airways. Although it was beyond the scope of our study to investigate the etiology of reduced TAC, our data suggest that the same remodeling process that occurs in the TBs may extend to the larger airways and be measured by MDCT.

We acknowledge that this was a retrospective study, and therefore it was not possible to access preoperative MDCT images to compare the relationship with TAC using clinical and explant CT images. The lung specimens have no chest wall and MDCT images were acquired at a fixed lung volume, without any motion artifacts, and therefore an increased number of airways may be quantified in specimen MDCT. MDCT LAA_{950} measurements may also be overestimated in lung specimens due to a lack of blood flow/volume. However, our primary objective was to investigate the association between TAC and TBs, which are not impacted by the lack of blood flow/volume. We also note that although we used random sampling to obtain cores for micro-CT analysis from donor lungs, we used selective sampling to avoid regions of severe emphysema in the COPD lungs, as such regions have been reported to lack TBs (1, 2). This may have resulted in biased estimates of the number of TBs in the COPD lungs and may partially explain the lack of correlation between TBs and TAC in COPD.

In conclusion, this study shows that TAC is associated with both the number of TBs and the distortion/remodeling that occurs in the TBs that remain in COPD lungs. Thus, TAC may be used as an imaging biomarker (9) to estimate the number and distortion of small airways and may provide a valuable outcome measure for clinical trials of new therapies aimed at the prevention and treatment of small airways disease. ■

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Impaired Right Ventricular–Vascular Coupling in Young Adults Born Preterm

To the Editor:

The improved survival of extremely preterm infants into adulthood has increased recognition of impaired right ventricular (RV) performance and evidence of pulmonary vascular disease (PVD) arising beyond the neonatal period. Because the efficiency of the right ventricle depends on proper hemodynamic coupling with the typically compliant pulmonary arteries (PAs), which constitutes its

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afterload, a comprehensive evaluation of RV–PA coupling is central in the characterization of cardiopulmonary function (1). Recent work from our group demonstrated that prematurity leads to RV dysfunction and early evidence of PVD in young adulthood, but little is known regarding the long-term impact on RV–PA coupling (2). This coupling interaction was not available to report in our original study or a previously reported abstract (2, 3). We hypothesize that young adults born preterm have subclinical RV dysfunction with impaired RV–PA coupling.

We analyzed prospectively acquired data from our original study (2), obtained from adults who were born premature ($n = 10$, five male; current age 26.9 ± 0.3 yr; gestational age 28.6 ± 0.9 wk) and were recruited from the Newborn Lung Project, which includes a cohort of infants who were born in Wisconsin and Iowa between 1988 and 1991 and were longitudinally followed. Control subjects were born at term ($n = 9$, seven male; current age 25.8 ± 0.3 yr; gestational age 40.2 ± 0.2 wk) and recruited from the general population. The Institutional Review Board of the University of Wisconsin–Madison School of Medicine and Public Health approved all procedures. Informed consent was obtained from all subjects.

RV–PA coupling can be calculated as the ratio of end-systolic elastance (Ees, a measure of contractility) to effective arterial elastance (Ea, a measure of RV afterload). In this study, RV and PA pressure traces were obtained using two 3.5F high-fidelity, solid-state pressure sensor catheters (Mikro-Cath; Millar) at a sampling rate of 1 kHz. Cardiac magnetic resonance (CMR) images were acquired on a clinical 3T scanner (M750; GE Healthcare). ECG-gated, balanced, steady-state, free-precession images through the entire heart and two-dimensional phase-contrast images of the main PA (MPA) and aorta (Ao) were acquired. Images were manually contoured using Segment software (Medviso) to measure RV volumes and the relative area change of the MPA and Ao, calculated as $[\frac{\text{Maximal area} - \text{Minimal area}}{\text{Maximal area}}]$. The ventricular stroke volume (SV) calculated as end-diastolic volume − end-systolic volume (ESV) was comparable to the SV derived from the MPA and Ao flow $[\frac{\text{Q}}{\text{Heart Rate}}]$.

The elastance relationship was calculated using the single-beat method from right heart catheterization, with Ees and Ea estimated as $[\frac{\text{Piso} - \text{Pes}}{\text{SV}}]$ and $[\frac{\text{Pes}}{\text{SV}}]$, respectively (4, 5), where Pes is the end-systolic pressure. Piso represents the peak value of the interpolated sine wave from the two isovolumic portions of the second derivative of the RV pressure waveform (6). Because $[\frac{\text{Ees}}{\text{Ea}}]$ can be simplified by omitting SV, RV–PA coupling becomes dependent on "pressure only" and can be calculated as $[\frac{\text{Piso}}{\text{Pes}} - 1]$. Similarly, $[\frac{\text{Ees}}{\text{Ea}}]$ can be simplified by omitting Pes and becomes dependent on "volume only" as calculated by $[\frac{\text{SV}}{\text{ESV}}]$ (4, 7). In addition, PA pressure and flow waveforms were used to determine the characteristic impedance, Z_C, a measure of proximal stiffness in the absence of wave reflections, and Z_0, the total pulmonary vascular resistance. Lastly, diastolic function was assessed via the relaxation time constant, τ_{weiss}.

All data are reported here as mean ± SE. Results were analyzed via two-sample *t* tests, and Grubbs' test was performed to remove outliers. A *P* value of <0.05 was used to indicate statistical significance. All analyses were conducted with IBM SPSS Statistics software version 23.

Baseline characteristics are recorded in Table 1. Volumes calculated from the CMR images revealed no statistical differences in the body surface area indexed chamber volumes (end-diastolic volume index and ESV index) between the preterm and term-born subjects.

Table 1. Baseline Characteristics

	Term-Born Young Adults	Preterm-Born Young Adults	*P* Value
Anthropometric data	$n = 9$	$n = 10$	
Gestational age, wk	40.22 ± 0.14	28.60 ± 0.86	**<0.001**
Current age, yr	25.78 ± 0.26	26.90 ± 0.27	**0.011**
BSA, m^2	1.90 ± 0.05	1.82 ± 0.07	>0.1
Sex, male, *n* (%)	7 (78%)	5 (50%)	>0.1
Structure and function	$n = 6$–9	$n = 8$–10	
HR, bpm	73 ± 4	85 ± 4	0.089
MPA max area, cm^2/m^2	3.95 ± 0.13	4.37 ± 0.10	**0.023**
MPA RAC	0.36 ± 0.02	0.33 ± 0.02	>0.1
Ao max area, cm^2/m^2	3.68 ± 0.20	3.56 ± 0.22	>0.1
Ao RAC	0.22 ± 0.03	0.21 ± 0.02	>0.1
(MPA/Ao)/BSA, m^{-2}	0.56 ± 0.03	0.71 ± 0.06	0.053
RV EDVi, ml/m^2	85.54 ± 2.45	80.55 ± 2.23	>0.1
RV ESVi, ml/m^2	32.55 ± 0.87	32.97 ± 0.98	>0.1
RV SVi, ml/m^2	52.99 ± 2.20	47.58 ± 1.36	0.056
RV EF	0.62 ± 0.01	0.59 ± 0.01	**0.041**
LV EDVi, ml/m^2	89.61 ± 3.51	82.39 ± 2.16	>0.1
LV ESVi, ml/m^2	33.95 ± 1.35	32.53 ± 1.03	>0.1
LV SVi, ml/m^2	55.66 ± 2.65	49.86 ± 1.29	0.075
LV EF	0.62 ± 0.01	0.61 ± 0.01	>0.1
LV SV/ESV	1.65 ± 0.07	1.54 ± 0.03	>0.1
Cardiopulmonary hemodynamics	$n = 5$–9	$n = 4$–10	
mPAP, mm Hg	14.0 ± 1.2	20.33 ± 1.3	**0.003**
Piso, mm Hg	29.3 ± 1.9	33.9 ± 4.5	>0.1
Pes, mm Hg	11.2 ± 1.6	17.9 ± 1.9	**0.030**
Ea, mm Hg/ml	0.11 ± 0.02	0.20 ± 0.02	**0.035**
Ees, mm Hg/ml	0.18 ± 0.02	0.16 ± 0.04	>0.1
Z_C, mm Hg · s/ml	1.22 ± 0.35	1.07 ± 0.27	>0.1
Z_0, mm Hg · s/ml	1.97 ± 0.25	2.96 ± 0.21	**0.014**
τ_{weiss}, ms	27.46 ± 2.76	42.25 ± 6.05	0.085

Definition of abbreviations: Ao = aorta; BSA = body surface area; Ea = effective arterial elastance; EDVi = end-diastolic volume index (EDV/BSA); Ees = end-systolic elastance; EF = ejection fraction (SV/EDV); ESVi = end-systolic volume index (ESV/BSA); HR = heart rate; LV = left ventricle; MPA = main pulmonary artery; mPAP = mean pulmonary artery pressure; Pes = end-systolic pressure; Piso = isovolumetric pressure obtained from the single-beat method; RAC = relative area change; RV = right ventricle; SVi = stroke volume index (SV/BSA); τ_{weiss} = time constant of ventricular relaxation; Z_C = characteristic impedance; Z_0 = zero Hz impedance.
Data are shown as mean ± SE. Bold indicates $P < 0.05$.

Pressure waveform analysis revealed that preterm subjects had increased total pulmonary vascular resistance (Z_0) that contributed to increased RV afterload (0.11 ± 0.02 vs. 0.20 ± 0.02 mm Hg/ml; $P = 0.035$). This contributed to increased Pes (11.2 ± 1.6 vs. 17.9 ± 1.9 mm Hg; $P = 0.030$) and reduced RV ejection fraction (0.62 ± 0.01 vs. 0.59 ± 0.01; $P = 0.041$) and RV stroke volume index (52.99 ± 2.20 vs. 47.58 ± 1.36 ml/m^2; $P = 0.056$), which could indicate the beginning stages of RV systolic dysfunction.

Analysis of the CMR phase-contrast images revealed increased PA dilation in preterm subjects, whereas the Ao area was comparable between the preterm and term-born subjects. However, no difference in the stiffness of the PA was measured between the preterm and term-born subjects, as estimated noninvasively via the relative area change and invasively by the characteristic impedance, Z_C.

Preterm subjects had an increased RV relaxation time constant, τ_{weiss} (27.46 ± 2.76 vs. 42.25 ± 6.05 ms; $P = 0.085$), suggesting reduced RV diastolic function. Lastly, no compensatory changes in RV contractility were observed in preterm subjects. Maintained contractility with increased RV afterload led to reduced RV–PA coupling as calculated by both the pressure- and volume-only methods (Figure 1). Good agreement was found between the two methods (Pearson coefficient $R^2 = 0.78$; $P < 0.001$).

Although the preterm subjects in this study were healthy, active individuals, they demonstrated early signs of RV systolic and diastolic dysfunction and decreased RV–PA coupling. Several preterm subjects also presented with PA pressures consistent with pulmonary hypertension (2). This study was not designed to address the causation or mechanistic progression of reduced RV–PA coupling; however, we previously demonstrated mitochondrial DNA damage and dysregulated biogenesis in a rat model of prematurity-related lung disease (8). These animals also developed RV–PA uncoupling in a setting of modest pulmonary hypertension, which we proposed represents an intrinsic RV insult of prematurity. Future studies are needed to test these mechanisms.

The results of this study should be interpreted within the framework of its inherent limitations, primarily the small sample size and the asynchronous acquisition of RV pressures and volumes. The single-beat method was not validated against the gold-standard, multibeat method with a preload reduction in subjects with PVD; however, the benefits associated with the single-beat method as a measure of RV–PA coupling have been well described (4).

In summary, otherwise healthy, young adults who were born preterm were found to have high-resistance/low-compliance pulmonary vascular beds with attenuated RV adaptation in the face of increased vascular load. This resulted in impaired RV–PA coupling, as demonstrated by two different methods. These findings add to the growing evidence that preterm birth has profound lifelong consequences that warrant further study. ■

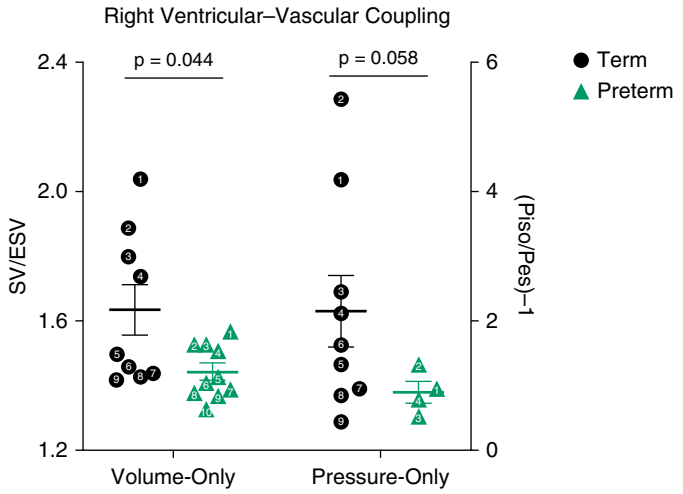

Figure 1. Right ventricular–pulmonary arterial coupling as estimated by a volume-only method (left) and a pressure-only method (right). Numbers within the symbols are used to denote specific patients to compare the two methods. Optimal mechanical coupling occurs when the end-systolic elastance (Ees) to effective arterial elastance (Ea) ratio is equal to 1, and optimal energy transfer occurs when Ees/Ea falls between 1.5 and 2.0 (9). ESV = end-systolic volume; Pes = end-systolic pressure; Piso = isovolumetric pressure obtained from the single-beat method; SV = stroke volume.

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Association of Sex Steroid Hormones with Adult Asthma in the United States, 2013–2016

To the Editor:

We read with great interest the article by Han and colleagues on the association between sex steroid hormones and asthma in U.S. adults (1). The sex disparity in asthma prevalence is well established, and compelling evidence links it to sex hormones (2). Using National Health and Nutrition Examination Survey (NHANES) data from 2013–2014 and 2015–2016, the authors found that elevated serum-free testosterone was significantly associated with lower odds of current asthma in women only. Analyses stratified by obesity showed a similar association only in obese women and nonobese men. Here, we raise some methodological considerations.

First, the statistical power is considered low (especially for men) because of the small number of subjects with current asthma (239 men and 450 women), as the authors indicated, but it could benefit from excluding fewer NHANES participants. In this study, 728 (6.0%) adults ⩾80 years of age were excluded for no specific reason. In addition, 1,623 (17.6%) adults were further excluded owing to missing data on annual household income ($n = 516$), body mass index ($n = 84$), smoking status ($n = 4$), second-hand smoke exposure ($n = 4$), pack-years ($n = 138$), family history of asthma ($n = 182$), or ever use of birth control pills or any form of female hormones ($n = 695$). However, the authors could have included the adults with missing data on certain covariates in the analyses by using several analytic strategies, including assigning an "unknown" category for missing values in a given covariate, and dealing with the missing data using multiple imputation (3). It would be of great interest to determine whether the results would vary if the sample size were increased by >20%. Also note that the information on ever use of female hormones was available only for females ⩾20 years of age. In this study, excluding women without this information actually restricted the analyses to women ⩾20 years of age.

Second, the session time of venipuncture and the season when the examination was performed were not considered in this study. Diurnal variations in serum testosterone levels (i.e., peaking in the morning and decreasing afterward) have been well documented in both men and women, although the amplitude of variation declines with age (4, 5). Despite these inconsistencies, the evidence suggested a significant seasonal variation in serum testosterone (6). Association studies on testosterone and health outcomes are expected to take these two covariates into account to minimize possible misclassifications. In NHANES, the time of venipuncture was classified as a morning, afternoon, or evening session and can be found in the Fasting Questionnaire file (Cycle 2013-2014: https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/FASTQX_H.htm and Cycle 2015-2016: https://wwwn.cdc.gov/Nchs/Nhanes/2015-2016/FASTQX_I.htm) (variable PHDSESN). The season when the examination was performed can be obtained from the Demographic Variables and Sample Weights file (Cycle 2013-2014: https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/DEMO_H.htm and Cycle 2015-2016: https://wwwn.cdc.gov/Nchs/Nhanes/2015-2016/DEMO_I.htm) (variable RIDEXMON) pertaining to a 6-month time period, either November 1 through April 30 or May 1 through October 31.

Third, the interaction between menopausal status and sex hormones on current asthma in women may not have been adequately investigated. The authors tried to explore this interaction using age with a cutoff of 51 years and serum estradiol in women, as they stated that there were no data on menopausal status in NHANES. However, menopausal information can be obtained in the Reproductive Health file (Cycle 2013-2014: https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/RHQ_H.htm and Cycle 2015-2016: https://wwwn.cdc.gov/Nchs/Nhanes/2015-2016/RHQ_I.htm) based on several questions, including "Have you had at least one menstrual period in the past 12 months?", "What is the reason that you have not had a period in the past 12 months?", and "How old were you when you had your last menstrual period?" Information on hysterectomy and bilateral oophorectomy were also available to help identify the subjects' menopausal status. Analyses stratified by menopausal status may help us better understand the association between sex hormones and current asthma in women. ■

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