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# 24-hour blood pressure monitoring and renal function evaluation at the predicted term of delivery in prematurely born children

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**Abstract:** Background: The cause of the increased risk of hypertension in children born prematurely is still unclear. The aim of this study was to analyze the results of blood pressure monitoring and the levels of variety of kidney function markers at the 40–42 weeks postmenstrual age in children born prematurely and to compare them with the values obtained from full-term newborns. The analysis of the differences in the observed parameters could be used to assess the risk of developing hypertension in preterm infants in the following years of life.
Methodology: Prospective cohort study included 37 children born prematurely (<35 weeks of gestation) and 20 full-term newborns. The 24-hour ambulatory blood pressure measurement, serum cystatin C and thrombomodulin levels, urine Neutrophil Gelatinase-Associated Lipocalin (NGAL) concentration, renal ultrasound and bioelectrical impedance were performed.
Results: Analysis of the blood pressure monitoring reveled lower values of diastolic (DBP) and mean blood pressure (MAP) in the preterm group (DBP: 47.69 ± 4.79 vs. 53.96 ± 5.3 mmHg; p <0.01; MAP 64 ± 6.7 vs. 68 ± 6 mmHg; p = 0.02), however the preterm children were significantly smaller at the time of evaluation. Moreover, the pulse pressure was significantly higher in the preterm group (44 ± 7.8 vs. 39.4 ± 5.7 mmHg; p = 0.017). In the preterm group serum cystatin C level was lower (1.397 ± 0.22 vs. 1.617 ± 0.22 mg/l; p <0.01) and NGAL urine concentration was higher (57 ± 84 vs. 15 ± 21 ng/ml; p = 0.04). There was substantial difference in body composition between groups - the total body water was lower in the preterm group (75.6 ± 13 vs. 82 ± 8%; p = 0.015).
Conclusion: At the predicted date of birth, preterm newborns show significant differences in blood pressure profile, body weight composition, and levels of cystatin C and NGAL compared to full-term babies.

**Key words:** prematurity, cystatin C, NGAL, blood pressure profile.

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## Introduction

Preterm birth has always been a major challenge in perinatal health care, mainly due to the various complications affecting these group of newborns. The most dynamic complications occur in the first few weeks of preterm infants' life, but prematurity also influences health issues later in life. Recently, many clinical research trials proved that children born prematurely and with low birth weight are at greater risk of arterial hypertension, however the cause of this phenomenon is still unclear. In published studies many hypotheses occur: reduction in the number of nephrons [1], deregulation of intrarenal renin-angiotensin system [2], the effect of metabolic imprinting [3, 4] etc. However, clinical studies in which these hypotheses were formulated concerned changes in various systems in children already diagnosed with hypertension. Moreover, reliable data on hypertension risk factors are not available from prospective clinical observations initiated prior to the onset of disease symptoms.

The plan of the study was to perform the wide assessment of cardiovascular and renal systems of children born prematurely at the 40–42 week of gestational age and compare the efficiency of this systems to children born on time. The project can be the introduction to prospective evaluation of children with proved increased risk of hypertension, and finally shed light on the pathogenesis of hypertension in newborns.

Our goal was to evaluate blood pressure profile, body composition and selected kidney injury markers in premature infants at the term of expected delivery and compare it to term controls.

## Materials and Methods

Prospective cohort study was performed in Neonatal Intensive Care Unit of University Children Hospital in Cracow between 01.01.2016 and 30.09.2018. Thirty seven children born before 35th week of gestational age with birth weight below 2500 grams were enrolled to the study group.

The control group consists of children born on time with birth weight over 2500 grams who were in good general condition at the time of evaluation (7–21 days of life). Exclusion criteria for children both groups were: lack of parents' consent, history of diabetes or hypertension during pregnancy, chromosome aberrations, multiple congenital malformations, severe intraventricular hemorrhage, birth asphyxia (APGAR $\leq$3 in 5 minute of life) and urinary tract infection at the history or/and at moment of assessment. Flowchart of the study is presented on Fig. 1. The Ethical Committee for Clinical Investigations of Collegium Medicum, Jagiellonian University, approved the study. All parents signed informed consent prior study procedures.

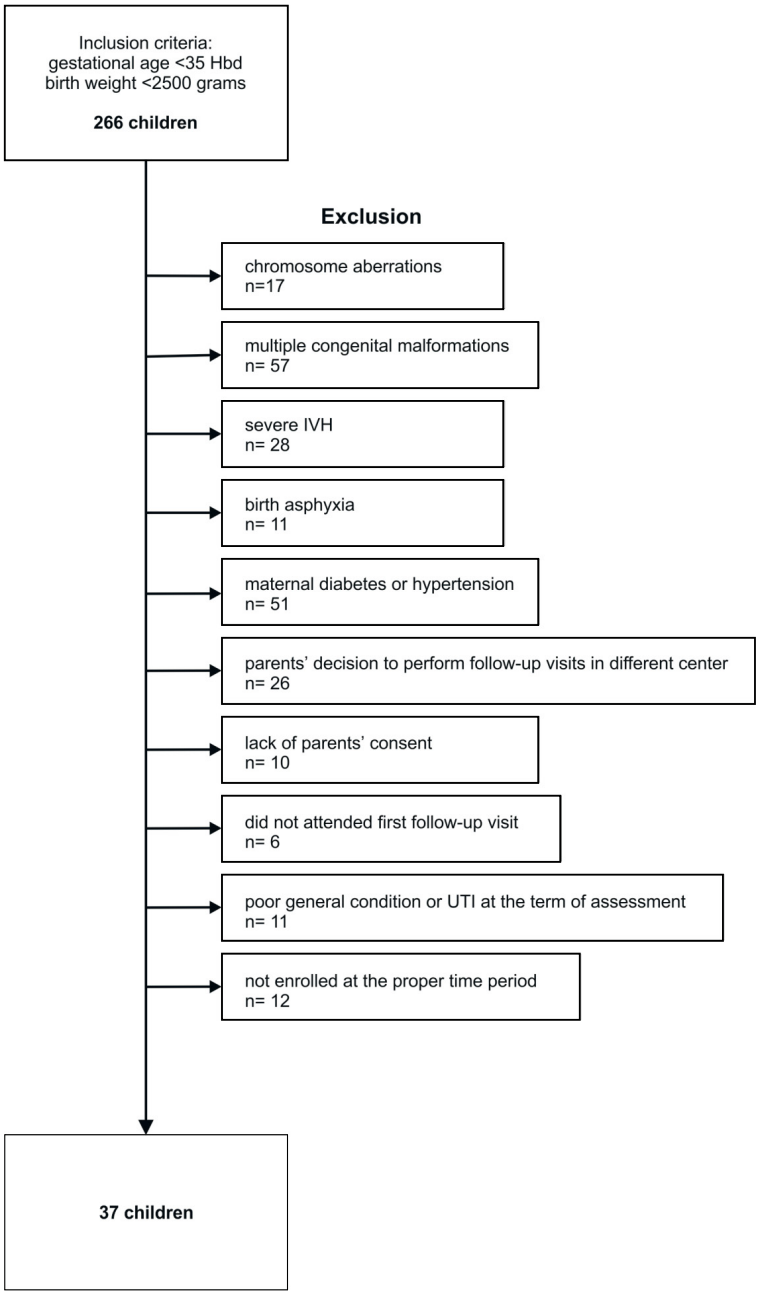


**Fig. 1.** Flowchart of the study inclusion.

All children were assessed between 40th and 42nd week of gestational age. After obtaining the parents' consent detailed information about possible risk factors of hypertension (pregnancy, perinatal period, the treatment in the neonatal unit) were taken. In each child following procedures were performed: anthropometric measurements, body composition assessment on basis of bioelectrical impedance, ambulatory blood pressure measurement, kidneys size assessment with the use of ultrasound, serum thrombomodulin and cystatin C levels, and urine NGAL concentration.

### *Anthropometric measurements*

Body length was estimated in the supine position with an accuracy of 0.5 centimeter. Body weight was evaluated with a precision of 1 g. For each patient body surface area (BSA) was calculated with the Du Bois and Du Bois formula:

$$BSA = weight(kg)^{0.425} \times height(cm)^{0.725} \times 0.007184$$

### *Bioelectrical impedance*

Bioelectrical impedance analysis is a noninvasive technique to estimate body composition based on the difference in electrical conductive properties of various tissues. Body composition was measured with the multi-frequency impedance body composition monitor (BCM; Fresenius Medical Care, Bad Homburg, Germany), and disposable electrodes BCM-FMC (<25 kg). The BCM measured resistance and reactance at 50 frequencies between 5 and 1000 kHz, amplitude of the electric current was 0.8 mA. The newborns were examined in the supine position with arms and legs extended. The electrodes were attached to each dorsal surface of left hand and foot [5]. On base of measured impedances following parameters were estimate: Total Body Water, Extracellular Water, Intracellular Water, Free Fat Mass, R5, R50 and R100 bioelectrical indexes.

### *24-hour Ambulatory blood pressure monitoring*

For 24-hour ambulatory blood pressure measurement (ABPM) holter ABPM50 device (Contec, Beijing, China, 2015) and appropriately fitted pediatric cuff were used. Blood pressure measurements were performed at an interval of 20 minutes during the day and every 30 minutes during the night. With help of a licensed ABPM program: mean systolic blood pressure (SBP), mean diastolic blood pressure (DBP), mean arterial blood pressure (MAP), mean heart rate (HR) and pulse pressure (PP) were calculated. Daytime and nighttime periods were not analyzed due to natural dysregulation of newborns' daily rhythm. Due to lack of z-score data of premature children blood

pressure regarding to weight and length, the obtained values were adjusted: ratio of SBP, DBP and MAP to weight as well as to length were calculated.

### *Abdominal ultrasound*

The kidney ultrasound was performed by a qualified ultrasonography specialist with the use of Philips EnVisor C HD system; (Koninklijke Philips N.V., Eindhoven, Netherlands). Measurements were performed in the supine position with convex probe and scanned in the para-coronal view with the transducer positioned to obtain the longest kidney dimension. Kidney length was calculated as the average of three measurements.

The reference values of kidney length were calculated using the formula of Dinkel *et al.* [6]. Renal length was adjusted to the patient's height. The formula used to calculate predicted renal length were:

$$Left\ kidney\ (mm):\ 0.51346\ x\ height\ (cm)\ +\ 17.659$$

$$Right\ kidney\ (mm):\ 0.49915\ x\ height\ (cm)\ +\ 18.381$$

The formula used to calculate relative kidney length was:

Relative kidney length = (actual kidney length measured by ultrasound / predicted kidney length) *100%

### *Laboratory blood test*

In each child 0.9 ml of blood was taken to assess levels of thrombomodulin and cystatin C. Cystatin C was measured by a particle-enhanced immunonephelometric assay (N Latex Cystatin C assay; Dade Behring, Deerfield, IL). Estimated glomerular filtration rate (eGFR) was calculated using Hoek *et al.* formula:

$$eGFR = -4.32 + \frac{80.35}{CysC}$$

The serum creatinine (SCr) level assessment was measured by using VITROS® Chemistry Products (Ortho Clinical Diagnostics, Raritan, NJ). Estimated glomerular filtration rate was calculated using George J. Schwartz [7] formula:

$$eGFR = 0,413x\frac{height}{SCr}$$

Thrombomodulin serum level was assessed with the use of prepared ELISA kit (Elabscience Biotechnology, China).

### *Laboratory urine test*

Neutrophil gelatinase-associated lipocalin (NGAL) level in single urine sample was checked with the use of prepared ELISA kit (Elabscience Biotechnology, China) with the sensitivity of 0.10 ng/mL. Urine was collected with the use of special newborn urine bags (no child was catheterized to collect sample).

### *Outcome variables*

1. Blood pressure profile assessment
   a) Systolic blood pressure (SBP)
   b) Diastolic blood pressure (DBP)
   c) Mean arterial pressure (MAP)
   d) Pulse pressure (PP)
   e) SBP (DBP, MAP) / weight ratio
   f) SBP (DBP, MAP) / length ratio
2. Renal parameters
   a) Kidneys size
   b) Cystatin C level (cysC-eGFR)
   c) Creatinine level (creat-eGFR)
   d) Urine NGAL concentration
3. Endothelium function
   a) Thrombomodulin level
4. Body composition parameters
   a) Total body water
   b) Lean body mass
   c) Free fat mass

### *Statistical analysis*

Statistical analysis was performed with the use of Statistica 13.0 software. Qualitative values were compared by Fischer exact test. To assume the differences in continuous variables between studied groups Student's t-test and Mann-Whitney U test were used. Logarithmic data were analyzed after transformation to linear form. Differences were found as statistically important if the probability of type I error alpha was lower than 0.05.

## Results

### *Population*

Study group comprised of 37 children born prematurely (mean gestational age 28.97 ± 3.15 weeks) with mean birth weight 1218 ± 467 grams). Mean children age at the moment of measurements was 115 days (Postmenstrual age — 41.2 ± 2.2). At the moment of assessment all prematurely born children were in good general condition for at least 2 weeks. Moreover, for at least 2 weeks they were not receiving any medications that could influence blood pressure or renal function. Control group comprised of 20 children born on time (mean gestational age 39.35 ± 1.18 weeks) with mean birth weight 3506 ± 370 g. Mean controls calendar age amounted 15 days (Postmenstrual age — 41.5 ± 1.7). The characteristic of the preterm group and control group is presented in Table 1. The group of premature babies was characterized by a moderately high number of risk factors for kidney damage.

**Table 1.** The characteristic of the preterm and control group.

| Birth parameters | | | |
|---|---|---|---|
| | Study group (n = 37) | Control group (n = 20) | P value |
| Gestational age (weeks) | 28.97 ± 3.15 | 39.35 ± 1.18 | <0.01* |
| Birth weight (g) | 1218 ± 487 | 3506 ± 370 | <0.01* |
| Birth length (cm) | 39 ± 6 | 54 ± 3 | <0.01* |
| Head circumference (cm) | 26 ± 3 | 35 ± 1 | <0.01* |
| Apgar score, first minute (Median, IQR) | 5 (3–7) | 9 (9–10) | <0.01# |
| | 6 | 0 | <0.01” |
| Perinatal period | | | |
| Respiratory therapy (days) | 14 ± 20 | 0,7 ± 1,5 | <0.01” |
| Total parenteral nutrition (days) | 29 ± 27 | 2 ± 6 | <0.01” |
| Surfactant administration (n) | 20 | 0 | <0.01” |
| Aminoglycosides administration (n) | 18 | 7 | 0.8” |
| Vancomycin administration (n) | 27 | 2 | <0.01” |
| Pharmacological / surgical therapy of persistent ductus arteriosus | 12/1 | 0 | <0.01” |
| Late onset sepsis (n) | 23 | 2 | <0.01” |
| Retinopathy of prematurity / laser therapy (n) | 8 | 0 | <0.01” |
| Necrotizing enterocolitis (n) | 7 | 0 | <0.01” |
| Bronchopulmonary dysplasia (n) | 22 | 0 | <0.01” |
| Moment of assessment | | | |
| Postmenstrual age (weeks) | 41.2 ± 2.2 | 41.5 ± 1.7 | 0.65* |
| Weight (g) | 3349 ± 589 | 3789 ± 560 | <0.01* |

**Table 1.** cont.

| Moment of assessment | | | |
|---|---|---|---|
| Length (cm) | 50.2 ± 4 | 54.9 ± 2.7 | <0.01* |
| BSA ($m^2$) | 0.23 ± 0.027 | 0.25 ± 0.024 | 0.01* |

Data are presented as mean ± SD, unless otherwise stated; IQR — interquartile range, BSA — body surface area
* p value for student-t test; # p value for Mann-Whitney U test; "chi2 test.

### *Anthropometric measurements*

Children from the study group at the predicted term of delivery were significantly lighter then children from the control group (3349 ± 589 g vs. 3794 ± 593 g; p <0.01). The difference was also visible in the assessment of length (50.2 ± 4 cm vs. 55 ± 3 cm; p <0.01) and BSA (0.23 ± 0.03 m2 vs. 0.25 ± 0.02 m2; p <0.01). Data presented in Table 1.

### *Blood pressure profile*

Ambulatory blood pressure measurement was performed in all children from study and control group. Data for two children are not available due to technical problems (ABPM was performed, but only few measurement was recorded). There was no difference in systolic blood pressure between groups (90.47 ± 9.19 mmHg in study group vs. 93.38 ± 7.62 mmHg in control group; p = 0.13). However, the diastolic blood pressure and mean arterial pressure were significantly lower in premature children (DBP: 47.69 ± 4.79 vs. 53.96 ± 5.3 mmHg; p<0.01; MAP 64 ± 6.7 vs. 68 ± 6 mmHg; p = 0.02). Moreover, there was a difference in pulse pressure between groups — PP was higher in the study group (44 ± 7.8 vs. 39.4 ± 5.7 mmHg; p = 0.017). Analysis of standard deviations of SBP, DBP and MAP did not show differences in BP variability between groups. Mean SD for SBP was 19.25 mmHg in the study group and 17.94 mmHg in controls; p = 0.49. As well as, SD for DBP and MAP were 12.73 and 15.43 mmHg in premature children, comparing to 13.12 and 14.89 mmHg in control group; p = 0.77 and 0.75.

After adjustment of blood pressure values to children weight and length, the increase SBP/kg and SBP/cm ratio were shown (p = 0.03 and p = 0.04 respectively). No differences were shown after DBP and MAP recalculation.

Heart rate was similar in both groups — 137 ± 10 beats per minute in premature and 134 ± 12 beats per minute in controls.

### *Renal outcomes*

The urine sample was obtained from 33 children from study group and 19 patients from control group. Lack of NGAL assessment was caused by problems with urine sample collection — no child was catheterized to obtain the sample. The assessed marker of kidney injury was significantly higher in the study group. Mean NGAL urine concentration was 57 ± 84 ng/ml in the group of children born prematurely and 15 ± 21 ng/ml in control group; p = 0.04.

Cystatin C and eGFR were analyzed in the whole study group and in 19 out of 20 children from the control group. One collected blood sample was two small for the assessment — the procedure was not repeated. Cystatin C was significantly lower in premature children (1.397 ± 0.22 vs. 1.617 ± 0.22 mg/l; p <0.01). As the result estimated cysC-GFR was higher in the study group (54.6 ± 9.6 vs. 46.2 ± 6.5 ml/min/1.73 $m^2$).

Creatinine was analyzed in 25 children from the study group and in 17 children from the control group. Creatinine was significantly lower in the study group (0.27 vs. 0.37 mg/dl; p <0.01) and creat-eGFR was higher in this group (80.8 vs. 63.9 ml/min/1.73 $m^2$; p <0.01).

Kidney length was assessed in 37 premature children and in 20 controls. There was no difference nor in actual neither relative kidneys size between children born prematurely and children born on time (data on request).

### *Cardiovascular and body composition outcomes*

Bioelectrical impedance was performed in all children from the study group and in 17 out of 20 cases from the control group. The procedure cannot be done in 3 children due to anxiety after attachment of electrodes.

Total body water was lower in prematurely born children (2.5 ± 0.46 vs. 3.1 ± 0.47 liter; p <0.01). The difference was also present when assessing as per cents of total body mass (75.6 ± 13 vs. 82 ± 8%; p = 0.015). The extracellular and intracellular were both decreased (ECV: 0.99 ± 0.17 vs. 1.12 ± 0.18 l; p <0.01; ICV 2.02 ± 0.51 vs. 2.3 ± 0.61 l; p = 0.048). As the result lean body mass index was higher in the study group (25.7 vs. 18%; p = 0.01). There was no difference between groups in assessment of resistance with the impedance variables R5, R50 R100. The free fat mass was lower in the children from the study group, but the difference was not present during assessment of FFM index (%).

The serum thrombomodulin level was assessed in 37 out of 39 children from the study group and in 19 out of 20 controls. Three collected blood samples were two small for the assessment — the procedure was not repeated. The serum concentration

of thrombomodulin did not differ between groups. It was 1209 ± 765 pg/mL in premature children and 1665 ± 1078 pg/mL in term babies; p = 0.08.

All results are presented in Table 2.

**Table 2.** Outcome variables in the study and control groups.

| | Study group (n = 37) | Control group (n = 20) | P value for tudent-t test |
|---|---|---|---|
| Mean SBP (mmHg) | 90.47 ± 9.19 | 93.38 ± 7.62 | 0.13 |
| Mean DBP (mmHg) | 47.69 ± 4.79 | 53.96 ± 5.3 | <0.01 |
| MAP (mmHg) | 64 ± 6.7 | 68 ± 6 | 0.02 |
| PP (mmHg) | 44 ± 7.8 | 39.4 ± 5.7 | 0.017 |
| HR (beats per minute) | 137 ± 10 | 134 ± 12 | 0.32 |
| Cystatin C (mg/l) | 1.397 ± 0.22 | 1.617 ± 0.22 | <0.01 |
| cysC-eGFR (ml/min/1.73m2) | 54.6 ± 9.6 | 46.2 ± 6.5 | <0.01 |
| Creatinine (mg/dl) | 0.27 | 0.37 | <0.01 |
| creat-eGFR (ml/min/1.73m2) | 80.8 | 63.9 | <0.01 |
| NGAL (ng/ml) | 57 ± 84 | 15 ± 21 | 0.04 |
| Right kidney length (cm) | 4.54 ± 0.47 | 4.66 ± 0.46 | 0.61 |
| Left kidney length (mc) | 4.46 ± 0.63 | 4.57 ± 0.47 | 0.71 |
| TBW (%) | 75.6 ± 13 | 82 ± 8 | 0.015 |
| LBM (%) | 25.68 ± 10.5 | 18.0 ± 8.13 | 0.01 |
| FFM (%) | 84.5 ± 2.1 | 83,9 ± 1.4 | 0.23 |
| FM (%) | 15.5 ± 2.1 | 16,1 ± 1.4 | 0.23 |
| Thrombomodulin (pg/mL) | 1209 ± 765 | 1665 ± 1078 | 0.08 |

Data are presented as mean ± SD; SBP — systolic blood pressure, DBP — diastolic blood pressure, MAP — mean arterial pressure, PP — pulse pressure, HR — heart rate, eGFR — estimated glomerular filtration rate, NGAL — neutrophil gelatinase-associated lipocalin, TBW — total body water, LBM — lean body mass, FFM — free fat mass, FM — fat mass.

## Discussion

Presented study focused on discovery of the pathophysiological changes present at term of delivery in children born prematurely, that could ultimately lead to the changes in their blood pressure profile. We proved that prematurely born children at the predicted term of delivery have elevated markers of tubular nephrons damage (urine NGAL), higher pulse pressure and lower total body water. These might be the cause of former preterms predisposition to hypertension and poorer renal outcomes later in life.

## *Renal dysfunction*

It was already proven that renal function in young adults born prematurely is poorer than in healthy controls [8]. Most authors associate this phenomenon with decreased radial glomerular counts that was proven in few autopsy studies [9, 10]. However, Sutherland *et al.* compered the glomerular count in prematures in comparison to stillborn control neonates at the same age range as the postconceptional age of the preterm neonates and proved that renal maturation accelerates after preterm birth with an increased number of glomerular generations, but the percentage of morphologically abnormal is higher [11]. They also proved that the kidney weight to body weight ratio are higher in premature group. In our study there was no difference in relative kidney length between groups, but the moment of assessment differ from mentioned study (40–42 Hbd vs. 24–38 Hbd).

Due to incapability in glomerular count prediction, the methods of the assessment of kidney injury in neonates is widely discussed nowadays [12]. There is no definite consensus about the diagnostic criteria of acute kidney injury (AKI) in this group of patients. Several proteins that are released from specific segments of the nephron and detectable in the blood and urine are now investigated as new biomarkers of kidney injury to identify AKI earlier, improve the diagnosis of AKI, and to aid in risk stratification. One of this proteins — Neutrophil Gelatinase-Associated Lipocalin (NGAL) is produced from distal tubular cells in response to injury [13, 14]. It was already proven, that kidney injury can occur in the absence of eGFR decrease, which represents an emerging condition called "subclinical AKI" [15, 16]. Subclinical AKI occurs when the effects of tubular injury and reduced GFR in some nephrons is compensated by other non-injured and functioning nephrons [14]. We show that in term of predicted delivery urine NGAL concentration was higher in premature children when comparing to controls. As the result premature children presented hyperfiltration (proven by lover cystatin C level and increased eGFR). This phenomenon can be explained on basis of study presented by Kiyoshi *et al.* They presented on a mouse models that in ischemia-reperfusion injury of kidneys, a single dose of NGAL, introduced during the initial phase of the disease, dramatically protects the kidney [17]. However, even with the protective value of NGAL protein, subclinical AKI is an early step in the spectrum of kidney injury and is associated with poor outcomes later in life [18].

## *Body composition*

We have shown that the main changes in body composition of prematurely born children concerns decreased amount of water in their organism. This phenomenon was previously observed in literature [19]. We assume that the chronic decrease in

both intra and extracellular water is caused via a phenomenon called "renal reserve" — mentioned above increased filtration in injured kidney.

### *Blood pressure*

The incidence of hypertension in former preterms in studies from last 10 years ranges from 6 to 25% [20–28]. Moreover it was proven that higher BP is determined more strongly by birth parameters than by any anthropometric measurement [29]. Most of this studies were performed in adolescence or in young adults and the higher SBP and/or DBP in former preterms was proved.

In our study both MAP and DBP were lower in the study group at the moment of predicted date of delivery and there was no difference in SBP. However the pulse pressure was significantly higher.

24 hour ambulatory blood pressure measurement in neonates is rarely performed therefore there are no specific norms for this age group. Interpretation of the obtained results is difficult, as it should be taken into account that at the time of the examination, premature babies had significantly lower body weight.

Previously performed pediatric studies did not concentrates on pulse pressure. However in last decades this parameter is widely analyzed in adults. It was already proven that mortality and higher cardiovascular risk are strongly related with pulse pressure increase [30–32]. Moreover it was proven that for a given systolic pressure, lower diastolic pressure was associated with greater mortality [33]. Furthermore, some study suggests that PP is a better predictor of adverse renal outcome than DBP or even SBP [34]. We suspect, that like in adults, in our group PP increase is a temporary mechanism that in the end will lead to arteriosclerosis and systolic hypertension as well as to renal function deterioration.

### *Further speculations*

We have performed the further analysis of blood pressure profile of presented study group. We suppose that the lack of difference in SBP between groups is caused by the difference in weight and length. Prematurely born children are both lighter and shorter than term controls. In the wide literature search no reference values for prematures BP regarding to weight or length were found — these data were not analyzed yet. We performed the simple analysis of SBP and DBP relation to weight and length of our newborns. We calculated that both SBP/weight and SBP/height ration was significantly higher in the study group ($p = 0.03$ and 0.04 respectively). There was no difference between groups after similar DBP and MAP recalculation.

We assume that this type of blood pressure profile might be the result by previously described lower TBW in the study group. The physiological reaction for

decreased blood volume and organ blood flow is an increase of heart constriction strength. This inotrope reaction can relatively increase the SBP, but is not influencing the DBP. The raw values of SBP are similar in both groups, because of children size — the actual difference starts to be visible after recalculation due to weight or length.

### *Further observation of the study group*

All children included to the study are nowadays patients of Pediatric and Neonatology Follow-up Department of our hospital. The protocol of the study assumed to perform reassessment of renal and cardiovascular parameters in second year of life. We performed the assessment in 7 children, but the technical issues (problems with ABPM performance and urine collection, parents' reluctance to take the blood sample) made us to postpone the moment of full follow-up till the preschool period. However, the medical condition of all children is monitored. Two of premature children died in first year of life — one due to complications after liver transplant, second due to heart failure. Eight children from the premature group (23%) are patients of the pediatric nephrology department due to kidney problems observed after discharge (asymmetric kidneys in ultrasound, twinkling artifact in ultrasonographic evaluation, nephrolithiasis). No child in the control group developed renal complications. None of children (premature or control) have developed hypertension yet.

### *Speculated presentation of pathophysiological pathway leading to prematurity related kidney injury and hypertension*

Further evaluation of presented group is needed, but we speculate that the observed values may indicate higher risk of tubular damage in preterm infants. This injury might lead to hyper filtration in glomerular part of not injured nephrons (subclinical AKI) and the decrease of total body water in premature children. Next step in proposed pathomechanism is the increase of pulse pressure. Subclinical AKI and high PP are well known factors of both hypertension and poorer renal outcomes later in life. The speculative pathway in relation to the observed results of laboratory tests are presented in Fig. 2.

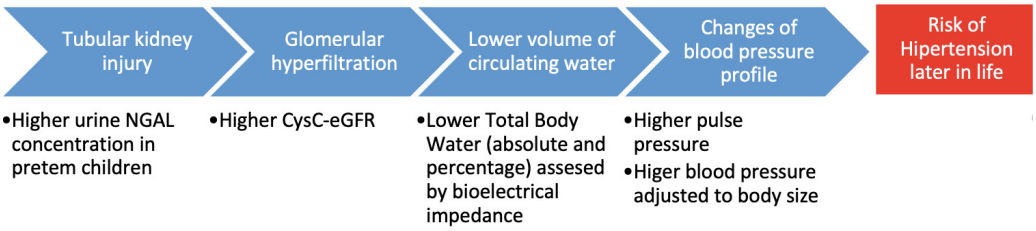


**Fig. 2.** The speculative pathway of higher risk of hypertension in premature children.

### *Strengths and limitations*

The main strength of our study is the complex assessment of premature children at the term of delivery, before well-known complications occur. Moreover, we performed ABPM in each child that gave us an opportunity to assess the blood pressure parameters more particularly — this type of BP assessment was never performed in such young patients.

The main limitation was small sample size. The main reason of small sample size was very rigorous exclusion criteria (pregnancy hypertension and diabetes — two well known risk factors of premature delivery). Exposure to high protein intake is known to increase eGFR, diuresis and induce renal hypertrophy, and may be partly responsible for the results obtained. The test point was chosen to minimize the impact of the diet. However, data on the type of nutrition, protein and caloric intake were not recorded on regular basis, which can be considered one of the limitations of the study.

## Conclusion

According to assessment between 40th and 42nd week of gestational age, in the group of children born prematurely, comparing to term controls, we observed: higher pulse pressure, higher NGAL concentration, lower cystatin C and creatinine levels (as the result — higher eGFR), lower total body water and higher lean body mass.

### *Conflict of interest statement*

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## *Author contribution*

M.G. and P.K. made substantial contributions to the design of the study. M.G. and D.W. collected, analyzed, and interpreted the research data and they were major contributors in drafting the initial version of the manuscript. P.K. reviewed and revised the manuscript. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

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