calcification plays a more significant role in driving progression of AS in men than in women. Of note, we did not observe any sex differences in the hemodynamic progression of AS on echocardiography, suggesting that fibrosis plays a more important role in women (5). Our data have some limitations, including the possible influence of partial volume effects on the valve ^{18}F-fluoride signal, and further larger studies will be required for confirmation of our findings. However, we believe they add to the existing published data, demonstrating that the pathophysiology of AS might be different in men and women and that the 2 sexes may therefore require different pharmacological interventions to reduce disease activity and slow progression of AS.

Frederique E.C.M. Peeters, MD, PhD
Mhairi K. Doris, MD
Timothy R.G. Cartlidge, MD
Jacek Kwiecinski, MD, PhD
Tania A. Pawade, MD, PhD
William S.A. Jenkins, MD, PhD
Bas L.J.H. Kietselaer, MD, PhD
Harry J.G.M. Crijns, MD, PhD
David E. Newby, MD, PhD
Marc R. Dweck, MD, PhD*

*Centre for Cardiovascular Science
University of Edinburgh
47 Little France Crescent, Edinburgh
Midlothian EH16 4TJ
United Kingdom
E-mail: marc.dweck@ed.ac.uk

https://doi.org/10.1016/j.jcmg.2020.02.034

Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Imaging* author instructions page.

REFERENCES

1. Peeters F, Meex SJR, Dweck MR, et al. Calcific aortic valve stenosis: hard disease in the heart: a biomolecular approach towards diagnosis and treatment. Eur Heart J 2018;39:2618–24.

2. Dweck MR, Jenkins WS, Vesey AT, et al. 18f-sodium fluoride uptake is a marker of active calcification and disease progression in patients with aortic stenosis. Circ Cardiovasc Imaging 2014;7:371–8.

3. Pawade TA, Cartlidge TR, Jenkins WS, et al. Optimization and reproducibility of aortic valve 18f-fluoride positron emission tomography in patients with aortic stenosis. Circ Cardiovasc Imaging 2016;9.

4. Pawade T, Clavel MA, Tribouilloy C, et al. Computed tomography aortic valve calcium scoring in patients with aortic stenosis. Circ Cardiovasc Imaging 2018;11:e007146.

5. Simard L, Cote N, Dagenais F, et al. Sex-related discordance between aortic valve calcification and hemodynamic severity of aortic stenosis: is valvular fibrosis the explanation? Circ Res 2017;120:681–91.

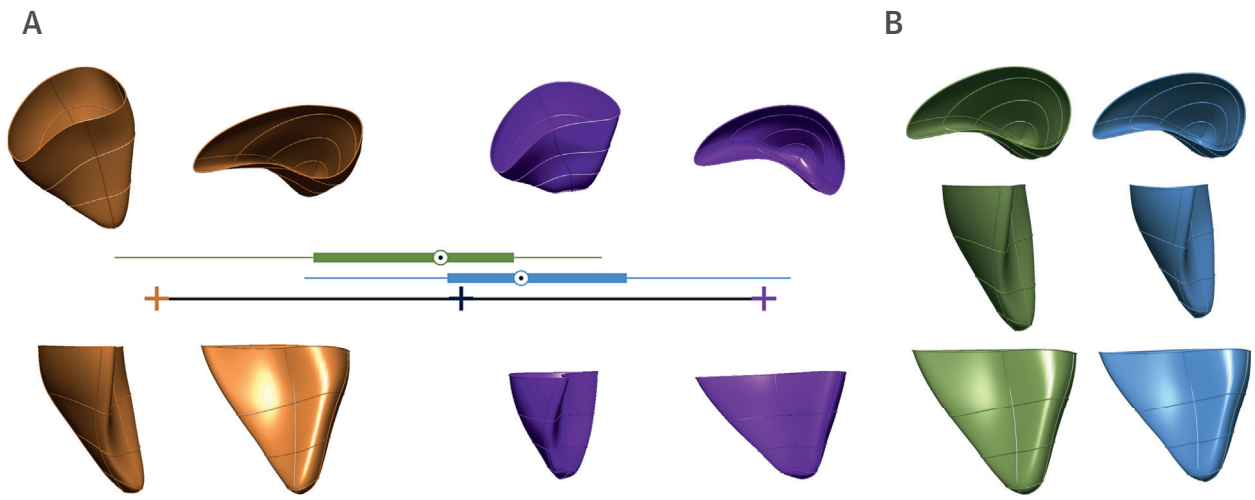
Multimodality Imaging Demonstrates Reduced Right-Ventricular Function Independent of Pulmonary Physiology in Moderately Preterm-Born Adults

Preterm-born individuals have altered right-ventricular (RV) structure and function in young adulthood (1). To what extent the pulmonary circulation impacts these findings remains largely unknown. However, unlike RV changes that are apparent across gestational ages of prematurity, acute and chronic pulmonary complications are primarily isolated to more extreme cases below 28 weeks' gestation (2). Given that more than 80% of preterm births are moderately preterm—between 32 and 36 weeks' gestation—understanding the extent of RV changes in this subpopulation are of increased public health interest. Accordingly, we used a detailed multimodal assessment to determine whether reductions in RV function are out of proportion to changes in pulmonary physiology in moderately preterm-born young adults.

We studied 101 normotensive participants aged 18 to 40 years (3). Of these, 54 were born at term (39.5 ± 1.4 weeks at birth), and 47 were born preterm (32.8 ± 3.2 weeks at birth). Echocardiography and cardiac magnetic resonance (CMR) were performed to characterize RV morphology, RV function, pulmonary hemodynamics, and RV-pulmonary arterial vascular coupling, as previously described (1,4). Creation of a RV statistical atlas of CMR images was undertaken adapting previously published methods (5). The end-diastolic frames of RV short-axis cine stacks with manually contoured endocardial contours were retrieved and rebuilt into binary segmentation images. Smooth meshes were fitted to the RV blood-pool anatomy, achieving subvoxel accuracy. The RV anatomy of each subject was then described with a mesh, and principal component analysis was undertaken to identify key modes of shape variation. Spirometry lung function tests were performed to measure forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC).

Statistical analysis was performed using SPSS Version 23 (IBM, Armonk, New York). All data were normally distributed, and Student's *t*-tests were used to compare continuous variables between the preterm-born and term-born adults, with adjustment for sex when appropriate. Multivariable linear regressions were completed to assess differences between groups for RV measures adjusting for sex, height, age, FEV_1, and FVC; p values < 0.05 were considered significant.

FIGURE 1 **Unique RV Geometry**



(A) Principal component analysis coordinates for mode 1. The average across all individuals is set at coordinate 0 (**dark blue cross**). The **orange cross** and **orange** RV mesh represent −3SD, whereas the **purple cross** and **purple** RV mesh represent +3SD. Box plots represent the median mode 1 coordinates for each group (**blue** = preterm-born, and **green** = term-born). **(B)** Statistical average shape of the right ventricle of term-born **(green)** and preterm-born **(blue)** young adults.

RV end-diastolic areas and volumes were lower in preterm-born individuals ($p \leq 0.001$). Measurements of RV function by echocardiography, including RV fractional area of change (FAC) and tricuspid annular plane systolic excursion (TAPSE), were lower in preterm-born compared with term-born adults (FAC: 38.91 ± 7.37% vs. 43.83 ± 7.01%; $p = 0.008$ and TAPSE: 1.84 ± 0.25 cm vs. 2.25 ± 0.35 cm; $p < 0.001$). Despite lower pulmonary artery acceleration times (PAATs) in those born preterm (141.1 ± 15.1 ms vs. 159.2 ± 21.6 ms; $p < 0.001$), indicating increased pulmonary vascular resistance, the RV remained coupled to its pulmonary circulation (TAPSE/PAAT: 0.13 ± 0.02 ms vs. 0.14 ± 0.03 m/s; $p = 0.153$). RV CMR revealed higher mass (21.20 ± 3.08 g/m^2 vs. 18.98 ± 2.32 g/m^2; $p < 0.001$) and lower ejection fraction (54.90 ± 5.17% vs. 57.48 ± 4.39%; $p = 0.008$) in those born preterm. Lower RV FAC, TAPSE, ejection fraction, and higher mass in preterm-born participants remained significant in multivariable regressions adjusting for pulmonary-function parameters ($p < 0.05$). Principal component analysis of the RV statistical atlas defined 5 anatomic modes of geometric variation within the study population, with mode 1 accounting for 25.3% of the variance. Preterm and term cohorts showed significant differences ($p < 0.001$) in mode 1, representing a smaller and shorter RV cavity in the preterm group, with no differences in other modes (Figure 1).

Although moderately preterm-born young adults exhibited structural and functional RV alterations, the RV remained coupled to the pulmonary vasculature. We speculate that uncoupling will be more likely to occur sooner in preterm-born individuals and may be gestational-age dependent. Our findings are of immediate public health concern and should be taken into clinical consideration, including regular, long-term follow-up of individuals born preterm. Future longitudinal research is needed to better understand individual patterns of cardiac remodeling throughout adulthood. Whether perinatal or later life clinical interventions known to improve RV physiology can modify the dysfunctional trajectory remains to be determined.

Afifah Mohamed, MSc
Pablo Lamata, PhD
Wilby Williamson, MBBS, DPhil
Maryam Alsharqi, MSc
Cheryl M.J. Tan, MRes
Holger Burchert, MSc
Odaro J. Huckstep, DPhil
Katie Suriano, PhD
Jane M. Francis, DCR(R), DNM
Joana Leal Pelado, BSc
Cristiana Monteiro, BSc
Stefan Neubauer, MD
Philip T. Levy, MD
Paul Leeson, PhD
Adam J. Lewandowski, DPhil*

*Oxford Cardiovascular Clinical Research Facility
Division of Cardiovascular Medicine
Radcliffe Department of Medicine
University of Oxford, John Radcliffe Hospital
Oxford OX39DU
United Kingdom
E-mail: adam.lewandowski@cardiov.ox.ac.uk

https://doi.org/10.1016/j.jcmg.2020.03.016

Please note: This study was funded by a British Heart Foundation (BHF) project grant (PG/13/58/30397), the Oxford BHF Centre for Research Excellence, and National Institute for Health Research (NIHR) Oxford Biomedical Research Centre. Afifah Mohamed is funded by a Malaysian Government Scholarship and the National University of Malaysia. Dr. Lewandowski is funded by a British Heart Foundation Intermediate Research Fellowship (FS/18/3/33292). Dr. Lamata is funded by a Wellcome Trust Senior Research Fellowship (209450/Z/17/Z). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Ethical approval for the study was granted by the South Central Berkshire Research Ethics Committee in the UK (14/SC/0275). Study registration was completed via www.clinicaltrials.gov (NCT02103231).
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Imaging* author instructions page.

REFERENCES

1. Lewandowski AJ, Bradlow WM, Augustine D, et al. Right ventricular systolic dysfunction in young adults born preterm. Circulation 2013;128:713–20.

2. Thebaud B, Goss KN, Laughon M, et al. Bronchopulmonary dysplasia. Nat Rev Dis Primers 2019;5:78.

3. Huckstep OJ, Williamson W, Telles F, et al. Physiological stress elicits impaired left ventricular function in preterm-born adults. J Am Coll Cardiol 2018;71:1347–56.

4. Levy PT, El Khuffash A, Woo KV, Hauck A, Hamvas A, Singh GK. A novel noninvasive index to characterize right ventricle pulmonary arterial vascular coupling in children. J Am Coll Cardiol Img 2019;12:761.

5. Lewandowski AJ, Augustine D, Lamata P, et al. Preterm heart in adult life: cardiovascular magnetic resonance reveals distinct differences in left ventricular mass, geometry, and function. Circulation 2013;127:197–206.

Impact of Agreement and Discrepancies in Interpretations of Stress Echocardiography

Insights From the PROMISE Trial

Stress echocardiography (SE) assesses for flow-limiting coronary artery disease (CAD) and requires expertise to interpret. Clinical trials use core laboratories to ensure that interpretations are accurate and reproducible. We determined agreement between site and core laboratory SE interpretations in the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) (1), identified factors associated with disagreement, and examined the relationship of disagreement with outcomes.

PROMISE randomized 10,003 symptomatic patients without known CAD to computed tomographic angiography or functional testing. For patients who had interpretable SE as their initial test (n = 986), we compared local and blinded core laboratory interpretations for rest and stress regional wall motion abnormalities (WMAs). Outcomes were referral for second noninvasive test or catheterization; the PROMISE primary endpoint of all-cause mortality, myocardial infarction (MI), and hospitalization for unstable angina and cardiovascular (CV) death or MI. Disagreement rates between site and core laboratory interpretations and kappa statistics were calculated overall and for resting and stress interpretations. Multivariable logistic regression (adjusted for characterization of chest pain, image quality, electrocardiographic stress changes, Atherosclerotic Cardiovascular Disease score [2013] [2], test conclusiveness, and site accreditation) identified associations between concordance and subsequent care. Analysis was performed using SAS 9.4 (SAS Institute, Cary, North Carolina).

The study protocol was approved by an institutional review board at each coordinating center and at each enrolling site in North America. Participants provided written informed consent; mean age was 59.6 ± 8.1 years; 51.8% were women. Most SEs (89.9%) used exercise stress, and 23.2% used a contrast agent. Sites reported limited or nondiagnostic studies in 103 (10.7%).

Overall, 122 of 986 (12.4%) studies had discordant interpretations (kappa 0.33; 95% confidence interval [CI]: 0.24 to 0.42). Of the 99 discordant resting studies, 18 were abnormal by site, whereas 81 were abnormal by core laboratory. Of the 66 discordant stress studies, 51 were abnormal by site and 15 by core laboratory (**Table 1**). Sites noted regional WMAs in 20 of 986 (2.0%) resting studies compared with 28 of 986 (2.8%) by core laboratory.

Only site-reported stress-related electrocardiographic changes differed (p = 0.01) between patients with concordant and discordant findings. A second noninvasive test was requested in 72, of whom 51 had concordant normal SE interpretations (7% of concordant normals), 10 were concordant abnormal (28% of concordant abnormals), and 11 had discordant interpretations (11% of discordants). There was no difference between concordant normal and discordant SE groups (odds ratio [OR]: 1.58; 95% CI: 0.78 to 3.20), whereas concordant abnormals received testing at a higher rate than normals (OR: 5.07; 95% CI: 2.21 to 11.64). Catheterization (total N = 45) was more frequent in the discordant group than concordant normals (19.8% vs. 1.0%; OR: 26.7; 95% CI: 10.3 to 68.8) and in the concordant abnormals than normals (50.0% vs. 1.0%; OR: 97.7; 95% CI: 32.3 to 295.7). Among the 20