

Management of End-Stage Heart Failure

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Heart failure (HF) is a highly prevalent, complicated clinical syndrome associated with extraordinary levels of morbidity and mortality. Lifetime risk for both men and women in the United States is currently estimated at 1 in 5¹, and ~300,000 annual US deaths are attributable to HF.² Implantable defibrillators and medications such as diuretics, ace inhibitors and beta-blockers provide significant mortality benefits. But even patients in clinical trials, who are considered to be receiving optimized medical therapy, have a 1-year mortality of 8-18%, making current therapy inadequate for long-term management.² Continued high mortality rates are the result of the relentlessly progressive nature of HF and the limited ability of current interventions to break this progression.

Until recently, cardiac transplantation was the only viable therapy with mortality benefit to offer to patients with end-stage HF. Given the difficulty in minimizing the progressive functional decline in HF patients, preventative measures are as important as new treatment modalities to the improvement of HF management. This paper will briefly describe the syndrome of HF and subsequently focus on developing management options, including ventricular assist devices, new pharmaceutical agents and cardiac regeneration.

Definition and Characterization of HF

Myocardial Failure vs. Heart Failure

In 1988, Packer defined HF as “a complex clinical syndrome characterized by abnormalities of left ventricular function and neurohormonal regulation, which are accompanied by effort intolerance, fluid retention and reduced longevity.”³ This description importantly differentiates HF from myocardial failure. Myocardial failure, as one component of HF, is secondary to a defect in myocardial contraction or relaxation, and is represented by systolic and diastolic failure respectively. Equally, myocardial failure can occur in either the left or right heart systems, and HF patients commonly suffer from dysfunctions in both.² Compensatory mechanisms for inadequate cardiac output resulting from myocardial failure, such as neurohormonal responses, initially correct for the unbalanced supply and demand. However, ultimately, these compensatory mechanisms drive further myocardial damage and thereby set the progressive nature of the HF syndrome.

A Vicious Cycle

The HF syndrome is a consequence of both myocardial failure and abnormal neurohormonal regulation. Complex neurohormonal changes result from hemodynamic changes produced by myocardial failure, mainly inadequate arterial volume and end-organ perfusion.⁴ Examples of these neurohormonal changes include enhancement of adrenergic drive, augmented activation of the renin-angiotensin-aldosterone axis and heightened vasopressin and endothelin release. Through enhanced vascular resistance and renal retention of sodium and water, these changes are initially sufficient to reestablish adequate levels of organ perfusion. Over time, these compensatory mechanisms become harmful through various deleterious effects, including enhanced afterload through vasoconstriction, electrolyte abnormalities from excessive sodium and water retention and arrhythmias (Figure 1). These deleterious effects contribute to many of the debilitating symptoms of heart failure, such as dyspnea and fatigue, and also add additional stress to the already failing myocardium. Thus, a “vicious cycle” is set in motion as compensatory mechanisms to myocardial failure require additional work from the heart, which in turn leads to additional injury and worsening myocardial failure.

Epidemiology

From a public health perspective, HF heavily contributes to the burden of disease in the United States, as can be immediately appreciated with a lifetime risk of 1 in 5 for both men and women.¹ Perhaps even more frightening is that despite improving management options, the incidence of HF has been steadily *increasing* over the past 2 decades.⁵ Per estimations from the American Heart Association (AHA) in 2002, there are nearly 550,000 new HF cases annually, and nationwide prevalence of ~5 million cases.⁶ Of these cases, between 300,000 and 800,000 patients can be characterized as having advanced HF, or New York Heart Association (NYHA) functional class III or IV despite medical management.^{7;8} Additionally alarming is that prevalence increases with age, with a prevalence of 1-2% in ages 50-59 but ~10% when older than 75 years.^{9;10} As the US population continues to age, we can expect both incidence and prevalence to continue to increase.

As well as being a very common syndrome, HF contributes to significant morbidity and mortality. HF is now recognized as the most common diagnosis-related group in the Medicare system and is responsible for more than 20% of all hospitalizations of patients older than 65 years.^{9;11} HF consumes more Medicare dollars than any other diagnosis as a result of nearly \$5500 per hospital discharge and additional monthly expense of \$1740 following discharge.^{9;12} As a whole, HF results in direct and indirect annual US costs of \$24.3 billion.⁶

HF mortality levels is also staggering. There are an estimated 300,000 annual US deaths with HF as a primary or contributory cause. HF patients enrolled in clinical trials typically have mild to moderate level disease and are considered to have access to the best available medical management, yet one-year survival rates continue to be devastating, ranging from 8-18%.² Expanding to an all-inclusive HF population, all patients with an index-diagnosis hospitalization in Scotland from 1986 to 1995 suffered 44.5% overall 1-year mortality. Median survival improved from the start (1.23 yr) to finish (1.64 yr) of the study period, likely as a result of new medications such as ace inhibitors, however this improvement is far from changing the scope of this disease process.¹³

Underlying Etiologies

Given the overwhelming disease burden of HF, recognition of risk factors and underlying etiologies is imperative to the provision of appropriate preventative measures and prompt medical management. The prospective cohort NHANES study identified numerous independent risk factors for the development of HF (Table I).⁵ Strikingly, ischemic heart disease is attributable to nearly 2/3 of all HF cases. Many risk factors of ischemic heart disease are independent risk factors for the development of HF, such as diabetes mellitus, hypertension, obesity and smoking cigarettes. Other recognized underlying etiologies not addressed in this study are thyroid disease and exposure to various cardiotoxins, such as alcohol. The appreciation of these risk factors will hopefully emphasize the importance of appropriate counseling and management of these issues.

Figure 1: The Cyclic Generation of Heart Failure

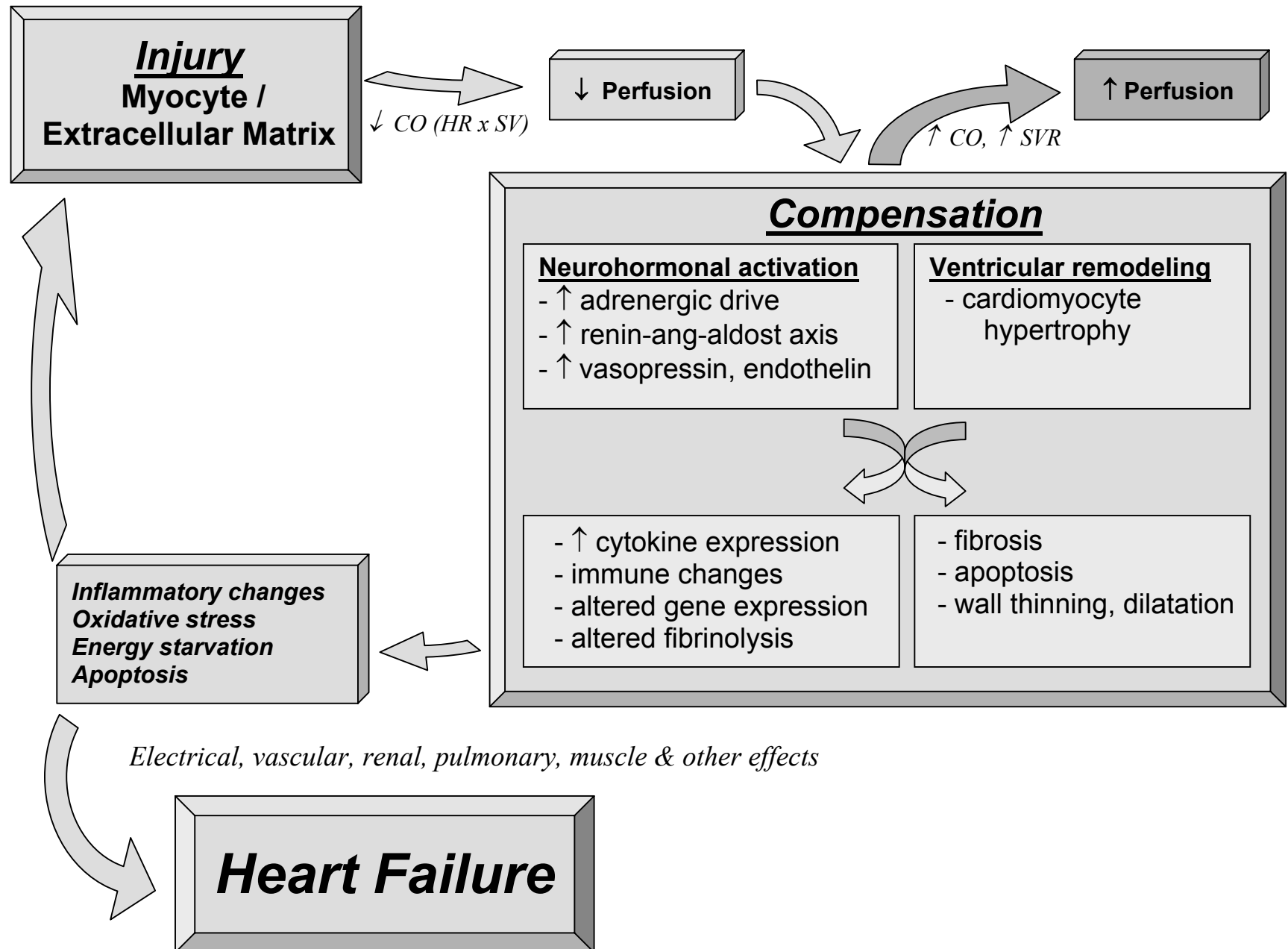


Table I. Independent Risk Factors of Heart Failure⁵

<u>Risk Factor</u>	<u>Relative Risk</u>	<u>Attributable Risk</u>
Coronary heart disease	8.11	61.6%
Diabetes mellitus	1.85	3.1%
Cigarette smoking	1.59	17.1%
Valvular heart disease	1.46	2.2%
Hypertension	1.40	10.1%
Overweight	1.30	8.0%
Male Sex	1.24	8.9%
Low physical activity	1.23	9.2%
Less than high school education	1.22	8.9%

Diagnosis and Clinical Presentation of HF

As described above, the clinical syndrome of HF is a combination of dysfunctional myocardium and unbalanced neurohormonal regulation. These combined deficits lead to a vast array of clinical signs and symptoms, which can be used for the diagnosis of the HF syndrome (Table II). The cardinal manifestations of HF are those physical signs and symptoms which we commonly associate with acute exacerbations of HF and although less appreciable, remain present in chronic HF. Physical signs of pulmonary congestion and peripheral edema derive from excessive fluid retention as a consequence of the compensatory neurohormonal mechanisms described above. Patients with advanced HF have a narrow functional fluid balance range. Minor fluid shifts can result in relative hypovolemia and hypoperfusion or hypervolemia and dyspnea. Accordingly, while one may be extremely symptomatic (dyspnea and fatigue), blatant physical signs such as edema and congestion may not be as obvious.

Table II. Framingham Diagnostic Criteria for CHF¹⁰

<u>Major Criteria*</u>	<u>Minor Criteria*</u>
Paroxysmal nocturnal dyspnea	Bilateral ankle edema
Neck vein distention	Nocturnal cough
Rales	Dyspnea on ordinary exertion
Radiographic cardiomegaly	Hepatomegaly
Acute pulmonary edema	Pleural effusion
S3 gallop	↓ vital capacity by 1/3 of previous max
Weight loss ≥ 4.5 kg in 5 days of CHF treatment	tachycardia (HR ≥ 120 beats/min)
At autopsy:	
- pulmonary edema or	
- visceral congestion or	
- cardiomegaly	

* (+) diagnosis with 2 major criteria OR 1 major and 2 minor criteria

Functional Classification and Staging of HF

The ability to characterize the severity of HF is certainly important in applying appropriately timed management options as well as describing prognosis. In 1994, the NYHA developed a classification system for HF patients designed to characterize disease severity based on functional status (Table III).¹⁴ Many clinical trials utilize this classification system for entry criteria as well describing the course of the intervention under study. Patients defined as having advanced heart failure are typically those considered to have sustained levels of Class III or IV functionality despite medical management. Of importance, this system is based on symptomatology and inherently allows rapid movement from class to class. A patient brought to the Emergency Department with pulmonary edema and respiratory distress at rest would qualify as class IV HF. Aggressive diuresis can drastically improve symptoms with reduction to class I or II, potentially leading to discharge from acute care within hours.

Table III. NYHA Functional Classification System¹⁴

<u>NYHA Class</u>	<u>Description</u>
I	asymptomatic with ordinary physical activity
II	symptomatic* with moderate physical activity
III	symptomatic with minimal physical activity
IV	symptomatic at rest

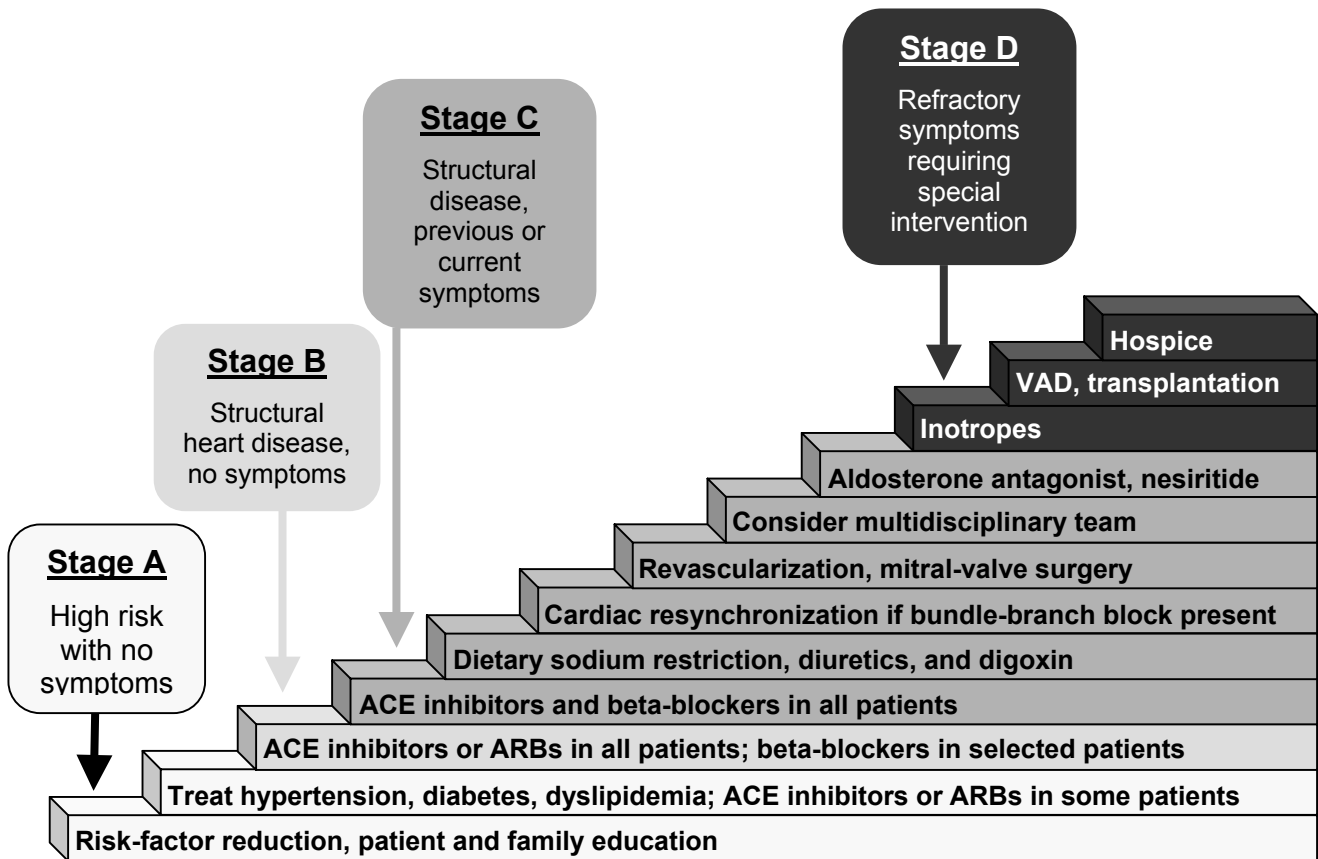
* symptoms include fatigue, dyspnea, palpitations and anginal pain

In 2001, the American College of Cardiology (ACC) and AHA provided updated guidelines for the management of chronic HF.² Within these guidelines, the AHA and ACC developed a new staging system to further assist clinicians in the characterization of HF patients. (Table IV) This staging system is meant to supplement the NYHA classification system, and emphasize the progressive nature of HF. In contrast to the NYHA classification system, this staging system characterizes HF in a unidirectional stepwise fashion, starting only with identifiable risk factors but no myocardial dysfunction. Similar to cancer staging, once disease severity has reached criteria for a specific stage, there is no reversal to a lesser stage. As above, primary care physician appreciation of these risk factors from the perspective of “health maintenance” is vital to preventative efforts, as nearly 2/3 of all HF patients receive their care from these physicians alone.¹² The staging system breaks HF patients into four groups: A, B, C, and D. An official and billable diagnosis of HF can in reality only be applied to Stage C and D patients, as it is these patients who have both structural heart disease and have developed symptoms consistent with the HF syndrome.² Patients who become refractory to standard medical therapies and require advanced support levels are characterized as Stage D (Figure 2). Coupled with Stage D disease severity (highest rates of mortality and worst quality of life), the limited additionally available therapeutic options make hospice planning an inevitable management decision for many such patients.

Table IV. ACC/AHA Staging System, HF as a Progressive Syndrome²

<u>ACC/AHA Stage</u>	<u>Description</u>
A	At risk for developing HF, but no functional cardiac disorder
B	Structural cardiac disorder but has never developed symptoms
C	Past or Present HF symptoms associated with underlying structural heart disease
D	end-stage disease requiring specialized treatment strategies such as mechanical circulatory support, continuous inotropic infusions, cardiac transplant or hospice care

Figure 2. Stages of Heart Failure and Treatment Options for Systolic Heart Failure (Adapted from reference 12)



Pathophysiology and Prognostic Indicators

As can be appreciated in Figure 2, the indications for available therapies are met upon reaching specific levels of disease severity. Given the relentlessly progressive nature of HF and limited treatment options for patients achieving Stage D severity, optimizing medical management to slow or prevent progression is of utmost importance. The development of successful specialized treatment strategies requires an understanding of the pathophysiological mechanisms involved in HF progression. The association of these mechanisms to objective parameters facilitates the design and subsequent improvement of such strategies. Equally essential in this undertaking is the elucidation of reliable prognostic parameters that would help in understanding when and how these strategies should be applied.

In revisiting the progressive nature of HF (Figure 1), the compensatory factors that develop after myocardial injury in turn add additional stress to the myocardium and result in its further damage. The compensatory affects and subsequent destructive affects of this cycle within myocardial tissue are defined as “Ventricular Remodeling”. Many medicines now considered standard therapy are effective because of their stabilization of ventricular remodeling and neurohormonal dysregulation. One such example is seen in ace inhibitors, in which the enhanced activation of the renin-angiotensin-aldosterone system is counterbalanced by the inhibition of conversion of angiotensin to aldosterone. The additional mortality benefit seen in the addition of an aldosterone-receptor antagonist (spironolactone) to NYHA class IV HF patients already treated with an ace inhibitor demonstrates that these individual medications are not sufficient countermeasures upon this single compensatory mechanism.¹⁵ The recognition of this disease mechanism has assisted in the utilization of ace inhibitors and aldosterone receptor antagonists in HF. The recently described mortality benefit from application of the aldosterone-receptor antagonist, eplerenone, to patients with HF symptoms and LVEF <40% following acute myocardial infarction¹⁶ suggests the further need for optimization of timing for utilization of HF therapies.

In looking for prognostic indicators for progression, many have been effective on the population level but not sufficient on an individual patient basis. One would expect that reduced left ventricular ejection fraction (LVEF), as a critical measure of systolic myocardial function, would provide prognostic information. Unfortunately, as LVEF falls below 25%, it loses such utility.² Likewise, the NYHA Class IV functional level is indicative of severe advanced disease. However for patients who resolve NYHA Class IV severity and maintain a congestion free state for one month have a two year survival rate of ~80%.¹⁷ Peak oxygen consumption is a parameter widely used to monitor functional status and applied to criteria for advanced treatment strategies such as cardiac transplant. However peak oxygen consumption is a measure of both cardiac reserve and peripheral conditioning, and has the ability to improve much like NYHA classification.^{18;19} Patients who become refractory to ace inhibition secondary to advanced HF symptoms (NYHA Class IV) have predictably increased mortality.²⁰ This is certainly important in identifying those patients in urgent need of additional specialized strategies or hospice care. However these patients have already progressed to severe disease, so this has little prognostic utility that could be helpful in earlier application of specialized strategies.

Prognostic applications of measures of neurohormonal regulation have also been found difficult to apply to individual patients. Small population based studies have shown certain biomarkers (norepinephrine, endothelin, BNP and troponin) to be successful in predicting mortality.²¹⁻²³ Application of these parameters to the individual is difficult in that many of these biomarkers have

labile levels and tracking them over time seems more useful. In predicting patients who will progress to end-stage HF and suffer early mortality, no one or combination of these parameters have been successful. Experienced practitioners thus rely on these parameters, especially in their fluctuations over time, to develop a subjective perception of individual disease progression.

Management of End-Stage Heart Failure

As described above, HF incidence and prevalence continue to increase despite the utilization of many medications to interfere with the pathophysiological cycle. As the numbers of HF cases continue to rise, it is reasonable to expect similar increases in patients who progress to stage D HF. As elucidated in Figure 2 above, there are limited therapeutic alternatives available to the hundreds of thousands of patients who qualify as having stage D HF. That hospice care is acceptable as a management choice for these patients is a sobering fact. Until recently, cardiac transplant was the only viable management option with proven mortality benefits. However due to limited numbers of usable donor hearts, there is a vast shortage in transplants completed compared to patients meeting eligibility indications. Nearly 100,000 patients have been estimated to meet criteria for cardiac transplant in a given year, however only ~2200 such transplants are performed annually.²⁴

Given this large gap in supply and demand, the remaining focus of this discussion will be on the available treatment options for stage D HF patients as well as potential therapeutic options for the future. In addition to heart transplant, other options include pharmaceutical agents both presently available and in development. Management efforts like heart transplant which focus on treating, supporting, or replacing the damaged myocardium will also be discussed, including mechanical circulatory support systems, widely known as ventricular assist devices (VADs) and the exciting future possibility of induced cardiac regeneration.

Intravenous Inotropes and Vasodilators

In conjunction with continuing medications started at earlier stages of HF, addition of intravenous inotropes (dobutamine, dopamine and milrinone) and vasodilators (nitroglycerin & nitroprusside) to the medical management of refractory (stage D) HF patients offer symptomatic benefits. These patients require frequent hospital admissions from clinical deterioration and frequently receive these medications to attempt improvement of cardiac performance and facilitate diuresis. Patients who require frequent utilization of these medications or are unable to be weaned from this intravenous support can obtain an indwelling catheter for at home infusion. This method is commonly employed in patients awaiting cardiac transplant but is also utilized as a method to allow patients to return home and die in relative comfort.² Positive inotropic medications are in essence compensating for the diseased myocardium much like the endogenous compensatory mechanisms as described above. Logic follows that while this approach can be successful in improving symptoms in refractory HF cases on a short-term basis, it is equally feeding back into the “vicious cycle”. In reality, IV inotropes offer no survival benefit, and in the absence of bridging support to additional therapy (i.e., transplant, VAD), this therapy is considered palliative in nature.²

Cardiac Transplantation

As mentioned above, heart transplant has until recently been the only viable choice for improving mortality in patients who have progressed to stage D or end-stage HF. See Table V below for absolute and relative indications as well as contraindications. Comparisons of patients who meet criteria for transplant and either receive or don't receive a transplant show a clear benefit in transplantation. One such case report identified one-year survival in patients meeting absolute indications for transplant but not receiving one as less than 50% compared to one-year survival following transplant of 83%.⁸ Equally impressive, once receiving a heart transplant, 10-year survival currently reaches ~50%.⁸ Table VI below demonstrates the estimated 50% survival time for various states of disease severity and transplant indications. These numbers are startling when compared to the average waiting time in 2000 for O-blood-type patients after being listed on the transplant list was 869 days (~29 months).²⁵ As is apparent by the large gap in transplants completed annually versus the number of patients who qualify for them, regardless of mortality benefits, cardiac transplant is not a sufficient management option in end-stage HF.

Certainly quality of life is as important, if not more so, than quantity of life. Many studies address the issues of quality of life post-cardiac transplant, with consistent findings of significant improvements in many quality of life measures. See Table VII and [Grady, 2003] for review.

Table V. Indications and Contraindications for Cardiac Transplantation²

Absolute Indications

1. Hemodynamic compromise due to HF
2. Refractory cardiogenic shock
3. dependence on IV inotropic support to maintain adequate organ perfusion
4. Peak VO₂ < 10 ml/kg/min c achievement of anaerobic metabolism
5. Severe symptoms of ischemia that consistently limit routine activity and are not amenable to CABG or PCI
6. Recurrent symptomatic ventricular arrhythmias refractory to all therapeutic modalities

Relative Indications

1. Peak VO₂ 11-14 ml/kg/min (55% predicted) and major limitation of daily activities
2. Recurrent unstable ischemia not amenable to other intervention
3. Recurrent instability of fluid balance/renal function not due to patient noncompliance with medical regimen

Contraindications

1. Fixed pulmonary vascular resistance
2. Irreversible renal failure
3. Respiratory failure
4. Sepsis
5. Severe neurologic deficit

Table VI. Estimated 50% Mortality Rates in Advanced HF⁸

<u>Functional Class</u>	<u>50% Mortality</u>
1. Acute cardiogenic shock	Imminent
2. Chronic CHF with organ dysfunction from low output state	1 mo, if factors non-reversible
3. Class IV, Inotrope dependent	3-6 months
4. Class IV, ACEI-intolerant	~ 6 months
5. Class IV on ACEI with risk factors: cachexia, peak VO ₂ <10, hypoNa ⁺ , progressive renal dysfunction	? 6-12 mo
6. Class IV on oral therapy, inc ACEI	+/- 12 mo
7. Class IV stabilized to Class III	> 24 mo

* patients in classifications 4-7 meet criteria for cardiac transplant,

* patients in classifications 1-4 meet criteria for LVAD support (see below)

Table VII. Changes in Quality of Life After Cardiac Transplant²⁶

Positive Effects

- *Functional status*
- health status
- domestic activities
- leisure activities

Emotional Issues

- Depression
- Anxiety
- symptom distress
- well-being
- life satisfaction
- body image
- perceived QOL
- emotional functioning
- mental functioning

Relationship Issues

- family relationships
- vocational functioning

Equivocal Effects

- * Level of stress
- * Coping use and effectiveness
- * Vocational functioning
- * Sexual functioning

Negative Effect

- * Financial situation

Mechanical Circulatory Support (Ventricular Assist Devices)

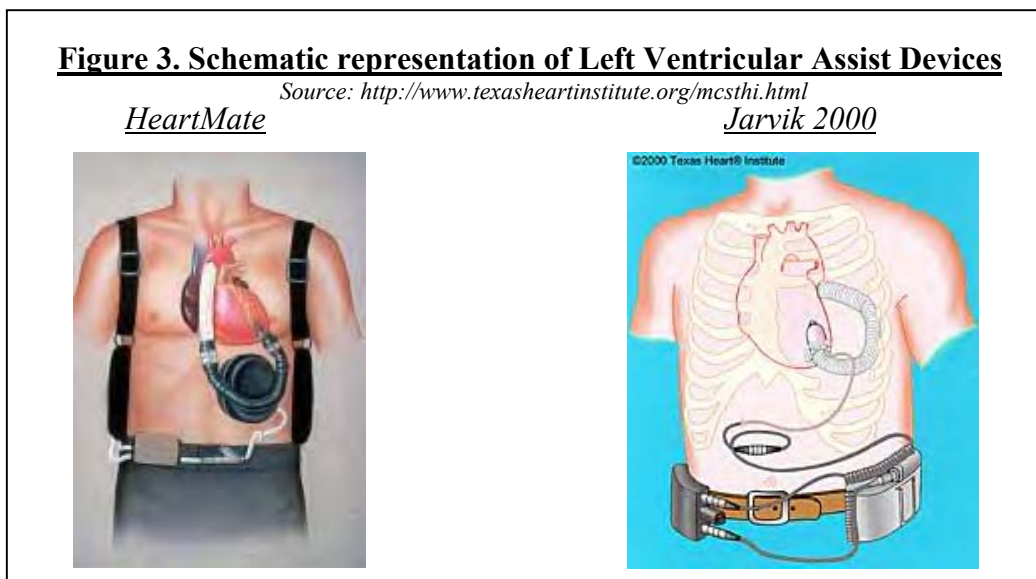
Mechanical Circulatory Support Systems were first envisioned in the mid-1970's when the NIH produced a request for proposal for the design and development of cardio-circulatory support systems with the potential to prolong life in end-stage HF patients for up to 2 years.²⁷ Current devices are approved for both short-term and long-term support. Patients with loss of >40% of LV mass after acute MI commonly develop cardiogenic shock and intra-aortic balloon pumps are commonly used for short-term support in such patients.²⁸ Multiple designs of both Left (and Bi-) Ventricular Assist Devices (LVAD) as well as Total Artificial Hearts (TAH) are in use and in development for long-term support. As this paper is focusing on chronic heart failure, the remainder of this section will focus on LVAD's as they are presently indicated for use as a "Bridge to Transplant" as well as "Destination Therapy". Small case reports also offer evidence that some patients survive and do well after explantation of an LVAD, leading to potential future use of LVAD's as a "Bridge to Recovery".

Indications for LVAD are similar to indications for heart transplant as described in Table VI above. Of note, age greater than 65 years is a relative contraindication to cardiac transplant, but not in use of LVAD. Although not exclusion criteria, age greater than 60 years and dependence on mechanical ventilatory support are associated with poor outcomes.²⁸ Specific inclusion criteria for use of LVAD as a "Bridge to Transplant" include hemodynamic deterioration despite IABP or maximal pharmacological therapy, as well as objective parameters such as: PCWP >20 mm Hg, CI \leq 2 L/min/m², or SBP \leq 80 mm Hg. In fact, LVAD's have now been successfully used as a bridge to transplant for more than 2 decades.²⁸ In 2001, nearly 20% of all patients receiving cardiac transplant received LVAD support prior to undergoing transplant.²⁷ Devices with current FDA approval as a bridge to transplantation include the Thoratec Ventricular Assist Device System, the Novacor Ventricular Assist System, and the HeartMate left ventricular assist device (Figure 3).

In comparison to cardiac transplantation, estimates from the Institute of Medicine in 1991 portrayed that long-term MCS could potentially benefit 35,000 to 70,000 US patients with severe HF annually²⁹, which is in stark contrast to the level of support offered by heart transplant yearly. LVAD utilization also provides significant benefits in mortality and quality of life. Reversal of ventricular remodeling and normalization of neurohormonal activation and renal and hepatic dysfunction are all contributory to the success of LVAD support.^{28;30} Indeed NYHA functionality often returns to class I with LVAD support.²⁸ As a bridge to transplant, mortality benefits are clear. Evaluation of efficacy in 1992 derived improved survivability to transplant if patients received support from the HeartMate 1000 IP LVAD, where 71% of patients with LVAD survived to transplant, while only 30% of patients survived to transplant without such support.³¹ In patients who did survive to transplant, one-year survival was equally impressive with 90% of patients surviving with pre-transplant LVAD support compared to only 67% without this support. Interestingly, patients not receiving LVAD but surviving to transplant had an average wait time of 5 days from meeting criteria to receiving their donor hearts. One can imagine even more impressive survival differences if the wait times for transplantation were equal.²⁷

Certainly there are drawbacks to LVAD support as well. Major complications include post-operative hemorrhage (60%), sepsis (30-40%) as well as thromboembolic events, renal failure, technical device failure and neurologic sequelae.²⁸ As new systems are continuing to be developed,

improvements in these complications are being made. The investigational device, Jarvik 2000 (Figure 3), has been successfully implanted without cardiopulmonary bypass, with subsequent significant reductions in post-operative hemorrhage. Likewise, this system uses a turbine design to push blood, limiting device surface – blood contact. This has resulted in drastically decreased levels of hemolysis, which in turn reduces levels of renal failure.²⁸ These promising results are reflected in Delgado’s comments that “As mechanical devices become smaller and less vulnerable to complications, the indications for their use will probably broaden to include patients not waiting transplantation and those with milder heart failure.”²⁸



Given the prolonged waiting times for donor hearts, many patients on the transplant waiting list have received LVAD support and far outlived predicted mortality levels. As of January 2001 numerous patients have had prolonged survival with different LVAD systems. 217 patients with the HeartMate system had survival > 1 year, with 33 surviving >2 years and 3 > 3 years. Equally impressive is one patient with the Novacor LVAD having survived greater than 4.5 years.²⁸ This observed prolonged survival triggered the REMATCH study to investigate the potential for patients to receive LVAD support as destination therapy in place of therapy as a bridge to transplant.³² In this study, 129 patients meeting criteria for cardiac transplant but having exclusion criteria (mostly age > 65 years) were randomized to receive continued maximal medical therapy +/- LVAD support. One-year survival analysis revealed an all cause death reduction of 48%, with 52% of patients with LVAD surviving compared to only 25% without LVAD support. Differences in 2-year survival were equally impressive, with 23% surviving with LVAD vs. only 8% without. This study demonstrates an estimated 270 lives saved for every 1000 treated with LVAD, compared to only 70 per 1000 for both ace inhibitors and β -blockers.^{33;34} When examining the cause of death in these patients, 50 of the 54 deaths in the medical management arm were attributed to LV dysfunction, compared to 1 of 41 deaths in the LVAD arm. Common causes of death in the LVAD arm were sepsis (17), device failure (7) and CVA (4), all of which might be expected to improve as LVAD systems continue to improve.

As in transplant, quality of life (QOL) is an important issue. Indeed, HeartMate patients had significantly better QOL, more satisfaction with health and functionality and significantly less symptom-related distress 1-2 weeks after surgery, but more self-care disability and economic-status dissatisfaction.²⁶ In a series of 44 HeartMate patients discharged home with an LVAD in place, 30% were able to rejoin society as productive members, through returning to work or school.³⁵

The evidence of benefits from mechanical circulatory support in the form of LVADs is very impressive and can be expected to only improve as system designs continue to be modified. Given the 1991 estimates of 35-70,000 patients could potentially receive benefit from such support, LVADs seem a reliable supplemental therapy to cardiac transplant in the management of end-stage HF.

Potential Management Options for the Future

Medications in development

Just as many medications are currently employed to counteract the compensatory mechanisms described above (i.e. β -blockers, ace inhibitors, aldosterone-receptor antagonists), additional agents are in development to attack other aspects within the HF cycle. These developmental classes of medications include endothelin antagonists, vasopeptidase antagonists, vasopressin antagonists, cytokine antagonists, and apoptosis inhibitors.

Endothelin antagonists. Endothelin-1 (ET-1) is a protein ligand to the endothelin receptors that are expressed by cardiomyocytes. ET-1 is thought to have limited function in normal cardiac physiology, but has an increased role within the pathophysiological state of HF.³⁶ In clinical and experimental HF, ET-1 and its precursor, big ET-1 have been shown to associate with hemodynamic and functional severity well as prognosis.^{37;38} Current thought is that ET-1 initially adds inotropic support but overexpression may eventually produce focal vasospasm, myocyte necrosis and increased fibrosis.³⁶ Initial studies with 2 endothelin antagonists (Bosentan and Enrasentan) yielded disappointing results³⁶, however trials of *tezosentan* applied in the acute HF setting have initially shown benefits in cardiac index, pulmonary capillary wedge pressure and vascular resistance.³⁹ Unfortunately, tezosentan is administered intravenously and is currently available only in the acute HF setting.³⁶

Vasopeptidase inhibitors are another class of medicines under current investigation for potential use in chronic HF. The up-regulated renin-angiotensin-aldosterone vasoconstrictor system is naturally balanced with an endogenous vasodilatory system. Initial data on the medication *omapatrilat* was encouraging, in showing decreased risk of mortality and HF progression as well as improved cardiac function.² However subsequent studies have shown increased risk of angioedema, which has at least for now, stalled the future development of this class of medicines.

Vasopressin Antagonists are another exciting medication class with future potential. Vasopressin plays multiple physiologic roles, including mediation of vasoconstriction (through the V_1 receptor) and water excretion (through the V_2 receptor).⁴⁰ At present diuretics are the only available agents to mediate fluid reduction, an important aspect in chronic heart failure management. A recent study of

the orally administered V₂-selective antagonist, *tolvaptan*, has shown significant benefit in reductions of edema, body weight and resolution of hyponatremia.⁴¹ No significant changes in quality of life were reported, however this study followed patients for only 4 weeks. Additional trials of this medication are certainly necessary to better characterize its future roles in HF management.

Cytokine Antagonists. Proinflammatory cytokine regulation has been associated with chronic HF as well. Overexpression of tumor necrosis factor (TNF) has been shown to induce a HF-type phenotype, including left ventricular dysfunction and remodeling, pulmonary edema, and fetal gene expression.³⁶ Initial studies in patients with dilated cardiomyopathy using the TNF transcriptional blocker pentoxifylline demonstrated improvement in LVEF and functional class compared to placebo.⁴² However subsequent large-scale trials of a TNF-chelator, *etanercept*, showed lack of efficacy.³⁶ As agents blocking TNF transcriptional activation appear useful, more studies are needed before this type of medication can be applied clinically.

Apoptosis Inhibitors. Cardiomyocyte apoptosis, or programmed cell death, significantly increases in patients with HF⁴³⁻⁴⁵ and multiple animal studies have now demonstrated apoptosis as having a direct causal role in some forms of HF.^{46,47} Caspases are intracellular proteins that function as the operating enzymes in the apoptosis cascade. Additional recent murine studies with the caspase inhibitor, *IDN 1965*, show improvement of cardiac function and delayed or prevented onset of HF in transgenic mice undergoing coronary artery ligation induced myocardial infarction.⁴⁸ Although these are exciting studies, apoptosis inhibitors have severe potential downsides, as apoptosis is critical in many commonly occurring processes, such as immune system regulation. One greatly feared side effect of apoptosis inhibitors is the potential of tumor induction, and these issues need to be resolved before such inhibitors can be applied clinically.

Cardiac Regeneration

Yet another exciting potential for future management of heart failure is cardiac regeneration. One piece of evidence that cardiomyocyte regeneration is a possibility comes from the observations made in male human recipients of female-donor hearts. Examination of myocardium after significant time post-transplant has identified cardiomyocytes containing Y-chromosomes. One reasonable explanation for their presence is that they have newly formed and originated from the recipient patient.^{49,50} However these findings remain controversial with the concept of cell fusion and phenotype adaptation, requiring additional work to further elucidate this process.

Skeletal myoblast percutaneous transplantation has been recently shown to be well tolerated in a small group of patients having suffered acute MI.⁵¹ Six month follow up subsequently revealed increasing LV wall thickening and LVEF. However many of these patients have developed life-threatening arrhythmias requiring implantable defibrillator deployment. Again, additional work is needed to determine the true clinical applicability of this new and exciting technology.

Mouse studies have had equally exciting results. Use of bone-marrow mesenchymal stem cells in the above percutaneous transplantation method may be a possibility in the future. Such murine stem cells have been harvested and induced to differentiate *in vitro* into a cardiomyocyte phenotype. Equally exciting is the application of various cytokines in an induced-infarct mouse model with the

goal of mobilizing these bone-marrow stem cells.⁵² Four week follow up studies identified significant levels of newly formed cardiomyocytes as well as decreased infarct size, decreased cavitory dilatation, increased LVEF and decreased mortality. Again, these studies are controversial in the formation of new cardiomyocytes vs. fusion. Regardless of these effects being secondary to fusion or new cell formation, the outcomes are tremendous and one can only hope for similar outcomes in human studies that are sure to follow.

Summary

In summary, heart failure is a highly prevalent and progressive disease with high levels of morbidity and mortality. The progressive nature of HF leads to the development of end-stage HF despite the optimal utilization of currently available medicines. Cardiac transplant and mechanical circulatory support systems are viable options to improve morbidity and mortality in these end-stage patients. As protocols and technology continue to improve, indications for application of these and new technologies will continue to develop with real hope for future patients developing end-stage HF.

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