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The dynamics of cardiac autonomic control in sleeping preterm neonates exposed *in utero* to smoking

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HIGHLIGHTS

- Prenatally smoke-exposed neonates have low vagal and elevated sympathetic activities during sleep.
- Maternal smoking during pregnancy disrupts heart rate control dynamics in the neonate.
- The observed effects can be attributed to exclusively prenatal smoking exposure.

ABSTRACT

Objective: We aimed to determine whether *in utero* exposure to smoking may influence the activity and dynamics of cardiac autonomic control in preterm infants. We hypothesized that cardiac autonomic control is altered in preterm infants exposed prenatally to smoking and that these effects may vary as a function of the sleep state. *Methods:* We studied healthy, preterm neonates born to mothers who had smoked throughout pregnancy but not since birth ($n = 16$). *In utero*-exposed neonates were matched with control preterm neonates born to non-smoking mothers ($n = 18$). Cardiac autonomic control was monitored as a function of the sleep state by assessing heart rate variability with both linear and non-linear methods. *Results:* Preterm neonates with *in utero* exposure to smoking displayed alterations (relative to control neonates) in short-term cardiac autonomic control in all sleep states. These alterations included low vagal activity, elevated sympathetic activity, and low complexity and adaptability in heart rate control dynamics. *Conclusions:* Our results constitute direct evidence that cardiac autonomic activity and control are altered in sleeping preterm infants exposed to smoking *in utero*. *Significance:* These alterations may place the affected infants at a higher risk of neurological and cardiovascular complications, which could conceivably persist throughout childhood and adulthood.

1. Introduction

Tobacco smoking during pregnancy has still a high prevalence worldwide, and is the most important potentially preventable cause of a range of adverse gestational and developmental outcomes (Salihu and Wilson, 2007). There is unequivocal evidence of a close relationship between maternal smoking during pregnancy on one hand and higher incidences of preterm birth, infant morbidity and infant mortality on the other (Green et al., 2005). Worldwide, nearly 10% of all deliveries are preterm (Beck et al., 2010). Preterm birth is the leading cause of neonatal death (27%) (Lawn et al., 2010) and is a risk factor for elevated blood pressure (Hack et al., 2005) and hypertension (Eriksson et al., 2001) later in life.

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Furthermore, a number of studies have found that smoking exposure at critical stages of fetal and infant development alters autonomic blood pressure control mechanisms (Browne et al., 2000; Cohen et al., 2008; Viskari-Lähdeoja et al., 2008), and that these effects persist for up to 1 year after birth (Cohen et al., 2010). Although a few studies have examined the influence of smoking exposure on heart rate variability (HRV), most failed to find a difference between control and smoke-exposed infants (Browne et al., 2000; Galland et al., 2000; Viskari-Lähdeoja et al., 2008). Other studies have yielded conflicting results, with either lower parasympathetic tone (Franco et al., 2000) or lower sympathetic tone (Thiriez et al., 2009) in infants born to smoking mothers. This discrepancy may be due to shortcomings in study design. The influence of sleep states has not always been considered (Browne et al., 2000; Thiriez et al., 2009; Viskari-Lähdeoja et al., 2008), even though active sleep (AS) and quiet sleep (QS) differ in terms of autonomic function (Frasch et al., 2007). Also, it has not been possible to determine whether the observed effects were due to prenatal exposure or postnatal exposure (Browne et al., 2000; Franco et al., 2000; Galland et al., 2000; Viskari-Lähdeoja et al., 2008).

There is now evidence to support the hypothesis championed by Goldberger et al. (1990), whereby the HR in the developing human infant is subject to non-linear and possibly chaotic-like changes (Sugihara et al., 1996). A conventional spectral analysis of HRV (as used in the above-cited studies) can provide information on cyclic variations but not on the dynamic properties of the fluctuations. Non-linear methods are typically designed to assess quality, scaling and correlation properties rather than the magnitude of variability assessed by conventional HRV methods. To the best of our knowledge, non-linear methods of HRV analysis have never been used to study the effects of smoking exposure. Importantly, non-linear methods are known to be suitable for analyzing non-stationary time series and may provide additional power in characterizing complex systems such as cardiac autonomic control in infants (Mäkikallio et al., 2002; Morren et al., 2005).

According to current literature, there is no direct evidence to show that *in utero* exposure to smoking alters cardiac autonomic control in neonates, and the underlying pathophysiological mechanisms remain poorly understood. The objective of the present study was to determine whether *in utero* exposure to smoking in preterm infants may influence the activity and dynamics of cardiac autonomic control. We hypothesized that cardiac autonomic control (as measured in an HRV analysis) is altered in preterm infants exposed prenatally to smoking and that these effects may vary as a function of the sleep state. The HRV's characteristics were examined with linear and non-linear methods, in order to extract more detailed quantitative and qualitative information.

2. Methods

2.1. Patients

Enrolment of preterm neonates, including eligibility requirements and informed consent, have been described in detail previously (Stéphan-Blanchard et al., 2013). None of the neonates had disorders or treatments (for at least the 7 days preceding the study) known to influence cardiac autonomic control. To control whether infants displayed an acid/base disturbance caused by a respiratory and/or metabolic problem, base excess was measured during the first 7 days of life. The local institutional review board approved the study, which complies with the Declaration of Helsinki.

Shortly after each infant's arrival in the NICU, a structured questionnaire on prenatal history and exposure to tobacco smoke was administered. Medical records were reviewed for any mention of smoking during pregnancy and were compared with the mother's statement. Neonates whose mothers reported (i) illicit substance abuse or (ii) passive smoking at home or at work during their pregnancy were excluded from the study. Only neonates born to women who reported smoking more than 1 cigarette per day throughout the entire pregnancy were included in the study. The included, exposed infants were matched for gestational age at birth and postmenstrual age at the time of the study with control infants born to non-smoking mothers.

2.2. Study protocol

The study protocol has been described in detail previously (Stéphan-Blanchard et al., 2013). Neonates were recorded polygraphically (two electro-encephalograms, eye movements, an electrocardiogram, respiratory signal, body movements, oxygen saturation) at thermoneutrality, in the supine position during a morning nap.

Sleep states were scored as recommended by the Pediatric Task Force (Grigg-Damberger et al., 2007). All artifacts or other events that might have influenced the infant's HR were identified manually and excluded from the analysis.

2.3. HRV analysis

Recording and calculation of linear HRV parameters have been described elsewhere (Stéphan-Blanchard et al., 2013). Briefly, electrocardiogram signals were sampled at 2000 Hz. R wave detection, calculation of RR intervals and HRV analysis were performed with Kubios HRV® software (Biosignal Analysis and Medical Imaging Group, Department of Physics, University of Kuopio, Kuopio, Finland).

Standardized time- (mean HR, SDNN, r-MSSD and pNN25) and frequency-domain (power spectra in the very low (VLF), low (LF) and high (HF) frequency bands, LF/HF ratio) HRV parameters were extracted in order to characterize both overall, short- and long-term cyclic components responsible for HR variability.

2.3.1. Detrended fluctuation analysis (DFA)

DFA quantifies the intrinsic, fractal-like correlation properties of dynamic systems (Peng et al., 1995). A scaling exponent α represents the time series' correlation properties (see Appendix A). If $\alpha < 0.5$, the signal is anti-correlated (i.e. there are negative correlations in the signal); if $\alpha = 0.5$, the signal is uncorrelated (white noise); lastly, if $\alpha > 0.5$, there are positive correlations in the signal. In the present study, we sought to characterize the scaling behavior of the fluctuation function on short and long timescales, in order to establish whether there were short- or long-range correlations. Therefore, two scaling exponents were estimated (with a linear fit) over a specific scaling range for each segment: α_1 in the range $4 \leqslant n \leqslant 16$ and α_2 in the range $16 \leqslant n \leqslant 64$, which respectively characterize correlation behavior on short and intermediate timescales.

2.3.2. Approximate entropy (ApEn) and sample entropy (SampEn)

ApEn quantifies the unpredictability of fluctuations in a time series (see Appendix A) and yields the logarithmic probability that patterns of observations will repeat themselves within determined tolerance limits on next incremental comparisons. A low value of ApEn corresponds to lower complexity and a more predictable time series. SampEn is similar to ApEn but does not take account of self-matches and thus reduces the superimposed bias. SampEn is also less dependent on the length of the time series (Richman and Moorman, 2000). Both ApEn and SampEn are estimates of the negative natural logarithm of the conditional probability that