D'. Pulse wave velocity was calculated as D/t. The radial pulse wave was generated after the acquisition of 20 to 30 reproducible sequential waveforms and central systolic, diastolic, and pulse pressures were calculated by using the generalized transfer function of the corresponding central aortic pressure waveform. The overall quality of the captured signal for all recordings were evaluated by an algorithm based on average pulse height, pulse height variation, diastolic variation, shape deviation, and maximum dP/dT included in the device. The difference between the peak systolic central pressure and the pressure at the onset of the reflected wave from the lower body was measured as time to reflection. The ratio between the augmented pressure and the central pulse pressure was referred as the aortic AIx and expressed as percent.

This study complied with the Declaration of Helsinki and was approved by the Local Ethical Committee in Kartal Kosuyolu Education and Research Hospital.

Statistical analysis

Statistical analyses were performed using SPSS for Windows version 15.0 software program (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± standard deviation for continuous variables and as proportions for categorical variables. A two-tailed $p<0.05$ was considered significant for all statistical analyses. Simple correlations were evaluated by Pearson's r correlation coefficients. Independent samples t test was used to test differences between groups. Linear regression analyses were performed to assess the independent association of aortic stiffness and wave reflections variables with strain parameters of left ventricular (LV) performance. Reproducibility of the measurements was assessed by calculating the intraclass correlation coefficients for absolute agreement and relative 95% confidence intervals.

RESULTS

There was no statistical difference between age, sex, weight, height, smoking, hypertension, and anti-hypertensive medication of patients with SLE and the control group. Demographic and clinical properties of both groups are shown in Table 1.

There were no significant differences between LV end diastolic volume and LV EF. However, absolute values of global circumferential strain, global radial

Table 1. Demographic and clinical properties of patients with systemic lupus erythematosus and control group

	SLE (n=43)			Control (n=30)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			42±12			41±15	0.653
Gender							
Female	35	81		23	76		0.628
Weight (kg)			70±11			74±11	0.431
Height (cm)			163±8.0			164±7.8	0.104
Hypertension	11	25		9	30		0.682
ACE inhibitor	2			2			
ACE inhibitor + diuretics	5			5			
Ca channel blockers	4			2			

SLE: Systemic lupus erythematosus; SD: Standard deviation; ACE: Angiotensin converting enzyme.

Table 2. Echocardiographic parameters of patients with systemic lupus erythematosus and control group

	SLE (n=43)	Control (n=30)	
	Mean±SD	Mean±SD	*p*
LVd (cm)	4.7±0.4	4.5±0.3	0.196
LVs (cm)	2.7±0.3	2.5±0.3	0.128
LVED volume (mL)	93±20	91±20	0.659
EF (%)	60±10	64±5.5	0.073
IVS (cm)	0.9±0.1	0.9±0.1	0.573
Posterior wall (cm)	0.8±0.1	0.8±0.1	0.675
Global CS (%)	–15±5.1	–20±3.6	0.001
Global RS (%)	40±19	51±15	0.015
Global LS (%)	–19±3.1	–21±3.3	0.009
E	82±18	91±13	0.030
A	73±17	71±14	0.479
E/e’	13±4.3	11±3.6	0.025
Sm lateral	9.4±2.0	12±2.2	0.001

SLE: Systemic lupus erythematosus; SD: Standard deviation; LVd: Left ventricle diastole; LVs: Left ventricle systole; LVED: Left ventricle end diastole; EF: Ejection fraction; CS: Circumferential strain; RS: Radial strain; LS: Longitudinal strain; Sm lateral: Peak systolic velocity at myocardial segments.

Table 3. Aortic stiffness parameters of patients with systemic lupus erythematosus and control group

	SLE (n=43)	Control (n=30)	
	Mean±SD	Mean±SD	*p*
Heart rate	71±15	77±9.5	0.054
Aorta SP	107±11	101±14	0.056
Aorta DP	68±9.1	65±7.1	0.166
Aorta MP	86±8.8	82±10	0.091
Aortic pulse pressure	43±11	37±12	0.028
PP amplification	134±18	151±23	0.001
Ejection duration	308±49	302±25	0.518
Radial SP	119±18	117±14	0.692
Radial DP	66±10	63±7.0	0.135
Radial MP	86±8.9	82±10	0.094
Radial pulse pressure	55±11	54±12	0.594
Aorta Tr	137±15	141±15	0.264
Aortic augmentation	11±6.6	6.9±8.0	0.013
AIX	25±11	15±17	0.005
PWV	10±2.9	8.4±2.0	0.014

SLE: Systemic lupus erythematosus; SD: Standard deviation; SP: Systolic pressure; DP: Diastolic pressure; MP: Mean arterial pressure; PP: Pulse pressure; Tr: Time to reflection; AIX: Aortic augmentation index; PWV: Pulse wave velocity.

strain, and GPSLS were significantly lower in SLE patients than the control group (–15±5.1 vs. –20±3.6, p=0.001; 40±19 vs. 51±15, p=0.015; –19±3.1 vs. –21±3.3, p=0.009, respectively). Also, Sm lateral with tissue Doppler echo was 9.4±2.0, whereas in the study population it was 12±2.2 (p=0.001). Left ventricular diastolic function was assessed by E/e’ and found higher in patients with SLE (13±4.3 vs. 11±3.6, p=0.025).

There were no statistically significant differences between heart rate, aortic and radial systolic and diastolic blood pressure, and mean pressure of patients with SLE and control group. However, aortic pulse pressure, aortic augmentation, AIx, and PWV were statistically significantly different between SLE patients and control group (Table 3).

Pulse wave velocity was negatively associated with GPSLS (β= –0.35, p=0.033). Also, PWV was positively correlated with SLE index (r=0.40, p=0.006) and E/e’ (r=0.431, p=0.001, Figure 1). Aortic augmentation was negatively correlated with GPSLS (r= –0.24, p=0.037) and positively correlated with E/e’ (r=0.23, p=0.046, Figure 2). Systemic lupus erythematosus index was negatively correlated with GPSLS (r= –0.45, p=0.002) and positively correlated with E/e’ (r= 0.42, p=0.005, Figure 3).

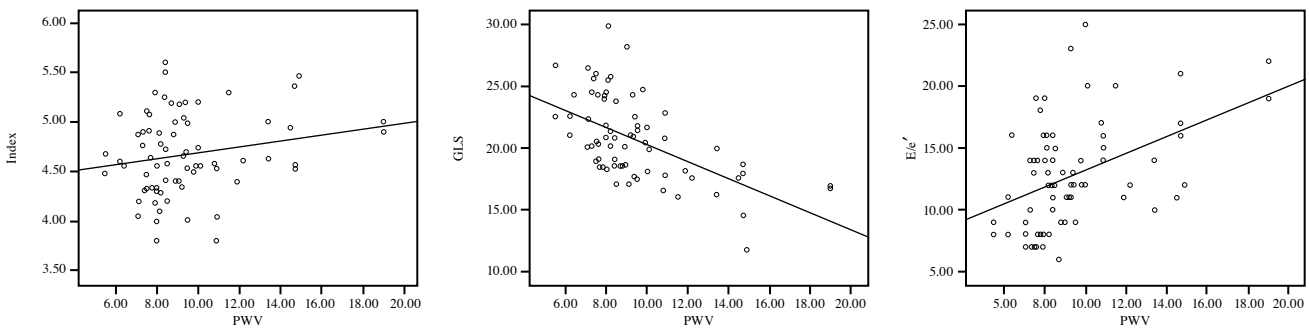

Figure 1. This figure shows that pulse wave velocity is associated with global peak systolic longitudinal strain and positively correlated with systemic lupus erythematosus index and E/e’.

GLS: Global longitudinal strain; PWV: Pulse wave velocity.

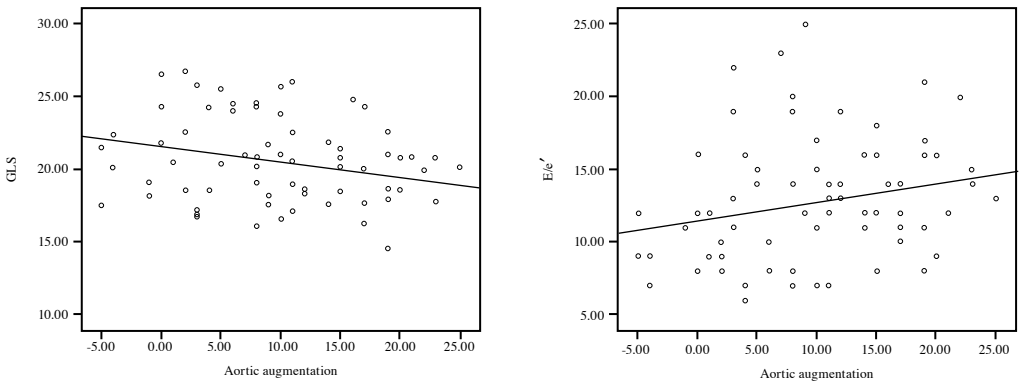

Figure 2. This figure shows that aortic augmentation is negatively correlated with global peak systolic longitudinal strain and positively correlated with left ventricular diastolic dysfunction.
GLS: Global longitudinal strain.

DISCUSSION

Systemic lupus erythematosus-specific variables were reported as independently associated with increased PWV in previous studies.[18,19] Increase in PWV seems to be caused by the presence of an accelerated atherosclerotic process, arising from the combination of traditional and lupus specific risk factors. Systemic lupus erythematosus is characterized by chronic vascular inflammation which may act as a contributing factor in the initiation or the progression of vascular stiffness. Potential stiffening mechanisms associated with increasing blood pressure include medial layer thickening, smooth muscle cell hypertrophy and hyperplasia, expansion of the extracellular matrix, and shifts in the collagen-to-elastin ratio.[20,21] There are several factors such as immune complexes associated with vascular function that may be the source of arterial injury. The mechanical vascular stimulation increases pulsatile shear and pressure, which causes vascular stiffening results in wide arterial pulse pressure. Ultimately, stiffened vessels become vulnerable to atherosclerosis and susceptible to increased lipoprotein and leukocyte permeability.[22,23]

To our knowledge, an association of aortic stiffness with LV functional parameters in patients with SLE has not been reported yet. Speckle tracking echo is a useful tool to quantify different components of complex cardiac motions such as longitudinal deformation. Using the speckle tracking method, our data demonstrated that SLE contributes to the impairment of systolic regional myocardial function. Also, it has been shown that arterial stiffness was related to the impairment of systolic function of the regional myocardium in hypertensive patients with normal EF. In this study, SLE patients with normal global EF as compared with controls had

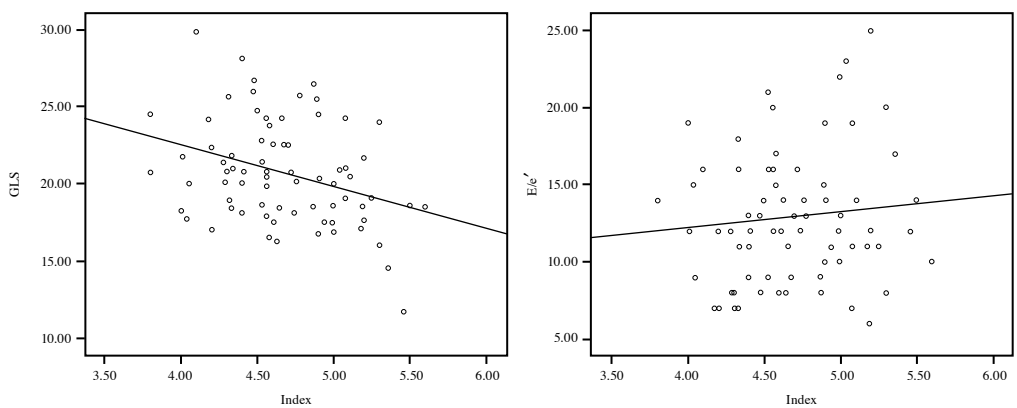

Figure 3. This figure shows that systemic lupus erythematosus index is negatively correlated with global peak systolic longitudinal strain and positively correlated with left ventricular diastolic dysfunction.
GLS: Global longitudinal strain.

a higher degree of PWV and aortic augmentation and a significant association between PWV and GPSLS was found. Also, we found that the PWV and aortic augmentation are positively correlated with SELENA-SLEDAI score which depicts to SLE disease severity. This result means that, as the disease activity accelerates, aorta stiffens and GPSLS -one of the most important markers of LV performance- decreases in patients with SLE. Because the subendocardium is more vulnerable to increased wall stress, ischemia, and interstitial fibrosis, longitudinal systolic dysfunction may already be seen at the early stages of progressive myocardial disease, including hypertrophy and myocardial ischemia.[24] Arterial stiffness increases the systolic load on the LV which predisposes to change in coronary perfusion patterns and reduction in LV systolic performance.[25] However, we did observe significant association between disease activity score, arterial stiffness, and GPSLS. Additionally, E/e' was correlated with the PWV, aortic augmentation, and the SELENA-SLEDAI score. In patients with SLE, subendocardium may be affected because of inflammation even at early stages which may lead to stiffness in large arteries with LV systolic and diastolic impairment.

There are several limitations of our study. First, our work may fail to show the effect of SLE specific factors and medical therapy on arterial stiffness. Second, we were unable to demonstrate the precise mechanism underlying the impairment of systolic function of the regional myocardium in patients with SLE. Third, sample size is small and further studies with larger SLE populations are required to assess the physiological principles of the problem and to move toward therapy.

In conclusion, our study suggests that the disease activity score is significantly associated with aortic stiffness, global peak systolic longitudinal strain, and left ventricular diastolic function in patients with systemic lupus erythematosus. Furthermore, patients with lower disease activity had lower pulse wave velocity and aortic augmentation, and higher global peak systolic longitudinal strain and E/e'.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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