Part IV

The future

14

Devices in heart failure: new approaches

MANDEEP MEHRA

Introduction

Therapy targeted towards neurohormonal aberrations in heart failure has served us well. In this regard, the strategy of using angiotensin-converting enzyme (ACE) inhibitors in concert with β-adrenergic blockade has demonstrated clinically important improvements in outcomes for patients with heart failure |**1**|. As investigators have sought to evaluate other incremental neurohormonal targets in further improving outcomes, it has become evident that a ceiling effect might exist in the serial exploitation of the neurohormonal model |**2**|. Thus, cytokine antagonism, endothelin receptor blockade and centrally acting sympatholytics (moxonidine) have demonstrated worse outcomes, while vasopeptidase inhibitors (omapatrilat) that enhance circulating natriuretic peptides have shown little additional benefits. Even angiotensin receptor blockers (ARBs) have shown divergent effects in the setting of β-adrenergic blockade, with one trial suggesting adverse outcomes (using valsartan) and another pointing to modest improvement (using candesartan) |**3**,**4**|. Only aldosterone antagonists have suggested a glimmer of hope, with a putative effect on sudden death reduction in the setting of post-myocardial infarction heart failure |**5**| (Fig. 14.1).

This emerging dilemma has led to the proposition that therapeutic targets beyond the neurohormonal model must be entertained if we are to derive ongoing incremental improvements in outcomes in heart failure. These specific strategies include modulation of myocardial metabolic substrate utilization, alleviation of myocardial ischaemia, and relief of arrhythmic burden. Other novel areas of investigation relate to identifying and treating sleep disordered breathing, amelioration of anaemia and renal dysfunction, and resynchronization of contraction as well as the use of other antiremodelling strategies such as mechanical ventricular assistance and passive restraint devices |**2**|.

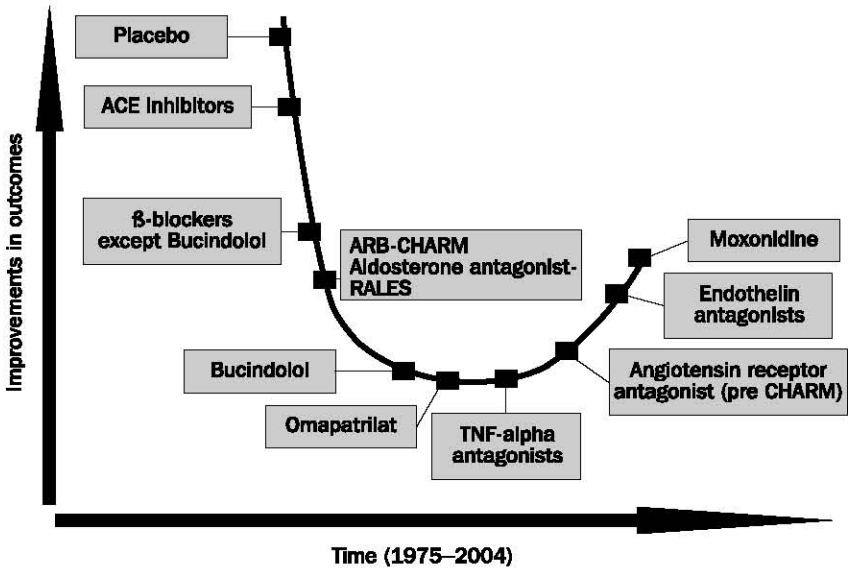

Fig. 14.1 A schema depicting a possible ceiling effect to the incremental targeting of the neurohormonal model. This exemplifies the need to investigate targets beyond the traditional concept of neurohormonal antagonism, thereby making the case for device therapy in the treatment of heart failure. Source: adapted from Mehra *et al.* (2003) |**2**|.

Cardiac resynchronization therapy

The concept of cardiac resynchronization therapy that seeks to harmonize ventricular contractility by decreasing areas of focal asynchrony is widely gaining clinical acceptance. Several recent clinical trials have provided support for the usefulness of cardiac resynchronization therapy using biventricular pacing |**6**|. Recent randomized clinical trials of cardiac resynchronization therapy have suggested that the application of this treatment modality in severe systolic heart failure despite optimal drug therapy yields benefits that result in improved functional capacity, reversal of adverse ventricular remodelling, and decreased hospitalizations. Indeed, a recent meta-analysis of these trials has even suggested decreased deaths from progressive heart failure as a consequence of cardiac resynchronization.

Cardiac resynchronization in chronic heart failure

Abraham WT, Fisher WG, Smith AL, *et al.* MIRACLE Study Group. *N Engl J Med* 2002; **346**(24): 1845–53

BACKGROUND. These investigators conducted a double-blind trial to evaluate cardiac resynchronization therapy in 453 patients with moderate to severe symptoms of heart failure associated with an ejection fraction (EF) of 35% or less and a QRS interval of 130 ms or more. The patients were randomly assigned to a cardiac resynchronization group (228 patients) or to a control group (225 patients) for 6 months, while conventional therapy for heart failure was maintained. As compared with the control group, patients assigned to cardiac resynchronization experienced an improvement in the distance walked in 6 min (+39 vs +10 m; *P* = 0.005), functional class (*P* <0.001), quality of life (–18.0 vs –9.0 points; *P* = 0.001), time on the treadmill during exercise testing (+81 vs +19 s; *P* = 0.001), and EF (+4.6 vs –0.2%; *P* <0.001). In addition, fewer patients in the group assigned to cardiac resynchronization than control patients required hospitalization (8 vs 15%) or intravenous medications (7 vs 15%) for the treatment of heart failure (*P* <0.05 for both comparisons). Implantation of the device was unsuccessful in 8% of patients and was complicated by refractory hypotension, bradycardia, or asystole in four patients (two of whom died) and by perforation of the coronary sinus requiring pericardiocentesis in two others.

INTERPRETATION. Cardiac resynchronization resulted in significant clinical improvement in patients who had moderate to severe heart failure and an intraventricular conduction delay.

Comment

This study was rigorously conducted and was constructed to maintain blinding in the heart failure specialist. One of the difficulties in translating this data to the 'real world' setting lies in the fact that this trial randomized patients only after pacemaker implantation was deemed successful (92% of patients). This study also brought to

Table 14.1 Problems and uncertainties with cardiac resynchronization therapy

QRS width fails to define site and magnitude of ventricular dys-synchrony
Electrical and mechanical dys-synchrony are not consistent, as 'normal' QRS width can also be associated with dys-synchrony
Failure to define the location and magnitude of mechanical dys-synchrony leads to a 'hit or miss' approach with a high non-responder rate
Uncertain if patients with atrial fibrillation benefit from resynchronization therapy
Risk–benefit ratio may be narrow: New York Heart Association class II might be 'too well' for cardiac resynchronization therapy or class IV might be 'too sick'
Unclear when cardiac resynchronization therapy should be performed alone or in conjunction with an implantable cardioverter defibrillator
Technical learning curve, cost and potential morbidity are substantial
Longevity of benefit not completely established

Source: Abraham *et al.* (2002).

light the importance of the placebo response that occurs in patients with heart failure who undergo device implantation. Once the placebo effect is adjusted for, only 30% of the study patients actually appeared to benefit primarily as a result of the device effect. This low response rate points out that there are several unknowns with cardiac resynchronization therapy and much needs to be understood with regards to appropriate patient selection by detecting mechanical dys-synchrony, optimal location of lead placement and correcting mechanical ventricular dys-synchrony by the pacing technique |6| (Table 14.1).

Cardiac resynchronization and death from progressive heart failure: a meta-analysis of randomized controlled trials

Bradley DJ, Bradley EA, Baughman KL, *et al. JAMA* 2003; **289**(6): 730–40

BACKGROUND. Progressive heart failure is the most common mechanism of death among patients with advanced heart failure. The objective of this meta-analysis was to determine whether cardiac resynchronization reduces mortality from progressive heart failure. Eligible studies were randomized controlled trials of cardiac resynchronization for the treatment of chronic symptomatic left ventricular dysfunction. Eligible studies reported death, hospitalization for heart failure, or ventricular arrhythmia as outcomes. Of the 6883 potentially relevant reports initially identified, eleven reports of four randomized trials with 1634 total patients were included in the meta-analysis. Pooled data from the four selected studies showed that cardiac resynchronization reduced death from progressive heart failure by 51% relative to controls (odds ratio [OR] 0.49; 95% confidence interval [CI] 0.25–0.93). Progressive heart failure mortality was 1.7% for cardiac resynchronization patients and 3.5% for controls. Cardiac resynchronization also reduced heart failure hospitalization by 29% (OR 0.71; 95% CI 0.53–0.96) and showed a trend towards reducing all-cause mortality (OR 0.77; 95% CI 0.51–1.18). Cardiac resynchronization was not associated with a statistically significant effect on non-heart failure mortality (OR 1.15; 95% CI 0.65–2.02). Among patients with implantable cardioverter defibrillators (ICDs), cardiac resynchronization had no clear impact on ventricular tachycardia or ventricular fibrillation (OR 0.92; 95% CI 0.67–1.27).

INTERPRETATION. Cardiac resynchronization reduced mortality from progressive heart failure in patients with symptomatic left ventricular dysfunction. This finding suggests that cardiac resynchronization may have a substantial impact on the most common mechanism of death among patients with advanced heart failure.

Comment

Caution must be exercised in interpreting the results of meta-analyses that seek to separate the mode of death in heart failure trials. Much controversy exists in adjudicating the mode of death in the context of clinical trials, and investigators agree that

distinguishing between different modes of death is not always crystal clear. Furthermore, this review lumped together trials in which patients received either pacemakers alone or in combination with implantable defibrillators. The natural history and prognosis of these different patient groups might not be similar. Also, when assessing treatments that have the capacity to be harmful, all-cause mortality is the appropriate end-point that deserves to be examined. In this regard it is vital to point out that all-cause mortality was not demonstrated to improve using cardiac resynchronization therapy.

More recently, the Comparison of Medical Therapy, Pacing and Defibrillation in Chronic Heart Failure (COMPANION) trial results were published |**6**,**7**|. This trial enrolled patients with moderate to severe heart failure despite maximized medical therapy. Inclusion criteria included a QRS duration >120 ms and a PR interval >150 ms. The trial had three treatment arms: one out of five patients was to receive optimal pharmacological therapy, two out of five were to receive optimal pharmacological therapy plus biventricular pacing, while the remaining two out of five were to receive biventricular pacing, plus backup ICD therapy. In contrast to all others, this study was powered to evaluate a primary end-point of combined all-cause mortality and hospitalization. Data were analysed using an intention to treat statistical approach. In total, 1520 patients were randomized (93%) and 1080 patients were implanted with a cardiac resynchronization therapy pacer (CRT group) or defibrillator (CRT-D group). Of these, 118 patients failed the initial implant (88% implant success for the CRT group and 92% for the CRT-D group). Left ventricular lead dislodgement was seen in 2 and 2.5% in the CRT and CRT-D groups, respectively. As compared with patients treated with medical therapy only, there was a statistically significant event rate reduction in the primary combined end-point of total hospitalization and total mortality at 1 year in the CRT/CRT-D group (OR 0.82; $P = 0.05$ and 0.81; $P = 0.015$, respectively), as well as in the combined end-point of hospitalization for heart failure and death (OR 0.64 and 0.60, respectively; $P = 0.05$). Mortality at 1 year decreased by 24% ($P = 0.059$, ns) in the CRT group and 36% ($P = 0.003$) in the CRT-D group. The effects of cardiac resynchronization therapy on hospitalization due to heart failure appeared to be more pronounced in patients with left bundle branch block (as opposed to intraventricular conduction defector right bundle branch block), patients with longer QRS duration (>148 ms) and in patients receiving β blockers. Despite the findings of this trial, little can be ascertained to help guide the clinician in the selection of patients who should receive cardiac resynchronization therapy alone, or in combination with a defibrillator since the study was not powered to detect differences between these two groups.

ICDs in heart failure: preventing sudden death

Because less than 20% of patients survive an episode of sudden cardiac death, the majority who experience a life-threatening ventricular tachyarrhythmia do not

survive to benefit from an ICD. Because of this, the concept of the ICD for primary prevention of sudden cardiac death has received considerable attention. Although β blockers and aldosterone antagonists in patients with heart failure, particularly in the post-myocardial infarction setting, have demonstrated benefits in reducing sudden death, prophylactic ICDs have shown the greatest promise in this regard.

Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction

Moss AJ, Zareba W, Hall WJ, *et al. N Engl J Med* 2002; **346**: 877–83

BACKGROUND. This trial was designed to determine if the ICD reduces mortality in patients with prior myocardial infarction and decreased left ventricular systolic function. The belief was that Holter monitoring and electrophysiological testing may not be necessary to identify patients who benefit from an ICD. In total, 1232 with prior myocardial infarction (56% with prior surgical revascularization) and left ventricular ejection fraction (LVEF) <0.30 were randomized to ICD or no ICD therapy. Exclusion criteria included myocardial infarction within 1 month, coronary artery bypass graft or percutaneous transluminal coronary angioplasty within 2 months, and any patient already satisfying criteria for receiving an automatic implantable cardiac defibrillator (AICD) by satisfying the entry criteria for the first Multicenter Automatic Defibrillator Implantation Trial II (MADIT II). The primary end-point was all-cause mortality. A 30% survival benefit with ICD therapy ensued at 20 months, but a trend to increased heart failure episodes was also seen in the device arm.

INTERPRETATION. In patients with myocardial infarction and an LVEF <0.30, strong consideration should be given to prophylactic placement of an ICD.

Comment

This investigation was designed to follow a simple clinical algorithm based on easily available diagnostic tests to identify the patients enrolled. Thus, unlike prior studies, no requirement for electrophysiological studies or ambient ventricular ectopy were required for entry into this study. Indeed, analyses of ICD discharges and electrophysiological studies performed in the subgroup of those patients who received the device confirmed the poor predictive capacity for formal testing in this population. Thus, whereas those patients with inducible ventricular tachycardia were more likely to receive shocks for sustained ventricular tachycardia, those who were non-inducible suffered as many shocks but for ventricular fibrillation. One of the most important issues with this technology is the cost implication. Before considering prophylactic ICD placement, patients should receive optimal medical therapy with β blockers, ACE inhibitors and aldosterone antagonists. Left ventricular function should be evaluated at a time remote from the time of the myocardial infarction, allowing sufficient time to elapse to allow recovery of ventricular function. Some have argued that we need to define subgroups within the context of the MADIT II

population who may be most likely to benefit, but a clear-cut subpopulation has been difficult to ascertain.

More recently, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) has been completed and presented by Dr Gust Bardy. The SCD-HeFT tested the hypothesis that either amiodarone or the automatic cardiac defibrillator improves survival compared to placebo in patients with heart failure. This study enrolled 2521 patients with New York Heart Association II or III heart failure and a LVEF <0.35 (either ischaemic or non-ischaemic aetiology) and randomly allocated them to a strategy of ICD, amiodarone or placebo. The patients were well treated with 87% on ACE inhibitors or ARBs and 78% on β blockers at last follow-up. This investigation suggested no benefit of amiodarone compared with placebo (hazard ratio [HR] 1.06; 97.5% CI 0.86–1.3; $P = 0.53$). On the other hand, ICD therapy decreased mortality by 23% compared to control, a finding consistent across ischaemic and non-ischaemic aetiology of heart failure (HR 0.77; 97.5% CI 0.62–0.96; $P = 0.007$). Interestingly, most of the benefit of the ICD strategy was confined to those with New York Heart Association II heart failure at study entry while no significant benefit was observed in the New York Heart Association III group. This study now suggests that patients with mild heart failure and left ventricular dysfunction should be strongly considered as candidates for automatic cardiac defibrillator implantation.

Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial

Wilkoff BL, Cook JR, Epstein AE, *et al.* Dual Chamber and VVI Implantable Defibrillator Trial Investigators. *JAMA* 2002; **288**(24): 3115–23

BACKGROUND. All of the prospective multicentre trials that support the use of implantable defibrillators have used single chamber pacemakers/ICDs. Despite the significantly increased cost of dual chamber pacemaker/ICD devices and the lack of outcome data, these devices accounted for approximately two-thirds of the ICDs implanted in the real world setting. Dual chamber pacemaker trials have not provided data that would support this trend, but the high incidence of atrial fibrillation, bradycardia, and congestive heart failure, as comorbid conditions, suggests that the situation could be different in the defibrillator patient population. The Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial, a single-blind, parallel-group, randomized clinical trial, enrolled 506 patients with indications for ICD therapy. All patients had an LVEF of 40% or less, no indication for antibradycardia pacemaker therapy, and no persistent atrial arrhythmias. Patients were randomly assigned to have the ICDs programmed to ventricular backup pacing at 40/min (VVI-40; $n = 256$) or dual chamber rate-responsive pacing at 70/min (DDDR-70; $n = 250$). Maximal tolerated medical therapy for left ventricular dysfunction, including ACE inhibitors and β blockers, was prescribed to all patients and the composite end-point of time to death or first hospitalization for congestive heart failure was evaluated. One-year survival free of the

composite end-point was 83.9% for patients treated with VVI-40 compared with 73.3% for patients treated with DDDR-70 (relative hazard 1.61; 95% CI 1.06–2.44). The components of the composite end-point, mortality of 6.5% for VVI-40 vs 10.1% for DDDR-70 (relative hazard 1.61; 95% CI 0.84–3.09) and hospitalization for congestive heart failure of 13.3% for VVI-40 vs 22.6% for DDDR-70 (relative hazard 1.54; 95% CI 0.97–2.46) also trended in favour of VVI-40 programming.

INTERPRETATION. For patients with standard indications for ICD therapy, no indication for cardiac pacing, and an LVEF of 40% or less, dual chamber pacing offers no clinical advantage over ventricular backup pacing and may be detrimental by increasing the combined end-point of death or hospitalization for heart failure.

Comment

This important trial suggests that the observed worsening of heart failure noted in trials of prophylactic ICD placement may be explained not only by post-shock stunning, but more commonly by the use of backup pacing. This is most likely due to the development of right ventricular pacing-induced left bundle branch block resulting in intra- and interventricular dys-synchrony with resultant further worsening of left and right ventricular systolic and diastolic function.

Laplace therapeutics in heart failure

The management of late-stage heart failure often frustrates seasoned clinicians and is fraught with oscillating haemodynamic instability coupled with multi-organ dysfunction. Even the option of cardiac transplantation is fraught with limitations due to a scarce donor organ pool and restrictive criteria. This difficult situation has led researchers to develop mechanical alternatives to provide palliation in the form of 'destination therapy' that is fundamentally designed to enhance quality of life. The lack of viable therapeutic strategies in treating the late-stage heart failure patient have led to a flurry of activity in the surgical domain to reshape an adversely remodelled ventricle. This premise seeks to decrease wall stress by exploiting Laplace's law that describes the stress and strain relationship as a measure of cavity size and wall thickness |**8**| (Fig. 14.2). One of the many surgical approaches to decreasing ventricular wall stress is perhaps the notion of ventricular assistance, which provides active assistance by serving as a 'ventricular vacuum' for providing rest to the cavity. Ventricular assist devices (VADs) have ushered in the era of 'ultimate haemodynamic unloading' by the use of pumps that either replace most of the native ventricular function, or partially unload the ventricle by assistance in parallel. Another approach is to attempt reshaping of the ventricle using passive cardiac restraint devices or actively altering the stress–strain relationships within the ventricular cavity by the use of myocardial splints (Table 14.2).

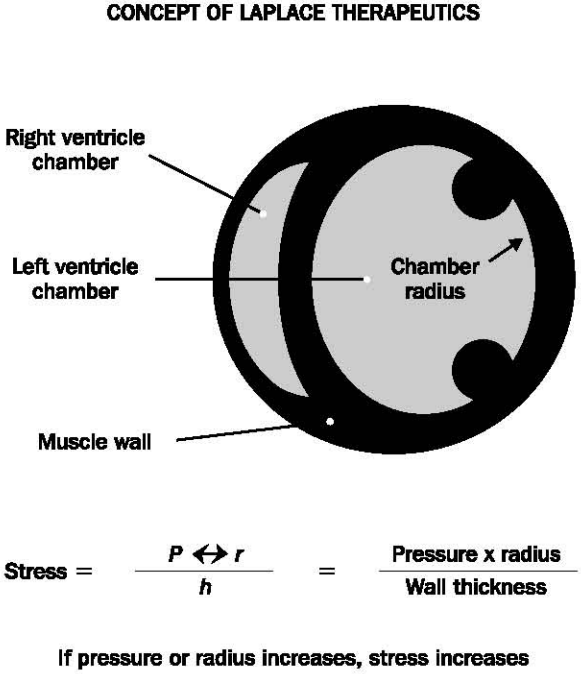

Fig. 14.2 Laplace's law defines the stress–strain relationship within a cavity. Therapeutic manoeuvres that decrease pressure or cavity size will decrease wall stress, as will thickening of the heart muscle.

Table 14.2 Laplace therapeutics: decreasing wall stress with device therapy

Target	Modality
Decrease pressure within cavity	Ventricular assist device
Decrease work of ejection	Cardiac resynchronization therapy
Decrease cavity size	Passive cardiac restraint
	Myosplint
Increase myocardial thickness	Myoblast transplantation
	Stem cell therapy

Long-term mechanical left ventricular assistance for end-stage heart failure

Rose EA, Gelijns AC, Moskowitz AJ, *et al.* Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Study Group. *N Engl J Med* 2001; **345**(20): 1435–43

BACKGROUND. Implantable left ventricular assist devices (LVADs) have been established as an important bridge to cardiac transplantation, although some devices have been placed long term and few have recovered enough to be weaned. This trial was designed to evaluate the suitability of LVADs as long-term myocardial replacement therapy in patients ineligible for cardiac transplantation. One hundred and twenty-nine patients with end-stage heart failure who were ineligible for cardiac transplantation were randomly assigned to receive an LVAD or optimal medical therapy, with a primary end-point of all-cause mortality. To be eligible, patients had to have New York Heart Association class IV heart failure for at least 90 days despite attempted therapy with an ACE inhibitor, diuretics, and digoxin; an EF ≤25%; and an exercise peak O_2 uptake ≤12 ml/kg/min (later increased to 14 ml/kg/min). Survival was significantly improved from 25% at 1 year in the medical therapy group to 52% in the LVAD group (relative risk 0.52; 95% CI 0.34–0.78; *P* = 0.001). However, at 2 years, only 23% in the LVAD group were alive (compared with 8% in the medical group).

INTERPRETATION. The use of an LVAD resulted in improved survival and quality of life in patients with extremely severe heart failure. An LVAD may be an acceptable alternative therapy in selected patients who are not candidates for cardiac transplantation.

Comment

Whereas a superficial evaluation of these trial findings suggests a remarkable survival advantage with LVAD therapy, a closer appraisal of the evidence points to the tremendous clinical cost that has to be borne in order to achieve these salutary results. Thus, at 2 years, only 23% in the LVAD group were alive (compared with 8% in the medical group). The modes of death in the LVAD group included sepsis (n = 17), VAD failure (n = 7), cerebrovascular disease (n = 4), pulmonary embolus (n = 2), and only one categorized as pump failure. Similarly, the probability of infection with the device was 28%, bleeding 42% and device failure 35%, requiring device replacement in ten of 68 patients. In regard to hospitalizations, device-treated patients spent more days in the hospital compared with the medical therapy arm. Thus, from a clinical standpoint, one could argue that device therapy 'delayed death compared with medical therapy' but at a very high rate of unpleasant and largely iatrogenic complications. In fact, the median prolongation in life with LVADs was 8 months, of which 3 months were spent in the hospital. Although the investigators suggested that quality of life was improved, no calculation of the 'quality of death' was ascertained in the overall equation to define benefit with device therapy. It should therefore be emphasized that appropriate patient selection for destination therapy is critical, as

application to less morbidly ill situations might alter the risk–benefit ratio adversely against such a therapeutic approach. More recently, proposals for care standards for destination therapy have been proposed which have led third party payers to adopt restricted coverage criteria that allow destination therapy to be performed only at centres with multidisciplinary experienced teams and demonstrated proficiency in using VAD therapy. Furthermore, coverage requirements include the transfer of centre-specific data to a central registry such that universal tracking of outcomes along with bench-marking of 'best practices' can be achieved.

Clinical experience with an implantable, intracardiac, continuous flow circulatory support device: physiologic implications and their relationship to patient selection

Frazier OH, Myers TJ, Westaby S, Gregoric ID. *Ann Thorac Surg* 2004; **77**(1): 133–42

BACKGROUND. Unlike pulsatile assist devices, continuous-flow pumps have a simplified pumping mechanism and they do not require compliance chambers or valves. In the 1980s, clinical experience with the Hemopump proved that a high-speed, intravascular, continuous-flow pump could safely augment the circulation. Subsequently, a decade of animal experiments with a larger, longer-term continuous-flow pump (the Jarvik 2000) confirmed the safety and efficacy of intraventricular placement, leading to its clinical application. In this observational study, the investigators analysed the physiological and anatomical effects of using the Jarvik 2000 pump for cardiac support in 23 patients in whom the device was applied as a bridge to transplant under the protocol approved by the Food and Drug Administration Investigational Device Exemption. The device was used as a bridge to transplantation in 20 patients and as destination therapy in three. In the bridge-to-transplant group, 14 patients underwent transplantation, five died during the circulatory support period and one is in an ongoing study. The support period lasted an average of 90 days. For the survivors, the follow-up period averaged 16 months. In the destination therapy group, one patient died unexpectedly from an accident 382 days after device implantation. The two survivors remain in New York Heart Association functional class I at 700–952 days after implantation.

INTERPRETATION. The Jarvik 2000 can offer effective long-term support for patients with chronic heart failure and New York Heart Association class IV status. However, the new physiology produced by continuous offloading of the heart throughout the cardiac cycle has introduced unique clinical problems. The understanding of the problems generated by this biotechnological interface is essential for obtaining optimal clinical outcomes.

Comment

As newer generation devices become available, the hope that the cost and morbidity associated with these devices will be lower will probably become a reality. Mechanical assist devices are increasingly evolving towards smaller devices that are associated

with lesser morbidity and transcutaneous energy sources that avoid the near universal risk of infection. Continuous-flow axial impeller pumps besides the Jarvik 2000 have been introduced to clinical application offering new advantages. Wieselthaler *et al.* |**9**| investigated six male patients (mean age 53 ± 11 years) with end-stage left heart failure who were implanted with a DeBakey VAD axial-flow pump for bridge to transplantation. Three patients were successfully transplanted after 74, 115 and 117 days. Two other patients died after 25 and 133 days. Noon and colleagues |**10**| have reported more extensively on the MicroMed DeBakey VAD. A detailed evaluation of the first 32 of more than 50 patients implanted with this device has been completed. With current data, the probability of survival at 30 days after implant is 81%. This preliminary experience suggests that this long-term axial-flow circulatory assist device is capable of providing adequate haemodynamic support in patients with severe heart failure, sufficient to recover and return to normal activities while awaiting heart transplantation. The concept of destination therapy using VADs is promising and validated. Yet, gaps in translating this information to the clinical realm exist, due to the device limitations of iatrogenic complications and durability. The field of mechanical assistance is progressing rapidly with the introduction of smaller devices that are more durable and with less risk of infection or haematological aberrances. The most important advance will occur with the structured implementation and development of strategies designed to achieve the maximal potential for device removal, ushering in a more universal opportunity for destination to recovery.

Recovery from heart failure with circulatory assist: a working group of the National Heart, Lung, and Blood Institute

Reinlib L, Abraham W. *J Cardiac Fail* 2003; **9**(6): 459–63

BACKGROUND. Anecdotal evidence suggests that heart failure patients fitted with mechanical assist devices experience direct cardiac benefits manifested by reverse remodelling and some are successfully separated from their device in follow-up. To investigate this phenomenon, on 2–3 August 2001, the National Heart, Lung, and Blood Institute convened the working group, 'Recovery from Heart Failure with Circulatory Assist' in Bethesda (Maryland, USA). The team included cardiac surgeons, cardiologists, and experts in experimental research. The goal was to prioritize recommendations to guide future programmes in: (1) elucidating the mechanisms leading to reverse remodelling associated with an LVAD; (2) exploring advanced treatments, including novel pharmacologies, tissue engineering, and cell therapies, to optimize recovery with LVAD therapy; and (3) identifying target genes, proteins, and cellular pathways to focus on for the production of novel therapies for myocardial recovery and cardiovascular disease.

INTERPRETATION. The working group made research and clinical recommendations to eventually translate findings into improved therapeutic strategies and device design: (1) support collaborations among clinical and basic scientists with an emphasis on

clinical/translational research that might eventually lead to clinical trials; (2) identify candidate patients most likely to benefit from LVAD as a destination therapy; (3) explore potential biomarkers indicating when patients could most successfully be weaned from devices; and (4) promote clinical and experimental study of mechanically assisted organs and the tissue derived from them.

Comment

The challenge in the notion of destination therapy is inherent in our ability to separate those likely to improve after cardiac reparation has been allowed from those who present an irreversible illness that requires ongoing mechanical support. Several recent lines of evidence suggest the potential for cardiac recovery, leading to the development of the notion that the 'destination' could in fact eventually be cardiac recovery, offering an opportunity for pump explantation. In this regard, it is useful to evaluate the cellular and biochemical effects of mechanical unloading using VAD support. It has been demonstrated that mechanically induced haemodynamic restoration is accompanied by regression of cellular hypertrophy, normalization of the neuroendocrine axis, improved expression of contractile proteins, enhanced cellular respiratory control, and decreases in markers of apoptosis and cellular stress |**11**|. Due to the mechanistic lines of evidence supporting the notion that device explantation is reasonable, several investigators have sought to develop algorithms whereby the VAD can be removed. The evidence in this regard is controversial, with some investigators reporting marked success along with others recommending great caution in this approach. One of the biggest dilemmas that confronts the clinician is in the optimal clinical evaluation of cardiac recovery. Because the negative pressure exerted by the mechanical device alters loading conditions unusually, investigators have yet to settle upon the best method for the determination of explant feasibility. Others have suggested active ways to facilitate cardiac recovery, a premise that is still experimental. Mancini and colleagues |**12**| used exercise testing and exercise haemodynamic evaluations to distinguish patients on VAD support who might be candidates for explantation due to significant recovery. These investigators reported a low rate of explant success (five of 111 implants). These researchers have recently reported two cases of successful device explantation only to suffer recrudescence of disease in late follow-up. Other groups in larger populations have reported better success. Muller *et al.* |**13**|, as well as Hetzer and colleagues |**14**|, reported on 28 explants among 96 VAD-treated patients. These investigators used routine echocardiographic parameters to assess recovery with devices turned on and then off for up to 20 min. Others have suggested that inotropic stimulation using dobutamine echocardiography might be useful in determining cardiac recovery. These same investigators also revealed variability in the clinical response and histological improvement as evidenced by inconsistency between clinical responses and collagen alteration in the myocardium. More recently, Gorcsan *et al.* |**15**| used on-line quantitative echocardiography alone or combined with exercise cardiopulmonary testing to assess myocardial recovery in patients receiving LVAD support and thereby identifying patients

who are clinical candidates for device removal. It should be noted that the scant support for device explantation in routine late-stage heart failure is further amplified by the inconsistency and lack of agreement in the best technique to identify those likely to be successful. A tantalizing concept proposed recently seeks to actively attempt maximal reverse ventricular remodelling by the use of pharmacological stimuli. The concept revolves around the induction of physiological cardiac hypertrophy using clenbuterol, a selective β2-adrenergic receptor agonist, in carefully selected patients, followed by device explantation |**16**|. This interesting approach remains under systematic investigation.

Initial experience with the AbioCor implantable replacement heart system

Dowling RD, Gray LA Jr, Etoch SW, *et al. J Thorac Cardiovasc Surg* 2004; **127**(1): 131–41

BACKGROUND. This study sought to evaluate the safety and efficacy of the first available totally implantable replacement heart (AbioCor implantable replacement heart system) in the treatment of severe, irreversible biventricular heart failure in human patients. Seven male adult patients with severe, irreversible biventricular failure (>70% 30-day predicted mortality) who were not candidates for transplantation met all institutional review board study criteria and had placement of the AbioCor implantable replacement heart. All were in cardiogenic shock despite maximal medical therapy, including inotropes and intra-aortic balloon pumps. Their mean age was 66.7 + 10.4 years (range 51–79 years). Four of seven patients had prior operations. Six had ischaemic and one had idiopathic cardiomyopathy. All had three-dimensional computer-simulated implantation of the thoracic unit that predicted adequate fit. At the time of the operation, the internal transcutaneous energy transfer coil, battery, and controller were placed. Biventriculectomy was then performed, and the thoracic unit was placed in an orthotopic position and attached to the atrial cuffs and outflow conduits with quick-connects. The flow was adjusted to 4–8 l/min. Central venous and left atrial pressures were maintained at 5–15 mmHg. The device is powered through transcutaneous energy transfer. An atrial flow-balancing chamber is used to adjust left/right balance. The balance chamber and transcutaneous energy transfer eliminate the need for percutaneous lines. There was one intra-operative death caused by coagulopathic bleeding and one early death caused by an aprotinin reaction. There have been multiple morbidities primarily related to pre-existing illness severity: five patients had prolonged intubation, two had hepatic failure (resolved in one), four had renal failure (resolved in three), and one each had recurrent gastrointestinal bleeding, acute cholecystitis requiring laparotomy, respiratory failure that resolved after 3 days of extracorporeal membrane oxygenation, and malignant hyperthermia (resolved). There were three late deaths: one caused by multiple systems organ failure (post-operative day 56), one caused by a cerebrovascular accident (post-operative day 142), and one caused by retroperitoneal bleeding and resultant multiple systems organ failure (post-operative day 151). This latter patient was not able to tolerate anticoagulation (no anticoagulation or antiplatelet therapy alone for 80% of the first 60 days) and had a

transient ischaemic attack on post-operative day 61 and a cerebrovascular accident on post-operative day 130. At autopsy, blood pumps were clean. The two patients who had large cerebrovascular accidents had thrombus on the atrial cage struts. These struts have been removed for future implants. There were no significant haemolysis or device-related infections. The balance chamber allowed for left/right balance in all patients (left atrial pressure within 5 mmHg of right atrial pressure). Three patients have taken multiple (>50) trips out of the hospital, and two have been discharged from the hospital. Total days on support with the AbioCor are 759.

INTERPRETATION. The initial clinical experience suggests that the AbioCor might be effective therapy in patients with advanced biventricular failure.

Comment

One of the most technologically advanced devices, the AbioCor totally implantable heart is designed to completely replace the human heart and not merely 'assist' it. As such, this technique is a true destination therapy with no opportunity for recovery of the native heart. Thus, this technology is best suited for those individuals who suffer from severe irreversible pulmonary hypertension and biventricular failure who have little potential for any meaningful recovery. The longest survivor with this total replacement heart lived 17 months and died due to device malfunction. In others, the results have been quite mixed with marked device-related morbidity of bleeding complications and stroke.

Myosplint implant and shape-change procedure: intra- and peri-operative safety and feasibility

Schenk S, Reichenspurner H, Boehm DH, *et al. J Heart Lung Transplant* 2002; **21**(6): 680–6.

BACKGROUND. To attempt a decrease in ventricular wall stress, transventricular tension members (Myosplint) were implanted to change the left ventricle effective radius and to reduce the left ventricle wall stress by 20%. Myosplints were implanted in seven patients, all diagnosed with dilated cardiomyopathy. New York Heart Association class ranged from III to IV, and left ventricular end-diastolic diameter ranged from 70 to 102 mm. Mitral valve regurgitation was classified as mild in three cases and moderate in four. Four patients underwent mitral valve annuloplasty. These investigators observed no significant device-related complications, such as thromboembolism, bleeding, device instability, or vascular damage, at 90 days. Early indications in a small patient population demonstrate some improvements in clinical parameters.

INTERPRETATION. From this initial experience, one may conclude that placement of the Myosplint devices can be safely performed without early, significant adverse events. In patients with significant mitral valve incompetence, concomitant mitral valve repair is indicated to realize the full benefit of the procedure. The long-term effect of each procedure on cardiac function and survival will require further evaluation.

Comment

The Myocor Myosplint is a transcavitary tensioning device designed to change left ventricular shape and reduce wall stress. Studies have shown that this technique reduces fibre stress without a decrement in the stress–strain relationship. The tension rods that are inserted within the ventricular cavity require precise estimates of location and placement in order to achieve optimal benefits in reducing wall stress. Data in humans are still quite limited and clinical trends and benefits with this device are unclear.

Global surgical experience with the Acorn cardiac support device

Oz MC, Konertz WF, Kleber FX, *et al. J Thorac Cardiovasc Surg* 2003; **126**(4): 983–91

BACKGROUND. Providing end-diastolic support with an innovative mesh-like cardiac support device reduces mechanical stress, improves function, and reverses cardiac remodelling in animal models without safety issues. The objective of this study was to review the global clinical safety and feasibility experience of this device. The Acorn CorCap cardiac support device has been implanted world-wide in more than 130 patients with dilated cardiomyopathy with or without concomitant cardiac surgery. The device is positioned around the ventricles and given a custom fit. A series of 48 patients were implanted with the device in initial safety and feasibility studies, of whom 33 also received concomitant cardiac surgery. At implantation, eleven patients were in New York Heart Association class II, 33 were in class III, and four were in class IV. The average CorCap implantation time was 27 min. The mean intra-operative reduction in left ventricular end-diastolic dimension was 4.6 ± 1%. There were no device-related intra-operative complications. Eight early and nine late deaths occurred during follow-up extending to 24 months. Actuarial survival was 73% at 12 months and 68% at 24 months. There were no device-related adverse events or evidence of constrictive disease, and coronary artery flow reserve was maintained. Ventricular chamber dimensions decreased, whereas EF and New York Heart Association class were improved in patients overall and in those patients implanted with the CorCap device without concomitant operations.

INTERPRETATION. The CorCap device appears safe for patients with dilated cardiomyopathy. Randomized clinical trials are underway in Europe, Australia, and North America.

Comment

Passive cardiac restraint devices attempt to reshape the heart over time. Concerns about the development of constrictive physiology and impediments to coronary blood flow have appeared unfounded in animal studies and initial human trials. Whether cardiac restraint devices can be beneficial in isolation or only in the context

of concomitant operations such as mitral valve repair remains unproven. This concept is currently under investigation in a randomized trial that will share preliminary results in late 2004 |**17**|.

Conclusion

The device era in heart failure therapeutics has now been realized. Never before have clinicians had as diverse a repertoire of treatment options as now. However, we must be careful that we do not rush to judgement in the application of device therapy before the accumulation of an appropriate evidence base to help refine our treatment approaches. The availability of devices ushers with it responsibility to weigh factors such as device-based complications, incremental benefit potential and cost-effectiveness. The populations who are most likely to benefit require clarification. Despite these limitations, device therapy represents a fulfilment of therapeutic principles in heart failure that seek to modify the problem at the 'heart' and not simply to target the peripheral consequences of the manifest disorder.

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Editors

ILEANA L PIÑA, MD, Professor of Medicine, Case Western Reserve University; Division of Cardiology, University Hospitals of Cleveland, Cleveland, Ohio, USA

SIDNEY GOLDSTEIN, MD, Division Head Emeritus, Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, Michigan, USA

MARK E DUNLAP, MD, Associate Professor of Medicine, Physiology and Biophysics, Louis B Stokes VA Medical Center, Case Western Reserve University, Cleveland, Ohio, USA

Contributors

KIRKWOOD F ADAMS, MD, Associate Professor, Departments of Medicine and Radiology, School of Medicine, University of North Carolina, Chapel Hill, North Carolina, USA

INDER S ANAND, MD, FRCP, DPhil(Oxon), FACC, Professor of Medicine, Division of Cardiology, University of Minnesota Medical School; Director, Heart Failure Clinic, Veterans Administration Medical Center, Minneapolis, Minnesota, USA

EMILY L BURKETT, MS, Research Associate and Genetic Counsellor, Division of Cardiology, Oregon Health and Science University, Portland, Oregon, USA

MARK E DUNLAP, MD, Associate Professor of Medicine, Physiology and Biophysics, Louis B Stokes VA Medical Center, Case Western Reserve University, Cleveland, Ohio, USA

SIDNEY GOLDSTEIN, MD, Division Head Emeritus, Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, Michigan, USA

RAY E HERSHBERGER, MD, Associate Professor, Division of Cardiology, Oregon Health and Science University, Portland, Oregon, USA

STEVEN J KETEYIAN, PhD, Program Director, Preventive Cardiology, Division of Cardiovascular Medicine, Henry Ford Heart and Vascular Institute, Detroit, Michigan, USA

Mikhail Kosiborod, MD, Fellow, Section of Cardiovascular Medicine, and Clinical Scholar, Robert Wood Johnson Clinical Scholars Program, Yale University School of Medicine, New Haven, Connecticut, USA

Harlan M Krumholz, MD, MSc, Professor of Medicine (Cardiology) and Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut, USA

Patrick M McCarthy, MD, Chief, Cardiothoracic Surgery, Co-Director, Northwestern Cardiovascular Institute, Galter; Professor of Surgery, Northwestern Medical School, Chicago, Illinois, USA

Mandeep R Mehra, MD, MBBS, Director, Ochsner Heart Failure and Cardiac Transplantation Program, Oschsner Clinic Foundation, New Orleans, Louisiana, USA

Maria Eugenia Natale, MD, Clinical Cardiologist, Hospital Italiano, Buenos Aires, Argentina

Carlos Eduardo Negrão, PhD, Professor of Medicine, Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil

James O O'Neill, MRCPI, Fulbright Scholar, Department of Cardiovascular Medicine, George M and Linda H Kaufman Center for Heart Failure, Cleveland Clinic Foundation, Cleveland, Ohio, USA

J Herbert Patterson, PharmD, Associate Professor of Pharmacy, School of Pharmacy, and Research Associate Professor, School of Medicine, University of North Carolina, Chapel Hill, North Carolina, USA

Ileana L Piña, MD, Professor of Medicine, Case Western Reserve University; Division of Cardiology, University Hospitals of Cleveland, Cleveland, Ohio, USA

Margaret M Redfield, MD, Director, Mayo Heart Failure Program and Mayo Cardiorenal Research Laboratory, Mayo Clinic College of Medicine, Rochester, Minnesota, USA

Matt Saval, MS, Research Coordinator, Henry Ford Heart and Vascular Institute, Division of Cardiovascular Medicine, Detroit, Michigan, USA

Ricardo Serra-Grima, MD, Professor of Cardiology and Sports Medicine, University of Barcelona; Director of Exercise Testing and Cardiac Rehabilitation, Holy Cross and St. Paul Hospital, Barcelona, Spain

James B Young, MD, FACC, Chairman, Division of Medicine, Professor and Academic Chair, Department of Medicine, Lerner College of Medicine of Case Western Reserve University; Medical Director, Kaufman Center for Heart Failure, Cleveland Clinic Foundation, Cleveland, Ohio, USA