Sustained Cardiac Recovery Hinges on Timing and Natural History of Underlying Condition

Abhishek Jaiswal, MD[1,*], Thierry H. Le Jemtel, MD[1], Rohan Samson, MD[1] and Donna Mancini, MD[2]

[1]Tulane University Heart and Vascular Institute, Tulane School of Medicine, New Orleans, Louisiana; [2]Division of Cardiology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York

ABSTRACT

The review underlines that advanced heart failure (AHF) patients who experience sustained cardiac recovery in the current left ventricular assist device (LVAD) era have similar clinical characteristics to those who experienced myocardial recovery in the pre-LVAD era. They are young, do not have coronary artery disease and were treated for idiopathic dilated cardiomyopathy within weeks to months of experiencing symptoms. As recently shown with progressive remodeling of the transverse tubular system, AHF results in myocyte and extracellular matrix alterations that with time become irreversible. Young age, short duration of symptoms and LV systolic dysfunction as evidenced by smaller LV cavity dimension are primary determinants of sustained cardiac recovery in patients with AHF. Mechanical circulatory support can be life saving in patients with low-cardiac output and end-organ dysfunction. However, the underlying condition and not mechanical circulatory support appears to be the primary determinant of sustained myocardial recovery.

Key Indexing Terms: Myocardial recovery; Sustained cardiac recovery; Left ventricular assist device; Advanced heart failure.
[Am J Med Sci 2018;356(1):47–55.]

INTRODUCTION

Sustained cardiac recovery (steady left ventricular [LV] performance and functional capacity for >3 years after device removal) is an attractive goal of prolonged mechanical circulatory support (MCS).[1] It may obviate the need for cardiac transplantation in a large cohort of patients with advanced heart failure and thus lessens the donor shortage issue.[2] However, the rate of sustained cardiac recovery during MCS remains extremely low and greatly differs from center to center.[3] Low-success rates of persistent cardiac recovery have been attributed to the lack of aggressive pharmacotherapy, bridge to recovery protocols and adequate LV unloading.[4] Apart from acute myocarditis and peripartum cardiomyopathy, the nature of the underlying condition is not routinely viewed as a major determinant of sustained recovery after long-term MCS.[5]

This review details the clinical profile and management of patients who experience sustained recovery in the pre-MCS era and after MCS with LV assist devices (LVAD). The effects of mechanical unloading with LVAD on cardiomyocytes and extracellular matrix are then reviewed. In the absence of a randomized study of long-term MCS versus optimal pharmacologic therapy (that cannot be conducted for ethical reasons) one cannot ascertain whether long-term MCS does affect sustained myocardial recovery rates in advanced heart failure (AHF). However, by restoring hemodynamics compatible with life, long-term MCS is likely to increase the pool of AHF patients who with dilated cardiomyopathy and short duration of symptoms and LV dysfunction may experience sustained myocardial recovery.

MATERIAL CONTENT

Sustained Recovery in the pre-MCS Era

Sustained recovery, which seldom occurs in ischemic cardiomyopathy (ICM), is not uncommon in myocarditis and toxic insults or idiopathic dilated cardiomyopathy.[6,7] Sustained recovery does also occur in a non-negligible proportion (15-50%) of patients with idiopathic dilated cardiomyopathy.[8]

Spontaneous cardiac recovery has been observed in patients in the pre-β adrenergic receptor blockade (BARB) era. Three decades ago, Figulla et al[9] reported that 7 of 52 patients (13%) with dilated cardiomyopathy with no histologic evidence of myocarditis experienced a sustained increase in LV ejection fraction (LVEF) from 32-51% while receiving digitalis, diuretics and vasodilators. None of the baseline clinical and hemodynamic characteristics predicted sustained LVEF increase. A decade later, Dec et al[10] noted spontaneous increases in LVEF (>10% points) and clinical stability in 20-45% of patients with dilated cardiomyopathy. The improvement in LVEF was independent of baseline LVEF and most often occurred within 6 months of the diagnosis of dilated cardiomyopathy. Steimle et al[11] confirmed that recovery is most likely to occur in patients with short

duration of symptoms. Among 297 consecutive patients with dilated cardiomyopathy who were referred for cardiac transplantation, 49 had symptoms for <6 months. Thirteen of the 49 patients (27%) experienced a LVEF increase from 22-49% that was sustained over a period of 44 months. As 4 patients with LVEF recovery had myocarditis, peripartum cardiomyopathy or alcoholism, the recovery rate was actually 18% (9/49) in patients with idiopathic dilated cardiomyopathy. Cicoira et al[12] reported improvement in LV function in 19% of patients (19/98) with idiopathic dilated cardiomyopathy during a median follow up of 37 months. A recent onset of symptoms and a history of hypertension were the strongest predictors of recovery.

Improvement in LVEF during BARB in patients with chronic heart failure was first reported by Waagstein et al[13] and Swedberg et al.[14] Subsequently, Cioffi et al observed an improvement in LVEF ≥ 10% in 31 of 87 elderly patients (35%) with recently diagnosed ischemic and non-ICM (NICM) after a mean follow up of 17 months. The improvement in LVEF was most notable in patients receiving BARB therapy.[15] Treatment with BARB increased the likelihood of recovery by 3.4 times. In 295 patients with recent onset ischemic and NICM, O'Keefe et al[16] reported normalization of LVEF during carvedilol therapy in 16% of patients. Similarly, Kawai et al[17] noted LV recovery in 26% of patients with dilated cardiomyopathy after BARB for 2 years. McNamara et al[18] demonstrated a similar normalization rate (25%) of LVEF in patients at 6-month follow up in a mixed population of 373 patients with idiopathic dilated cardiomyopathy and myocarditis with symptoms for <6 months. However, Merlo et al[19] reported a recovery rate of 37% in 361 patients with dilated cardiomyopathy after BARB for 2 years. Zou et al[20] reported normalization of LVEF in nearly 50% of patients after a mean follow-up of 31 months. A younger cohort with shorter duration of symptoms and higher baseline LV function might have contributed to the high recovery rate in the last 2 reports. Reviewing LV recovery in patients with new onset dilated cardiomyopathy, Givertz et al[7] noted normalization of LV function in 7-25% of patients.

Predictors of LVEF recovery during BARB have been previously reviewed.[21] O'Keefe et al[16] observed approximately 2-fold greater improvement in LVEF in patients with recent onset NICM than in patients with ICM. Approximately, 30% of patients with a nonischemic cause improved LVEF by ≥ 21 points, compared with only 10% of ICM patients. Binkley et al[6] showed that younger women with dilated cardiomyopathy and normal QRS duration were more likely to experience LVEF recovery than elder men with abnormal QRS duration. Similarly, short duration of symptoms, nonischemic etiology, narrow QRS duration, smaller LV end-diastolic diameter (<6 cm), hypertension and higher presentation LVEF predicted improvement in LVEF.[18-20,22]

Overall, it appears that the frequency and clinical profile of patients who experience LV recovery are similar in both pre- and contemporaneous BARB era. Interestingly, Givertz et al[7] pointed out that while implementation of guidelines directed medical therapy (GDMT) facilitates LV recovery it does not primarily determine full LV recovery, supporting the view that normalization of LV function primarily depends on the nature of the underlying disease process. The recently reported low LV recovery rate (7-25%) in patients with idiopathic dilated cardiomyopathy receiving GDMT corroborates this assumption.[22-25] Relapse of LV dysfunction on discontinuation of BARB in patients with recovered LV function suggests that BARB may result in remission rather than recovery.[26,27]

Whether long-term GDMT induces recovery remains unresolved at present time.[6,7,27] Mortality increases in patients who experienced improvement in LVEF after BARB withdrawal without decrease in LVEF.[28] Further, recurrence of LV systolic dysfunction has been noted in patients who once had recovered LVEF while receiving GDMT. Gupta et al[25] reported a recurrence rate of 36% in patients with dilated cardiomyopathy with wider QRS duration. The authors noted that most patients had a relapse after 5 years. A wider QRS duration identifies a subset of dilated cardiomyopathy patients with significant cardiac remodeling.

For HF patients with a wide QRS complex, cardiac resynchronization therapy (CRT) significantly improves LVEF and LV volumes lessening morbidity and mortality.[21] In MADIT-CRT population, LVEF improved from a mean of 29.5-40.5% at 12 months and 7.3% patients achieved an LVEF of >50%.[29] Super responders of CRT, (defined as LVEF normalization), are young females with NICM of short duration and smaller left atrial size.[30,31] However, the beneficial effect of CRT seems to be present as long as it is continued.[32] In a single center experience, Kay et al noted significant deterioration of LVEF at 6 months after discontinuation of CRT.[33] The sustainability of cardiac recovery after cessation of CRT warrants further investigation.

In summary, sustained recovery does occur in patients with idiopathic dilated cardiomyopathy (Table 1). Younger patients with smaller LV cavity dimension and normal QRS duration—signifying recent onset dilated cardiomyopathy are the most likely candidates for sustained recovery.

TABLE 1. Characteristics of patients with heart failure and subsequent cardiac recovery during the pre-β adrenergic receptor blockade, β adrenergic receptor blockade era and left ventricular assist device support eras.

Young age
Female
Nonischemic etiology
Short duration of symptoms
Smaller cardiac dimension
Narrow QRS
Hypertension