Vascular Function and Myocardial Performance Indices in Children Born Small for Gestational Age

Maria Felicia Faienza, MD; Giacomina Brunetti, PhD; Maurizio Delvecchio, MD, PhD;
Annapaola Zito, MD; Fabrizia De Palma, MD; Francesca Cortese, MD; Adriana Nitti, MD;
Elena Massari, MD; Michele Gesualdo, MD; Gabriella Ricci, MD; Santa Carbonara, MD;
Paola Giordano, MD; Luciano Cavallo, MD; Pietro Scicchitano, MD; Marco Matteo Ciccone, MD

Background: Small-for-gestational-age (SGA) children have increased cardiovascular risk, but the mediating factors are poorly understood. We hypothesized that birth size could affect the cardiovascular system since childhood in the absence of other risk factors. We investigated endothelial and myocardial function in SGA children with regular catch-up growth.

Methods and Results: Biochemical markers, blood pressure, flow-mediated vasodilation (FMD), common carotid intima-media thickness (cIMT), anteroposterior diameter of the infrarenal abdominal aorta (APAO) and echocardiographic parameters of left and right ventricular (LV and RV) function were studied in 27 SGA and 25 appropriate-for-gestational-age (AGA) subjects. SGA subjects had a higher homeostasis model assessment index than controls (2.61 ± 1.27 vs. 1.56 ± 0.40 , $P=0.01$), higher cIMT (0.51 ± 0.04 mm vs. 0.45 ± 0.07 mm, $P=0.007$) and APAO (1.31 ± 1.35 cm vs. 1.30 ± 0.16 cm, $P=0.005$), and lower FMD ($10.11 \pm 4.17\%$ vs. 12.34 ± 4.28 , $P=0.04$) than controls. On echocardiography SGA had higher Tei index both at LV and RV than controls ($P=0.001$). Reduced RV systolic function was also observed in SGA subjects.

Conclusions: SGA subjects had vascular morphological and function abnormalities compared with AGA, which increase their cardiovascular risk profile. Furthermore, a subtle cardiac alteration in both RV and LV functions was seen in SGA patients compared with AGA. (*Circ J* 2016; **80**: 958–963)

Key Words: Anteroposterior diameter; Carotid intima-media thickness; Flow-mediated vasodilation; Infrarenal abdominal aorta; Small for gestational age

Small for gestational age (SGA) is a condition that affects approximately 3–10% of newborns whose birth weight and/or length are at least 2 SD below the mean for gestational age.¹ Most SGA children have catch-up growth during the first 2–4 years of life, but approximately 15% of them continue to be short throughout childhood, adolescence and adulthood.² Children born SGA have an increased risk of developing permanent metabolic changes as a consequence of intra-uterine reprogramming, which lead to increased cardiovascular (CV) risk, excess abdominal fat and type 2 diabetes in adulthood.^{3,4} Additionally, low birth weight combined with rapid postnatal growth appears to be associated with impaired glucose tolerance,⁵ obesity⁵ and non-alcoholic fatty liver disease,^{6,7} whereas rapid growth after 2 years of age may increase the risk for CV disease (CVD).⁸ In particular, childhood weight

gain rather than birth size seems to affect both blood pressure and common carotid intima-media thickness (cIMT) in young adults.^{9–11}

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Increased vascular IMT has been demonstrated in SGA aged 3–6 years,¹² irrespective of the presence or absence of prenatal risk factors for intrauterine growth restriction.¹³

Furthermore, early endothelial dysfunction has been demonstrated in young adults born with low birth weight, particularly in those who did not have other CV risk factors.¹⁴

These findings support the hypothesis that the CV alterations in children born SGA are due to fetal CV reprogramming rather than to prenatal and postnatal risk factors. Therefore,

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Department of Biomedical Sciences and Human Oncology, Section of Pediatrics (M.F.F., M.D., F.D.P., A.N., P.G., L.C.), Department of Basic and Medical Sciences, Neurosciences and Sense Organs, Section of Human Anatomy and Histology (G.B.), Cardiovascular Diseases Section, Department of Emergency and Organ Transplantation (A.Z., F.C., M.G., G.R., S.C., M.M.C.), University “A. Moro”, Bari; Department of Pediatric Cardiology, Giovanni XXIII Pediatric Hospital, Bari (E.M.); and Cardiology Unit, Hospital “F. Perinei”, Bari (P.S.), Italy

Mailing address: Maria Felicia Faienza, MD, Department of Biomedical Science and Human Oncology, Section of Pediatrics, University “Aldo Moro” Bari, Piazza G. Cesare, 11, 70124 Bari, Italy. E-mail mariafelicia.faienza@uniba.it

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subjects born SGA could develop early impairment in vascular morphology and function. One more interesting question is whether SGA children are at increased risk for myocardial function alterations, a subtle cardiomyopathy whose future evolution is still unknown. The literature contains contrasting results: some authors reported altered cardiac performance in SGA individuals as compared with subjects born appropriate for gestational age (AGA),^{15–17} while others found no influence of low birth length and/or weight on future development of early cardiac dysfunction.^{18,19}

We hypothesized that birth size could affect the CV system since childhood in the absence of other risk factors. We therefore investigated endothelial and myocardial function by evaluating cIMT, flow-mediated dilatation (FMD) of brachial artery, anteroposterior diameter of infra-renal abdominal aorta (APAO) and echocardiographic tissue Doppler imaging (TDI) markers in a group of children born SGA with regular catch-up growth within the first year of life.

Methods

Patients

Twenty-seven children (15 male; mean age, 10.03±3.0 years) out of 30 meeting the inclusion criteria agreed to participate to this study. All children were born at term at the Neonatology Unit at University “Aldo Moro” Bari, Italy, and were classified as SGA (birth weight and/or length <3rd percentile for gestational age).²⁰ In particular, 11 subjects were SGA for weight, 13 for weight and length and the remaining 3 only for length. They were followed up for the first 4 years of life at the Pediatric Endocrinology Unit according to established follow-up in SGA subjects. Between January and September 2014, they were invited by telephone to participate in the study. All subjects had weight gain equally distributed in the first 6 months of life and continued to have regular growth during the first year of life. Catch-up growth was defined as attainment of height centile within the midparental height range.²¹

Medical and family history was obtained from all subjects. Exclusion criteria were renal, liver and/or CVD, hypertension, metabolic and/or endocrine disorders, genetic syndromes, history of chronic allergy, and acute infectious or inflammatory disease during the 3 months preceding the study. Physical examination, including anthropometric parameters (height, weight, body mass index-standard deviation score; BMI-SDS) using Italian growth charts,²² and assessment of pubertal stage according to Tanner criteria were performed.²³ Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in all patients from the right brachial artery using a mercury gauge in the supine position prior to examination after resting for a minimum of 5 min.

The control group consisted of 25 healthy children born at term and AGA (birth weight >−2 SDS and <+2 SDS), matched for age, gender and BMI-SDS. The control group was recruited on a voluntary basis in the outpatient clinic and consisted of children referred to hospital for minor surgery or electrocardiography for minor trauma to head, limbs, or chest pain. All subjects were in good general health and were not taking drugs in the last 3 months.

Written informed consent was obtained from the children's parents. All procedures were in accordance with the guidelines of the Helsinki Declaration on Human Experimentation and were approved by the local ethics committee.

Biochemistry

Blood glucose, insulin, total cholesterol (TC), high-density

lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) were measured after overnight fasting in all subjects.

TC, LDL-C, HDL-C and TG within the 5th and the 95th percentiles were defined as normal.²⁴ Insulin resistance (IR) was measured using the homeostasis model assessment (HOMA) index, calculated as insulin (μU/ml)×blood glucose (mmol/L)/22.5.²⁵ IR was defined as HOMA-IR >2.5.²⁵

Ultrasonography

SGA children and controls underwent high-definition vascular and cardiac ultrasound assessment according to the following protocols in order to identify arteries with early atherosclerotic lesions and/or early signs of cardiac function impairment.

cIMT Ultrasonographic echo-color Doppler study of left and right common carotid arteries was performed bilaterally by the same physician with a Philips Sonos 5500 using a 7.5-MHz high-resolution probe. The patients were placed in the supine position, with the neck extended and rotated contralaterally by 45°, and the common carotid arteries were examined on the sagittal axis in lateral view. cIMT was defined as a low-level echo gray band not projecting into the arterial lumen, and was measured during end-diastole according to the method described by Pignoli et al.²⁶ The measurements were performed bilaterally 1 cm proximally to the carotid bulb, 3 times, and then mean cIMT was calculated.^{27,28} Intra-observer variability was good (intraclass correlation coefficient [ICC]=0.99; good if >0.80).²⁹

FMD of the Brachial Artery All the patients were fasted (including avoidance of stimulants such as coffee/tea, chocolate) and physical exercise free for at least 8–12 h before the examination in order to avoid negative influences on test results. The tests were carried out in a quiet air conditioned room (22–24°C), early in the morning. We performed a preliminary scan in order to explore the anatomy and identify landmarks. The scan was done at the right brachial artery on long-axis projection between 5 and 10 cm above the elbow using a ≥7.0-MHz linear probe. The study was performed using a high-resolution ultrasonograph (Philips Sonos 5500) connected to an image analysis system, certified by the National Research Council of Pisa (MVE II), for computing the brachial artery diameter in real-time by analyzing B-mode ultrasound images.³⁰ All the ultrasound examinations were performed by the same physician in order to reduce observer bias. With the subject in a supine position for at least 10 min, the arm was positioned comfortably in order to identify the humeral artery. A sphygmomanometer cuff was placed distally to the artery. After 1 min of flow image baseline acquisition, the artery was occluded by inflating the cuff to a pressure of 200–220 mmHg for exactly 5 min. After deflation, the following increased shear stress provides the stimulus for the dilatation of the humeral artery. Within 15 s from the end of ischemia, the flow rate was measured and then the degree of hyperemia. The image of the artery was then recorded continuously for 2–3 min after ischemia. Reactive hyperemia was calculated as the ratio of the change in diameter (maximum dilatation after deflation-baseline) divided by the baseline, which corresponds to maximum FMD recovery. FMD was analyzed as the percentage increase in brachial artery diameter after the application of a pressure stimulus.^{28,31} Intra-observer variability was good (ICC=0.93).

APAO To improve the image acquisition, subjects were asked to keep fasting for at least 8–12 h and to follow a fiber diet for the 2 days prior to the examination to reduce intestinal bloating (diet preparation). Ultrasonography of the infra-renal abdominal aorta was performed by a single operator using a

Table 1. Clinical and Biochemistry Characteristics

	SGA	Controls	P-value
Subjects (n)	27	25	—
Age (years)	10.03±3.0	10.41±3.9	0.17
Gender (M/F)	15/12	13/12	0.25
Tanner (I/II)	15/12	12/13	0.33
Birth weight (kg)	2.268±0.4	3.25±0.37	0.0001
Birth length (cm)	45.9±3.6	49.71±3.81	0.01
Weight-SDS	0.23±1.05	0.22±0.67	0.40
Height-SDS	0.34±0.91	0.31±0.74	0.21
BMI-SDS	0.09±1.23	0.1±0.64	0.32
SBP (mmHg)	103.65±2.28	107±2.54	0.51
DBP (mmHg)	63.26±6.29	64.04±3.39	0.33
Glucose (mg/dl)	85±12	81.16±8.14	0.20
Insulin (μU/ml)	12.15±5.25	9.74±4.59	0.27
HOMA-IR	2.61±1.27 (1.01–5.27)	1.56±0.40 (0.96–2.00)	0.01
Triglycerides (mg/dl)	73±44	57.24±19.16	0.46
TC (mg/dl)	165±31	144.8±28.32	0.20
HDL-C (mg/dl)	55±9	58.67±9.30	0.252
LDL-C (mg/dl)	83.4±23.5	78.10±21.03	0.39

Data given as mean±SD (range). BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment; IR, insulin resistance; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SDS, standard deviation score; SGA, small for gestational age; TC, total cholesterol.

single high-resolution vascular ultrasound Philips 5500 equipped with a 3-MHz electronic probe. With the patient in a supine position, the electronic probe was placed 1 cm left of the umbilicus. The best image in long-axis projection of the abdominal aorta was then obtained. APAO was defined as the maximum external cross-sectional measurement.³⁰ It was calculated as the distance between the near and the far walls of the abdominal aorta. Measurements were performed 2 cm above and distal to the umbilicus and expressed in centimeters.³⁰ Intra-observer variability was good (ICC=0.97).

M-Mode, B-Mode Echocardiography and TDI

All patients underwent echocardiography of both the left and right chambers, in agreement with international guidelines.³² Pulsed-wave TDI was used in order to evaluate the velocity of the ventricle walls and the related parameters of systolic and diastolic function of both the left and right ventricles (LV and RV).³³ TDI information is less load dependent than standard Doppler.³⁴ On apical 4-chamber projection, the cardiac structures examined were the mitral valve annulus, both lateral and medial, the basal and mid part of the LV lateral wall and interventricular septum, the basal part of the RV lateral wall and the lateral tricuspid annulus.³⁵ We considered as main parameters: systolic velocity (S'); early diastolic velocity (E'); and late diastolic velocity (A'). We calculated E'/Av for all the anatomic territories considered and E'/E' at the lateral and medial parts of the mitral annulus. Systolic and diastolic time parameters related to both the RV and LV were measured throughout the entire cardiac cycle:^{33–36} for the LV, isovolumetric contraction time (l-IVCT), ejection time (l-ET), isovolumetric relaxation time (l-IVRT) were used to obtain the LV Tei index [(l-IVRT+l-IVCT)/l-ET]; and for the RV, isovolumetric contraction time (r-IVCT), ejection time (r-ET), and isovolumetric relaxation time (r-IVRT) were used to obtain the RV Tei index [(r-IVRT+r-IVCT)/r-ET].

In order to evaluate the reproducibility of the echocardiographic evaluations, we calculated the intra-observer variability:

ICC=0.87.

Statistical Analysis

For statistical analysis, SPSS for Windows, version 22.0 (SPSS, Chicago, IL, USA) were used. Results are given as mean±SD. The Kolmogorov-Smirnov test was applied to test normality of distribution. In parameters with normal distribution, means were compared using unpaired Student t-test, whereas linear correlations were calculated using Pearson's correlation coefficient; in parameters with skewed distribution, significance was assessed with the Mann-Whitney test and Spearman's correlation coefficient, respectively. Finally, multiple regression analysis was used to determine the relative strength of each biochemical and clinical variable in predicting CV parameters. The limit of statistical significance was set at 0.05.

Results

Baseline clinical characteristics, biochemical markers of glucidic and lipid metabolism, and HOMA-IR index are listed in **Table 1**. No significant differences were found between SGA children and controls according to age, sex, pubertal stage, weight, height, BMI-SDS, SPB and DBP. Blood glucose level was normal in all examined subjects, but HOMA-IR was significantly higher in SGA children compared with controls (2.61±1.27 vs. 1.56±0.40, P=0.01). No statistically significant differences for TC, HDL-C and LDL-C, and TG were seen between SGA children and controls. We did not observe any differences between SGA groups according to metabolic and cardiovascular risk parameters.

Vascular Assessment

c-IMT, FMD and APAO are listed in **Table 2**. Mean cIMT was significantly higher in SGA children than controls (0.51±0.04 mm vs. 0.45±0.07 mm, P=0.007). Furthermore, SGA subjects had statistically significantly worsened endothelial function as compared with healthy controls (10.11±4.17% vs.

Table 2. Vascular and Echocardiographic Parameters

Ultrasound parameters	SGA	Controls	P-value
Mean cIMT (mm)	0.51±0.04	0.45±0.07	0.007
FMD (%)	10.11±4.17	12.34±4.28	0.04
APAO (cm)	1.31±1.35	1.30±0.16	0.005
TAPSE (mm)	21.54±4.75	27.03±1.89	0.002
LVEF (%)	62.55±6.29	59.62±0.10	0.001
LV Tei index	0.41±0.07	0.24±0.20	0.001
RV Tei index	0.41±0.09	0.16±0.10	0.001
Left E/A ratio	2.14±0.47	1.50±0.89	0.001
Right E/A ratio	1.94±1.83	1.33±0.10	0.001
E/e' ratio	8.10±1.59	11.91±0.89	0.001

Data given as mean±SD. APAO, anteroposterior diameter of the infrarenal abdominal aorta diameter; cIMT, carotid intima-media thickness; FMD, flow-mediated dilatation; LV, left ventricular; LVEF, LV ejection fraction; RV, right ventricular; SGA, small for gestational age; TAPSE, tricuspid annular plane systolic excursion.

12.34±4.28%, $P=0.04$). There was also a statistically significant increase in APAO in SGA patients compared with controls (1.31±1.35 cm vs. 1.30±0.16 cm, $P=0.005$).

Mean cIMT was positively related to age ($r=0.367$, $P=0.05$), while FMD was inversely correlated with age ($r=-0.660$, $P=0.0003$), and TC ($r=-0.231$, $P=0.001$).

Echocardiography

Interesting insights came from the echocardiographic evaluation of both RV and LV function. SGA subjects had increased left Tei index (0.41±0.07 vs. 0.24±0.20, $P=0.001$) and right Tei index (0.41±0.09 vs. 0.16±0.10, $P=0.001$) compared with healthy controls (Table 2). Furthermore, even indirect markers of systolic RV function (ie, tricuspid annular plane systolic excursion [TAPSE]) were reduced in SGA subjects as compared with controls (21.54±4.75 mm vs. 27.03±1.89 mm, $P=0.002$). We also observed an increase in both left (2.14±0.47 vs. 1.50±0.89, $P=0.001$) and right (1.94±1.83 vs. 1.33±0.10, $P=0.001$) E/A for the 2 groups (Table 2). SGA subjects had higher LV ejection fraction (LVEF) as compared with AGA subjects (62.55±6.29% vs. 59.62±0.10% $P=0.001$). As regards the influence of birth weight, we found a negative correlation with LVEF ($r=-0.320$, $P<0.0001$) and RV Tei index ($r=-0.230$, $P<0.0001$).

Multiple Regression Analysis

In SGA subjects, cIMT was significantly influenced by HOMA-IR ($\beta=0.159$) and LDL-C ($\beta=0.294$; $r=0.359$, $P=0.0001$), while left E/A was negatively influenced by HOMA-IR ($\beta=-0.333$) and positively by HDL-C ($\beta=0.360$; $r=0.480$, $P=0.0001$), on multiple regression analysis. Multiple regression analysis also showed that metabolic parameters did not influence APAO and TAPSE.

Discussion

The present study has shown that SGA subjects have an early, subtle impairment of the CV system, the implications of which for overall growth and outcomes are still unknown.

Vascular and echocardiographic comparisons of SGA and AGA controls identified the following: (1) morphological alterations in the systemic arterial vessels in SGA subjects, as reflected by increased cIMT and APAO; (2) reduced endothelial function in SGA subjects; and (3) right and left cardiac chamber alterations in both systolic and diastolic function in SGA subjects, as reflected by left and right Tei index and/or

TAPSE.

It is well established that the atherosclerotic process starts in childhood and proceeds silently over a long period of time before clinical manifestations.³⁷ SGA is associated with the risk of atherosclerosis,^{38,39} probably due to the increase of risk factors for the development of metabolic syndrome, particularly in SGA subjects with spontaneous catch-up growth.⁴⁰ The present SGA subjects had statistically significantly higher HOMA-IR compared with the AGA subjects, indicating an insulin-resistant condition that is well known to induce acceleration of the systemic atherosclerotic process.³⁰ The present SGA subjects had reduced FMD. In our previous study such endothelial dysfunction in SGA patients was found to be related to a dysfunction in endothelial progenitor cells resulting in reduced proliferation and migration of such cells.⁴¹ Such a condition might be triggered by an anti-angiogenic state enhanced by the low birth weight via alteration of the vascular endothelial growth factor pathway.⁴¹ Unfortunately, this explanation of endothelial dysfunction in the present subjects is an hypothesis only, because we did not evaluate endothelial progenitor cells.

The role of birth weight on endothelial vasodilatation was also supported by Touwslager et al,⁴² who demonstrated that the vessels' dilatation after acetylcholine use was related to anthropometric parameters of the newborns such as birth weight, length and head circumference. Therefore, SGA patients could effectively be characterized by early signs of systemic atherosclerosis represented by altered endothelial function.

Furthermore, the morphology of the vessels could also be impaired in SGA subjects as compared with healthy controls. We observed marked alterations in cIMT and APAO in the present SGA subjects. These results are in line with those of Stergiotou et al, who noted increased carotid and aortic IMT in SGA subjects, even after adjusting for neonatal weight and vessel diameter.¹³ Furthermore, low birth weight has been associated with increased cIMT in young adults who had severe fetal growth restriction and in those who had exaggerated postnatal growth.⁴³ Martyn et al calculated a 5.3-fold increased risk of carotid stenosis and a 2.3-fold increased incidence of atherosclerotic disease in the lower limbs in patients with the lowest birth weight.⁴⁴ The present data seem to confirm such a trend in SGA subjects. Such a condition is very dangerous because these data are strongly associated with cardiac disease. As outlined by Vågerö and Leon, low birth weight could increase the risk for ischemic heart disease, and such a condition may be triggered by early onset of atherosclerosis.

rotic disease.⁴⁵

The association between morphological and function alterations of systemic arterial vessels and the function alterations of both cardiac chambers is well-established. Bekkers et al observed that increased abdominal aorta diameter is directly related to increased ascending aorta diameter, larger LV dimensions, higher LV mass index, and lower LVEF.⁴⁶ The same relationships were noted between endothelial function and myocardial performance indices. Akgul et al found that TDI determines LV performance changes in acromegaly, as well as endothelial dysfunction assessed using FMD.⁴⁷ Other studies noted the relationship between alteration in vascular endothelial function and myocardial performance indices.^{48,49} Such correlations have also been observed in pediatric patients,⁵⁰ although the present study is the first to investigate all these vascular and cardiac function indices in SGA patients.

One of the most interesting research fields emerging with regard to the clinical background of SGA is related to the possible alterations of cardiac performance. The literature is undecided with regard to such matters, although the majority of studies support the present data. Most of the data relate to the neonatal period but they do not include follow-up.^{18,51,52} Significant variations were observed in myocardial performance indices of both RV and LV within the first month after delivery in very low-birth-weight infants.⁵²

It is possible that the reduced anthropometric characteristics of SGA subjects may impair the development of cardiomyocytes and the intracellular molecular signaling useful for the regulation of cardiac cell proliferation, apoptosis and final differentiation.⁵³ Moreover, subjects with very low birth weight for gestational age have a 2.0-fold risk increase in myocardial infarction occurrence, especially if combined with increase in body weight in adulthood (increasing the risk to 10.8-fold).⁵⁴

The present data indicate that there is reduced performance of myocardial fibers in SGA patients as compared with AGA. We found that both right and left Tei indices were higher in SGA as compared with AGA; that is, it seems that the SGA patients had reduced performance of both RV and LV in term of systolic and diastolic function. The finding that SGA patients express higher troponin I in umbilical cord blood as compared with AGA⁵⁵ supports the hypothesis of original damage to cardiomyocytes, the impact of which on future cardiac performance is still unknown. Nevertheless, in the present study the subtle alteration in cardiomyocytes was reflected by TAPSE: this indirect marker of RV systolic function was reduced in SGA patients compared with controls. Although the values were all in the normal range for age and sex, the statistically significant difference could be considered a marker of future negative evolution of cardiac performance.

The most important echocardiography finding is that SGA patients had a more favorable diastolic filling pattern (elevated E/A, reduced E/e') compared with controls, but they also had impaired overall myocardial function as assessed on Tei index. The great increase in SGA E/A ratio could be considered a predisposing factor for reduced ventricle compliance rather than an amelioration of it. We considered it as a pseudonormalization pattern of the ventricle diastolic pattern. Nevertheless, E/e ratio appears to contradict such a hypothesis, although the diastolic alteration is corroborated by the increased Tei index. There may be a subtle fiber impairment in SGA patients that could alter TDI measurements, and speckle tracking may be more useful in such cases. Nevertheless, the finding of better LVEF in SGA patients compared with healthy controls is in contrast to the supposed impairment in cardiac performance in the former compared with controls. The present SGA

patients had an LV function ($62.55 \pm 6.29\%$) higher than their counterpart ($59.62 \pm 0.10\%$, $P < 0.001$). Although LVEF was within the normal range (ie, higher than 55%) in both groups, the meaning of this statistically significant difference is still a matter of debate. Further studies are needed in order to clarify the underlying mechanisms of subtle cardiac performance imbalance in SGA patients, although linked to improved LVEF.

Conclusions

SGA subjects have subtle cardiac and vascular impairment compared with healthy AGA controls. The implications of such alterations for the immediate CV future of such individuals are still unknown. Long-term follow-up is necessary in order to evaluate the effects of these alterations on morbidity and mortality.

Conflict of Interest

The authors declare no conflicts of interest.

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