Bridge to Recovery and the Search for Decision Nodes

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It is the great glory as well as the great threat of science that everything which is in principle possible can be done if the intention to do it is sufficiently resolute.

—Peter Medawar
The Threat and the Glory, 1977

Heart failure is a major global problem that continues to defy attempts at offering solutions based on a comprehensive understanding of its basic mechanisms. Insertion of left ventricular assist devices (LVADs) in patients with advanced heart failure can result in profound changes in the structure and function of the myocardium that are referred to as “reverse remodeling.” Occasionally, this process can result in sufficient improvement in myocardial function to enable explantation of the device, with prolonged reversal of heart failure (“bridge to recovery”). Studies of the timing and the relationship between changes in structure to function at different levels offer unprecedented opportunities in unraveling the secrets of heart failure while fine-tuning bridge to recovery. By necessity, these studies rely largely on in depth analysis of scarce, often minute human myocardial tissue followed by integrating the results to equally detailed clinical studies. Unfortunately, most of the literature relating to this subject is derived from studies on samples taken at the time of transplantation rather than clinical “recovery.” Because the timing of transplantation depends on the availability of donor organs, the period of support and degree of recovery is extremely variable.

The study of myofilament function could be of value in explaining some of the events and inconsistencies observed in bridge to recovery. The lack of changes in myofilament sensitivity or cooperativity after LVAD implantation reported

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by Ambardekar is difficult to explain. Studies in animal models show that unloading is associated with time-dependent changes in myofibrillar function.9

Bridge-to-recovery studies have shown that the observed reverse remodeling is associated with changes in gene expression involving a large number of genes.10 These studies used techniques to detect and/or quantify changes in candidate or global gene expression. Ambardekar and colleagues used real-time polymerase chain reaction to examine changes in gene expression in several selected genes encoding sarcomeric proteins. In addition, they evaluated posttranslational modifications (phosphorylation of some of these genes). Previous studies of LVAD-induced changes in sarcomeric, nonsarcomeric, and linker proteins suggest an important role of these molecules in the process of reverse remodeling.10–13 Attempts at defining global gene expression using progressively more sophisticated tools have yielded useful information regarding the possible contribution of different networks, operating at different levels, in orchestrating reverse remodeling. Although many of the changes induced by prolonged unloading of the myocardium are beneficial, others can be harmful. The concept and time frame of atrophy of the myocardium is poorly studied and deserves more attention.

The rapidly accumulating knowledge in the field is bringing us nearer to understanding the fundamental mechanisms of heart failure, its progression, and, importantly, regression. The emerging picture is that of a series of complex biological networks, which, in common with other complex networks,14 are governed by a large number of interconnected nodes acting as decision nodes or hubs, with time-dependent bidirectional flow of information between the different nodes. Recent studies of complex biological networks have shown that information from decision nodes does not necessarily go through hubs.14 Defining the topology of the network as well

Figure 1. Isolated ventricular myocytes from patients at the time of insertion of a left ventricular assist device (LVAD) (middle horizontal panel) showing severe hypertrophy as compared with normal controls (top horizontal panel). Bottom panel, “Normalization” of the size of the myocytes after LVAD. Reproduced from Reference 5 (Yacoub MH. A novel strategy to maximize the efficacy of left ventricular assist devices as a bridge to recovery. Eur Heart J. 2001;22:534–540), by permission of Oxford University Press.

Figure 2. Photomicrograph of ventricular myocytes before (A) and after (B) recovery using left ventricular assist device combination therapy.
as the type and hierarchy of the decision nodes is mandatory for achieving progress in the fields of bridge to recovery and identifying novel mechanistic therapeutic targets for the treatment of heart failure.

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None.

**References**


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