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Original Article

Histopathologic correlates of myocardial improvement in patients supported by a left ventricular assist device

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Abstract

Background: Left ventricular assist devices unload the failing heart and improve hemodynamic function and tissue architecture. In some patients improvement allows for left ventricular assist device removal. We retrospectively compared histologic features in patients who were weaned off left ventricular assist device support with those who remained on support without evidence of clinical remission. **Methods:** We graded left ventricular core samples taken at implantation on a scale we designed for evaluating severity and extent of fibrosis and hypertrophy. We correlated the grades with a computerized semiquantitative analysis of picrosirius-red and Masson's trichrome-stained sections. We evaluated interstitial (10×), perivascular (20×), and replacement (4×) fibrosis. Hypertrophy was assessed by myocyte diameter, cytoplasmic area, and nuclear/cytoplasmic ratio. **Results:** All patients (N=17) underwent left ventricular assist device implantation for heart failure. In eight patients improvement allowed left ventricular assist device removal. The groups did not differ in age (24.1 vs. 25 years, P=.4) or mean time on left ventricular assist device support (506 vs. 414 days, P=.24). All mean measures showed significantly less hypertrophy in the left ventricular assist device-removal group than in the nonremoval group, respectively (cytoplasmic area, 58.00 vs. 77.18 μm^2, P=.021; myocyte diameter, 20.32 vs. 25.35 μm, P=.004; nuclear/cytoplasmic ratio, 11.04 vs. 8.69, P=.053). Although not statistically significant, the left ventricular assist device-removal group tended toward less overall fibrosis than the nonremoval group (11.57 vs. 13.24, P=.214). **Conclusions:** Left ventricular assist device-removal patients had less hypertrophy and fibrosis overall than did nonremoval patients. These findings may help identify patients with a higher probability of left ventricular assist device removal and myocardial recovery.

Keywords: Heart-assist device; Hypertrophy; Myocardium; Myocyte; Remodeling; Transplantation

1. Introduction

With the advent of cyclosporine, left ventricular assist devices (LVADs), originally developed for long-term support, have became clinically effective as a bridge to transplant [1,2]. Since the early 1900s, resting the heart has been the method of treatment for heart failure [3,4]. The LVAD is the most effective method currently available for resting the heart while allowing normal activity for the patient. Our group has reported on the histologic, anatomic, and physiologic improvements in the hearts of patients who were bridged to transplant in the early 1990s [5].

Unloading the failing heart initiates mechanisms and pathways that lead to beneficial changes in the cellular and tissue architecture of the heart and to improved hemodynamic function [6–8]. In some patients in whom the LVAD was removed because of infection or device failure, native cardiac function improved sufficiently to avoid subsequent device replacement or transplantation. However, this phenomenon has been studied prospectively in only a limited fashion [1,8–11].

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No clinical guidelines are currently available to reliably predict outcome in patients with LVADs. Although histologic features such as fibrosis and hypertrophy have been associated with deterioration of myocardial function, their usefulness as markers of clinical status has not been established. To quantify the extent and severity of fibrosis and hypertrophy, we developed a semiquantitative grading scale to help determine histologic features that may be useful in predicting clinical outcome. In this study, using both a semiquantitative grading scale and morphometric evaluation, we (a) evaluated histologic parameters at LVAD implantation in patients with clinical myocardial improvement who were weaned from mechanical support, (b) correlated the severity and extent of fibrosis and hypertrophy at implantation of the device with the clinical course, and (c) compared the histopathologic features of patients in whom myocardial function improved enough to allow device explantation with those who did not have significant clinical recovery and who remained on LVAD support or died.

2. Methods

2.1. Patients

We studied patients with idiopathic cardiomyopathy who required LVAD implantation for heart failure at the Texas Heart Institute at St. Luke's Episcopal Hospital. Patients with ischemic cardiomyopathy were excluded. We studied two groups: those who showed sufficient echocardiographic and clinical improvement in native heart function to suggest weaning from mechanical support (LVAD-removal group) and a similar cohort of randomly selected patients who lacked evidence of echocardiographic improvement and who remained on support or died (nonremoval group). We retrospectively reviewed the data from the charts of all patients. The following information at the time of implantation and histologic specimen retrieval was recorded: age, gender, duration of heart failure, hemodynamic parameters, and type of LVAD. Both groups of patients (removal and nonremoval) were maintained on their regular heart failure therapy.

2.2. Histologic assessment

We blindly evaluated biopsy specimens of the left ventricular apex taken at the time of LVAD implantation in all patients. Specimens were fixed in formaldehyde, embedded in paraffin, serially sectioned, and stained with hematoxylin and eosin (H&E). We designed a grading system (see below) to evaluate the presence and severity of interstitial, perivascular, and replacement fibrosis, and the severity of hypertrophy. The extent and severity of fibrosis were determined by a computerized quantitative analysis of positive Picrosirius red-stained areas and Masson's trichrome-stained slides (Microsuite Biological Suite, Olympus BX61). At low power (1.25×), we studied the overall amount of fibrosis on each slide. Perivascular fibrosis (10×) (Fig. 1A) was defined as the amount of fibrous tissue localized within 1 diameter of each vessel and was evaluated in all perivascular spaces of five randomly selected areas of each slide. Interstitial fibrosis (20×) was measured in five randomly selected areas of each slide. Replacement fibrosis (4×), defined as deposits of fibrous tissue that replaced myocytes, was studied by measuring the percentage of myocardial compromise in areas of replacement fibrosis (Fig. 1B).

To assess hypertrophic changes, we studied three variables: myocyte diameter, myocyte area, and nuclear/cytoplasmic (N/C) ratio. All measurements were obtained on at least 10 randomly selected myocytes in five sections of H&E-stained slides (20×). Myocyte diameter was obtained by measuring the length of a cross-sectional diameter perpendicular to the nucleus (Fig. 2). Nuclear/cytoplasmic ratio and myocyte area were measured by delineating the

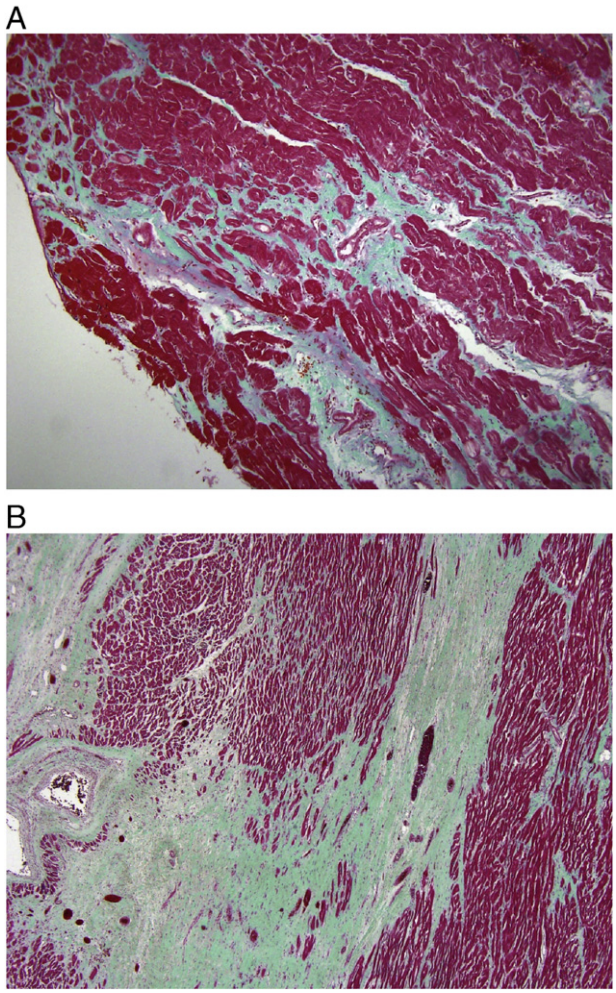

Fig. 1. Left ventricular core at implantation stained with Masson's trichrome (10×) showing (A) perivascular fibrosis extending into the interstitium and (B) replacement fibrosis with extensive fibrous tissue deposited in the interstitium replacing myocytes.