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 LAAo300 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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Miranda Kirby, Ph.D.*
Ryerson University
Toronto, Canada
and
St. Paul’s Hospital
Vancouver, Canada

Naoya Tanabe, M.D.*
Dragoș M. Vasilescu, Ph.D.*
St. Paul’s Hospital
Vancouver, Canada

Joel D. Cooper, M.D.
University of Pennsylvania
Philadelphia, Pennsylvania

John E. McDonough, Ph.D.
Stijn E. Verleden, Ph.D.
Bart M. Vanaudenaerde, Ph.D.
Katholieke Universiteit Leuven
Leuven, Belgium

Don D. Sin, M.D.
Wan C. Tan, M.D.
Harvey O. Coxson, Ph.D.
James C. Hogg M.D., Ph.D.
St. Paul’s Hospital
Vancouver, Canada

*These authors contributed equally to this work.

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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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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Correspondence 615
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 afterload (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 calculated from the CMR images revealed no statistical differences 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.

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\frac{\text{Maximal area}}{\text{Minimal area}}.
\]

The elastance relationship was calculated using the single-beat method from right heart catheterization, with Ees and Ea estimated as \[
\frac{\text{Pmax} - \text{Pes}}{\text{SV}}
\]
and \[
\frac{\text{Pzero}}{\text{SV}},
\]
respectively (4, 5), where Pes is the end-systolic pressure. Peso 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 \[
\frac{\text{Pmax} - \text{Pes}}{\text{SV}}
\]
can be simplified by omitting SV, RV–PA coupling becomes dependent on "pressure only" and can be calculated as \[
\frac{\text{Pzero}}{\text{SV}} - 1.
\]
Similarly, \[
\frac{\text{Pzero}}{\text{SV}}
\]
can be simplified by omitting Pes and becomes dependent on "volume only" as calculated by \[
\frac{\text{Zzero}}{\text{SV}}.
\]
(4, 7). In addition, PA pressure and flow waveforms were used to determine the characteristic impedance, Zc, a measure of proximal stiffness in the absence of wave reflections, and Zo, the total pulmonary vascular resistance. Lastly, diastolic function was assessed via the relaxation time constant, \(\tau_{\text{relax}}\).

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>
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<th>Table 1. Baseline Characteristics</th>
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<tr>
<td><strong>Anthropometric data</strong></td>
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<td>Gestational age, wk</td>
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<td>Current age, yr</td>
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<td>BSA, m²</td>
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<td>Sex, male, n (%)</td>
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<td><strong>Structure and function</strong></td>
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<td>HR, bpm</td>
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<td>MPA max area, cm²/m²</td>
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<td>MPA RAC</td>
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<td>Ao max area, cm²/m²</td>
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<td>Ao RAC</td>
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<td>(MPA/Ao)/BSA, m⁻²</td>
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<td>RV EDVi, ml/m²</td>
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<td><strong>Cardiopulmonary hemodynamics</strong></td>
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<td>mPAP, mm Hg</td>
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<td>Pes, mm Hg</td>
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<td>Ea, mm Hg/ml</td>
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<td>Ees, mm Hg/ml</td>
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<td>Zc, mm Hg · s/ml</td>
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<td>Z0, mm Hg · s/ml</td>
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<td>(\tau_{\text{relax}}), ms</td>
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Definition of abbreviations: Ao = aorta; BSA = body surface area; Ee = effective arterial elastance; EDVi = end-diastolic volume index (EDV/BSA); Ees = end-systolic elastance; EF = ejection fraction (SV/EDVi); 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; SV = stroke volume index (SV/BSA); \(\tau_{\text{relax}}\) = time constant of ventricular relaxation; Zc = characteristic impedance; Z0 = zero Hz impedance.

Data are shown as mean ± SE. Bold indicates \(P < 0.05\).
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, \( \tau_{\text{weiss}} \) (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. 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.

Author disclosures are available with the text of this letter at www.atsjournals.org.

Ashley Mulchrone, Ph.D.
University of Wisconsin–Madison
Madison, Wisconsin

Alessandro Belloffore, Ph.D.
San José State University
San José, California

Johannes M. Douwes, M.D., Ph.D.
University Medical Center Groningen
Groningen, the Netherlands

Neal Duong
Arij G. Beshish, M.B. B.Ch., Ph.D.
Gregory P. Barton, Ph.D.
Christopher J. Francois, M.D.
Marlowe W. Eldridge, M.D.
Kara N. Goss, M.D.
Naomi C. Chesler, Ph.D.*
University of Wisconsin–Madison
Madison, Wisconsin

ORCID ID: 0000-0002-7612-5796 (N.C.C.).

*Corresponding author (e-mail: naomi.chesler@wisc.edu).

References
information can be obtained in the Reproductive Health 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_H.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.

Author disclosures are available with the text of this letter at www.atsjournals.org.

Yuewei Liu, M.D., Ph.D.*
Sun Yat-sen University
Guangzhou, China

Yun Zhou, Ph.D.
Guangzhou Medical University
Guangzhou, China

ORCID IDs: 0000-0001-5970-4262 (Y.L.); 0000-0002-1758-7499 (Y.Z.).

*Corresponding author (e-mail: liuyuewei@mail.sysu.edu.cn).

References