Paediatrica Indonesiana

VOLUME 51 May • 2011 NUMBER 3

Original Article

The influence of intrauterine growth retardation on cardiac function, left ventricular mass and superior vena cava return in newborns

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Abstract

Background Low birth weight (LBW) in neonates is a problem leading to high morbidity and mortality. Barker hypothesized that fetal cardiac remodeling during hypoxic conditions or maternal under-nutrition is a risk factor for coronary heart disease in the young. Early vascular changes may influence cardiac function and newborns' cerebral blood flow.

Objective The aim of this study was to determine the effects of being small for gestational age (SGA) on newborns' cardiac function, left ventricular (LV) mass and superior vena cava (SVC) return.

Methods This cross-sectional study was conducted in Cipto Mangunkusumo Hospital from February to June 2008. LBW and normal newborns who fulfilled the inclusion criteria were recruited as subjects. Maternal history, infant physical examination, and echocardiography were obtained within 48 hours of life to exclude those with congenital heart disease, and assess cardiac function and SVC flow.

Results Subjects were 21 preterm appropriate for gestational age (AGA), 19 SGA and 19 normal newborns. SGA newborns showed lower LV mass, stroke volume and cardiac output than normal newborns. However, these SGA parameters were not different from preterm AGA babies. In addition, LV mass index was significantly different but no difference of SVC return between the three groups.

Conclusion SGA newborns' LV function was lower than that of normal newborns, as low as preterm AGA newborns. Normal SVC return was observed in the three groups. This finding may be due to a brain-sparing effect to maintain sufficient cerebral blood flow in the fetus. **[Paediatr Indones. 2011;51:170-7]**.

Keywords: *low birth weight, cardiac function, SVC return*

Low birth weight (LBW) newborns are classified as those whose birth weight is 1,500-2,499g.[1] Small for gestational age (SGA) is defined as a birth weight of lower than the 10th percentile of the Lubchenco curve.[2] SGA is a high risk condition, with high morbidity and mortality. A 2002 profile from the Indonesian National Health System revealed the LBW prevalence to be 6%, with a neonatal mortality rate as high as 17:1,000 survival births.[1] In America, 7.6% of births were LBW, 30% of which were full term newborns with intrauterine growth retardation (IUGR).[3]

From May-December 2007, 1,875 babies were born in Cipto Mangunkusumo Hospital, an average of 281 babies born every month, of which 35 were LBW and 6 of the LBW were SGA. Some factors that may contribute to this high prevalence are poverty, crowded urban areas, maternal malnutrition and low education. Similar conditions were reported by Barker fifteen years ago in poor urban areas of various

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ethnicities in many countries.[4] Barker hypothesized that the IUGR fetus adapts to maternal undernutrition by changing the cell program signaling pathway during fetal growth and development. This change promotes fetal vascular remodeling that may lead to coronary heart disease in young.[5] Postnatally, this protective effect would become maladaptive if the child's nutritional state rapidly improved. Changes in cardiac function, blood flow pattern, oxygenation and thermoregulation occuring in IUGR fetuses may influence hemodynamics in the transitional neonatal period.[6,7]

The vascular remodeling process develops early in the IUGR fetus, and may disturb cardiac function by altering the metabolic environment at the distal vasculature. Remodeling may be precipitated by prostaglandin metabolites, leukotriene blockers, bradykinin, angiotensin-II, histamine and nitric oxide, which results in arterial vasoconstriction.[8,9] Those changes may also influence cerebral blood flow. Since the brain is a vital organ, sufficient blood must be supplied to meet cerebral metabolic demands. Cerebral blood flow supply comprises 80% of SVC returns, estimated indirectly by measuring SVC return with echocardiography.

Cardiovascular problems in IUGR newborns occur during fetal development. We aim to determine if SGA LBW influences LV geometry, cardiac function and superior vena cava return in newborns during the first 48 hours of life.

Methods

We conducted an observational, cross-sectional study in Cipto Mangunkusomo Hospital, Jakarta from February to June 2008. LBW and normal babies born in Cipto Mangunkusumo Hospital were recruited as subjects. A consecutive sampling method was performed until the target number of samples was fulfilled. We calculated that 19 subjects were required for each group to obtain 90% power with a 5% significance level. Subjects were newborns fulfilling the following inclusion criteria: birth weight of 1,500 - 2,500 grams, gestational age of 28 weeks or more, not suffering from severe illness, including severe asphyxia, sepsis, respiratory distress, pulmonary hypertension or congenital heart defects.

Twenty normal newborns were recruited as the control group. Subjects were then divided into three groups: SGA, preterm AGA and normal babies, according to Lubchenco's chart.[2] Parents provided written informed consent. The Medical Research Ethics Committee of the Faculty of Medicine, University of Indonesia approved the protocol.

Patient history and physical examination were obtained. Subjects also underwent 2-D and M-mode echocardiography, as well as color Doppler. Echocardiography was performed on a clean, warm table while the babies were calm or sleeping. Echocardiography was performed using Phillips HD11XE machine in order to exclude congenital heart disease, assess LV geometry and function, as well as SVC return. We obtained LV geometry three times before calculating LV systolic function.

LV geometry parameters were obtained through the parasternal long axis view, including interventricular septum systolic and diastolic dimensions (IVSs, IVSd), LV end systolic and diastolic diameters (LVES, LVED), left posterior wall dimensions (LPWs, LPWd), and cross- sectional area of aorta (CSA Ao). Stroke volume was obtained by measuring the velocity trans-annular index of aorta flow (VTI Ao) through

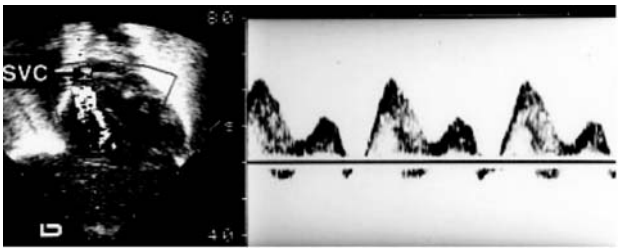

Figure 1. PW-Doppler placed at the SVC right atrial junction, revealing S, D, and A waves of SVC return.

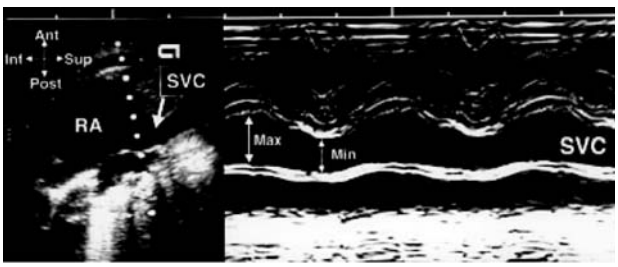

Figure 2. M-mode of SVC return at the SVC-RA junction revealed anterior and posterior walls of SVC and anterior wall movement. Variation of diameter was approximately 20% (SD 8).

an apical five chamber view. LV systolic function including fractional shortening (FS), ejection fraction (EF), stroke volume (SV), cardiac output (CO), LV mass index, and SV index were assessed. We also measured the peak of the E and A waves, E/A ratio and deceleration time (DT) tp assess LV diastolic function. Every measurement was obtained three times and the means calculated.

Pulse wave (PW) color Doppler of SVC return was obtained from a coronal sub-costal view as far as possible from the umbilicus, by tilting the transducer slightly anteriorly until the maximal SVC flow was seen entering the right atrium. The transducer was then placed at the left parasternal site to take a parasternal long axis view. In this view, adjustment was sometimes required by tilting the transducer to the left anterior and angling to the right, to avoid the lung shadow. SVC diameter was measured in this view at the point where the SVC joined with the right atrium.

SVC flow consists of three waves. The first is the S wave that reveals ventricle systole, the second and smaller is the D wave, which reveals early diastolic phase of the ventricle, and the third is the A wave in the opposite direction which reveals systolic phase of the atrium (**Figure. 1**). Pulsation of SVC flow was dynamically altered by respiration (**Figure. 2**). We calculated the mean of three maximum SVC flow amplitudes.

Echocardiographic examination was performed in conjunction with electrocardiography to record the cardiac cycle and heart rate. We were unable to obtain respiratory cycle data due to the lack of probes, so we obtained the largest S wave of SVC flow three times and took the mean of results, as well as the other measurements.

Differences in cardiac function and SVC flow were analyzed with ANOVA, followed by post hoc analysis. Correlation between anthropometry and LV function was analyzed with Pearson's and Spearman's tests.

Results

Fifty-nine newborns (28 male and 31 female) were recruited as subjects. They were divided into three groups, 21 AGA LBW newborns, 19 SGA newborns and 19 normal weight newborns. LBW babies were often born to high risk mothers with severe preeclampsia. Other risk factors for LBW were maternal undernutrition, infection, and bleeding due to placenta previa and oligohydramnios, as well as twin gestation. Characteristics of subjects, and their LVs and SVCs are shown in **Tables 1 and 2**.

Table 1. Characteristics of subjects

	AGA LBW (n=21) Mean (SD)	SGA LBW (n=19) Mean (SD)	Normal (n=19) Mean (SD)
Gestational age (weeks)	33.9 (2.45)	38.3 (2.85)	38.8 (1.62)
Birth weight (g)	2,031 (266)	2,010 (254)	2,904 (382)
Length at birth (cm)	43.8 (2.3)	43.1 (2.49)	46.9 (2.17)
Body surface area (m2)	0.16 (0.125)	0.16 (0.132)	0.19 (0.016)
Ponderal index	2.4 (0.34)	2.5 (0.34)	2.8 (0.22)

Table 2. Parameters of geometry and function of LV and SVC in the three groups

Parameters	AGA LBW (n=21) Mean (SD)	SGA LBW (n=19) Mean (SD)	Normal(n=19) Mean (SD)
IVSd (cm)	0.46 (0.07)	0.51 (0.08)	0.55 (0.1)
LVED (cm)	1.31 (0.19)	1.35 (0.20)	1.55 (0.29)
LPWd (cm)	0.48 (0.1)	0.52 (0.06)	0.59 (0.08)
IVSs (cm)	0.52 (0.09)	0.58 (0.11)	0.60 (0.13)
LVES (cm)	0.72 (0.17)	0.75 (0.17)	0.87 (0.23)
LPWs(cm)	0.53 (0.08)	0.60 (0.08)	0.63 (0.08)
Diameter Ao (cm)	0.68 (0.08)	0.72 (0.08)	0.79 (0.09)
VTI Ao (cm)	9.5 (2.10)	9.8 (1.37)	11.00 (2.39)
CSA Ao	0.54 (0.06)	0.56 (0.07)	0.62 (0.07)
E (m/s)	0.52 (0.11)	0.55 (0.11)	0.60 (0.14)
A (m/s)	0.54 (0.09)	0.53 (0.07)	0.56 (0.15)
VTI SVC (cm)	12.1 (2.96)	10.9 (1.72)	13.80 (2.96)
SVC diameter (cm)	0.55 (0.13)	0.61 (0.14)	0.66 (0.13)

Two-D and color Doppler echocardiography examination revealed a closing ductus arteriosus in 40 newborns (20 AGA LBW, 14 SGA, and 6 normal newborns). In the other 19 babies the ductus arteriosus was closed.

The mean heart rate of SGA newborns was significantly slower than that of preterm AGA (95% CI -13.22 to -1.5, P=0.015) and normal newborns (95% CI -12.9 to 0.95, P=0.024). Both SGA and preterm AGA newborns had lower LV mass, stroke volume and cardiac output than normal newborns, but there were no differences between SGA and preterm AGA newborns.

LV geometry and function parameters were different between SGA and normal newborns, as well as preterm AGA and normal newborns, as seen in **Table 3**. No differences were found between SGA and preterm AGA newborns, except systolic left posterior wall (LPWs) thickness was significantly thicker in SGA than in preterm AGA babies (95% CI -0.11 to -0.02, P=0.004). LV mass index of preterm AGA was less than in normal infants (95 % CI 29.7 to -7.3). Meanwhile, the mean LV mass index in SGA newborns was between that of preterm AGA and normal infants, but not statistically different from either group.

We analyzed the correlation of anthropometric parameters, including the Ponderal index (PI), birth weight (BW), length of birth and body surface area (BSA), with LV mass, LV function and SVC return. PI was abnormally distributed, so we analyzed the correlation of PI with each cardiac parameter using Spearman's test. For other anthropometric parameters that were normal in distribution,

Table 3. Mean heart rate, LV mass, LVfunction, and SVC return in the three groups

	AGA LBW	SGA LBW	Normal	P
Heart rate	131 (SD 8.3)	123 (SD 10.9)	130 (SD 8.3)	0.06
LV mass (g)	8.5 (SD 2.29)	10.1 (SD 2.77)	14.3 (SD 5.56)	*0.0001
LV diastolic function				
E/A	0.98 (SD 0.192)	1.05 (SD 0.216)	1.10 (SD 0.240)	0.226
DT	0.10 (SD 0.021)	0.10 (SD 0.135)	0.11 (SD 0.022)	0.301
LV systolic function				
EF (%)	69.3 (SD 9.46)	69.1 (SD 2.77)	68.8 (SD 8.53)	0.985
FS (%)	45.3 (SD 8.74)	45.2(SD 9.11)	44.7 (SD 8.25)	0.973
Stroke volume (mL)	5.1 (SD1.23)	5.5 (SD 0.70)	9.8 (SD 1.51)	*0.0001
Cardiac output (CO) (mL/min)	665.1 (SD 170.10)	678.7 (SD 122.23)	890.3 (SD 227.78)	*0.0001
Cardiac index (mL/min/m2)	4.3 (SD 0.98)	4.4 (SD 0.98)	4.5 (SD 0.90)	0.729
LV mass index	53.8 (SD 13.47)	64.64 (SD 15.21)	72.3 (SD 23.2)	*0.006
SV index	32.4 (SD 7.66)	35.6 (SD 5.74)	34.7 (SD 5.8)	0.27
SVC return (mL/kg/min)	153.1 (CI 82.1-433.8)	182.4 (CI 62.12-352.81)	230.9 (CI 88.16-468.12)	0.4
SVC flow/CO ratio	0.25 (CI 0.12-0.61)	0.30 (CI 0.104-0.626)	0.24 (CI0.123-0.431)	0.255

ANOVA analysis; *=significant, P< 0.05;

Table 4. Correlation between birth weight, length at birth, and body surface area to LV mass, LV function and SVC flow

	Birth weight		Length at birth		Body surface area (BSA)	
	R	P	r	P	r	P
LV mass	0.7*	<0.0001*	0.6**	<0.0001*	0.7*	<0.0001*
LV diastolic function:						
E/A	0.1	0.6	0.04	0.8	0.1	0.7
DT	0.3	0.05	0.2	0.3	0.2	0.1
LV systolic function:						
EF	0.02	0.8	-0.1	0.3	-0.03	0.8
FS	0.01	0.9	-0.2	0.2	-0.04	0.7
Stroke volume	0.6**	<0.0001*	0.5**	<0.0001*	0.6**	<0.0001*
Cardiac output	0.6**	<0.0001*	0.5**	<0.0001*	0.6**	<0.0001*
Cardiac index	-0.03	0.8	0.03	0.8	0.01	0.9
SVC return	0.2	0.2	0.2	0.2	0.2	0.1
SVC/CO ratio	-0.1	0.3	-0.1	0.4	-0.1	0.3

Pearson's analysis. * significantly correlated. Abbreviations: LV, left ventricle; E/A, E and A wave ratio; EF, ejection fraction; FS, fractional shortening; SVC, superior vena cava; CO, cardiac output

Pearson's correlation test was performed. No correlation was found between PI and LV mass, systolic and diastolic LV function, CO, cardiac index, and SVC flow return.

LV mass strongly correlated with birth weight and BSA ($r=0.7$; $P< 0.0001$), and moderately correlated with length at birth ($r=0.6$; $P<0.0001$). Stroke volume and cardiac output were each also moderately correlated with birth weight, BSA ($r=0.6$; $P<0.0001$) and length at birth ($r=0.5$; $P<0.0001$). (**Table 4**)

Discussion

A total of 59 babies were included in our study, 40 of which were LBW. The mean PI of SGA infants was 2.5 (SD 0.34). PI is one of anthropometric parameters usually used to assess fetal growth, formulated as 100 x BW (g)/length.[3] SGA infants with PI < 2.6 is associated with increased risk of coronary heart disease[10] and hypertension[11] in adulthood and even childhood.[12] Another study found that adolescents with a history of IUGR were prone to dyslipidemia.[13] Their risk of vascular dysfunction in adulthood reportedly increased to as high as that of a smoker who smokes 4.5 boxes/year, even with no other risk factor.[14] Boys born with PI < 2.6 and who quickly caught up in their growth were reported to have an increased risk of coronary heart disease and hypertension in adulthood.[5,6] Dietetic counseling is important for mothers, so they can provide healthy, appropriate food for their SGA babies to prevent fast catch up growth and avoid the risk of endothelial injury.

Stroke volume and cardiac output in SGA neonates was lower than that of normal neonates, but not different from preterm AGA neonates. However, after correcting for body surface area values, no differences in stroke volume or cardiac index were found between the three groups.

Severe maternal preeclampsia is one of the greatest risk factors for SGA LBW newborns in a recent study. Early onset of this maternal condition may influence fetal cardiovascular function and promote the remodeling process and pathological signaling pathways which act as a compensatory mechanism during fetal life. Preeclampsia may lead to fetal hypoxia, resulting in arterial stiffness and vasoconstriction. This mechanotransduction process promotes myocyte signaling of compensatory pathways and leads to LV wall hypertrophy during the fetal stage. Changes in the signaling pathway result in sarcomere reorganization, altered gene expression, stimulated protein synthesis and increased myocyte size. However, released humoral stimulating factors, including endothelin-1, angiotensin II, and TGF-β, stimulate fibroblasts, endothelium and smooth muscle of the vasculature.[15] If chronic afterload is sustained after birth and stimulates a hypertrophic response, cardiac output would decrease, leading to insufficient oxygen transport and advanced vascular endothelial response.[16]

Our study showed that the mean heart rate (HR) of SGA LBW newborns was slower (123x/min, SD 10.9) than both the normal group (130x/min SD 8.3) and the AGA LBW group (131x/min SD 8.3). Ou results are consistent with a study reporting the median HR of newborns to be 145x/min while awake and 120 – 125 x/min while asleep.[17] Johnson *et al.* found that heart rate was faster in preterm than in normal babies.[18] However, we could not find any references of heart rate in SGA newborns.

Other differences between SGA, preterm AGA and normal newborns were LV mass and LV mass index. LV mass in SGA and AGA LBW newborns was significantly lower than that of normal newborns. However, no differences were found between SGA and preterm AGA newborns.

The normal value of LV mass index in children 2 – 17 years of age is 60.8 (SD 12)/m^2. LV is considered hypertrophic if the LV mass index is > 103 g/m^2 for boys or > 84.2 g/m^2 for girls.[12] We did not find references of LV mass index for neonates. It was interesting that the SGA LBW neonates' LV mass index was slightly higher than that of preterm AGA neonates, but not statistically different from normal newborns. This observation could be due to the maturation process or a compensatory response to increased afterload. Any compensatory effort of the ventricle could be detected indirectly by measuring blood levels of N-terminal-pro brain natriuretic peptide (NT-proBNP). In healthy newborns, NT-proBNP concentration may spike immediately after delivery, then gradually decrease to adult levels by the age of three years.[15] However, we did not assess NT-proBNP levels.

Thickened LPWs in SGA newborns [0.60 cm (SD 0.08)] may reveal the heightened LV effort to pump blood at systole against systemic vascular resistance (SVR), suggesting that SVR was higher in SGA than in AGA LBW newborns, even though birth weight may be similar.

No significant differences of LPWd were found between the three groups, even though the thinnest dimension was found in the AGA LBW group. However, we found in normal newborns and SGAs that LPWd was higher than that of a previous study which reported LPWd of 3.5 (1.5-5.5) mm in newborns with 3 kg birth weight.[19] However, LPWs in the SGA group were significantly more thickened than in the AGA LBW group [0.60 cm (SD 0.08) vs 0.53 cm (SD 0.08), P=0.004, respectively], but not different from the normal group. Differences in maturation of SGA and AGA (preterm) newborns or the high LV effort in SGA newborns to pump blood against highly restricted arteries may explain this difference in thickness.

Previous study showed that maternal protein deficiency is a predisposing factor for cell program disturbance.[20,21] Changes in peripheral vasculature may occur as result of trophoblast invasion, maternal vascular transformation and disturbances in the differentiation and developmental processes of feto-placental vasculature.[13] Han *et al.* showed that in ovines, gene transcription upregulation in the left ventricle occurring during fetal life and maternal undernutrition was sustained.[22] Thicker LPWs in our study may also be associated with maternal preeclampsia since this was the greatest risk factor for LBW babies, possibly increasing fetal systemic vascular resistance.

LV diastolic function was assessed by measuring the E/A wave ratio of transmitral flow during diastole using pulse wave (PW) Doppler. E wave reveals LV early diastolic filling and A wave reveals atrial contraction on late diastolic period. We found no differences in E and A waves in SGA LBW and preterm AGA newborns. However, the E wave in preterm AGA newborns (0.52 SD 0.11) was lower than that of normal newborns, similar to a study by Johnson *et al.* that reported an E wave of 0.55 (SD 0.1).[18] Fetuses and newborns normally have smaller E waves than A waves, so the E/A ratio is less than one. [23] However, in adults the E wave is taller than the A wave. Higher A waves in preterm newborns are caused by less compliance of immature ventricles. As such, the E/A ratio should increase with age as the A wave decreases.[23] Less LV compliance leading to SGA newborns prone to diastolic dysfunction resulting in congestive heart failure. Diastolic function in SGA LBW newborns was not available.

There are three levels of diastolic dysfunction:[24] 1) level 1, mild diastolic dysfunction caused by failure of LV relaxation, 2) level 2, moderate dysfunction or pseudonormalization, with LV end diastolic pressure increases because of abnormal LV compliance, 3) Level 3, severe dysfunction or restrictive pattern. The normal E/A ratio in the SGA LBW group might be due to the pseudo-normalization process, but further investigation will be required.

SVC return reflects the amount of blood going to the upper body, particularly the brain. In SGA LBW newborns, selective peripheral vasculature changes develop, resulting in increasing or optimizing cerebral blood flow rather than lower body blood flow. A decrease in cerebral vascular resistance is responsible for this action, a process called "brain-sparing" effect.[25,26] Mori *et al.*[27] found that communal carotid arteries and abdominal aortas changed their stiffness index because of cerebral preferential perfusion overflow. This compensatory response could severely affect lower body perfusion leading to neonatal complications, for example, hyperbilirubinemia, hypocalcemia, hypoglycemia, and enterocolitis necroticans. Since we observed no difference in SVC flow between the three groups, this may indicate presence of positive brain-sparing effects in the SGA group. No clinical complications occurred in the first 48 hours, despite slow HR and SGA LBW itself, but we did not measure effects on carotid and abdominal arteries.

No correlation was found between the Ponderal index and LV mass, function and SVC return. LV mass was strongly correlated to birth weight and body surface area, and moderately correlated to length at birth. Stroke volume and cardiac output were moderately correlated with birth weight, body surface area and length at birth. Jiang *et al.*[28] studied 216 children aged 9 years. Echocardiography at birth was performed in order to assess the effect of IUGR on heart structure (i.e., coronary artery, aortic root, left atrium and left ventricle outflow tract diameter, as well as LV mass). At repeat echocardiography at

9 years of age, they found that the aortic diameter in previously SGA LBW children remained smaller than in those of normal cohorts. We did not measure aortic diameter, a possible topic for further cohort studies of SGA LBW newborns.

LV mass, stroke volume, and cardiac output in the SGA group was smaller than that of the normal group, but not different from the AGA LBW newborn group. After correcting with body surface area to find the LV mass index, stroke volume index and cardiac output index, interestingly, we found the LV mass index in the SGA group to not be different from the normal group.

No differences in SVC return between the three groups seemed to reflect that preferential perfusion cerebral blood flow occurred during the fetal period, meaning that blood flow to other organs may be reduced. Altered cardiac function in SGA babies was considered to be subclinical in nature since all subjects were in doing well clinically. However, good clinical status may change if SGA newborns are prone to physical stress or diseases. Further study is required determine if this is the case.

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