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# Myocardial Atrophy and Chronic Mechanical Unloading of the Failing Human Heart

## Implications for Cardiac Assist Device–Induced Myocardial Recovery

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## ABSTRACT

**BACKGROUND** In animal models of heterotopic transplantation, mechanical unloading of the normal, nonhypertrophic heart results in atrophy. Primarily on the basis of these animal data, the notion that chronic left ventricular assist device (LVAD)-induced unloading will result in atrophy has dominated the clinical heart failure field, and anti-atrophic drugs have been used to enhance the cardiac recovery potential observed in some LVAD patients. However, whether unloading-induced atrophy in experimental normal heart models applies to failing and hypertrophic myocardium in heart failure patients unloaded by continuous-flow LVADs has not been studied.

**OBJECTIVES** The study examined whether mechanical unloading by continuous-flow LVAD leads to myocardial atrophy.

**METHODS** We prospectively examined myocardial tissue and hemodynamic and echocardiographic data from 44 LVAD patients and 18 untransplanted normal donors.

**RESULTS** Cardiomyocyte size (cross-sectional area) decreased after LVAD unloading from 1,238 ± 81 $\mu m^2$ to 1,011 ± 68 $\mu m^2$ ($p = 0.001$), but not beyond that of normal donor hearts (682 ± 56 $\mu m^2$). Electron microscopy ultrastructural evaluation, cardiomyocyte glycogen content, and echocardiographic assessment of myocardial mass and left ventricular function also did not suggest myocardial atrophy. Consistent with these findings, t-tubule morphology, cytoplasmic penetration, and distance from the ryanodine receptor were not indicative of ongoing atrophic remodeling during LVAD unloading. Molecular analysis revealed no up-regulation of proatrophic genes and proteins of the ubiquitin proteasome system.

**CONCLUSIONS** Structural, ultrastructural, microstructural, metabolic, molecular, and clinical functional data indicated that prolonged continuous-flow LVAD unloading does not induce hypertrophy regression to the point of atrophy and degeneration. These findings may be useful in designing future investigations that combine LVAD unloading and pharmaceutical therapies as a bridge to recovery of the failing heart. (J Am Coll Cardiol 2014;64:1602–12) © 2014 by the American College of Cardiology Foundation.

Left ventricular assist devices (LVADs) are increasingly used to bridge end-stage heart failure patients to heart transplantation or implanted as a lifetime therapy (1,2). Although LVADs have established utility in increasing cardiac output and reversing end-organ damage, this intervention's consequences for myocardial structure and function are uncertain (3). Animal models of

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mechanical unloading of nonfailing and nonhypertrophic myocardium by means of: 1) heterotopic transplantation (4); 2) LVAD (5); and 3) severing the mitral papillary muscle chordae tendineae (6) suggested that chronic unloading could lead to myocardial atrophy. Whether this phenomenon applies only to unloaded nonfailing and nonhypertrophic myocardium or also to hypertrophic and failing human myocardium unloaded by continuous-flow LVADs is unknown. Available clinical data are inconclusive and are limited to two human studies with first-generation, pulsatile LVADs that evaluated left ventricular (LV) mass as assessed by echocardiography (7,8).

SEE PAGE 1613

On the basis of these limited animal and clinical data, chronic LVAD unloading in patients with heart failure (HF) was postulated to induce regression of cardiac hypertrophy to the point of atrophy and degeneration (8–12). This notion dominated the field to the point that specific anti-atrophic drugs (e.g., clenbuterol) were repeatedly used to prevent the presumed atrophic remodeling in LVAD studies and thus enhance the myocardial recovery observed in a subset of patients during LVAD unloading (3,10–16).

In this prospective study, we investigated whether mechanical unloading of the failing human heart induced by continuous-flow LVADs is associated with myocardial atrophy and degeneration at the functional, microstructural, ultrastructural, metabolic, and molecular levels.

## METHODS

**STUDY POPULATION.** We prospectively enrolled 44 consecutive patients with clinical characteristics consistent with chronic HF who required circulatory support with continuous-flow LVAD as bridge to transplantation between 2008 and 2011. Patients who required LVAD support for acute HF (acute myocardial infarction, acute myocarditis, post-cardiotomy cardiogenic shock, and so on) were excluded. The patients were enrolled at the institutions comprising the UTAH Cardiac Transplant program (University of Utah Health Science Center, Intermountain Medical Center, and the George E. Wahlen VA Medical Center, Salt Lake City, Utah). After LVAD implantation, the device speed was adjusted to achieve adequate flows (cardiac output) and LV decompression. The pump speed was adjusted under echocardiographic guidance during the post-implantation hospitalization (and at subsequent outpatient clinic visits) to achieve a midline position at the interventricular and interatrial septa and minimal mitral valve regurgitation. Normal control samples were 18 normal donor hearts (mean age 33.6 ± 3.5 years), not allocated for heart transplantation for noncardiac reasons (size, infection, etc.). The institutional review board of the participating institutions approved the study, and all patients provided informed consent.

**TISSUE ACQUISITION.** Myocardial tissue was prospectively collected from the LV apical core at LVAD implantation. To avoid any reactive foreign body inflammatory changes, tissue was obtained from the apex at the time of cardiac transplantation, at least 1.5 to 2 cm distant from the LVAD inflow cannula site. Control samples were acquired from hearts that were not transplanted for noncardiac reasons. Normal donor LV apical tissue was harvested and processed in the same manner as the failing hearts. For tissue processing details, see the supplemental Methods section in the Online Appendix.

**CARDIOMYOCYTE SIZE EVALUATION.** Cardiomyocyte size evaluation was previously described (17)

**ABBREVIATIONS AND ACRONYMS**

**ANP** = atrial natriuretic peptide
**HF** = heart failure
**LV** = left ventricular
**LVAD** = left ventricular assist device
**PAS** = periodic acid Schiff
**PASD** = periodic acid Schiff with diastase
**RyR** = ryanodine receptor
**UBB** = ubiquitin
**UBE2** = ubiquitin-conjugating enzyme E2
**UPS** = ubiquitin proteasome system

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