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The Preterm Heart in Adult Life: Cardiovascular Magnetic Resonance Reveals Distinct Differences in Left Ventricular Mass, Geometry and Function

Running title: *Lewandowski et al.; Preterm Birth and the Adult Left Ventricle*

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Abstract:

Background—Preterm birth leads to an early switch from fetal to postnatal circulation before completion of left ventricular *in utero* development. In animal studies this results in an adversely remodeled left ventricle. We determined whether preterm birth is associated with a distinct left ventricular structure and function in humans.

Methods and Results—234 individuals aged 20-39 years underwent cardiovascular magnetic resonance. 102 had been followed prospectively since preterm birth (gestational age=30.3±2.5weeks and birthweight=1.3±0.3kilograms) and 132 were born at term to uncomplicated pregnancies. Longitudinal and short-axis cine images were used to quantify: left ventricular mass, three-dimensional geometric variation by creation of a unique computational cardiac atlas, and myocardial function. We then determined whether perinatal factors modify these left ventricular parameters. Individuals born preterm had increased left ventricular mass (66.5±10.9 vs 55.4±11.4g/m^2, P<0.001) with greater prematurity associated with greater mass (r=-0.22, P=0.03). Preterm-born individuals had short left ventricles with small internal diameters and a displaced apex. Ejection fraction was preserved (P>0.99) but both longitudinal systolic (peak strain, strain rate and velocity, P<0.001) and diastolic (peak strain rate and velocity, P<0.001) function, as well as rotational (apical and basal peak systolic rotation rate, P=0.05 and P=0.006, and net twist angle, P=0.02) movement, were significantly reduced. A diagnosis of preeclampsia during the pregnancy was associated with further reductions in longitudinal peak systolic strain in the offspring (P=0.02, n=29).

Conclusions—Individuals born preterm have increased left ventricular mass in adult life. Furthermore, they exhibit a unique three-dimensional left ventricular geometry as well as significant reductions in systolic and diastolic functional parameters.

Clinical Trial Registration Information—clinicaltrials.gov; Identifier: NCT01487824.

Key words: cardiac dysfunction; cardiac magnetic resonance imaging; cardiac remodeling; preeclampsia; preterm birth

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Introduction

Recent improved survival of infants born premature has led to a growing cohort of very preterm infants now entering adulthood.[1] Before birth such adults have often been exposed to a suboptimal intrauterine environment and, following delivery, key developmental stages that would normally occur *in utero* during the third trimester, have to take place under *ex utero* physiological conditions.[2] As 10% of births are preterm any adverse health impact of this unusual developmental pattern are relevant to a large population of adults.

Cardiac development may be particularly affected. Birth is associated with a switch in cardiomyocyte phenotype from a fetal hyperplastic pattern to neonatal hypertrophic response and animal models demonstrate this switch also occurs at the time of preterm delivery.[2, 3] These cardiomyocytes, which are still relatively immature during the last trimester, are then exposed to significant flow changes as the low-resistance placental circulation transforms into a high-resistance arterial system.[4] Experimental studies demonstrate that, in this setting, cardiomyocytes undergo accelerated hypertrophy with an increase in interstitial myocardial collagen deposition and that the induced changes are sufficient to remodel the left ventricle.[2, 3, 5]

Cardiovascular magnetic resonance allows for accurate non-invasive assessment of left ventricular structure and function in humans.[6] Computational atlas formation has also introduced the possibility to capture three-dimensional geometric variation within populations to explore risk factor influences.[7, 8] We used these techniques to reveal for the first time the impact of preterm birth on left ventricular structure and function in humans. Furthermore, we investigated whether key perinatal factors associated with preterm birth, such as maternal preeclampsia, growth restriction and variation in postnatal weight gain, had additional impacts on the left ventricle relevant to adult cardiovascular health.

Methods

Study population

We have prospectively followed individuals born preterm between 1982 and 1985 since recruitment at birth to randomized feeding regimes.[9] The initial cohort of 926 subjects (birthweight <1850g)[10, 11] underwent subgroup review during childhood and adolescence.[12-14] 240 had agreed to be recontacted and 102 of these subjects, aged between 23 and 28 years, were able to attend an appointment in Oxford for detailed cardiovascular phenotyping.[10, 11] 102 young adults born term to uncomplicated pregnancies with similar age and sex distribution to the preterm-born young adults were recruited to undergo identical investigations. An older group (30 term-born individuals a decade older with similar sex distribution) was also recruited to characterize normal aging-related cardiovascular changes. All data was coded with subject and study-specific IDs (e.g. EVS001) to ensure anonymity and blinded analysis. The study was registered with ClinicalTrials.gov (NCT01487824) and the protocol and recruitment strategy have previously been reported.[10, 11] The study was approved by the relevant ethics committee (Oxfordshire Research Ethics Committee A: 06/Q1604/118) and all participants provided signed informed consent.

Study visit

Anthropometry and lifestyle questionnaire

Subjects attended in the morning following a 12-hour overnight fast. Height was measured to the nearest centimeter and weight to the nearest 0.2 kilogram, with subjects wearing light clothing, using a combined digital height and weight measurement station (Seca, UK). Data on medical history, smoking, parental medical history and lifestyle were obtained using a validated questionnaire.[15]

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Blood samples

Blood samples were drawn, centrifuged and separated within 30 minutes, then stored for later analysis at -80^{o}C. Fasting blood biochemistry was measured at the Oxford John Radcliffe Hospital Biochemistry Laboratory using routine validated assays, with clinical level quality controls.

Blood pressure

Three brachial blood pressure measurements were recorded on the left arm with an automatic digital monitor (HEM-705CP, OMRON, Japan) and the second and third measurements averaged for analysis.[9-11] Aortic blood pressure was assessed by left radial artery applanation tonometry to derive ascending aortic pressure waveforms (SphygmoCor Analysis System, Australia).

Cardiovascular magnetic resonance

Cardiovascular magnetic resonance was performed on a 1.5T Siemens Sonata scanner. Steady-state free precession (SSFP) cine sequences were used to acquire localization images followed by optimized left ventricular horizontal and vertical long-axis cines. From these a left ventricular short-axis cine stack was obtained with standardized basal slice alignment with a 7mm slice thickness and 3mm inter-slice gap. All cardiovascular magnetic resonance imaging was prospectively ECG-gated with a precordial three-lead ECG and acquired during end-expiration breath holding. Image acquisition parameters for the SSFP images were: echo time 1.5ms, repetition time 3.0ms, and flip angle 60°. The short- and long-axis SSFP images were stored on a digital archive for post-processing, which was undertaken as detailed below.

Quantification of left ventricular mass

Image analysis for left ventricular volumes and mass was performed offline on the short-axis

cine stack using Siemens analytical software (Argus, Siemens Medical Solutions, Germany). Left ventricular short-axis epicardial and endocardial borders were manually contoured at end-diastole and end-systole to allow automated calculation of left ventricular mass and volumes. Mass represents (end-diastolic epicardial - endocardial volume)*1.05, stroke volume is end-diastolic - end-systolic volume and ejection fraction is (stroke volume/end-diastolic volume)*100%. Wall thickness was measured on the mid-ventricular short-axis slice at end-diastole, and internal and external cavity diameters on the mid-ventricular short-axis slice at end-diastole between septum and inferolateral wall. Ventricular length was measured at end-diastole on the horizontal long-axis cine between the left ventricular apex and middle of the mitral annulus. Relative wall thickness was calculated as (2*inferior wall thickness)/end diastolic diameter.

Creation of cardiac atlas for assessment of left ventricular geometry

Creation of a cardiac statistical atlas of all cardiovascular magnetic resonance images was undertaken in collaboration with the Department of Computer Science, University of Oxford and Department of Biomedical Engineering, King's College London based on recently published methods.[8] The end-diastolic frame from the DICOM file for each slice of the left ventricular short-axis cine stack that included the manually contoured endocardial and epicardial contours drawn using Argus were retrieved and rebuilt into a single DICOM file with MatLab R2011b (The Mathworks, Natick, USA). The file was converted into a binary segmentation image representing the left ventricle, and a mesh was fitted to this myocardial anatomy, achieving sub-voxel accuracy (average fitting error of 1.24mm).[8] The left ventricular anatomy of each subject was then described with a mesh defined by a set of 3456 nodal variables (or degrees of freedom). Principal component analysis was undertaken to identify the key modes of variation of the shape,

reducing the parametric space for comparisons from 3456 to six-dimensions. The left ventricular meshes for the population have been made available to the scientific community at: amdb.isd.kcl.ac.uk.[16]

Assessment of left ventricular systolic and diastolic function

In addition to gross volumetric measures of systolic left ventricular function (ejection fraction and stroke volume), we evaluated both systolic and diastolic function, including cardiac rotational movement, based on myocardial deformation parameters assessed with TomTec 2D Cardiac Performance Analysis MR (TomTec Diogenes, Germany). The endocardial borders of the left ventricular SSFP horizontal long-axis cine as well as basal, mid and apical left ventricular short-axis cines were manually contoured on the end-diastolic frame. The software then tracked motion of related features adjacent to this endocardial line, such as the cavity tissue boundary or individual tissue patterns, over the cardiac cycle to produce endocardial strain parameters.[17] The averages of segmental strains from the short-axis planes were used for endocardial circumferential strain and average of segmental strain in the horizontal long-axis view for global endocardial longitudinal strain. Net twist angle was calculated as peak apical endocardial circumferential rotation minus peak basal endocardial circumferential rotation.

Statistical analysis

Statistical analysis was carried out using SPSS Version 19. Normality of variables was assessed by visual assessment of normality curves and Shapiro-Wilk test. Comparison between groups for continuous variables was performed using a two-sided, independent-samples student T-test for normally distributed data and Mann Whitney and Kruskal-Wallis tests for skewed data. For categorical variables, comparison was done using a Chi-Square test. Linear regression models were performed using a Forced Entry Method. Pearson correlations (r) were used for bivariate

associated and unstandardized regression coefficients (B) were used for bivariate and multivariate regression models. Analysis was repeated with and without inclusion of six sets of preterm-born twins, but as no differences were observed, results are presented with twins included in the preterm-born cohort.102 subjects per group provided us with 80% power at *P*=0.05 to identify a 0.38SD difference between groups, equivalent to a 10g difference in left ventricular mass, and a 0.58SD difference between each young adult group and the older adults. Results are presented as Mean±Standard Deviation. Where multiple comparisons were performed between groups, P-values were adjusted using the Bonferroni method. Comparisons between preterm-born young adults with term-born young adults were adjusted for age and sex, while comparisons between preterm-born young adult and term-born young adults with the older term-born older adults were adjusted for sex. P-values <0.05 were considered statistically significant.

Results

Study Population Characteristics

Compared to the original cohort of preterm-born individuals recruited at birth, those followed up in young adulthood were similar in perinatal characteristics (**Online Data Supplement, Table I**) apart from a small 70g (5%) difference in birthweight. This is accounted for by a marginally more preterm cohort such that birthweight z-score is identical between groups. Of the 102 individuals in the cohort, 14 (13.7%) were born extremely preterm (<28w), 56 (54.9%) were born very preterm (28-31w), and 32 (31.4%) were born moderate to late preterm (32-36w). In adult life, there were no significant differences in number of smokers, personal and family medical history, or lifestyle factors such as socioeconomic status, physical activity or diet

(results not shown). Adults born preterm were shorter and weighed more than the young adult term-born cohort (**Table 1**) and had a distinct metabolic profile. Total and low-density lipoprotein cholesterol, triglyceride, glucose, and insulin levels were significantly increased (**Online Data Supplement Table II**). Brachial and aortic blood pressure parameters were also elevated compared to the term-born cohort of similar age, with levels similar to individuals a decade older (**Online Data Supplement Table II**).

Elevated left ventricular mass in preterm-born young adults

Those born preterm had a 19g higher left ventricular mass and significantly increased mass indexed to body surface area compared to term-born young adults (left ventricular mass: 121.1±27.3 vs 102.1±26.8 g, $P<0.001$ and mass index: 66.5±10.9 vs 55.4±11.4 g/m^2, $P<0.001$) (**Figure 1, Panel A**). Within the preterm group, the more premature their birth the greater their left ventricular mass in young adult life (r=-0.22, $P=0.03$).

Blood pressure was associated with left ventricular mass in all study groups with brachial pulse pressure the most closely related parameter in the preterm-born (r=0.54, $P<0.001$), term-born (r=0.54, $P<0.001$), and older (r=0.68, $P<0.001$) adults. Therefore, as blood pressure in young adulthood was higher in those born preterm, we explored to what extent this accounted for their higher left ventricular mass. Initially, as the older term-born adults had similar blood pressure levels to the preterm group, we compared levels of left ventricular mass between these groups and found mass and mass index were significantly higher in the younger preterm-born adults ($P<0.001$ and $P<0.001$) (**Figure 1, Panel A**) consistent with an impact of prematurity on left ventricular mass independent of absolute blood pressure levels alone. To ensure the variation in age between these groups did not confound the comparison we also carried out a complementary analysis based on a comparison of the impact of prematurity with the study

participants stratified into high and low blood pressure groups around the median brachial pulse pressure within the cohort (**Figure 1, Panel B**). Left ventricular mass was higher in those in the higher blood pressure group consistent with an impact of blood pressure on left ventricular mass. However, those born preterm had additional significant increases in mass index, irrespective of blood pressure level, compared to both term-born young adults as well as the older adults (61.2±9.8 vs 51.1±10.7g/m^2, *P*<0.001, and vs 49.6±10.3g/m^2, *P*<0.001 in those with pulse pressure <46mmHg and 70.5±10.0 vs 61.2±9.8g/m^2, *P*<0.001, and vs 62.1±10.4g/m^2, *P*=0.003 in those with a pulse pressure ≥46mmHg).

Finally, we used a linear regression model to take account of other potential factors related to left ventricular mass within the preterm-born and term-born young adult groups. Within sets of interrelated variables, such as blood pressure, the variable with the strongest correlation was included, leaving six independent variables significantly related to mass index (*P*<0.05, **Online Data Supplement Table III**) to be included in the model (glucose level, high density lipoprotein cholesterol, waist to hip ratio, gender, brachial pulse pressure, and premature birth as a dichotomous categorical variable with young adults born at term as '1' and preterm as '2'). In this model prematurity remained an independent predictor of mass index (B=10.23g/m^2/group, *P*<0.001, 95% CI: 7.48 to 12.98).

Geometric Changes of the Preterm Left Ventricle

We then studied variation in left ventricular geometry. Principal component analysis was used to identify the major modes of variation within the three-dimensional meshes generated from each of the cardiac datasets. All identified modes were numbered in order based on the amount of variation within the population each accounted for (with mode 1 accounting for the greatest proportion, 29.8%). When we compared the preterm cohort to the term-born individuals of

similar age, significant differences were observed between groups in the first six modes, with levels of significance for modes 1, 2 and 5 being in the order $P=1x10^{-11}$ to $P=1x10^{-13}$ (**Figure 2, Panel A**). These first six modes accounted for 84.2% of the variance in left ventricular geometry within the study population (**Figure 2, Panel B**). Four of these modes also reached significance for differences between the preterm group and the older term-born adults, but no modes reached significance when the two term-born cohorts were compared (**Figure 2, Panel A**). **Figure 2, Panel C** demonstrates where the mean of each group lies relative to the other groups in the principal component analysis parametric space. Separation between preterm and term-born offspring is also evident when individual subject data is plotted in three dimensions (**Figure 2, Panel D**).

We visually assessed models that corresponded with +/-2 standard deviations of the mean variation for the six modes that differed between preterm and term-born individuals. The geometric difference each describes are shown in **Figure 2, Panel C.** Preterm-born individuals had significantly shorter ventricles, increased left ventricular wall thickness, a shift in apex away from the right ventricle, and reduced internal left ventricular cavity diameter (**Figure 2, Panel C** and **Figure 3**). Several of these features could be captured by standard clinical left ventricular measures; specifically, left ventricular length, cavity diameters and wall thickness at end-diastole. We confirmed differences in these standard measures between preterm-born young adults and term-born individuals (**Table 2**). In view of the combination of increased wall thickness with reduced ventricular cavity size we also calculated relative wall thickness and left ventricular mass relative to end-diastolic volume (left ventricular mass/end-diastolic volume) (**Table 2**). 21 individuals born preterm (20.6%) had a relative wall thickness >0.42 compared to none in either term-born group. Furthermore, those born preterm had increased left ventricular

mass/end-diastolic volume compared to both term-born groups (*P*<0.001, **Table 2**), with an inverse association between gestational age and left ventricular mass/end-diastolic volume (r=-0.36, *P*<0.001).

Altered Left Ventricular Systolic and Diastolic Function

We then evaluated whether there were also changes in left ventricular function related to prematurity. End-systolic volume was reduced in the preterm group and stroke volume was smaller, with the reduction graded according to the degree of prematurity (r=-0.20, *P*=0.05). Although ejection fraction did not differ, myocardial deformation patterns were significantly altered in those born preterm (**Table 3**). Longitudinal peak systolic strain and peak systolic strain rate were reduced compared to both term-born groups (**Figure 4, Panels A and B**). Furthermore, systolic rotational behavior varied with reduced basal and apical rotation rates (**Table 3**). Diastolic myocardial relaxation was also reduced with slower longitudinal peak diastolic strain rates compared to term-born individuals of similar age. Interestingly, longitudinal peak diastolic strain rates were reduced in the older adults to a similar degree as measured in those born preterm (**Figure 4, Panels A and B**).

Preterm Birth Risk Factors and Left Ventricular Geometry and Function

To understand whether prematurity *per se* or factors linked with prematurity accounted for the variation in the key geometric (left ventricular mass index, length, and end-diastolic volume) and functional (longitudinal peak systolic strain, peak systolic strain rate and diastolic strain rate) variables that differed in those born preterm, we performed further regression analyses. For each outcome variable, we performed two regression models. As our sample size was 102 individuals, we limited the number of variables included to five key perinatal characteristics (gestational age, birthweight z-score, postnatal weight gain in the first two weeks, days of ventilation, and

maternal preeclampsia). Those characteristics that were significant in this model were included in a second model which incorporated potentially relevant cardiovascular risk factors in young adulthood (high-density lipoprotein, gender, waist to hip ratio, glucose, and brachial pulse pressure).

Gestational age was associated with left ventricular structure in this preterm group (**Online Data Supplement, Table IV**). For left ventricular mass index, gestational age was the only independent predictor in model 1 (P=0.02) and remained an independent predictor in model 2 (P=0.03). For left ventricular length, gestational age and birthweight z-score were both independent predictors in model 1 (P=0.03 and P=0.04) but only gestational age remained significant in model 2 (P=0.02 and P=0.11). For end-diastolic volume, gestational age approached significance in model 1 (P=0.08) and was significant in model 2 (P=0.05).

Interestingly, when we modeled functional variables, maternal preeclampsia, but not other variables, accounted for a proportion of variation in longitudinal peak systolic strain within the preterm group in model 1 (P=0.05), and remained significant in model 2 (P=0.05). Nearly a third (n=29) of our preterm group were born to a pregnancy complicated by preeclampsia. The absolute global peak longitudinal systolic strain in those born preterm to a preeclamptic pregnancy was -13.8%±2.2 compared to -15.2±3.4% in those born preterm to normotensive mothers (P=0.02). This appeared to be additional to any impact of prematurity on longitudinal peak systolic strain, as individuals born preterm to normotensive pregnancies still showed a significant reduction in longitudinal peak systolic strain compared to term-born individuals of similar age (P<0.001).

Discussion

This study demonstrates for the first time that young adults born preterm have a unique adverse left ventricular structure and function. Left ventricular mass is significantly increased while the left ventricles are shorter, with reduced cardiac volumes and apical displacement. Furthermore, prematurity is associated with reductions in systolic, diastolic and rotational function. The variation in structure appears to be determined by preterm birth, with the severity of changes graded according to the degree of prematurity, and not by any specific associated perinatal exposures such as preeclampsia, variation in birthweight or growth. In contrast, maternal preeclampsia had an impact on cardiac systolic function in addition to that associated with preterm birth.

Increased left ventricular mass index is an independent predictor for cardiovascular morbidity and mortality.[18] The average 19g higher left ventricular mass in young adults born preterm is equivalent to that associated with a 9kg/m^2 increase in body mass index,[19] and in longitudinal studies would equate to greater than 50% increased risk of cardiovascular clinical events in later adult life.[20, 21] The major cardiovascular risk previously identified in those born preterm is their higher blood pressure,[9] which could have accounted for a proportion of the increased left ventricular mass. However, we found for any given level of blood pressure prematurity was associated with additional significant increases in left ventricular mass and that the increase in left ventricular mass was graded according to the degree of prematurity independent of other perinatal factors. The presence of increased left ventricular mass in those with hypertension or pre-hypertension is known to have independent prognostic significance,[21, 22] and those born preterm appear to have a disproportionate increase in left ventricular mass relative to their blood pressure.

At birth, there is a change in cardiomyocyte development from fetal to adult

arrangement,[3, 23] which coincides with an increase in cardiac output and left ventricular end-diastolic pressure.[4, 24, 25] In preterm birth this occurs before complete *in utero* development and, in lambs born preterm, exposure of a relatively immature heart to the sustained increase in afterload and fluctuating preload of postnatal circulation resulted in accelerated cardiomyocyte hypertrophy while cardiomyocyte number remained static.[2, 18] Consistent with this experimental data, Kozák-Bárány et al found left ventricular mass in humans born preterm increases 56% in the first month postnatally compared to 35% in those born at term.[23] It is possible the increase in those born preterm merely reflected the expected *in utero* cardiac growth rate for this point in development. However, our data are consistent with the rapid increase in neonatal left ventricular mass being a pathological event that persists into adult life.

Our decision to use novel computational techniques to build the first atlas of the adult preterm heart provided a valuable tool to capture and analyze three-dimensional variation in left ventricular geometry in addition to changes in mass. The method we applied was chosen as it, for the first time, allowed use of a standard 12-slice left ventricular short-axis stack. This meant some smoothing of the meshes occurred to account for slice gap and shift, but is potentially more widely clinically applicable than other mesh creation strategies. The atlas analysis avoided specific presuppositions about likely measures of relevance and we demonstrate that it was powerful enough to identify and quantify variation in a range of geometric factors, such as apical position, that we would not have captured with standard clinical measures. The last trimester is important for cardiac growth and it seems plausible that the short ventricle and reduced cavity size relates to the interruption in development and flow changes seen at preterm birth.[23] Changes in flow patterns within the heart could additionally account for alterations in apical position. However, apical position was also displaced in older adults suggesting other factors may be

relevant.

Preterm-born lambs have a five- to seven-fold increase in interstitial, but not perivascular, collagen deposition,[2] characteristic of myocardial pressure-overload.[18] The inflammatory cascade of preterm labor has also been proposed to lead to myocardial fibrosis.[26, 27] These myocardial patterns would be expected to result in changes in diastolic relaxation, as we observed in the preterm-born young adults.[28] The older adults had similar reductions in diastolic function and it is possible there are changes in extracellular matrix, as well as cardiomyocyte appearance and function, within the preterm group, equivalent to changes observed with aging.

In addition to diastolic abnormalities, preterm-born young adults showed unique changes in longitudinal, circumferential and rotational systolic function.[29] Additionally, maternal preeclampsia was associated with further reductions in left ventricular systolic strain. Preeclampsia is indicative of placental pathology and insufficiency, which may not be a feature of other pregnancies that lead to preterm birth, and offspring of preeclamptic pregnancies develop with reduced uterine perfusion and relative hypoxia from early in gestation.[30] In newborn pigs, short-term exposure to hypoxemia leads to sustained reduction in longitudinal peak systolic strain,[31] thought to be because longitudinal movement is primarily mediated by subendocardial and subepicardial fibers, which are most susceptible to ischemia.[32, 33] While animal models of preeclampsia and pregnancy hypoxia have consistently shown cardiac effects in the offspring, this is the first study in humans to confirm a cardiac specific impact of preeclampsia.

We were not able to follow up all those initially recruited to the preterm study in the 1980s. Nevertheless, there were no significant differences in demographics or perinatal records between those who took part and the full cohort to suggest any selection bias was introduced. We

can be confident of this as a major strength of the study is the prospective nature of data collection with very detailed information collected at birth. This also allowed us to study the impact of key perinatal factors on later cardiac structure. Previous work has shown that birthweight is a risk factor for coronary heart disease in later life in term-born individuals.[15] It will be of interest to determine whether the haemodynamic changes seen in small for gestational age term-born individuals also lead to cardiac remodelling patterns similar to those we have seen in preterm-born young adults. The study size, although the largest cardiac study of preterm infants, meant we remained conservative with the number of factors included in our multiple regression analyses. It is likely other key parameters that may influence left ventricular development will be of interest to investigators and will require subsequent investigation. For example, we have previously investigated the impact of preterm birth on the vasculature,[10, 11] and it will be of interest to understand to what extent there is adverse cardiac and vascular coupling within preterm infants. At present we have also not addressed whether preterm birth influences right ventricular structure and function or left ventricular radial strain. There are technical challenges in creation of an accurate three-dimensional model of the geometrically complex right ventricle, but in due course we expect to undertake similar analysis. Reproducibility of radial strain analysis is currently relatively poor[34] and further development is needed before results can be confidently reported.

In summary, we have demonstrated for the first time that individuals born preterm have a unique left ventricular geometry and function. There is a continuous shift in the demographic of individuals born preterm, with a greater number of younger, smaller preterm-born individuals surviving. Approximately 10% of births are now preterm,[1, 35] and with the first generation of very preterm-born survivors now reaching young adulthood, our findings are of considerable

public health interest. We believe understanding whether modifications of these variations in left ventricular structure and function prevents development of cardiac disease in a growing subgroup of the population will be of interest.

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Conflict of Interest Disclosures: None.

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Table 1. Characteristics of Cohorts

	Preterm-born Young Adults (n=102)	Term-born Young Adults (n=102)	P-Value ψ	Term-born Adults (n=30)	P-Value ¥	P-Value Δ
Demographics						
Gestational Age (wks)	30.3±2.5	39.6±0.9		39.8±0.8		
Age(years)	25.1±1.4	25.0±2.6		35.5±1.8		
Males, n(%)	47(46.1)	47(46.1)		14(46.7)		
Smokers, n(%)	20(19.6)	20(19.6)	>0.99	3(10.0)	0.63	0.63
Anthropometrics						
Birthweight(g)	1297.0±286.8	3460.0±417.0		3301.9±423.9		
Height(cm)	169.1±10.0	173.5±9.0	**<0.001**	169.3±9.6	>0.99	**0.01**
Weight(kg)	73.0±20.5	69.3±12.5	0.33	79.8±28.9	0.46	**0.01**
BMI(kg/m^2)	24.9±5.4	22.9±3.1	**0.003**	27.1±9.6	0.33	**<0.001**
BSA(/m^2)	1.81±0.21	1.83±0.20	>0.99	1.84±0.21	>0.99	>0.99
Waist:Hip	0.78±0.10	0.81±0.06	0.91	0.81±0.08	>0.99	>0.99

Values as Mean±Standard Deviation unless stated otherwise. P-values were adjusted using the Bonferroni method.
ψ=Preterm-born Young Adults vs. Term-born Young Adults. Comparisons adjusted for age and sex.
¥=Preterm-born Young Adults vs. Term-born Adults. Comparisons adjusted for sex.
Δ=Term-born Young Adults vs. Term-born Adults. Comparisons adjusted for sex.

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Table 2. Left Ventricular Volumes and Dimensions

	Preterm-born Young Adults (n=102)	Term-born Young Adults (n=102)	P-Value ψ	Term-born Adults (n=30)	P-Value ¥	P-Value Δ
End-Diastolic (ED) Volume (mL/m^2)	72.2±9.3	80.2±11.7	**<0.001**	81.5±12.9	**<0.001**	>0.99
End-Systolic Volume(mL/m^2)	25.7±5.4	29.1±6.4	**<0.001**	29.0±6.4	**0.01**	>0.99
Stroke Volume(mL/m^2)	46.6±7.4	51.3±8.9	**<0.001**	52.5±8.4	**<0.001**	>0.99
Length(cm)	9.20±0.65	9.81±0.73	**<0.001**	9.70±0.64	**<0.001**	>0.99
Luminal Diameter(cm)	5.20±0.47	5.64±0.48	**<0.001**	5.66±0.34	**<0.001**	>0.99
External Diameter(cm)	7.33±0.65	7.19±0.64	0.16	7.26±0.43	>0.99	>0.99
Global ED Wall Thickness (WT)(mm)	9.26±1.40	7.46±1.26	**<0.001**	7.93±1.26	**<0.001**	0.07
Anterior ED WT(mm)	8.21±1.51	6.87±1.51	**<0.001**	7.39±1.45	**0.009**	0.15
Anterolateral ED WT(mm)	8.89±1.74	6.89±1.45	**<0.001**	7.11±1.50	**<0.001**	>0.99
Inferolateral ED WT(mm)	9.40±1.75	7.13±1.53	**<0.001**	7.52±1.38	**<0.001**	0.44
Inferior ED WT(mm)	9.17±1.73	7.22±1.60	**<0.001**	8.03±1.45	**0.003**	**0.01**
Inferoseptal ED WT(mm)	10.29±1.80	8.56±1.34	**<0.001**	8.96±1.58	**<0.001**	0.40
Anteroseptal ED WT(mm)	9.63±1.79	8.10±1.78	**<0.001**	8.56±1.68	**0.003**	0.51
Relative Wall Thickness(RWT)	0.35±0.07	0.26±0.05	**<0.001**	0.28±0.05	**<0.001**	**0.02**
RWT > 0.42, n(%)	21(20.6)	0(0)	**<0.001**	0(0)	**<0.001**	>0.99
Mass/ED Volume(g/mL)	0.93±0.14	0.70±0.12	**<0.001**	0.70±0.13	**<0.001**	>0.99

Values as Mean±Standard Deviation unless stated otherwise. P-values were adjusted using the Bonferroni method.
ψ=Preterm-born Young Adults vs. Term-born Young Adults. Comparisons adjusted for age and sex.
¥=Preterm-born Young Adults vs. Term-born Adults. Comparisons adjusted for sex.
Δ=Term-born Young Adults vs. Term-born Adults. Comparisons adjusted for sex.

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Table 3. Left Ventricular Systolic and Diastolic Function

	Preterm-born Young Adults (n=102)	Term-born Young Adults (n=102)	P-Value ψ	Term-born Adults (n=30)	P-Value ¥	P-Value Δ
Systolic Function						
Ejection Fraction(%)	64.5±6.1	64.1±4.9	>0.99	64.3±4.8	>0.99	>0.99
Longitudinal						
Strain(%)	-14.8±3.2	-17.9±4.1	**<0.001**	-17.7±5.3	**0.003**	>0.99
Strain Rate(%/s)	-0.90±0.21	-1.06±0.31	**<0.001**	-1.08±0.31	**0.009**	>0.99
Displacement(cm)	3.80±1.47	4.71±2.54	**0.01**	4.23±1.56	0.68	>0.99
Velocity(cm/s)	2.25±0.78	3.09±0.97	**<0.001**	3.17±1.18	**<0.001**	>0.99
Circumferential						
Basal Strain(%)	-21.2±2.9	-21.8±3.2	0.45	-22.2±3.4	0.38	>0.99
Basal Strain Rate(%/s)	-1.26±0.21	-1.28±0.24	>0.99	-1.32±0.28	0.63	>0.99
Basal Rotation(°)	-7.21±4.59	-8.81±5.22	0.08	-7.65±4.12	>0.99	0.88
Basal Rotation Rate(°/s)	-46.2±26.4	-60.2±35.4	**0.006**	-52.1±29.2	>0.99	0.83
Mid Strain(%)	-17.9±2.2	-17.7±2.2	>0.99	-18.3±2.2	>0.99	0.61
Mid Strain Rate(%/s)	-1.06±0.14	-1.04±0.19	>0.99	-1.09±0.18	>0.99	0.97
Apical Strain(%)	-21.6±3.8	-22.1±3.8	>0.99	-22.8±4.0	0.45	>0.99
Apical Strain Rate(%/s)	-1.30±0.24	-1.25±0.24	0.39	-1.33±0.24	>0.99	0.40
Apical Rotation(°)	7.04±4.35	7.95±5.54	0.63	6.13±4.66	>0.99	0.42
Apical Rotation Rate(°/s)	46.3±26.2	56.1±30.1	**0.05**	42.0±22.8	>0.99	**0.04**
Net Twist Angle(°)	14.0±6.4	16.9±7.8	**0.02**	13.5±6.3	>0.99	0.18
Diastolic Function						
Longitudinal						
Strain Rate(%/s)	0.95±0.35	1.31±0.52	**<0.001**	1.07±0.31	0.41	**0.01**
Velocity(cm/s)	-2.38±0.81	-3.22±1.36	**<0.001**	-2.60±1.14	0.84	0.09
Circumferential						
Basal Strain Rate(%/s)	1.42±0.24	1.62±0.39	**<0.001**	1.55±0.42	0.11	>0.99
Basal Rotation Rate(°/s)	56.7±37.5	71.4±40.5	**0.03**	73.3±45.7	0.16	>0.99
Mid Strain Rate(%/s)	1.13±0.18	1.13±0.19	>0.99	1.18±0.21	0.59	0.67
Apical Strain Rate(%/s)	1.45±0.36	1.44±0.39	>0.99	1.42±0.34	>0.99	>0.99
Apical Rotation Rate(°/s)	-45.5±27.7	-52.3±41.8	0.57	-48.0±35.3	>0.99	>0.99

Values as Mean±Standard Deviation unless stated otherwise. P-values were adjusted using the Bonferroni method.
ψ=Preterm-born Young Adults vs. Term-born Young Adults. Comparisons adjusted for age and sex.
¥=Preterm-born Young Adults vs. Term-born Adults. Comparisons adjusted for sex.
Δ=Term-born Young Adults vs. Term-born Adults. Comparisons adjusted for sex.

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Figure Legends:

Figure 1. Panel A – Left ventricular mass indexed to body surface area (LVMI). LVMI was higher in preterm-born young adults (PTYA, blue; 66.5±10.9g/m^2) than young adults born at term (YAT, green; 55.4±11.4 g/m^2, *P*<0.001) and adults a decade older born at term (AT, red; 57.0±11.9 g/m^2, *P*<0.001). LVMI of the older term-born adults did not differ from the young adults born at term (*P*>0.99). **Panel B** – Comparison of left ventricular mass indexed to body surface area (LVMI) by equivalent blood pressure groups. The median brachial pulse pressure (46mmHg) for the entire population was used as a cutoff point to divide each subgroup (PTYA=preterm-born young adults, blue; YAT=term-born young adults, green; AT=term-born adults a decade older, red) into two. Comparison of those with brachial pulse pressure <46mmHg (n=44 PTYA, n=58 YAT, and n=13 AT) showed that PTYA had significantly higher LVMI compared to YAT and AT (61.2±9.8 vs 51.1±10.7 g/m^2, *P*<0.001, and vs 49.6±10.3 g/m^2, *P*<0.001). Comparison of those with brachial pulse pressure ≥46mmHg (n=58 PTYA, n=44 YAT, and n=17 AT) showed that PTYA had a similar magnitude of elevation of LVMI compared to both YAT and AT (70.5±10.0 vs 61.2±9.8 g/m^2, *P*<0.001, and vs 62.1±10.4 g/m^2, *P*=0.003).

Figure 2. Panel A – Comparison of differences in shape between groups by modes of variation of the Principal Component Analysis (PCA). Comparison between groups was performed using a two-sided student T-test. The red line indicates *P*=0.01. The panel on the left shows a comparison of the preterm-born young adults (PTYA) and young adults born at term (YAT), demonstrating that the first six modes of variation differed significantly between groups. The

middle panel shows a comparison of the PTYA and older adult term-born (AT) groups, demonstrating that modes 1, 2, 5, and 6 were significantly different between groups. The panel on the right shows a comparison of the YAT and AT groups, demonstrating no significant differences between groups. **Panel B –** Cumulative variance explained by each mode of variation. The first six modes of variation, which differed between the PTYA and YAT groups (see panel C), explained 84.2% of the variance in LV geometry within the entire population, with mode 1 explaining the majority of variance (29.8%). **Panel C –** The first six independent modes of variation resulting from the PCA. In all six cases, the average is at coordinate 0, and is represented by a dark blue cross and the dark blue LV mesh overlaid to the orange and purple meshes. The orange cross and orange LV mesh represent -2 SD for each mode of variation, and the purple cross and purple LV mesh represent +2 SD for each mode of variation. As illustrated here, the modes of variation represent changes in: 1=primarily ventricular length, with a proportion of diameter change; 2=wall thickness; 3 and 4=apex orientation; 5 = primarily diameter, with a proportion of apex position; 6=primarily diameter, with a proportion of length change. The stars represent the PCA coordinates for the average for each group (PTYA=blue; YAT=green; AT=red), for each mode of variation. **Panel D –** Distribution of all subjects in the PCA coordinates. Averages for the group are indicated by a circle. The panel on the left represents the first three modes of variation (1, 2, and 3) and the panel on the right represents the next three modes of variation (4, 5, and 6).

Figure 3. Statistical average shape for each group. PTYA, blue = preterm-born young adults; YAT, green = term-born young adults; AT, red = older term-born adults.

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Figure 4. Panel A – Longitudinal peak systolic and diastolic strain rate. Preterm-term born young adults (PTYA, blue) have reduced longitudinal peak systolic strain rate (-0.90±0.21%/s) compared to both the young adults born term (YAT, green; -1.06±0.31%/s, *P*<0.001) and the older term-born adults (AT, red; -1.08±0.31%/s, *P*=0.003). However, while longitudinal peak diastolic strain rate in the PTYA was still reduced compared to the YAT (0.95±0.35%/s vs 1.31±0.52%/s, *P*<0.001), it did not differ from the AT (1.07±0.31%/s, *P*=0.41). **Panel B –** Example longitudinal strain rate curves for each group. YAT and AT showed similar longitudinal strain rates in systole, which differed from the PTYA. In diastole, longitudinal strain rates were similar for the PTYA and AT, which differed from the YAT.

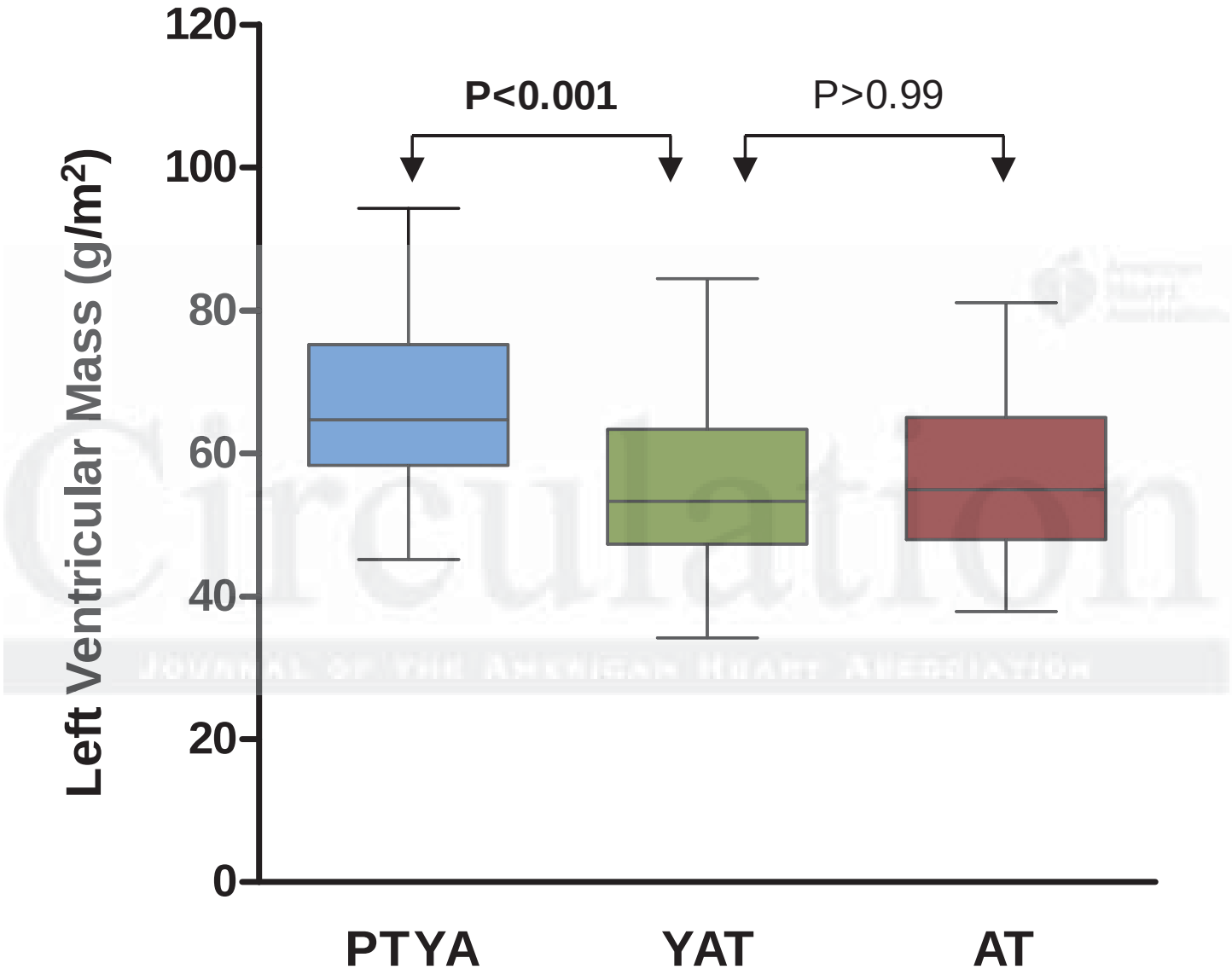


Figure 1, Panel A

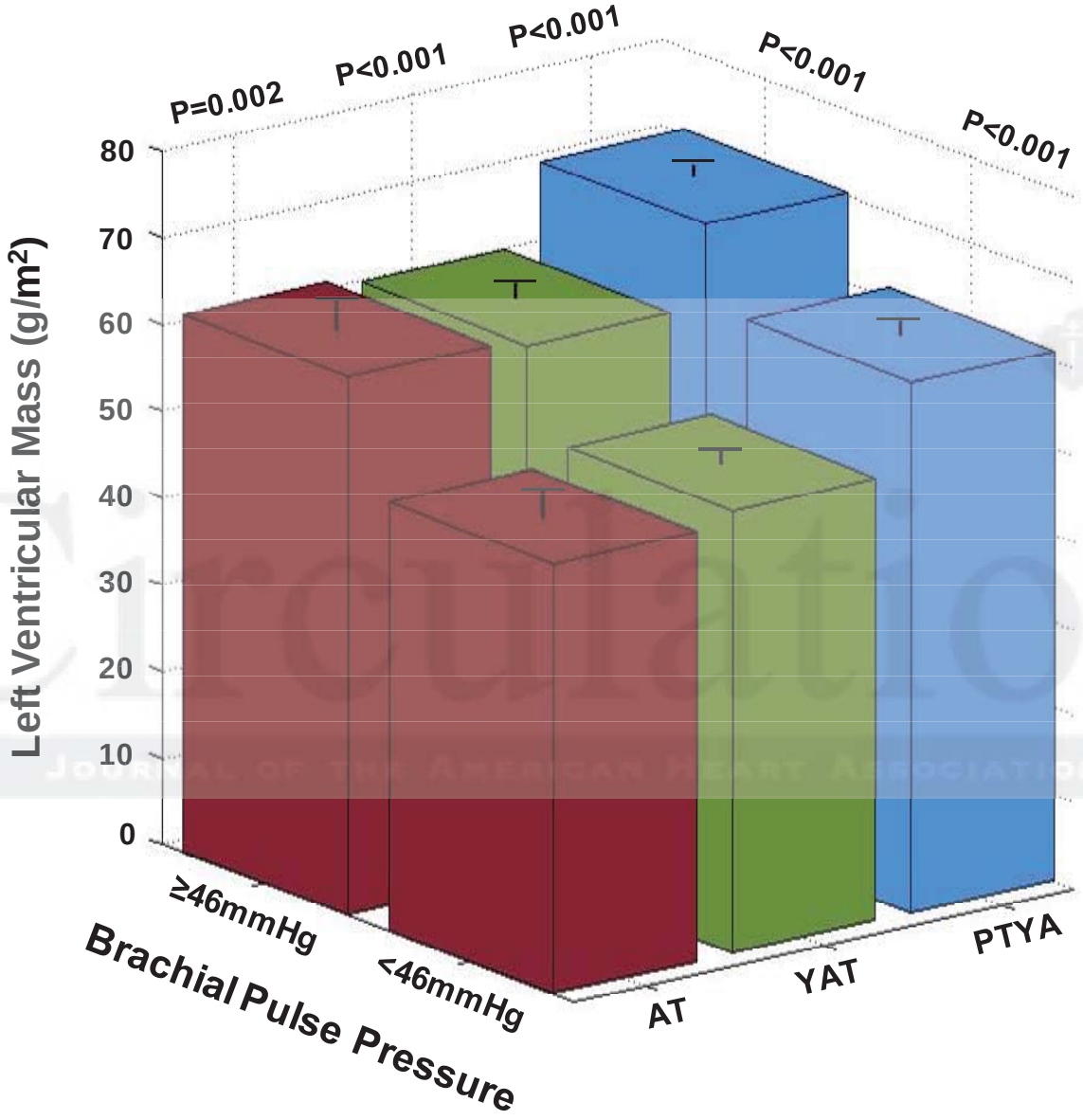
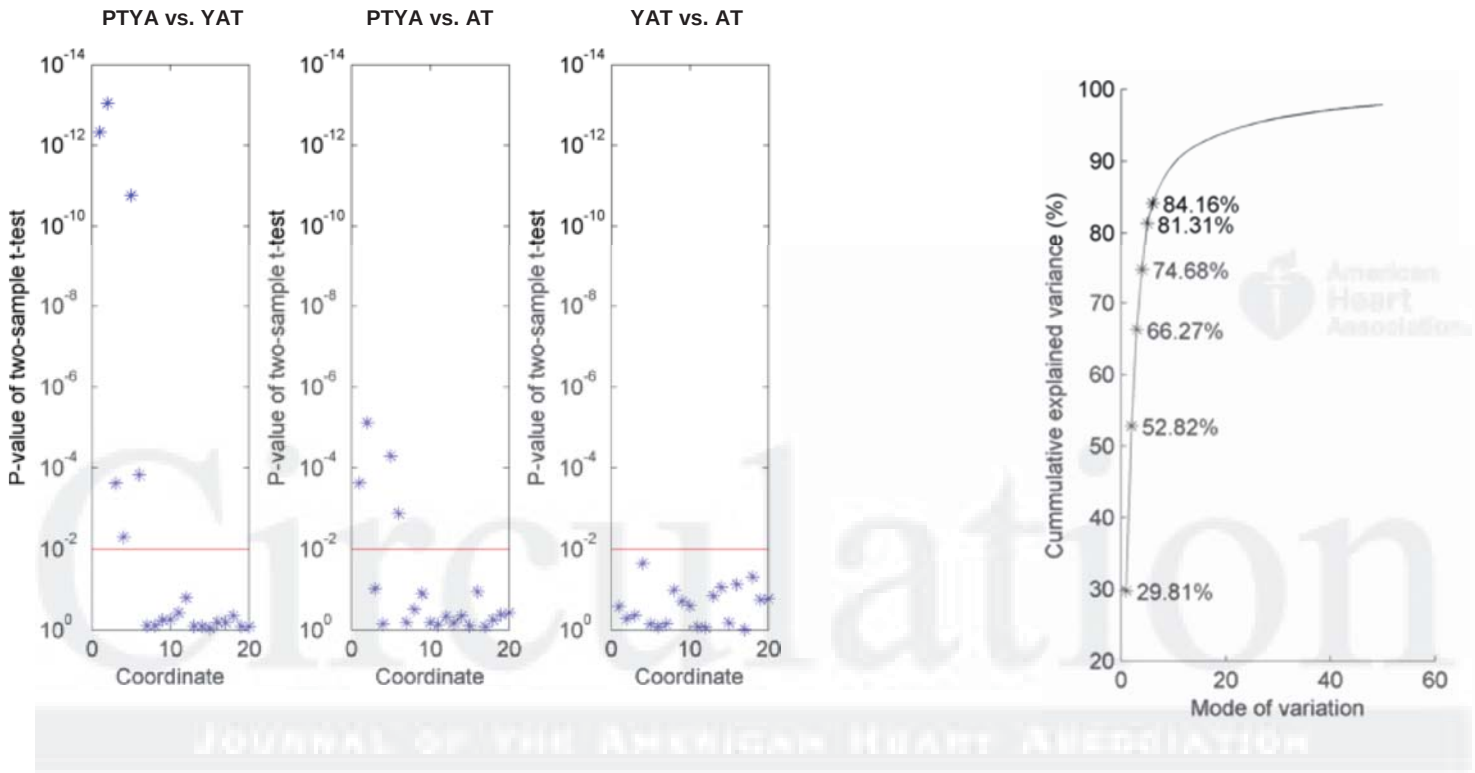


Figure 1, Panel B



Panel A **Panel B**

Figure 2

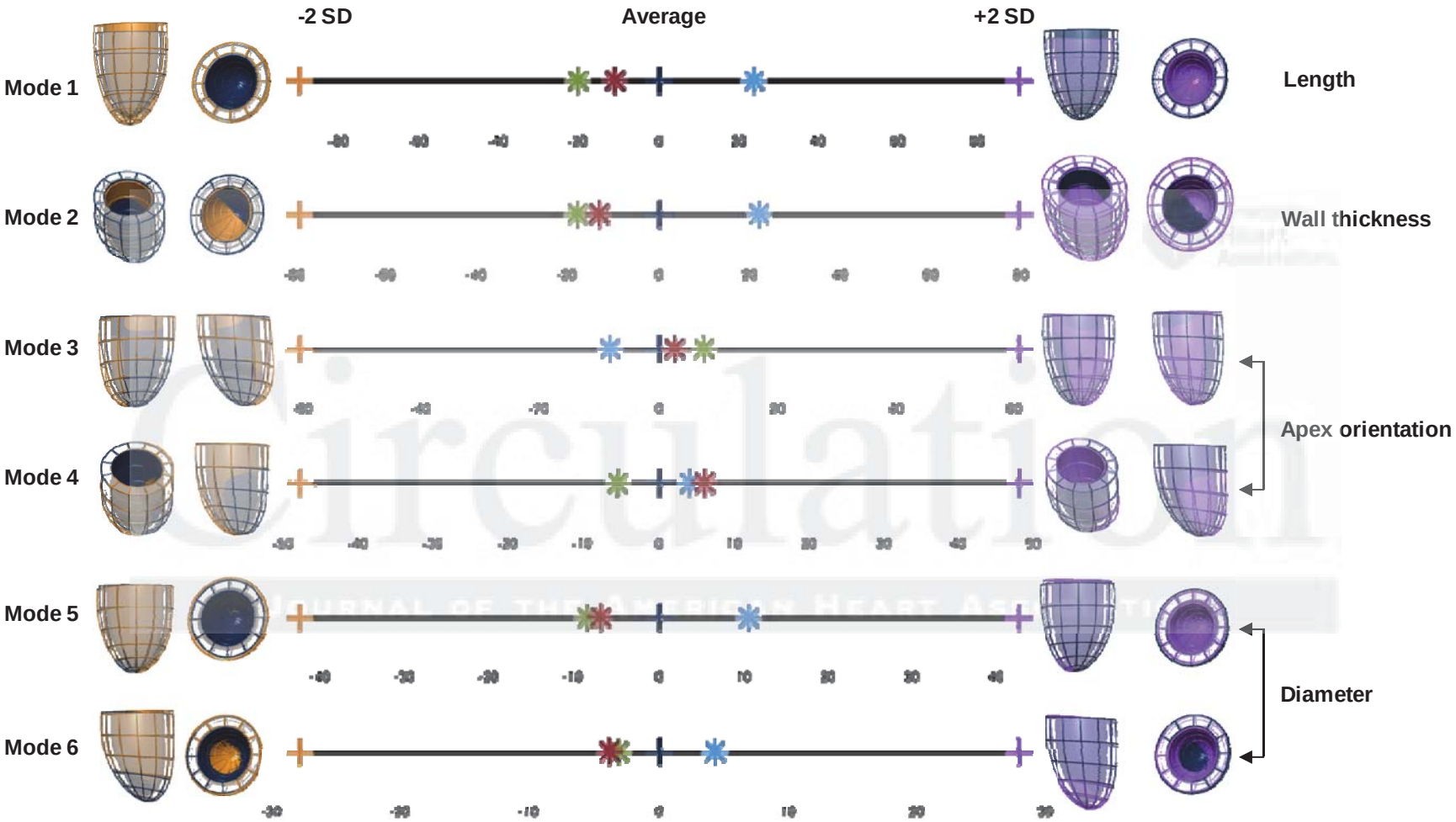


Figure 2, Panel C

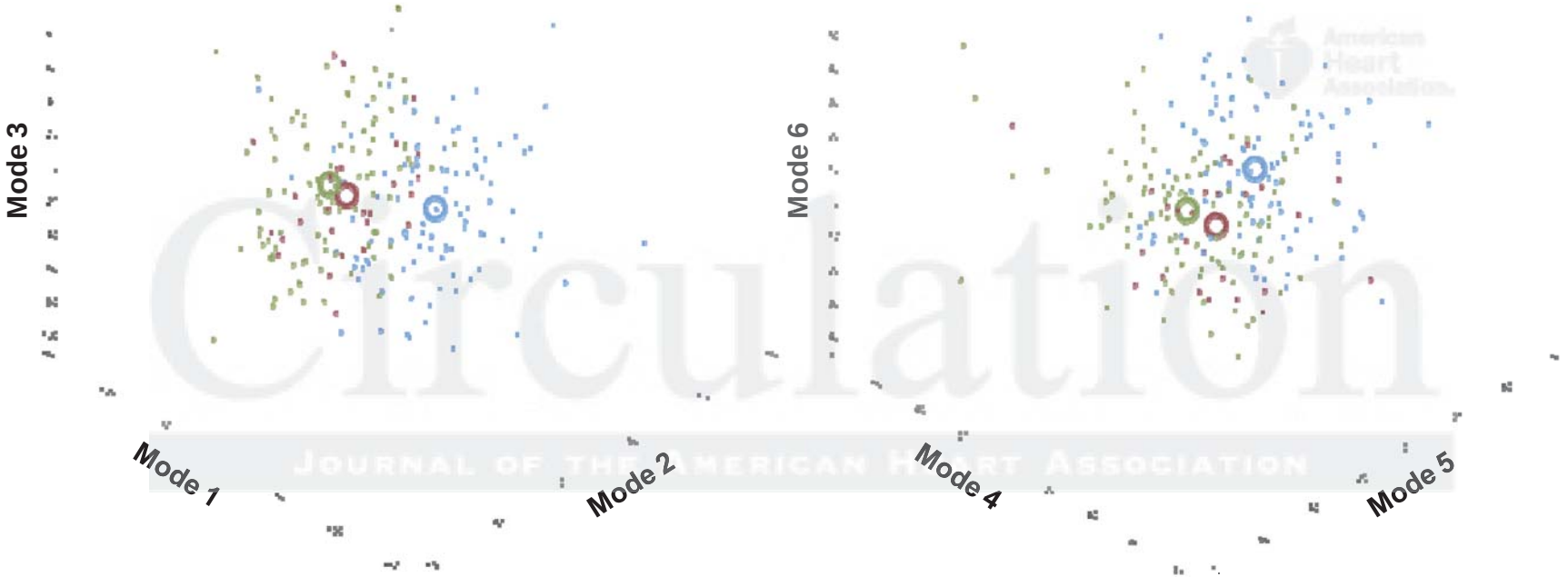


Figure 2, Panel D

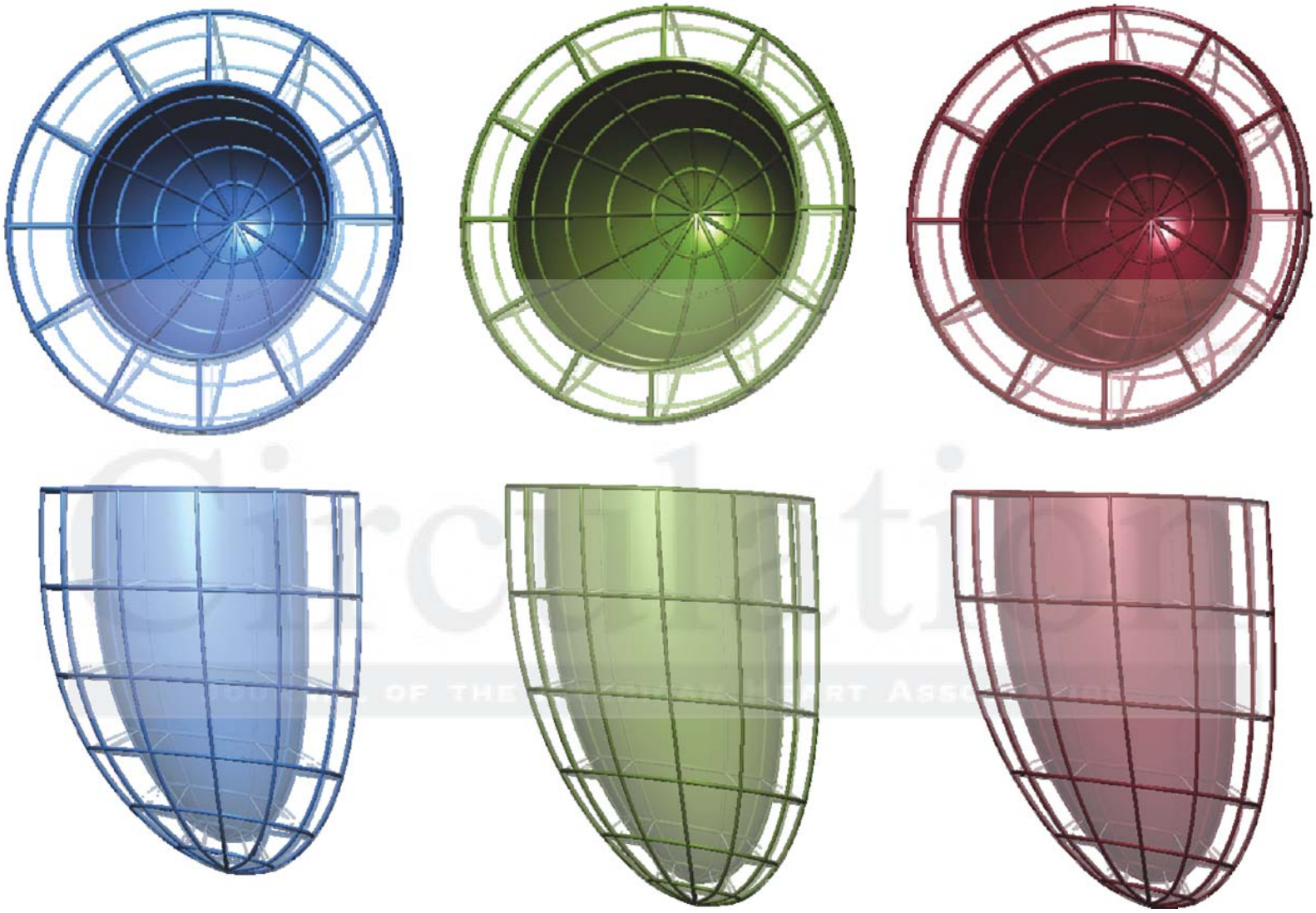


Figure 3

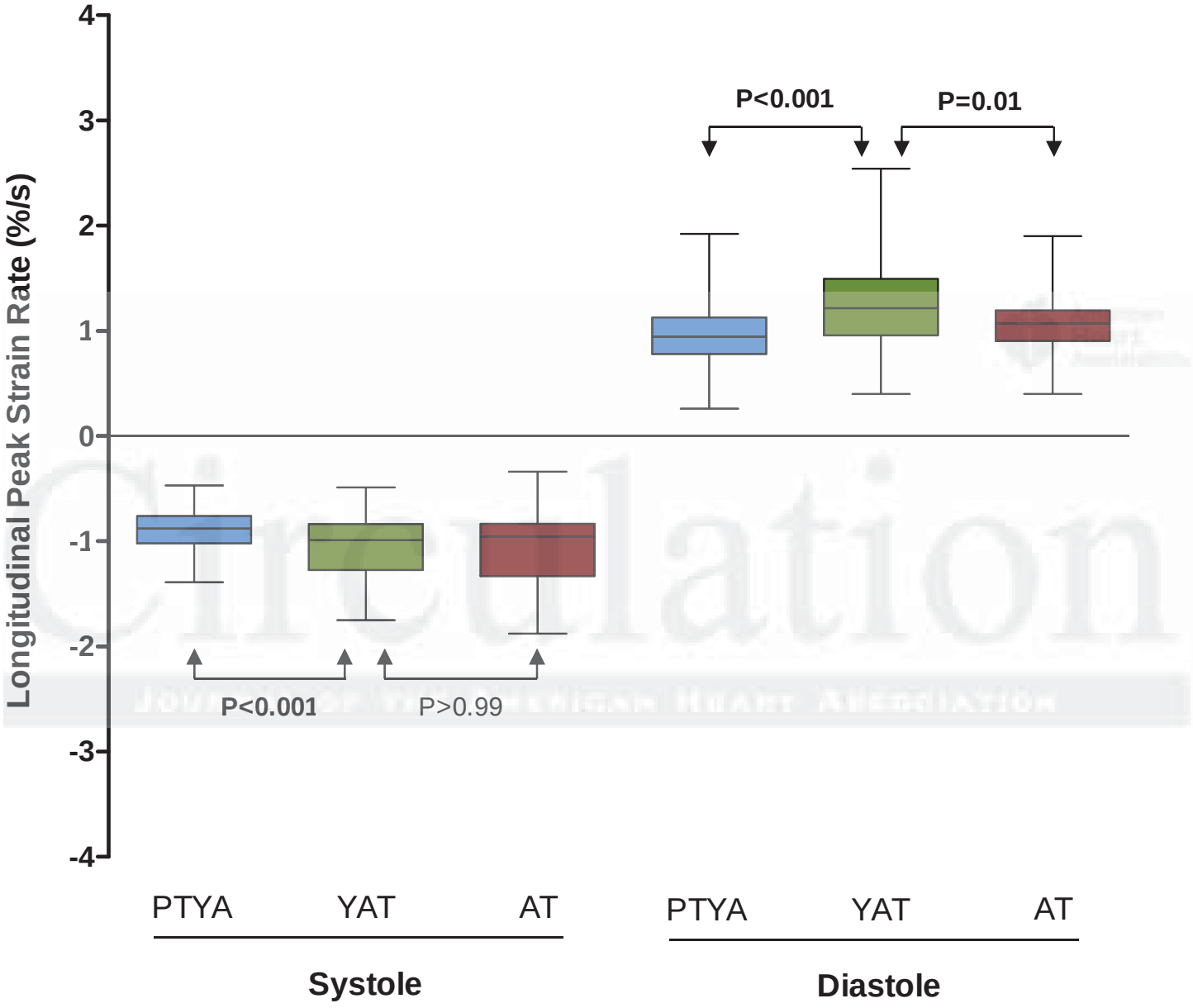


Figure 4, Panel A

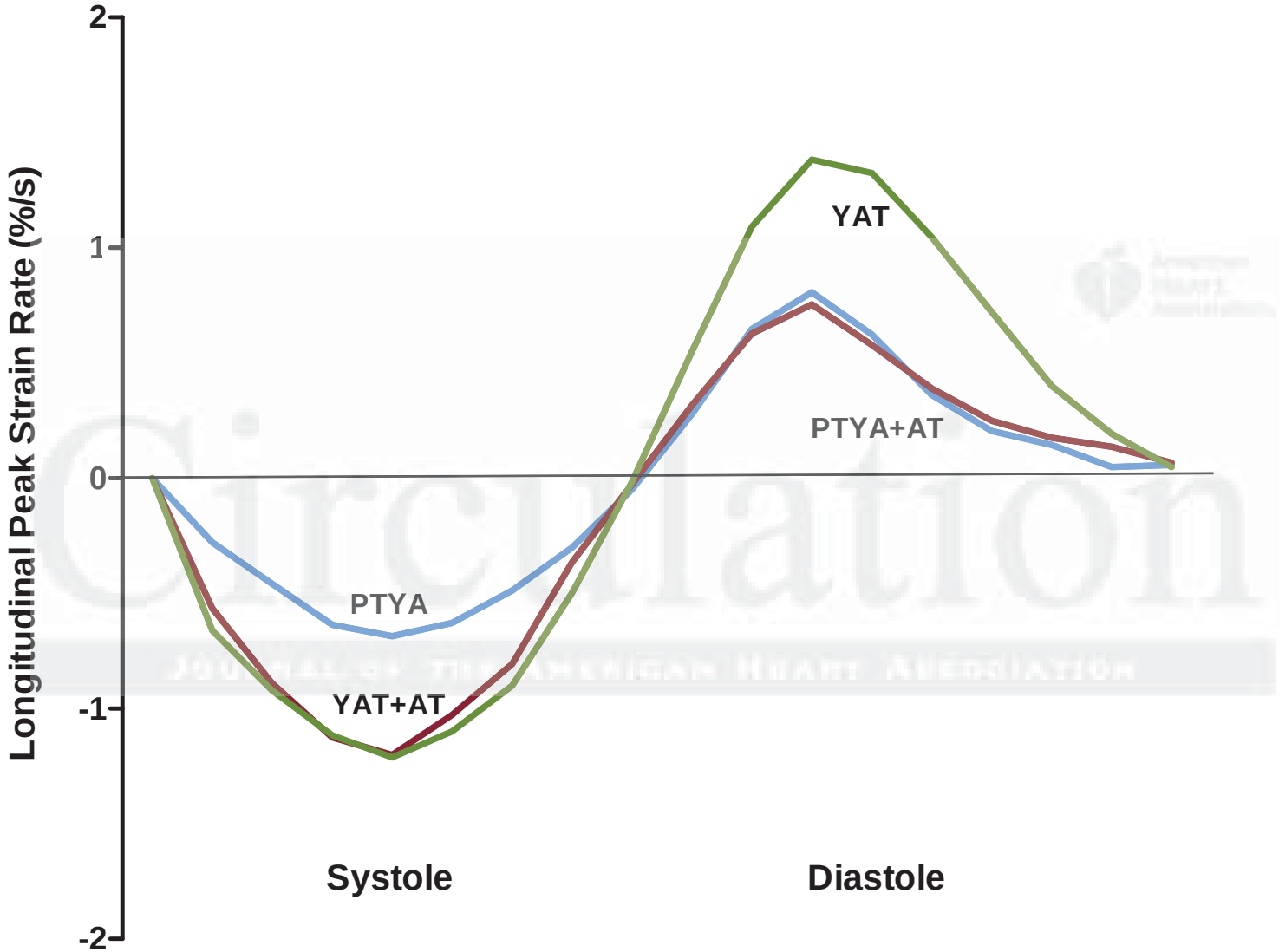


Figure 4, Panel B

SUPPLEMENTAL MATERIAL

Table I: Comparison of Key Perinatal Characteristics between Birth Cohort and Follow-up Cohort

	Original cohort (n=926)	Follow-up cohort (n=102)	P-Value
Males, n (%)	463 (49.8)	47 (46.1)	0.48
Gestational age (weeks)	30.8±2.8	30.3±2.5	0.30
Birth weight (grams)	1369.8±315.5	1297.0±286.8	0.03
Birth weight z score	-0.81±1.32	-0.84±1.21	0.83
Small for gestational age, n (%)	310 (33.5)	32 (31.4)	0.67
Maternal smoking during pregnancy, n (%)	299 (32.3)	25 (24.5)	0.11
Paternal smoking during pregnancy, n (%)	224 (24.2)	31 (30.4)	0.17
Maternal preeclampsia, n (%)	259 (28.0)	29 (28.4)	0.92
Ventilation (days)	4.65±9.84	4.14±7.43	0.61
Number of individuals on ventilation, n (%)	476 (51.4)	55 (53.9)	0.63

Values as Mean±Standard Deviation unless stated otherwise.

Table II: Biochemistry and Blood Pressure

	Preterm-born Young Adults (n=102)	Term-born Young Adults (n=102)	P-Value ψ	Term-born Adults (n=30)	P-Value ¥	P-Value Δ
Biochemistry						
Total Cholesterol (mmol/L)	4.89±1.05	4.23±0.86	**<0.001**	5.48±1.18	**0.03**	**<0.001**
HDL-C (mmol/L)	1.53±0.40	1.47±0.41	0.54	1.46±0.39	0.98	>0.99
LDL-C (mmol/L)	2.81±0.93	2.37±0.66	**<0.001**	3.39±1.00	**0.02**	**<0.001**
Triglycerides (mmol/L)	1.12±0.79	0.87±0.40	**0.02**	1.38±0.91	0.39	**0.003**
CRP (mmol/L)	2.27±4.02	1.53±3.35	0.50	3.99±7.97	0.12	0.11
Glucose (mmol/L)	5.01±0.43	4.61±0.30	**<0.001**	5.65±1.60	**0.003**	**<0.001**
Insulin (pmol/L)	64.4±42.8	35.6±15.9	**<0.001**	104.4±89.0	**0.006**	**<0.001**
Brachial Blood Pressure						
Systolic	121.3±10.9	112.9±10.1	**<0.001**	121.7±13.5	>0.99	**<0.001**
Diastolic	73.0±7.2	68.8±7.0	**<0.001**	73.9±6.0	>0.99	**<0.001**
Mean Arterial Pressure	89.1±7.4	83.5±7.1	**<0.001**	89.8±7.5	>0.99	**<0.001**
Pulse Pressure	48.4±9.1	44.1±8.5	**0.001**	47.8±11.3	>0.99	0.12
Aortic Blood Pressure						
Systolic	108.0±10.0	97.4±8.8	**<0.001**	109.1±10.9	>0.99	**<0.001**
Diastolic	74.5±7.4	69.6±7.7	**<0.001**	75.3±7.3	>0.99	**<0.001**
Mean Arterial Pressure	85.7±7.7	78.9±7.6	**<0.001**	86.5±8.0	>0.99	**<0.001**
Pulse Pressure	33.5±7.1	27.7±5.6	**<0.001**	33.8±7.3	>0.99	**<0.001**

Values as Mean±Standard Deviation unless stated otherwise. P-values were adjusted using the Bonferroni method.
ψ=Preterm-born Young Adults vs. Term-born Young Adults. Comparisons adjusted for age and sex.
¥=Preterm-born Young Adults vs. Term-born Adults. Comparisons adjusted for sex.
Δ=Term-born Young Adults vs. Term-born Adults. Comparisons adjusted for sex.

Table III: Relationship of Variables with Left Ventricular Mass Index (LVMI) in Preterm-born and Term-born Young Adults using Bivariate Regression

Variable	Unstandardized Coefficient (B)	95% Confidence Interval		P-Value
		Lower Bound	Upper Bound	
Premature Birth	**11.10**	**3.99**	**7.11**	**<0.001**
Age	-0.48	-1.31	0.36	0.26
Gender	**13.39**	**10.44**	**16.34**	**<0.001**
Smoking	-1.70	-6.05	2.66	0.44
Waist:Hip Ratio	**47.31**	**22.55**	**72.06**	**<0.001**
Total Cholesterol	-0.20	-2.06	1.66	0.83
LDL Cholesterol	0.75	-1.49	2.99	0.51
HDL Cholesterol	**-8.13**	**-12.43**	**-3.83**	**<0.001**
Insulin	0.001	-0.06	0.06	0.99
Glucose	**8.37**	**4.15**	**12.58**	**<0.001**
Triglycerides	2.55	-0.38	5.31	0.09
Brachial Systolic BP	**0.52**	**0.38**	**0.66**	**<0.001**
Brachial Diastolic BP	-0.003	-0.24	0.23	0.98
Brachial Mean Arterial Pressure	**0.35**	**0.13**	**0.57**	**0.002**
Brachial Pulse Pressure	**0.80**	**0.64**	**0.96**	**<0.001**
Aortic Systolic BP	**0.40**	**0.25**	**0.56**	**<0.001**
Aortic Diastolic BP	0.040	0.18	0.26	0.72
Aortic Mean Arterial Pressure	**0.24**	**0.03**	**0.45**	**0.02**
Aortic Pulse Pressure	**0.92**	**0.69**	**0.69**	**<0.001**

Bolded variables are statistically significant.

Table IV: Multivariate Regression Coefficient for Gestational Age in Multiple Regression Models of Key Left Ventricular Parameters

	Model 1				Model 2			
		95% Confidence Interval				95% Confidence Interval		
	B (/gestational week)	Lower Bound	Upper Bound	P Value	B (/gestational week)	Lower Bound	Upper Bound	P Value
LV Mass Index (g/m^2)	-0.98	-1.92	-0.21	**0.02**	-0.93	-1.72	-0.14	**0.03**
LV Length (cm)*	0.078	0.010	0.154	**0.03**	0.068	0.011	0.125	**0.02**
LV End-Diastolic Volume (mL/m^2)	0.68	-0.09	1.44	0.08	0.77	0.02	1.56	**0.05**

Model 1 independent variables: gestational age, birthweight z-score, postnatal weight gain in the first two weeks, days of ventilation, and maternal preeclampsia.

Model 2 independent variables: gestational age, high-density lipoprotein, gender, waist to hip ratio, glucose, and brachial pulse pressure.

***When modelling LV length, birthweight z-score also reached significance in model 1 (*P*=0.04) and was therefore included in model 2, but did not reach significance (*P*=0.11).**

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