Size at Birth and Autonomic Function During Psychological Stress

Alexander Jones, Alessandro Beda, Alexandra M.V. Ward, Clive Osmond, David I.W. Phillips, Vivienne M. Moore, David M. Simpson

Abstract—Small size at birth is associated with exaggerated blood pressure responses to psychological stressors, which increase the risk of developing sustained hypertension in adult life. Explanatory mechanisms for this association are not well characterized. We investigated the hypothesis that an adverse fetal environment, reflected by small size at birth, persistently alters autonomic nervous system and baroreflex control of cardiovascular function, resulting in exaggerated blood pressure and heart rate responses to stressors. Men and women from an Australian prospective cohort study underwent a series of 3 psychological stressors (Stroop, mirror-tracing, and speech) while their blood pressure was recorded continuously using a Portapres. Indices of autonomic function were derived using spectrum analysis (wavelet packet transform), and baroreflex function was estimated using an adaptive autoregressive model. We found that women who were small at birth demonstrated increased levels of low-frequency blood pressure variability at rest ($r = -0.28; P < 0.05$) and during stress ($r = -0.42; P < 0.001$), reduced levels of high-frequency heart period variability ($r = 0.22; P < 0.05$), and reduced baroreflex sensitivity ($r = 0.34; P < 0.01$). These findings were not present in the men. This study provides evidence that markers of impaired fetal growth are related to autonomic cardiovascular control involving modulation of both sympathetic and parasympathetic function but in a sex-specific manner. We also provide the first human evidence of a relationship between size at birth and baroreflex function. (Hypertension. 2007;49:1-8)

Key Words: baroreflex ■ epidemiology ■ fetal ■ physiology ■ stress

There is now substantial epidemiological evidence that small size at birth is associated with a greater prevalence of hypertension and related conditions including coronary artery disease. Animal and preliminary human studies suggest that individuals who were small at birth have an enhanced biological response to stress. There is evidence that increased blood pressure responses to psychological stress may predict subsequent hypertension and coronary artery disease. Notwithstanding the failure of earlier studies to show similar associations and the suggestion that factors such as race, age, sex, and type of stressor might have important moderating roles, these findings point toward a potential coherent explanation for the association between fetal growth and the development of heart disease.

In 1997, an association was described between size at birth and resting pulse rate, a crude index related to sympathetic activity. Subsequent studies have reported associations between size at birth and more specific measures of sympathetic function. In a study of 114 adolescent twin pairs, pre-ejection period shortening (a marker of cardiac sympathetic stimulation) accounted for 63% to 83% of the association between birth weight and blood pressure. Recently, we demonstrated that low birth weight is associated with enhanced blood pressure and heart rate (HR) responses to psychological stressors. However, the associations were sex specific, being confined to women and not observed in men. A strikingly similar sex specificity was found in a more recent study from the Netherlands using the same psychological stressors. In contrast, direct recordings of muscle sympathetic nerve activity in 2 studies seem to be contradictory, providing evidence of both positive and negative associations between muscle sympathetic nerve activity and birth weight in men and women. However, both studies were small, and neither group reports their results separately by sex.

Although human studies are often limited to general indicators of prenatal adversity, such as size of the offspring at birth, animal studies implicate a number of processes that may account for the findings in human studies. Manipulations of the maternal environment, such as exposure to stress, reduced environmental temperature, or low-protein diet, and the fetal environment, such as hypoxia or surgical induction of placental insufficiency, produce evidence of increased sympathetic nervous system (SNS) function at rest and during stress and alterations in target organ innervation in
the adult offspring. However, the picture of associations between prenatal insults and later SNS function emerging from animal studies, as with the human studies, is not without its apparent contradictions, which may be accounted for by variations in the species or sex of the animals, type, timing or duration of insult, or methodologic approach used. Thus, further clinical studies that account for factors such as the sex of subjects are required to establish the impact that programming of SNS function might have on human health.

In this study, we used spectral analysis to derive indices of sympathetic and parasympathetic HR and blood pressure control in a large group of men and women. The actions of these limbs of the autonomic nervous system on the heart and vasculature are partially separable in the frequency domain, with distinct low- and high-frequency bands associated with HR and blood pressure variability. Estimates of spectral power in these bands yield indices relating to autonomic cardiovascular control. We assessed baroreflex function using a model that quantifies the strength with which spontaneous variations in blood pressure influence subsequent variations in HR.

**Methods**

For this study, 103 men and 76 women with a mean age of 26.3 (SD: 0.4) years, drawn from a larger cohort of adults, as described previously, underwent a set of 3 psychological stress tasks engaging the subjects in different cognitive challenges. They were born between June 1975 and July 1976 at the Queen Victoria Hospital in Adelaide, Australia, and established in 1984 as part of a World Health Organization collaborative study of ischemic heart disease risk factors in families. Information available from birth records was derived from parents’ postcode, and information about health, socioeconomic status, smoking and alcohol consumption, and mood (Centre for Epidemiologic Studies Depression Scale) was determined as the time difference between consecutive beat arrival times for which the manufacturer reports an accuracy of 10 ms (nonaccumulating). The servo adjust mode (Physicaloc) was switched off during the key measurement periods. The data processing used to derive indices of autonomic function is detailed in a data supplement available online at http://hyper.ahajournals.org.

**Statistical Analysis**

For all of the parameters, mean values for the 5-minute rest and stress task periods were obtained. Stress-induced increments in parameters were calculated with respect to the first rest period. Normalization of HP variability was carried out by dividing the low-frequency (LF) or high-frequency (HF) component by the sum of these components. Parameters with a skewed distribution were log transformed before parametric testing. Results in Table 1 are expressed as geometric means and geometric SDs. Body mass index, menstrual cycle phase, investigator; and resting HR were associated with cardiovascular responses to stress. Therefore, we adjusted for these potential confounders using multiple linear regression. As subjects were challenged with multiple stressors, analysis was carried out using a repeated-measures approach (generalized least squares random effects linear regression). This gives an improved estimate, for example, of the relationship between size at birth and overall stress response to the 3 tasks by accounting for differences between the tasks as a cofactor in the model. We transformed parameters to their z scores, providing normalized regression coefficients analogous to correlation coefficients.

**Results**

Table 1 shows SAP, HR, and derived parameters at rest and during the stress tasks. The mean finger arterial pressure measures were 122.4 mm Hg (SD: 14.7 mm Hg) in men and 122.9 mm Hg (SD: 15.2 mm Hg) in women, which, as expected, were significantly higher than pressures measured by brachial artery oscillography (men: 118 mm Hg; SD: 10.8 mm Hg; women: 106 mm Hg; SD: 10.3 mm Hg). Both sexes show marked increases of SAP and HR during stress compared with rest. LF variability of both HP (LF-HF) and SAP (LF-SAP), indicators of sympathetic activation declined during the Stroop and mirror tasks but rose above resting levels during the speech task. HF-HF variability (HF-HF), an indicator of parasympathetic activation, declined with respect to rest across all of the tasks. The ratio between LF-HF and HF-HF is often used as an indicator of sympathovagal balance with higher values representing a shift toward sympathetic activation. Both sexes showed a significant shift toward sympathetic activation during the speech task with respect to rest, but men (Table 1a) also showed a significant shift in the opposite direction during the mirror task. The use of normalized values for HF-HF and LF-HF (NHF-HF and NLF-HF)
gave similar results. In both sexes, baroreflex sensitivity ($\alpha$) was significantly lower during the 3 stress tasks than at rest, representing diminished baroreflex cardiovascular control as HR and blood pressure increased. Table 1 also shows the salivary cortisol concentrations during the stress tasks. In both sexes, cortisol concentrations fell after the Stroop and mirror tasks and rose in men, but not women, after the speech task.

There were no significant relationships between birth weight and the cardiovascular parameters in men (Table 2). However, in women (Table 2), low birth weight was associated with greater SAP during the stress tasks and greater stress-induced increases in SAP and HR with respect to resting levels. Both sympathetic activation, indicated by LF-SAP and the ratio between LF-HP and HF-HP, and parasympathetic withdrawal, indicated by HF-HP, were greater in low birth weight women. Similar relationships were observed using normalized values (data not shown). Furthermore, low birth weight women demonstrated reduced baroreflex sensitivity ($\alpha$) during the Stroop and speech tasks. Because evidence for increased sympathetic activation was also present at rest in the low birth weight women, this may represent an underlying characteristic that explains their exaggerated HR and blood pressure responses. The 3 key findings of increased sympathetic activation (LF-SAP), greater parasympathetic withdrawal (HF-HP), and decreased baroreflex control ($\alpha$) in the low birth weight women are illustrated in the Figure, together with comparative data from the men. There were no relationships between the cortisol measurements and birth weight during any of the tasks.

Of 76 women in the study, 68 had provided adequate information to calculate the phase of their menstrual cycle based on the date of their last menstrual period and their cycle length. Thirty-seven women were in the follicular phase, and 31 were in the luteal phase. Further analysis of the data showed that statistically significant relationships between birth weight and all of the cardiovascular parameters were confined to women in the luteal phase of their menstrual cycle. In subgroup analysis, this finding remained significant regardless of hormonal contraception use. However, formal testing of the interaction between birth weight and menstrual phase showed that this reached statistical significance ($P = 0.04$) for blood pressure but not for the other variables.

To elucidate the pattern of fetal growth that predicts these cardiovascular responses in women, we examined the associations between other neonatal measurements and cardiovascular function during stress. Table 3 shows relationships between size at birth and estimates of the combined effect of
the 3 stress tasks on cardiovascular parameters. These were calculated using a repeated-measures approach. Gestational age was not found to be a significant predictor of cardiovascular outcomes. The effects of low birth weight were paralleled by short body length and small head circumference. In further multiple regression analysis, we allowed for the confounding factors previously adjusted for in Table 2 (body mass index, investigator, phase of menstrual cycle, and resting HR) together with other potential confounding factors (smoking status, oral contraceptive pill use, index of relative socioeconomic disadvantage, Centre for Epidemiologic Studies depression score, and educational achievement). The findings presented in Table 3 remained largely unaltered in this further analysis. Relationships between birth weight, for example, and SAP ($r=0.37$; $P<0.05$), SAP increment from rest to stress ($r=0.28$; $P<0.05$), LF-SAP increment from rest to stress ($r=0.33$; $P<0.05$), LF-HP ratio ($r=0.28$; $P<0.05$), ratio between LF-HP and HF-HP ($r=0.34$; $P<0.05$), and $\alpha$ ($r=0.28$; $P<0.05$) during stress were similar or strengthened, whereas relationships between birth weight and HR ($r=-0.09$; $P$ value not significant), HR increment from rest to stress ($r=-0.21$; $P$ value not significant), and HF-HP ($r=0.19$; $P$ value not significant) were somewhat weakened.

**Discussion**

In this study, we have shown that the associations between small size at birth and increased HR and SAP responses to psychological stressors in women may have their origins in autonomic cardiovascular control and baroreflex function. The major findings (Figure) were that those with low birth weight showed increased indicators of sympathetic activation particularly during stress (as evidenced by LF-SAP in Tables 2 and 3), reduced parasympathetic activity (reduced HF-HP), and reduced baroreflex sensitivity ($\alpha$). These findings were strongly statistically significant and in multiple regression analysis were independent of potential confounders, such as obesity, smoking, socioeconomic status, and depression. The similar associations found with other measures of neonatal size and the absence of significant relationships with gestational age suggest that these associations are because of growth restriction rather than prematurity. In contrast, no significant relationships between size at birth and these cardiovascular parameters were found in the men (Table 2).

These findings add to the previously published human evidence showing that indices of sympathetic function, including resting pulse rate$^{10}$ and pre-ejection period,$^{11}$ are associated with fetal growth. That these associations only become apparent during psychological stress tasks may explain the reported discrepancies in the literature, particularly with respect to the studies of muscle sympathetic nerve activity, which were carried out either at rest$^{14}$ or during pharmacological stimulation.$^{11}$ The human data are also supported by evidence from animal studies showing that, in models of placental restriction in sheep$^{50}$ and rats,$^{21}$ the developing SNS is modified such that the adult animals display different SNS function during stress.

Both men and women showed significant increases of HR and SAP in response to the stressors that we used (Table 1). However, as we have noted previously,$^4$ responses were greater in men than women. A striking finding in our data was that women showed strong relationships between size at birth and both blood pressure and the underlying autonomic or baroreflex parameters, which were not observed at all in men (Table 2). An identical sex difference was reported in a recent study in the Netherlands, which seems to confirm our findings.$^{12}$ This sex difference is also a feature of many of the animal studies. For example, in the study of placental restriction in rats,$^{21}$ the association between birth weight and SNS function was limited to females, supporting the sex differences found in our study.

These differences are likely to reflect the different hormonal milieu of men and women. There is substantial evidence of a sex difference in autonomic cardiovascular control mechanisms in both animals$^{31}$ and in humans.$^{32}$

**TABLE 2. Normalized Regression Coefficients Relating Birth Weight to Cardiovascular Parameters at Rest and During 3 Stress Tasks**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Men (N=103)</th>
<th>Women (N=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Stroop</td>
</tr>
<tr>
<td>SAP</td>
<td>-0.05</td>
<td>0.03</td>
</tr>
<tr>
<td>I-SAP†</td>
<td>—</td>
<td>0.10</td>
</tr>
<tr>
<td>LF-SAP</td>
<td>-0.06</td>
<td>-0.02</td>
</tr>
<tr>
<td>HR</td>
<td>0.00</td>
<td>0.05</td>
</tr>
<tr>
<td>I-HR</td>
<td>—</td>
<td>0.13</td>
</tr>
<tr>
<td>LF-HP</td>
<td>0.01</td>
<td>-0.08</td>
</tr>
<tr>
<td>HF-HP</td>
<td>-0.09</td>
<td>-0.17</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>0.09</td>
<td>0.06</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>0.00</td>
<td>-0.07</td>
</tr>
<tr>
<td>Cortisol</td>
<td>-0.23</td>
<td>-0.04</td>
</tr>
</tbody>
</table>

*P<0.01.  
†P<0.05.  
‡Increment of SAP from rest to stress.  
§P<0.001.  
||Increment of HR from rest to stress.
healthy individuals, the evidence is consistent with a lower sympathoadrenal response to stressors in women than in men, probably as a result of estrogens. Our previous analysis of the blood pressure data from the present study suggested that low birth weight had abrogated the sex differences in the response to stress. This suggested that early growth restriction might impair the protective mechanisms that exist in women because of their higher levels of circulating estrogens. Because there is no clear evidence that early growth restriction is associated with lower circulating estrogen concentrations, this could represent a reduction in the tissue response to estrogens. This is governed by the nuclear receptors estrogen receptor-α and estrogen receptor-β, the latter in many instances inhibiting gene transcription. The distribution of these receptors differs widely in various tissues, especially within the brain, and could alter central regulation of blood pressure. Our finding that the association between birth weight and cardiovascular control in the women was confined to the luteal phase of the menstrual cycle is also highly suggestive of the involvement of gonadal steroids. Several studies suggest that hormonal responses to stressors are increased in the luteal as compared with the follicular phase. It is, therefore, of great interest that some recent animal studies also show that menstrual phase influences the effects of early growth restriction on hormonal responses to stressors.

A novel finding in our study was that measures of birth size were associated with altered cardiac baroreflex sensitivity in women. Although this is the first evidence of such a relationship in humans, it is supported by a recent study of sheep. In addition, peripheral sympathetic baroreflex sensitivity has been evaluated in humans by measuring the muscle sympathetic nerve activity response to infused nitroprusside, and although no direct birth weight effect was observed, the low

Key cardiovascular parameters in women (N=68; top) and men (N=103; bottom) during the Stroop task in relation to birth weight. To allow for the skewed nature of the variables plotted on the vertical axes, a logarithmic scale was used. Regression lines, r², and P values are given.
and normal birth weight groups had markedly different relationships between cortisol concentrations and sympathetic activity. Evidence is now emerging that the baroreflex may play a vital role in the long-term regulation of autonomic cardiovascular control. Lifelong effects on baroreflex function resulting from fetal growth restriction might explain some of the associations found between size at birth and adult SNS and parasympathetic nervous system function.

In the present study, cortisol concentrations declined after the Stroop and mirror tasks (Table 1), which accords with recent observations that these tasks do not reliably stimulate the hypothalamic–pituitary–adrenal axis (HPAA). The fall in the Stroop and mirror tasks (Table 1), which accords with previous investigators using similar tasks. In contrast, the more stressful speech task in our study, which caused greater blood pressure and HR responses, may have stimulated a more dominant response of the SNS and an overall increase in LF power. Support for this comes from growing evidence that disparate psychological stressors may produce blood pressure responses through distinct but stereotypical mechanisms. For example, cognitive tasks similar to the Stroop and mirror tasks appear generally to stimulate a blood pressure response by increasing cardiac output. In contrast, speech stressors may produce the response by increasing systemic vascular resistance, whereas cardiac output may actually fall (a hemodynamic response similar to that typically produced by the cold pressor test). However, these observations are not universal and may be modified by the age, sex, and race of individuals.

It has also been suggested that tasks that involve speech may produce respiratory frequencies outside the HF band. Although this might have an impact on assessment of the difference between measures taken at rest and those during stress, we have reported consistent associations between size at birth and measures of autonomic function within each task, which, if anything, might be weakened by the effect of speech. Finally, some care should be taken in drawing a comparison between the values for LF and HF power in our study with those of other studies. The wavelet packet transform technique that we used (for more detail, see the data supplement available online at http://hyper.ahajournals.org) separates these 2 bands at 0.18 Hz rather than the more typical 0.15 Hz leading to potential differences in the quantification of power in these bands. However, we found that the higher cutoff still fell close to the minimum power between the 2 spectral peaks and, therefore, was unlikely to have a significant impact on estimates of power in the 2 bands.

### Perspectives
This study shows strong relationships between impaired fetal growth and autonomic cardiovascular control, which are
restricted to women. There is evidence of modulation of sympathetic, parasympathetic, and baroreflex function (Fig- 
ure). Because these findings seem to be affected by the menstrual cycle, it is likely that interactions between fetal 
growth and adult gonadal hormone secretion mediate these effects. Our findings are the first to demonstrate developmental-
programming of baroreflex function in humans and to show that this programming may be sex dependent, raising
the exciting possibility of sex-specific pathways from prenatal adversity to later hypertension and disease. In the light
of a recently published study showing associations between size at birth and an enhanced adrenocortical stress response in
boys but not girls, the limited available data suggest that women and girls who were small at birth have greater sympathoadrenal
activity than their higher birth weight peers, whereas men and boys who were small at birth have an enhanced adrenocortical
response to stress, although this needs confirmation.

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Disclosures

None.

References


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