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Physiological Stress Elicits Impaired Left Ventricular Function in Preterm-Born Adults

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ABSTRACT

BACKGROUND Experimental and clinical studies show that prematurity leads to altered left ventricular (LV) structure and function with preserved resting LV ejection fraction (EF). Large-scale epidemiological data now links prematurity to increased early heart failure risk.

OBJECTIVES The authors performed echocardiographic imaging at prescribed exercise intensities to determine whether preterm-born adults have impaired LV functional response to physical exercise.

METHODS We recruited 101 normotensive young adults born preterm (n = 47; mean gestational age 32.8 ± 3.2 weeks) and term (n = 54) for detailed cardiovascular phenotyping. Full clinical resting and exercise stress echocardiograms were performed, with apical 4-chamber views collected while exercising at 40%, 60%, and 80% of peak exercise capacity, determined by maximal cardiopulmonary exercise testing.

RESULTS Preterm-born individuals had greater LV mass (p = 0.015) with lower peak systolic longitudinal strain (p = 0.038) and similar EF to term-born control subjects at rest (p = 0.62). However, by 60% exercise intensity, EF was 6.7% lower in preterm subjects (71.9 ± 8.7% vs 78.6 ± 5.4%; p = 0.004) and further declined to 7.3% below the term-born group at 80% exercise intensity (69.8 ± 6.4% vs 77.1 ± 6.3%; p = 0.004). Submaximal cardiac output reserve was 56% lower in preterm-born subjects versus term-born control subjects at 40% of peak exercise capacity (729 ± 1,162 ml/min/m^2 vs. 1,669 ± 937 ml/min/m^2; p = 0.021). LV length and resting peak systolic longitudinal strain predicted EF increase from rest to 60% exercise intensity in the preterm group (r = 0.68, p = 0.009 and r = 0.56, p = 0.031, respectively).

CONCLUSIONS Preterm-born young adults had impaired LV response to physiological stress when subjected to physical exercise, which suggested a reduced myocardial functional reserve that might help explain their increased risk of early heart failure. (Young Adult Cardiovascular Health sTudy [YACHT]; NCT02103231) (J Am Coll Cardiol 2018;71:1347–56)

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ABBREVIATIONS AND ACRONYMS

BSA = body surface area

CI = cardiac index

CMR = cardiovascular magnetic resonance

COR = cardiac output reserve

CPET = cardiopulmonary exercise test

EDV = end-diastolic volume

EF = ejection fraction

ESV = end-systolic volume

LV = left ventricular

Preterm birth rates range from 5% to 18% worldwide (1). The population of adults born preterm has risen sharply in recent decades because modern perinatal care often achieves 95% survival rates (2). Multiple studies have described a distinct preterm cardiovascular phenotype, including altered cardiac structure and function (3–5) and impaired exercise capacity (6), as well as increased risk for hypertensive disorders and stroke (7). However, as the modern cohorts of preterm-born survivors now approach middle age, the long-term epidemiological consequences of prematurity remain largely unknown. A recently reported study of >2.6 million individuals born between 1987 and 2012 identified preterm birth as a novel risk factor for incident heart failure in childhood and adolescence (8), emphasizing the importance of research into the underlying mechanisms responsible for increased risk in this population.

Acute cardiac insufficiency is uncommon in young adults (9) and a previous cardiovascular magnetic resonance (CMR) study confirmed that preterm-born young adults maintain a fully preserved resting left ventricular (LV) ejection fraction (EF) despite significant functional and anatomical LV remodeling (4). Stress echocardiography is a powerful tool used to unmask underlying cardiac dysfunction that is well-compensated at rest by assessing the cardiac response to physiological stressors such as exercise (10). Because those born preterm have well compensated resting LV function despite significant structural modifications and moderate changes in myocardial deformation at rest (4), investigating cardiac functional responses to physiological stress is essential to more fully understand the impact of being born preterm on LV function (10). We therefore used 2-dimensional echocardiography to test the hypothesis that the LV of preterm-born young adults has reduced myocardial reserve that results in functional impairment in response to the physiological stressor of physical exercise.

SEE PAGE 1357

METHODS

STUDY DESIGN. We completed YACHT (Young Adult Cardiovascular Health sTudy), an observational, case–control study to investigate cardiovascular structure, function, and physiological stress response in preterm and term-born young adults. Participants age 18 to 40 years completed a detailed multimodal set of study measures, including 24-h ambulatory blood pressure monitoring, cardiopulmonary exercise testing, and cardiac imaging. Ethical approval for YACHT was granted by the South Central Berkshire Research Ethics Committee (14/SC/0275). Study registration was completed via ClinicalTrials.gov (NCT02103231).

STUDY POPULATION. A total of 149 participants were recruited into YACHT through open recruitment in the local Oxford community using posters, mailed invitations from the John Radcliffe Hospital birth registries, word of mouth, patient invitation through the John Radcliffe Hospital Specialist Hypertension Clinic, and invitations to previous study participants who had indicated interest in future study participation. In total, 48 participants were excluded from this analysis to prevent confounding: 32 diagnosed hypertensive participants recruited through the John Radcliffe Hospital Hypertension Clinic, and 16 additional participants with awake ambulatory blood pressure measures in the hypertensive range. Therefore, 101 nonhypertensive young adult participants (47 preterm-born, 54 term-born) who met the following criteria were recruited and included in this analysis: 1) aged 18 to 40 years; 2) body mass index <40 kg/m^2; 3) awake ambulatory blood pressure <135/85 mm Hg; and 4) verified birth history (preterm or term-born). Exclusion criteria included: 1) unwilling or unable to give informed consent; 2) pregnant or lactating; 3) history of acute cardiac or cerebrovascular event; 4) diagnosis with a disease or disorder that could influence study participation or outcome measures; 5) hypertension diagnosis; and 6) treatment with antihypertensive medication. Participants were assessed with a wide range of measures to achieve deep cardiovascular phenotyping, including clinic and 24-h ambulatory blood pressure, biochemistry, anthropometry, cardiopulmonary exercise testing, vascular stiffness, multiorgan magnetic resonance imaging, as well as a full clinical resting echocardiogram and stress echocardiogram using apical 4-chamber views while exercising at 40%, 60%, and 80% of peak exercise capacity. Cohort characteristics are provided in **Table 1**.

STUDY VISIT. Overview. Participants were instructed to fast overnight for 12 h but encouraged to drink water to remain hydrated before attending a study visit at the University of Oxford Centre for Clinical Magnetic Resonance Research and Oxford Cardiovascular Clinical Research Facility in the John Radcliffe Hospital (Oxford, United Kingdom). All measurements were completed by trained study investigators.

Anthropometry. Using an integrated height and weight measurement station (Seca, Birmingham,