The greatest impediments to survival in heart transplant recipients in the first year post-transplant are infection and rejection. Over time, transplant coronary artery disease (a form of chronic rejection) and malignancy (resulting from inadequate immune surveillance of cancer cells) emerge as threats. Balancing immune response is one of the most serious challenges for the transplant cardiologist: over-immunosuppression results in an increased risk for infection and malignancy, while under-immunosuppression results in increased risk for rejection and transplant CAD.

It has been no simple matter to monitor the effect of immunosuppressive therapy on transplant recipients’ immune response. Drug monitoring values, while useful for preventing drug toxicity, do not measure the immune response state nor the risk for rejection or infection. Recently, however, two new blood tests have emerged as important tools for these very purposes.

Measuring immunosuppression
ImmuKnow®, approved by the U.S. Food and Drug Administration for the detection of cell-mediated immunity in an immunosuppressed population, measures adenosine triphosphate (ATP) release from activated lymphocytes. A low score reflects low production of ATP, indicating that the patient is more immunosuppressed. The test has shown promise in assessing infection and rejection risk in several types of solid organ transplants, including kidney, pancreas and small bowel recipients. In previous research, my colleagues and I were among the first to investigate the utility of this assay in a large number of heart transplant patients.

Between November 2005 and July 2008, we studied 296 heart transplant recipients who had 864 assays of ATP production performed at two weeks to 10 years post-transplant and correlated to infection and rejection events that occurred within one month after testing. All patients received standard triple-drug immunosuppressive therapy with tacrolimus, mycophenolate and corticosteroids without induction therapy.

There were 39 infectious episodes and eight rejection episodes. The average ImmuKnow score was significantly lower during infection than steady state (187 vs. 280 ATP ng/mL, p<0.001). The average ImmuKnow score was not significantly different during rejection than steady state (327 vs. 280 ATP ng/mL, p=0.30). Interestingly, 3 of the 8 rejection episodes were antibody-mediated rejection accompanied by compromised cardiac function, and for these, the mean ImmuKnow score was significantly higher than for steady state patients (491 vs. 280 ATP ng/mL p < 0.001). Based on these results, testing of ATP production appears to predict infection risk in heart transplant patients. The association between high ImmuKnow scores and rejection risk, however, was inconclusive due to the small number of patients experiencing rejection.

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Directions in Heart Failure Care
Michele Hamilton, MD

Heart failure (HF) has become an increasingly large healthcare problem, with more than 500,000 new cases each year in the United States alone. It has an expected mortality of as high as 50 percent within five years of diagnosis, higher than many cancers, and treatment of HF is now the single greatest Medicare expenditure. In fact, HF remains the most common diagnosis in hospitalized Medicare patients.

The impaired systolic cardiac performance characteristic of HF leads to maladaptive compensatory activation of the renin-angiotensin-aldosterone, sympathetic and other vasoconstriction systems, causing adverse remodeling and further worsening of cardiac function. HF therapy has evolved as a multi-pronged approach to counteract these factors. Angiotensin-converting enzyme inhibitors (or angiotensin receptor blockers for patients with cough), beta blockers and aldosterone antagonists have all been shown in large randomized trials to improve survival, and together these drugs provide the foundation for the treatment of systolic HF. Numerous trials have shown that it is imperative to employ these medications, even in the sickest, New York Heart Association Class IV (American Heart Association Stage D) patients and to upward titrate to target doses as tolerated.

The A-HeFT study, a large U.S. multi-center trial, showed that the addition of isordil and hydralazine may lead to a further reduction in mortality and HF symptoms in African-Americans. Omega-3 fatty acids also provide a small additional survival advantage when added to the other therapies. Diuretics, useful in reducing volume overload and symptoms of congestion, must be used with care to avoid development of cardiorenal syndrome. Implantable defibrillators improve survival in patients with reduced systolic function, with additional benefit from resynchronization therapy in a still-to-be-clarified subset of this population.

Although studies of endothelin and cytokine antagonists have not been favorable, other agents, such as direct renin and vasopressin antagonists, continue to be evaluated. Ventricular assist devices and other surgical options are becoming more practical, and may ultimately be useful in preventing the progression of ventricular dysfunction before advanced symptoms develop. Finally, exciting stem-cell research is also in progress.

Reducing re-hospitalizations

Despite the significant advances in HF therapy, many patients continue to have recurrent hospitalizations, with rates as high as 50 percent at six months. This happens so frequently and is so costly, in fact, that the Center for Medicare and Medicaid Services has targeted HF re-hospitalizations for possible reduction in Medicare reimbursements. Contributing factors to avoidable hospital readmission include submaximal treatment of the initial episode, inadequate transition and follow-up care, medication non-compliance, and dietary indiscretion.

The patient who has been hospitalized with acute heart failure provides a unique opportunity for optimizing medical therapy, reinforcing HF education and establishing close follow-up care. HF disease management programs focusing in these areas have consistently demonstrated sustained clinical benefit. At the Cedars-Sinai Heart Institute, we have sought to optimize initial hospitalization by creating a HF-specific inpatient unit with highly specialized staff and equipment, including hemodynamic monitoring and ultrafiltration. We are also keenly aware of the need to provide ongoing support to such patients once they leave the hospital. We see great potential for specialized outpatient HF programs, working in partnership with community-based cardiologists, to improve clinical outcomes.

In one such effort undertaken previously at another institution, we assigned dedicated physician/nurse teams to provide six months’ longitudinal care to HF patients following their intensive inpatient medical therapy. The longitudinal care emphasized sodium and fluid restriction, with daily weights and a flexible diuretic regimen.

The results were highly encouraging: my colleagues and I observed an 80 percent reduction in re-hospitalizations among our HF patients after launching this program. We are currently testing other approaches to follow-up care, including home visits, electronic scales and frequent phone contact.

Proven Therapies for HF

- Angiotensin-converting enzymes and receptor blockers
- Beta blockers
- Aldosterone antagonists
- Isordil/hydralazine (for African-Americans)
- Omega-3 fatty acids
- Defibrillators and resynchronization therapy
- Mechanical assist devices
- Cardiac transplantation
- Comprehensive management programs

Potential Therapies for HF

- Vasopressin antagonists
- Renin antagonists
- c-GMP PDE inhibitors (sildenafil)
- Iron or erythropoietin
- Hormonal supplementation
- Stem-cell therapy
- Implantable hemodynamic monitoring
- Percutaneous valve procedures
- Total Artificial Heart
Advances in Mechanical Circulatory Support

Jaime D. Moriguchi, MD

An estimated 250,000 Americans have disabling symptoms of congestive heart failure despite optimal medical therapy. While transplantation represents an excellent option for those fortunate enough to qualify, this life-saving procedure can only be offered to some 2,100 recipients annually.

Mechanical circulatory support (MCS), a relatively new surgical discipline, includes any mechanical device that is capable of pumping blood to support circulation. Over the past two decades, these pumps have been surgically implanted in thousands of patients with end-stage heart disease and cardiogenic shock as a bridge to transplantation or as destination therapy. For example, the HeartMate® XVE (also referred to as HeartMate I) left ventricular assist device (LVAD) offers marked improvement in survival and quality of life over medical therapy. The majority of patients are able to resume near-normal activities in an outpatient setting. However, due to its relatively large size, this particular device cannot be offered to children or most adults with a body surface area of less than 1.7 meters squared. Furthermore, its durability is limited: typically 12 to 18 months.

Recent technological advances in nonpulsatile or continuous flow axial devices, which resemble jet turbines, have resulted in quantum improvements in LVAD options. The HeartMate III® (Fig. 1) is the most celebrated device in its class and has been implanted in nearly a thousand individuals in the United States alone. It is extremely simple in design, with only one moving part and no valves. The pump, which is magnetically driven, is about the size of a D-cell battery and is capable of providing 4 to 8 liters of blood flow per minute. The infl ow cannula is placed in the left ventricular apex and the outflow graft anastomosed to the ascending aorta. Blood thinners are required, but stroke rates have been extremely low. Infectious complications of the percutaneous driveline have also been very low.

Even more impressive are the success rates for HeartMate II. More than 75 percent of implanted patients are successfully bridged to heart transplantation, with a one-year post-transplant survival rate of nearly 90 percent in most series. Furthermore, one-year survival of patients supported on this pump is approaching 90 percent, and pump durability is conservatively projected to be five to eight years. Not surprisingly, successful outcomes are tightly linked to appropriate patient selection, as well as center experience. Quality of life for recipients is improved on average by 2.1 functional classes (NYHA Class IV to II), and patients are extremely mobile. Improvements in lithium ion battery technology have extended battery life to nearly 12 hours. This device, the only LVAD in its class approved by the Centers for Medicare and Medicaid Services (CMS) as a bridge to transplantation, was approved in January 2010 as destination therapy.

The MCS Program at Cedars-Sinai has been extremely active over the past three years, averaging more than 30 VAD implants annually. Devices currently available include the Thoratec pneumatic BiVAD (paracorporeal pumps that sit outside the body, connected by cannulae supporting both left and right ventricles); Abiomed AB5000; and HeartMate I XVE and HeartMate II LVADs. Short-term support devices that can be implanted percutaneously in the cath lab include the Impella 2.5 and the TandemHeart®.

In the very near future, we hope to begin offering the Total Artificial Heart (Fig. 2). This device, which originated more than 25 years ago, has undergone multiple revisions and is the only implantable total artificial heart that is CMS-approved as a bridge to transplantation. It is a true heart replacement, not an assist device, capable of pumping 10 liters/minute with very low stroke and infection rates. More than 79 percent of patients who receive a Total Artificial Heart are successfully bridged to transplantation. P lovers, thanks to new investigational drivers weighing under 12 lbs., patients can be discharged home to lead quite active lives until suitable donor hearts become available.

Over the past several years, the field of mechanical circulatory support has literally exploded with a dazzling array of technological advances. Extremely miniaturized and durable pumps can be implanted with minimal morbidity and mortality, providing outstanding quality of life and improved survival. More significantly, this technology can be offered to all who qualify. What does the future hold? The answer may lie with the next generation of devices, which incorporate magnetically levitated rotors, and have no valves or bearings that can wear down. Anticipated durability extends beyond 15 to 20 years.

In summary, we now have a therapeutic option that represents a truly viable and attractive alternative to heart transplantation. There are many experts in the fields of mechanical circulatory support and transplantation who are thoroughly convinced, as I am, that MCS represents the future therapy of choice for end-stage heart disease.

Figure 1: The HeartMate II. Reprinted with permission from Thoratec Corporation.

Figure 2: Syncardia temporary Total Artificial Heart. Image courtesy of syncardia.com
Cardiac resynchronization therapy (CRT) is a relatively recent development that has further improved outcomes in the heart failure population. Electrical conduction abnormalities are commonly seen in heart failure and are associated with an increased mortality. Patients with wide QRS complexes have been noted to experience delayed activation of the free left ventricular wall, resulting in mechanical dyssynchrony—a process associated with adverse pathophysiologic and hemodynamic profiles. Cardiac dyssynchrony results in a decrease in stroke volume, facilitation of mitral regurgitation, increased wall stress and delayed relaxation.

The primary objective of CRT is restoration of a more normal ventricular activation pattern by providing almost simultaneous contraction of the left ventricular septum and free wall. A number of studies have demonstrated improvements in hemodynamics with CRT, including increases in cardiac output, systolic pressure and contractility, and decreases in left atrial pressure, myocardial oxygen consumption and mitral regurgitation.

Multiple randomized trials have conclusively demonstrated that the use of CRT in appropriately selected heart failure patients is associated with improvement in objective measures, including six-minute walk test, health-related quality-of-life scores, peak oxygen consumption and New York Heart Association (NYHA) functional class. Importantly, major randomized trials have also demonstrated a significant reduction in mortality and hospitalizations with CRT. Based on this data, CRT is recommended in patients with systolic dysfunction and heart failure resulting from either ischemic or nonischemic cardiomyopathy who have a left ventricular ejection fraction (LVEF) <0.35, are in NYHA functional class III or IV, are on maximal medical therapy, have a QRS complex duration >120 ms and are in sinus rhythm. More recent studies and meta-analysis of older data also suggests that CRT may be of benefit in patients with mild heart failure (NYHA II), although to date CRT is not currently an accepted recommendation in this population.

The role of CRT in patients with atrial fibrillation or patients with “induced dyssynchrony” from right ventricular pacing is unclear. Data suggests that patients with atrial fibrillation and complete atrioventricular block may fare better with CRT compared to right ventricular pacing alone, and a number of studies demonstrate that patients with cardiac defibrillators who undergo right ventricular pacing have a higher risk of heart failure exacerbation.

To date, QRS duration has represented the most reliable marker for mechanical dyssynchrony, and current guidelines recommend QRS duration—not QRS morphology—as a criteria for CRT. In clinical trials, most patients had left bundle branch morphology, and it remains unclear as to whether there is a relative difference in benefit in patients with left versus right bundle branch morphology. Imaging modalities such as tissue Doppler or magnetic resonance imaging may be useful in identifying who is likely to benefit from CRT, although further data is needed to justify routine use of these techniques.

Implantation of a CRT device is associated with a very low risk of morbidity and mortality. In clinical trials, mortality was less than 0.5 percent and complications of bleeding, infection, pneumothorax and cardiac tamponade were extremely low (<1 percent). Transvenous placement of a left ventricular lead, however, was associated with risk of failure as high as 10 percent. The most frequent complications were due to lead dislodgment or extracardiac stimulation. Improvements in techniques, equipment and expertise have led to a decline in failure rates.

Tests: continued from page 1

**Predicting rejection without biopsy**

Signs and symptoms of transplant rejection are non-specific, a fact that has made surveillance heart biopsies the cornerstone of post-transplant management for more than 30 years. The procedure has its disadvantages, however. Heart biopsy is limited by sub-optimal inter-observer reproducibility and a lack of histological findings in patients with compromised cardiac function. Moreover, heart biopsies are invasive and uncomfortable for patients, and are accompanied by significant morbidity (0.3 to 0.5 percent rate of serious complication).

AlloMap®, a noninvasive blood test, has the potential to refine diagnostic and prognostic accuracy. Using microarray technology to simultaneously analyze the expression of thousands of genes, AlloMap has correlated a pattern of gene expression to histologic cardiac rejection.

In clinical testing to date, AlloMap scores of greater than 34 have demonstrated a high correlation to rejection. Scores less than 34 were found to have a high negative predictive value (98%) for rejection. This test might even be used to determine which heart transplant patients could forego biopsies, since a very low score (less than 20 in the first six months after transplant) can predict an ensuing rejection-free three-month period.

The Cedars-Sinai Heart Institute plans to conduct a randomized trial of AlloMap versus heart biopsy to assess the routine use of AlloMap in heart transplant patients (IRB #21046). If AlloMap is shown to be equivalent to heart biopsy, this could drastically change the way heart transplant patients receive care—and improve their quality of life if routine heart biopsies are eliminated.

Despite the risks of rejection and infection, heart transplantation remains the preferred treatment for select patients with end-stage heart disease. The advent of the ImmunoKnow and AlloMap blood tests provide transplant cardiologists with powerful new tools to reduce these risks and improve outcomes for our heart transplant patients.

1 Some of the human research activities described in this article were initiated at non-Cedars-Sinai institutions prior to the investigators’ arrival at Cedars-Sinai.