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Baroreflex Sensitivity and Blood Pressure in Premature Infants – Dependence on Gestational Age, Postnatal Age and Sex

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Summary

To characterize the differences in baroreflex sensitivity (BRS), blood pressure (BP), heart rate (HR) and respiration rate (RR) in preterm infants with a similar postconceptional age reached by various combinations of gestational and postnatal ages. To detect potential sex differences in assessed cardiovascular parameters. The study included 49 children (24 boys and 25 girls), postconceptional age 34.6±1.9 weeks. Two subgroups of infants were selected with the similar postconceptional age (PcA) and current weight, but differing in gestational (GA) and postnatal (PnA) ages, as well as two matched subgroups of boys and girls. Blood pressure (BP) was recorded continuously using Portapres device (FMS). A stationary segment of 250 beat-to-beat BP values was analyzed for each child. Baroreflex sensitivity (BRS) was calculated by cross-correlation sequence method. Despite the same PcA age and current weight, children with longer GA had higher BRS, diastolic and mean BP than children with shorter GA and longer PnA age. Postconceptional age in preterm infants is a parameter of maturation better predicting baroreflex sensitivity and blood pressure values compared to postnatal age. Sex related differences in BRS, BP, HR and RR were not found in our group of preterm infants.

Key words

Premature infants • Volume-clamp photoplethysmography • Baroreflex sensitivity • Blood pressure • Postconceptional age • Sex differences

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Introduction

The development of blood pressure (BP) and heart rate (HR) in newborns in the early stages of postnatal life is well-known. Newborns with lower gestational age and lower birth weight have lower BP values and higher HR in the early postnatal period compared to full-term infants (Versmold *et al.* 1981, Javorka and Zavarská 1983, LeFlore and Engle 2002, Strambi *et al.* 2004, Lehotská *et al.* 2007, Keijzer-Veen *et al.* 2010, Lazdam *et al.* 2010, Metz *et al.* 2012, and others). These differences are particularly expressed in the first postnatal weeks. After reaching the 44th-48th week of postconceptional age (sum of gestational and postnatal age), differences in systolic BP between preterm and full-term infants disappear and since then the systolic BP does not increase significantly until the end of the first year (de Swiet *et al.* 1980, Northern Neonatal Nursing Initiative 1999, Lurbe *et al.* 2007).

A given value of the postconceptional age (PcA) can be reached by a shorter gestational age with a longer postnatal age and vice versa. The question therefore arose as to whether these cardiovascular parameters, including basic quantitative characteristic of basic blood pressure reflex control mechanism – baroreflex sensitivity would differ in children of the same PcA, depending on whether they reached PcA with various contributions of gestational

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and postnatal ages – i.e. with a shorter gestational age and a longer postnatal age, or with a longer gestational age and a shorter postnatal age. To solve this question, the postconceptional age must be lower than 44 weeks in order to still be able to determine the dependence of blood pressure and other parameters on gestational age.

There is also a missing information on the potential sex related differences in baroreflex sensitivity, blood pressure and heart rate in premature infants. Therefore, the objectives of the study were: 1) To characterize the effect of gestational age on baroreflex sensitivity, blood pressure, heart rate and respiratory rate in children with the same postconceptional age. This approach is aimed to determine the possible existence of different maturation rates of the cardiovascular system during intra- and extrauterine conditions. 2) To determine whether there are sex differences in the assessed cardiovascular parameters of premature infants in early postnatal life.

Methods

Subjects

A total of 49 children (24 boys, 25 girls) were examined, born in the 26^{th}-36^{th} gestational week, with a birth weight of 650-2700 g. At the time of examination, the children had a postconceptional age (gestational age + postnatal age) in the range of 31.3-40.9 weeks, a postnatal age of 4-56 days and a current weight of 1170-2540 g. The mean values and standard deviations of the whole study group characteristics are presented in Table 1.

Table 1. Study group basic characteristics and cardiorespiratory parameters (n=49).

	Arithmetic mean	**SD**
Gestational age (weeks)	31.5	2.8
Birth weight (g)	1605	475
Postnatal age (days)	21.8	13.5
Postconceptional age (weeks)	34.6	1.9
Current weight (g)	1931	334
BRS (ms/mm Hg)	5.7	3.8
BP syst. (mm Hg)	57.1	7.3
BP diast. (mm Hg)	31.3	7.3
BP mean (mm Hg)	41.1	7.1
HR (min^{-1})	148	14
RR (min^{-1})	50	8

SD – standard deviation, BRS – baroreflex sensitivity, BP syst. – systolic blood pressure, BP diast. – diastolic blood pressure, BP mean – mean blood pressure, HR – heart rate, RR – respiratory rate.

Criteria for inclusion of newborns in the study included: children born prematurely, postnatal age greater than 4 days and wrist circumference 45-75 mm. Only children who were calm during investigation were included in the study. The child's motor restlessness together with any symptom of respiratory or cardiovascular disorders, as well as taking drugs potentially affecting the cardiovascular and respiratory systems belonged to the exclusion criteria.

The study was approved by the Ethics Committee of the Jessenius Faculty of Medicine, Comenius University in accordance with the Declaration of Helsinki (2000) of the World Medical Association. All parents of the infants enrolled in the study gave their written informed consent prior to the examination.

Standardization of measurement conditions

We performed the examination of children and data collection between 8 a.m. and 3 p.m. under standard conditions: 1-2 h after feeding, in quiet environment with constant ambient temperature and with minimization of visual and auditory stimuli. During recording of cardiovascular parameters, the child was in the supine position in the incubator, or on a warming mattress.

Instrumentation and software

We used a Portapres device (FMS, Netherlands) for noninvasive and continuous blood pressure recording.

Beat-to-beat recordings of blood pressure and heart rate/pulse rate were stored in the device memory, later transferred to a computer and processed by FMS software (BeatScope 1.1a, PRVBRS). A pulse oximeter (Nellcor Oximax M560, USA) was used to monitor the oxygen saturation of hemoglobin.

Measurement procedure

Blood pressure registration was preceded by a choice of a Portapres cuff with the appropriate size according to the circumference of the infant´s wrist. After placing the cuff on the wrist of the right hand, which was supported and kept at heart level, the infants was left at rest in a horizontal supine position for at least 5 min without inflating the cuff. After this adaptation period, we recorded beat-to-beat blood pressure values for 2-5 min. During each measurement, we recorded the child's behavior, respiratory rate, and oxygen saturation of blood. The average value of oxygen saturation in the whole group was 97 % (range 93-100 %). Respiratory rate was counted visually at 30 s intervals using stopwatch.

Processing of blood pressure recordings

A stationary segment containing 250 continuous beat-to-beat blood pressure values was selected from each recording. As a next step, we calculated average values of systolic, diastolic and mean BP and heart rate in the selected segment.

Baroreflex sensitivity was calculated from spontaneous oscillations of systolic BP and pulse intervals (PI) by cross-correlation sequence method. This method searches for sequences of at least four consecutive beats with the changes in systolic BP and PI in the same direction. The correlations between beat-to-beat values in the detected sequences were calculated for variable delays between blood pressure and PI values (Parati *et al.* 2004). The delay with the highest coefficient of determination was selected for a given sequence – this approach increases the degree of mutual correlation and provides more instantaneous BRS values (a criterion for inclusion of given sequence as baroreflex sequence was having coefficient of determination r^2 associated with $P<0.01$). The mean BRS value for each child was calculated as the average of all instantaneous BRS values inside analyzed segment. On average, 24 instantaneous BRS values were found in each recording.

Statistical analysis

We used the Shapiro-Wilk normality test to decide whether the evaluated variable have a normal (Gaussian) distribution. For between groups comparison, parametric two-sample *t*-test or non-parametric Kruskal-Wallis test were applied in accordance with data distribution.

We considered the values $P<0.05$ as statistically significant. The results are presented as arithmetic mean ± standard deviation (SD).

Results

Cardiovascular parameters in children with the similar postconceptional age – an effect of different gestational and postnatal ages

From the whole group of children (n=49), 38 children were divided into two sex and postonceptional age matched subgroups with different gestational and postnatal ages. (i.e. two subgroups differed in the duration of intrauterine and extrauterine life). The postconceptional age and current weight did not differ statistically between subgroups. Subgroup A consisted of 22 children (11 girls and 11 boys) with shorter gestational age and longer postnatal age. Subgroup B consisted of 16 children (8 girls and 8 boys) and had longer gestational and shorter postnatal age (Table 2).

Although the infants were of similar postconceptional age and did not significantly differ in current weight, children with longer gestational age (subgroup B) had almost twice as high baroreflex sensitivity, significantly higher diastolic and mean blood pressure and lower respiratory rate compared to children with shorter gestational age and longer postnatal age (subgroup A).

Sex differences in cardiorespiratory parameters

Searching for sex differences, we compared the assessed variables between two subgroups (16 subjects in each subgroup) paired according to postconceptional, gestational and postnatal age and birth weight and current weight (Table 3).

Statistical analysis showed that in subgroups classified by sex, no significant differences between boys and girls in baroreflex sensitivity, blood pressure or respiratory rate were found. Although the heart rate in girls tended to be higher, the difference was not significant.

Table 2. Basic characteristics and cardiorespiratory parameters in two subgroups of children (**A, B**) with the same postconceptional age and different gestational and postnatal ages.

	A	B	P
Postconceptional age (weeks)	34.91 ± 1.78	34.98 ± 1.72	0.884
***Gestational age** (weeks)*	**30.95 ± 2.1**	**34.0 ± 1.9**	**<0.001**
***Postnatal age** (days)*	**27.4 ± 10.9**	**7.1 ± 2.7**	**<0.001**
***Birth weight** (g)*	**1462 ± 365**	**2044 ± 313**	**<0.001**
Current weight (g)	1935 ± 312	2001 ± 302	0.520
***BRS** (ms/mm Hg)*	**4.64 ± 1.74**	**8.12 ± 5.16**	**0.018**
BP syst. (mm Hg)	56.1 ± 7.1	58.0 ± 8.1	0.657
***BP diast.** (mm Hg)*	**29.8 ± 5.3**	**34.6 ± 8.7**	**0.034**
***BP mean** (mm Hg)*	**39.6 ± 5.0**	**44.2 ± 8.6**	**0.015**
HR (min^{-1})	149.5 ± 12.8	146.3 ± 14.7	0.475
RR (min^{-1})	**52 ± 9**	**47 ± 6**	**0.034**

BRS – baroreflex sensitivity, BP syst. – systolic blood pressure, BP diast. – diastolic blood pressure, BP mean – mean blood pressure, HR – heart rate, RR – respiratory rate. Values are presented as arithmetic mean ± SD – standard deviation. P-values correspond to between groups comparison and significant differences are highlighted in bold.

Table 3. Comparison of variables between boys and girls.

	Boys n=16	**Girls** n=16	**P**
Postconceptional age (weeks)	34.5 ± 1.6	34.7 ± 1.7	0.726
Gestational age (weeks)	31.6 ± 2.2	31.6 ± 2.9	1.000
Postnatal age (days)	20.1 ± 10.9	21.1 ± 15.5	0.835
Birth weight (g)	1713 ± 353	1577 ± 440	0.343
Current weight (g)	2023 ± 237	1918 ± 197	0.184
BRS (ms/mm Hg)	5.2 ± 2.5	5.6 ± 3.3	0.836
BP syst. (mm Hg)	56.0 ± 6.3	58.4 ± 8.0	0.407
BP diast. (mm Hg)	31.7 ± 6.9	31.5 ± 8.8	0.706
BP mean (mm Hg)	41.5 ± 6.9	41.6 ± 8.5	0.598
HR (min^{-1})	147 ± 12	154 ± 14	0.138
RR (min^{-1})	50 ± 7	50 ± 10	0.664

BRS – baroreflex sensitivity, BP syst. – systolic blood pressure, BP diast. – diastolic blood pressure, BP mean – mean blood pressure, HR – heart rate, RR – respiratory rate. Values are presented as arithmetic mean ± SD. No statistically significant differences were found.

Discussion

In the present study, we registered non-invasively continuously blood pressure in preterm infants using volume-clamp plethysmography method (Peňáz 1973) to obtain a representative average blood pressure and heart rate values and to evaluate baroreflex sensitivity at rest for each studied infant. Several studies (e.g. Andriessen *et al.* 2004, Yiallorou *et al.* 2006) have shown that this method can be applied not only to adults but also to newborns – if the cuff is applied to infant's wrist instead of an adult's finger. The relevance and validity of this modified method was verified by comparison with the invasive intraarterial blood pressure measurement method (Andriessen *et al.* 2004), as well as by comparison with the blood pressure values obtained by oscillometric method (Jagomägi 1996, Lemson 2009).

Relationship of cardiovascular parameters to gestational age in infants at the same postconceptional age

The level of maturation of organ and organ systems and their control mechanisms is very heterogeneous in premature infants. Baroreflexes are principal reflex mechanisms in the short term blood pressure control in postnatal life and their development in children and adolescents is well known (Dietrich *et al.* 2005, Svačinová *et al.* 2015). However, baroreflex control mechanisms are of lesser physiological importance during intrauterine life (Wood and Tong 1999). Several authors (Gournay *et al.* 2002, Yiallourou *et al.* 2010) found that BRS values in newborns are low and increase with gestational and postnatal age. These relations were confirmed by Haskova *et al.* (2017) and they also observed an increase of BRS with birth weight and current weight. Our results indicate the importance of intrauterine baroreflex maturation because we observed markedly decreased values of BRS in infants with lower gestational age despite having similar postconceptional age. In accordance with our observation, slower extrauterine maturation of BRS in preterm babies up to the age of 5-6 months was observed in previous studies. It can be one of the important factors in the pathogenesis of cardiovascular instability in this high risk groups of newborns (Gournay *et al.* 2002, Witcombe *et al.* 2012, Fyfe *et al.* 2015).

In premature infants, a relationship between blood pressure values and gestational age and birth weight was known already several decades ago (e.g. Versmold *et al.* 1981, Javorka and Zavarská 1983, Metz *et al.* 2012, and others) – the lower the gestational age at birth and the lower the birth weight, the lower their blood pressure. With increasing gestational, postnatal and postconceptual age, blood pressure rises levelling off at the postconceptual age of 44-48 weeks (Northern Neonatal Nursing Initiative 1999). Lurbe *et al.* (2007) studied blood pressure from birth to the first year of life in neonates with various birth weights. Multiple regression analysis found that birth weight was a positive independent determinant of systolic blood pressure at birth and a negative independent determinant of systolic blood pressure increase during the first month of life.

These results indicate that premature newborns, especially infants with very low birth weight, undergo a faster development of blood pressure in the first months of age (Georgieff *et al.* 1996, Pejovic *et al.* 2007). Similar relations were also observed in animal studies in various species. As early as 1968, Dawes stated that the less mature the newborn, the more prominently and faster their blood pressure increases in the early postnatal period regardless of the animal species.

We found, evaluating two subgroups of premature infants with the same postconceptional age (35th week), that children with longer gestational age had significantly higher baroreflex sensitivity, higher diastolic and mean blood pressure, as well as lower respiratory rate, compared to children with shorter gestational and longer postnatal age. In other words, infants with shorter gestational age were unable to reach the cardiorespiratory parameters values of infants with longer intrauterine development despite being in the same postconceptional week. Cardiovascular maturation appears to be faster during intrauterine life, and postnatal maturation must take longer for more premature infants to get to the similar BRS, blood pressure, and heart rate values as infants with higher gestational age.

From a practical point of view, it appears that focusing on the length of postnatal age when estimating the maturity of the cardiovascular system can be misleading if the gestational age is too low. We confirmed the findings of Zubrow *et al.* (1995) that in preterm infants, postconceptional age is the primary determinant of blood pressure and has a greater predictive value than postnatal age. Our study extended these findings to relations with baroreflex sensitivity.

Sex differences in cardiovascular measures of premature infants

Although this issue has been addressed for a long time on heart rate and blood pressure values, the existing data are ambiguous. In addition, there is currently no information about potential sex differences in baroreflex sensitivity.

No sex differences in heart rate were found in fetuses up to 41st gestational week (Robles de Medina *et al.* 2003). Several papers report no sex differences in the blood pressure values of the full-term newborns during the first week (Zinner *et al.* 1980, Kellerová and Andrásyová 1988, Alves *et al.* 1999, Nwokoye *et al.* 2015). However, Elsmén *et al.* (2007) found in more than 230 premature infants that boys on the first day of life not only have lower mean blood pressure (on average by 3 mm Hg), but also need inotropic heart support more often than girls. Although Kent *et al.* (2007a) found lower mean and diastolic blood pressure in healthy full-term boys at postnatal age of two days, blood pressure values no longer differed between boys and girls at 6 or 12 months of age (Kent *et al.* 2007b).

When evaluating heart rate and its variability in newborns, Nagy *et al.* (2000) and Kantor (2003) found that boys have slightly lower heart rate and larger magnitude of heart rate variability than girls. On the other hand, Lehotská *et al.* (2007) did not find any sex related differences in either HR or its variability in full-term newborns in the first four postnatal days, although girls tended to have higher heart rate.

It should be noted that the results of previous studies focused on blood pressure differences between boys and girls were obtained by intermittent measurement. In our study, we determined the values of blood pressure by continuous measurement, which also enabled the determination of baroreflex sensitivity. After unification of postconceptional age and pairing by gestational and postnatal age, as well as birth and current weight, we did not find any significant sex differences in blood pressure, heart rate, or respiratory rate. Only a non-significant trend towards a higher heart rate was observed in girls. Novelty of our study is also in its focus on a detection of potential sex differences in baroreflex sensitivity – to the best of our knowledge a relation between sex and BRS values in newborns was not analyzed so far. However, no significant differences in BRS between premature boys and girls with the postconceptional age of 35 weeks were observed.

Conclusions

Premature newborns with longer gestational age have higher baroreflex sensitivity, higher diastolic and mean blood pressure, as well as lower respiratory rate compared to their counterparts with shorter gestational age and longer postnatal age despite being at the same postconceptional age. It points towards an importance of intrauterine environment for the development of cardiovascular and respiratory system and their control. No sex related differences were observed in cardiorespiratory measures between male and female newborns. It indicates similar development of infants in the terms of their blood pressure and its control regardless of the sex.

Conflict of Interest

There is no conflict of interest.

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