Effect of Maternal use of Labetalol on the Cerebral Autoregulation in Premature Infants

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Abstract Hypertensive disorders of pregnancy (HDP) are normally treated to avoid maternal complications. In this study we aimed to investigate if there was an effect of maternal HDP treatment on the cerebral autoregulation of the neonates by analyzing measurements of mean arterial blood pressure (MABP) and $rScO_2$ by means of correlation, coherence and transfer function analysis. We found that these infants presented higher values of transfer function gain, which indicates impaired cerebral autoregulation, with a decreasing trend towards normality. We hypothesized that this trend was due to a vasodilation effect of the maternal use of labetalol due to accumulation, which disappeared by the third day after birth. Therefore, we investigated the values of pulse pressure in order to find evidence for a vasodilatory effect. We found that lower values of pulse pressure were present in these infants when compared with a control population; which, together with increased transfer function gain values, suggests an effect of the drug on the cerebral autoregulation.

1 Introduction

Hypertension is the most common medical disorder encountered during pregnancy and is estimated to occur in about 6-8% of pregnancies [1]. Hypertensive disorders of pregnancy (HDP) should be treated in order to prevent maternal complications and improve fetal maturity by permitting prolongation of pregnancy and minimizing fetal exposure to possible adverse effects of antihypertensive treatment. There are several advantages and disadvantages of HDP treatment [1]. In pregnancy longer than 34 weeks, induction of labour in the occurrence of

hypertension and pre-eclampsia is generally considered the best treatment to improve maternal and neonatal outcome. However, there is considerable morbidity in late preterms explained by the mode of delivery and gestational age [2]. Labetalol is a selective α-1 (peripheral vasodilation) and non-selective β receptoragonist (preventing reflex tachycardia and maintaining cardiac output), which is often used in HDP treatment. Due to its lipophilic properties it easily passes the placental barrier, which is in essence a lipid membrane. Hypotension, bradycardia and hypoglycaemia are possible neonatal side effects, but may also occur in (preterm) infants regardless of labetalol exposure. Labetalol's half-life in adults is approximately 6 hours but accumulation occurs. However, half-life after maternal use in a preterm baby with clinical signs of β-blockage was 24 hours [3]. Conflicting evidence exists for specific neonatal side effects described after use of labetalol for maternal hypertension. Nevertheless oral and intravenous labetalol is used as a first or second-line treatment in HDP due to its highly effective antihypertensive properties and because it has a better profile than hydralazine and other β-blockers [4, 5]. Scarce information on neonatal cerebral haemodynamics in gestational hypertension and pre-eclampsia is available. However, not much is known about the true influence of maternal use of labetalol on the neonatal hemodynamic parameters (bradycardia, hypotension) in the brain, mainly since cerebral fetal circulation is subject to changes due to brainsparing in severe pre-eclampsia. We aimed to investigate labetalol-induced effects on neonatal cerebral autoregulation mechanisms during the first three days of life.

2 Methods

Data. The study was performed in 56 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) grams. In all infants peripheral oxygen saturation (SaO_2) was measured continuously by pulse oximetry, mean arterial blood pressure (MABP) by an indwelling arterial catheter. With NIRS, regional oxygen saturation ($rScO_2$) was continuously and noninvasively recorded using the INVOS4100 (Somanetics). MABP, SaO_2 and NIRS signals were simultaneously measured during the first three days of life. From the 56 infants 16 correspond to control subjects, and 40 correspond to the group of mothers who were treated for HDP. From the HDP group 21 neonates correspond to mothers treated with labetalol (HPD+Lab) and 19 correspond to mothers with other treatment (HPD-Lab). The subjects from the three groups were matched for gestational age, birth weight and gender.

Signal Analysis. Artifacts shorter than 30 seconds were removed and corrected by interpolation using robust least squares support vector machines for function estimation [6]. Artifacts longer than 30 seconds were truncated. Remaining artifacts, if any, were removed manually. Hence, a single continuous measurement was replaced by a set of continuous artifact-free segments. The resulting signals

were filtered with a mean average filter and then downsampled to 1Hz in order to obtain a common sampling frequency.

Mathematical Tools. Cerebral autoregulation was assessed by means of correlation, coherence and transfer function analysis between MABP and $rScO_2$. The correlation, coherence and transfer function scores were calculated using a time-sliding window of length 15 minutes and overlapping time of 1 minute. Coherence and transfer function analysis were performed using the Welch method for the calculation of the respective cross-power and auto-power spectral densities. This method involves a further segmentation of the signals into 5-minute epochs with an overlapping of 4.5 minutes. The average of the coefficients in the frequency ranges 0.003Hz-0.02Hz (very low frequency range: VLF), 0.02Hz-0.05Hz (low frequency range: LF) and 0.05Hz-0.1Hz (high frequency range: HF) were calculated [7] for further analysis. The transfer function was calculated with the following formula:

$$H(f) = \frac{G_{io}(f)}{G_{ii}(f)}$$

where $G_{io}(f)$ represents the input-output cross-power spectrum and $G_{ii}(f)$ represents the input auto-power spectrum. In addition, the pulse pressure was calculated as the difference between the systolic and diastolic blood pressure measurements. Figure 1 shows a representative set of measurements for a control subject.

Statistical Analysis. To assess whether the scores and pulse pressure values were different between the populations the non-parametric Kruskal-Wallis test was used, due to the lack of normality in the data distributions. The 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 as statistically significant.

3 Results

When comparing the correlation, coherence and gain values for the three different populations, taking the complete measurements for the first three days of life per group, no statistically significant differences between the scores were found. However, when the analysis was performed in a day-by-day basis, the HDP+Lab presented higher values of gain during the first day of life, in the VLF and LF bands, when compared with the gain values for the Control and the HDP-Lab group ($p<0.05$). In addition, the gain values during the first day of life, in the VLF and LF bands, for the HDP+Lab population were higher than the values in the second and third day ($p<0.05$). This behaviour indicates a progression towards normality. Figure 2 shows the gain for a representative subject from the HBP+Lab group. Correlation, coherence and phase were still not statistically significant.

Pulse pressure values were lower for the HDP+Lab group when compared with the other groups. In addition, for the three populations the pulse pressure values were lower during the first day of life and presented an increased profile in the second and third day. Figure 3 shows the median values of pulse pressure for the three different populations and its evolution during the first three days of life. In Table 1 the median values of pulse pressure and its range of variation (minimum – maximum values) are indicated.

Table 1. Pulse pressure values for the different populations during the first three days of life (all values are given in mmHg).

	Day 1	**Day 2**	**Day 3**
Control	16.08 (5.97-27.54)	21.50 (10.25-28.47)	23.07 (15.73-32.64)
HDP+Lab	12.94 (9.32-20.17)	16.10 (8.24-25.11)	17.47 (7.67-27.11)
HDP-Lab	16.76 (9.05-23.18)	17.45 (9.87-27.34)	19.76 (10.04-27.87)

4 Discussion and Conclusion

In this study we found that the maternal use of labetalol induces high values of the transfer function gain between MABP and $rScO_2$. These high values are concomitants with low values of pulse pressure. In [8] low values of pulse pressure indicate the presence of vasodilation due to the use of drugs for hypertension treatment. However, labetalol is a non-selective β antagonist; its action also reduces cardiac contractility which is reflected as a reduction in pulse pressure. When comparing pulse pressure values from the HDP+Lab and HDP-Lab group a stronger reduction is observed in the HDP+Lab group, this may be caused by a combination of vasodilation and reduction in cardiac contractility. We hypothesized that vasodilation was present in this group due to the concomitant reduction in pulse pressure and increase in transfer function gain values. Vasodilation reduces the effect of the myogenic mechanism responsible for cerebral autoregulation, which increases the transfer function gain. This vasodilation may be produced by the accumulation of labetalol due to its maternal use [9]. Interestingly, a trend towards normality can be seen in the gain and pulse pressure values. The gain values return to normality by the end of the third day, while the pulse pressure values were still lower than normal by then. This may be due to a decrease in labetalol. This vasodilatory effect might also be caused by brainspairing. In [10] higher mean values in cerebral blood flow velocity were reported in children with evidence of brainsparing. However, no differences were found in the amount of neonates that presented brainsparing between the HDP+Lab and HDP-Lab groups.

Correlation, Coherence and transfer function phase didn't present differences between the studied populations. This may be due to the fact that impaired

cerebral autoregulation is reflected not only by a coupled dynamics between MABP and cerebral blood flow, but also by the strength of this relation. This strength is assessed by the gain of the transfer function but not by the correlation and coherence scores. Moreover, in a recent study carried out in our group [11], we found that, among the aforementioned methods, transfer function analysis is the most robust method for cerebral autoregulation assessment. This result is in agreement with the results provided by [12].

In conclusion, there is evidence indicating that labetalol induces changes in the cerebral autoregulation mechanism of the neonates possibly due to its accumulation. This accumulation of labetalol might produce vasodilation, which leads to high values of gain, impairing the myogenic mechanism of cerebral autoregulation. Further studies are necessary to evaluate whether this phenomenon also has an effect on the later neurological outcome of the patients.

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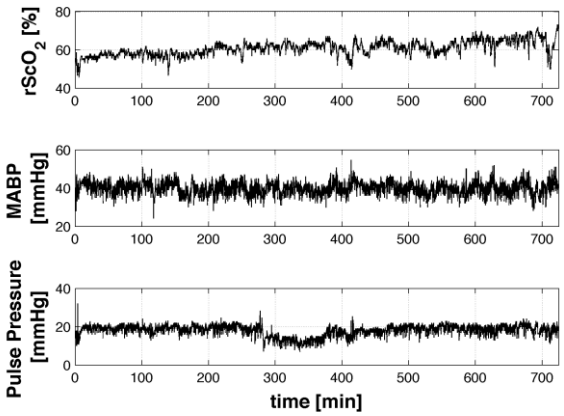

Fig. 1. Measurements of $rScO_2$, MABP and Pulse pressure for one of the subjects during the first day of life.

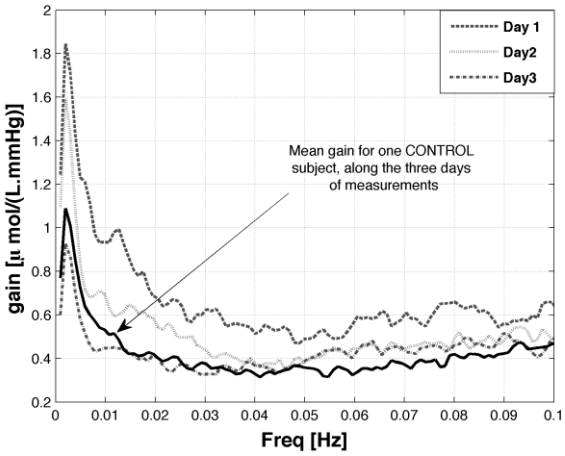

Fig. 2. Gain values for a representative subject from the HDP+Lab group. Gain values during the first, the second, and third day are shown together with the values from a control subject for comparison.

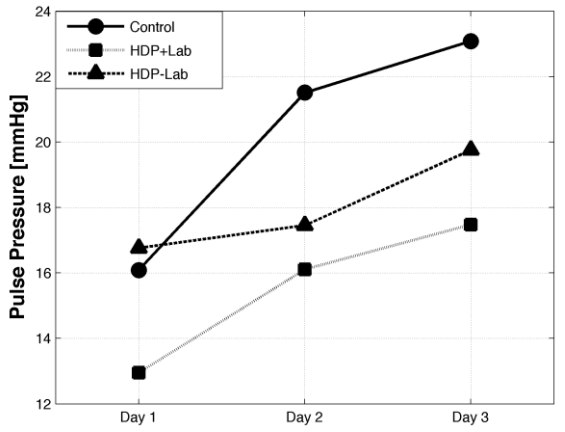

Fig. 3. Median values of pulse pressure for the three different groups, Control, HDP+Lab and HDP-Lab, during the first three days of life.