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ORIGINAL ARTICLE

Assessing variability in neonatal blood pressure, notably in hypotension*

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Summary
New reports corroborate our prior finding that hypotension in infancy is associated with impaired neurodevelopment later in childhood. We had also found that neurological deficit is further associated with a more pronounced circadian variation in transcutaneous pO_2 ($tcpO_2$). New evidence in adulthood prompts the recommendation to automatically monitor vital signs for continued surveillance, relying on the methods of chronobiology for data analysis as-one-goes. This applies notably early in extra-uterine life when infants may be particularly sensitive to ischemic cerebral injury secondary to systemic hypotension. Monitoring at this sensitive lifetime stage has also provided a glimpse of unseen effects of the cosmos on the patterns of blood pressure variability, detected by chronomics.

Key words: blood pressure; chronomics; circadian; ischemic cerebral injury; hypotension; neurological development

** Dedicated affectionately, on the occasion of his 91st birthday, to Prof. Dr. med. Theodor Hellbrügge, Dr. h. c. mult., chronopediatrician par excellence, by his 1960 contribution in Cold Spring Harbor, mapping the development of the circadian system, ushering in concerns about the newborn's and subsequently the child's unseen yet discernible risks in developing cardiovascular disease.*

INTRODUCTION

Irrespective of treatment, infants with low blood pressure (BP) have worse neurodevelopment than infants with acceptable BP (Batton et al. 2009). Metabolite ratios from near-term proton magnetic resonance spectroscopy were not predictive of Bailey scores at 18 to 24 months adjusted age (Augustine et al. 2008). These relatively recent reports prompt us to revisit results from an earlier study (Syutkina et al. 1999) to illustrate how the methods of chronobiology may be useful for risk assessment, so that prophylactic measures may be implemented in a timely manner.

In the case of cardiovascular disease risk assessment, population studies suggested that circadian characteristics of BP and heart rate (HR) in early extrauterine life may be influenced by much lower-frequency cycles spanning decades (Halberg et

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al. 1990, Syutkina et al. 2003), verifiable on an individualized basis in adulthood (Halberg et al. 2008b). Whereas circadians are our focus herein, the merit of keeping the data archived serves not only for an individualized assessment of neurological development later in infancy, but it also provides for population-based meta-analyses examining a host of putative influences, including those from the cosmic environment (Halberg et al. 2001).

SUBJECTS AND METHODS

Eight infants (6M, 2F) born at gestational ages 35–37 weeks with a birth weight between 1750 and 2400 g were monitored each for 25 hours between the ages of 2 and 14 days. All infants were clinically stable. None had serious neurological problems or abnormal ultrasound findings.

Blood gases (pO_2 and pCO_2) were continuously recorded transcutaneously using the TCM-222 monitor (Radiometer, Denmark). Records were digitized for consecutive 2-minute intervals. Systolic (S) and diastolic (D) BP and HR were measured non-invasively at 20- to 30-minute intervals with the BX5 monitor (Colin Medical Instruments, Komaki, Japan).

Each record was analyzed by cosinor (Halberg 1980, Cornélissen and Halberg 2005), involving the least squares fit of a 24-hour cosine curve to the data, yielding estimates of the MESOR (M, a rhythm-adjusted mean), double amplitude (2A, a measure of the extent of predictable change within a day), and acrophase (Φ, a measure of the timing of overall high values recurring each day). Trough and peak values were assessed as the bathymetron (= M–A) and acrometron (= M+A), respectively to approximate the lowest and highest values anticipated to recur each day.

Six years later, the same children had neurological and psychological exams, including electro-encephalography, on the basis of which they were classified into two groups with more (N=5) or less (N=3) severe abnormalities.

Results from monitoring during the perinatal span were compared by Student t-test between the two groups at the significance level $2\alpha=0.05$.

RESULTS

A statistically significantly lower circadian trough of SBP (64.2 ± 2.2 vs. 79.7 ± 4.8 mmHg) and DBP (38.8 ± 1.7 vs. 48.5 ± 3.1 mmHg) and a statistically significantly higher circadian $tcpO_2$ peak (92.0 ± 2.9 vs. 78.0 ± 2.4 mmHg) between the ages of 2 and 14 days predicted future neurological deficit assessed at 6 years of age. Neurological deficit was also associated with a statistically significantly more prominent circadian variation in $tcpO_2$.

DISCUSSION

Preterm infants may be susceptible to ischemic cerebral injury, secondary to systemic hypotension, because of the occurrence of a pressure-passive cerebral circulation (Lou et al. 1979). Spans of relative ischemia tend to occur regularly as part of the circadian variation of cerebral blood volume determined by near-infrared spectrophotometry (Syutkina et al. 1999).

In adulthood, an excessive circadian amplitude of BP carries a risk greater than that associated with high BP (Cornélissen et al. 2007, Halberg et al. 2007). This condition and other vascular variability disorders can greatly increase cardiovascular disease risk beyond that of an elevated BP MESOR (Halberg et al. 2009). A cosinor approach (Halberg 1980, Cornélissen and Halberg 2005) separated groups of children and newborns with a positive vs. negative family history of high BP and/or related vascular disease, a positive history being associated with a larger BP variability (Halberg et al. 1986). One must be aware, however, for vascular disease risk assessment of the long cycles that can jeopardize a test based solely on circadian variability (Halberg et al. 1990). In the future, a minimal 7-day record of BP is recommended for routine neonatal screening (Cornélissen et al. 1987, Syutkina et al. 2003) as soon as affordable unobtrusive instrumentation permits.

CONCLUSION

The availability of automatic BP monitoring in the NICU and of methodology to easily assess the circadian and infradian variation from around-the-clock week-long measurements could be taken advantage of to draw guidelines for the important, yet still problematic decision when to provide therapy for low BP in preterm infants (Batton et al. 2009), and to monitor the response to treatment. Conclusions from this more recent study are in keeping with our original report (Syutkina et al. 1999). While they are particularly pertinent during the

neonatal span, they apply equally at all ages, as apparent from an international consensus (Halberg et al. 2008a).

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