

CASE REPORT

INTERMEDIATE

CLINICAL CASE

Unmasking Hydroxychloroquine Cardiotoxicity in a Patient With Heart Failure and Chronotropic Incompetence



Fatima M. Ezzeddine, MD,^a John R. Giudicessi, MD,^a Joseph J. Maleszewski, MD,^b Peter T. Lin, MD,^b Barry A. Borlaug, MD,^a Jeffrey B. Geske, MD^a

ABSTRACT

Chronic use of hydroxychloroquine can result in cardiomyopathy and conduction disturbances. Here, we describe a case of hydroxychloroquine cardiotoxicity in a patient with heart failure with preserved ejection fraction and severe chronotropic incompetence. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2021;3:997-1001) © 2021 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

A 69-year-old female patient presented with progressive exertional dyspnea of 1 year in duration, associated with fatigue and lightheadedness, which now limited her active lifestyle inclusive of hiking. She had been diagnosed with decreased central hypoxic drive and had been using supplemental oxygen with some improvement of her dyspnea.

PAST MEDICAL HISTORY

The patient's past medical history was significant for hypertension, asthma, obstructive sleep apnea (OSA),

hypothyroidism, and discoid lupus erythematosus. She had been treated previously for hypertension with valsartan for approximately 20 years but had not required antihypertensive therapy for approximately 9 years. The patient's discoid lupus erythematosus was diagnosed in her 30s, and it had been well controlled on hydroxychloroquine (HCQ) 200 mg daily since that time. The diagnoses of asthma and OSA were made after the initiation of HCQ therapy. Asthma was well controlled with albuterol and mometasone/formoterol inhalers. The patient was compliant with continuous positive airway pressure therapy for treatment of her OSA.

LEARNING OBJECTIVES

- To recognize the cardiotoxic effects of hydroxychloroquine use.
- To highlight the importance of endomyocardial biopsy in establishing the diagnosis of hydroxychloroquine-induced cardiomyopathy.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of dyspnea in this case is broad and includes cardiac and pulmonary etiologies (coronary artery disease, cardiomyopathy, conduction abnormalities, arrhythmias, valvular heart disease, asthma, chronic obstructive pulmonary disease, and interstitial lung disease).

From the ^aDepartment of Cardiovascular Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota, USA; and the ^bDepartment of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, Minnesota, USA. 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](#).

Manuscript received November 6, 2020; revised manuscript received February 12, 2021, accepted March 11, 2021.

ABBREVIATIONS AND ACRONYMS

- HCQ** = hydroxychloroquine
- LVH** = left ventricular hypertrophy
- OSA** = obstructive sleep apnea

INVESTIGATIONS

Physical examination was remarkable for bradycardia with a heart rate of 49 beats/min. Body mass index was 23.72 kg/m². No cardiac murmurs were noted. The electrocardiogram showed sinus bradycardia and left ventricular hypertrophy (LVH) (Figure 1). Plasma N-terminal pro-B-type natriuretic peptide was modestly elevated, at 966 pg/ml (normal range: ≤202 pg/ml). Initial transthoracic echocardiogram revealed a left ventricular ejection fraction of 60% to 65%, mild concentric LVH, elevated filling pressures with medial mitral E/e' of 28, moderate left atrial enlargement by visual assessment, and absence of hemodynamically significant valvular disease or dynamic left ventricular obstruction. Repeat transthoracic echocardiography 5 months after HCQ discontinuation revealed a left ventricular ejection fraction of 66%, mild to moderate concentric LVH with an indexed left ventricular mass measurement of 123 g/m², grade 2/4 left ventricular diastolic dysfunction with medial mitral E/e' ratio 16, biatrial enlargement with an indexed left atrial volume of 48 ml/m², estimated right ventricular systolic pressure of 32 mmHg, and absence of hemodynamically significant valvular disease or dynamic left

ventricular obstruction (Figure 2, Videos 1 and 2). Cardiac magnetic resonance imaging showed nonspecific mild concentric LVH (maximal wall thickness: 16 mm) and very mild late gadolinium myocardial enhancement without other evidence to suggest myocardial infarction, infiltrative process, or myocarditis (Figure 3). Cardiopulmonary exercise testing revealed a peak oxygen consumption of 22.2 ml/kg/min (91% predicted), with a peak heart rate of 111 beats/min and blunted chronotropic response in the absence of atrioventricular nodal blocking agents. Findings of pulmonary studies, including pulmonary function testing and chest computed tomography scan, were unremarkable. The H₂FPEF score (1) was 2, suggesting low likelihood of heart failure with preserved ejection fraction based on the available workup/clinical picture.

In light of the patient's unexplained exertional dyspnea, she subsequently underwent invasive hemodynamic cardiopulmonary exercise testing. Furthermore, given a nearly 30-year history of chronic HCQ use and documented chronotropic incompetence, the patient also underwent right ventricular endomyocardial biopsy to rule out HCQ-related cardiotoxicity. Hemodynamic catheterization was diagnostic of heart failure with preserved ejection fraction with severe chronotropic incompetence.

FIGURE 1 Resting Electrocardiogram Showing Sinus Bradycardia, Left Ventricular Hypertrophy, and a Premature Atrial Contraction Beat

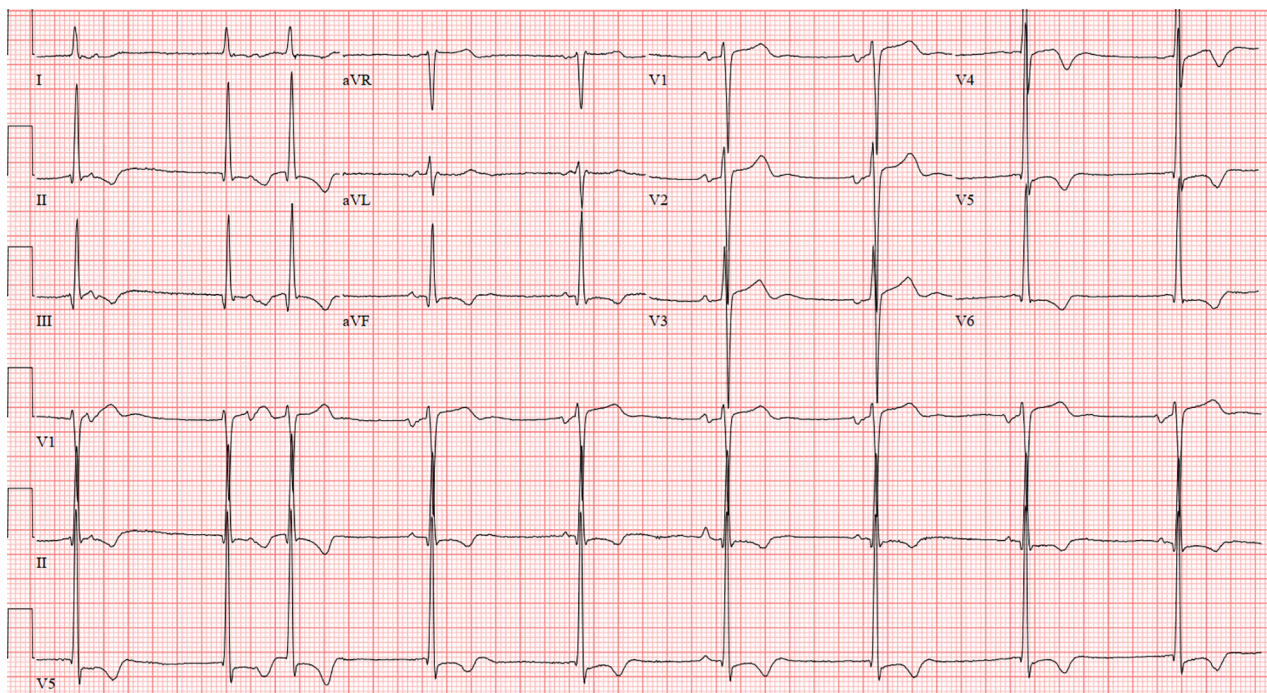
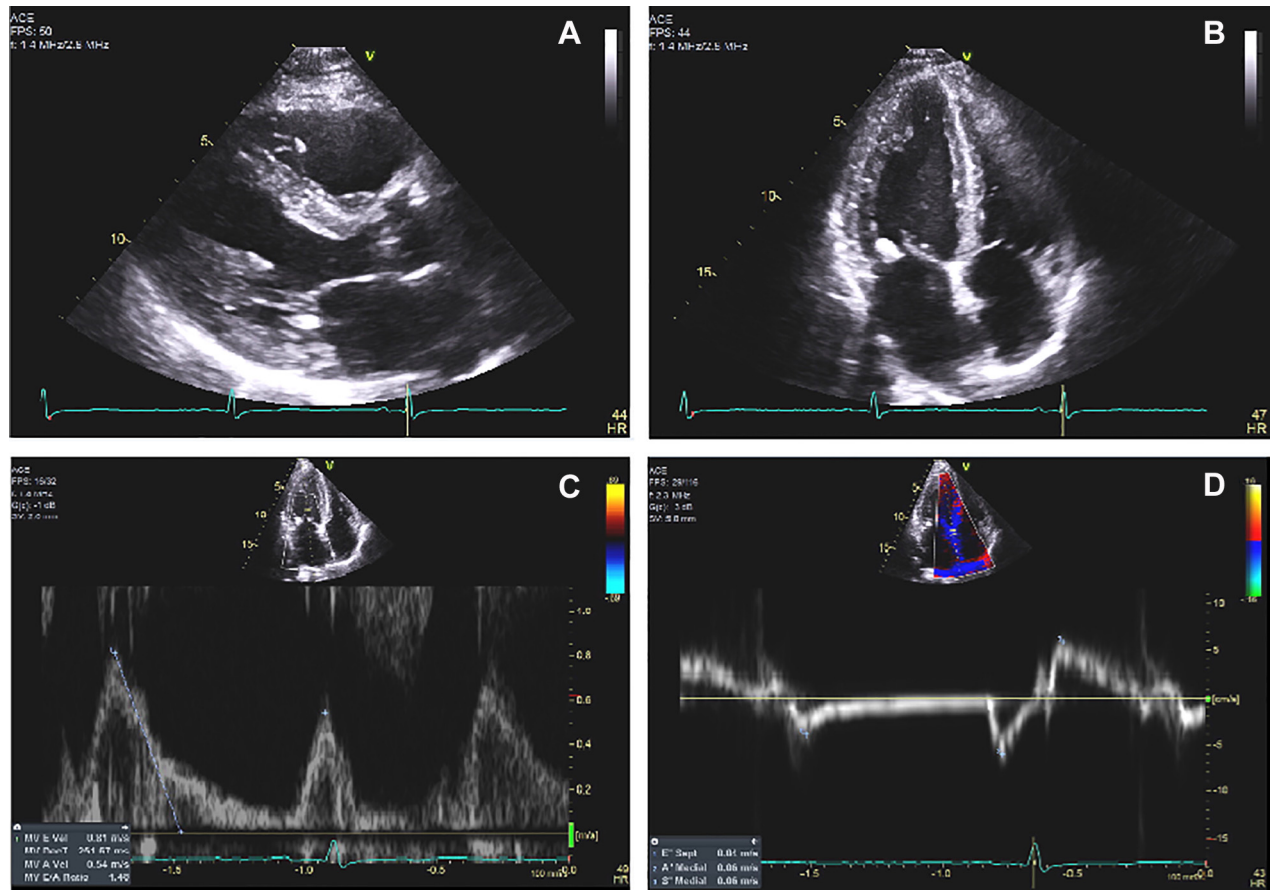
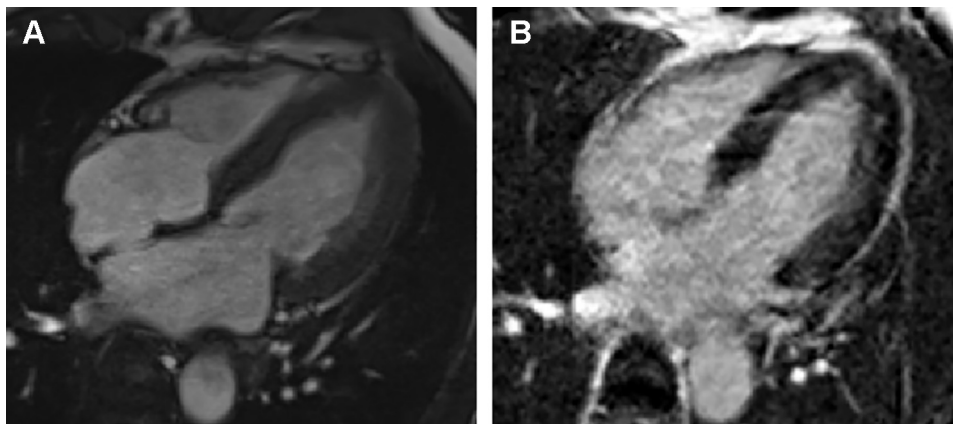


FIGURE 2 2-Dimensional Echocardiography Showing Mild Left Ventricular Hypertrophy, Biatrial Enlargement, and Diastolic Dysfunction

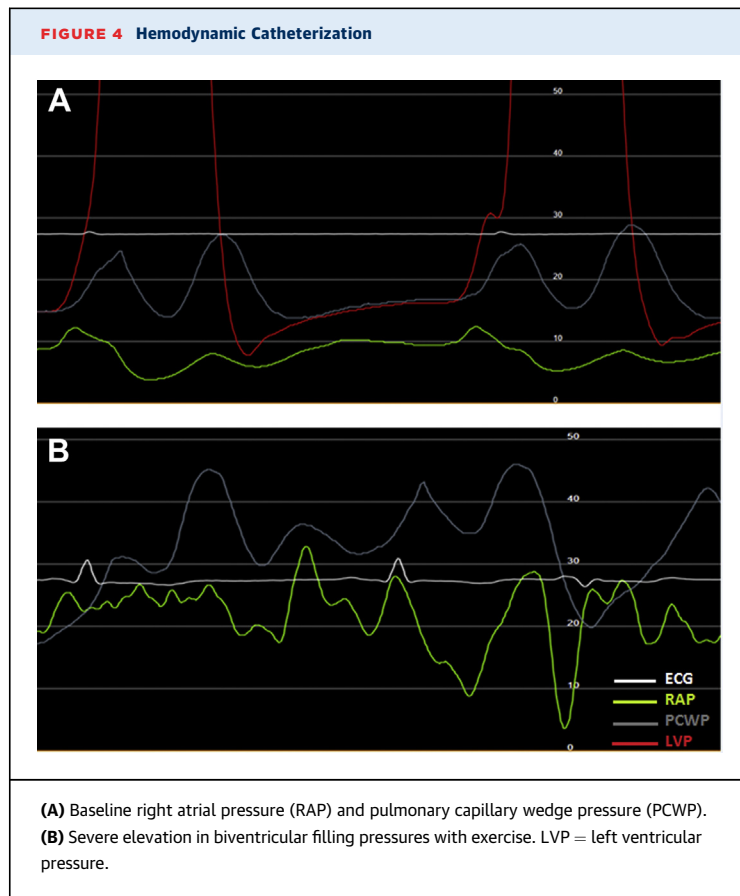


(A) Parasternal long-axis view. (B) 4-chamber view. (C) Mitral inflow view. (D) Mitral medial tissue Doppler measurements.

FIGURE 3 Cardiac Magnetic Resonance Images Showing Mild Left Ventricular Hypertrophy and Biatrial Enlargement



Cardiac magnetic resonance 4-chamber steady state free precession (A) and late gadolinium enhancement (B) sequences. Late gadolinium enhancement was absent, reducing the likelihood of an underlying infiltrative process, myocarditis, or sequelae of myocardial infarction.

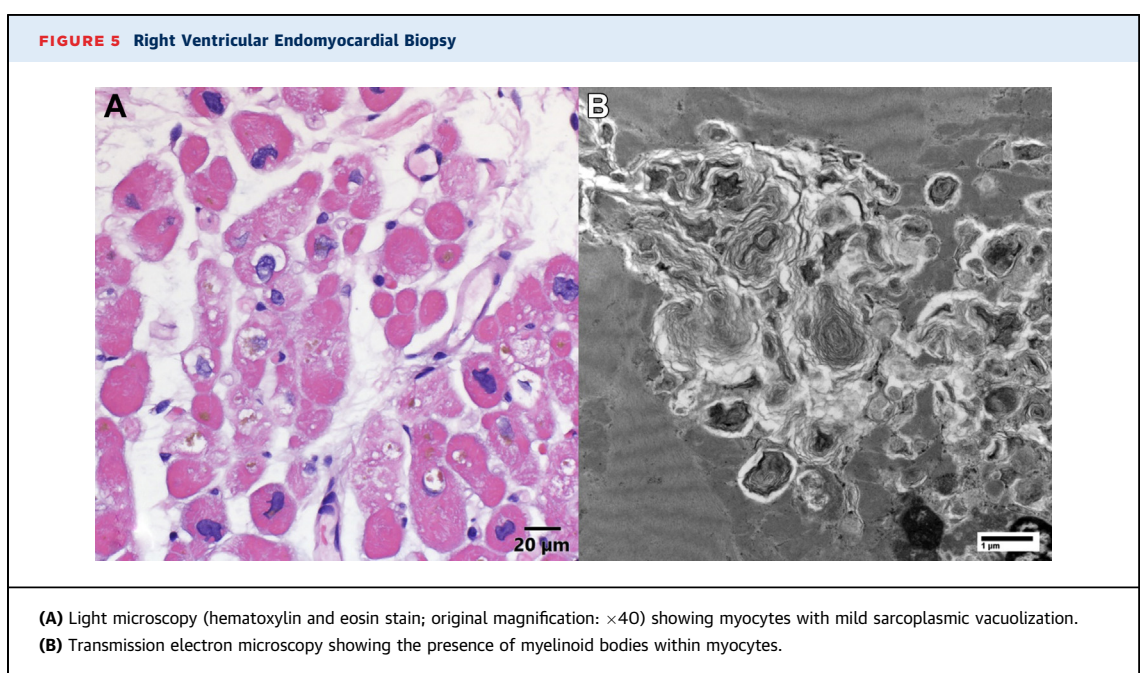


Baseline right atrial pressure and pulmonary capillary wedge pressure were mildly elevated, at 7 mm Hg and 18 mm Hg, respectively (Figure 4A), with a resting heart rate of 38 beats/min. With exercise, there was severe elevation in biventricular filling pressures and severe exercise-induced pulmonary hypertension (Figure 4B). Peak exercise capacity was depressed because of chronotropic incompetence. Peak oxygen consumption (V_{O_2}) was 948 ml/min (13.35 ml/kg/min), peak heart rate was 95 beats/min, peak cardiac output was 7.5 l/min, and peak cardiac index was 3.54 l/min/m² (26% of the predicted increase based on metabolic demand).

Right ventricular endomyocardial biopsy findings were consistent with HCQ cardiotoxicity, and hematoxylin and eosin staining showed myocytes with mild sarcoplasmic vacuolization (Figure 5A). Furthermore, transmission electron microscopy showed the presence of myelinoid bodies within myocytes (Figure 5B).

MANAGEMENT

After the initial evaluation, HCQ was discontinued because of a high clinical suspicion that it may be contributing to the patient's symptoms. After completion of the hemodynamic study, the patient underwent permanent pacemaker implantation because of the persistence of severe symptomatic



chronotropic incompetence despite HCQ discontinuation for 5 months.

DISCUSSION

Chronic HCQ use can cause lysosomal dysfunction, which results in restrictive or hypertrophic cardiomyopathy with or without dilatation and/or conduction abnormalities, including atrioventricular blocks and bundle branch blocks (2). A high index of suspicion is needed to make the diagnosis of HCQ cardiotoxicity. The echocardiographic features of HCQ cardiotoxicity include diffusely thickened ventricular walls, biatrial enlargement, and diastolic dysfunction (2,3). Restrictive physiology is also frequently seen (3). Cardiac magnetic resonance imaging is usually helpful in biventricular structural and functional assessment, ruling out infiltrative cardiomyopathies and defining the myocardial substrate in restrictive cardiomyopathy (4). Endomyocardial biopsy remains the standard diagnostic test of HCQ cardiotoxicity. The pathological findings include enlarged and vacuolated cells on light microscopy and the presence of myelinoid and curvilinear bodies on transmission electron microscopy, which are due to the accumulation of metabolic products, such as glycogen and phospholipids (2-5). Curvilinear bodies are more specific for HCQ cardiotoxicity, but they are not always seen (2). Therefore, in the proper clinical context, myelinoid bodies alone would be considered sufficient for making the diagnosis of HCQ cardiotoxicity. Enlarged mitochondria may also be seen (6).

Risk factors for HCQ cardiotoxicity include older age, female sex, longer duration of therapy (>10 years), pre-existing cardiac disease, and renal insufficiency (2). Prognosis of HCQ cardiotoxicity can vary

from complete reversibility to lack of reversibility requiring cardiac transplantation (2). Early recognition of HCQ cardiotoxicity is crucial to prevent late irreversible stages of the drug toxicity.

FOLLOW-UP

Several months after the cessation of HCQ, the patient noticed a substantial improvement in her dyspnea. This symptomatic improvement continued after the pacemaker implantation. Two weeks after pacemaker implantation, she was found to have atrial fibrillation on cardiac device interrogation and was then started on anticoagulation with apixaban.

CONCLUSIONS

The present case underlines the importance of endomyocardial biopsy in confirming the diagnosis of HCQ-induced cardiomyopathy. It is unclear in this case the extent of diastolic dysfunction and chronotropic incompetence that were solely due to the cytopathic effects of HCQ, as opposed to overlap with unrelated heart failure with preserved ejection fraction. Regardless, HCQ cessation is indicated to treat a potentially reversible contributor to the patient's symptoms.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. Jeffrey B. Geske, Mayo Clinic, Cardiovascular Diseases, 200 1st Street SW, Rochester, Minnesota 55905, USA. E-mail: geske.jeffrey@mayo.edu.

REFERENCES

1. Reddy YN, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation* 2018;138:861-70.
2. Joyce E, Fabre A, Mahon N. Hydroxychloroquine cardiotoxicity presenting as a rapidly evolving biventricular cardiomyopathy: key diagnostic features and literature review. *Eur Heart J Acute Cardiovasc Care* 2013;2:77-83.
3. Cotroneo J, Sleik KM, Rodriguez ER, Klein AL. Hydroxychloroquine-induced restrictive cardiomyopathy: correlation between clinical, echocardiographic and pathologic findings. *Eur J Echocardiogr* 2007;8:247-51.
4. Yogasundaram H, Putko BN, Tien J, Paterson DI, Cujec B, Ringrose J, Oudit GY. Hydroxychloroquine-induced cardiomyopathy: case report, pathophysiology, diagnosis, and treatment. *Can J Cardiol* 2014;30:1706-15.
5. Rattiff NB, Estes ML, Myles JL, Shirey EK, McMahon JT. Diagnosis of chloroquine cardiomyopathy by endomyocardial biopsy. *N Engl J Med* 1987;316:191-3.
6. Soong TR, Barouch LA, Champion HC, Wigley FM, Halushka MK. New clinical and ultrastructural findings in hydroxychloroquine-induced cardiomyopathy—a report of 2 cases. *Hum Pathol* 2007;38:1858-63.

KEY WORDS cardiomyopathy, chronotropic incompetence, exercise, heart failure, hydroxychloroquine

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