Retinal and Renal Microvasculature in Relation to Central Hemodynamics in 11-Year-Old Children Born Preterm or At Term

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ORIGINAL RESEARCH

Retinal and Renal Microvasculature in Relation to Central Hemodynamics in 11-Year-Old Children Born Preterm or At Term

Fang-Fei Wei, MD, PhD; Anke Raaijmakers, MD, PhD; Jesus D. Melgarejo, MD; Nicholas Cauwenberghs, MSc; Lutgarde Thijs, MSc; Zhen-Yu Zhang, MD, PhD; Cai-Guo Yu, MD; Elena Levtchenko, MD, PhD; Harry A. J. Struijker-Boudier, PhD; Wen-Yi Yang, MD, PhD; Tatiana Kuznetsova, MD, PhD; Sean Kennedy, MD, PhD; Peter Verhamme, MD, PhD; Karel Allegaert, MD, PhD; Jan A. Staessen, MD, PhD

BACKGROUND: Prematurity disrupts the perinatal maturation of the microvasculature and macrovasculature and confers high risk of vascular dysfunction later in life. No previous studies have investigated the crosstalk between the microvasculature and macrovasculature in childhood.

METHODS AND RESULTS: In a case-control study, we enrolled 55 children aged 11 years weighing <1000 g at birth and 71 matched controls (October 2014–November 2015). We derived central blood pressure (BP) wave by applanation tonometry and calculated the forward/backward pulse waves by an automated pressure–based wave separation algorithm. We measured the renal resistive index by pulsed wave Doppler and the central retinal arteriolar equivalent by computer-assisted program software. Compared with controls, patients had higher central systolic BP (101.5 versus 95.2 mm Hg, $P<0.001$) and backward wave amplitude (15.5 versus 14.2 mm Hg, $P=0.029$), and smaller central retinal arteriolar equivalent (163.2 versus 175.4 µm, $P<0.001$). In multivariable analyses, central retinal arteriolar equivalent was smaller with higher values (+1 SD) of central systolic BP (–2.94 µm; 95% CI, –5.18 to –0.70 µm [$P=0.011$]) and forward (–2.57 µm; CI, –4.81 to –0.32 µm [$P=0.026$]) and backward (–3.20 µm; CI, –5.47 to –0.94 µm [$P=0.006$]) wave amplitudes. Greater renal resistive index was associated with higher backward wave amplitude (0.92 mm Hg, $P=0.036$).

CONCLUSIONS: In childhood, prematurity compared with term birth is associated with higher central systolic BP and forward/backward wave amplitudes. Higher renal resistive index likely moves reflection points closer to the heart, thereby explaining the inverse association of central retinal arteriolar equivalent with central systolic BP and backward wave amplitude. These observations highlight the crosstalk between the microcirculation and macrocirculation in children.

REGISTRATION: URL: http://www.clinicaltrials.gov. Unique Identifier: NCT02147457.

Key Words: central hemodynamics ■ children ■ microcirculation ■ prematurity ■ retina

Prematurity disrupts the perinatal maturation of the microcirculation[1] and macrocirculation[1] and predisposes to impairment of the arterial structure and function later in life,[2] as exemplified by the well-known narrower retinal arteriolar diameters in children[3,4] or young adults[5] born prematurely compared with their peers born at term. The brain and kidney are continually perfused at high volume flow throughout

Correspondence to: Jan A. Staessen, MD, PhD, Studies Coordinating Centre, Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Sciences, Campus Sint Rafaël, University of Leuven Kapucijnenvoer 7, Box 7001, BE-3000 Leuven, Belgium. E-mail: jan.staessen@med.kuleuven.be

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CLINICAL PERSPECTIVE

What Is New?

- In childhood, prematurity compared with term birth is associated with higher central systolic blood pressure and forward/backward wave amplitudes in the central circulation.
- The higher renal resistive index likely moved reflection points closer to the heart, thereby explaining the inverse association of the retinal arteriolar diameter with the central systolic blood pressure and the backward wave amplitude.
- These observations highlight a disturbed crosstalk between the microcirculation and macrocirculation in prematurely born children.

What Are the Clinical Implications?

- Vascular dysregulation and high blood pressure predispose to adverse cardiovascular outcome.
- The clinical relevance of our findings lies in a life-course approach in the prevention of vascular illness, which must start in childhood, particularly in prematurely born individuals.

Nonstandard Abbreviations and Acronyms

AVR	arteriole to venule diameter ratio
BMI	body mass index
BP	blood pressure
CRAE	central retinal arteriolar equivalent
CRVE	central retinal venular equivalent
DBP	diastolic blood pressure
MAP	mean arterial pressure
PP	pulse pressure
PREMATCH	Prematurity as Predictor of Children's Cardiovascular and Renal Health
PWV	pulse wave velocity
RRI	renal resistive index
SBP	systolic blood pressure

systole and diastole, so that pulsations are transmitted through the capillary network up to the venous efflux,[6] in particular if the elastic properties of the aorta degrade. The arterial pressure wave consists of a forward component generated by the heart and reflected waves returning from peripheral branching sites to the central aorta.[7] In stiff compared with elastic arteries, reflected waves return faster, reach the proximal aorta during systole, and augment the late systolic blood pressure (SBP).[8] A recently published case-control study demonstrated that preterm-born 18-year-old adolescents had higher central SBP than controls attributable to increased wave reflection in the central aorta.[9] However, studies on how premature birth affects the central hemodynamics in children at a younger age are scarce,[10] and, according to our review of the literature, no previous study has addressed how premature birth affects the crosstalk between the retinal or renal microcirculation and central hemodynamics. We addressed this knowledge gap in a case-control study of 11-year-old children born with extremely low birth weight or delivered at term.[11,12] We hypothesized that the association of retinal and renal microvascular traits in young children might be modulated by prematurity.

METHODS

Study Participants

The PREMATCH (Prematurity as Predictor of Children's Cardiovascular-Renal Health; NCT02147457) case-control study[11,12] complies with the Declaration of Helsinki for research in humans.[13] The ethics committee of the University Hospitals Leuven approved the protocol. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure, because informed consent did not cover this option. Based on good clinical practice guidelines and national legislation, parents or custodians provided written informed consent and the children informed assent. We recruited cases from a cohort of 140 children, who survived prematurity (birth weight <1000 g; gestation length ranging from 23 to 33 weeks) and who were initially admitted (2000–2005) at the Neonatal Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium. Of 140 invited children who survived premature birth, 93 participated (66.4%). The 87 healthy controls were born at term with a birth weight averaging 3391 g and ranging from 2300 to 5000 g. They were friends of the cases (n=41) or recruited at an elementary school close to the examination center (n=46). Cases and controls were examined at ≈11 years of age. However, cases and controls could not be matched for age on a 1-to-1 basis, but within a narrow age range. We excluded participants from analysis if the quality of their retinal photographs was too low to be reliably graded (7 cases), if tonometric measurements had not been obtained (9 cases and 2 controls), or if the quality of their pulse wave analysis (6 cases and 5 controls) or wave separation analysis (16 cases and 9 controls) did not meet quality standards (see section Clinical and Hemodynamic Measurements). Thus, the current analysis included 55 cases and 71 controls (Figure S1).

Clinical and Hemodynamic Measurements

Body weight was measured using an Omron Karada Scan HBF-511 device (Omron Healthcare Inc) and body height with a wall-mounted ruler. Body mass index (BMI) was body weight in kilograms divided by height in meters squared. We converted the anthropometric measurements to *Z* scores based on Centers for Disease Control and Prevention growth charts.[14]

For blood pressure (BP) measurement, European guidelines were applied.[15] After the children rested for at least 5 minutes in the supine position, immediately before the hemodynamic measurements, observers obtained 2 consecutive auscultatory BP readings (phase V diastolic pressure) to the nearest 2 mm Hg on the right arm, using a standard mercury sphygmomanometer (Rudolf Riester GmbH) fitted with a 9×18 cm cuff. The second of the 2 measurements was used for analysis and calibration of the pulse wave analysis by diastolic BP (DBP) and mean arterial pressure (MAP). Pulse pressure (PP) was SBP minus DBP. MAP was DBP plus 40% of the PP (the difference between SBP and DBP).[16] Prehypertension and hypertension were classified as BP levels exceeding the 90th and 95th percentiles, respectively, of the reference distributions stratified by sex, age, and body height.[17]

Next, experienced observers (F.-F.W. and Z.-Y.Z.) recorded the radial arterial waveform on the patient's dominant arm during an 8-second period by applanation tonometry. They used a high-fidelity SPC-301 micromanometer (Millar Instruments Inc.) interfaced with a laptop computer running SphygmoCor software version 9.0 (AtCor Medical Pty Ltd.). Recordings were discarded when BP variability of consecutive waveforms exceeded 5% or the amplitude of the pulse wave signal was <80 mV. From the radial signal, SphygmoCor software calculates the aortic pulse wave by means of a validated generalized transfer function.[18,19] The software returns the central systolic pressure, diastolic pressure, PP, and the pressure at the first and second peak (shoulder) of the central waveform (Figure S2). The augmentation ratio and index are quotients of the second over the first peak of the central BP wave and of the absolute difference between the second and first peak over central PP, both expressed as a percentage. From the central waveform, a triangular-flow pressure-based wave separation algorithm,[20] as implemented in the SphygmoCor software, allows computing of the forward/backward PP amplitudes (Figure S2) and the timing of their peak height relative to the ECG QRS complex. The reflection index is the ratio of the backward to the forward PP amplitude expressed as a percentage.

Aortic pulse wave velocity (PWV) was measured by sequential ECG-gated recordings of the arterial pressure waveform at the carotid and femoral arteries. The observers measured the distance from the suprasternal notch to the carotid sampling site (distance A), and from the suprasternal notch to the femoral sampling site (distance B). Pulse wave travel distance was calculated as distance B minus distance A.[21] Pulse transit time was the average of 10 consecutive beats.[22] Carotid-femoral PWV is the ratio of the travel distance in meters to transit time in seconds. PWV was discarded if the SEM of 10 beats was >10%. The short-term intrasession reproducibility of carotid-femoral PWV was 2.61%.[23]

Retinal Photography

We applied a noninvasive nonmydriatic approach in a dimly lit room to acquire retinal photographs, 1 image per eye in each participant, with a Canon Cr-DGi retinal visualization system combined with a Canon D 50 digital camera (Canon Medical Systems USA, Inc.). We determined the central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE), which represent the retinal arteriolar and venular diameters, respectively. We used the validated computer-assisted program SIVA (Singapore I Vessel Assessment, version 3.6; Singapore Eye Research Institute) based on formulae published by Parr and Spears[24] and Hubbard et al.[25] The software returns average vessel diameters according to the revised Knudtson formula.[26] The arteriole to venule diameter ratio (AVR) was CRAE divided by CRVE. For analysis, we averaged measurements in both eyes. Intraobserver variability (F.-F.W.) and interobserver variability (F.-F.W. and Z.-Y.Z.) were assessed from repeated measurements in 30 children, using intraclass correlation coefficients.[27] For the intraobserver correlation, coefficients were 0.98, 0.99, and 0.98 for CRAE, CRVE, and AVR, respectively, and the corresponding interobserver correlation coefficients were 0.94, 0.93, and 0.87, respectively.[27]

Renal Doppler Ultrasound

With participants in the supine, left or right decubitus, experienced ultrasonographers obtained renal grayscale images and color Doppler recordings, using a Vivid 7 Pro (GE Vingmed) interfaced with a 1.5- to 4.5-MHz convex transducer according to a standardized protocol.[28] The observers attempted to record the intrarenal blood flow of at least the superior, middle, and inferior segmental or interlobar renal arteries at both kidneys over 5 cardiac cycles. One observer (N.C.) postprocessed the digitally stored images using a workstation running EchoPac software (version 4.0.4; GE Vingmed). Good-quality images were averaged for analysis. The renal resistive index (RRI) was the ratio of the difference between peak systolic minus end-diastolic peak blood velocity divided by the peak systolic blood velocity. The absolute and relative interobserver

variability was 0.001±0.038 and −0.01±6.46%, respectively.[29]

Statistical Analysis

For database management and statistical analysis, we used SAS software version 9.4 (SAS Institute Inc). We applied the Shapiro–Wilk test to evaluate normality of distributions. For comparison of means, we used *t* test or Wilcoxon–Mann–Whitney test depending on the distribution of the variables and χ^2 statistic for comparison of proportions. Statistical significance was a 2-sided α-level <0.05.

Using linear regression analysis, we standardized the augmentation ratio and index, the aortic PWV, the forward/backward wave amplitudes, and peak times to a heart rate of 70 beats per minute (approximately the mean in cases and controls). In unadjusted and multivariable-adjusted analyses, we expressed association sizes of the retinal microvascular phenotypes with a 1-SD increment of central hemodynamic measurements. Association sizes were therefore expressed as standardized regression coefficients. In multivariable-adjusted analyses, we adjusted for sex, age, BMI, brachial DBP, heart rate, and prematurity, if appropriate (0,1). In sensitivity analyses, the models relating CRAE to central hemodynamic traits were additionally adjusted for CRVE to provide unbiased results.[30] Additionally, we substituted BMI as a covariable by body weight and height and computed the odds of having hypertension at 11 years old in relation to CRAE. Finally, in multivariable-adjusted analyses, we preformed mediation analysis, using PROC CAUSALMED as implemented in the SAS software. CRAE was the outcome variable, central hemodynamic measurements were the exposure variables, and prematurity was the mediator.

RESULTS

Characteristics of Participants

Table 1 and Table S1 list the characteristics of the 55 cases and 71 controls. The number of girls was similar among cases and controls (28 [50.9%] versus 41 [57.8%], respectively; *P*=0.44). Compared with controls, cases were 0.55 years (95% CI, 0.06–1.03; *P*=0.028) older. Cases compared with controls had lower *Z* scores (*P*<0.001) for body height (difference [Δ], 0.77; CI, 0.46–1.08) and body weight (Δ, 0.71; CI, 0.36–1.05), but higher *Z* scores (*P*≤0.002) for peripheral SBP/DBP (Δ, 0.72/0.31; CI, 0.43–1.02/0.11–0.51). Compared with controls, cases had higher SBP values (112.3 mm Hg versus 103.3 mm Hg, respectively; *P*<0.001) and MAP (82.7 mm Hg versus 78.2 mm Hg, respectively; *P*=0.015) standardized by age and body height.

Central Hemodynamics and Retinal and Renal Microvascular Traits

Compared with controls (Table 2), cases had higher central SBP/DBP values (Δ, 6.25/3.02 mm Hg; CI, 3.32–9.17/0.75–5.28 mm Hg), MAP (Δ, 4.10 mm Hg; CI, 1.90–6.29 mm Hg), PP (Δ, 3.31 mm Hg; CI, 0.74–5.89 mm Hg), and backward wave amplitude (Δ, 1.20 mm Hg; CI, 0.08–2.33 mm Hg), but smaller (*P*<0.001; Table 2) CRAE (Δ, −12.2 µm; CI, −16.5 to −7.94 µm) and AVR (Δ, −0.036; CI, −0.052 to −0.020). However, there was no difference in aortic PWV (*P*=0.20) and RRI (*P*=0.34) between cases and controls.

Unadjusted Analyses

CRAE was inversely correlated with central MAP, PP, and forward/backward wave amplitudes (*P*≤0.006; Figure 1). In unadjusted analyses, a 1-SD increment in central SBP/DBP (+8.7/+6.5 mm Hg), MAP (+6.5 mm Hg), PP (+7.4 mm Hg), and forward/backward wave amplitudes (+7.6/+3.3 mm Hg) was associated with smaller CRAE, with association sizes −5.51/−3.12 µm, −4.58 µm, −3.81 µm, and −3.28/−3.92 µm, respectively (*P*≤0.009; Table 3). In unadjusted analyses (Table S2), CRVE was inversely correlated (*P*≤0.038) with central systolic pressure (−3.60 µm), PP (−4.49 µm), and forward/backward wave amplitudes (−4.47/−3.19 µm). The associations between AVR and central hemodynamic traits were directionally similar compared with CRAE, with the exception of aortic PWV (−0.009; *P*=0.038), but lost significance for central PP and forward/backward wave amplitudes (Table S3). In unadjusted analysis (Figure 2), a 1-SD increment in RRI (+0.04) was associated with 1.13 mm Hg (*P*=0.006) higher backward wave amplitude.

Adjusted Analyses

With adjustments applied for sex, age, BMI, heart rate, and prematurity (Table 3), a 1-SD increment in central SBP and MAP was associated with smaller CRAE, with association sizes −3.59 µm (*P*=0.002) and −2.94 µm (*P*=0.011). With additional adjustment for brachial DBP (Table 3), CRAE was −2.57 µm (*P*=0.026) and −3.20 µm (*P*=0.006) lower in relation to forward/backward wave amplitudes. In multivariable-adjusted analyses (Table S2), CRVE was −3.75 µm (*P*=0.018) and −3.99 µm (*P*=0.014) smaller in relation to central PP and forward wave amplitude. The multivariable-adjusted association sizes of the AVR with central DBP (*P*=0.044), aortic PWV (*P*=0.012), backward wave amplitude (*P*=0.035), and reflection magnitude (*P*=0.008) were significant (Table S3), with association sizes ranging from −0.008 to −0.011. In multivariable-adjusted analysis (Figure 2), a 1-SD increment in RRI (+0.04) was

Table 1. Characteristics of Cases and Controls

Characteristics	Cases (n=55)		Controls (n=71)		*P* Value
	No.	Mean±SD	No.	Mean±SD	
Anthropometric measurement					
Female sex, %	55	28 (50.9)	71	41 (57.8)	0.44
Age, y	55	11.5±1.4	71	10.9±1.3	0.028
Body height, cm	55	147.0±8.6	71	149.5±10.2	0.14
Z score for height	55	−0.46±0.78	71	0.31±0.94	<0.001
Percentile for height (IQR)	55	27.9 (17.4–56.5)	71	64.2 (29.3–84.0)	<0.001
Body weight, kg	55	38.1±9.6	71	40.8±9.8	0.12
Z score for weight	55	−0.64±1.0	71	0.07±0.91	<0.001
Percentile for weight (IQR)	55	23.1 (6.9–50.1)	71	49.8 (30.1–79.8)	<0.001
BMI, kg/m^2	55	17.4±3.2	71	18.1±2.8	0.22
Z score for BMI	55	−0.56±1.2	71	−0.06±1.0	0.014
Percentile for BMI (IQR)	55	31.5 (11.1–63.1)	71	46.7 (24.0–77.1)	0.024
Peripheral BP					
Systolic, mm Hg	55	112.4±10.5	71	105.4±7.3	<0.001
Z score for systolic pressure	55	0.68±0.99	71	−0.045±0.68	<0.001
Percentile for systolic pressure (IQR)	55	77.0 (46.6–91.1)	71	49.5 (31.2–69.4)	<0.001
Diastolic, mm Hg	55	63.3±6.8	71	60.4±6.0	0.012
Z score for diastolic pressure	55	0.13±0.59	71	−0.18±0.53	0.002
Percentile for diastolic pressure (IQR)	55	58.4 (37.1–67.2)	71	43.3 (29.8–57.9)	0.002
Prehypertension, %	55	21 (38.2)	71	2 (2.8)	<0.001
Hypertension, %	55	11 (20.0)	71	0 (0)	<0.001

Values are expressed as mean (±SD) or median (interquartile range [IQR]). *Z* scores were based on Centers for Disease Control and Prevention growth charts.[14] Prehypertension and hypertension were classified as blood pressures (BPs) exceeding the 90th and 95th percentiles, respectively, of the distributions stratified according to sex, age, and body height.

BMI indicates body mass index.

associated with 0.92 mm Hg (*P*=0.036) higher backward wave amplitude.

Sensitivity Analyses

Sensitivity analyses relating CRAE to the central hemodynamic indexes, with additional adjustment for CRVE, produced confirmatory results (Table S4). In unadjusted models, per 1-SD increment in central SBP, CRAE was 4.15 µm (CI, 0.77–7.52 µm; *P*=0.017) smaller in cases and 3.11 µm (CI, 0.50–5.72 µm; *P*=0.020) in controls. The corresponding association sizes in multivariable-adjusted models, per 1-SD increment in central SBP, CRAE were 3.26 µm (CI, 0.38–6.15 µm; *P*=0.027) smaller in cases and 3.25 µm (CI, 0.21–6.72 µm; *P*=0.065) in controls. In multivariable analyses, in which BMI was replaced by body weight and height, the association sizes of CREA expressed per 1-SD increment in the explanatory variables were −3.81 µm (CI, −6.12 to −1.49 µm; *P*=0.022) for central SBP, −2.66 µm (CI, −4.92 to −0.40 µm; *P*=0.021) for forward wave amplitude, and −3.18 µm (CI, −5.45 to −0.91 µm; *P*=0.006) for backward wave amplitude. With adjustment for covariables and body weight and height instead of BMI, a 1-SD increment in the RRI was also associated with a 1.03 mm Hg higher backward wave amplitude (CI, 0.13–1.93 mm Hg; *P*=0.025). The prevalence of hypertension was 16.7%. The odds of having hypertension at 11 years old in relation to a 1-SD smaller CRAE was 2.42 (CI, 1.43–4.07; *P*=0.001). With adjustments applied for sex, age, body height and weight, heart rate, CRVE, and prematurity, the odds ratio was 2.24 (CI, 1.03–4.87; *P*=0.043).

Mediation Analysis

In multivariable-adjusted analyses, CRAE was directly and indirectly associated via prematurity with central SBP (*P*=0.013/*P*=0.003), MAP (*P*=0.006/*P*=0.004) and backward wave amplitude (*P*=0.003/*P*=0.040).

DISCUSSION

A literature review revealed that no studies have addressed the possible association of retinal or renal microvascular traits with central hemodynamics in prematurely born children compared with those born at term. We addressed this knowledge gap in 11-year-old children born prematurely or

Table 2. Central Hemodynamics and Retinal Microvascular Traits

Characteristics	Cases (n=55)	Controls (n=71)	*P* Value
SBP, mm Hg	101.5±9.1	95.2±7.4	<0.001
DBP, mm Hg	64.8±6.9	61.7±5.9	0.010
MAP, mm Hg	77.0±6.6	72.9±5.8	<0.001
Central PP, mm Hg	36.7±8.2	33.4±6.4	0.012
Augmentation pressure, mm Hg	2.69±3.6	1.68±2.7	0.074
Augmentation ratio, %	102.9±3.7	102.0±2.9	0.15
Augmentation index, %	9.65±6.5	7.98±5.7	0.13
PWV, m/s	4.13±0.86	4.37±0.98	0.20
Forward wave amplitude, mm Hg	33.5±8.2	31.2±7.0	0.090
Backward wave amplitude, mm Hg	15.6±3.7	14.4±2.6	0.036
Reflection magnitude, %	46.4±7.8	46.0±8.7	0.81
Central retinal arteriolar diameter, µm	163.2±12.9	175.4±11.3	<0.001
Central retinal venular diameter, µm	237.2±17.6	242.4±16.6	0.097
Arteriole to venule diameter ratio	0.69±0.05	0.72±0.04	<0.001

Values are expressed as mean±SD. Pulse wave velocity was available in 46 cases and 54 controls. The time-dependent hemodynamic variables (augmentation ratio and index, pulse wave velocity [PWV], and forward/backward wave amplitudes) were standardized to a heart rate of 70 beats per minute (approximately the mean in cases and controls).

DBP indicates diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; and SBP, systolic blood pressure.

delivered at term. The retinal arteriolar diameters were smaller, with higher central systolic and mean arterial BP and with greater forward/backward wave amplitude. The observation that retinal diameters were smaller[3–5] and central BP levels were higher[9] in cases than controls is in line with existing knowledge and provides an external validation of our results. What our study added to existing knowledge is that prematurity compared with term birth was associated with higher central SBP and forward/backward wave amplitudes in the central circulation, an observation highlighting a disturbed crosstalk between the microcirculation and macrocirculation in prematurely born children. The clinical relevance of our findings can be gauged from studies showing that central hemodynamic characteristics, including wave reflection,[31–33] and arterial stiffness[34,35] predict cardiovascular complications over and beyond traditional risk factors. Moreover, numerous studies have demonstrated that the diameters of the retinal microvessels carry important prognostic information,[36,37] smaller CRAE[37] and lower AVR,[36] predicting cardiovascular mortality[37] and coronary heart disease.[36]

For the mechanistic interpretation of the inverse association between CRAE and central SBP and the backward wave amplitude, we hypothesized that higher renal vascular resistance might bring reflection points closer to the heart, thereby moving the backward wave into systole and increasing the central SBP. Both CRAE and the RRI[38] are microvascular traits and both might be clinically useful markers for the early detection of microvascular alterations. This mechanistic hypothesis was substantiated by the positive association between the backward wave amplitude and the RRI in both unadjusted and multivariable-adjusted analyses. Renin is highly expressed during perinatal kidney development.[39,40] In keeping with other studies,[39] we previously reported that in the PREMATCH (Prematurity as Predictor of Children's Cardiovascular and Renal Health) study,[12] plasma renin activity was 0.54 ng/mL per hour (CI, 0.23–0.85; *P*=0.001) lower in cases compared with controls. Furthermore, abundance of elastin fibers in the aortic wall determines its elasticity. Synthesis of elastin is deficient in prematurely born infants.[41] Loss of aortic compliance leads to a rise in PP and an increase in circumferential stress,[41] making them vulnerable to arterial stiffening later in life. Over time, cyclic stress on the aortic wall promotes further fragmentation of the elastin fibers, so that stiff collagen has to bear the pulsatile load. The higher BP in prematurely born children and adults likely accelerates this process, predisposing them to a higher risk of cardiovascular complications. However, aortic stiffening is a process that requires many years to develop, thereby explaining why there was no relation between CRAE and PWV in our 11-year-old patients. Previous case-control studies compared aortic[10] or carotid-radial[42] PWV after premature birth and at term birth at the age of 11[10] or 18[42] years. In keeping with the current results, aortic PWV was not different between the groups either before or following adjustment for sex and MAP.[10,42] A study of children with or without chronic kidney disease (girls 40%; mean age, 15.1 years) confirmed that at young age there was no difference in aortic PWV between cases and controls.[43]

Strength and Limitations

The current study must be interpreted within the context of its strengths and potential limitations. First, the sample size was small and the cross-sectional case-control design precludes direct causal inferences. Second, BP was measured on only 1 occasion and the BP analyzed was a single measurement taken immediately before the hemodynamic examination to calibrate the central BP. However, the correlation between the average of this single measurement and the average of 3 consecutive readings with the children in the seated position, obtained as previously

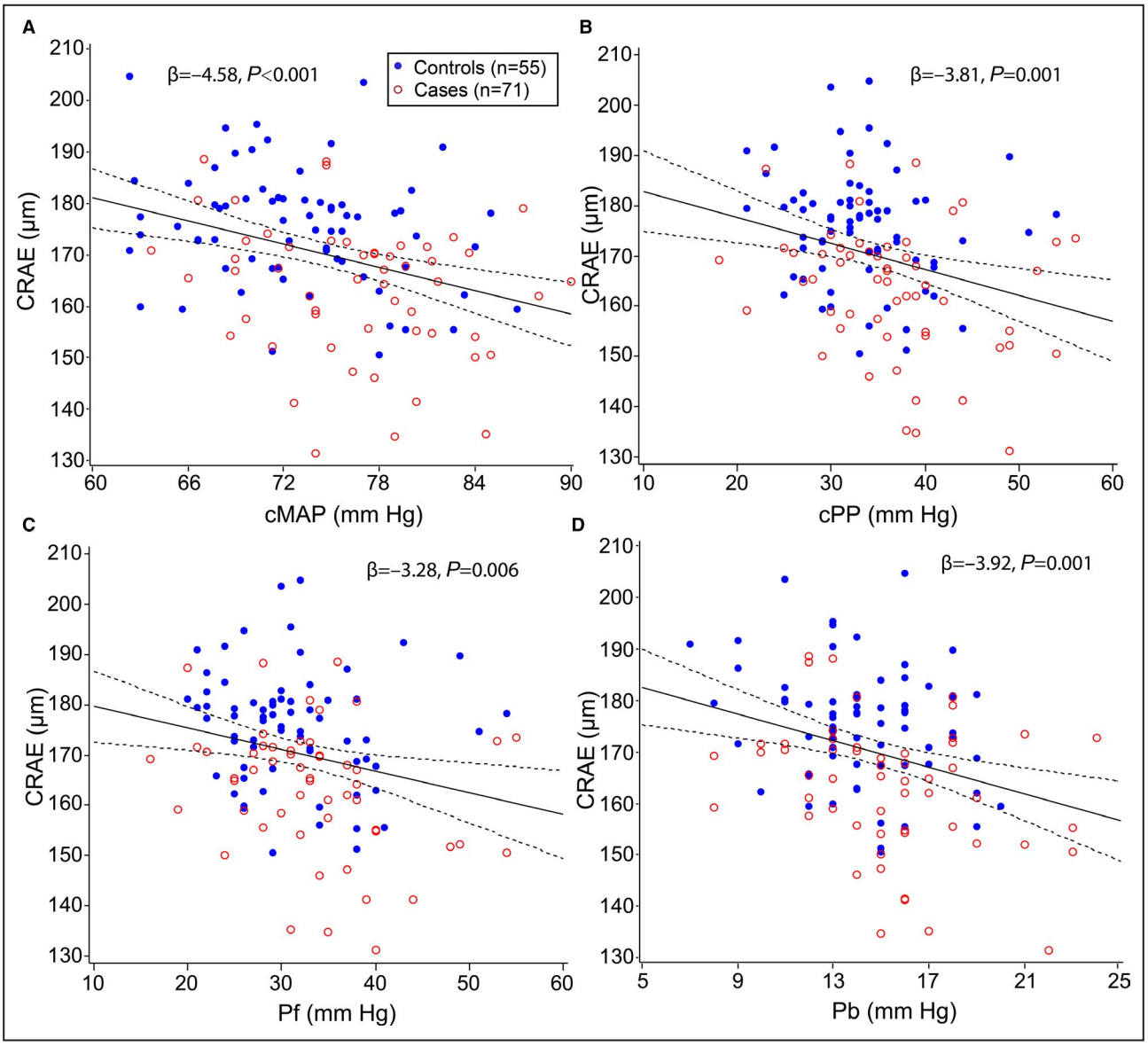

Figure 1. Unadjusted associations of the central retinal arteriolar equivalent (CRAE) with central mean arterial pressure (cMAP, A), central pulse pressure (cPP, B), forward wave amplitude (Pf, C), and backward wave amplitude (Pb, D).
β expresses the change in the dependent variable for a 1-SD increment in the explanatory variable.

described,[12] was 0.74 SBP and 0.77 DBP. In the 55 cases, the systolic/diastolic levels of the seated BP averaged 112.0/67.9 mm Hg and in the 71 controls averaged 105.5/63.8 mm Hg, demonstrating that the single measurement analyzed was representative of the children's BP. Third, although quality criteria were the same in cases and controls, more cases were excluded because of quality issues of the central hemodynamic measurements (38/93 [40.9%] versus 16/87 [18.4%]; $P<0.001$). However, CRAE (163.2 versus 162.0 μm; $P=0.68$) and CRVE (237.2 versus 230.2 μm; $P=0.075$) were similar in the 55 cases analyzed and 31 cases removed from analysis excluded because of poor central hemodynamic measurements, suggesting that the selection bias had no major influence on the results. Fourth, cases were on average 6.56 months (Table 1) older than controls, but this small difference unlikely biased our results, in particular because the regression models were adjusted for age, sex, BMI, and heart rate. Finally, we did not adjust for multiple testing. Adjustment for multiple testing is usually recommended to avoid rejecting the null hypothesis too readily.[44,45] However, as in the present study, the explanatory hemodynamic variables were highly correlated, and each new test does not provide a completely independent opportunity for a type I error and does not necessitate adjusting the significance levels for multiple testing.[44,45]

Table 3. Central Retinal Arteriolar Diameter in Relation to Central Hemodynamics

Hemodynamics (+ 1 SD)	Unadjusted Models		Adjusted Models	
	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value
Central systolic pressure (+8.7 mm Hg)	−5.51 (−7.69 to −3.33)	<0.001	−3.59 (−5.87 to −1.32)	0.002
Central diastolic pressure (+6.5 mm Hg)	−3.12 (−5.45 to −0.79)	0.009	−1.98 (−4.19 to 0.23)	0.079
Central mean pressure (+6.5 mm Hg)	−4.58 (−6.83 to −2.33)	<0.001	−2.94 (−5.18 to −0.70)	0.011
Central pulse pressure (+7.4 mm Hg)	−3.81 (−6.11 to −1.52)	0.001	−2.14 (−4.38 to 0.10)	0.061
Augmentation pressure (+3.2 mm Hg)	0.06 (−2.33 to 2.45)	0.96	0.31 (−0.41 to 1.02)	0.40
Augmentation ratio (+3.3 %)	0.46 (−1.93 to 2.85)	0.70	0.88 (−1.40 to 3.16)	0.45
Augmentation index (+6.2 %)	0.70 (−1.69 to 3.09)	0.56	1.42 (−0.74 to 3.57)	0.20
PWV (+0.95 m/s)	−0.57 (−3.24 to 2.10)	0.67	−0.93 (−3.45 to 1.59)	0.46
Forward wave amplitude (+7.6 mm Hg)	−3.28 (−5.60 to −0.96)	0.006	−2.57 (−4.81 to −0.32)	0.026
Backward wave amplitude (+3.3 mm Hg)	−3.92 (−6.21 to −1.64)	0.001	−3.20 (−5.47 to −0.94)	0.006
Reflection magnitude (+8.3 %)	−0.38 (−2.77 to 2.01)	0.75	−0.39 (−2.66 to 1.88)	0.74

Association sizes (95% CI) express the difference in central retinal arteriolar diameter associated with 1-SD increment in the hemodynamic indexes. All analyses included 126 children (55 cases and 71 controls) with the exception of pulse wave velocity (PWV), which was available in 100 children (46 cases and 54 controls). Adjusted models accounted for sex, age, body mass index, heart rate, and prematurity (0.1). The augmentation ratio and index, PWV, forward/backward wave amplitudes, and reflection magnitude were also adjusted for brachial diastolic blood pressure.

Conclusions

Vascular dysregulation and high BP predispose to adverse cardiovascular outcomes. In our current study, there was an inverse association of CRAE with central systolic and mean arterial BP and with forward/backward wave amplitudes in 11-year-old children. Prematurity predisposes to central and peripheral hypertension and dysregulation of the cross-talk between microcirculation and macrocirculation.[12] High

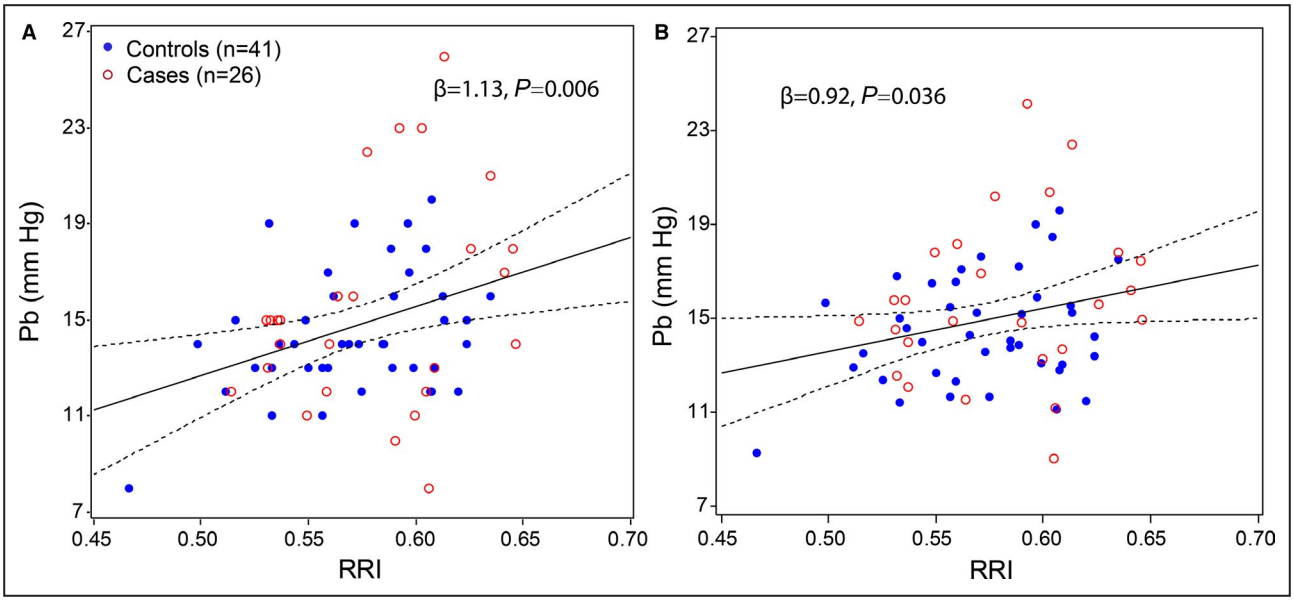

Figure 2. Unadjusted (A) and multivariable-adjusted (B) associations of backward wave amplitude with the renal resistive index (RRI).
The multivariable association was adjusted for sex, age, body mass index, brachial diastolic blood pressure, heart rate, and prematurity (0,1). β expresses the change in backward wave amplitude for a 1-SD increment in RRI.

BP behaves as the motor driving the structural and functional alterations of the vasculature, forerunning premature cardiovascular complications in young and middle-aged adults.[46] The translational value of our findings lies in a life-course approach[47] in the prevention of vascular illness, which must start in childhood, particularly in prematurely born individuals.

ARTICLE INFORMATION

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Affiliations

From the Studies Coordinating Centre, Research Unit Hypertension and Cardiovascular Epidemiology (F.-F.W., J.D.M., N.C., L.T., Z.-Y.Z., C.-G.Y., W.-Y.Y., T.K., J.A.S.); Center for Molecular and Vascular Biology (P.V.), KU Leuven Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium; Department of Cardiology, the First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, Guangdong, China (F.-F.W.); Department of Pediatrics, University Hospitals Leuven, Leuven, Belgium (E.L.); KU Leuven Department of Development and Regeneration, University of Leuven, Leuven, Belgium (A.R., K.A.); Department of Endocrinology, Beijing Luhe Hospital and Key Laboratory of Diabetes Prevention and Research, Capital Medical University, Beijing, China (C.-G.Y.); Department of Pharmacology (H.A.J.S.-B.) and Cardiovascular Research Institute Maastricht (H.A.J.S.-B., J.A.S.), Maastricht University, Maastricht, The Netherlands; Department of Cardiology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China (W.-Y.Y.); Department of Clinical Pharmacy, Erasmus MC, Rotterdam, The Netherlands (K.A.); NPA Alliance for the Promotion of Preventive Medicine, Mechelen, Belgium (J.A.S.).

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Disclosures

None.

Supplementary Materials

Tables S1–S4
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Characteristics of 55 Cases.

Characteristics	Values
Perinatal characteristics, n (%)	
Tocolysis	15 (28.8)
Pre-eclampsia	17 (30.9)
Chorioamnionitis	2 (3.7)
Antenatal lung maturation	46 (86.8)
Premature rupture of membranes	10 (18.5)
Gestational age (weeks)	27.6 (25.0 to 31.0)
Birth weight (g)	808.9 (530.0 to 995.0)
Postnatal characteristics	
Ventilation (days)	11.4 (0 to 41)
Oxygen need (days)	37.3 (1.0 to 87.0)
Ibuprofen, n (%)	24 (43.6)
Postnatal steroids, n (%)	26 (47.3)
Retinopathy of prematurity ≥3, n (%)	7 (12.7)
Intraventricular hemorrhage, n (%)	9 (16.4)

Values are mean (95% confidence interval) or n (%). To accelerate antenatal lung maturation, mothers received intramuscular betamethasone on two consecutive days.

Table S2. Central Retinal Venule Diameter in Relation to Central Hemodynamic Traits.

Hemodynamics (+ 1 SD)	Unadjusted Models		Adjusted Models	
	Estimate (95%CI)	*P*	Estimate (95%CI)	*P*
Central systolic pressure (+8.7 mm Hg)	–3.60 (–6.58 to –0.61)	0.019	–3.22 (–6.47 to 0.04)	0.053
Central diastolic pressure (+6.5 mm Hg)	0.16 (–2.89 to 3.21)	0.92	0.23 (–2.90 to 3.35)	0.89
Central mean pressure (+6.5 mm Hg)	–1.51 (–4.55 to 1.53)	0.33	–1.21 (–4.42 to 2.00)	0.46
Central pulse pressure (+7.4 mm Hg)	–4.49 (–7.43 to –1.54)	0.003	–3.75 (–6.85 to –0.65)	0.018
Augmentation pressure (+3.2 mm Hg)	0.66 (–2.39 to 3.71)	0.67	0.42 (–0.58 to 1.42)	0.41
Augmentation ratio (+3.3 %)	0.82 (–2.23 to 3.87)	0.59	1.46 (–1.76 to 4.67)	0.37
Augmentation index (+6.2 %)	2.36 (–0.66 to 5.39)	0.12	2.90 (–0.12 to 5.91)	0.059
Pulse wave velocity (+0.95 m/s)	2.22 (–1.00 to 5.43)	0.17	2.18 (–1.16 to 5.52)	0.20
Forward wave amplitude (+7.6 mm Hg)	–4.47 (–7.42 to –1.52)	0.003	–3.99 (–7.15 to –0.83)	0.014
Backward wave amplitude (+3.3 mm Hg)	–3.19 (–6.19 to –0.19)	0.038	–1.52 (–4.81 to 1.77)	0.36
Reflection magnitude (+8.3 %)	1.70 (–1.33 to 4.74)	0.27	3.07 (–0.09 to 6.22)	0.057

Association sizes (95% confidence interval) express the difference in central retinal venular diameter associated with 1-SD increment in the hemodynamic indexes. The analyses included 126 children with the exception of pulse wave velocity, which was available in 100 children. Adjusted models accounted for sex, age, body mass index, heart rate, and prematurity (0,1). The augmentation ratio and index, pulse wave velocity, forward and backward wave amplitudes and reflection magnitude were also adjusted for brachial diastolic blood pressure.

Table S3. Arteriole-to-Venule Diameter Ratio in Relation to Central Hemodynamic Traits.

Hemodynamics (+ 1 SD)	Unadjusted Models		Adjusted Models	
	Estimate (95%CI)	*P*	Estimate (95%CI)	*P*
Central systolic pressure (+8.7 mm Hg)	–0.012 (–0.020 to –0.003)	0.006	–0.005 (–0.014 to 0.004)	0.26
Central diastolic pressure (+6.5 mm Hg)	–0.013 (–0.021 to –0.004)	0.003	–0.008 (–0.016 to –0.0002)	0.044
Central mean pressure (+6.5 mm Hg)	–0.014 (–0.022 to –0.006)	0.001	–0.008 (–0.016 to 0.0003)	0.059
Central pulse pressure (+7.4 mm Hg)	–0.003 (–0.011 to 0.006)	0.56	0.002 (–0.006 to 0.010)	0.61
Augmentation pressure (+3.2 mm Hg)	–0.003 (–0.011 to 0.006)	0.55	–0.0002 (–0.003 to 0.002)	0.88
Augmentation ratio (+3.3 %)	–0.001 (–0.010 to 0.007)	0.75	–0.003 (–0.011 to 0.005)	0.51
Augmentation index (+6.2 %)	–0.004 (–0.013 to 0.004)	0.34	–0.002 (–0.010 to 0.006)	0.54
Pulse wave velocity (+0.95 m/s)	–0.009 (–0.018 to –0.0005)	0.038	–0.011 (–0.019 to –0.002)	0.012
Forward wave amplitude (+7.6 mm Hg)	–0.0002 (–0.009 to 0.008)	0.96	0.001 (–0.007 to 0.010)	0.75
Backward wave amplitude (+3.3 mm Hg)	–0.007 (–0.016 to 0.001)	0.096	–0.009 (–0.017 to –0.001)	0.035
Reflection magnitude (+8.3 %)	–0.007 (–0.016 to 0.001)	0.099	–0.011 (–0.019 to –0.003)	0.008

Association sizes (95% confidence interval) express the difference in retinal arteriole-to-venule diameter ratio associated with 1-SD increment in the hemodynamic indexes. The analyses included 126 children with the exception of pulse wave velocity, which was available in 100 children. Adjusted models accounted for sex, age, body mass index, heart rate, and prematurity (0,1). The augmentation ratio and index, pulse wave velocity, forward and backward wave amplitudes and reflection magnitude were also adjusted for brachial diastolic blood pressure.

Table S4. Association of Central Retinal Arteriolar Diameter with Central Hemodynamic Traits Additionally Adjusted for Central Retinal Venular Diameter.

Hemodynamics (+ 1 SD)	Adjusted Models	
	Estimate (95%CI)	*P*
Central systolic pressure (+8.7 mm Hg)	–2.27 (–4.15 to –0.39)	0.018
Central diastolic pressure (+6.5 mm Hg)	–2.08 (–3.83 to –0.32)	0.021
Central mean pressure (+6.5 mm Hg)	–2.43 (–4.22 to –0.63)	0.008
Central pulse pressure (+7.4 mm Hg)	–0.54 (–2.40 to 1.32)	0.56
Augmentation pressure (+3.2 mm Hg)	0.13 (–0.45 to 0.70)	0.66
Augmentation ratio (+3.3 %)	0.24 (–1.57 to 2.06)	0.79
Augmentation index (+6.2 %)	0.16 (–1.58 to 1.90)	0.86
Pulse wave velocity (+0.95 m/s)	–2.03 (–3.93 to –0.14)	0.036
Forward wave amplitude (+7.6 mm Hg)	–0.87 (–2.73 to 0.99)	0.36
Backward wave amplitude (+3.3 mm Hg)	–2.56 (–4.35 to –0.76)	0.006
Reflection magnitude (+8.3 %)	–1.78 (–3.58 to 0.01)	0.052

Association sizes (95% confidence interval) express the difference in central retinal arteriolar diameter associated with 1-SD increment in the hemodynamic indexes. The analyses included 126 children with the exception of pulse wave velocity, which was available in 100 children. Adjusted models accounted for sex, age, body mass index, heart rate, and prematurity (0,1). The augmentation ratio and index, pulse wave velocity, forward and backward wave amplitudes and reflection magnitude were also adjusted for brachial diastolic blood pressure.

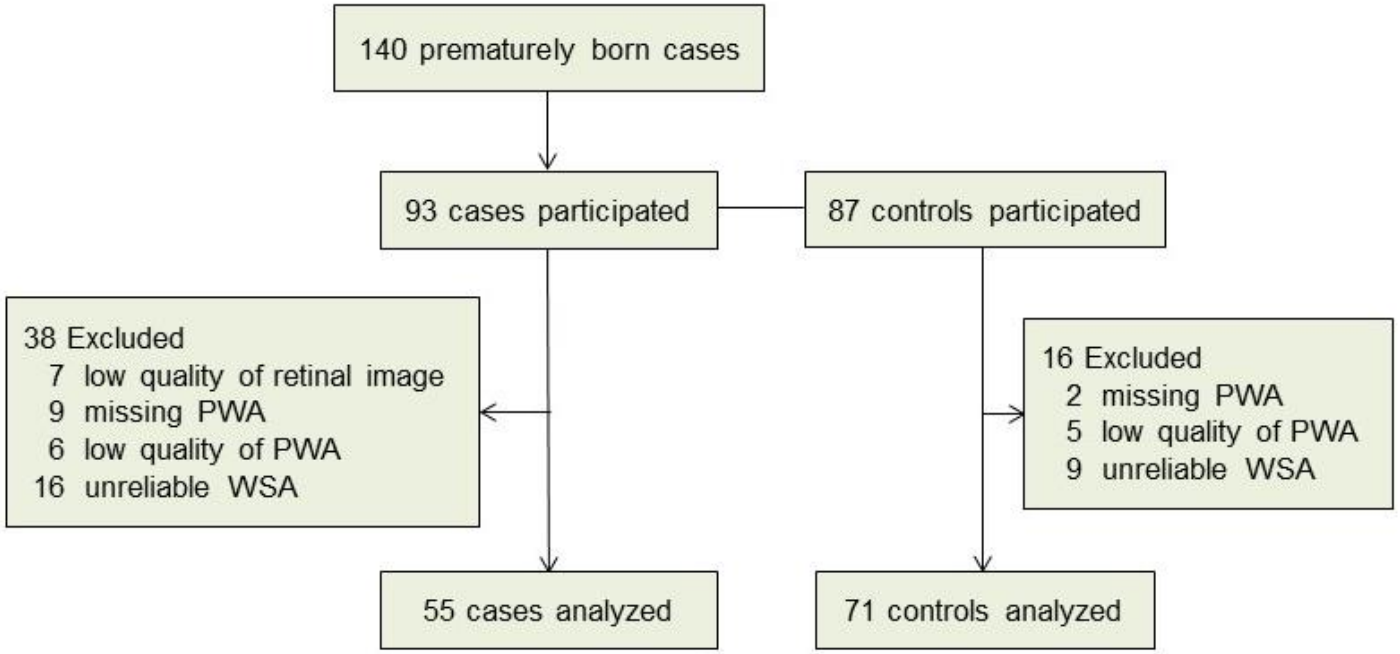

Figure S1. Flowchart. All cases had a birth weight of <1000 g. Controls were were born at term with a birth weight averaging 3391 g. Children were 11 years old at the time of the examination. PWA and WSA indicate pulse wave analysis and wave separation analysis, respectively.

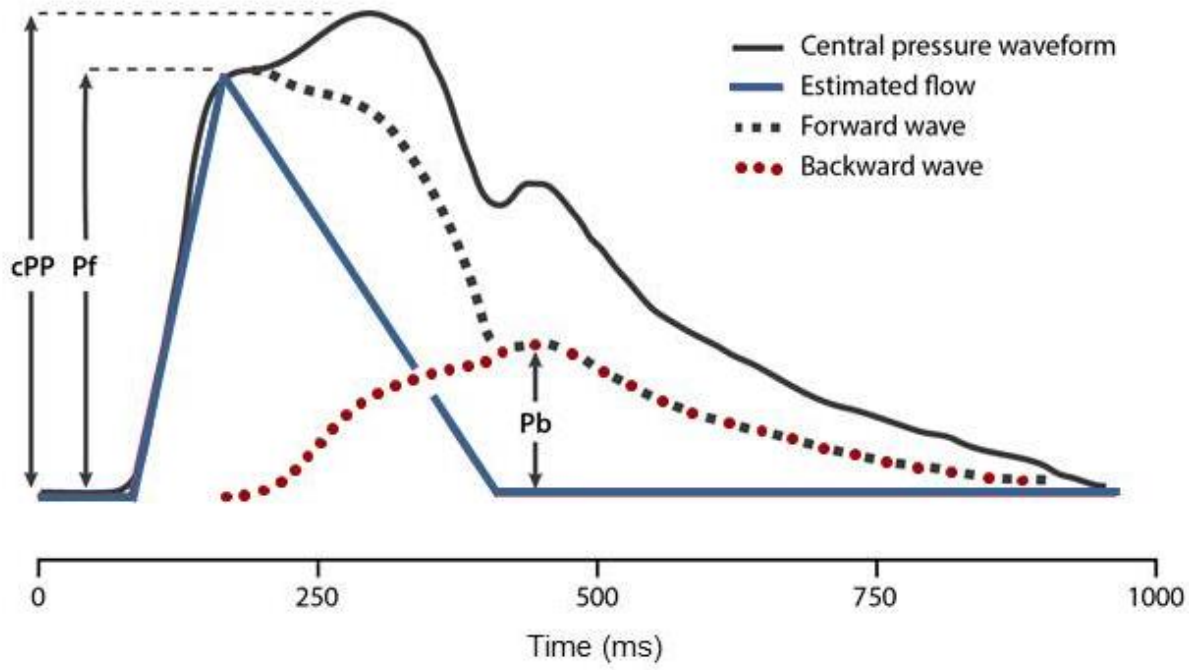

Figure S2. Pressure-based wave separation algorithm. The central pressure waveform was separated in its forward and backward component, using a triangular-shaped flow estimate. Start, peak and end of the estimated flow curve were derived from the ejection period and the first shoulder of the central pressure curve. cPP indicates central pulse pressure; Pb, backward wave amplitude; Pf, forward wave amplitude.