Chapter 23
Influence of the Maternal Use of Labetalol on the Neurogenic Mechanism for Cerebral Autoregulation Assessed by Means of NIRS

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Abstract Labetalol is a drug used in the treatment of hypertensive disorders of pregnancy (HDP). In a previous study we investigated the influence of the maternal use of labetalol on the cerebral autoregulation (CA) mechanism of neonates. In that study, we found that labetalol induces impaired CA during the first day of life, with CA returning to a normal status by the third day after birth. This effect was hypothesized to be caused by labetalol-induced vasodilation. However, no strong evidence for this claim was found. In this study we aim to find stronger evidence for the vasodilation effect caused by labetalol, by investigating its effect on the neurogenic mechanism (NM) involved in CA. The status of the NM was assessed by means of transfer function analysis between the low frequency content of the autonomic control activity (LFA), obtained by processing of the heart rate (HR), and the regional cerebral oxygen saturation ($rScO_2$). We found that neonates from mothers treated with labetalol presented a lower LFA and an impaired NM response during the first day of life, with values returning to normal by the end of the third day. These results reflect a vasodilation effect caused by labetalol, and indicate that the impaired CA observed in the previous study is caused by vasodilation.

Keywords Labetalol • Hypertensive disorders of pregnancy • Vasodilation effect • Neurogenic mechanism • Cerebral autoregulation

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1 Introduction

Labetalol is an α_1 and non-selective β adrenergic antagonist that is normally used for the treatment of hypertensive disorders of pregnancy (HDP) [1]. Since labetalol easily passes the placental barrier, it accumulates in the neonate [2]. Therefore, its effects on the cerebral circulation of neonates should be studied. In the literature scarce information can be found about the influence of the maternal use of labetalol on the neonatal cerebral autoregulation (CA).

CA is a complex process that refers to the maintenance of a constant cerebral blood flow (CBF) over a broad range of arterial blood pressures. Several mechanisms are involved in CA; in the literature the myogenic, metabolic and neurogenic mechanisms have been described [3]. The myogenic mechanism is responsible for reactions to changes in MABP and has been extensively studied. The metabolic mechanism reacts to changes in the concentration of gases in the blood, especially to changes in CO_2 concentrations. Concerning the neurogenic mechanism (NM), only a few studies can be found in the literature where its influence on CA has been investigated. Purkayastha et al. studied the influence of the sympathetic activity on CA, which is related to the NM [4]. They conclude that increases in sympathetic activity have a role in establishing cerebral vascular tone in humans. In addition, they found that an α_1 adrenergic receptor blockade 'impairs' CA. Since labetalol is an α_1 adrenergic antagonist, we hypothesized that the maternal use of labetalol impairs the NM involved in CA. However, since labetalol is also a nonselective β adrenergic antagonist, it has a direct effect on the heart rate (HR), suppressing the influence of the autonomous system on heart activity. In this study we aimed to investigate the effect of maternal use of labetalol on the NM of neonates during the first 3 days of life.

2 Methods

Data. The study was performed in 49 infants from the Wilhelmina's Children's Hospital Utrecht (the Netherlands), with a gestational age of 29 (24.7–31.9) weeks and a birth weight of 960 (540–1585) g. In all infants, the peripheral oxygen saturation (SaO_2), MABP, HR, and the regional cerebral oxygen saturation ($rScO_2$) were continuously and noninvasively recorded using the INVOS4100 (Somanetics). All signals were simultaneously measured during the first 3 days of life and were resampled to 1 Hz. From the 49 infants, 14 correspond to control subjects, and 35 correspond to the group of mothers who were treated for HDP. From the HDP group, 19 neonates correspond to mothers treated with labetalol (HPD+Lab) and 16 correspond to mothers who followed other treatment (HPD−Lab). Among the other treatments we can find the use of Adalat, Aldomet, Ketanserine, Nepressol and Magnesium sulfate.

Signal Analysis. Artifacts shorter than 30 s were removed and corrected by interpolation using robust least squares support vector machines for function estimation [5]. Whereas artifacts longer than 30 s were removed from the signals. Only segments free of artifacts were used for further processing.

Mathematical Tools. The status of the neurogenic mechanism was assessed by means of transfer function analysis between the low frequency content of autonomic control activity (LFA) and $rScO_2$. The transfer function scores were calculated using a time-sliding window of length 15 min and overlapping time of 1 min. The cross-power and auto-power spectral densities needed for the estimation of transfer function values were computed using the Welch method. In this method a further segmentation of the signals into 5-min epochs with an overlap of 4.5 min was used.

In HR variability studies, the sympathetic activity (SA) and parasympathetic activity (PA) are quantified using the power contained in the low frequency (LF) and high frequency (HF) bands. The LF band contains information from the SA and PA, while the power in the HF is attributed mostly to PA. For neonates, these frequency bands are defined as follows: LF (0.04–0.24 Hz) and HF (0.24–1.0 Hz) [6]. According to [4], an increase in SA has a role in establishing cerebral muscular tone in humans; therefore, in this study we are interested in the information contained in the LF of the HR, which might reflect sympathetically mediated activity. To obtain a continuous estimation for the low frequency activity (LFA), we used the discrete wavelet transform [7]. In summary, LFA was estimated by decomposing the HR using a five level discrete wavelet transform, with Daubechies 4 as mother wavelet, and computing the root mean square value of the sum of the 2nd to the 4th level detail coefficients, using five samples for the mean average. The 2nd to the 4th level detail coefficients contain information on the HR located in the frequency range 0.031–0.25 Hz, which includes the LF range, as indicated in [6]. An approximation to the high frequency activity (HFA) was obtained as the root mean square value of the sum of the 1st level detail coefficients, which contains information in the frequency range 0.25–0.5 Hz. The upper frequency range was limited by the sampling frequency used to acquire the signals. The mean average of the transfer function gain in the LF range was used as a score to quantify the status of the NM. Figure 23.1 shows a representative set of measurements for a control subject where the MABP, $rScO_2$, HR and the estimated LFA and HFA are presented.

Statistical Analysis. Transfer function gain values, and the variance of the LFA and HFA for the three different populations were compared during the first, second and third day of life by means of the Kruskal–Wallis test. Statistical analysis was performed using the statistics toolbox from MATLAB. All reported p-values were two-tailed and a nominal p-value <0.05 was considered to be statistically significant.

3 Results

Figure 23.2 shows the median, 25 %, and 75 % percentiles of the LFA variance for the three different populations during the first 3 days of life. LFA was found to be significantly higher during the first day of life in the Control group than in the HDP+Lab group ($p=0.01$). In addition, higher values of LFA were found in the HDP+Lab population during the third day of life when compared to the first day ($p=0.01$). HFA values behave similarly to LFA (they are not shown here due to space limitations).

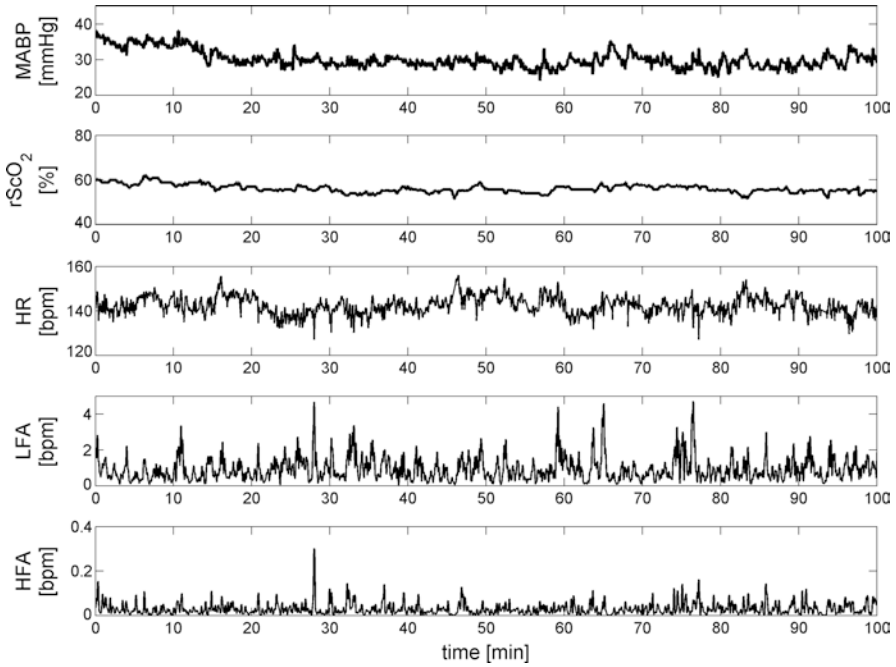


Fig. 23.1 Measurements of MABP, $rScO_2$, HR and the low frequency and high frequency autonomic control activity (LFA and HFA, respectively) for one control subject during the first day of life

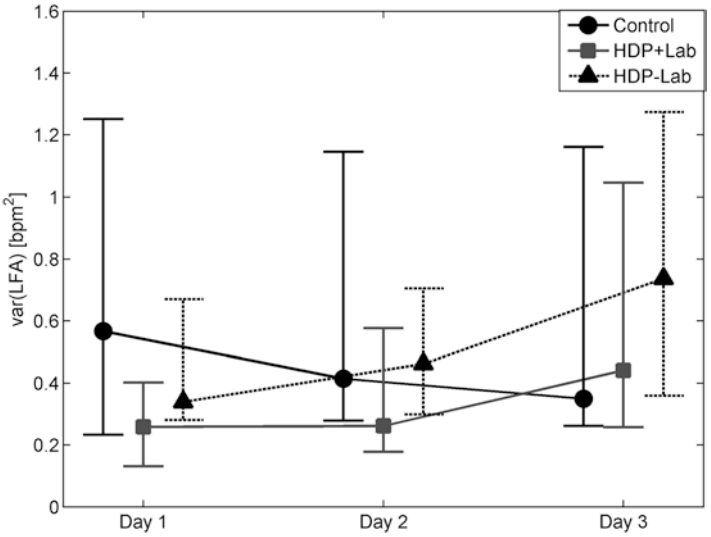


Fig. 23.2 Variance of the low frequency components in the autonomic control activity, var(LFA), for the three different populations during the first 3 days of life. The *solid circle*, *square* and *triangle* represent the median value for the control, HDP+Lab, and HDP−Lab populations, respectively. The *bar line* indicates the 25 and 75 % percentiles

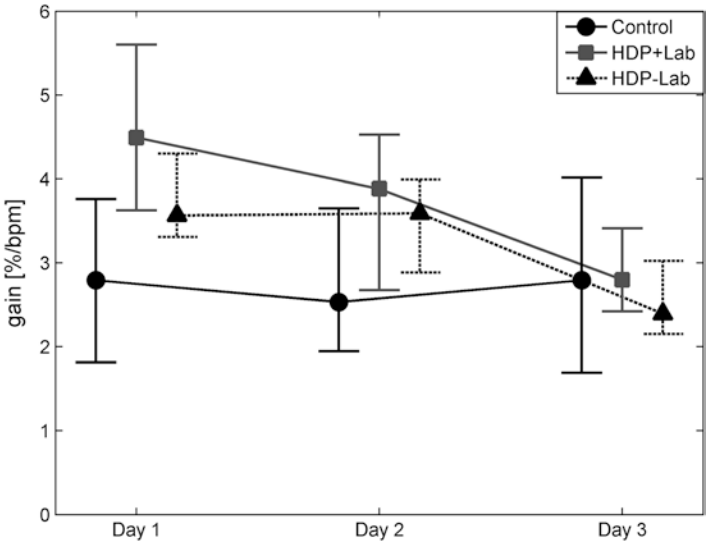


Fig. 23.3 Gain values indicating the status of the neurogenic mechanism for the three different populations during the first 3 days of life. The *solid circle*, *square* and *triangle* represent the median value for the control, HDP+Lab, and HDP−Lab populations, respectively. The *bar line* indicates the 25 and 75 % percentiles

Figure 23.3 shows the median, 25 %, and 75 % percentiles of the transfer function gain between LFA and $rScO_2$. When comparing the Control group with the HDP+lab group, significant differences were found during the first and second day ($p=0.001$, and $p=0.049$, respectively). In addition, when comparing the scores for the same population during the different days, in the HDP+Lab group the gain values during the first day and second day of life were significantly higher than the gain values during the third day of life ($p<0.001$ and $p=0.048$, respectively). Moreover, in the HDP−Lab group, the gain values during the first day and second day of life were significantly higher than the gain values during the third day of life ($p=0.009$, and $p=0.023$, respectively). No significant differences were found between the Control group and HDP−Lab group, or for the gain values in the Control group during the first 3 days of life.

4 Discussion and Conclusion

In this study we found that the activity in the low frequency and high frequency of the autonomic control, assessed by processing of the HR signals, was suppressed during the first day of life, with an increasing trend towards normality in the HDP+Lab group. In addition, we found that the gain values for the NM were higher during the first day of life in the same group, with a decreasing trend towards

normality. LFA, HFA and gain values in the HDP+Lab group were comparable to Controls by the third day of life.

Purkayastha et al. found that α_1 adrenergic receptor blockade reduced dynamic CA [4]. In [8], we performed a study with the same population analyzed in this paper; we found that the maternal use of labetalol impairs CA. In [8] the myogenic mechanism involved in CA was assessed by means of transfer function gain between MABP and $rScO_2$. By merging the results presented in this paper with the results published in [8], and using as support the results presented in [4], the effects of the maternal use of labetalol on the neonatal CA mechanisms can be summarized as follows: due to accumulation of labetalol in the neonates, the β and α_1 adrenergic receptors are blocked. On the one hand, β blockage produces as result a reduction of the influence of the autonomic nervous system in the heart, represented by a reduced LFA and HFA in the neonates. On the other hand, α_1 blockage reduces the muscular tone in the cerebral vascular bed, producing as a consequence vasodilation. Since the half-life time of labetalol in neonates is around 24 h [2], these effects are expected to disappear by the third day of life. Results provided in this paper indicate that as the LFA increases the NM is re-established, which corresponds to a concomitant reduction in α_1 and β adrenergic receptor blockade. In summary, in this paper we have found strong evidence that links the maternal use of labetalol with impaired CA caused by a vasodilation effect.

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