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HEART FAILURE AND CARDIOMYOPATHIES

CLINICAL CASE

Advanced Biventricular Heart Failure Precipitated by Large Territory Stroke in a Patient With Carvajal Syndrome

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ABSTRACT

Stroke-heart syndrome describes the neurocardiogenic mechanisms that lead to the development of poststroke cardiovascular complications. We describe a 25-year-old man with Carvajal syndrome who developed advanced biventricular heart failure 2 months after a large territory ischemic stroke. His condition was managed with inotropic support initially and required biventricular assist devices as a bridge to possible heart transplantation. This case highlights the increased risk of cardiovascular complications after stroke through dysregulation of the brain-heart axis. Poststroke neuron death leads to systemic and local inflammation through noradrenaline, interleukin-1, and other proinflammatory cells. This cumulatively leads to endothelial dysfunction and cardiomyocyte fibrosis/necrosis within the heart. (JACC Case Rep. 2025;30:103191) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

This case is of a 25-year-old man with Carvajal syndrome, a rare cardio-cutaneous syndrome known to cause dilated cardiomyopathy (DCM). He was followed up closely in our Heart Function Clinic and was initiated and maintained on guideline-directed medical therapy (GDMT) with sacubitril-valsartan 100 mg twice daily, carvedilol 18.75 mg twice daily, eplerenone 25 mg daily, and dapagliflozin 10 mg daily with NYHA functional class I symptoms.

He presented to the hospital a few months before his scheduled follow-up with significant right-sided upper and lower limb deficits. He was diagnosed with an acute occlusion of the left M1 and proximal left A1 segment (**Figure 1**) and underwent a successful thrombectomy (Thrombolysis In Cerebral Infarction scale Grade 2b). There was evidence of a large apical thrombus on transthoracic echocardiography (TTE), which was the most likely etiology for his stroke. He was anticoagulated with heparin before being transitioned to therapeutic warfarin and transferred to a

LEARNING OBJECTIVES

- To understand the proposed pathophysiology and burden of SHS
- To recognize the role of advanced multidisciplinary heart failure care, including using RVADs and LVADs to address advanced RV and LV dysfunction, respectively
- To acknowledge the need for further collaborative preclinical and clinical work between neurology and cardiology to develop preventative therapies to reduce poststroke cardiovascular complications

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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 Author Center.

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ABBREVIATIONS AND ACRONYMS

DCM = dilated cardiomyopathy

ECG = electrocardiogram

GDMT = guideline-directed medical therapy

IL = interleukin

LV = left ventricle

LVAD = left ventricular assist device

LVEF = left ventricular ejection fraction

RV = right ventricle

RVAD = right ventricular assist device

SHS = stroke-heart syndrome

TTE = transthoracic echocardiography

rehabilitation hospital. He was discharged home in stable condition after rehabilitation.

Our patient then represented to care shortly after his discharge (2 months after the initial stroke) with significant shortness of breath and worsening orthopnea while having significant diarrhea at home. Physical examination revealed elevated jugular venous pulse at the angle of the jaw and reduced air entry to his bases bilaterally. He had minimal peripheral edema. He was admitted to the cardiology unit to facilitate diuresis and for consideration of advanced therapies.

PAST MEDICAL HISTORY

The patient had Carvajal syndrome secondary to a mutation (c.1865T>C leading to substitution of Leucine by Proline at amino acid 622) in the spectrin repeat 6 domain of the *desmoplakin* gene. His manifestations of Carvajal syndrome included arrhythmogenic dilated cardiomyopathy, palmoplantar keratoderma, woolly hair, and tooth agenesis. He had never been assessed formally for heart transplantation because he was clinically asymptomatic on GDMT.

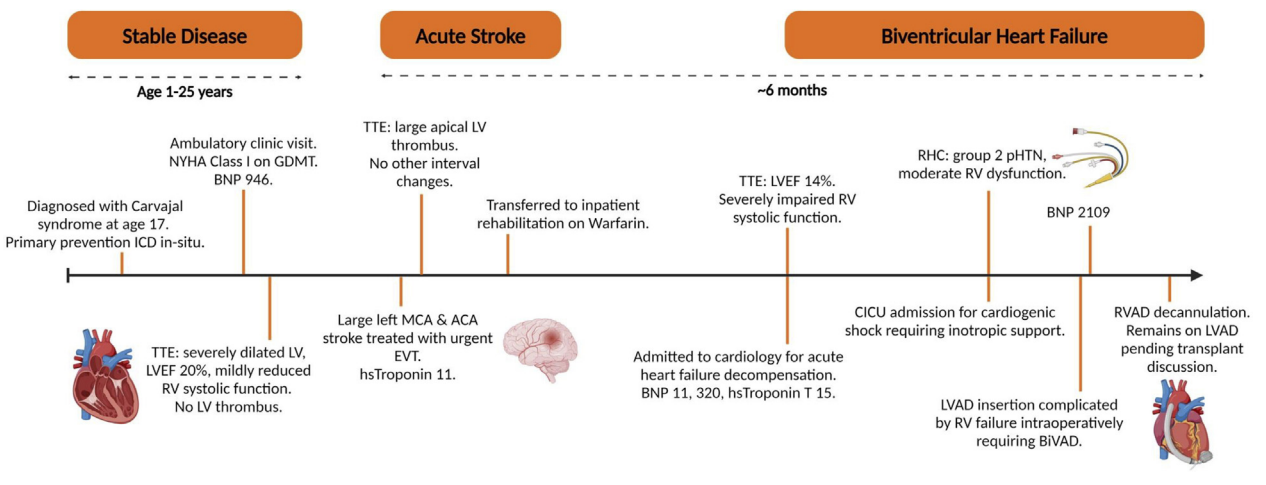
DIFFERENTIAL DIAGNOSIS

The trigger for his significant heart failure decompensation was not clear. The differential diagnosis included a possible systemic infection (considerable diarrhea before presentation), acute valvular dysfunction, arrhythmia-related, increased salt intake/under-diuresis at home, or likely due to his recent ischemic stroke.

INVESTIGATIONS

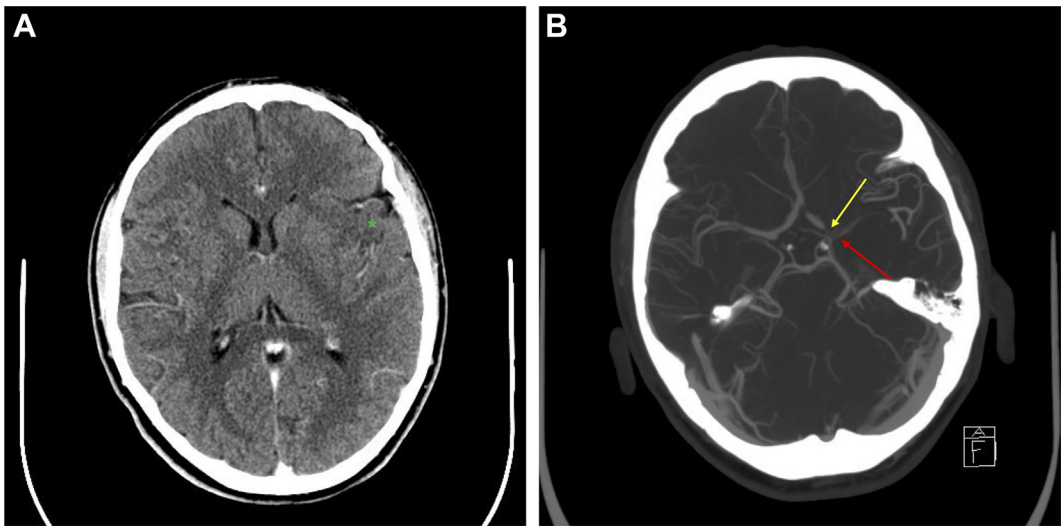
Investigations revealed a white blood cell count of 7.6 × 10⁹/L, C-reactive protein of 18.1 mg/L, hemoglobin of 149 g/L, and an estimated glomerular filtration rate of 91 mL/min. Baseline electrocardiogram (ECG) (Figure 2) showed sinus rhythm, left-axis deviation, and nonspecific intraventricular conduction delay. This was similar to the ECG at the time of the stroke and subsequent heart failure admission, but both of the latter ECGs showed new evidence of left atrial enlargement (Figures 3 and 4). Baseline

VISUAL SUMMARY **Various Phases of Disease Including Stable Disease, During Acute Stroke, and During the Development and Management of Biventricular Heart Failure**



This figure was generated using BioRender software. ACA = anterior cerebral artery; BiVAD = biventricular assist device; EVT = endovascular thrombectomy; ICD = implantable cardioverter-defibrillators; LV = left ventricle; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; MCA = middle cerebral artery; RV = right ventricle; RHC = right-sided heart catheterization; RVAD = right ventricular assist device.

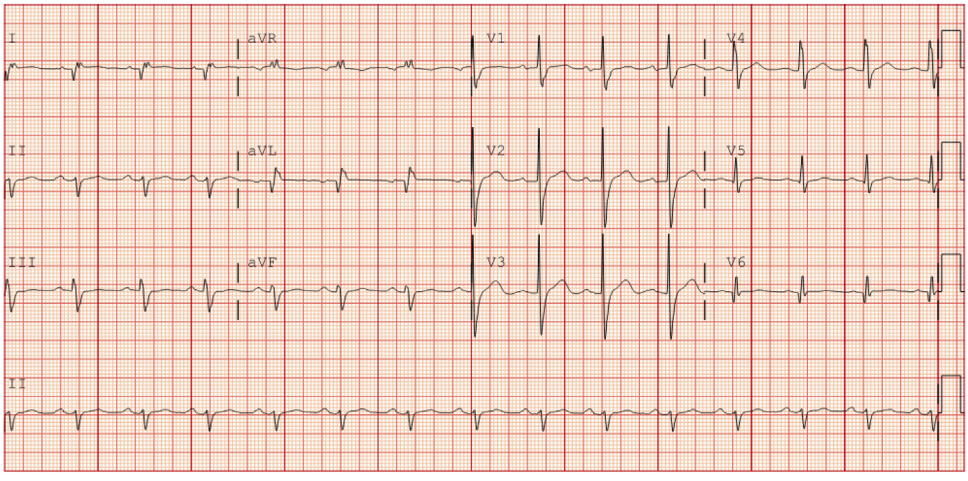
FIGURE 1 **Computed Tomography Angiography**



Computed tomography angiography of the head during initial ischemic stroke presentation. Faint region of hypoattenuation in the left frontal operculum and subtle blurring of gray-white differentiation in the subinsular ribbon (green asterixis) (A). Focal nonopacification of proximal left A1 segment (yellow arrow) and nonopacification of left M1 segment (red arrow) (B).

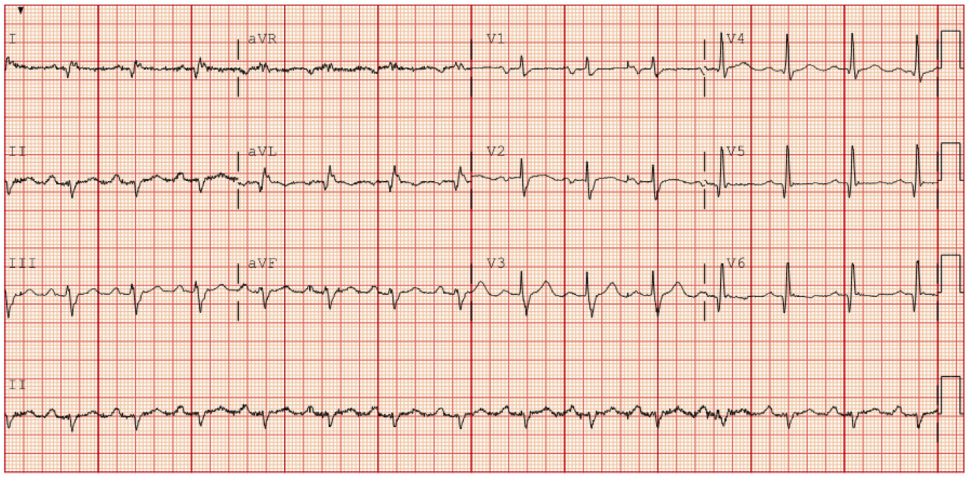
TTE in the clinic revealed a severely dilated left ventricle (LV) with eccentric hypertrophy (left ventricular ejection fraction [LVEF]: 20%) and mildly reduced right ventricle (RV) systolic function (**Figure 5**, Videos 1 to 3). TTE during the work-up of his stroke showed similar LV and RV systolic dysfunction but evidence of a new pedunculated LV thrombus (**Figure 6**, Videos 4 and 5). The TTE during his presentation for decompensated heart failure showed a severely dilated LV with severe global LV dysfunction (LVEF: 14%), a significant reduction of RV function with RV dilation, and evidence of residual thrombus (**Figure 7**). Cardiac biomarkers revealed a marked elevation of N-terminal

FIGURE 2 **Baseline ECG**



ECG showed sinus rhythm, left-axis deviation, and nonspecific intraventricular conduction delay. ECG = electrocardiogram.

FIGURE 3 ECG During Work-Up of Stroke



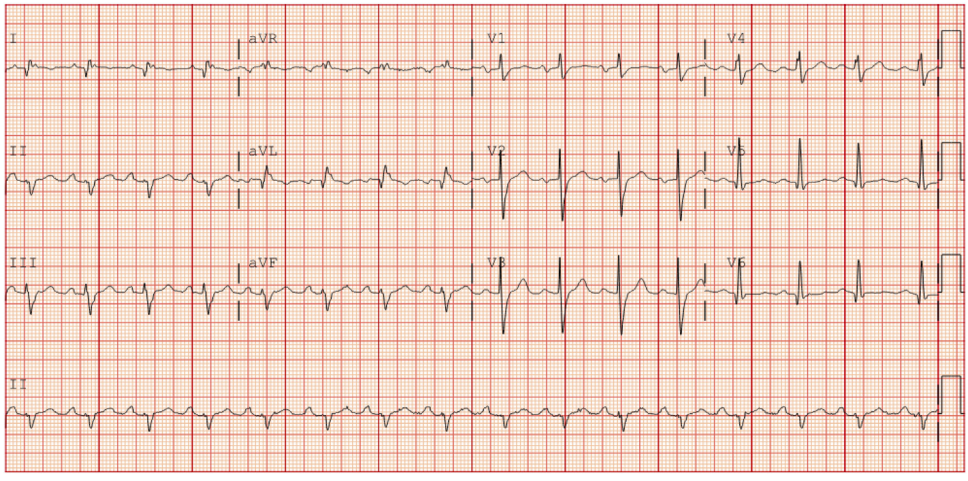
ECG showed sinus rhythm, left-axis deviation, nonspecific intraventricular conduction delay, left atrial enlargement, and QTc was 476 ms. Abbreviation as in Figure 2.

prohormone of brain natriuretic peptide to 11,320 ng/L with normal high-sensitivity troponin T (15 ng/L). Right-sided heart catheterization during his heart failure admission demonstrated group 2 pulmonary hypertension, significantly elevated right and left filling pressures, and associated low cardiac output (Table 1). Although he seemed reasonably compensated with a normal RV stroke work index and right atrial/pulmonary wedge ratio, there was evidence of moderate RV dysfunction (pulmonary artery pulsatility index: 1.22).

MANAGEMENT

Diuresis was challenging on the ward and limited by hypotension, end-organ hypoperfusion evidenced by worsening renal and liver function, and runs of symptomatic ventricular tachycardia (180-220 beats/

FIGURE 4 ECG During Decompensated Heart Failure Presentation



ECG showed sinus rhythm, left-axis deviation, nonspecific intraventricular conduction delay, with evidence of left atrial enlargement. Abbreviation as in Figure 2.

min). Given the right-sided heart catheterization findings and continued clinical deterioration, ventricular assist device as a bridge to candidacy/transplantation was scheduled. HeartMate 3 left ventricular assist device (LVAD) insertion was performed and the LV was also closely inspected intraoperatively followed by surgical removal of the residual LV thrombus. As the cardiopulmonary bypass circuit was being weaned off, there was evidence of significant RV dysfunction intraoperatively, requiring significant inotrope and vasopressor support, including additional boluses of epinephrine to maintain his hemodynamics. Due to ongoing hemodynamic instability despite significant vasopressor/inotropic support and poor RV function at baseline, the decision was made to implant a right ventricular assist device (RVAD) CentriMag. He was quickly weaned off pressors and inotropes postoperatively in the Cardiovascular Intensive Care Unit. RVAD was slowly and successfully weaned over the next month and then decannulated.

OUTCOME AND FOLLOW-UP

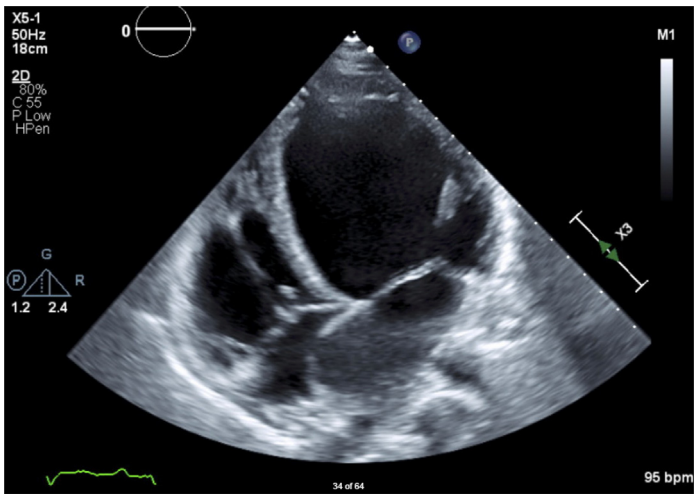
Following RVAD decannulation, this patient underwent significant rehabilitation before eventual discharge home. He will undergo complete cardiac rehabilitation now and will be reassessed for a heart transplantation in the next year. An expedited transplantation work-up would be considered if he developed symptomatic ventricular arrhythmias or refractory RV failure in the interim.

DISCUSSION

We describe the first reported case of a patient with moderately advanced arrhythmogenic cardiomyopathy from Carvajal syndrome who decompensated after a large ischemic stroke. Stroke-heart syndrome (SHS) is a framework describing the neurocardiogenic mechanisms leading to poststroke cardiovascular complications.[1-3] These complications include ischemic and nonischemic myocardial injury, acute coronary syndromes, left ventricular dysfunction, electrical abnormalities, and neurogenic sudden death.[1]

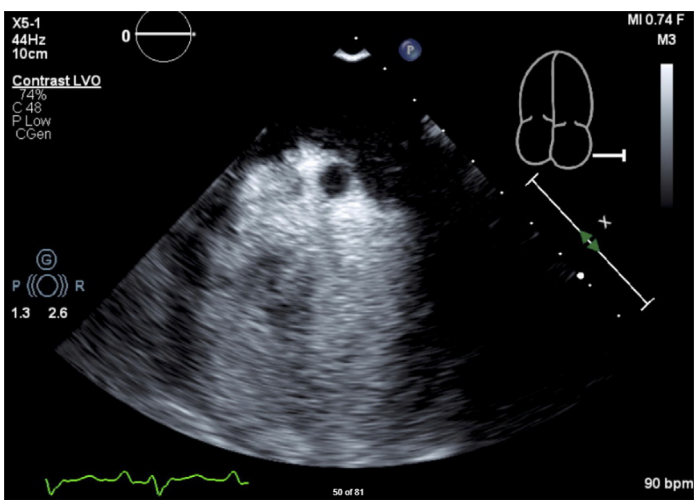
The mechanism by which these events occur is still being elucidated, but evidence from animal and human models suggests local and systemic mechanisms of injury, which have been well described previously by Sposato et al.[1] Systemically, poststroke neuron death leads to local inflammation that activates microglia, stimulates cytokines and chemokines release, and converts pro-interleukin-1 (IL-1) into IL-1 by caspases. Sympathetic stimulation of the adrenal gland, in addition to IL-1 and cytokine stimulation, leads to a systemic surge of humoral catecholamines. This is further enhanced by the release of macrophages, neutrophils, and cytokines

FIGURE 5 Baseline TTE



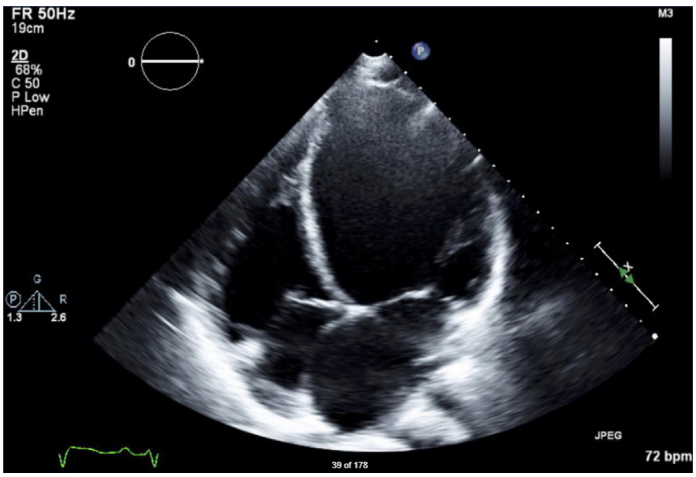
TTE had evidence of severely dilated left ventricle with eccentric hypertrophy and severe global LV dysfunction with LVEF by biplane Simpson's with contrast being 20%. There was also evidence that RV systolic function is mildly reduced and dilated. Left atrium was severely enlarged. TTE = transthoracic echocardiogram.

FIGURE 6 TTE During Work-Up of Stroke



TTE had evidence of severely dilated LV with eccentric hypertrophy and severe global LV dysfunction with LVEF by biplane Simpson's with contrast being 20%. RV systolic function was mildly reduced and the RV was dilated. Left atrium was severely enlarged and there was evidence of a pedunculated LV thrombus. Abbreviations as in Figure 5.

FIGURE 7 TTE During his Presentation in Severe Decompensated Heart Failure



TTE had evidence of a severely dilated LV with eccentric hypertrophy and severe global LV dysfunction with LVEF by biplane Simpson's with contrast being 14%. RV systolic function was severely reduced and dilated. The pedunculated residual LV thrombus was still present but smaller than previously shown. Abbreviations as in Figure 5.

systemically from the spleen and bone marrow. Locally, noradrenaline reaches the heart because of the significant sympathetic neural response, leading to cardiomyocyte damage. Noradrenaline, IL-1, and other proinflammatory cells further stimulate myofibroblast and macrophage activation, leading to profound local inflammation. Sequalae of this local inflammation include endothelial dysfunction and cardiomyocyte fibrosis/necrosis. Immune cells play a crucial role in dilated cardiomyopathy showing increased myeloid cells in the heart in patients with arrhythmogenic cardiomyopathy.[4] Recent translational work by Simats et al[5] provides further evidence that stroke can trigger systemic inflammation via innate immune memory and IL-1β-mediated epigenetic changes can drive cardiac fibrosis and dysfunction up to 3 months after ischemic stroke. Central autonomic network dysregulation and hypothalamic-pituitary-adrenal axis activation also contribute to the development of SHS through catecholamine surge.[6] Catecholamine release further enhances immune regulation, increasing cytokine release and further exacerbating the local and systemic inflammatory response.

TABLE 1 Right Heart Hemodynamics by Invasive Catheterization

Heart rate, beats/min	104
Noninvasive blood pressure (MAP), mm Hg	87/64 (72)
Right atrial pressure (mean), mm Hg	23/18 (18)
Right ventricular pressure (end-diastolic pressure), mm Hg	51/15 (22)
Pulmonary artery pressure (mean), mm Hg	49/27 (39)
Wedge pressure (mean), mm Hg	34/39 (32)
Wedge pressure saturation, %	91
Cardiac output/cardiac index by thermal dilution (BSA), L/min	2.8 (1.7)
Cardiac output/cardiac index by Fick (BSA), L/min	2.3 (1.4)
Transpulmonary gradient, mm Hg	7
Pulmonary vascular resistance, dynes/sec/cm^{-5}	245
Systemic vascular resistance dynes/sec/cm^{-5}	1,542
RVSWI, g × m/m^2	4.67
RA/PW ratio	0.56
PAPi	1.22
CPO/CPI, W/(W/m^2)	0.45/0.27
Systemic saturation, %	91
Pulmonary artery saturation, %	42
Body surface area, m^2	1.66
Hemoglobin, g/L	145
Estimated oxygen consumption, mL O_2/M^2	135

BSA = body surface area; CPO/CPI = cardiac power output/cardiac power index; MAP = mean arterial pressure; PAPi = pulmonary artery pulsatility index; RA/PW = right atrial/pulmonary wedge; RVSWI = right ventricular stroke work index.

SHSs are well described in animal models, but few human studies or cases highlight this phenomenon. Our present case demonstrates an example of a patient who, despite significant LV dysfunction at baseline, was still relatively asymptomatic and functioning well on GDMT for several years until his significant ischemic stroke. Our patient had a mutation in the *desmoplakin* gene, a protein for preserving cardiac cellular integrity, resisting mechanical stress, and anchoring the cytoskeleton to the plasma membrane at the desmosome junction.[7] Before his stroke, our patient had a severely dilated LV with global systolic dysfunction, but only mildly reduced RV systolic function. We suspect that the poststroke inflammatory cascade likely overwhelmed our patient's pre-existing weak desmosome cell-adhesion junction, driving adverse cardiac remodeling, electrical dysfunction, and biventricular failure. This case also highlights the increased prevalence of RV dysfunction in patients with DCM, which may exhibit a genotype-dependent effect.[8] Specifically, previous work has demonstrated that DCM patients with non-*titin* mutations had a relative lack of reverse remodeling in RV function and an overall poor prognosis compared with patients with *titin* mutations/genotype-negative.[8]

Despite SHS becoming increasingly well recognized in stroke literature during the past 5 years, we still have limited data on specific therapies targeting the brain-heart axis to prevent cardiovascular complications after stroke.[1-3,6] Proposed therapies for preventing poststroke cardiovascular complications include inhibiting IL-1 and preventing sympathetic overactivation by blocking ß-adrenergic receptors.[5,9] The CANTOS (Canakinumab Anti-inflammatory

Thrombosis Outcome Study) trial demonstrated that anti-inflammatory therapy with canakinumab targeting the IL-1β innate immunity pathway led to a lower rate of recurrent cardiovascular events compared with placebo.[10] However, the primary efficacy endpoints of this study were nonfatal myocardial infarctions, nonfatal strokes, or cardiovascular death. Further work is required to determine if there is any role for IL-1β inhibition in reducing the incidence or progression of heart failure after stroke.

CONCLUSIONS

Patients who experience ischemic strokes are at significant risk of developing cardiovascular complications through dysregulation of the brain-heart axis. Patients with genetic mutations may be at increased risk for the development or progression of heart failure after an acute ischemic stroke. This case highlights the importance of advanced multidisciplinary care between neurologists and cardiologists and the need for further preclinical and clinical studies on possible preventative therapies to reduce the risk of poststroke cardiovascular complications.

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KEY WORDS Carvajal syndrome, genetic cardiomyopathy, heart failure, stroke-heart syndrome, ventricular assist device

APPENDIX For supplemental videos, please see the online version of this paper.