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 authors present a retrospective analysis of 8 patients with paired samples taken at the time of device implantation and at transplantation. They examined several clinical parameters before LVAD implantation and before transplantation; the latter studies were performed during device support. The myocardial samples were examined for cell size and contractile characteristics measured in cell fragments obtained from frozen LV samples by mechanical homogenization. In addition, they examined myofilament function and sensitivity to Ca$^{2+}$ as well as the expression of a number of cardiac sarcomeric proteins, posttranslational modification, and isoform shift. What have we learned from this study? The first lesson is that the clinical characterization of cardiac function before explantation must be standardized both in terms of timing and, importantly, methodology. The latter should eliminate, as much as possible, the confounding influence of the simultaneously functioning device. Several methods of testing cardiac function after switching off pulsatile devices or reducing the RPM in continuous-flow pumps have been devised and used in some series. Further refinement of these methods is required to allow them to act as good correlates to the basic science studies and, importantly, to predict short- and longer-term outcome after explantation of the device.

With regard to evaluating the changes in myocardial cell size and their relevance, there is a pressing need to compare the different methods used for this purpose and attempt to relate them to changes in myocardial wall thickness. Ambardekar and colleagues measured the size of cell fragments after tissue homogenization; other studies measured cellular diameter or volume in intact tissue sections or in single cells (Figure 1), using standard morphometric (Figure 2) or electrophysiological techniques. Without exception, all these studies reported varying degrees of reduction in cell size. Hypertrophy at organ and cellular levels is well documented in patients with heart failure and is associated with poor prognosis. It is widely assumed that regression in hypertrophy improves prognosis. This notion was supported by the observation that regression in cellular hypertrophy after LVAD support was associated with varying degrees of improvement in cellular contractility as measured by shortening fraction, force frequency, or calcium force relationship. In contrast, previous studies from our laboratory showed that unlike sarcomplasmic reticulum calcium content and other related parameters, regression in hypertrophy was not invariably associated with recovery. This highlights the fact that myocardial function is governed by a complex network of interacting factors that must be taken into consideration. Another intriguing aspect of interpreting the observed diminution in cell size in LVAD patients is the possibility that these cells represent stem cells recruited from local or distant sites. Previous studies from our laboratory showed an increase in myocardial expression of insulin-like growth factor-1 and stromal cell-derived factor-1 (SDF-1) after bridge to recovery using LVAD combination therapy. These 2 molecules are associated with recruitment of progenitor cells. This important issue must be investigated further both in humans and experimental models.

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 myofibrillar sensitivity or cooperativity after LVAD implantation reported...
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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