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Abnormal Regional Myocardial Deformation Properties and Increased Aortic Stiffness in Normotensive Patients with Aortic Coarctation Despite Successful Correction: An ABPM, Standard Echocardiography and Strain Rate Imaging Study.

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ABSTRACT

The long-term follow-up data subsequent to a successful repair of aortic coarctation (AoC) show that life expectancy remains reduced. Previous standard echocardiographic studies demonstrated normal or increased systolic cardiac function in patients after successful repair of AoC. Strain rate (SR) imaging is a new technique able to detect subclinical myocardial abnormalities. We investigated whether young patients late after successful AoC repair, without hypertension, as assessed by ABPM and exercise test, already show abnormal myocardial deformation properties and their relationship with aortic stiffness. We studied 166 subjects: 83 AoC non-hypertensive patients (mean age 12±4 years) late after successful repair of AoC; 83 age-sex comparable subjects as controls. Peak systolic SR (1/sec) for both regional longitudinal and radial function was assessed. Aortic (AO) stiffness index was calculated from the echocardiographically derived thoracic AO diameters and the measurement of blood pressure obtained by cuff sphygmomanometry. Left ventricular (LV) ejection fraction was significantly increased in AoC patients, while regional longitudinal SRs were significantly reduced (SR: -1.1±0.9 vs –2±0.5, $p<0.0001$) in patients. Ao stiffness index was significantly increased in AoC patients (12±9, $p<0.0001$). At multilinear regression analysis, age at repair (p:0.005; Coeff.: -0.201; SE: 0.027) and aortic stiffness index (p=0.0029; Coeff.: 0.334; SE: 0.423), predicted longitudinal SR. Despite the presence of a successful repair for AoC, in absence of hypertension, longitudinal deformation properties are significantly impaired. Moreover, the degree of longitudinal SR impairment is correlated with age at repair and aortic stiffness. Early repair can delay the onset of hypertension in postcoarctectomy patients, but cannot prevent the innate structural and functional abnormalities of the aorta and their deleterious effect on myocardial deformation properties.

Key-words: Aortic coarctation; ventricular function; strain rate imaging.

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Introduction. The long-term follow-up data subsequent to a successful repair of aortic coarctation (AoC) show that life expectancy remains reduced in AoC patients [1-2]. Late arterial hypertension, more often systolic, which occurs in nearly one third of patients after repair, and atherosclerosis are the main determinants of cardiovascular events [1-3]. Coronary heart disease, stroke, sudden cardiac death, and heart failure account for the majority of premature deaths [1-3] , and prognosis is related to the age at intervention [1-3] . Other studies suggest that AoC might not be simply a mechanical obstruction of the aorta, but more likely a generalized disease of the cardiovascular system [4].

Despite this, previous studies based on standard echocardiography demonstrated normal or increased systolic cardiac function in patients after successful repair of AoC [5-9] . New tools, such as the ultrasonically derived strain rate (SR) imaging, have been added to our capabilities [10-11] and it is now possible to detect early subclinical myocardial abnormalities [12-17].The myocardial deformation properties in patients after AoC repair have not yet been described. We have sought to evaluate the myocardial deformation properties in normotensive AoC children late after successful repair and to assess their relationship with arterial stiffness.

Methods

Study Sample. We studied consecutive AoC patients regularly followed at our out-patient clinic from June 2003 to September 2006 without: 1. major associated cardiovascular abnormalities (such as ventricular septal defect and aortic and mitral valve functional abnormalities); 2. evidence of recoarctation (>20 mmHg pressure gradient at continuous Doppler in the aortic arch and the presence of a diastolic tail) [18-19]; 3. evidence of aortic aneurysm at the last outpatient visit, and 4. hypertension.

A patient was assumed to be “normotensive”, if: 1. he was without anti-hypertensive drug treatment, 2. showed systolic (SBP) and diastolic blood pressure (DBP) < 90° percentile for age, sex, and height at office measurements; 3. 24h-SBP and DBP were < 90° percentile for age, sex, and height, and 4. showed no hypertension during exercise.

If at least one of these signs were positive, the patient was classified to be “hypertensive” and excluded from the study.

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Control group. We also studied, by identical protocol, 83 age- and sex-comparable subjects without detectable cardiovascular risk factor. Volunteer controls were all recruited in Naples (Italy), were selected from our departments of pediatric cardiology among children investigated for dizziness, or minor orthostatic complaints, or for sport eligibility. None of the control subjects had family history of cardiomyopathy, cardiovascular structural or functional abnormalities or received any medication.

All studies were performed in accordance with the rules of the Ethical Committee, Second University of Naples. All parents gave their written informed consent to participate in the study.

Clinical Assessment. During a one-day stay, anamnestic and anthropometric data were reviewed. Resting BP was measured at all extremities by an automatic oscillometric cuff device (Dinamap, Critikon Inc., Tampa, FL, USA).

Ambulatory Blood Pressure Measurements. The 24-h ambulatory blood pressure (BP) was measured on the right arm (Space Labs Inc., Issaquah, WA, USA). BP measurements were recorded automatically every 15 min from 8:00 a.m. to 20:00 p.m. and every 30 min from 20:00 p.m. to 8:00 a.m.. BP studies were excluded if there was an interval of 2 h of invalid or absent measurements. Hypertension at ABPM was defined as 24 hSBP or 24h-DBP over the 90th percentile of the reference values provided by Soergel et al. (20). To allow interpretation of data, by ABPM normative data [20] only patients with a height between 115 and 185 cm were included.

Exercise test. An exercise test was performed on a bicycle in a sitting position according to international guidelines [21]. The WHO protocol was used starting with 25 Watt and increasing work load by 25 Watt every 2 minutes [22] . ECG was monitored continuously; blood pressure was measured manually every 2 minutes.
Hypertension during exercise was present when the peak systolic blood pressure [mmHg] was more than 2 SD above the age and work load dependent reference value [23]:

$$\text{mean} \pm 2 \cdot SD = [111.2 + (0.310 \cdot \text{age [years]})] + (0.334 \cdot \text{work rate [Watt]}) \pm 2 \cdot 17.9$$

Standard Echocardiographic Evaluation. Echocardiography measurements were taken with a System Seven (GE, Norway).

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In this studies 2 echocardiographers were involved. All the echocardiographic examinations were performed by the same observer (echocardiographer 1). All the echo measurements were performed off-line on digitally stored raw data by another investigator (echocardiographer 2) who was blind to the clinical status of the studied subjects. The ascending aorta and the aortic arch were visualized by means of high, long axis view and suprasternal view. Left ventricular measurements were taken from two-dimensional guided M-mode tracings.

Parameters measured by echocardiography were pressure gradient throughout the former coarctation region and the left ventricular and aortic morphology. Left ventricular mass indexed for height $^{2.7}$ (LVMI) was calculated [24]. LV end-diastolic and end-systolic volumes and the LVEF at rest were computed from apical 4 and 2 chamber views, using a modified Simpson's biplane method. Each representative value was obtained from the average of three measurements. The endocardial mean velocity of circumferential fiber shortening corrected for the heart rate (VCFc) and end systolic circumferential stress [25] were calculated.

To assess global LV and right ventricular (RV) longitudinal function, from the standard apical view, the atrioventricular ring displacement was measured for the septal and lateral mitral ring (MAPSE) and lateral tricuspid ring (TAPSE) by conventional M-mode methods.

Using pulsed-wave Doppler, mitral inflow velocities, peak early diastolic velocity (E), peak late diastolic velocity (A), E/A ratio, E deceleration time (DT), A duration, and isovolumic relaxation time (IVRT) were measured.

Echocardiography of the Aorta. Thoracic aortic diameters (mm/m^2) were measured 3 cm above the aortic valve by two dimensional guided M-mode transthoracic echocardiography of the aortic root at left parasternal long-axis view. Aortic systolic diameter (AoS) was measured at the time of full opening of the aortic valve, and diastolic diameter (AoD) at the peak of the QRS complex at the simultaneous electrocardiogram recording. Aortic stiffness index was calculated as follows:

$$(\ln(SBP/DBP) \times (AoS-AoD)/AoD \quad [26].$$

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Color Doppler Myocardial Imaging Study (CDMI). CDMI data to assess longitudinal function were recorded from the interventricular septal and the left ventricular (LV) lateral walls from standard apical view.

Radial function for the LV posterior wall was recorded using parasternal long axis view. All data were acquired at a frame rate of 200±15 frames/s (GE Vingmed System Seven; 3.5 MHz). This frame rate was necessary to resolve cardiac mechanical events and to average out the influence of any random noise in the Doppler velocity signal. An appropriate velocity scale was chosen in order to avoid CDMI data aliasing. The narrowest image sector angle possible (usually 30°) was used to achieve the maximum color Doppler frame rate possible. For apical views, care was taken to maintain each wall in the center of the ultrasound sector in an attempt to align at as near as possible to the direction of longitudinal motion. For parasternal long axis view, care was paid to keeping the posterior LV wall perpendicular to the ultrasound beam in order to be aligned as near as possible to radial motion.

As breath holding is not feasible in young patients data from 3 consecutive cardiac cycles (to be used for subsequent analysis) were recorded during normal quiet respiration.

CDMI data were stored in digital format and transferred to a computer workstation for the off-line analysis of regional SR curves. This was carried out using dedicated software (GE Workstation). Longitudinal SR's were estimated by measuring the spatial velocity gradient over a computation area of 10 mm. LV regional longitudinal function was evaluated on the apical, mid and basal segments of septal and lateral LV walls. We chose those LV walls because we had the best alignment with the ultrasound beam.

LV radial SR's were estimated using a computation area of 5 mm, from the mid segment of the LV posterior wall.

To derive SR profiles from the different segments, the region of interest was maintained in a constant position within the segment being interrogated by using a semi-automatic tracking algorithm.

The timing of ventricular ejection and relaxation was obtained using an anatomic grey scale M-mode cursor positioned visually in the underlying grey scale data set. The timing of these events was measured by placing the cursor at the level of aortic cusps,

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and mitral valve. From the averaged SR data, peak systolic SR was measured. We decide to measure only SR because this is the less-load dependent contractility index obtained by CDMI data [27-28].

Pulsed-wave tissue Doppler of the septal annulus was used for the measurement of early peak diastolic mitral annular velocity (e'). The E/e' ratio was calculated.

Statistical Analysis. All the analyses were performed using a commercially available package (SPSS , Rel 11.0 2002. Chicago: SPSS inc).
Data are presented as the mean value ± SD. The normality Kolmogorov-Smirnov test was performed to determine whether continuous variables were normally distributed. Age at the time of repair, which presented a skewed distribution, is presented as the median value (range). Qualitative data were compared using Mantel-Haenszel' s test. Continuous variables were compared using paired t-test and Wilcoxon matched pairs test. The correlations were studied by linear regression analysis. In addition, to identify significant predictors of average LV peak systolic SR in AoC patients, their individual association with clinical relevant variables was assessed by multiple regression analyses. The following variables were included into the analysis: clinical data (age, age at repair, 24h-systolic blood pressure) and echocardiographic-Doppler indexes (LVMI, aortic stiffness index, E wave-DT, A wave duration, E\e'). These variables were selected according to results of univariate analysis and to their clinical relevance and potential impact on prognosis, as shown by earlier studies [1-9]. The assumption of linearity was checked graphically by studying the smoothed martingal residuals from the null model plotted against the covariate variables. The linearity assumptions were satisfied. The Hosmer-Lemeshow goodness of fit test was used to check that the model adequately fit the data. Model was cross validated by the bootstrap technique (200 runs) [29].
The null hypothesis was rejected for a p value <0.01.

Reproducibility between the 2 echocardiographers was determined in 60 randomly selected subjects (30 patients and 30 controls). Inter- and intraobserver variability was examined by using both Pearson's bivariate two-tailed correlations and Bland-Altman analysis. Relation coefficients, ninety-five percent confidence limits and percent errors were reported.

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Results

In this study 83 AoC normotensive patients were included, of these, 45% had a bicuspid aortic valve without significant functional abnormalities (only trivial to mild aortic regurgitation, or peak pressure gradient at continuous Doppler < 20 mmHg). AoC repair had been performed at a median age of 4 months (range 0.1 to 156 months), with 58% of subjects undergoing surgery within the 4 months of life (mean age 12 ± 4 years, male 70%). All were in the typical juxtaductal position. Repair was by end-to-end anastomosis in 48% of patients, by subclavian flap in 13%, by patch angioplasty in 16%, and by primary percutaneous stent implantation in 19%. The median time from coarctation repair to the study was 100 months (range 16 to 216 months).
Clinical characteristics of the study sample are shown in Table 1.

Standard echocardiographic study (Table 2) demonstrated an increased wall thickness and a significant increase in LVMI in AoC patients. LV ejection fraction, VCFc, were significantly increased in AoC patients. End systolic stress was significantly reduced in AoC patients (Table 2).
Among the studied diastolic parameters, E wave, DT, and A wave duration were significantly prolonged in AoC patients. The E\e' ratio was significantly increased in patients.

The stiffness of the aortic wall as assessed by aortic stiffness index was significantly increased in patients ($p<0.0001$).

Radial peak systolic SR was significantly increased in AoC patients (Table 3), while regional longitudinal peak systolic SRs were significantly reduced in AoC patients (Table 3). Among AoC patients, 16 (19%) were outside the 95% lower confidence limits in the normal group.

Patients surgically treated showed a LV EF of 72 ± 8%, a MAPSE-septal wall of 13±3mm, a LVMI of 47±17 g/m $^{2.7}$,and an average peak systolic longitudinal SR of 1.4±0.5 1\s. AoC patients who underwent primary stent implantation showed LV EF of 74 ± 7%, a MAPSE-septal wall of 13±5 mm, a LVMI of 55±16 g/m $^{2.7}$, and an average peak systolic longitudinal SR of 1.5±0.6 1\s.

Determinans of Diastolic Function.

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E\A was significantly correlated with age at repair (p:0.004; r: -45), LVMI (p:0.001; r: -36), and 24h-DBP (p:0.002; r: -48). E\e' was significantly correlated with age at surgery (p:0.003; r: -34), LVMI (p:0.004; r: -33), and aortic stiffness index (p:0.001; r: -55).

Determinans of Myocardial Deformation Properties.

At univariate analysis, average peak systolic longitudinal SR showed a significant correlation with age at repair (r^2: 0.68; $p< 0.001$), age (r^2: 0.13; $p<0.001$), LVMI (r^2: 0.20; $p<0.001$), aortic stiffness index (r^2: 0.61; $p<0.001$, and 24h-SBP (r^2: 0.15; $p<0.001$) (Figure 1).

At multilinear regression analysis, the only independent predictors of LV average peak systolic longitudinal SR were age at correction (p: 0.005; Coeff.: -0.201; SE: 0.027) and aortic stiffness index (p=0.0029; Coeff.: 0.334; SE: 0.423).

Reproducibility. Pearson's correlations: Peak systolic SR: $r = 0.88$, $p = 0.0001$; Peak systolic S: $r = 0.92$, $p = 0.00001$. Bland–Altman analysis: Peak systolic SR (95% CI+3.1, per cent error 3.5%); Peak systolic S (95% CI+2.5, per cent error 2.3%).

Discussion

To the best of our knowledge, this is the first published study of SR imaging in AoC patients. Regional longitudinal systolic myocardial deformations are significantly reduced in a large sample of AoC young patients, despite a successful correction and in presence of a (super) normal LV ejection fraction and an increased VCFc/stress. The degree of this impairment is significantly related with age at correction and aortic stiffness.

Left Ventricular Function in AoC Patients: Increased systolic function and enhanced standard echocardiographic indexes of contractility have been reported in patients after successful repair of AoC during childhood [5-8], a group known to have an increased incidence of LV hypertrophy, systemic hypertension, and a significant late mortality risk [1-4]. However, the mechanism underlying this apparent persistent elevation of myocardial contractility is difficult to explain. Chronic ventricular hypertrophy is known to be associated with contractile dysfunction [30-33], thus the enhanced myocardial contractility found in AoC patients may be artifactual [34] . Indeed, all those studies [5-9] suggesting elevation of myocardial contractility after successful

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repair of AoC are in contrast with results of both animal models - with experimentally induced pressure overload [35-37] - and studies on humans with hypertension [38-39]. In those studies LV hypertrophy is commonly associated with a gradual deterioration of LV function and contractility.

Most of the previous studies assessing myocardial contractility in AoC patients used endocardial stress-velocity indexes which can overestimate myocardial performance and contractility, especially in hypertrophied hearts [27;29;31; 39-40].
This misrepresentation of fiber mechanics by those standard echocardiographic derived indexes has been found to be clinically important in subjects with LV hypertrophy caused by systemic hypertension [30;32;34;39-40] resulting in a failure to recognize depressed fiber shortening.

Other studies using midwall index of contractility, thus providing a physiological correction, still showed evidence of an unexplained hypercontractile state in AoC patients [34]. However, it has been demonstrated that midwall stress-velocity relationship at low afterload has a similar behavior to the endocardial stress–velocity relationship [39].

Myocardial Deformation Properties in AoC patients. Using for the first time peak systolic SR we demonstrated the presence of an abnormal longitudinal systolic function in AoC patients. SR is a new parameter recently proposed as a strong index of LV contractility [27-28]. In several studies the new ultrasonic derived deformation indexes demonstrated a higher ability than standard echocardiography to unmask preclinical systolic abnormalities [12-17]. In hypertensive patients with apparently normal systolic function, and in presence of a normal diastolic function, the application of SR imaging demonstrated the presence of a preclinical LV systolic abnormalities [13-17].

Of note, in our study abnormal systolic function was detected studying myocardial deformation along the longitudinal axis, while myocardial deformation properties along the radial axis were increased. Indeed, peak systolic radial SR is expression of midwall fiber contraction and in presence of low afterload has a similar behavior to the endocardial stress–velocity relationship, showing evidence of an unexplained hypercontractile state in AoC patients [40].

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This is in agreement with a recent report demonstrating increased midwall fractional shortening and decreased longitudinal shortening in 15 AoC patients late after successful correction, using magnetic resonance imaging [40].

In our study sample endocardial end systolic stress, index of afterload [4], was reduced. This finding is not surprising and is in agreement with previous studies [4,7] . In a mathematical model [10], keeping normal myocardial contractility and reducing afterload, SR increased. Conversely in our study, longitudinal peak systolic SR was significantly reduced even in presence of a reduced end-systolic stress, suggesting an impairment in myocardial longitudinal function. This finding may explain, at least in part, the reduced exercise duration in AoC patients compared to controls (Table 1).

Aortic stiffness in AoC patients. Aortic stiffness index was significantly increased in AoC patients in agreement with previous studies demonstrating abnormalities in vascular structure and function in patients after successful decoarctectomy.

These abnormalities are more frequently found in the precoarctation aorta and proximal arteries even in patients after early and successful repair [18; 41-42].

In our study, longitudinal deformation impairment was significantly correlated with the age at correction and aortic stiffness index .

These findings suggest that although early repair has a beneficial effect, it cannot change the innate structural and functional abnormalities of the proximal aorta and their deleterious effect on myocardial function [42].

Indeed, despite early repair the estimated survival in postedecoarctectomy patients is still reduced with 80% of the surgical patients alive at 40-50 years after surgery [1; 43].

Study Limitations. This study carries some limitations: 1- Patient sample: We included in our study also AoC patients in medical treatment but this corresponds to the usual clinical situation encountered in hospital practice. However, we excluded patients under beta blockers to avoid any effect of drugs on myocardial contractility. 2- Echo study: The usual limitations inherent in the angle dependency of all echocardiographic Doppler techniques also apply to ultrasound derived SR imaging. In this study, care was taken to always align the ultrasound beam with the direction of myocardial deformation to be interrogated and we included in the study only the walls with the best alignment.

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Clinical implications. Our findings have potential implications for management strategies aimed at reducing late morbidity and mortality in this high-risk group. Aortic coarctation is associated with reduced life expectancy and increased morbid events even after successful repair. Aortic stiffness is increased in postcoarctectomy patients and myocardial deformation properties are significantly influenced by age at repair and aortic stiffness index. The current data suggest to correct AoC early and to consider the use of drugs able to improve aortic stiffness in postcoarctectomy patients, independently of blood pressure values.

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Table 1. General Characteristics of Studied Sample.

	AoC Patients (n=83)	Controls (n=83)	P Value
Age (years)	12± 4	12± 4	0.9
Male (%)	70	70	0.9
BSA	1.2±0.3	1.2±0.3	0.9
SBP (mmHg)	118± 17	115± 10	0.15
DBP (mmHg)	66± 9	65± 6	0.38
24h-SBP (mmHg)	114± 10	111± 12	0.0001
24h-DBP (mmHg)	66± 6	64± 10	0.10
Resting Heart rate (bpm)	85 ± 8	85 ± 5	0.9
Peak exercise SBP (mmHg)	156±16	140±16	0.0001
Exercise Duration (min)	9±3	11±3	0.0001

SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

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Table 2. Standard Echocardiographic Characteristics of Studied Sample.

	AoC Patients (n=83)	Controls (n=83)	P Value
IVS end-diastole (mm)	11±2	7±2	<0.0001
LV end-diastole (mm)	40±7	40±7	0.9
LVPW end-diastole (mm)	9±2	7±2	<0.0001
LV ejection fraction (%)	68±8	64±7	0.0001
LVMI ($g/m^{2.7}$)	49± 20	33± 14	<0.0001
VCFc (circ/sec)	1.3±0.2	1.1±0.2	<0.0001
End Systolic Stress (g/cm^2)	38±14	46±12	0.001
MAPSE-septal wall (mm)	12±5	13±3	0.05
MAPSE-lateral wall (mm)	12±4	15±6	0.11
TAPSE (mm)	24±5	22±6	0.14
E/A	1.8± 0.6	1.7±0.1	0.06
E-DT (msec)	239 ± 57	150 ± 15	<0.0001
A duration (msec)	97 ± 22	86 ± 17	0.001
E/e’	7 ± 2	5 ± 1	<0.0001
IVRT (msec)	48± 19	50±16	0.36
Aortic stiffness index	12±9	6±4	<0.0001

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Table 2 legend. IVSd: interventricular septum; LV: left ventricle; PW: posterior wall; VCFc: velocity of circumferential fiber shortening corrected for the heart rate. MAPSE: Mitral annulus peak systolic excursion; TAPSE: Tricuspid annulus peak systolic excursion.E-DT: E wave deceleration time; IVRT: Isovolumic relaxation time. E\A: ratio between early (E) and late (A) transmitral peak diastolic velocities. E\e': ratio between peak early transmitral diastolic velocity (E) and peak early diastolic mitral annular velocity (e').

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Table 3. Peak Systolic Strain Rate (1/s) Values of the Studied Sample.

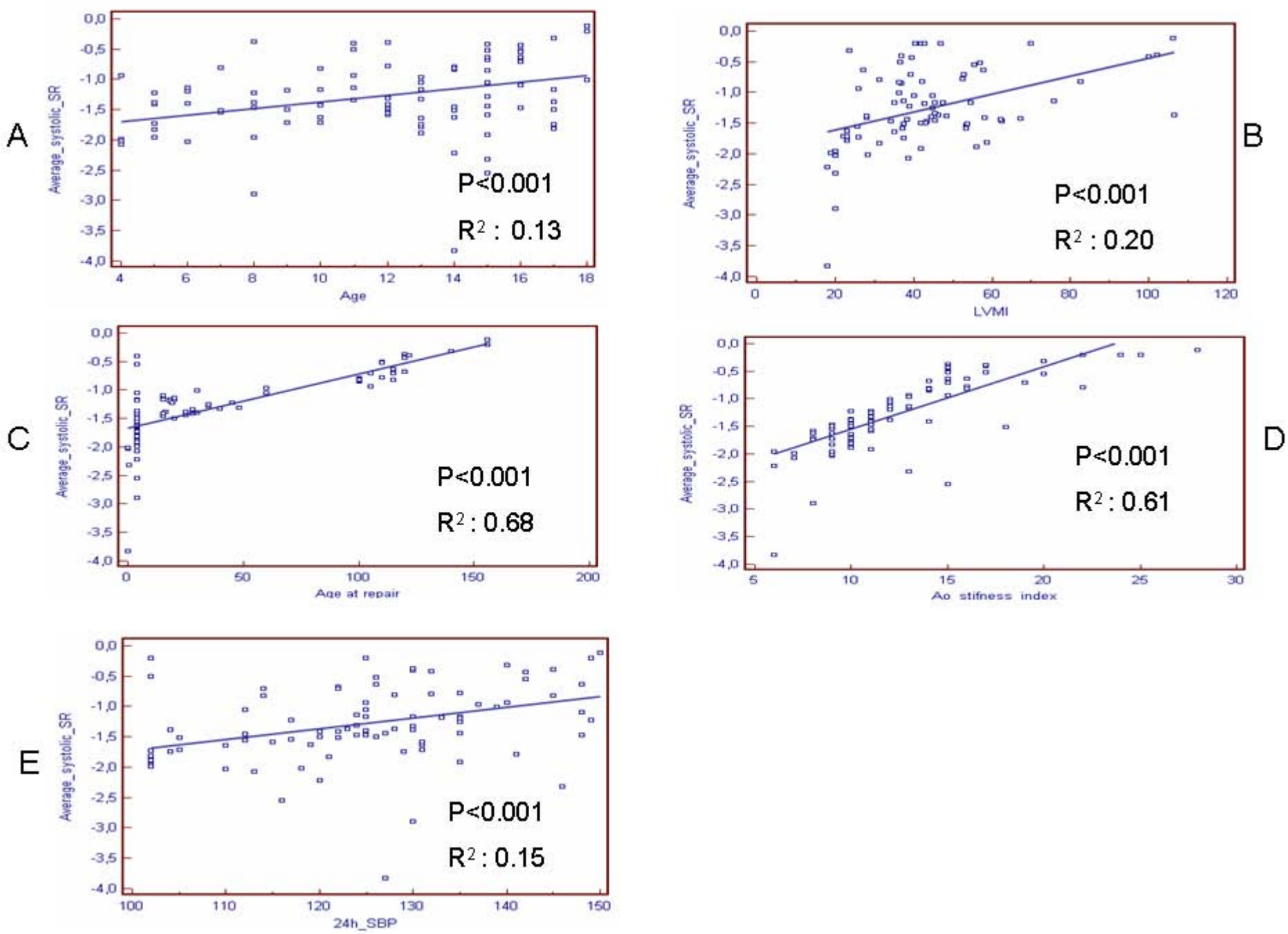
	AoC Patients (n=83)	Controls (n=83)	P Value
Posterior Wall			
Parasternal Short Axis View	3.1 ± 0.7	2.8± 0.5	0.001
Parasternal Long Axis View	3.2 ± 0.6	2.7± 0.5	0.001
Apical 4 Chamber View			
Basal Septum	-1.1± 0.9	-2± 0.5	<0.0001
Mid Septum	-1.2± 0.5	-1.9± 0.4	<0.0001
Apical Septum	-1.3± 0.7	-2.1± 0.7	<0.0001
Basal LV Lateral Wall	-1.4± 0.7	-1.9± 0.7	0.001
Mid LV Lateral Wall	-1.3± 0.6	-1.9± 0.5	0.001
Apical LV Lateral Wall	-1.6± 0.6	-2.0± 0.6	0.001

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Figure legend.

Figure 1. Linear regression between: **A** average peak systolic longitudinal strain rate (SR) and age (years); **B** average peak systolic longitudinal strain rate (SR) and left ventricular mass/ height 2.7; **C** average peak systolic longitudinal strain rate (SR) and age at repair (months); **D** average peak systolic longitudinal strain rate (SR) and aortic stifness; **E** average peak systolic longitudinal strain rate (SR) and 24h systolic blood pressure (24h-SBP).

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