

TableData for the 3 Patients in the Current Series and Comparison With the Series Described by da Silva et al.¹

	Age, y	Weight, kg	ECC, min	Clamping, min	CTI Ablation	Follow-up, mo	Functional Class	Tricuspid Insufficiency
Case 1	13	51	125	80		38	NYHA I	Mild
Case 2	17	58	125	85		18	NYHA I	Mild-moderate
Case 3	56	92	114	82	Yes	6	NYHA I	Mild
Da Silva et al. ¹	17 (1-49)	?	104	70	9/40	49 (3-143)	NYHA I	Mild

Abbreviations: ECC, extracorporeal circulation; CTI, cavotricuspid isthmus; NYHA, New York Heart Association functional class.

of the mitral valve. As a preventive measure, da Silva et al. recommended not implanting the annulus in the tricuspid position, particularly in young patients.

Wolff-Parkinson-White-type arrhythmias are common in patients with Ebstein anomaly. Of the 40 patients in the series reported by da Silva et al., 9 underwent ablation of anomalous pathways during surgical repair. The most recent guidelines recommend prophylactic ablation during surgery for adult patients.²

The surgical procedure for Ebstein anomaly is one of several new surgical techniques being introduced in Spain.⁶ Our initial experience is very limited, as we had only 3 cases over a period of 3 years. This frequency, however, is in line with rates described by other authors (mean of 1 case per year⁵). The technique is reproducible, as evidenced by the similarities in surgical times (Table). Our early results are promising, although we acknowledge that longer follow-up is needed. We consider that the central flow and full coaptation between valvular tissue achieved with the modification described by da Silva et al.¹ may be key to the success of the technique. Finally, prophylactic ablation of the cavotricuspid isthmus is a simple and technique that can be recommended, particularly in adult patients.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found in the online version available at <http://dx.doi.org/10.1016/j.rec.2017.04.019>

Juan-Miguel Gil-Jaurena,^{a,b,*} María-Teresa González-López,^{a,b} Ana Pita-Fernández,^{a,b} Ramón Pérez-Caballero,^{a,b} Raquel Prieto,^{b,c} and Constanco Medrano^{b,d}

^aServicio de Cirugía Cardíaca Infantil, Hospital Universitario, Gregorio Marañón, Madrid, Spain

^bInstituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain

^cServicio de Cardiología, Hospital Universitario Gregorio Marañón, Madrid, Spain

^dServicio de Cardiología Pediátrica, Hospital Universitario Gregorio Marañón, Madrid, Spain

* Corresponding author:

E-mail address: giljaurena@gmail.com (J.-M. Gil-Jaurena).

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Dilated Cardiomyopathy and Hydroxychloroquine-induced Phospholipidosis: From Curvilinear Bodies to Clinical Suspicion



Miocardopatía dilatada y fosfolipidosis inducida por hidroxiquinona: de los cuerpos curvilíneos a la sospecha clínica

To the Editor,

Hydroxychloroquine is widely used to treat rheumatoid arthritis and lupus erythematosus. When administered orally, the drug has high bioavailability, long elimination half-life (30–60 days), and large volume of distribution and steady-state concentrations are reached after 4 to 6 months of treatment.¹ Retinal toxicity is a well-known adverse effect and screening recommendations have been established for its prevention.² Rarely, the drug can cause

cardiomyopathy, which can be fatal unless it is suspected at an early stage. Hydroxychloroquine induces phospholipidosis (phospholipid accumulation in the cytoplasm) through inhibition of lysosomal phospholipase to form indigestible complexes visible under an electron microscope. Depending on their morphology, these are denoted myeloid bodies (forming concentric layers) or curvilinear bodies (comma shape). These depositions lead to vacuolization of the cytoplasm, disorganization of the myofibrils, cell hypertrophy, and, finally, fibrosis (Figure). Definitive diagnosis of hydroxychloroquine-induced cardiomyopathy requires the presence of pathognomonic curvilinear bodies³ (these can also be found in neuronal ceroid lipofuscinosis, but without involvement of the myocardium). Myeloid bodies are very suggestive of hydroxychloroquine-induced cardiomyopathy but they are not pathognomonic because they can be present in phospholipidosis induced by cationic amphiphilic drugs (amiodarone, aminoglycosides, and fluoxetine, among others) and also in genetic

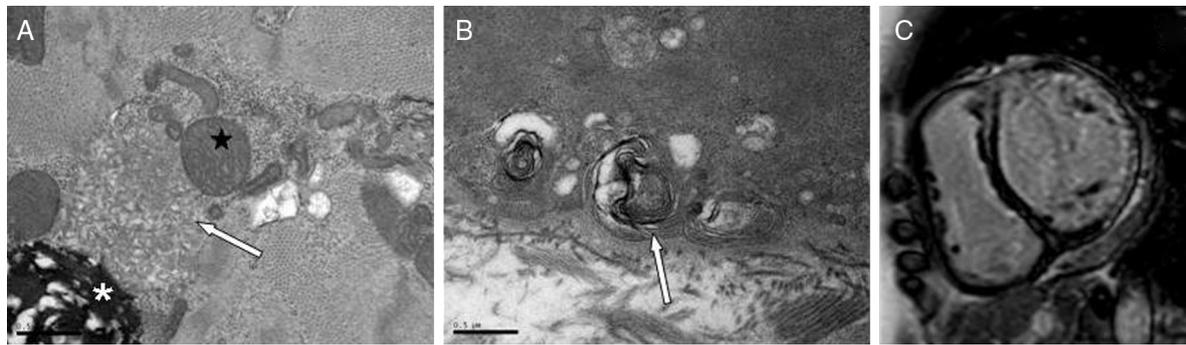


Figure. A, Endomyocardial biopsy and electron microscopy for patient 1. Characteristic curvilinear bodies (arrow), along with myelin figures (asterisk, left inferior margin) and abnormal mitochondria (star). B, Endomyocardial biopsy and electron microscopy for patient 2. Myeloid body (arrow), structure formed by concentric layers of electron-dense membranous material surrounded by a single limiting membrane. C, Magnetic resonance imaging, late contrast enhancement sequence, short axis, corresponding to patient 2. Inferolateral transmural fibrosis and linear septal intramural fibrosis can be observed.

phospholipidoses (Fabry disease and Niemann-Pick disease). It is therefore necessary to rule out these diseases before relating myeloid bodies to hydroxychloroquine. From the practical point of view, hydroxychloroquine-induced cardiac toxicity should be suspected if ventricular dysfunction develops in a patient who is taking this drug, and should be grounds for discontinuation. Most cases reported in the literature correspond to the restrictive cardiomyopathy phenotype with increased wall thickness as the most common structural finding. The ventricular dilatation phenotype without wall thickening is less frequent. However, in the 3 cases thought to have occurred in our cardiomyopathy unit, presentation was always in the form of dilated cardiomyopathy (Table). The certainty of diagnosis varied from pathognomonic demonstration of curvilinear bodies in endomyocardial biopsy (patient 1) to mere clinical suspicion given the temporal relationship with drug administration (patient 3). In patient 2, the presence of myeloid bodies was observed without curvilinear ones. Although hydroxychloroquine rarely causes conduction disorders in the electrocardiogram, it can reduce heart rate by a similar mechanism to Ivabradine; consequently, it is beginning to be discussed as a possible antianginal drug.⁴ There is considerable variability in the minimum dose required to cause cardiac toxicity reported in the literature, and this observation is reflected in the 3 cases described below.

Patient 1 was a 60-year old man with rheumatoid arthritis (under treatment with methylprednisolone and hydroxychloroquine for 27 months). Echocardiography prior to treatment showed no abnormalities. He presented with heart failure and dilated cardiomyopathy with severely depressed ejection fraction, and no increased wall thickness. His status normalized after treatment discontinuation. Endomyocardial biopsy showed myeloid and curvilinear bodies under electron microscopy, which confirmed the diagnosis of hydroxychloroquine-induced cardiomyopathy.

The second patient was a 41-year-old woman with lupus erythematosus. She initiated treatment with hydroxychloroquine with no renal insufficiency or other history of interest. Three months later, she presented with acute pulmonary edema. Cardiac magnetic resonance imaging showed dilated ventricular volumes with severely depressed ejection fraction, no wall hypertrophy, and late gadolinium enhancement in the inferolateral transmural and septal intramural region. Endomyocardial biopsy showed myeloid bodies but not curvilinear ones. Given the clinical context, the phenotype of cardiomyopathy, and sequencing of the *GLA* gene, which showed no variants with respect to the reference genome, other phospholipidoses mentioned above were ruled out. Despite withdrawal of the drug, ejection fraction had not improved after 2 years of follow-up.

Table
Characteristics of the 3 Patients With Hydroxychloroquine-Induced Cardiomyopathy in the Cardiomyopathy Unit

	Patient 1	Patient 2	Patient 3
Age, Sex	60 y, male	41 y, female	66 y, female
Underlying disease	Rheumatoid arthritis	Lupus erythematosus	Lupus erythematosus
Cumulative dose of hydroxychloroquine	324 g	36 g	300 g
Cardiomyopathy phenotype	Dilated cardiomyopathy (echocardiography: LV EDD, 83 mm; EF, 26%; hypokinetic RV)	Dilated cardiomyopathy (MRI: LV EDV, 110 mL/m ² ; EF, 28%; RV EDV, 61 mL/m ² ; EF, 53%)	Dilated cardiomyopathy (MRI: LV EDV, 106 mL/m ² ; EF, 45%; RV EDV, 63 mL/m ² ; EF, 77%)
Conduction disorders in ECG	No, nonspecific repolarization disorder (T wave flattening in precordial leads)	No, nonspecific repolarization disorder (T wave flattening in precordial leads)	Left-bundle-branch block
CMRI	Not performed	With fibrosis	Without fibrosis
Coronary angiography	No significant lesions	No significant lesions	Not performed
Diagnosis	Endomyocardial biopsy: curvilinear bodies, confirmed diagnosis	Endomyocardial biopsy: myeloid bodies, highly suspected diagnosis	No biopsy, clinical diagnosis
Reversibility	Yes	No	Yes

CMRI, cardiac magnetic resonance imaging; ECG, electrocardiogram; EDD, end-diastolic diameter; EDV, end-diastolic volume; EF, ejection fraction; LV, left ventricular; MRI, magnetic resonance imaging; RV, right ventricular.

Patient 3 was a 66-year-old woman with lupus erythematosus and normal echocardiogram prior to initiating therapy who developed dilated cardiomyopathy after 25 months of treatment. The patient presented with exercise-induced dyspnea. Magnetic resonance imaging showed left ventricular dilatation with a slightly depressed ejection fraction, normal wall thickness, and no focal or segmental fibrosis in the late enhancement sequences. The drug was withdrawn and ventricular volumes returned to normal during subsequent follow-up. Hydroxychloroquine-induced cardiomyopathy was therefore suspected clinically. Endomyocardial biopsy was not performed.

These 3 cases of hydroxychloroquine-induced myocardial toxicity highlight the importance of periodic clinical assessment of these patients (even those who have been under treatment for a few months). In the event of minimal clinical suspicion, the use of imaging techniques should be considered to assess whether myocardial involvement is present.

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Francisco Di Girolamo,^a Eduard Claver,^{a,*} Montse Olivé,^b Joel Salazar-Mendiguchía,^a Nicolás Manito,^a and Ángel Cequier^a

^aÀrea de Malalties del Cor, IDIBELL, Hospital de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain

^bServicio de Anatomía Patológica (Neuropatología) y Unidad de

Patología Neuromuscular, IDIBELL, Hospital de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain

* Corresponding author:

E-mail address: eclaver@bellvitgehospital.cat (E. Claver).

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Percutaneous Ventricular Assist Device for Circulatory Support During Ablation of Atrial Tachycardias in Patients With Fontan Circulation



Soporte circulatorio mediante asistencia ventricular percutánea durante la ablación de taquicardias auriculares en pacientes con circulación de Fontan

To the Editor,

In this article, we describe 2 patients with Fontan circulation who underwent successful ablation of a hemodynamically unstable atrial arrhythmia with the aid of a continuous flow percutaneous ventricular assist device (VAD).

A 34-year-old man was referred to our clinic for an ablation for symptomatic, frequently-recurring intra-atrial reentrant tachycardia (IART). He was diagnosed with tricuspid atresia and atrial and ventricular septal defect. At the age of 8 years, a Fontan circulation had been created and resulted in a pulmonary homograft between the right atrium and a hypoplastic right ventricle (Björk modification). Preprocedure examination revealed moderately reduced left ventricular function and a mildly stenosed homograft. The first ablation procedure was discontinued due to hemodynamic instability. During the repeat procedure, we decided to use hemodynamic support through a percutaneous VAD (Impella 3.5 CP catheter, Abiomed Inc, Danvers, MA, United States), which was placed via the right femoral artery in a retrograde approach across the aortic valve in the left ventricle (Figure 1A). A dense bipolar voltage map (Figure 1B) of the right atrium identified scarring in multiple locations. An IART was induced and ablation was performed during tachycardia. During ablation on the lateral wall, the tachycardia terminated. However, multiple different IARTs could be reinduced. After ablation of all

channels in the scar, no IART could be induced at the end of the procedure.

Initially, during atrial tachycardias, the patient was hemodynamically unstable. With a continuous blood flow of 2.7 L per minute, the tachycardias were tolerated, but only after correction of the preload. There have been no recurrences during a 30-month follow-up.

A 21-year-old man born with tricuspid valve atresia underwent a bidirectional Glenn anastomosis at 9 months. Completion of the Fontan circulation followed at the age of 2 when the right atrium was connected to the pulmonary artery.

The patient was referred for catheter ablation because of multiple episodes of drug-resistant IART. The patient had deteriorated left ventricular function and subsequently overt congested heart failure. Because he was hemodynamically unstable during his tachycardias, we used hemodynamic support with an Impella 3.5 CP catheter (Abiomed Inc, Danvers, MA, United States) that was placed via the left femoral artery.

Bipolar voltage mapping illustrated an area of low voltage on the lateral wall of the right atrium, most probably the result of the atriotomy. Entrainment mapping suggested that the area of low voltage on the lateral right atrial wall was part of the induced IART circuit. Consequently, an ablation line in the target area led to termination of the IART. With the use of the percutaneous VAD and preload correction by administering 1.5 L lactated ringer's solution to obtain a left ventricular end diastolic pressure of more than 12 mmHg, the patient maintained stable hemodynamics (Figure 2) and a urine production of > 200 mL per hour.

The patient continued to receive sotalolol twice daily and experienced a single episode of atrial tachycardia in the subsequent year. In addition, his ventricular function improved, symptoms of heart failure ceased, and his functional class remained stable.