Cambridge City Publishers

Case Reports in Clinical Cardiology Journal

Case Report | Vol 5 Iss 4

Coronary Microvascular Dysfunction and Exercise-Induced ST Changes Following Trauma in a Young Adult Born Preterm: A Case Report

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Received: August 21, 2025; **Accepted:** September 06, 2025; **Published:** September 15, 2025

Abstract

Background: Moderate to extreme preterm birth affects nearly 3% of all live births in the United States and is associated with increased lifetime cardiovascular risk. However, the mechanisms are poorly understood.

Case Summary: A 27-year-old male with history of extreme preterm birth (27 weeks gestation) presented with acute chest pain, dyspnea and exercise intolerance following trauma. When symptoms persisted, exercise testing revealed focal ST depression, prompting coronary evaluation. Left heart catheterization demonstrated decreased coronary flow reserve and adenosine stress MRI demonstrated borderline coronary perfusion reserve, leading to a diagnosis of coronary microvascular dysfunction. Symptoms resolved with isosorbide mononitrate.

Discussion: Extreme preterm birth impairs systemic microvascular development. Impact on the coronary arteries has never been documented but is likely. Coronary microvascular dysfunction should be considered in the differential of chest pain or dyspnea in young adults born preterm, even in the absence of classic risk factors.

Keywords: Coronary microvascular dysfunction; Exercise; Prematurity; Young adults

Introduction

Moderate to extreme preterm birth (≤32 weeks gestation) affects nearly 3% of all live births in the United States. Improved neonatal care practices have lowered the age of viability from ~32 weeks in the 1970s down to 22-24 weeks currently, with most extremely preterm infants now surviving to adulthood. There is a growing awareness of potential cardiac comorbidities across the lifespan including increased risk for heart failure, ischemic heart disease, and systemic and pulmonary hypertension [1-5]. Whether abnormal cardiac development contributes to increased risk for coronary dysfunction after preterm birth is unknown.

Case Presentation

A 27-year-old male presented to the emergency department (ED) following a motor vehicle accident (MVA). His head and chest impacted with the steering wheel without loss of consciousness. Initial ED complaints included nausea, dizziness, and headache with concern for concussion. However, after leaving the ED, the patient experienced sharp ripping and squeezing chest pain lasting <2 minutes. The next day he experienced acute onset dyspnea, chest pain, and erratic heart rate (between 120-150 bpm) occurring with very minimal exertion (walking). His heart rate would slowly return to baseline (60-70 bpm) and symptoms resolve upon standing still or sitting. These symptoms persisted for the next 17 months, significantly interfering with daily activities and quality of life.

The patient was born extremely preterm (gestational age 27 weeks, birth weight 1 lb. 6 oz.). His 155-day Neonatal ICU course was complicated by bronchopulmonary dysplasia with pulmonary hypertension (PH) requiring supplemental oxygen until 19 months of age. At 18 months, his family relocated from altitude to sea level. His echocardiogram subsequently showed recovery of PH and right ventricular (RV) dysfunction (from RV systolic pressure 40-50 mmHg, mild RV dilation, and mild RV hypertrophy to normal RV pressures and size). Growing up, he was very active, swimming long distances and playing soccer without cardiopulmonary symptoms. Prior to the MVA, he was running 1-2 miles multiple days per week (10-12 min/mile pace). Post-MVA, he was unable to walk more than 10-20 yards or pick up his backpack without debilitating symptoms.
Clinical management involved a multi-faceted approach with both invasive and non-invasive testing performed over the course of 20 months, summarized in Table 1.

Initially, the patient was diagnosed with inappropriate sinus tachycardia (IST) due to chest pain, heart palpitations, and tachycardia (>130 bpm) which persisted for nearly 4 months following his MVA. Postural orthostatic tachycardia syndrome (POTS) was also considered along with concerns for autonomic dysreflexia. Beta blockers, calcium-channel blockers, and ivabradine were trialed to blunt symptoms, but all pharmaceutical interventions failed due to worsening fatigue, lightheadedness, and persistent exertional tachycardia.

The patient was referred to the Heart and Lung Center for Adults Born Preterm at UT Southwestern Medical Center (Dallas, TX) for further testing. Stress ECHO demonstrated nonspecific ST changes, but no wall motion abnormalities or exercise-induced PH. Cardiopulmonary exercise testing (CPEX) at the Institute for Exercise and Environmental Medicine (Dallas, TX) identified a high heart rate at rest and during submaximal exercise with mildly blunted stroke volume reserve, consistent with history of prematurity. Cardiac output increased appropriately but was dependent on heart rate. Reproducible focal ST depression in V3 was observed during submaximal and maximal exercise. Normal HR recovery during exercise suggested the absence of autonomic dysfunction (i.e., IST and POTS).

Based on reproducible ST changes on CPEX, a coronary CT angiography (CTA) was obtained to evaluate for anomalous origin of coronary arteries (AOCA) but was normal. Left/right heart catheterization (L/RHC) with IV fluid challenge was performed to rule out PH, LV diastolic filling impairment, or myocardial bridging, demonstrating angiographically normal coronary arteries and no evidence of PH or LV diastolic impairment (Table 2). Dobutamine/adenosine stress LHC demonstrated no myocardial bridging. Mild, non-obstructive coronary artery disease was observed, with left anterior descending fractional flow reserve (LAD FFR) of 0.94 at rest, and 0.81 at maximal hyperemia with IV adenosine (normal 0.94 to 1.0). Cardiac stress MRI with adenosine was performed to evaluate for coronary microvascular dysfunction, demonstrating reduced global resting myocardial blood flow of 1.7 ml-min-g (normal >2 ml-min-g) and low normal myocardial perfusion reserve of 2.6 ml-min-g at peak stress (normal >2.5 ml-min-g), suggestive of coronary microvascular dysfunction.

The patient was prescribed isosorbide mononitrate, 30mg once daily, and reported complete resolution of exertional dyspnea, chest pain, and tachycardia. He was able to resume exercise training. Six months following initiation of isosorbide mononitrate daily, the patient remains symptom free. Repeat CPEX performed after 3 months on isosorbide mononitrate demonstrates improve exercise tolerance and resolution of exertional angina (Figure 1).

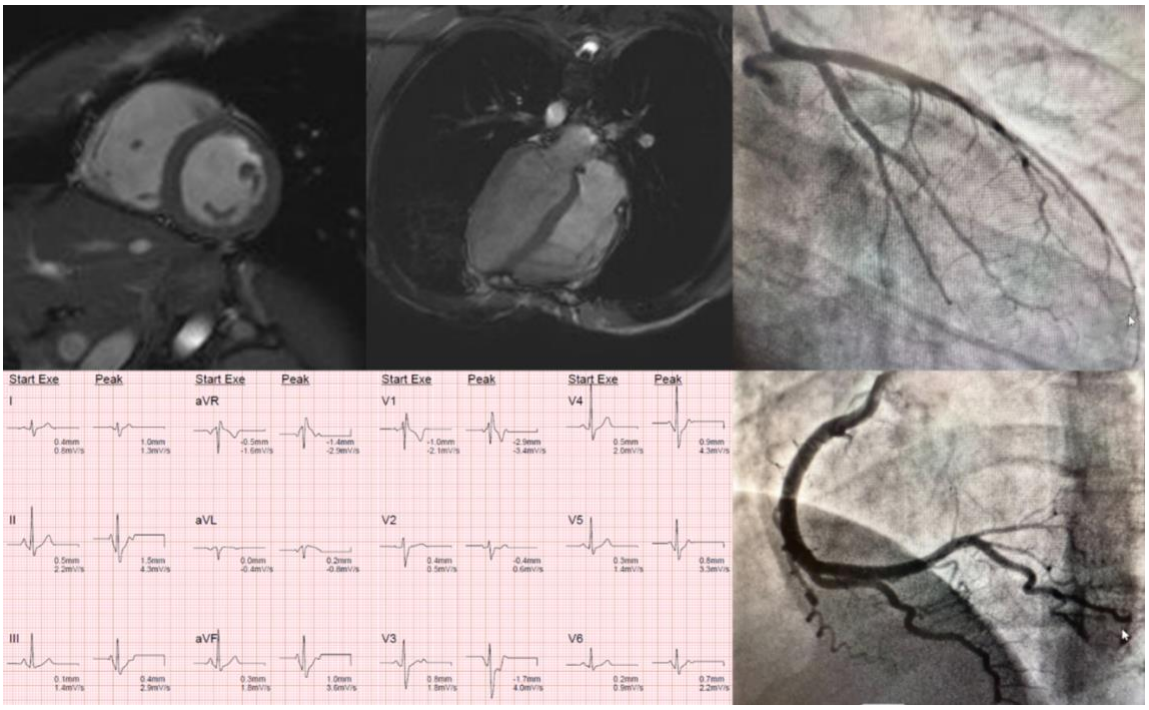

Figure 1: Cardiac MRI demonstrated a small heart with normal function in the absence of structural abnormalities (short axis top left, 4 chamber center; LVEF 63% with LVEDVi 62 ml/m^2; RVEF 57% with RVEDVi 79 ml/m^2; septal wall thickness 7 mm; LV mass index 52 g/m^2; no late gadolinium enhancement; no pericardial effusion; no wall motion abnormalities). Exercise EKG demonstrated focal ST depressions in V3, which resolved post-exercise (bottom left). Coronary angiogram demonstrated mild diffuse nonobstructive coronary artery disease, with a reduced post-adenosine fractional flow reserve of 0.81 (right top/bottom). A diagnosis of coronary microvascular disease in an ex-27 week preterm-born young adult was made, with improvement in symptoms with isosorbide mononitrate.

Table 1: Patient Timeline of Clinical Management.

Time from symptom onset	Test Performed	Associated Differential Diagnosis	Notable Findings
0 mo.	12-Lead ECG	IST, POTS, Autonomic dysreflexia Arrhythmia, Accessory pathway, and SA nodal dysfunction	Resting HR 85 bpm, normal sinus rhythm, right bundle branch; short PR interval
1 mo.	Treadmill Cardiac Stress Test	-----	Resting HR 89 bpm; normal sinus rhythm; right bundle branch, accelerated HR response to exercise
4 mo.	Transthoracic ECHO	HFpEF, PH, Pericardial effusion	Small LV and RV; normal LV and RV function, no pericardial effusion
6 mo.	Cardiac MRI w/wo contrast	HFpEF, PH, Pericardial effusion	LVEF 63% with LVEDVi 62ml/m^2; RVEF 57% with RVEDVi 79 ml/m^2; septal wall thickness 7 mm; LV mass index 52g/m^2; no late gadolinium enhancement; no pericardial effusion; no wall motion abnormalities
8 mo.	14-Day Holter Monitor	IST, POTS, Autonomic dysreflexia Arrythmia, accessory pathway, and SA nodal dysfunction	Min HR 38 bpm, max HR 161 bpm, average HR 77 bpm; sinus rhythm, rare isolated supraventricular beats (<1%)
12 mo.	Stress ECHO	Impaired stroke volume reserve; Exercise induced PH; Exercise induced wall motion abnormalities	No wall motion abnormalities; no indication of exercise induced PH.
12 mo.	CPEX	Impaired stroke volume reserve; Arrhythmia; Noncardiac etiologies of dyspnea	Reduced $\dot{V}O_{2max}$ (78% predicted); Focal ST depression in V3 observed during submaximal and maximal exercise. Normal HR recovery after exercise.
13 mo.	Coronary CT Angiography	Anomalous origin of coronary arteries (AOAC), myocardial bridge	Coronaries arise normally with no ostial narrowing; small coronaries but no significant coronary atherosclerosis; no myocardial bridge
14 mo.	R/L Heart Catheterization with IV fluid challenge	HFpEF, Diastolic impairment; Myocardial bridging; PH	Normal coronary arteries, no evidence of myocardial bridge. No PH.
17 mo.	Invasive microvascular dysfunction study with adenosine and IV dobutamine challenge	Myocardial bridging; Coronary microvascular dysfunction	Diffuse, mild non-obstructive coronary artery disease in all vessels. Post-adenosine fractional flow reserve (FFR) 0.81.
17 mo.	Cardiac Stress MRI with myocardial flow quantification	Coronary microvascular dysfunction	Low global myocardial blood flow (1.7 ml-min-g) and low myocardial perfusion reserve (2.6 ml-min-g) with stress
20 mo.	CPEX	Coronary microvascular dysfunction, treated with isosorbide mononitrate	Normal $\dot{V}O_{2max}$ (97% predicted);

Abbreviations: bpm: beats per minute; CPEX: cardiopulmonary exercise test; ECG: electrocardiogram; ECHO: echocardiogram; HFpEF: heart failure with preserved ejection fraction; HR: heart rate; IST: inappropriate sinus tachycardia; LVEDVi: left ventricular end-diastolic volume indexed to body surface area; LVEF: left ventricular ejection fraction; PH: pulmonary hypertension; POTS: postural orthostatic tachycardia syndrome; RVEDVi: right ventricular enddiastolic volume indexed to body surface area; RVEF: right ventricular ejection fraction; SA: sinoatrial; V̇ O2max: maximal oxygen consumption.

Table 2: Hemodynamics from Left and Right Heart Catheterization.

	Baseline	**Post-Fluid Challenge**
RA (mmHg)	6	5
RV (mmHg)	25-Jul	35/4
PAP (mmHg)	22/13	29/13
mPAP (mmHg)	18	21
PCWP (mmHg)	11	17
LVEDP (mmHg)	17	17
PVR (dynes)	152	80
SVR (dynes)	1621	1643
CO (Fick; l/min)		5.12
CI (Fick; l/min/m^2)		3.44
CO (Thermo; l/min)		5.53
CI (Thermo; l/min/m^2)		3.72
	Baseline	**Post-IV adenosine**
LAD FFR	0.94	0.81 (maximal hyperemia)

Abbreviation: CI: cardiac index; CO: cardiac output; FFR: fractional flow reserve; LAD: left anterior descending; LVEDP: left ventricular end-diastolic pressure; PAP: pulmonary arterial pressure; mPAP; mean pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; RA: right atrium; RV: right ventricle; SVR: systemic vascular resistance.

Discussion

To our knowledge, coronary microvascular dysfunction in adults born preterm has not been described. We acknowledge that trauma, as present in this case, is considered a risk factor for developing coronary microvascular dysfunction and based on the timeline likely contributed. However, based on the underlying pathophysiology of impaired cardiac and coronary development in preterm birth, we propose that this patient had a reduced myocardial reserve that made him significantly more susceptible. Under normal in utero conditions, fetal cardiac growth transitions from hyperplastic growth to hypertrophic growth at 32-36 weeks gestation. Preterm birth at earlier gestations forces premature cardiomyocyte cell cycle arrest, leading to a reduced cardiomyocyte endowment for the lifetime [5,6]. Structurally, this leads to smaller cardiac chamber sizes, which is one of the most consistent findings across cohort studies. Gross cardiac hypertrophy is variably reported, and LV fibrosis may be present [4].

Smaller stroke volume reserve results in increased chronotropic dependence in this population, and likely accounts for this patient's poor tolerance of rate-controlling medications. Currently, the impacts of extreme preterm birth on coronary development and maturation are very poorly understood. Coronary microvascular rarefaction may play a role, as microvascular rarefaction has been reported in peripheral systemic, pulmonary vascular, and retinal microvascular beds in both children and adults born preterm [7,8]. Alternatively, impaired flow mediated dilation and endothelial dysfunction may contribute [7,9]. Regardless, impaired coronary microvascular function is now recognized as a risk factor for major adverse cardiovascular events and warrants further risk factor modification and treatment [10].

As we collectively learn how the extremely preterm heart ages, a high index of suspicion and understanding of the impact of developmental pathology on cardiac aging is critical. Impaired coronary development and function may accompany the impaired development of the myocardium associated with extreme preterm birth. Thus, coronary microvascular dysfunction should be considered in the differential of chest pain or dyspnea in young adults born preterm, even in the absence of classic risk factors or clinical findings on diagnostic workup. Further, due to chronotropic dependence, caution is advised with the diagnosis of "inappropriate sinus tachycardia" and a thorough evaluation of potential physiologic contributors to sinus tachycardia is recommended. If necessary, IST can be excluded by demonstrating normal heart rate slowing at night. The preterm heart should be considered "high risk" for the lifetime due to higher rates of heart failure, ischemic heart disease, systemic and pulmonary hypertension, and cardiorenal disease.

Acknowledgements and Disclosures

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors have no conflicts of interest to disclose.

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