Elevated Blood Pressure with Reduced Left Ventricular and Aortic Dimensions in Adolescents Born Extremely Preterm

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Objective To evaluate the long-term cardiovascular effects of extremely preterm birth in a cohort of adolescents followed prospectively, who were largely free from intrauterine growth restriction.

Study design Central blood pressures, aortic and cardiac dimensions, left ventricle (LV) function, pulse wave velocity, augmentation index, and microvascular reactive hyperemia were measured in 18-year-old subjects born extremely preterm at <28 weeks' gestation (n = 109) and term-born controls (n = 81).

Results Compared with controls, preterm adolescents had higher systolic (124 ± 13 vs 118 ± 10 mm Hg, $P = .002$) and diastolic (72 ± 8 vs 67 ± 7 mm Hg, $P < .001$) blood pressures, but lower ascending aortic z-scores (0.13 ± 0.89 vs 0.42 ± 0.78, $P = .02$), LV diastolic (48.5 ± 4 vs 50.3 ± 4.5 mm, $P = .007$) and systolic (30.2 ± 3.5 vs 31.9 ± 4.0 mm, $P = .003$) diameters, and a reduced LV mass (130 ± 34 vs 145 ± 41 g, $P = .01$) and mass index (75 ± 14 vs 81 ± 16 g/m^2, $P = .02$). However, LV relative wall thickness, LV function, pulse wave velocity, augmentation index, and microvascular reactive hyperemia were similar. Within the ex-preterm group, there were no significant relationships between birthweight z-scores and any cardiovascular measures, once the latter were adjusted for current body size.

Conclusions Extremely preterm birth had relatively minor cardiovascular effects in late-adolescence, with increased blood pressures, decreased LV, and aortic size, but preserved LV function, macrovascular properties, and microvascular function. In utero growth was not independently related to cardiovascular function within the ex-preterm cohort. *(J Pediatr 2016;172:75-80)*.

Low birthweight and prematurity predispose to higher cardiovascular morbidity and mortality in adulthood.[1-4] Indeed, vascular abnormalities may be evident by adolescence or early adult life, including an elevated pulse wave velocity (PWV),[5,6] increased carotid intima-media thickness (cIMT),[6,7] aortic narrowing,[5,8,9] and impaired microvascular function.[7,9,10] More recently, increased left ventricle (LV) mass with increased LV wall thickness and reduced luminal diameter has been reported in ex-preterm young adults.[11]

Ex-preterm subjects are heterogeneous, however, as they may have in utero growth restriction (IUGR), be small for gestational age (SGA) or appropriate weight for gestational age (AGA) at birth, and also because prematurity can span moderately preterm (32-36 weeks' gestation), very preterm (28-31 weeks' gestation), and extremely preterm (<28 weeks' gestation) categories. The latter category is increasingly relevant as survival of babies born extremely preterm has improved dramatically over recent years.[12] Thus, studies in ex-preterm adolescents and adults born at varying gestations and with varying in utero growth impairment have suggested that increasing prematurity is associated with greater vascular dysfunction[6,7] and LV mass.[11] By contrast, evidence from small cohorts of extremely preterm but AGA infants and children suggests that, even though blood pressures may be elevated,[13] no differences exist between AGA ex-preterm and control groups in LV mass index,[13] PWV,[14] or microvascular dilation.[15] However, whether additional cardiovascular abnormalities emerge as extremely preterm subjects progress toward adulthood is unknown.

The main aim of the study was to define longer-term cardiovascular sequelae of being born extremely preterm, comparing results with term-born controls, who have been followed since birth as part of the Victorian Infant Collaborative

AGA	Appropriate weight for gestational age
AI_x	Augmentation index
BSA	Body surface area
cIMT	Carotid intima-media thickness
IUGR	In utero growth restriction
LV	Left ventricle
PWV	Pulse wave velocity
SGA	Small for gestational age

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Study.[16] In addition, we aimed to assess the effect of IUGR on the cardiovascular measures within the extremely preterm cohort alone.

Methods

After study approval from the institutional Human Research Ethics Committee and written informed consent, participants were recruited from the Victorian Infant Collaborative Study cohort, which included all extremely preterm (gestation <28 weeks) or low birthweight (<1000 g) survivors born in Victoria, Australia in 1991-1992.[16] The original cohort was comprised of 298 preterm survivors and 262 control infants. Control infants were born in maternity hospitals housing neonatal intensive care units, had birthweights of >2499 g, were randomly selected from births on the due date of the preterm survivor, and were matched for sex.

Of the original cohort, only a subset of 109 subjects born <28 weeks' gestation and 81 control subjects were able to attend the Royal Children's Hospital for anthropometric and blood pressure measurements, echocardiography, and vascular assessment at 18.0 ± 0.9 (mean ± SD) years of age. Anthropometric and blood pressure data at 18 years from both cohorts have been reported elsewhere.[17] All the measurements were performed in a single session by the same technologist who was unaware of subjects' group classification.

Presence of renal disease, diabetes mellitus, smoking status, and family history of hypertension were recorded after taking a clinical history. Subjects were asked to abstain from alcohol, tobacco, and caffeine for ≥24 hours, and were fasted for ≥6 hours prior to study. Body surface area (BSA) was calculated by the formula of Dubois and Dubois,[18] with body mass index defined as weight (kg)/height $(m)^2$. After 10 minutes of semirecumbent rest in a quiet darkened room, right brachial blood pressure was recorded in triplicate using a blood pressure cuff width that was greater than 40% of the upper arm circumference, with a digital oscillometric monitor (HEM 705-CP; Omron, Kyoto, Japan).[19] Ambulatory blood pressure was measured for 24 hours using the Oscar 2 ambulatory blood pressure monitor (SunTech Medical Inc, Morrisville, North Carolina). Measurements were performed one-half hourly when awake, and hourly when asleep, and generated systolic, diastolic, and mean blood pressure values at each time point.

Echocardiography (Vivid 7; GE Medical Systems, Horten, Norway) was performed in semirecumbent patients according to American Society of Echocardiography guidelines,[20,21] using a 5 MHz transducer for cardiac and aortic sonography, and a 10 MHz linear probe for carotid imaging. Ascending aortic, left atrial, and LV diameters were obtained using M-mode and normalized by z-scores.[22] To assess LV systolic function, fractional shortening was calculated from M-mode and ejection fraction with Simpson biplane method, and diastolic function was evaluated with transmitral Doppler velocities, isovolumic relaxation time, and tissue Doppler analysis. LV mass was indexed to BSA.[23] Relative wall thickness was calculated as (LV posterior wall + interventricular septal dimensions)/LV end-diastolic dimension.

Right common carotid and radial artery pressure waveforms were obtained with an applanation tonometer (SPT-301 Transducer, Millar Instruments, Houston, Texas) interfaced to a SphygmoCor system (AtCor Medical, Sydney, Australia). The central aortic pressure profile was obtained by mathematical transformation of the radial signal and augmentation index (AI_x) then derived after determination of the ascending limb inflection point.[24]

The carotid pulse-to-sternal notch and sternal notch-to-right radial artery distances were measured to the nearest cm, with carotid-radial PWV calculated as carotid-to-right radial artery path-length divided by the difference between arrival time of the pressure wave foot at these two sites.[25]

The cIMT was measured offline in the right common carotid artery posterior arterial wall, 1 cm proximal to the carotid bulb,[21] using wall-tracking software (EchoPAC, GE Vingmed Ultrasound, Norway).

Microcirculatory responses were assessed using the Endo-PAT system (Itamar Medical, Caesarea, Israel), with probes placed on the tips of both index fingers. After a period of equilibration, a left arm blood pressure cuff was inflated to 50 mm Hg above systolic pressure for 5 minutes, with reactive hyperaemia recorded after cuff deflation.[26]

Statistical Analyses

Data were analyzed with SPSS (v 20; IBM Corp, Armonk, New York), with normality assessed using Levene's test. Between-group data were compared with an independent Student *t* test for continuous normally distributed data and χ^2 analysis for categorical variables, with results presented as mean differences (95% CI). To detect if differences between groups were sex-specific, we ran regression models including an interaction term for sex and group; if the interaction term was significant, group differences were compared within each sex separately. To assess the associations of the cardiovascular measures with IUGR within the ex-preterm cohort, we regressed the various measures against the birthweight SD score, calculated relative to the British Growth Reference.[27]

With 109 preterm subjects and 81 controls, the study had 80% power to detect a mean difference between groups as small as 0.41 SD. Within the ex-preterm cohort alone, the study had 80% power to detect a correlation coefficient between continuous variables as small as 0.26.

Results

As expected, although predominantly AGA, ex-preterm subjects were smaller at birth, with a trend toward lower birthweight z-scores (**Table I**). Only 2% of our pre-term study cohort were born SGA (birthweight z-score <−2 SD), with no SGA patients in the control group. At the time of the cardiovascular study, corrected age, weight, and body mass