Small-for-gestational-age birth is linked to cardiovascular dysfunction in early childhood

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Background The aim of this study was to assess clinical and echographic markers of cardiovascular dysfunction in infants born small for gestational age (SGA) compared to a control group of subjects born adequate for gestational age (AGA).

Methods This was a single-center cross-sectional case-control study. We recruited 20 SGA and 20 gestational age–matched AGA subjects at 24 months of age.

The study population underwent anthropometric and Doppler 2-dimensional echocardiographic assessments, and carotid artery intima-media thickness (cIMT) and endothelium-dependent vasodilation evaluation (FMD).
The pressure-volume curve during diastole was calculated using the algorithm for the elastance calculation on 1 single beat.

Results SGA children showed lower stroke volume, lower left ventricle (LV) dimensions and volume, and greater LV thickness. Diastolic function was impaired in SGA with lower capacitance and higher elastance.

Birth weight standard deviation score was positively associated with capacitance and negatively associated with *E/E'* ratio and elastance, and in SGA infants, the end-diastolic pressure-related volume curve was shifted to the left compared to AGA. cIMT and systemic vascular resistance were significantly higher, while FMD was lower, in SGA compared to AGA; birth weight standard deviation score was directly correlated with FMD and inversely correlated with cIMT.
Finally, a longer breastfeeding duration was associated to a lower cIMT even after correction for confounding factors.

Conclusions This study shows that infants born SGA present an early and subtle cardiovascular dysfunction compared to AGA controls. These alterations are strongly related to weight at birth. Finally, breastfeeding exerts an important protective and beneficial cardiovascular effect. (Am Heart J 2019;217:84-93.)

The term *small for gestational age* (SGA) identifies newborns with a birth weight below the 10th percentile for sex and gestational age due to fetal, maternal, or placental factors that affect the normal intrauterine growth.[1]

SGA birth is a widespread condition associated with both an increased risk of neonatal morbidity and mortality and a higher risk of long-term complications.[2]

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Acknowledgements of grant support: No financial assistance was received in support of the study.
Conflicts of interest: none.
Submitted February 24, 2019; accepted August 1, 2019.

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https://doi.org/10.1016/j.ahj.2019.08.004

In 1989, David Barker's group found a correlation between low birth weight and cardiovascular (CV) diseases and mortality, prompting many researches focused on the effects of intrauterine life on future health.[3] These findings support the theory of a fetal programming of later diseases, according to which the intrauterine exposure to particular conditions, such as chronic hypoxia and undernutrition, can lead to morphological and epigenetic changes during a critical developmental window that could persist through life leading to an increased risk of CV diseases.[4] Moreover, SGA infants usually perform a catch-up growth to achieve a normal stature and weight in the first years of life that might be related to an increased risk of adiposity, metabolic disease, and CV risk factors later in life.[5-7] In this perspective, SGA infants represent a population at great risk of CV morbidity and mortality. Furthermore, some studies have shown the presence of CV and endothelial dysfunction in children and young adults born SGA even if the earliest window at which a CV impairment could be detected is still unknown. Moreover, in clinical practice, the clinical care of infants born SGA is usually focused on long-term neurological and endocrinological follow-up overshadowing CV diseases.

Therefore, we believe that the detection of a high CV risk profile associated with SGA birth and the identification of early echographic markers of CV damage during infancy would lead to an early diagnosis of CV complications, allowing prompt preventive therapeutic measures that might reduce CV morbidity and mortality at long-term follow-up.

Aims of this study were (1) to evaluate early CV abnormalities in infants born SGA at 24 months of age compared to an age-matched group of subjects born adequate for gestational age (AGA) and (2) to investigate the effect of catch-up growth and the role of breastfeeding on CV risk.

Subjects and methods

Study design and population

This was a single-center cross-sectional study conducted at the Division of Pediatrics of Maggiore della Carità University Hospital, Novara, Italy. We consecutively enrolled 20 SGA infants, born at term, aged 24 months with adequate catch-up growth, and 20 AGA, age-matched controls. *SGA* was defined as a birth weight <10th percentile for gestational age and *AGA* as a birth weight between the 10th and the 90th percentile for gestational age, according to Italian neonatal anthropometric charts.[8] The *catch-up growth* was defined as the achievement of normal stature and weight at the age of 24 months.

Exclusion criteria were heart, respiratory, liver, and kidney diseases; congenital malformations; genetic diseases; neonatal asphyxia; parenteral nutrition; congenital inborn error of metabolism; and preterm and twin birth.

SGA subjects were enrolled at 24 months of age during the auxological follow-up, and we longitudinally included patients who matched inclusion and exclusion criteria until we reached the number of 20. AGA children were retrospectively enrolled by reviewing medical records of healthy newborns.

The protocol was conducted in accordance with the Declaration of Helsinki, was approved by the Local Ethic Committee (CE 106/18), and was registered at www.clinicaltrials.gov (NCT03758092). Informed written consent was obtained from all subjects' parents.

No extramural funding was used to support this work.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Clinical and anthropometric variables

The infants' prenatal and neonatal data were retrospectively recorded, namely, a history of gestational diabetes and hypertension, the presence of intrauterine growth restriction,[9] maternal weight gain during pregnancy, Apgar score, gestational age and birth weight, length, and head circumference. All subjects' parents completed a questionnaire including family history, maternal smoking during pregnancy, and breastfeeding duration. At the time of enrollment, anthropometric data were evaluated by trained physicians according to standard procedures and based on the WHO growth charts.[10] Height, weight, and systolic (SBP) and diastolic (DBP) blood pressure were measured as previously described.[11] Body mass index (BMI) was calculated as weight (kg)/height $(cm)^2$, and weight gain in the first 2 years of life was calculated as the Δ between birth weight and weight at 24 months. Target height, based on the parents' measured height, was determined according to Tanner.

Echocardiographic assessment

Transthoracic echocardiogram using a Vivid 7 Pro ultrasound scanner (General Electric Healthcare, Chicago, IL) was performed by one expert pediatric cardiologist blinded to patients' clinical data. Measurements of left ventricle (LV end-diastolic diameter [LVEDD], LV end-systolic diameter [LVESD], interventricular septum at end diastole [IVSD], and LV posterior wall at end diastole [LVPWD]) were obtained from a 2D short-axis view and averaged over 3 consecutive cardiac cycles.[12] Left atrium diameter (LAD) was the maximum anteroposterior dimension during systole obtained from a 2D parasternal long-axis view.[13] LA volume was measured using the biplane area-length method.[12] The tricuspid annular plane systolic excursion (TAPSE) was acquired by placing an M-mode cursor through the tricuspid annulus in an apical 4-chamber view.[12,14]

Relative wall thickness (RWT) was calculated as the ratio (LV posterior wall thickness at end diastole × 2)/LV internal dimension at end diastole.[12]

LV volume and LV ejection fraction (EF) were obtained using the biplane Simpson method from an apical 4-chamber and 2-chamber views.[12] LV mass (LVM) was derived from the Devereux formula and indexed to body surface area (left ventricular mass index [LVMI]). Left ventricular output (LVO) was obtained with the velocity time integral (VTI) from a 5-chamber view, calculated as LVO = [(VTI) × (heart rate) × (cross-sectional area)], and indexed to body weight.[15]

Using pulsed wave Doppler, mitral inflow velocities, peak early diastolic velocity (*E*), peak late diastolic velocity (*A*), and *E/A* ratio were measured. Pulsed wave tissue Doppler of the lateral mitral annulus was used for the measurement of early peak diastolic mitral annular velocity (*E'*). The *E/E'* ratio was calculated. End-diastolic pressure (EDP) was calculated from the *E/E'* ratio with the formula $EDP = 1.91 + 1.24 \times E/E'$[14]; and the pressure-volume curve during diastole, with the formula $EDP = \alpha \times EDV^{\beta}$ (end-diastolic volume [EDV]).[16] Volume parameters were corrected to fixed values of EDP ($V_{30\ mm\ Hg}$). The coefficient "β" (beta), indicating the slope of the end-diastolic pressure-volume relationship (EDPVR), was calculated with the formula $\beta = [\log_{10}(EDP/30)]/[\log_{10}(EDV/V_{30mm\ Hg})]$.[17]

Table I. Clinical data at birth of 20 SGA and 20 AGA subjects

	SGA	AGA	*P* value
Subjects	20	20	
Gestational age (wk)	38.3 (1.2)	39.0 (1.2)	NS
Female	10 (50%)	12 (60%)	NS
Target height (cm)	171.4 (7.9)	169.3 (9.4)	NS
Birth weight (g)	2202 (219)	3242 (381)	<.001
Birth weight (SDS)	-2.09 (0.49)	0.14 (0.78)	<.001
Birth length (cm)	46.2 (2.0)	49.8 (1.6)	<.001
Birth length (SDS)	-1.33 (0.73)	0.23 (0.76)	<.001
Birth head circumference (cm)	32.5 (1.4)	34.4 (0.9)	<.001
Birth head circumference (SDS)	-1.09 (1.03)	0.24 (0.79)	<.001
Apgar score at 1 min	8.2 (0.8)	8.5 (0.8)	NS
Apgar score at 5 min	8.9 (0.3)	8.9 (0.4)	NS

Values are number (%) or mean (error measures).
NS, not significant.

Table II. Clinical and echocardiographic data at 24 months of age of 20 SGA and 20 AGA subjects

	SGA	AGA	*P* value
Subjects	20	20	
Age (m)	22.8 (1.7)	23.1 (2.5)	NS
Weight (kg)	11.2 (1.2)	11.8 (2.0)	NS
Weight (SDS)	–0.89 (0.90)	–0.44 (1.56)	NS
Height (cm)	84.2 (3.5)	85.2 (3.6)	NS
Height (SDS)	–0.30 (0.79)	–0.15 (0.83)	NS
BMI (kg/m^2)	15.74 (1.15)	16.19 (2.07)	NS
2-y weight gain (kg)	8.96 (1.11)	8.61 (1.91)	NS
2-y weight gain SDS	1.25 (0.98)	–0.22 (1.56)	<.001
SBP (mm Hg)	94.7 (8.9)	92.4 (7.5)	NS
DBP (mm Hg)	66.3 (9.1)	66.9 (7.6)	NS
Heart rate (beat/min)	118.1 (24.2)	115.6 (14.6)	NS
FS (%)	34.6 (3.5)	35.2 (4.0)	NS
EF (%)	59.9 (4.2)	62.2 (4.3)	NS
LV stroke volume (mL/kg)	1.35 (0.37)	1.53 (0.22)	.02
LVO (mL/kg/min)	160.1 (57.0)	176.1 (27.8)	NS
LVEDD (mm)	28.5 (2.1)	30.4 (2.9)	.01
LVEDD (*z* score)	–0.25 (0.86)	0.36 (0.69)	.009
LVESD (mm)	18.6 (1.5)	19.8 (1.9)	.02
LVESD (*z* score)	0.12 (0.71)	0.22 (0.65)	NS
IVSD (mm)	5.8 (1.0)	5.5 (0.8)	NS
IVSD (*z* score)	0.99 (0.72)	0.62 (0.70)	<.05
LVPW (mm)	4.8 (0.7)	4.3 (0.5)	.02
LVPW (*z* score)	0.85 (0.73)	0.29 (0.58)	.006
LAD (mm)	19.7 (3.1)	21.8 (3.2)	.02
LAD (*z* score)	0.91 (1.0)	1.54 (1.1)	.03
Ao (mm)	14.7 (2.4)	17.1 (1.4)	<.001
LA/Ao	1.36 (0.23)	1.24 (0.16)	<.05
LV mass (g)	30.8 (5.2)	31.7 (8.3)	NS
LV mass index (g/m^2)	59.6 (8.2)	59.4 (12.5)	NS
LV mass (*z* score)	–0.80 (0.81)	–0.83 (1.15)	NS
RWT	0.34 (0.06)	0.29 (0.04)	.001
LV area (cm^2)	4.80 (0.48)	5.04 (0.25)	.02
LV volume (mL)	23.9 (6.4)	28.2 (5.3)	.01
LA area (cm^2)	0.52 (0.09)	0.62 (0.07)	<.001
LA volume (mL)	8.8 (2.2)	11.5 (2.1)	<.001
Mitral *E* peak (cm/s)	106.6 (12.2)	103.0 (13.3)	NS
Mitral *A* peak (cm/s)	62.8 (17.6)	59.6 (15.1)	NS
E/A ratio	1.82 (0.56)	1.84 (0.51)	NS
Mitral lateral *E'* velocity (cm/s)	12.7 (2.3)	14.3 (2.1)	.003
E/E' ratio	8.59 (1.65)	7.25 (1.03)	.005
TAPSE (mm)	16.9 (2.3)	19.2 (2.7)	.003
TAPSE (*z* score)	0.32 (2.35)	1.89 (2.67)	.002
$V_{30mm\ Hg}$ (mL)	28.13 (7.37)	34.03 (6.84)	.006
Coefficient β	5.90 (0.05)	5.87 (0.03)	.005

Values are mean (error measures).
FS, LV fractional shortening; *LVPW*, LV posterior wall diastolic dimension.

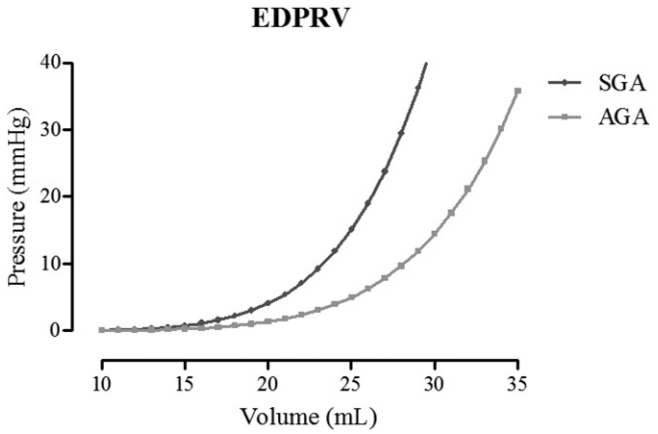
Vascular assessment

Vascular measurements were performed with a high-resolution ultrasonography (Esaote MyLab25 Gold, Esaote, Italy) using a 8-mHz linear transducer and a 5-mHz convex transducer for the abdominal aorta by one expert vascular surgeon blinded to patients' clinical status. Carotid artery intima-media thickness (cIMT), abdominal aortic diameter at maximum systolic expansion (Ds) and minimum diastolic expansion (Dd), brachial artery diameters, and brachial artery peak systolic velocity (BAPSV) and end-diastolic velocity (BAEDV) were measured as previously described,[18,19] and aortic strain (*S*), pressure strain elastic modulus (Ep), pressure strain normalized by diastolic pressure (Ep*), and brachial artery flow-mediated dilation (FMD) were calculated. Whereas *S* is the mean strain of the aortic wall, Ep and Ep* are the mean stiffness.[18] Arterial wall stiffness index (β index) was calculated with the formula β index = ln(SBP/DBP)/[(Ds − Dd) /Dd)][20]; and systemic vascular resistance (dynes/s/cm^2), with the formula SVR = (mean BP − right atrial pressure)/LVO, with an estimated right atrial pressure of 5 mm Hg.[21] The brachial artery maximum diameter recorded following reactive hyperemia was reported as a percentage change of resting diameter (FMD = peak diameter − baseline diameter/baseline diameter).[22]

Statistical analysis

All data were expressed as mean ± SD, absolute values, or percentages. A sample of 20 individuals was estimated to be sufficient for demonstrating a difference of 10% in cIMT with an SD of 0.1 mm with 90% power and a significance level of 95% in the Mann-Whitney test between SGA and controls according to published data.[23] Wilcoxon-Mann-Whitney test was used to determine the differences between SGA and control subjects. Covariate was birth weight standard deviation score (SDS). Correlations of CV parameters with continuous values were examined using Spearman correlation coefficients. Partial correlation was used to correct for covariates. The stepwise regression model with 2-tailed probability values and 95% CIs was used to measure the strength of the association between CV variables and prenatal and neonatal variables (birth weight SDS, birth length SDS, head circumference SDS, history of hypertension, gestational diabetes, cigarette smoking, maternal weight gain during pregnancy: model 1) and other

Figure 1



EDPVR curve in 20 SGA and 20 AGA infants at 24 months of age.

clinical and auxological variables (model 2: model 1 + weight gain SDS, length SDS, weight SDS, BMI SDS, duration of breastfeeding). Statistical significance was assumed at $P < .05$.

Intraobserver reliability was evaluated using the intraclass correlation coefficient (ICC), and we found adequate intraobserver reliability for all CV measures (ICCs = 0.787-0.987). The statistical analysis was performed with SPSS for Windows version 17.0 (SPSS Inc, Chicago, IL).

Results

Neonatal characteristics

Table I shows the auxological data at birth of 20 SGA (mean gestational age 38.3±1.2 weeks, 50.0% females) and 20 gestational age-matched AGA subjects (gestational age 39.0±1.2 weeks, 60.0% females).

Thirteen (65.0%) SGA subjects had a birth weight <3rd percentile and 7 (35.0%) between the 3rd and the 10th percentile.[8] Nineteen (95.0%) SGA subjects were also intrauterine growth restricted (IUGR). No differences were present in family history of hypertension, diabetes, hypercholesterolemia, obesity, and CV diseases and in gestational history of maternal cigarette smoking and gestational diabetes, whereas the prevalence of gestational hypertension was higher in SGA compared to AGA (6 vs 1; $P = .05$). The breastfeeding duration was longer in AGA than in SGA (12.9 vs 6.0 months; $P = .01$).

Anthropometric and CV characteristics at 24 months of age

The anthropometric and echocardiographic data at the age of 24 months are shown in Table II. All the SGA subjects underwent an adequate catch-up growth. No differences between SGA and AGA were found in SBP and DBP.

SGA infants showed lower LV stroke volume ($P = .02$), LV dimensions (LVEDD z score $P = .009$), area ($P = .02$), volume ($P = .01$), LAD (LAD z score $P = .03$), area ($P < .0001$), volume ($P < .0001$), and aortic dimensions (Ao $P < .0001$; LA/Ao $P = .05$) and greater LV thicknesses (IVSD z score $P = .05$; LVPWD z score $P = .025$; RWT $P = .001$) compared to AGA subjects. The study of diastolic function showed lower E' ($P = .003$) and $V_{30mm\ Hg}$ ($P = .006$) and higher E/E' ratio ($P = .005$) and β ($P = .005$) in SGA compared to AGA, whereas no difference was found in the E/A ratio, S and A' waves. TAPSE ($P = .003$) and TAPSE z score ($P = .002$) were lower in the SGA group. No differences were shown in the LV systolic function, LVM, LVMI, and heart rate.

Figure 1 shows the pressure-volume curve during diastole (end-diastolic pressure-related volume). In SGA infants, the curve was shifted toward the left compared to AGA; namely, for the same EDP, they showed lower EDV than AGA.

Vascular findings are shown in Table III. cIMT ($P = .003$) was significantly higher, whereas abdominal aortic diameters (AoDs $P = .009$; AoDd $P = .01$), Ep* ($P = .02$), basal and after ischemia brachial artery diameters (BAD basal $P = .01$; BAD after $P = .002$), BAPSV (basal $P = .004$; after $P = .002$), flow (basal $P = .006$; after $P = .01$), FMD ($P = .005$), and SVR ($P = .05$) were lower, in SGA compared to AGA. No differences between the 2 groups were found in aortic S and stiffness.

Associations between CV measurements and birth weight, weight gain, and duration of breastfeeding

Correlation analyses are shown in Tables IV and V. In the whole population of SGA and AGA infants, birth weight SDS was positively correlated with LVEDD, LVESD, LV area, LV volume, LAD, LAD z score, LA area, LA volume, Ao, E' wave, TAPSE, TAPSE z score, $V_{30mm\ Hg}$,

AoDs, AoDd, BAPSV, and FMD. A negative correlation was found between birth weight SDS and LVPWD *z* score, RWT, *E/E'* ratio, coefficient β, and cIMT.

Weight gain SDS was positively correlated with LVM, LVMI, and LVM *z* score.

After adjusting for birth weight SDS, breastfeeding duration was directly associated to BA flow basal and after and negatively associated to cIMT.

Impact of birth weight and duration of breastfeeding

Stepwise multiple regression analysis showed that birth weight SDS was an independent predictor of the *E/E'* ratio and coefficient β (model 1 and 2). $V_{30mm\ Hg}$ was predicted by birth weight SDS (model 1). In model 2, birth weight SDS and weight SDS were found as significant predictors. cIMT was predicted by birth weight SDS (model 1). In model 2, birth weight SDS and the duration of breastfeeding were found as significant predictors. Only in model 2 was breastfeeding duration found as a significant predictor of FMD (Table VI).

Model 2: Independent variables were those of model 1 plus weight gain SDS, length SDS, weight SDS, BMI SDS at 24 months of age, and the duration of breastfeeding.

Table III. Vascular data at 24 months of age of 20 SGA and 20 AGA subjects

	SGA	AGA	*P* value
cIMT (mm)	0.48 (0.10)	0.39 (0.10)	.003
AoDs (mm)	6.5 (1.5)	7.9 (1.3)	.009
AoDd (mm)	5.6 (1.2)	6.6 (0.9)	.01
S	0.16 (0.07)	0.19 (0.07)	NS
Ep	202.1 (96.8)	172.3 (119.2)	NS
Ep*	38.5 (20.8)	26.7 (18.9)	.02
β index	2.25 (0.44)	2.09 (0.47)	NS
BAPSV basal (cm/s)	57.4 (16.5)	77.4 (15.6)	.004
BAEDV basal (cm/s)	6.4 (3.6)	5.5 (6.4)	NS
BAD basal (mm)	2.06 (0.41)	2.44 (0.21)	.01
BAF basal (mL/min)	50.1 (28.6)	82.8 (26.5)	.006
BAPSV after (cm/s)	60.9 (16.3)	76.4 (15.8)	.002
BAEDV after (cm/s)	7.3 (3.3)	5.5 (6.9)	NS
BAD after (mm)	2.28 (0.44)	2.88 (0.26)	.002
BAF after (mL/min)	67.8 (42.6)	119.4 (56.6)	.01
FMD (%)	13.0 (1.5)	17.3 (3.5)	.005
Change in BA flow (%)	34.1 (21.8)	40.4 (27.8)	NS
SVR (dynes/s/cm^2)	503 (233)	411 (85)	<.05

Values are mean (error measures).
BAF, brachial artery flow.

Discussion

In this study, we found that SGA birth negatively affects cardiac remodeling and impairs vascular structure in infants aged 2 years. Furthermore, breastfeeding might play a beneficial role during heart remodeling among young children.

CV alterations in infants born SGA

Our study shows a marked variation in the cardiac structure of SGA infants, with higher ventricular parietal thickness and lower diameters and volumes compared to AGA. The increased placental resistance together with after-birth peripheral and vascular remodeling is responsible for the increased after-load affecting SGA patients resulting in eccentric cardiac hypertrophy that could be sustained by an "extra growth" of the myocardial muscular mass or by an increase of the connective tissue with a rearrangement of the ventricular wall.[24]

In this study, SGA children showed a greater *E/E'* ratio that was negatively correlated to birth weight. According to this finding, we developed the pressure-volume curve during diastole (EDPVR) and studied the capacitance and elastance to clarify if the increase of the *E/E'* ratio was a marker of diastolic dysfunction or was affected by the presence of smaller ventricles with higher filling pressures. SGA subjects showed a reduction of $V_{30mm\ Hg}$ and of capacitance and a significant increase of β compared to their AGA counterpart. Moreover, we found that birth weight was positively related to $V_{30mm\ Hg}$ and negatively related to β and that birth weight was an independent predictor of these parameters. The increase of the ventricular elastance in SGA infants indicates a change in myocardial material properties that might be due to physiological or pathological remodeling. Previous autoptic studies showed that growth-restricted fetuses have thinner cardiomyocytes, hypoplasia of the myocardial fibers, a slight maturational delay of the cardiomyocytes, and reduced glycogen storage,[25,26] and certainly, the structural subversion of cardiac histology could persist even in later life and could be precociously evaluated with echocardiographic parameters like EDV, *E/E'*, and elastance.

In human studies and in many animal models, impaired left ventricular function has been linked to IUGR, whereas right ventricular function has been poorly investigated. In line with previous studies conducted in IUGR baboons[27] and IUGR newborns and older children,[28,29] we found that TAPSE and its *z* score were lower in SGA infants compared to AGA. This reflects an alteration of the RV longitudinal shortening that is not related to LV impairment and might be caused by an affected pulmonary vascular growth causing a degree of pulmonary hypertension.[29,30]

Regarding vascular dysfunction, the assessment of cIMT is a sensitive clinical marker of atherosclerosis, predictive of CV morbidity and mortality in adulthood and high-risk population. Interestingly, we found higher cIMT in SGA patients, related to birth weight and probably linked to an altered development of the vascular system that affects the vascular structure and

Table IV. Partial correlation for birth weight SDS, weight gain SDS, and breastfeeding duration (months) with echocardiographic measurements

	Birth weight SDS		Weight gain SDS		Breastfeeding (m)	
	r	*P* value	*r*	*P* value	*r*	*P* value
Heart rate (beat/min)	0.113	NS	−0.396	NS	−0.001	NS
FS (%)	−0.097	NS	0.152	NS	−0.176	NS
EF (%)	−0.154	NS	−0.012	NS	−0.085	NS
LV stroke volume (mL/kg)	0.225	NS	−0.256	NS	−0.040	NS
LVO (mL/kg/min)	0.214	NS	−0.451	.01	−0.005	NS
LVEDD (mm)	0.305	.05	0.062	NS	0.185	NS
LVEDD (*z* score)	0.269	NS	−0.236	NS	0.258	NS
LVESD (mm)	0.354	.02	0.004	NS	0.236	NS
LVESD (*z* score)	0.054	NS	−0.143	NS	−0.043	NS
IVSD (mm)	0.011	NS	0.414	.01	0.038	NS
IVSD (*z* score)	−0.094	NS	0.204	NS	−0.035	NS
LVPW (mm)	−0.253	NS	0.326	.04	−0.104	NS
LVPW (*z* score)	−0.334	.03	0.045	NS	−0.177	NS
LAD (mm)	0.415	.008	−0.098	NS	0.020	NS
LAD (*z* score)	0.359	.02	−0.235	NS	0.013	NS
Ao (mm)	0.617	<.001	−0.143	NS	0.240	NS
LA/Ao	−0.199	NS	0.095	NS	−0.147	NS
LV mass (g)	0.033	NS	0.664	<.001	0.123	NS
LV mass index (g/m^2)	0.009	NS	0.374	.02	0.084	NS
LV mass (*z* score)	0.010	NS	0.433	.005	0.078	NS
RWT	−0.379	.02	0.224	NS	−0.197	NS
LV area (cm^2)	0.303	.05	−0.027	NS	0.278	NS
LV volume (mL)	0.361	.02	0.094	NS	0.158	NS
LA area (cm^2)	0.599	<.001	−0.191	NS	0.076	NS
LA volume (mL)	0.616	<.001	0.094	NS	0.158	NS
Mitral E peak (cm/s)	−0.091	NS	−0.054	NS	−0.150	NS
Mitral A peak (cm/s)	−0.126	NS	0.089	NS	−0.046	NS
E/*A* ratio	0.105	NS	−0.128	NS	0.144	NS
Mitral *E*′ velocity (cm/s)	0.456	.003	−0.404	.01	0.100	NS
E/*E*′ ratio	−0.363	.02	0.123	NS	0.042	NS
TAPSE (mm)	0.473	.003	−0.090	NS	0.079	NS
TAPSE (*z* score)	0.491	.002	−0.090	NS	0.079	NS
$V_{30mm\ Hg}$ (mL)	0.387	.02	0.085	NS	0.156	NS
Coefficient β	−0.360	.01	0.250	NS	0.051	NS

function and increases the later CV risk. As an underlying condition, impaired elastin synthesis seems conceivable. The synthesis of elastin peaks during the perinatal period has a half-life of several decades. Insufficient synthesis due to chronic substrate deprivation could cause long-lasting CV impairment,[31] although the duration of this effect is still unknown. In fact, although there is strong evidence that IUGR and SGA newborns have an increased arterial wall thickness and cardiac remodeling,[32,33] evidences that these alterations persist into later childhood and adulthood are controversial and probably affected by confounding factors that interfere later in life, like postnatal growth, hormonal status, nutrition, physical activity, weight, and blood pressure. Indeed, 2 large cohort studies have recently found no association between SGA birth and arterial wall thickening in children and adolescents aged 11 and 19 years, respectively.[34,35] Conversely, Stroescu et al have shown that cIMT was higher in SGA compared with AGA obese children with a mean age of 15 years and was related to adipokines levels and markers of inflammation that could play an additional role in arterial remodeling in the growing subject.[36] Furthermore, in a large group of young adults, cIMT was higher in subjects born SGA who performed the catch-up growth compared to patients born SGA with short stature, confirming the interfering role of postnatal factors.[37] Probably, at the age of 2 years, the effect on cIMT is mediated by both peri- and postnatal factors, and future perspective studies, beginning in the first years of life, enrolling even SGA without the catch-up growth will better clarify these contributing factors.

Moreover, we showed that SGA had lower FMD of the brachial artery compared to AGA, and this was related to birth weight, highlighting the presence of endothelial dysfunction in this subset, according to previous findings in children and young adults that showed the link between FMD and birth weight,[38] suggesting the correlation between an impaired fetal growth and altered arterial endothelial function.[39,40]

Table V. Partial correlation for birth weight SDS, weight gain SDS, and breastfeeding duration (months) with vascular measurements

	Birth weight SDS		Weight gain SDS		Breastfeeding (m)	
	r	*P* value	*r*	*P* value	*r*	*P* value
cIMT (mm)	–0.471	.002	0.179	NS	–0.451	.004
AoDs (mm)	0.273	.009	0.061	NS	0.202	NS
AoDd (mm)	0.200	.01	0.035	NS	0.124	NS
S	0.234	NS	0.083	NS	0.124	NS
Ep	–0.213	NS	–0.053	NS	–0.133	NS
Ep*	–0.283	NS	–0.036	NS	–0.185	NS
β index	–0.206	NS	–0.082	NS	–0.172	NS
BAPSV basal (cm/s)	0.462	.026	–0.119	NS	0.322	NS
BAEDV basal (cm/s)	–0.228	NS	0.118	NS	0.070	NS
BAD basal (mm)	0.130	NS	–0.306	NS	0.455	.03
BAF basal (mL/min)	0.218	NS	–0.318	NS	0.475	.03
BAPSV after (cm/s)	0.071	NS	–0.281	NS	0.535	.01
BAEDV after (cm/s)	–0.532	.01	0.236	NS	0.001	NS
BAD after (mm)	0.298	NS	0.438	.04	0.535	.01
BAF after (mL/min)	0.236	NS	–0.391	NS	0.497	.02
FMD (%)	0.542	.009	–0.501	.02	0.376	NS
Change in BA flow (%)	–0.175	NS	–0.240	NS	0.172	NS
SVR (dynes/s/cm^2)	–0.218	NS	0.456	.01	–0.026	NS

Impact of the catch-up growth and breastfeeding on CV dysfunction in infants born SGA

The catch-up growth of SGA infants required to achieve a normal final stature and neurocognitive outcome has been related to an adiposity rebound leading to a higher risk of obesity and metabolic impairment during childhood. In our study, weight gain SDS was positively related to LV mass, LV mass index, and LV mass *z* score, whereas no relationship with myocardial thicknesses and diameters, *E/E'* ratio, $V_{30\text{mm Hg}}$, cIMT, FMD, aortic strain, and stiffness was found, suggesting no correlation between weight gain and early CV damage. It is more likely that CV changes occurring during intrauterine life in SGA/IUGR fetuses persist postnatally, suggesting the intriguing hypothesis of an intrauterine CV programming with implications for future adult diseases.[29]

Nutrition and body weight have a strong effect on CV development during childhood.[41] High dietary intake of polyunsaturated fatty acids has been related to a lower cIMT in children with IUGR.[42] In particular, a breastfeeding duration longer than 4-6 months is associated with a lower cIMT and seems to have a protective role on future CV diseases.[43] According to this, our study showed a significant correlation between a longer breastfeeding duration and a lower cIMT even after correction for birth weight. This finding highlights the impact of breastfeeding on body composition and inflammation leading to a protective effect on the vascular system. Conversely, we did not find any relationship between breastfeeding and cardiac parameters. The effects of nutrition and body weight on CV remodeling have been longitudinally evaluated in one cohort of IUGR newborns followed until childhood showing a positive effect only for a breastfeeding duration longer than 6 months.[44] Furthermore, both animal and human studies have shown that breastfeeding could restore cardiomyocyte number after placental insufficiency with a protective effect on CV system reducing the risk of hypertension, diabetes, obesity, and dyslipidemia.[45,46] The real mechanisms linking breastfeeding with cardiac remodeling still need to be clarified; however, they might be partially related to the positive effect of growth factors, adipokines, and hormones and a favorable lipid profile of breast milk. Moreover, breastfeeding could modify growth pattern and body composition, lowering the risk of overweight[47] and improving endothelial function, in comparison with formulas. Studies in adults show conflicting results on the role of breastfeeding on vascular function. In the Cardiovascular Risk in Young Finns Study, breastfeeding was associated with an improvement of FMD in 1,667 adult male subjects,[48] whereas Leeson et al showed that prolonged breastfeeding was related to a greater brachial artery stiffness in 331 young adults.[49] In our population, breastfeeding duration was a significant predictor of FMD. As discussed above, breastfeeding could have a crucial impact on CV function through a modulation of the inflammatory cascade, and the increase of FMD could be the hemodynamic mechanism behind its protective effect.

Study limitations

Our study has several potential limitations. The major limit is the relatively small size of our population. Moreover, our study was not a randomized controlled

Table VI. Stepwise multiple regression analysis of neonatal and 24-month clinical variables (as independent variables) on *E/E'* ratio, $V_{30mm\ Hg}$, β, cIMT, and FMD (dependent variables)

Dependent variable	Significant effects	*B* (95% CI)	β	*P* value
Model 1				
E/E' ratio	Birth weight SDS	−0.636 (−0.828 to −0.444)	0.517	.002
R: 0.517				
Model 2				
E/E' ratio	Birth weight SDS	−0.636 (−0.828 to −0.444)	0.517	.002
R: 0.517				
Model 1				
$V_{30mm\ Hg}$	Birth weight SDS	3.558 (2.659-4.457)	0.586	<.001
R: 0.586				
Model 2				
$V_{30mm\ Hg}$	Birth weight SDS	3.049 (2.442-3.876)	0.503	.001
	Weight SDS	2.158 (1.430-2.886)	0.405	.006
R: 0.708				
Model 1				
Coefficient β	Birth weight SDS	−0.017 (−0.220 to −0.012)	0.501	.003
R: 0.501				
Model 2				
Coefficient β	Birth weight SDS	−0.017 (−0.220 to −0.012)	0.504	.004
R: 0.504				
Model 1				
cIMT	Birth weight SDS	−0.044 (−0.057 to −0.031)	0.527	.002
R: 0.527				
Model 2				
cIMT	Birth weight SDS	−0.036 (−0.049 to −0.023)	0.427	.01
	Breastfeeding	−0.004 (−0.006 to −0.002)	0.327	.04
R: 0.612				
Model 2				
FMD	Breastfeeding	0.003 (0.002-0.004)	0.465	.04
R: 0.465				

Model 1: Independent variables were birth weight SDS, birth length SDS, birth head circumference SDS, family history of hypertension, gestational diabetes, cigarettes smoking, and maternal weight gain during pregnancy.

trial. We performed a prospective data collection, which is certainly susceptible to selection bias. Another main limitation is that the echographic measurements and formulas used in our study came from adult studies, not validated in pediatric populations. Furthermore, in our study, CV variables were measured by a single operator. To limit this bias, all measurements were taken by the same reader blinded to patients' clinical data and showed good intraobserver reliability. Moreover, the end-diastolic pressure-related volume formula has been validated on humans and smaller hearts (rats and dogs) and appears to be generally applicable to normal and diseased hearts of different species and could be used in clinical and research settings where assessment of the differences in passive ventricular properties between groups of patients is performed.

Another limit of this study is the use of multiple comparisons, which are susceptible of spurious findings especially when the *P* values are marginal.

Furthermore, the inclusion of a third group of infants born SGA who did not perform the catch-up growth would have helped to better understand the CV effects of pre- and postnatal factors.

Finally, multiple blinded readers and a more extensive use of vascular imaging modalities including speckle tracking echocardiography and cardiac magnetic resonance imaging would have certainly improved the results of the current study.

Conclusion

Our study clearly shows the presence of CV dysfunction in term infants born SGA at 2 years of age, resulting in great implications for later morbidity and mortality. These data suggest the need for timely strategies to prevent or reverse CV abnormalities in an early stage. The markers of CV disease adopted in our study protocol might represent a potential effective monitor for a diagnosis in the early phase guiding future interventions. In this view, the pediatric age is a "window of opportunities" for the future public health.

In conclusion, we believe that infants born SGA present an early initial CV dysfunction compared to AGA controls and that these alterations are strongly related to birth weight. Finally, breastfeeding exerts an important protective and beneficial CV effect. Further larger studies and randomized trials are warranted to confirm our findings.

Funding

No funding was secured for this study

Conflict of interest

None declared.

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