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Devices in the management of advanced, chronic heart failure

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Abstract

Heart failure (HF) is a global phenomenon, and the overall incidence and prevalence of the condition are steadily increasing. Medical therapies have proven efficacious, but only a small number of pharmacological options are in development. When patients cease to respond adequately to optimal medical therapy, cardiac resynchronization therapy has been shown to improve symptoms, reduce hospitalizations, promote reverse remodelling, and decrease mortality. However, challenges remain in identifying the ideal recipients for this therapy. The field of mechanical circulatory support has seen immense growth since the early 2000s, and left ventricular assist devices (LVADs) have transitioned over the past decade from large, pulsatile devices to smaller, more-compact, continuous-flow devices. Infections and haematological issues are still important areas that need to be addressed. Whereas LVADs were once approved only for 'bridge to transplantation', these devices are now used as destination therapy for critically ill patients with HF, allowing these individuals to return to the community. A host of novel strategies, including cardiac contractility modulation, implantable haemodynamic-monitoring devices, and phrenic and vagus nerve stimulation, are under investigation and might have an impact on the future care of patients with chronic HF.

Introduction

Heart failure (HF) is a global epidemic,[1,2] and the lifetime risk of developing HF is 20%.[3] Medical therapy with angiotensin-converting-enzyme inhibitors,[4,5] β-blockers,[6–9] aldosterone antagonists,[10,11] and angiotensin-receptor blockers[12,13] has significantly improved morbidity and mortality in patients with HF. Despite these improvements, the rates of hospitalization for HF have improved little, and readmission rates remain high at 23–27% within 30 days.[14–16] In addition, the 5-year age-adjusted mortality from HF is 59% and 45% for men and women, respectively.[17] Remote monitoring is a promising management strategy for ambulatory patients with HF,[18] but many individuals with chronic HF require advanced mechanical therapies just to survive. Nevertheless, causes for optimism exist. Cardiac resynchronization therapy (CRT) has been an important addition to our armamentarium for the treatment of HF, and left ventricular assist devices (LVADs) have quickly revolutionized and improved the care of the sickest patients with HF. In this Review, we discuss the development and latest indications for the use of these devices in the management of patients with advanced, chronic HF.

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Cardiac resynchronization therapy

As the inherent limitations of medical therapy and the lack of game-changing options on the horizon became clear, the search began for nonpharmacological methods to treat advanced HF. Astute clinicians discovered that intraventricular dyssynchrony was prominent in left bundle branch block (LBBB), and the abnormal interventricular septal motion in LBBB corresponded to periods of asynchrony in contraction and a reduction in the left ventricular ejection fraction (LVEF).[19] Autopsy studies revealed that conduction abnormalities are common in HF and, in one report, >80% of patients with idiopathic dilated cardiomyopathy had electrocardiographic evidence of intraventricular conduction abnormalities.[20] Furthermore, intraventricular conduction delay in patients with chronic HF has been shown to be a marker of increased mortality.[21] In the early 1990s, these discoveries served as the impetus for French investigators to place pacemaker leads into all four cardiac chambers of a man with severe HF and LBBB, with the goal of restoring the natural mechanical activation sequence.[22] Remarkably, his NYHA classification improved from class IV to class II.[22] In a small study, multisite biventricular pacing acutely improved haemodynamics in patients with severe HF and marked QRS prolongation.[23] This improvement was thought to occur by an increase in left ventricular (LV) filling time, a decrease in septal dyskinesis, and a reduction in mitral regurgitation brought about by resynchronization of ventricular contraction.[24,25]

Experimentation with biventricular pacemakers began to emerge as a means to restore synchronous left and right ventricular contraction. The additional LV lead was initially placed surgically, but eventually the coronary sinus route was shown to be efficacious and safe and, therefore, is now the standard method of implantation (Figure 1).[26] The clinical efficacy and safety of this novel therapy was initially tested in 67 patients with severe HF (NYHA class III) resulting from chronic LV systolic dysfunction.[27] Investigators in this study enrolled patients with a QRS interval >150 ms. The mean distance walked, quality of life score, and peak oxygen uptake all significantly improved in the patients with active biventricular pacing.[27] These very encouraging results led to the first large, prospective, double-blind study of CRT in patients with moderate-to-severe HF (NYHA class III or IV with a LVEF ≤35%) and a prolonged QRS interval (≥130 ms). The landmark MIRACLE study[28] demonstrated that patients who received CRT (with the device set to deliver pacing therapy) experienced significant improvements in the distance walked in 6 min, NYHA functional class, quality of life, time on the treadmill during exercise testing, peak maximal oxygen uptake, and cardiac structure and function, compared with control patients (who received a biventricular pacemaker that was not programmed to deliver pacing therapy) over the course of 6 months.[28–30] This study led to the approval of the first CRT device in the USA and laid the groundwork for further investigation into the utility of CRT as adjunctive therapy for advanced systolic HF.

Evolution of CRT: severe HF

The treatment of severe LV dysfunction rapidly gained interest, and novel therapies for advanced HF, such as implantable cardioverter–defibrillators (ICDs), began to be explored. In MADIT II,[31] ICDs were shown to reduce mortality in patients with a history of myocardial infarction and severe LV dysfunction. Therefore, MIRACLE ICD[32] was designed to test whether combined ICD therapy and CRT was safe in patients with advanced, symptomatic HF. CRT improved the quality of life, exercise capacity, and functional status of patients without being proarrhythmic. However, not until the COMPANION study[33] was the combination of an ICD and CRT shown to reduce all-cause mortality compared with medical therapy in patients with severe, symptomatic HF. These finding were instrumental in advancing the role of CRT for the treatment of severe HF, but the results of the CARE-HF trial[34] showed definitively that CRT with optimal medical

therapy, but without an ICD, was superior to medical therapy alone in decreasing morbidity and mortality (36% reduction in the risk of death with CRT versus medical therapy alone). Additionally, the number needed to treat to reduce the combined end point was six patients, which suggests that CRT is also a cost-effective strategy in the management of HF.[34]

The culmination of data from the aforementioned studies in severe HF led to the initial criteria for CRT therapy: NYHA class III/IV, a QRS interval ≥130 ms, and a LVEF ≤35% while receiving optimal medical therapy.[35] Subsequent studies showed acute and persistent (>6 months) haemodynamic benefits—improved systemic blood pressure, central venous pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, ventricular–arterial coupling, mechanical efficiency, and chronotropic responses—of CRT in severe HF.[36,37] Even for gravely ill patients in NYHA class IV, CRT is beneficial and reduces morbidity and mortality if individuals are ambulatory and are not inotrope-dependent.[38] Additionally, CRT with or without an ICD in patients with severe, advanced HF was associated with marked reductions in all-cause, cardiac, and HF hospitalization rates compared with optimal pharmacological therapy.[39]

Despite the use of CRT, mortality in patients in NYHA class IV remains exceptionally high (25% and 38% at 1-year and 2-years, respectively).[40] CRT should not be withheld if these individuals are ambulatory, because studies have shown that CRT can decrease LV volumes and improve cardiac function in these patients.[40] If the disease is advanced, however, a robust improvement in overall functional status should not be expected.[41] A systematic review of 14 randomized trials involving a total of 4,420 patients with a LVEF ≤35% and a QRS duration ≥120 ms, who were in NYHA class III–IV and receiving optimal medical therapy, showed that CRT increased LVEF by 3%, enhanced LV remodelling, quality of life, and exercise capacity, and nearly 60% of patients improved by at least one NYHA class.[42] Hospitalizations were decreased by 37%, and all-cause mortality was reduced by 22%.[42] These data clearly show that CRT is immensely beneficial in patients in NYHA class III–IV. Subsequently, the search began to determine whether CRT was beneficial in mild-to-moderate HF.

CRT in mild-to-moderate HF

The MIRACLE ICD II study[43] was the first trial in which researchers exclusively investigated the role of CRT in patients in NYHA class II. The goal was to examine whether CRT limited disease progression and improved exercise performance in patients with mild HF symptoms. Ultimately, the study revealed that CRT did not alter exercise capacity, but did significantly improve LVEF, LV systolic and diastolic volumes (markers of reverse remodelling), and NYHA class.[43] A second study in patients in NYHA class II showed similar findings (significant improvements in LVEF and ventricular volumes), and only 8% of patients had progression of HF symptoms.[44] These results led to the large-scale REVERSE study,[45] which included patients in NYHA class I (17.5%) or class II (82.5%) with a history of HF symptoms. The primary end point was the HF clinical composite response, which scored patients as ‘improved’, ‘unchanged’, or ‘worsened’, and included ventricular volumes and hospitalizations for HF as secondary end points. This pivotal, double-blinded study showed that CRT (with or without an ICD), in combination with optimal medical therapy, reduced the risk of hospitalization for HF and improved ventricular structure and function, but the improvement in the HF clinical composite score did not reach statistical significance.[45]

MADIT-CRT[46] was the first study in which researchers assessed whether CRT reduced the risk of death or HF events in patients with mild HF. The investigators enrolled patients with ischaemic or nonischaemic cardiomyopathy and NYHA class I (14.5%) or class II (85.5%) symptoms to receive either an ICD, or an ICD with CRT (CRT-D). Importantly, this study

was not blinded. No significant difference in the overall risk of death was evident between the two groups, but patients who received CRT had a significant reduction in HF events and experienced an improvement in LVEF and ventricular volumes.[46] In the CRT-D group, 17.2% of patients reached the primary end point (death from any cause or a nonfatal HF event) compared with 25.3% of participants in the ICD-only arm. The benefit of CRT-D was completely driven by a 41% reduction in hospitalizations.[46] This landmark study in the evolution of CRT led the FDA to expand their criteria and approve CRT with devices made by Boston Scientific for patients with LBBB and who were in NYHA class II or ischaemic class I, with a LVEF <30% and a QRS duration >130 ms.[47] In a *post hoc* analysis of MADIT-CRT,[48] the presence of LBBB was a strong factor when determining benefit from CRT with an ICD. Patients in NYHA class II had a greater prevalence of LBBB and QRS duration ≥150 ms than patients in NYHA class I, and a meta-analysis suggested that the benefit of CRT with an ICD is limited to those patients with a QRS duration >150 ms.[49]

RAFT[50] differed from the REVERSE trial and MADIT-CRT in that, initially, patients in NYHA class II or III were included (Table 1). However, after data from the CARE-HF trial showed a clear reduction in mortality for patients in NYHA class III, the protocol was revised to include only patients in NYHA class II. Importantly, this CRT study was the first to show a mortality benefit of CRT-D over ICD alone, particularly in patients in NYHA class II.[50] In all previous studies showing a mortality benefit, CRT had been compared with medical therapy. The primary outcome (death from any cause or hospitalization for HF) in RAFT[50] occurred in 40% and 33% of the ICD and CRT-D groups, respectively, with a significant delay in time to occurrence of the primary outcome in the CRT-D group. Overall, 23.5% of the patients died. The 5-year actuarial death rate was lower (28.6% versus 34.6%) and the time to death was longer in the patients receiving CRT-D than in those receiving an ICD. On the basis of these results, 14 patients would need to be treated with CRT-D for 5 years to prevent one death.[50] Notably, these benefits were at the expense of an increased rate of procedure-related adverse events. Nevertheless, the results from RAFT and the REVERSE trial resulted in the FDA expanding the indication for particular CRT devices to include patients with mildly symptomatic HF (NYHA class II), with a LVEF ≤30%, LBBB, and a QRS duration ≥130 ms.[51] Subsequent studies have bolstered the evidence that CRT has a definitive role in patients with mild (NYHA class II) HF.[52–58] Because only 17.5% and 14.5% of patients in the REVERSE trial and MADIT-CRT, respectively, were in NYHA class I, CRT is not universally endorsed for this subset of patients, but the FDA has approved CRT for patients with LBBB in ischaemic class I. Further, definitive evidence is needed that individuals with mild HF truly derive a benefit from CRT.

QRS duration and morphology with CRT

QRS prolongation on the surface electrocardiogram is used as a surrogate marker of LV dyssynchrony and is the main criterion for determining whether a patient with HF is eligible for CRT. However, the marker might be an imperfect estimate, and many patients with HF could be deprived of beneficial CRT. In a study involving patients with underlying cardiomyopathy, tissue Doppler imaging showed that dyssynchrony was present in >60% of patients with a narrow QRS interval (<120 ms).[59] Small, single-centre, prospective studies have suggested that a clinical benefit (improved symptoms and reversed LV remodelling) of CRT exists in patients with a narrow QRS interval.[60–62]

The RethinQ study[63] was the first multicentre, randomized, controlled trial designed to assess the role of CRT in patients with moderate HF and a narrow QRS. Patients enrolled in this study were in NYHA class III, and had a LVEF ≤35% and a QRS duration <130 ms, although they were then stratified into prespecified subgroups of patients with a QRS interval <120 ms or ≥120 ms. In this study, CRT did not improve peak oxygen consumption (the primary end point) in patients with moderate-to-severe HF.[63] Data from two

subsequent, small, single-centre studies refute these results and suggest that patients with HF and a narrow QRS duration still receive haemodynamic and symptomatic benefit from CRT.[64,65] To date, only 244 patients with a QRS interval <120 ms have been enrolled in studies of CRT (Table 2). A benefit seems to exist in this population, but the severely limited number of patients studied precludes definitive recommendations. Ideally, the results of the ongoing EchoCRT trial[66] will clarify the role of CRT in these patients. The EchoCRT study will be the largest randomized, controlled trial by far in which the role of CRT will be examined in patients who are in NYHA class III–IV and have a narrow QRS and a LVEF <35%. Morbidity and mortality in patients with echocardiographic signs of ventricular dyssynchrony will be assessed.

The data on QRS duration are not conclusive; however, the effect of QRS morphology on CRT outcome is clearer. Patients with LBBB have been shown to benefit more from CRT than those with right bundle branch block—whether from relief of HF symptoms, improved quality of life, slowed HF progression, or reduced risk of ventricular tachyarrhythmias—whereas right bundle branch block has been shown to be a marker of worse outcomes and a poorer response to CRT.[48,67–69] The 2011 guidelines from the Heart Failure Society of America state that CRT is recommended for patients in sinus rhythm with a widened QRS interval (≥150 ms) not resulting from right bundle branch block, who have severe LV systolic dysfunction and persistent NYHA functional class II–III symptoms despite optimal medical therapy (Table 3).[70]

Impact of CRT on mitral regurgitation

Mitral regurgitation can be present in up to 90% of individuals with HF.[71] Causes of primary mitral regurgitation include myxomatous degeneration, rheumatic disease, endocarditis, fibroelastic degeneration and, in rare instances, systemic disease processes.[72] By contrast, functional mitral regurgitation in HF usually results from abnormal LV geometry because of remodelling, which induces an imbalance between the closing and the tethering forces that act on the mitral valve leaflets.[73–75] The results of several studies suggest that CRT has the potential to reduce functional mitral regurgitation in patients with HF.[76–79] The mechanism can be either improved papillary muscle synchronization, or an acute increase in the transmitral pressure gradients (mediated by an increased maximal rate of rise in LV systolic pressure caused by improved coordination of LV contraction, which can facilitate effective mitral valve closure).[76–79]

An observational study showed that an improvement in the grade of mitral regurgitation with CRT did not have an impact on event-free survival.[80] A subsequent, single-centre, prospective study showed that CRT can cause an early reversal (within days of initiation) of functional mitral regurgitation, and that the improvement is most profound in patients with moderate-to-severe functional mitral regurgitation at baseline. Additionally, the improvement in severe functional mitral regurgitation was associated with reverse LV remodelling and increased survival.[81] These results are the most- convincing to date that CRT has a marked impact on mitral regurgitation and can improve outcomes. The data need to be replicated in a randomized, multicentre trial, but CRT could be considered as a potential treatment option for functional mitral regurgitation.

Molecular benefits of CRT

CRT clearly reduces morbidity and mortality in patients with HF and systolic dysfunction, but additional benefits from this therapy occur at the cellular and molecular levels. Several studies strongly suggest that CRT improves myocardial oxidative metabolism and efficiency, and restores homogeneous myocardial glucose metabolism.[82–85] CRT, therefore, is likely to improve ventricular function without increasing global LV oxidative metabolism,

thereby improving LV efficiency. Ukkonen and colleagues postulated that successful resynchronization is indicated by increased oxidative metabolism of the interventricular septum relative to the lateral wall, which reflects enhanced work of the septum.[82] Additionally, CRT has been shown to restore the balance between collagen type I synthesis and degradation (increased collagen production is a marker of increased fibrosis, which portends worse outcomes). This change, and the reduction in interstitial remodelling with CRT, might determine the overall response to therapy of patients with HF.[86–92] Likewise, changes in myocardial gene expression have been described in patients with chronic HF receiving CRT, including an upregulation of β_1-adrenoreceptors, myosin-6, and sarcoplasmic/endoplasmic reticulum calcium ATPase 2α, which suggests that CRT induces reverse remodelling at the molecular level.[93–95] The benefit of upregulating these contractile proteins can be seen in the anterior wall of the myocardium away from the pacing site of the LV lateral wall, which supports the concept of a global benefit of CRT at the molecular level.[96]

Optimizing the response to CRT

The main challenge with the implementation of CRT in advanced HF is that 20–30% of patients have either a suboptimal or no response to CRT, despite meeting the clinical indications for therapy.[18,28,32,97] Advanced echocardiographic measures have been explored as a possible means of identifying patients who will respond to CRT, and an important study using tissue Doppler imaging described the presence of increased LV dyssynchrony at baseline as a marker of individuals likely to respond to CRT and have a good overall prognosis.[98] The main problem with wide-scale implementation of tissue Doppler imaging and echocardiographic techniques to detect dyssynchrony is that many studies show an inability to predict a positive response, and the sensitivity and specificity of the techniques are not strong enough to justify routine clinical use.[63,99]

Several baseline factors have been identified that might indicate which patients are ‘super responders’ to CRT (defined as an increase in LVEF ≥14.5%). These markers include female sex, no history of myocardial infarction, QRS duration ≥150 ms, presence of LBBB, BMI <30 kg/m^2, and low baseline left atrial volume index.[100] Interestingly, CRT was associated with greater reductions in death or HF, with consistent echocardiographic evidence of more reverse cardiac remodelling, in women (25% of the study population) than men in MADIT-CRT.[101] Some of the benefit might have been driven by the fact that more women than men had LBBB at baseline.

These data increase the complexity of identifying the patients that will benefit most from CRT. The future role of echocardiography with CRT might be to identify the site of latest activation (the LV segment with the greatest delay in mechanical activation) as a possible ‘sweet spot’ for LV lead implantation to improve the overall response to CRT.[102–104] Device optimization, which is focused on how the device is set to resynchronize, also remains challenging, and is likely to improve once our ability to identify responders is enhanced. The best approach might include a comprehensive, echocardiography-guided strategy, but time constraints in clinical practice might make such a scheme too challenging to implement.[105] An alternative approach might be to develop an optimization clinic with a standardized protocol to treat nonresponders. Every effort should be made to achieve biventricular pacing as close to 100% of the time as possible, which has been shown to reduce mortality.[106,107]

Left ventricular assist devices

Despite optimal medical therapy and CRT, many patients deteriorate to end-stage refractory HF (defined as symptoms at rest or on minimal exertion, including profound fatigue,

inability to perform most activities of daily living, requirement of repeated or prolonged hospitalizations for intensive management, or evidence of refractory cardiogenic shock).[108] Cardiac transplantation is the best treatment option for end-stage HF, but a severe shortage of donor organs exists (only 3,742 heart transplantations were reported worldwide in 2009),[109] and many patients are poor candidates for transplantation.

Bridge to transplantation

Mechanical circulatory support for ventricular unloading and assistance has been available in various forms since the 1960s, beginning with the extracorporeal left heart bypass pump, which led to the first implantation of a pneumatic total artificial heart in the mid 1980s.[110,111] Eventually, interest shifted towards LVADs with an external power source. From 1989 to 1992, single-centre and multicentre trials established that LVADs could serve as a 'bridge to transplantation' by showing a 65% rate of survival to transplantation, compared with a 50% rate in patients receiving medical therapy.[112,113] In 1994, the FDA approved the use of an LVAD with an external power source as a bridge to transplantation.[114]

These early devices were implanted through a median sternotomy with an inflow cannula inserted into the LV apex and an outflow tube anastomosed to the ascending aorta. The pneumatically-driven pumping chamber was placed within the abdominal wall (Figure 2a).[115] These devices were set to an automatic mode that created pulsatile flow; the device ejected blood when the pump was 90% full, or when it sensed a decreased rate of filling.[116] The aortic valve rarely opens when the heart is being supported by an LVAD, and the left ventricle is truly decompressed. A single drive line containing the electrical cable and the atmospheric air vent was tunnelled transcutaneously from the implanted pump to the exterior. These early devices were powered by two rechargeable batteries that provided 4–6 h of power and were usually worn in a shoulder holster, vest, or belt.[117] Importantly, improvements to the design of the HeartMate® 1000 IP LVAD (Thoratec Corporation, Pleasanton, CA, USA), such as textured interior surfaces that formed a pseudointima to eliminate direct contact between device surfaces and blood elements, reduced the rate of thromboembolism.[118] With advancements in technology, a transition occurred from pneumatically-driven devices to vented electrical LVADs, in particular the HeartMate® VE, which received FDA approval as a bridge to transplantation in 1998.[119]

Destination therapy

The use of LVADs in patients deemed unsuitable for transplantation is commonly called 'destination therapy'. The HeartMate® VE had been approved as suitable for bridge to transplantation, but a randomized, multi-centre trial was conducted to assess the role of LVADs as destination therapy. In May 1998, investigators in REMATCH[120] began enrolling extremely morbid patients in NYHA class IV (LVEF <25%, peak oxygen consumption <12 ml/kg/min, or inotrope-dependent) and who were ineligible for cardiac transplantation, to receive a HeartMate® VE LVAD ($n = 68$) or optimal medical management ($n = 61$). LVAD placement led to a 48% relative reduction in the risk of death during 30-month follow-up, and a 27% absolute reduction in 1-year mortality.[120] Patients with an LVAD also experienced a marked improvement in quality of life; all the individuals with an implanted device who survived to 1 year improved to NYHA class II.[120]

However, these findings must be put into perspective. These patients were critically ill, and survival was still only 52% and 23% after 1 year and 2 years with LVAD support, respectively.[120] Sepsis was the leading cause of death in patients who received an LVAD, most likely because of the external percutaneous drive line; LVAD failure was the second leading cause of death. Furthermore, the neurological event rate with LVAD therapy was not

trivial (4.35-fold higher than with medical therapy).[120] Nevertheless, REMATCH was a major step forward in the field of mechanical circulatory support, and the FDA approved the HeartMate® VE for destination therapy in 2003.

Unfortunately, long-term follow-up revealed that these devices were not very robust—the 1-year and 2-year freedom from device replacement was 87% and 37%, respectively.[121] The HeartMate® XVE model had several enhancements that had the potential to improve device reliability compared with the HeartMate® VE. In particular, the HeartMate® XVE showed a significant reduction in percutaneous lead breaks, and 97% and 82% of patients were free from serious mechanical failures at 6 months and 1 year, respectively—a significant improvement compared with the HeartMate® VE.[122] These advances were encouraging, but a need for improved devices for long-term mechanical circulatory support remained.

Continuous-flow LVADs

The concept of continuous-flow LVADs arose from the desire to reduce the size of the pump and to move away from the external venting. Continuous-flow pumps work by an axial mechanism (second-generation pumps with cylindrical rotors and a helical motor, causing the blood to be accelerated and aligned with the rotor's axis) or a centrifugal mechanism (third-generation pumps whose rotors are shaped to move the blood circumferentially and thereby cause it to move from the centre towards the outer rim of the pump), with the rotor impeller being levitated magnetically in both types of pump (Figure 2b).[123] This allowed LVADs to be smaller and simpler because they contained no valves, consumed less power, and had a shaft seal to extend their performance life. Consequently, fewer overall complications were reported than with pulsatile-flow devices.[124,125]

HeartMate® II axial pump—The HeartMate® II was designed as an axial-flow pump and, after two pivotal trials, was shown to be superior to the pulsatile HeartMate® XVE (significantly improved probability of survival free from stroke and device failure at 2 years; actuarial survival 58% and 24% with the HeartMate® II and the HeartMate® VXE, respectively).[126,127] The FDA approved the HeartMate® II for bridge to transplantation in 2008, and for destination therapy in 2010. Consequently, no pulsatile LVADs have been implanted for destination therapy since January 2010.[128] The benefits of the HeartMate® II extended up to at least 18 months (72% actuarial survival), and patients had marked improvements in their NYHA functional class and quality of life.[129] The incidence of right heart failure with the HeartMate® II was low, and right heart function (in particular the right atrial pressure and right ventricular stroke work index—a surrogate for right ventricular function) might actually improve with this device.[130,131] The favourable changes seen in right ventricular function are likely to be the result of the haemodynamic benefits of LV unloading.[132] These are all important considerations because right ventricular failure is an important cause of increased morbidity and mortality after LVAD implantation.[133]

Importantly, both overall quality of life and functional capacity have been shown to improve in patients in NYHA class IV with the HeartMate® II.[134] Prospective patient enrolment and data collection in the Interagency Registry For Mechanical Circulatory Support (INTERMACS) began in June 2006, and the Center for Medicaid and Medicare Services mandated that all US hospitals approved for mechanical circulatory support as destination therapy enter patient data into this database.[135] The fourth annual report shows that current actuarial survival with continuous-flow pumps exceeds 80% and 70% at 1 year and 2 years, respectively (Table 4).[128,136] The report also lists several important risk factors for death after LVAD implantation—advanced age at the time of implantation, large body size, female sex, a high bilirubin level, and elevated right-sided pressures. Notably, patients were at increased risk of death if they presented with critical cardiogenic shock or had a history of

CABG surgery, stroke, ascites, pulmonary hypertension, or renal dysfunction (elevated level of blood urea nitrogen, creatinine, or both) at the time of LVAD implantation.[128]

HeartWare® HVAD centrifugal pump—Another continuous-flow LVAD that is being investigated as a possible option for bridge-to-transplantation and destination therapy is the HeartWare® Ventricular Assist System, which includes a centrifugal pump, the HVAD® (HeartWare, Inc., Miami Lakes, FL, USA; Figure 3). This is an innovative system with a hydro-magnetically levitated rotor that is the only moving part, creating a stable, frictionless impeller system that, unlike the axial pumps, has no mechanical bearings. A short inflow cannula integrated into the pump itself allows intrapericardial placement, which avoids abdominal surgery. The device was initially investigated in a bridge-to-transplantation, multicentre, nonrandomized trial in Europe. A total of 23 patients in NYHA class IV who were taking inotropes received the HVAD®.[137] After 1 year, 87% of the patients were still alive. The advanced design of the pump allowed for full cardiac support (estimated mean HVAD® pump flow 6.1 ± 1.1 l/min) with low power consumption by the device (mean power consumption 4.8 ± 1.0 W at a mean rotational speed of 2,741 ± 195 rpm). Infections were the most-common adverse event, but of greater concern was that a thrombus was detected in the pump in six of the first 13 patients to receive the device. Follow-up reports stated that this problem had been resolved.[137] After 2-year follow-up in Europe, haemodynamic status, quality of life, and neurocognitive function were improved in the majority of patients with the HVAD®.[138]

The ADVANCE trial[139] was a study conducted in the USA to test the HVAD® as a bridge-to-transplantation device. Patients who received the HVAD® were compared with individuals implanted with commercially available devices (mostly the HeartMate® II). At 1 year, 86% of the 140 enrolled patients were still alive, and the device was shown to be noninferior to established LVADs.[139] Bleeding, infections, and perioperative right heart failure were the most-common adverse events, which are typical in patients with all types of LVAD.[126,127,129]

Haematological issues

Anticoagulation is necessary with all continuous-flow LVADs. Case reports of gastrointestinal bleeding with continuous-flow LVADs have increased awareness of this adverse event.[140,141] Subsequent studies strongly indicate that gastrointestinal bleeding is a frequent source of morbidity in patients with the HeartMate® II (incidence 19–40%), but no deaths have been attributed to this adverse effect, and so a negative impact on survival has not been reported.[142–145]

A possible explanation for the increased incidence of gastrointestinal bleeding is that the HeartMate® II might be associated with impaired platelet aggregation and, therefore, an increased tendency to bleed. Exposure of the blood to high shear stress in the HeartMate® II might cause a qualitative defect in von Willebrand factor, with an increased risk of bleeding even in the 24–48 h postoperative period.[146–148] In one study, high-molecular-weight von Willebrand factor multimers were measured in 31 patients with a HeartMate® II and were found to be reduced in all the patients, 58% of whom experienced bleeding.[145] The relationship between sheer stress, acquired abnormalities in von Willebrand factor, and arterio–venous malformations has been demonstrated in patients with aortic stenosis, so the same pathological process might occur with the HeartMate® II.[149] The bleeding rates might be high with the HeartMate® II from systemic anticoagulation and impaired platelet aggregation, but the thromboembolic rate remains low (2.0–2.5%).[150,151]

Molecular benefits of LVADs

Patients in NYHA functional class IV have benefited tremendously from LVADs, both as a bridge-to-transplantation and as destination therapy, with reductions in morbidity and mortality, and improved quality of life. Additional benefits at the molecular and cellular levels might accompany LV unloading. Several studies have suggested that LVAD support improves rate-dependent contractility by causing faster decay of the myocyte calcium transient, but this early benefit might not be sustained.[152,153] Additionally, LVADs seem to have a favourable impact on the expression and upregulation of genes that improve cardiac function.[154–157] Tissue analysis has revealed significant reductions in myocyte size, collagen content, and cardiac tumour necrosis factor with LVAD support.[158] From a clinical perspective, LVADs improve end-organ perfusion, and unloading might decrease the number of ICD shocks.[159–161]

Future directions

CRT and LVADs have ushered in an era of device management of HF. Substantial gains have been made since the introduction of these devices, but further progress is needed in the treatment of HF. In addition to making LVADs smaller,[162] other future goals will be to gain an improved understanding of the altered aortic valve biomechanics in patients with an LVAD,[163] and to increase the ability to explant the device because several reports describe low rates of device explantation.[158,164] Despite the tremendous benefits displayed at the cellular level, explantation of an LVAD has been accomplished in only a small subset of selected patients who are receiving aggressive medical regimens (mostly those with a nonischaemic aetiology or small ventricles before LVAD implantation).[165–167]

Device-based approaches for the treatment of HF or its comorbidities currently under investigation include cardiac contractility modulation (CCM),[168,169] percutaneous ventricular partitioning,[170] transvenous phrenic nerve stimulation for central sleep apnoea in HF,[171] chronic extra-aortic counterpulsation,[172] and a variety of noninvasive and implantable telemonitoring devices.[173] Some of these devices will be briefly described, but detailed discussion is beyond the scope of this Review.

Calcium transients and contractions induced by action potentials at 0.5 Hz exhibit phasic and tonic components, known as CCM signals.[174] These signals can prolong the action potential and, therefore, increase sarcoplasmic reticulum calcium loading and calcium cycling. Consequently, CCM signal stimulation is a novel mechanism that can be used to enhance myocardial contractility in HF.[175] The CCM signal is delivered via a device that resembles a dual-chamber pacemaker (one right atrial and two right ventricular leads are placed transvenously). The device can deliver signals during the absolute refractory period of the cardiac cycle to enhance contractility.[176] CCM therapy has been shown to be safe, and a subgroup analysis suggested that patients with a LVEF ≥25% and NYHA class III symptoms might gain the most benefit.[168,169]

Ventricular partitioning devices divide the dysfunctional and functional portions of the left ventricle in patients with a previous anterior myocardial infarction. The goal is to attenuate or reverse LV remodelling via mechanical reduction, thereby leading to reduced LV volumes and wall stress.[170] Preliminary studies suggest that the device is safe and that patients experience an improvement in NYHA class and quality-of-life scores.[170]

Transvenous phrenic nerve stimulation is being investigated as a possible therapeutic option for patients with HF and concomitant central sleep apnoea. A transvenous lead is placed in the right brachiocephalic vein, left brachiocephalic vein, or left pericardiophrenic vein to stimulate the adjacent phrenic nerve. An implanted pulse generator then provides low-

energy nerve stimulation to regulate breathing.[171] This therapy has been shown to reduce central sleep apnoea in patients with HF, and is an attractive novel therapy that requires further investigation.

Vagus nerve stimulation is an alternative novel mechanism to treat patients with moderate-to-severe HF. Reduced vagal activity is associated with increased mortality in patients with chronic HF, which makes vagal stimulation an attractive physiological therapy.[177] Under anaesthesia, the right vagus is exposed via a surgical incision and an electrode is placed. The implantable vagal neurostimulator system delivers low-current electrical impulses via a pulse stimulation lead. Preliminary studies suggest that implantation is feasible and patients can experience an improvement in their quality of live and overall LV function.[178]

Conclusions

CRT and LVADs have made a huge impact in the care of patients with chronic HF. Both therapies have decreased morbidity and mortality and, just as importantly, have improved the quality of life for thousands of patients. In our current medical climate, where cost containment and resource utilization are paramount, we must continue to improve upon these therapies to reduce hospitalization and readmission rates in HF. Each therapy also imposes unique challenges that require further research. Optimization of devices and identification of the patients who will benefit most are key areas of current research in CRT. The continued development and miniaturization of devices, and the elimination of external drive lines, are crucial for the long-term durability of LVADs. We are now in an era of mechanical therapy for HF, and the future is promising for all patients affected by this often-devastating condition.

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Key points

- Cardiac resynchronization therapy (CRT) has evolved as an effective therapy for many patients with chronic heart failure, especially those with left bundle branch block
- CRT device optimization remains challenging, and is an area of intense investigation
- Left ventricular assist devices can serve as a bridge to cardiac transplantation or destination therapy for critically ill patients with heart failure, and the use of the latest devices has increased patient survival
- Physicians must be aware of various complex issues, including haematological and infectious concerns, when treating patients with chronic heart failure
- Several novel, investigational devices for chronic heart failure are on the horizon and hold substantial promise to improve patient outcomes

Review criteria

The PubMed database was searched for articles using the terms: “chronic heart failure”, “left ventricular assist device”, and “cardiac resynchronization therapy”, combined with “bleeding”, “treatment”, “optimization”, and “management”. We mainly selected full-text, original articles that were written in English and published between 1990 and 2012, and also searched the reference lists of these papers for further leads.

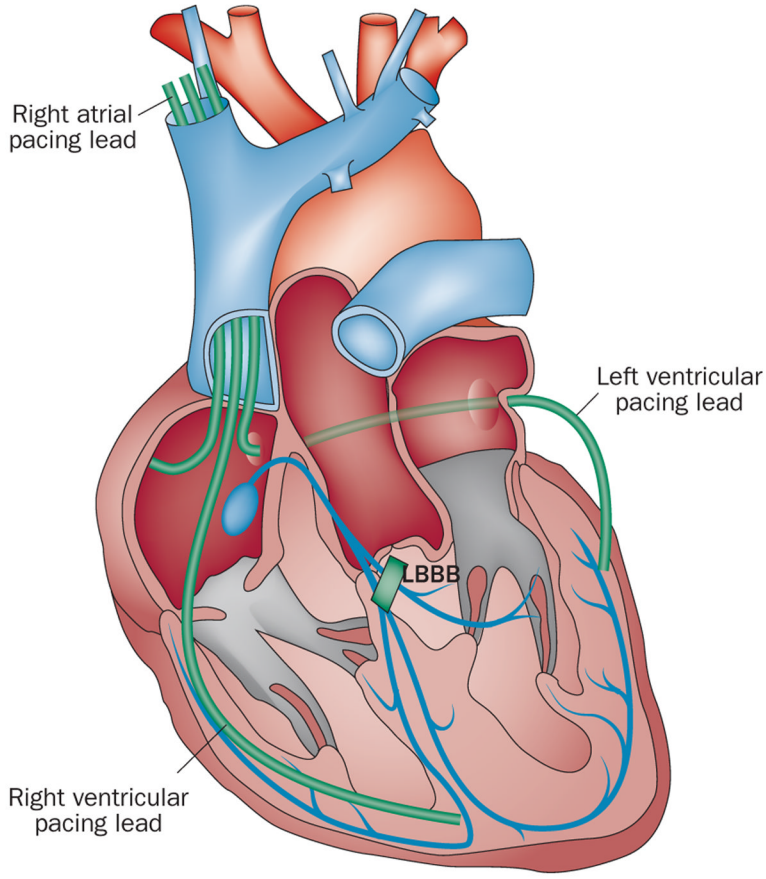

Figure 1.

CRT lead placement. A standard CRT system consists of a right atrial lead, a right ventricular lead (in CRT pacemaker systems) or a right ventricular defibrillation lead (in CRT defibrillator systems), and a left ventricular lead. The left ventricular lead is placed in a tributary of the coronary sinus on the left lateral or posterolateral wall. Abbreviations: CRT, cardiac resynchronization therapy; LBBB, left bundle branch block. Reprinted from *Lancet* **378** (9792), Holzmeister, J. & Leclercq, C. Implantable cardioverter defibrillators and cardiac resynchronisation therapy, 722–730 © (2011), with permission from Elsevier.

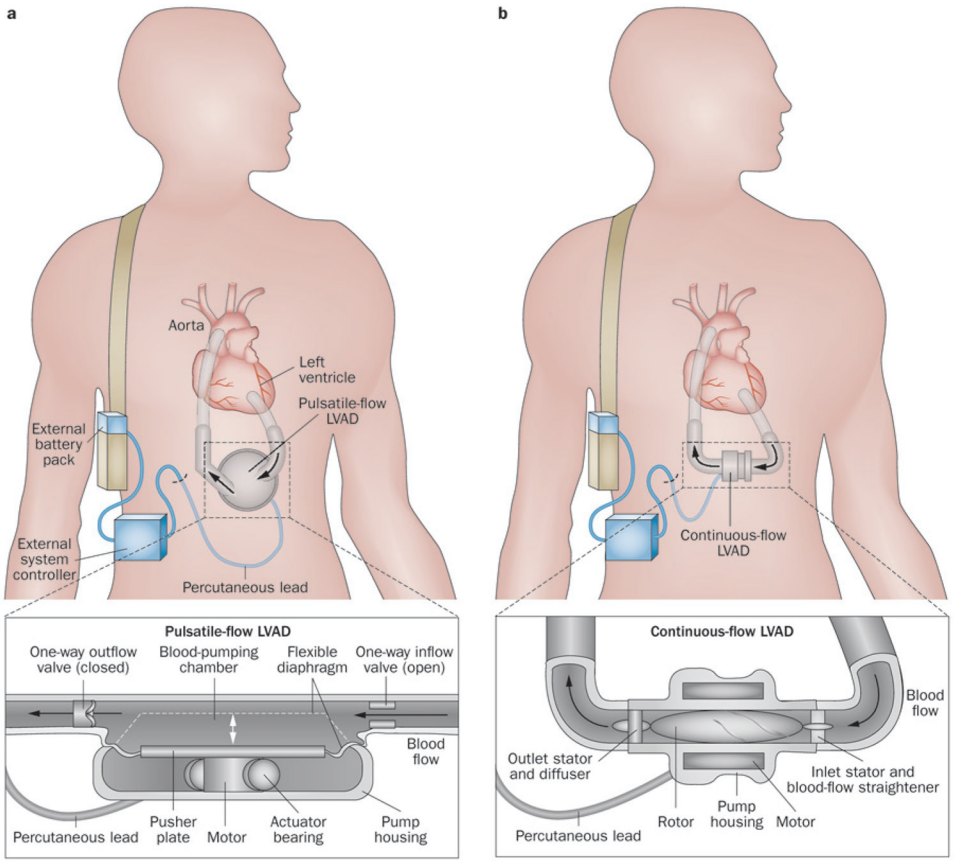

Figure 2.

Designs of LVADs. **a** | Pulsatile-flow devices use positive displacement pumps to propel blood throughout the body as a healthy ventricle would do. Although pulsatile flow is seemingly more physiological, left ventricular unloading and haemodynamic improvement is comparable to that achieved with continuous-flow pumps. **b** | Continuous-flow devices use either centrifugal or axial-flow pumps to propel blood continuously throughout the body. These devices are more reliable, have a longer functional life, and operate more quietly than pulsatile devices. Abbreviation: LVAD, left ventricular assist device.

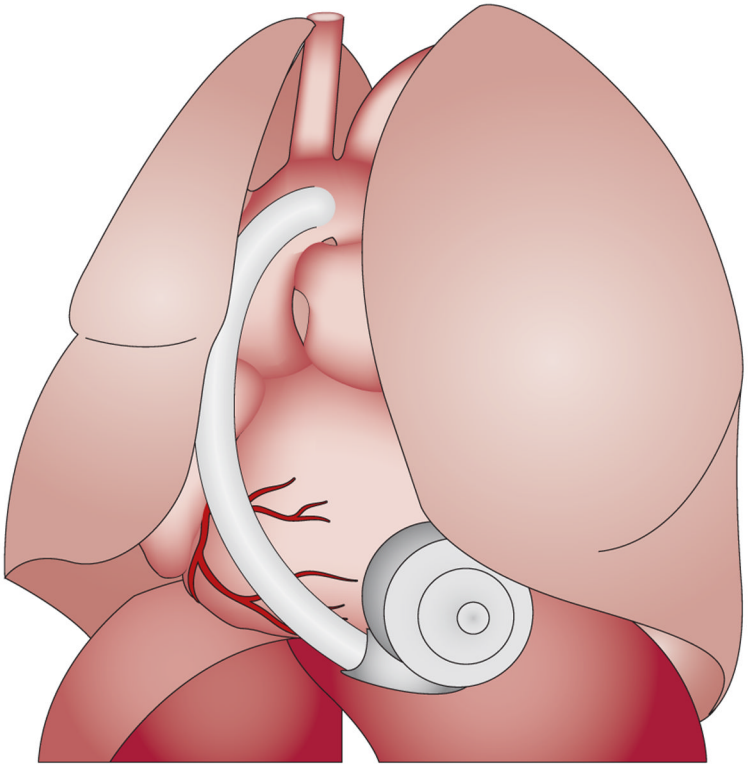

Figure 3.
The positioning of the HVAD® pump (HeartWare, Inc., Miami Lakes, FL, USA) within the pericardial space. Abbreviation: HVAD, HeartWare® Ventricular Assist Device. Reprinted from *J. Am. Coll. Cardiol.* **57** (12), Strueber, M. *et al.* Multicenter evaluation of an intrapericardial left ventricular assist system, 1375–1382 © (2011), with permission from Elsevier.

Table 1

Cardiac resynchronization therapy in patients with mild HF

Study	Number of patients	NYHA class	LVEF (%)	QRS duration (ms)	Primary end point	Effect on primary end point
REVERSE[45]	610	I–II	≤40%	≥120	HF clinical composite score	Not significant
MADIT-CRT[46]	1,820	I–II	≤30%	≥130	Death from any cause or a nonfatal HF event	Significant
RAFT[50]	1,798	II–III	≤30%	≥130	Death from any cause or hospitalization for HF	Significant

Abbreviations: HF, heart failure; LVEF, left ventricular ejection fraction.

Table 2

CRT in patients with heart failure and a narrow QRS

Study	Number of patients with narrow QRS (<120 ms)	Average QRS duration (ms)	NYHA class	End point	Outcomes
Achilli *et al.* (2003)[60]	14	110.0±10.9	III–IV	Functional capacity and echocardiographic outcomes	Improvements in NYHA class, LVEF, functional capacity, and reverse remodelling
Yu *et al.* (2006)[61]	51	103±13	III–IV	Clinical parameters and echocardiographic outcomes	Improvements in reverse remodelling, mitral regurgitation, NYHA class, exercise capacity, and LVEF
Bleeker *et al.* (2006)[62]	33	110±8	III–IV	Clinical parameters and echocardiographic outcomes	Improvements in 6-min walking distance, quality of life, LVEF, and reverse remodelling
RethinQ (2007)[63]	87	107±12	III	Increase of ≥1 ml/kg/min in peak oxygen consumption during cardiopulmonary exercise	Improvement in NYHA class, but not in peak oxygen consumption, quality-of-life scores, 6-min walking distance, or echocardiographic measures
Williams *et al.* (2009)[65]	30	Not reported (all <120)	III–IV	Short-term haemodynamic improvement in catheterization laboratory	Improvements in cardiac index, left ventricular stroke work, dP/dt_{max}, with increase in left ventricular filling
RESPOND (2011)[64]	29	91.5±10.6	III–IV	Change in 6-min walking distance	Improvement in 6-min walking distance, NYHA class, quality of life, and a composite clinical score

Abbreviations: CRT, cardiac resynchronization therapy; dP/dt_{max}, maximum rate of change in left ventricular pressure over time; LVEF, left ventricular ejection fraction.

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Table 3

2011 update of CRT guidelines from the Heart Failure Society of America[70]

Recommendation	QRS duration (ms)	NYHA class	LVEF	Strength of evidence
CRT is recommended for patients in sinus rhythm with a widened QRS interval that is not a result of right bundle branch block, who have severe LV systolic dysfunction and persistent, mild-to-moderate HF despite optimal medical therapy	≥150	II–III	≤35%	A
CRT can be considered for ambulatory, severely symptomatic patients with HF and a widened QRS interval and LV systolic dysfunction despite optimal medical therapy	≥150	IV	≤35%	B
CRT can be considered for patients with a widened QRS interval and severe LV systolic dysfunction who have persistent, mild-to-severe HF despite optimal medical therapy	≥120 to <150	II–IV	≤35%	B
CRT can be considered for patients with atrial fibrillation with a widened QRS interval and severe LV systolic dysfunction who have persistent, mild-to-moderate HF despite optimal medical therapy	≥120	II–III	≤35%	B
In patients with a reduced LVEF who require chronic pacing and in whom frequent ventricular pacing is expected, CRT can be considered	No comment	No comment	No comment	C

Abbreviations: CRT, cardiac resynchronization therapy; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction. Adapted from *J. Card. Fail.* **12** (2), Stevenson, W. G. *et al.* Indications for cardiac resynchronization therapy: 2011 update from the Heart Failure Society of American Guideline Committee, 94–106 © (2012), with permission from Elsevier.

Table 4

Survival with primary continuous-flow LVADs[128]*

Year of implantation	Number of patients	Survival (%)‡		
		1 month	6 months	12 months
2008§	458	95.8	88.3	83.4
2009	808	93.8	87.8	82.8
2010	1,445	95.1	87.0	81.4
2011//	692	95.4	88.7	Not available

*With or without a right ventricular assist device.

‡$P = 0.0001$.

§Two implantations with continuous-flow devices occurred before 2008 (one in 2006 and one in 2007).

//Includes January–June 2011.

Abbreviation: LVADs, left ventricular assist devices.