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## Reply to Tello et al.: Pending Right Heart Failure in Healthy Preterm-Born Subjects?

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from the pulmonary circulation by >50% is associated with increased right heart dimensions and decreased ejection fractions (EFs) to  $\geq 35\%$ , heralding the transition from maladaptation to failure (4).

The extraordinary RV–PA uncoupling in preterm-born subjects disclosed in the study by Mulchrone and colleagues is probably methodological. The authors applied a recently developed automatic second derivation of rate of pressure rise (dP/dt) (5) instead of a single derivation of dP/dt with manual identification of the end and onset of diastole, which traditionally has been used to determine the isovolumic portions of the RV pressure curve and extrapolate an estimation of Pmax (3, 4). As acknowledged by the authors, the second-derivative approach may reduce variability (i.e., increase precision) but underestimates Pmax by some 13% (5). This would obviously increase Pes, probably in a similar proportion. Calculating the EF from the pressure-only method as  $1 - \text{Pes}/\text{Pmax}$  with 13–15% corrections of the reported Pmax and Pes in the study by Mulchrone and colleagues would bring it back around the normal value of 60%.

Mulchrone and colleagues claim that there was good agreement between the pressure- and volume-only methods, with a Pearson coefficient of  $R^2 = 0.78$  ( $P < 0.001$ ) (1). However, as repeatedly underscored by Bland and Altman, correlation coefficients largely reflect the variability of the subjects being measured, such that if one measurement is always twice as big as the other, they are highly correlated but do not agree (6). The large differences in the means of Ees/Ea obtained by different methods in the preterm-born subjects indicate considerable biases, which would have been disclosed by a correct Bland and Altman analysis.

In conclusion, we believe that preterm-born healthy subjects can be reassured that they are not in a state of pending right heart failure. This discussion also underscores how difficult it is to measure the gold-standard Ees/Ea ratio to assess RV–PA coupling, and the importance of using a rigorous methodology, including the EF, as an indispensable internal control. ■

**Author disclosures** are available with the text of this letter at [www.atsjournals.org](http://www.atsjournals.org).

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## Reply to Tello et al.



From the Authors:

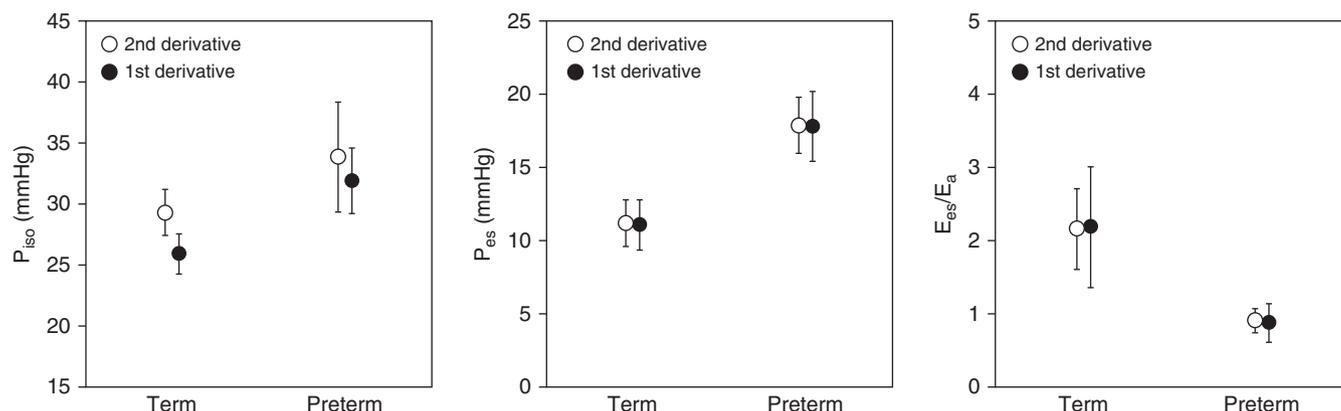
We appreciate the opportunity to further discuss cardiopulmonary differences between adults born preterm and adults born at term (1). Tello and colleagues raise two important points in their letter that we will address here. First, the “extraordinary” right ventricular–pulmonary arterial (RV–PA) uncoupling in the preterm-born subjects we reported is not the result of our use of the second-derivative approach to the single-beat method (2), as they suggest. The first author of this letter, who is an experienced user of both first- and second-derivative approaches, reanalyzed the hemodynamic data reported by Mulchrone and colleagues and found similar results (Figure 1) that led to a similar conclusion: preterm birth leads to a decrease in the RV–PA end-systolic elastance to arterial elastance ratio (Ees/Ea) that is clinically relevant. With either approach, the decrease is not statistically significant, most likely because of the small sample size.

Second, although data support that uncoupling of the right ventricle from the pulmonary circulation by more than 50% predicts RV failure in pulmonary hypertension (3), preterm birth causes a fundamentally different cardiopulmonary pathology. In particular, preterm birth results in morphologically different ventricles with smaller biventricular chamber size and subtle left ventricular (LV) dysfunction (4, 5). Herein lies a critically important methodological consideration in using RV–PA Ees/Ea to predict RV failure. As elegantly demonstrated decades ago (6, 7), although LV pump function is largely insensitive to RV pump function, the reverse is not true. As we recently showed in a mouse model of pulmonary hypertension secondary to left heart failure, impaired LV function depresses RV–PA Ees/Ea even if the right ventricle itself is in an adaptive, not maladaptive, state of remodeling (8). We anticipate that this is the case in our cohort of preterm-born subjects but must await invasive LV hemodynamic data to prove the point.

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**Figure 1.** Maximum isovolumic pressure ( $P_{iso}$ ), end-systolic pressure ( $P_{es}$ ), and right ventricular–pulmonary arterial end-systolic elastance to arterial elastance ratio ( $E_{es}/E_a$ ) for term-born and preterm-born subjects obtained with the second-derivative single-beat method (as reported in Reference 1) compared with the first-derivative approach. Mean  $\pm$  SE is shown.

In conclusion, we agree that preterm-born subjects are not in a state of pending right heart failure, but they do show significant RV–PA uncoupling due to a combination of ventricular dysfunction and elevated RV afterload revealed by our analysis. We previously demonstrated the clinical relevance of this uncoupling by reporting reduced exercise tolerance in the subjects included in the current analysis (9). Furthermore, should these subjects follow the trajectory of progressive RV dysfunction identified in our animal model (10, 11), careful clinical monitoring is warranted. Finally, we urge users of the gold-standard multibeat  $E_{es}/E_a$  ratio, as well as various single-beat methods, to consider LV function in their physiological and clinical interpretations of RV–PA coupling. ■

**Author disclosures** are available with the text of this letter at [www.atsjournals.org](http://www.atsjournals.org).

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## The American Thoracic Society/European Respiratory Society 2019 Spirometry Statement and Occupational Spirometry Testing in the United States



To the Editor:

U.S. occupational settings, in which hundreds of thousands of workers are tested each year, have scrupulously adhered to American Thoracic Society (ATS) statements since the

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