Fetal Programming

Long-Term Reprogramming of Cardiovascular Function in Infants of Active Smokers

Gary Cohen, Heather Jeffery, Hugo Lagercrantz, Miriam Katz-Salamon

Abstract—Newborn infants of smokers show symptoms of cardiovascular stress hyperreactivity. Persistent hyperreactivity could increase the risk of short- and/or long-term complications, such as hypertension. Here we determined whether incipient dysfunction in a smoker’s infant persists or worsens with age, by comparing cardiovascular reflex function of control and tobacco-exposed infants longitudinally from birth to 1 year. We compared infants born at term to nonsmoking couples (controls; n=19) and mothers who smoked moderately (average consumption=15 cigarettes per day; n=17). All were tested at 1 to 3 weeks, 3 months, and 1 year during sleep. We recorded blood pressure and heart rate noninvasively during passive repositioning (60° head-up tilt). Tilting control infants raised blood pressure slightly above baseline at 1 week (+2%) and much more at 1 year (+10%). This trend was reversed in the tobacco-exposed cohort (+10% at 1 week but only +4% at 1 year). At 3 months and 1 year, the heart rate response of tobacco-exposed infants to tilt was also abnormal (highly exaggerated). Our study reveals that maternal smoking leads to long-lasting “reprogramming” of infant blood pressure control mechanisms. The underlying dysfunction in a smoker’s infant could plausibly be a precursor or early marker of long-term susceptibility to complications, such as raised blood pressure. (Hypertension. 2010;55:722-728.)

Key Words: tilt ■ blood pressure ■ vasoconstrictor ■ vagus ■ nicotine

Recently we showed that cardiovascular stress reactivity is heightened in newborn infants of active smokers, much as it is in habitual smokers themselves.1 Because sympathetic overreactivity and autonomic dysfunction more generally are involved in the initiation and progression of disease,2–5 we undertook a 1-year follow-up study to track the natural history and to assess the likely impact of the incipient hyperreactivity seen in a smoker’s newborn infant.

We studied heart rate and blood pressure reactivity to abrupt repositioning (tilt from lying to upright then back to lying). Rapid adjustments are needed to stabilize blood flow to the brain when the body’s long axis is aligned with or perpendicular to gravity. These include changes in parasympathetic (vagal) and sympathetic tone to raise or lower heart rate, systemic vascular resistance, and blood pressure.6–9 Position-compensating reflexes are important during active maneuvers (standing, sitting, and turning) but probably also when we are stationary.10 Although a neonate responds qualitatively like an adult to a head-up tilt,1 we do not know how the circuits involved in this circulatory compensation develop as the capacity to stand and walk independently develops. Understanding this process and how it is disturbed by events before or around the time of birth may shed new light on how alterations in the body’s regulatory mechanisms contribute to sudden death in infancy or accelerate disease onset.4,11 The purpose of the longitudinal follow-up study reported on here was to determine whether “second-hand” exposure to tobacco products from conception is associated with persistent, age-dependant anomalies in positional cardiovascular control.

Methods

Subjects

Our cohort was composed of control infants born at term to nonsmokers (both parents; n=19) and term-born infants of women who smoked (n=17). All were appropriately grown (>10th birth-weight percentile for gestational age), and all were breastfed from birth (Table 1). None of the mothers had preeclampsia, diabetes mellitus, or hypertension, and all denied using illicit substances. Smokers and their partners estimated the number of cigarettes smoked per day during each trimester of pregnancy and subsequently (questionnaire). Each infant was studied as soon as possible after birth (half just before discharge, the remainder at 2 to 3 weeks), at 3 months, and again at 1 year. Data collection (and analysis) was unblinded. The study complied with the Declaration of Helsinki. The relevant institutional ethics review committees approved all of the procedures, and written informed consent was obtained from the parents of all of the infants who participated.

Procedures

Infants were studied during a daytime nap. They lay supine in a warm (20°C to 21°C) room and were lightly dressed. Blood pressure and heart rate were recorded from a wrist cuff (Finometer, FMS), as

Received September 13, 2009; first decision September 28, 2009; revision accepted December 22, 2009.
From the Department of Women and Child Health (G.C., H.L., M.K.-S.), Karolinska Institute, Stockholm, Sweden; Department of Neonatal Medicine (G.C., H.J.), Royal Prince Alfred Hospital, Sydney, Australia.
Correspondence to Gary Cohen, Department of Women and Child Health, Neonatal Unit, Karolinska Institute, Elevhemmet H1-02, S-171 76 Stockholm, Sweden. E-mail Gary.Cohen@ki.se
© 2010 American Heart Association, Inc.
Hypertension is available at http://hyper.ahajournals.org
DOI: 10.1161/HYPERTENSIONAHA.109.142695

722
Table 1. Study Population

<table>
<thead>
<tr>
<th>Age Group</th>
<th>GA, wk</th>
<th>PNA, d</th>
<th>PMA, wk</th>
<th>Birth Weight, g</th>
<th>Study Weight, g</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1 wk</td>
<td>39±0.5</td>
<td>4±1</td>
<td>40±0.4</td>
<td>3300±94</td>
<td>3238±90</td>
<td>46</td>
</tr>
<tr>
<td>Tobacco, n=9</td>
<td>39±0.3</td>
<td>4±1</td>
<td>40±0.4</td>
<td>3103±144</td>
<td>2967±153</td>
<td>20</td>
</tr>
<tr>
<td>2 to 3 wk</td>
<td>40±0.6</td>
<td>19±3</td>
<td>42±0.4</td>
<td>3475±195</td>
<td>3728±220</td>
<td>13</td>
</tr>
<tr>
<td>Tobacco, n=8</td>
<td>39±1</td>
<td>15±2</td>
<td>41±1</td>
<td>3147±163</td>
<td>3244±168</td>
<td>18</td>
</tr>
<tr>
<td>3 mo</td>
<td>39±0.4</td>
<td>91±5</td>
<td>52±0.6</td>
<td>3435±125</td>
<td>5772±241</td>
<td>28</td>
</tr>
<tr>
<td>Tobacco, n=17</td>
<td>39±0.3</td>
<td>91±8</td>
<td>53±1</td>
<td>3121±121</td>
<td>5726±391</td>
<td>33</td>
</tr>
<tr>
<td>1 y</td>
<td>39±1</td>
<td>375±8</td>
<td>93±1</td>
<td>3364±158</td>
<td>10 688±584</td>
<td>23</td>
</tr>
<tr>
<td>Tobacco, n=11</td>
<td>39±0.5</td>
<td>380±10</td>
<td>94±1</td>
<td>3034±166</td>
<td>10 556±428</td>
<td>25</td>
</tr>
</tbody>
</table>

Infants of nonsmokers (controls) and mothers who actively smoked (tobacco) were studied during a daytime nap. The total No. of tilt tests analyzed is indicated in column 7 (n). GA indicates gestational age at birth; PNA, postnatal age; PMA, postmenstrual age (gestational + postnatal ages). Data are mean±SD. There were no significant differences between groups at any age (ANOVA). See also Figure 1.

Results

The study cohort is described (Table 1). Although not all of the attempts at each age succeeded, each infant was success-
controls) and did not increase further with age: at 3 months and still at 1 year it was 50% to 65% below that of age-matched controls (Figure 3A and 3B).

Tobacco Exposure Amplifies the Effect of Improved Venous Return

Reversing posture from semiupright back to horizontal boosts venous return and cardiac preload. This maneuver triggered a biphasic heart rate response like that seen when tilting to upright (see Figure 2) but no rise in blood pressure, which normally fell slowly back to baseline over 10 to 15 beats (controls). The same maneuver in a smoker’s infant caused blood pressure to surge, especially at 1 year (Figure 3C).

Adjustment for Potential Confounders

Birth weight (slightly lower in the tobacco-exposed cohort) and body mass index at study did not contribute significantly (0.05% to 1.15%) to the total variance in outcome at any age. We also failed to observe any significant male-female differences at any age ($P=0.13$ to 0.53).

Reproducibility of the Pressor Response

The within-subject coefficient of variation for the mean blood pressure rise during tilt-up was 23% (range: 12% to 35%), and between-subject coefficient of variation was 11% (range: 6% to 14%), with no differences between controls and infants of smokers at any age.

Discussion

Our study revealed long-lasting reprogramming of circulatory control in infants of women who smoke. Cardiac and vasoconstrictor mechanisms, both of which are needed for effective short-term, seconds-to-minutes blood pressure regulation, were impaired as a result. By the time a smoker’s infant begins to stand and remain upright, therefore, routine blood pressure compensation is inadequate. This orthostatic dysfunction could be an early symptom of long-term susceptibility to a variety of complications, including raised blood pressure.12,13

Why does blood pressure rise slightly when an infant (or an adult for that matter) is upright? One reason is surely that a higher systemic driving pressure guarantees that the brain can continue to draw off sufficient blood flow via local autoregulatory mechanisms to meet its needs. In infants, as in adults, this is achieved by increasing heart rate briefly and narrowing the blood vessels to shift blood away from organs that can best tolerate reduced flow. The first component reflects vagal withdrawal reactivation9 and the second (quantitatively the more important), sympathetic peripheral vasoconstriction.6,14 Vasoconstriction also helps counteract the lower body hydro-

---

**Table 2. Parental Smoking Status and Estimated Daily Cigarette Consumption**

<table>
<thead>
<tr>
<th>Parent</th>
<th>During Pregnancy (n=17)</th>
<th>At 1 to 3 wk (n=17)</th>
<th>At 3 mo (n=1)</th>
<th>At 1 y (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother smoked, %</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>90*</td>
</tr>
<tr>
<td>Father smoked, %†</td>
<td>77</td>
<td>77</td>
<td>77</td>
<td>70</td>
</tr>
<tr>
<td>Average daily cigarette consumption, mean±SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mothers</td>
<td>15±5</td>
<td>14±5</td>
<td>16±6</td>
<td>18±5</td>
</tr>
<tr>
<td>Fathers</td>
<td>16±4</td>
<td>16±3</td>
<td>14±5</td>
<td>17±4</td>
</tr>
<tr>
<td>Smoked 1 cigarette per day in the house, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mothers</td>
<td>77</td>
<td>35</td>
<td>35</td>
<td>60</td>
</tr>
<tr>
<td>Fathers</td>
<td>63</td>
<td>56</td>
<td>63</td>
<td>70</td>
</tr>
</tbody>
</table>

*Smokers were recruited through antenatal clinics and quizzed about their and their partner’s smoking habits at each visit. The proportion (percentage) of mothers/fathers in these households still smoking at each visit and mean±SD daily consumption as reported by the mother, are shown.

†One father who lived apart from his spouse was excluded.
static pressure effects of gravity (capillary fluid filtration and venous pooling). Modulation of sympathetic constrictor tone is consequently the key to keeping pace with the considerable hemodynamic stress that develops when upright. If this mechanism is weak and blood pressure fails to rise enough, (a smoker’s infant) cerebral underperfusion and postural edema could worsen. Cross-sectional studies of adults, furthermore, suggest that the risk of developing hypertension is increased if positional blood pressure changes are either too high or too low.

Although the resting blood pressure of a smoker’s infant is in fact mildly elevated early, it appears to “normalize” over time. Diastolic/systolic pressures are reportedly up to 15% higher at 6 months but only 5% to 8% higher at 1 year and close to normal at 2 to 5 years. Our data from 1-year-olds indicate that even if this is so there may still be significant underlying dysfunction. This dysfunction resembles in some respects classical orthostatic “intolerance.” It may be a sign of irreversible programming of inherent blood pressure control mechanisms, in which case overt symptoms, such as a persistently elevated blood pressure, may reappear much later on. Disease does, after all, develop in stages. In adults, the progression of cardiovascular pathophysiology is resolved but lead to others, establishing a slow, inexorable pathological progression.

The issue of whether nicotine or other constituents/actions of tobacco are mostly to blame for infant dysfunction is unresolved and controversial. We suggested previously that the stress hyperreactivity in a smoker’s newborn infant is a residual sympatho-mimetic effect of nicotine.1 With considerably more data, we can now say that this hyperreactive state is already waning at 2 to 3 weeks and is completely and persistently reversed by 3 months. Normally after birth sympathetic drive is subject to increasing parasympathetic restraint, which is why heart rate slows and sympathetic reactivity “dips” after the first month (Figures 1 and 3, controls). A smoker’s infant is unusual, because these changes are exaggerated, with sympathetic reactivity becoming too weak and counteracting vagal tone too strong. Similar changes are described in immature animals exposed to nicotine at levels that simulate human exposure and can be traced to nicotine-induced disruption of sympathetic (adrenergic) and parasympathetic (cholinergic) signaling. The functional parallel between animal data and our data are intriguing because infants, unlike animals, are exposed to many other toxic constituents of tobacco, and most exposure to nicotine and its metabolites occurs in utero, with very little occurring after birth via breast milk and inhaled smoke. The postnatal decline in stress hyperreactivity in a smoker’s infant is also reminiscent of another nicotine-related phenomenon. Adults who abstain from nicotine experience a partial reversal of the hyperadrenergic state that it causes, which contributes to the rapid reduction in cardiovascular disease risk among ex-smokers. A sudden switch from high to low nicotine exposure at birth could partly explain why stress reactivity in a smoker’s infant is paradoxically heightened for a week or so after birth and why, as a new postexposure homeostasis is achieved, “rebound” depression develops. If this is so, it may be difficult to separate delayed effects

---

**Figure 2.** Immediate postural circulatory compensation. Beat-by-beat changes during the initial 20s (average of all tilts) are shown (A through C) and peak responses compared (D). An abrupt rise and fall in heart rate was always followed by a rise and fall in systolic (SBP) and diastolic (DBP) blood pressure. Peak heart rate (HR) and blood pressure responses progressively strengthened after 3 months (D). For infants of smokers, the HR and blood pressure changes were exaggerated at 3 months and 1 year (B and C). Data are mean±SD; *P<0.05. Note: HR profiles were comparable at 1 and 3 weeks, so for clarity only an average is shown (A).
attributed to nicotine withdrawal from those arising de novo from ongoing low-level exposure.

Vagally induced slowing of the heart is common in infancy and may be elicited by movement (Figure 2), as well as noxious stimuli (eg, eye pressure, facial immersion, gastric reflux, airway obstruction, and asphyxia).31–33 The heart must not slow excessively, however, otherwise dangerous circulatory depression could ensue. For this reason, vagal potentiation is considered a likely lethal predisposing factor in sudden infant death syndrome.4,24,34 Here we show that it indeed meets key criteria for a putative circulatory mechanism involved in sudden infant death syndrome for the following reasons: it occurs in a cohort known to be at high risk35; (2) it develops at a time (1 to 3 months after birth) that coincides with a peak in unexplained death35,36; and (3) it is unmasked by sleep and mild stress. A longer-term consequence of excessive vagal tone is that resting heart rate of a smoker’s infant is reduced considerably by 1 year (Figure 1). Because ventricular filling time and the force of contraction increase as the heart slows, postural maneuvers that boost cardiac filling pressures may then trigger undesirable surges in stroke volume, cardiac output, and blood pressure (Figure 3C). Such events could occur often, may be amplified by dysfunction in other pressure-regulating systems,37 and could place additional stress on the heart and vasculature of these infants.20,38

**Limitations**

We did not verify tobacco exposure biochemically because it is difficult, expensive, and resisted by some parents. Biomarkers are useful but have limitations, especially in quantifying long-term exposure, and do not invalidate assessment by questionnaire.39 Self-reporting does provide a reliable index of exposure of/ by self-confessed smokers.27 Were our control infants truly nonexposed? We believe so. We did not enrol parents who were ex-smokers because they may relapse, misreport their status, and bias the data. Moreover, the main
source of environmental exposure for children of the age that we studied is the home. In Sweden, where our study was done, paid parental leave is generous (18 months, costs shared between the state and the employer). We can be confident, therefore, that our nonsmokers did not routinely leave their infants with others (eg, grandparents) who inadvertently exposed them to tobacco smoke. We did not investigate whether cardiovascular dysfunction in a smoker’s infant is further modified by preterm birth, a recognized complication of maternal smoking. Perhaps because the number of subjects was small, we found no significant effects either of sex or size (at birth or follow-up), although both factors are known to program the development of the cardiovascular system.40,41 One thing our study was not designed to do was to disentangle the effects of prenatal and postnatal exposure, that is, to determine whether dysfunction in a smoker’s infant is an enduring effect of passive smoking before birth, after birth, or both. All of our infants of smokers were exposed to low levels of tobacco after birth via breast milk and environmental smoke. Although most smokers these days claim not to smoke near their baby, biomarker studies reveal that exposure continues, albeit at low levels.42 Even low-level environmental exposure could still complicate effects that originate before birth.43

Perspectives
Passive smoking later in life increases the risk of cardiovascular disease, but could the seeds of adult disease be planted early on, in infancy and early childhood? At least 10% to 15% infants worldwide are exposed to the danger of tobacco smoke before they are born, and, for many, exposure will continue after birth at home. Our study reveals for the first time that this early life exposure does indeed lead to long-lasting reprogramming of infant blood pressure control mechanisms. The resulting dysfunction is not necessarily manifested, at least in the early stages, by accompanying clinical symptoms, such as altered resting blood pressure. The long-term significance of reprogramming is uncertain at present, but by increasing vulnerability to stress it could open the door to such problems as hypertension later on. Identifying precursors or early markers of susceptibility to these complications has broad public and global health implications because it may lead to earlier diagnosis, treatment, and perhaps prevention of cardiovascular disease.

Acknowledgments
We thank Lena Legnevall and for her skilful and dedicated assistance, Håkan Eriksson and Björn Hellberg for their engineering brilliance, and the parents of those infants who participated for their enthusiastic cooperation.

Sources of Funding
This work was supported by the Flight Attendants Medical Research Institute, Stiftelsen Frimurare Barnhuset, Sällskapet Barnavärd, Karolinska Institute Research Fund, Stiftelsen Samariten, the Laerdal Foundation for Acute Medicine, Heart and Lung Foundation, and the Financial Markets Foundation for Children.

Disclosures
None.

References


