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Young Adults Born Small for Gestational Age: Is Reduced Baroreceptor Sensitivity a Risk Factor for Hypertension?

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Summary

Background: Adults born small for gestational age (SGA) are at increased risk for the metabolic syndrome and cardiovascular disease.

Hypothesis: Impaired short-term blood pressure regulation may contribute to the development of hypertension in patients born SGA.

Methods: In all, 43 patients born SGA (18 female, age 19.4 ± 0.3 years) were evaluated by beat-to-beat blood pressure and heart rate registration during rest and mental and orthostatic stress. The study group was divided into Group 1 with normal resting blood pressure (n = 32) and Group 2 with slightly elevated blood pressure (n = 11). Baroreceptor sensitivity (BRS) was calculated. Fasting insulin as well as lipid levels were correlated with hemodynamic parameters.

Results: Eleven of the 43 study patients (25%) had a slightly elevated resting systolic blood pressure (SBP) rising during mental and orthostatic stress. Body mass index (BMI) and fasting insulin levels correlated strongly with SBP in Group 2. Baroreceptor sensitivity was lower in Group 2 at rest ($p < 0.05$).

Conclusions: Three components of metabolic syndrome (elevated BP, high BMI, elevated insulin levels) correlate strongly in young adolescents born SGA; BRS is reduced in prehypertensive patients. Close follow-up is warranted during adult life as they are predisposed for developing a metabolic syndrome with elevated cardiovascular risk.

Key words: beat-to-beat blood pressure, baroreceptor sensitivity, cardiovascular risk

Introduction

The association between patients born small for gestational age (SGA) and increased blood pressure in adulthood has been shown extensively.[1–9] Large epidemiologic studies have addressed low birth weight as a risk factor for arterial hypertension, insulin resistance, and dyslipidemia,[1–3] three factors known as the metabolic syndrome and contributing to the development of cardiovascular disease.[6, 10–14] These findings led to the so-called Barker hypothesis that malnutrition during fetal life contributes to disturbances in physiologic and metabolic regulation in the growing organism.[7, 15]

Impaired baroreceptor sensitivity (BRS) has been advocated to be involved in the development of systemic hypertension.[16] This study was performed in 43 postpubertal patients born SGA to investigate baroreceptor function on a beat-to-beat basis.

Methods

Patients

The study group consisted of 43 healthy patients (18 female) born SGA; 11 of these were born SGA at term. All patients were recruited from a tertiary health care center (Ludwig-Maximilians-University Children's Hospital, Munich). All patients fulfilled the following inclusion criteria: birth length and/or birth weight below the 10th percentile for gestational age according to Largo[17] and postpubertal stage defined as Tanner stage V for boys and girls. Patients with chromosomal aberrations, syndromal abnormalities, and severe neuro-

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logical deficits were excluded. The family histories were negative for hypertension. All patients had been followed up closely until the age of 8 years, as they were included in the Bavarian Neurodevelopmental Study. Patients with arrhythmias such as supraventricular or ventricular premature beats during the test were excluded. The ethnicity was Caucasian for all patients. All patients gave their informed consent for participation in this study. The patients were subdivided into two groups according to their resting systolic blood pressure (SBP): Group 1 consisted of those with normal blood pressure and Group 2 of those with an SBP between 120 and 139 mmHg defined as prehypertension.[18]

Study design

Measurements

The following hemodynamic parameters were recorded and calculated:

- Heart rate was registered by a 6-lead electrocardiogram (ECG) with measurement of each RR-interval in milliseconds (ms) during the whole test; the values were given as mean over the respective test phase (see below for duration).
- Beat-to-beat blood pressure was measured by a finger cuff device positioned on the second and third finger of the right hand using the method of vascular unloading. The pulse wave obtained was calibrated with a conventional Dynamap® system (Critikon, Inc., Costa Mesa, Calif., USA) on the left upper arm. The right hand was positioned at heart level. For each heart beat, SBP and diastolic blood pressure (DBP) was measured; mean values (mmHg) as well as standard deviations were calculated over the respective test phases.[19, 20]
- Baroreceptor sensitivity was calculated according to the sequence method by the changes in RR interval (ms) divided by the changes in beat-to-beat SBP (mmHg). A minimum of three consecutive slopes of prolonged RR interval and increased SBP ("slope up") or shortened RR interval and decreased SBP ("slope down") were considered for the calculation. The cut-off level of measurements was 6 ms for RR interval and 1 mmHg for beat-to-beat blood pressure. The values were given as mean over the measurement time.[19, 21]

All measurements and calculations were done on a central computer device ("Task-Force-Monitor," CNS Systems, Graz, Austria) and on a beat-to-beat basis.

Protocol

A test lasting 30 min was performed, which consisted of a first phase with the patient supine in a quiet room after an overnight fast. After 20 min of recording, a psychological stress test was performed as second phase with the patient supine again (spelling of complicated words and counting of a prepared formula within 4 min). After 5 min of relaxation, the patient stood up and the circulatory variables were recorded during the first minute of upright posture as the third phase of the test.

Biochemical Markers

Blood samples were taken after a 12-h overnight fast. Insulin levels were measured using radioimmunoassay (Adaltis, Bologna, Italy). Total cholesterol and high-density and low-density cholesterol were obtained by standard methods.

Statistics

Calculations were performed using the Statistical Package for Social Sciences for Windows, version 12.0 (SPSS, Inc., Chicago, Ill., USA). Differences within the group were tested using the independent sample *t*-test and the nonparametric Mann-Whitney test. Correlations were analyzed using Spearman's correlation coefficient. All significance testing was fixed at $p < 0.05$ (two-sided).

Results

Blood Pressure and Heart Rate

Of the 43 patients, 11 (25%) showed a resting SBP of > 120 mmHg but < 140 mmHg; those patients formed Group 2 and were compared with the remaining subjects (Group 1). There were no differences regarding birth weight, birth length, ponderal index, gestational age, and catch-up growth at 1 year of age (Table I). All patients suffered an increase in their SBP

TABLE I Anthropometric data and biochemical profile

	SBP > 120 mmHg (n = 11)	SBP ≤ 120 mmHg (n = 32)
Sex	7 M, 4 F	18 M, 14 F
Age (years)	19.4 ± 0.3	19.4 ± 0.3
Weight (kg)	67.0 ± 9.1	56.3 ± 9.9 [a]
Height (cm)	170.9 ± 9.3	169.0 ± 8.3
BMI (kg/m^2)	23.0 ± 3.4	19.6 ± 2.3 [b]
Birth weight (kg)	1.85 ± 0.52	1.77 ± 0.64
Birth length (cm)	43.2 ± 3.7	43.3 ± 5.4
Ponderal index (kg/m^3)	22.5 ± 2.6	21.5 ± 2.9
Gestational age (week)	35.6 ± 3.4	34.5 ± 4.2
Weight at age 1 year (kg)	8.7 ± 1.5	8.4 ± 0.8
Catch-up growth at age 1 year	6.8 ± 1.4	6.5 ± 0.7
Cholesterol (mmol/l)	4.97 ± 0.89	4.53 ± 0.84
LDL (mmol/l)	3.04 ± 0.75	2.72 ± 0.56
HDL (mmol/l)	1.44 ± 0.35	1.42 ± 0.30
Insulin (mU/l)	7.9 ± 3.41	7.9 ± 3.10
HOMA-index	1.54 ± 0.71	1.58 ± 0.84

[a] $p < 0.05$.
[b] $p < 0.001$.
Abbreviations: M = male, F = female, SBP = systolic blood pressure, BMI = body mass index, Ponderal index = birth weight (kg) / birth length (m)3, Catch-up growth = weight at age 1 year − birth weight (kg), LDL = low-density lipoprotein, HDL = high-density lipoprotein, HOMA-index = insulin (mU/l) × glucose (mmol/l) / 22.5.

values during psychological stress (spelling), whereas it remained unchanged during upright posture (Table II). Diastolic blood pressure differed significantly during all test phases between the two groups. Heart rate increased in both groups during both challenges, and significant differences were seen only during mental stress. Although patients in Group 2 had a significantly elevated BMI compared with that in Group 1, a correlation between BMI and resting SBP was seen in Group 2 ($r = 0.53$, $p = 0.002$), but not in Group 1 ($r = -0.25$, $p = 0.44$).

Baroreceptor Sensitivity

Baroreceptor sensitivity decreased in both groups during the test; resting values were significantly lower in Group 2 than in Group 1 (Fig. 1).

Correlations between Hemodynamic Parameters and Biochemical Profile

The fasting insulin level correlated with resting as well as SBP during mental stress in Group 2 ($r = 0.74$ $p < 0.05$, and $r = 0.87$, $p < 0.05$, respectively), whereas there was no correlation with total or low-density lipoprotein cholesterol. A correlation of fasting insulin levels and BMI was observed as well ($r = 0.47$, $p = 0.05$). These correlations could not be found in Group 1.

Discussion

Large epidemiological studies have demonstrated a clear correlation between low birthweight and risk factors for cardiovascular disease such as obesity, hypertension, dyslipidemia, and type 2 diabetes in adulthood.[1–9] The same was shown in smaller patient groups with children born SGA tested in their pre- and postpubertal life.[10, 13, 21] In our study group of young adults born SGA, we observed that the prevalence of prehypertension as a predisposition for hypertension later in life is nearly the same as in the normal population (25 vs. 31%);[18, 23] however, as patients born SGA may develop further risk factors for cardiovascular disease, they may be at increased risk.

Our findings of slightly elevated blood pressure have been confirmed in other studies. Arends *et al.* found a resting SBP of 1.3 standard deviations in 28 prepubertal patients born SGA compared with normal control children.[10] Strambi *et al.* found an elevated resting SBP in 228 patients born SGA compared with 204 controls, with a marked rise between the ages of 7 and 18 years.[22]

According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, SBP deserves more attention as it is a major risk factor of cardiovascular disease.[18] By lowering the mean SBP in a population by 3.5 mmHg, cardiovascular mortality could be reduced by 26%.[8, 24, 25] Therefore; our study group could represent a population at increased risk for systolic hypertension and cardiovascular disease and should be monitored closely.

TABLE II Blood pressure, heart rate, and baroreceptor sensitivity during rest, during mental stress and during orthostatic challenge

	SBP > 120 mmHg (n = 11)	SBP ≤ 120 mmHg (n = 32)
SBP at rest	126.0 ± 5.9	109.9 ± 7.7 [a]
SBP during mental stress	135.1 ± 5.8	119.2 ± 10.3
SBP upright	136.0 ± 7.2	117.6 ± 14.3
DBP at rest	77.6 ± 5.5	67.7 ± 7.9 [b]
DBP during mental stress	86.4 ± 5.6	77.6 ± 9.9 [b]
DBP upright	91.9 ± 8.6	80.8 ± 12.1 [b]
HR at rest	72.7 ± 10.7	68.1 ± 10.1
HR during mental stress	88.8 ± 16.1	80.1 ± 10.2 [a]
HR upright	88.7 ± 10.5	91.3 ± 7.3
BRS at rest (ms/mmHg)	25.5 ± 10.3	34.9 ± 14.0 [a]
BRS during mental stress	14.1 ± 3.9	21.0 ± 11.8
BRS upright	9.5 ± 4.7	12.0 ± 6.4

[a] $p < 0.05$.
[b] $p < 0.001$.
Abbreviations: SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, BRS = baroreceptor sensitivity.

In our study group, we found no significant correlation between birth weight, gestational age, catch-up-growth in the first year of life, ponderal index at birth, and hemodynamic parameters. This might be due to the fact that this dependency would develop later in life. A large epidemiologic survey detected a decrease in SBP by 5.2 mmHg for each kilogram increase in birth weight among patients aged 64–71 years.[5] Therefore, our study group was probably too small and too young to detect any strong correlation at this young age.

As fasting insulin levels correlated strongly with resting SBP and BMI, we performed BRS testing in order to detect even slight changes in autonomic function of baroreceptor control. Such changes are well known among patients affected

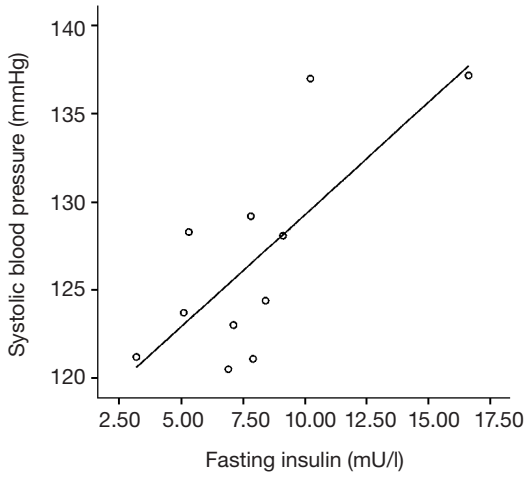

FIG. 1 Correlation of resting systolic blood pressure and fasting insulin levels in prehypertensive patients born SGA ($r = 0.74$, $p < 0.05$).

by diabetes mellitus type 2, even in the absence of autonomic neuropathy, and could play a key role in the development of systolic hypertension in these subjects.[26–29] Levels of BRS were significantly lower in prehypertensive patients at rest, indicating an impaired function of baroreceptor control. Whether this is due to a reduced response of the carotid baroreceptor itself or represents autonomic neuropathy at its initial stage remains to be determined. Surely, compared with normotensive individuals, beat-to-beat blood pressure regulation is less effective. One can therefore speculate that decreased baroreceptor control, which becomes worse throughout life, may contribute to the development of systolic hypertension as an additional factor.[8, 26–29]

Conclusion

We demonstrated that in a group of adolescents born SGA, SBP levels correlate with BMI as well as fasting insulin levels in individuals with prehypertension. Baroreceptor control was significantly reduced. Limitations of our study were the relatively small number and the heterogeneity of the group of patients, as SGA can be caused by several factors.

We speculate that impaired short-term blood pressure control in prehypertensive patients could play a key role in the development of hypertension. These patients may represent a group at risk for cardiovascular disease worsened by the development of a metabolic syndrome later in life, and we propose that these patients should be followed closely lifelong.

References

1. Eriksson J, Forsen T, Tuomilehto J, Osmond C, Barker D: Fetal and childhood growth and hypertension in adult life. *Hypertension* 2000;36:790–794
2. Eriksson JG, Forsen T, Tuomilehto J, Winter PD, Osmond C, Barker DJP: Catch-up growth in childhood and death from coronary heart disease: Longitudinal study. *Br Med J* 1999;318:427–431
3. Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJP: Early growth and coronary heart disease in later life: Longitudinal study. *Br Med J* 2001; 322:949–953
4. Huxley RR, Shiell AW, Law CM: The role of size of birth and postnatal catch-up growth in determining systolic blood pressure: A systematic review of the literature. *J Hypertens* 2000;18:815–831
5. Lackland DT, Egan BM, Ferguson PL: Low birth weight as a risk factor for hypertension. *J Clin Hypertens* 2003;5:133–136
6. Jaquet D, Czernikow P: Born small for gestational age: Increased risk of type 2 diabetes, hypertension and hyperlipidemia in adulthood. *Horm Res* 2003;59(S1):131–137
7. Barker DJ, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS: Fetal nutrition and cardiovascular disease in adult life. *Lancet* 2003;341: 938–941
8. Martyn CN, Barker DJ, Jespersen S, Greenwald S, Osmond C, Berry C: Growth in utero, adult blood pressure, and arterial compliance. *Br Heart J* 1995;73:116–121
9. Law CM, de Swiet M, Osmond C: Initiative of hypertension in utero and its amplification throughout life. *Br Med J* 1993;306:24–27
10. Arends NJT, Boonstra VH, Duivenvoordent HJ, Hofman PL, Cutfield WS, Hokken-Koelega ACS: Reduced insulin sensitivity and the presence of cardiovascular risk factors in short prepubertal children born small for gestational age (SGA). *Clin Endocrinol* 2005;62:44–50
11. Potau N, Gussinye M, Sanchez Ufarte C, Rique S, Vicens-Calvet E, Carrascosa A: Hyperinsulinemia in pre- and post-pubertal children born small for gestational age. *Horm Res* 2001;56:146–150
12. Lee PA, Chernausek SD, Hokken-Koelega ACS, Czernikow P: International Small for Gestational Age Advisory Board Consensus Development Conference Statement: Management of Short Children born Small for Gestational Age, April 24–October 1, 2001. *Pediatrics* 2003;111:1253–1261
13. Veening MA, Van Weissenbruch MM, Delemarre-Van de Waal HA: Glucose tolerance, insulin sensitivity, and insulin secretion in children born small for gestational age. *J Clin Endocrinol Metab* 2002;87:4657–4661
14. Soto N, Bazaes RA, Pena V, Salazar T, Avila A, Iniguez G, Ong KK, Dunger DB, Mericq V: Insulin sensitivity and secretion are related to catch-up growth in small-for-gestational-age infants at age 1 year: Results from a prospective cohort. *J Clin Endocrinol Metab* 2003;88:3645–3650
15. Barker DJP: Fetal programming of coronary heart disease. *Trends Endocrinol Metabol* 2002;13:364–368
16. Lucini D, Mela GS, Malliani A, Pagani M: Impairment in cardiac autonomic regulation preceding arterial hypertension in humans. *Circulation* 2002; 106:2673–2679
17. Largo RH: Catch-up growth during adolescence. *Horm Res* 1993;39(S3): 41–48
18. U.S. Department of Health and Human Services: National Institute of Health, National Heart, Lung and Blood Institute, National High Blood Pressure Education Program. Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *NIH Publication* 2004;No 04-5230
19. Fortin J, Habenbacher W, Gruellenberger R, Wach P, Skrabal F: Real-time monitor for hemodynamic beat-to-beat parameters and power spectra analysis of the biosignals. Proceedings of the 20th Annual International Conference of the IEEE Engineering in Medicine and Biology *Society* 1999;20: 360–363
20. Parati G, Ognaro G, Bilo G, Glavina F, Castiglioni P, Di Rienzo M, Mancia G: Non-invasive beat-to-beat blood pressure monitoring: New developments. *Blood Press Monit* 2003;8:31–36
21. Parati G, Omboni S, Frattola A, Di Rienzo M, Zanchetti A, Mancia G: Dynamic evaluation of the baroreflex in ambulant subject. In *Blood Pressure and Heart Rate Variability* (Ed. Di Rienzo M) , pp. 123–137. Amsterdam: IOS Press, 1992
22. Strambi M, Vezzosi P, Buoni S, Berni S, Longini M: Blood pressure in the small-for-gestational age newborn. *Minerva Pediatr* 2004;56:603–610
23. Stassen JA, Asmar R, De Buyzere M, Imai Yutaka, Parati G, Shimada K, Stergiou G, Redon J, Verdecchia P, and the Participants of the 2001 Consensus Conference on Ambulatory Blood Pressure Monitoring: Task Force II: Blood pressure measurement and cardiovascular outcome. *Blood Press Monit* 2001;6:355–370
24. Svetkey LP: Management of prehypertension. *Hypertension* 2005;45: 1056–1061
25. Sleight P: The HOPE-study (Heart Outcomes Prevention Evaluation). *J Renin Angiotensin Aldosterone* Syst 2000;1:18–20
26. Emdin M: The autonomous nervous system in diabetes. *Ital Heart J* 2001;2: 857–864
27. Ziegler D, Laude D, Akila F, Elghozi JL: Time- and frequency-domain estimation of early diabetic cardiovascular autonomic neuropathy. *Clin Auton Res* 2001;11:369–376
28. Frattola A, Parati G, Gamba P, Paleari F, Mauri G, Di Rienzo M, Castiglioni P, Mancia G: Time and frequency domain estimates of spontaneous baroreflex sensitivity provide early detection of autonomic dysfunction in diabetes mellitus. *Diabetologia* 1997;40:1470–1475
29. Riva P, Martini G, Rabbia F, Milan A, Paglieri C, Chiandussi L, Veglio F: Obesity and autonomic function in adolescence. *Clin Exper Hypertens* 2001;23:57–67