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Clinical Case Report

Morphological changes in mitochondria during mechanical unloading observed on electron microscopy: a case report of a bridge to complete recovery in a patient with idiopathic dilated cardiomyopathy

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ABSTRACT

The recovery of the cardiac function under mechanical support has not been well documented from a histopathological point of view. We herein report a case of idiopathic dilated cardiomyopathy in which the patient showed a complete recovery of the systolic function following treatment with a left ventricular assist device (LVAD) for deteriorated heart failure. A light microscopic observation showed marked regression of hypertrophic myocytes with significant intracellular vacuolization and scarcity at the time of LVAD implantation after the administration of mechanical support. Furthermore, an electron microscopic observation revealed that these findings were regulated primarily by volumetric regression and morphometric improvements in cardiomyocytic mitochondria.

1. Introduction

Left ventricular assist devices (LVADs) are widely used as a bridge to heart transplantation in end-stage heart failure (HF) patients or as destination therapy. In addition, providing hemodynamic support for unloading the LV using an LVAD can facilitate a sufficient myocardial recovery to allow for explantation, known as a "bridge to recovery" (BTR), in some patients. The success of BTR varies significantly across reported studies, presumably due to a variety of factors affecting both clinical and biological outcomes. Biological parameters of cardiac remodeling have been shown to be favorably altered during LVAD treatment, including cardiac hypertrophy, contractile dysfunction, sympathetic denervation, metabolic changes, autophagy, a decreased microvascular density, neurohumoral and cytokine dysregulation, and denaturation of the extracellular matrix [1]. Most such investigations have been directed towards identifying functional and molecular mechanisms; however, few detailed reports have been conducted from a histological point of view. We herein present a case of idiopathic dilated cardiomyopathy (IDCM) in which a complete recovery from decompensated HF was achieved with the temporal use of an LVAD. Serial histological evaluations revealed unique morphological alterations, particularly mitochondrial transformation.

2. Case report

A 29-year-old male was hospitalized at our institute for refractory HF diagnosed as IDCM (Fig. 1). He had no family history of cardiomyopathy or previous events of HF based on a medical interview. On admission, an electrocardiogram showed sinus tachycardia, with no evidence of intraventricular conduction block and a QRS duration of 104 ms. In addition, a chest X-ray disclosed moderate cardiomegaly and pulmonary congestion, and the initial echocardiogram demonstrated an enlarged LV cavity with an LV end-diastolic dimension of 74 mm, as well as a severely reduced systolic function and LV ejection fraction (EF) of 15% (Fig. 2A). The serum B-type natriuretic peptide (BNP) level was 1159 pg/ml. Despite the administration of intensive pharmacotherapy, including intravenous diuretics, antineurohumoral agents, and inotropic drugs, additional support with an intraaortic balloon pump was required due to the patient's deteriorated hemodynamic state. His condition progressively worsened, with an increase in the serum total bilirubin level to 3.3 mg/dl and a cardiac index of 1.8 l/min/m^2. We therefore decided to place a temporary pulsatile LVAD (Nipro, Tokyo, Japan) (LVADim) with concomitant intensified pharmacotherapy, including an uptitrated beta-blocker and renin–angiotensin–aldosterone system inhibitors, in combination with incremental cardiac rehabilitation. The patient's systemic condition and hemodynamic and laboratory data gradually returned to normal in association with improved LV contractions over several months (Fig. 2B).

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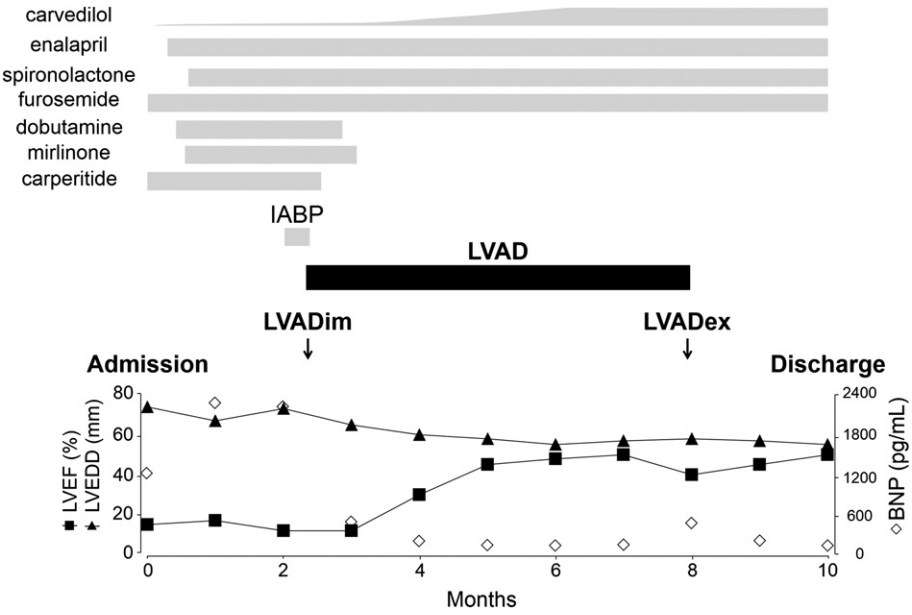

Fig. 1. Time course of heart failure management including left ventricular assist device (LVAD). Time courses of left ventricular ejection fraction (LVEF), LV end-diastolic dimension (LVEDD), and serum B-type natriuretic peptide (BNP) relative to the administration of drug and mechanical support. Despite the use of intensive treatment, including intravenous diuretics, antineurohumoral agents, and inotropic drugs, and additional support with an intraaortic balloon pump (IABP), the patient's hemodynamic state progressively deteriorated. After LVAD implantation (LVADim), his systemic condition improved in association with the hemodynamic and laboratory data, gradually accompanied by a recovery in the LV contractions, over several months. Finally, he was able to undergo LVAD explantation (LVADex) 6 months after LVADim.

Finally, he was able to undergo LVAD explantation (LVADex) 6 months after LVADim and was subsequently discharged. He remained free from symptoms, including exertional dyspnea, and his functional activity recovered to baseline, with an LVEF of 65%, according to the regular ambulatory workup performed 6 months after LVADex.

During hospitalization, myocardial tissue specimens were obtained from the apical core of the LV free wall under both LVADim and LVADex. Under LVADex, a sample was obtained approximately 1.5 cm from the operative scar from the LVAD inflow cannula in order to avoid including tissue with characteristics of reactive inflammation and degeneration. Consequently, there were no significant signs of inflammatory cell infiltration in any of the myocardial samples on immunohistological staining with CD3, CD68, or tenascin C. In addition, light microscopy (LM) showed that the cardiomyocytes in the sample obtained under LVADim were severely hypertrophied, thus exhibiting marked intracellular vacuolization and scarcity (Fig. 3A–B). Under treatment with hemodynamic support using LVAD for 6 months, the cardiomyocyte hypertrophy markedly regressed, with a change in diameter from 28±4 μm to 18±4 μm, in addition to discreet intracellular vacuolization and scarcity in the samples obtained during LVADex (Fig. 3E–F). Transmission electron microscopy (EM) (Hitachi H-7650, Tokyo, Japan) of the sample obtained using LVADim showed that the hypertrophied cardiomyocytes contained preserved myofibrils with an increased amount of myocytoplasm and a significant number of enlarged mitochondria with various morphological abnormalities, such as varying sizes and shapes with disorganized cristae (Fig. 3C–D, obtained from an intermediate zone of the LV wall on LVADim). In the samples obtained from the intermediate zone of the LV wall on LVADex, the fraction of myocytoplasm was markedly decreased in association with a decrease in number and uniform size of the mitochondria, whereas there were almost no morphological changes in the myofibrils (Fig. 3J–K), in parallel with the LM findings of regressed cardiomyocyte hypertrophy with discreet intracellular vacuolization and scarcity. The statistical analyses conducted using Wilcoxon rank sum test (JMP 10.0 software program for Windows) showed significant decreases in the number of mitochondria (131±52 vs. 75±33/100 μm^2, $P<.05$) and the size (0.9±0.6 vs. 0.5±0.3μm, $P<.05$) and volume ratio of mitochondria/myocyte (35%±11% vs. 20%±10%, $P<.05$; Adobe Photoshop ver. 11.0.2 and Lumina Vision ver. 3.3.2.0 software programs) on the basis of an observation of 30 randomly selected sections (100 μm^2) at a magnification of ×10,000 on LVADim compared with those observed on LVADex, respectively. Regarding intersectional diversity, we compared the endocardium side, the intermediate zone, and the epicardium side of the LV wall on the basis of an observation of 10 randomly selected sections for each side. More significant improvement of mitochondrial denaturation was observed toward the endocardium side (Fig. 3E as endocardium side on LVADim, Fig. 3F as intermediate zone on LVADim, Fig. 3G as epicardium side on LVADim, Fig. 3L as endocardium side on LVADex, Fig. 3M as intermediate zone on LVADex, and

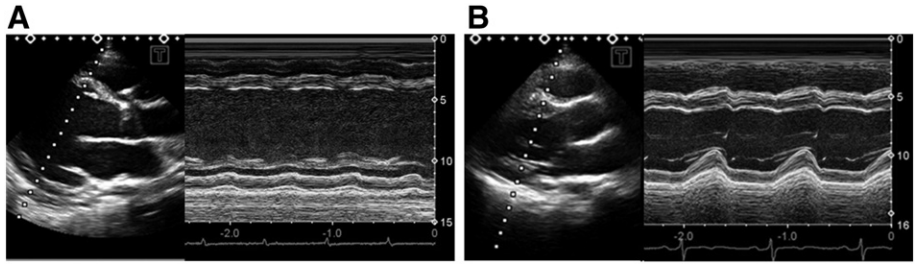

Fig. 2. Echocardiographic improvement during the mechanical support. These figures of the left ventricular (LV) were recorded using B mode (left side) and M mode (right side) from the parasternal long-axis views, respectively. During mechanical support, the LV ejection fraction (LVEF) dramatically improved in association with a decrease in the LV end-diastolic dimension (LVEDD) on LV assist device (LVAD) explantation (B) compared with that observed on LVAD implantation (A).