Journal of the American College of Cardiology
© 2011 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 58, No. 22, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.09.007

EDITORIAL COMMENT

Myocardial Expression Levels of Micro-Ribonucleic Acids in Patients With Left Ventricular Assist Devices

Signature of Myocardial Recovery, Signature of Reverse Remodeling, or Signature With No Name?*

Douglas L. Mann, MD,†
Daniel Burkhoff, MD, PHD‡
St. Louis, Missouri; and New York, New York

Clinical studies have shown that medical and device therapies that reduce heart failure morbidity and mortality also lead to a decreased left ventricular (LV) volume and mass and restore a more normal elliptical shape to the ventricle. These changes are due to the changes in myocyte size, structure, and organization that, on a global level, are reflected in shifts of the LV end-diastolic pressure–volume relationship toward normal. For want of better terminology, these changes, which encompasses myriad changes at the molecular, cellular, tissue, and organ level, have been referred to as "reverse remodeling" (1,2). More recently, it has also become clear that a subset of patients whose hearts have undergone reverse remodeling after support with a mechanical circulatory ventricular assist device (VAD) are able to be weaned from their VADs, which has been referred to as "myocardial recovery" (3). These observations have engendered a great deal of interest, insofar as they may provide insight into developing novel therapies that actually reverse heart failure, as opposed to preventing it from progressing (4).

See page 2170

In this issue of the *Journal*, Ramani et al. (5) examined the expression levels of noncoding ribonucleic acids (RNAs), termed microRNAs (miRs [see Topkara and Mann (6) for a review of microRNA biology]) in 28 patients with nonischemic heart failure who underwent VAD placement, to determine whether there was a relationship between the expression levels of microRNAs at the time of VAD implantation and the ability of the heart to recover after VAD support. This study included a test cohort of 14 patients and a validation cohort of 14 patients from a separate institution. Fourteen of the patients underwent removal of their VAD (LV recovery group, n = 7 from the test cohort and 7 from the validation cohort), whereas the other 14 patients remained VAD dependent. Apical myocardial cores, obtained at the time of implantation, were examined with respect to expression levels of 376 miRs by polymerase chain reaction (PCR)-based array and real-time (RT)-PCR methods at the time of VAD implantation. MicroRNA levels were also obtained from 7 nonfailing hearts. Moreover, microRNA levels were also examined in the hearts of patients at the time of VAD implantation, as well as at the time of VAD removal. Ramani et al. (5) noted that the levels of 4 miRs, namely, miR 15b, miR 23a, miR 26a, and miR 195, were significantly decreased in the LV recovery hearts when compared to VAD-dependent patients in the test cohort. Importantly, the validation cohort revealed similar findings with respect to microRNA expression levels in the LV recovery group. Of interest, there was no difference in the expression of miR 15b, miR 23a, miR 26a, and miR 195 levels before and after VAD implantation. Moreover, the expression levels of miR 23a and 195 in the LV recovery group were similar to those of nonfailing hearts. The hearts from the LV recovery group had significantly smaller cardiomyocytes at the time of VAD implant by quantitative histology. Ramani et al. (5) concluded that the lower cardiac expression of miRs 23a and 195 at the time of VAD placement was associated with subsequent LV functional recovery and that the differential expression of microRNAs at the time VAD placement may serve as a potential biomarker to assess the potential of myocardial recovery after VAD implantation.

Before discussing the clinical implications of this carefully done study, it is helpful to digress for a moment to discuss what is known and what is not known about myocardial recovery in the failing heart.

Myocardial recovery and the failing heart. Despite the frequent use of the term "myocardial recovery" to describe the reversal of various aspects of the heart failure phenotype after medical and device therapy, myocardial recovery has never been defined in the medical literature. The concept that the failing heart could "recover" became enmeshed in the lexicon of heart failure terminology in the mid 1990s after the observation was made that mechanical circulatory support with VADs was consistently associated with decreased LV size and marked leftward shifts toward normal

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the †Center for Cardiovascular Research, Division of Cardiology, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri; and the ‡Division of Cardiology, Columbia University, New York, New York. This research was supported by research funds from the National Institutes of Health (RO1 HL58081, RO1 HL61543, and RO1 HL-42250 to Dr. Mann). Dr. Mann is on the Scientific Advisory Board of miRagen. Dr. Burkhoff is the medical director of Circulite.

of the LV end-diastolic pressure–volume relationship, indicating that the heart was not simply unloaded but, rather, that there were fundamental changes in the biological properties of the heart that allowed the ventricle to return toward normal size, shape, and function (2). Moreover, there were anecdotal reports that some patients could be weaned from their VAD (7,8). These early observations were later complemented by studies of heart failure patients treated with angiotensin-converting enzyme inhibitors and beta-blockers, in whom significant decreases in LV end-diastolic volume where noted compared to placebo controls (9–11), although not to the same degree as observed with left ventricular assist devices. Viewed together, these studies challenged the prevailing dogma that heart failure was irreversible and, in turn, fostered a greater interest in understanding the biological processes responsible for restoration of normal cardiac structure and function. However, our understanding of myocardial recovery has been challenged by perplexing studies in patients showing that while mechanical unloading of the heart leads to restoration of LV size, shape, and pressure-volume relationships, and partial reversal of many aspects of the molecular and cellular heart failure phenotype (12), the vast majority of patients cannot be weaned from mechanical circulatory support (13,14). Thus, although myocardial recovery is always accompanied by reverse remodeling, reverse remodeling does not always result in myocardial recovery, despite the apparent similarities of these 2 processes at the anatomic, cellular, and molecular levels (15,16). So, what exactly is myocardial recovery?

In the absence of a previously established working definition, we propose that myocardial recovery of a failed heart be defined as the normalization of the molecular, cellular, myocardial, and LV geometric changes that provoked cardiac remodeling, that allow the heart to maintain preserved LV structure and function in the face of normal and/or perturbed hemodynamic loading conditions. Thus, although reversal of the heart failure phenotype at the cellular (myocyte) and molecular levels is necessary for the initiation of myocardial recovery, and is responsible for the restoration of normal LV size and shape (i.e., reverse remodeling), the sustainability of myocardial recovery will likely depend on the ability of the heart to maintain preserved structure and function in response to normal and/or perturbed hemodynamic loading conditions (Fig. 1). Although there has been significant work in understanding many aspects of reverse remodeling at a phenomenological level, there has been essentially no prior work on understanding the factors that allow the reverse remodeled heart to maintain preserved LV structure and function in the face of normal and/or perturbed hemodynamic loading conditions. Unfortunately, the extant literature does not suggest which of the myriad changes that occur during reversal of the heart failure phenotype is most important and/or necessary to preserve LV structure and function. Intuitively, one can speculate that changes within the myocardium, including both progressive loss of cardiac myocytes, as well as the organization of the extracellular matrix are likely to be extremely important (17). Although current efforts have largely focused on the changes in the type and/or volume fraction of collagen in the reverse remodeled heart, it is likely that changes in the 3-dimensional organization of collagen matrix, as well as interactions between the collagen matrix and the resident cardiac myocytes, will be critically important in terms of preserving LV structure and function.

In light of the foregoing discussion, what insights can be gleaned from the study of Ramani et al. (5) with respect to our understanding of myocardial recovery? The observation that the expression levels of the 4 of the microRNAs that predicted recovery in VAD patients did not change in the subset of patients who had microRNA levels determined before and hemodynamic unloading, and that 2 of the microRNAs identified (miRs 23a and 195) were similar to the levels found in nonfailing myocardium suggests that

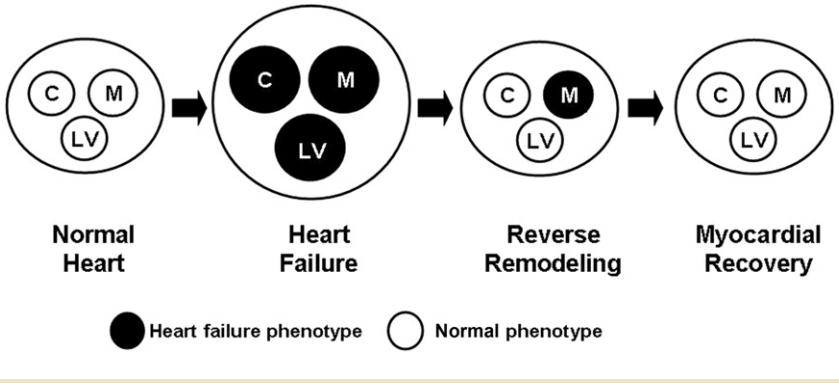

Figure 1 Myocardial Recovery of the Failing Heart

Myocardial recovery of a failed heart can be defined as the normalization of the molecular, cellular, myocardial, and left ventricular (LV) geometric changes that provoked cardiac remodeling. **Solid circles** = heart failure phenotype; **open circles** = normal phenotype; C = cardiac myocyte biology; LV = left ventricular geometry; M = myocardium (cardiocytes and extracellular matrix).

"recoverability," at least in this study, may relate more to the severity and nature of the underlying heart failure at the time of VAD implantation, rather than to the effect of mechanical unloading and/or concomitant medical therapy per se.

Although Ramani et al. (5) matched the clinical heart failure characteristics of the recovery and the VAD dependent groups meticulously, and were careful to exclude heart failure etiologies that are known to recover (e.g., myocarditis), it is possible that the stability of the miR 23a and miR 195 levels in the recovery group is a biomarker that identifies patients with less advanced heart failure, who are more or most likely to recover with device and/or medical therapies when compared to patients with more advanced disease. Indeed, the microRNAs that were identified in this study did not have in silico-based mRNA targets that are thought to be involved in either reverse remodeling or myocardial recovery, suggesting that the microRNAs were not involved mechanistically in recovery.

Thus, the provocative question raised by this study is whether at some point the failing heart "crosses the Rubicon," and that when damage to the heart eventually becomes advanced, even though reverse remodeling may be possible, the heart cannot maintain preserved LV structure and function in the face of normal and/or perturbed hemodynamic loading. Our lack of understanding regarding the key biological differences between reverse remodeling and myocardial recovery may be 1 of the root causes for our inability to design, develop, and implement new medical therapies for heart failure over the past decade. Given that the economic burden imposed by the epidemic of heart failure is rapidly approaching the tipping point, there has likely never been a better time for funding agencies, industry, and academia to work together to address the broader questions raised in the important study by Ramani et al. (5).

Reprint requests and correspondence: Dr. Douglas L. Mann, Division of Cardiology, Washington University, 660 South Euclid Avenue, Campus Box 8086, St. Louis, Missouri 63110. E-mail: dmann@dom.wustl.edu.

REFERENCES

1. Kass DA, Baughman KL, Pak PH, et al. Reverse remodeling from cardiomyoplasty in human heart failure. External constraint versus active assist. Circulation 1995;91:2314–8.
2. Levin HR, Oz MC, Chen JM, Packer M, Rose EA, Burkhoff D. Reversal of chronic ventricular dilation in patients with end-stage cardiomyopathy by prolonged mechanical unloading. Circulation 1995;91:2717–20.
3. Westaby S, Jin XY, Katsumata T, Taggart DP, Coats AJ, Frazier OH. Mechanical support in dilated cardiomyopathy: signs of early left ventricular recovery. Ann Thorac Surg 1997;64:1303–8.
4. Shah AM, Mann DL. In search of new therapeutic targets and strategies for heart failure: recent advances in basic science. Lancet 2011;378:704–12.
5. Ramani R, Vela D, Segura A, et al. A micro-ribonucleic acid signature associated with recovery from assist device support in 2 groups of patients with severe heart failure. J Am Coll Cardiol 2011;58:2270–8.
6. Topkara VK, Mann DL. Role of microRNAs in cardiac remodeling and heart failure. Cardiovasc Drugs Ther 2011;25:171–82.
7. Frazier OH. First use of an untethered, vented electric left ventricular assist device for long-term support. Circulation 1994;89:2908–14.
8. Levin HR, Oz MC, Catanese KA, Rose EA, Burkhoff D. Transient normalization of systolic and diastolic function after support with a left ventricular assist device in a patient with dilated cardiomyopathy. J Heart Lung Transplant 1996;15:840–2.
9. Konstam MA, Kronenberg MW, Rousseau MF, et al. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dilatation in patients with asymptomatic systolic dysfunction. SOLVD (Studies of Left Ventricular Dysfunction) Investigators. Circulation 1993;88:2277–83.
10. Greenberg B, Quinones MA, Koilpillai C, et al. Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction: results of the SOLVD echocardiography substudy. Circulation 1995;91:2573–81.
11. Australia/New Zealand Heart Failure Research Collaborative Group. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. Lancet 1997;349:375–80.
12. Margulies KB, Matiwala S, Cornejo C, Olsen H, Craven WA, Bednarik D. Mixed messages: transcription patterns in failing and recovering human myocardium. Circ Res 2005;96:592–9.
13. Mancini DM, Beniaminovitz A, Levin H, et al. Low incidence of myocardial recovery after left ventricular assist device implantation in patients with chronic heart failure [see comments]. Circulation 1998;98:2383–9.
14. Itchhaporia D, Snow PB, Almassy RJ, Oetgen WJ. Artificial neural networks: current status in cardiovascular medicine. J Am Coll Cardiol 1996;28:515–21.
15. Hall JL, Fermin DR, Birks EJ, et al. Clinical, molecular, and genomic changes in response to a left ventricular assist device. J Am Coll Cardiol 2011;57:641–52.
16. Drakos SG, Kfoury AG, Selzman CH, et al. Left ventricular assist device unloading effects on myocardial structure and function: current status of the field and call for action. Curr Opin Cardiol 2011;26:245–55.
17. Mann DL. Mechanisms and models in heart failure: a combinatorial approach. Circulation 1999;100:999–1088.

Key Words: cardiomyopathy ■ heart assist device ■ hypertrophy ■ microRNA.