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Devices in heart failure; diagnosis, detection and disease modification

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Abstract

Introduction/background: Implantable cardiac devices are widely used in chronic heart failure (CHF) therapy. This review covers current CHF treatment with electronic cardiac devices, areas of discussion and emerging technologies.

Sources of data: A comprehensive search of available literature resources including Pubmed, MEDLINE and EMBASE was performed. National and international guidelines were accessed.

Areas of agreement: Excessive right ventricular pacing is detrimental to cardiac function. Cardiac resynchronisation therapy is beneficial in specific individuals with CHF.

Areas of controversy: Implantable cardioverter defibrillators might not benefit all. Optimising CRT delivery. Remote monitoring seems not to be of benefit in CHF.

Growing points: Device based optimisation.

Areas timely for developing research: Personalisation of device therapy. Focussing implantable cardioverter defibrillator therapy. What to do at implantable cardioverter defibrillator box change?

Introduction

Chronic heart failure is a common condition characterised by symptoms of breathlessness and fatigue in the presence of cardiac dysfunction, most frequently impairment of contraction of the left ventricle (left ventricular systolic dysfunction). The management of heart failure due to left ventricular systolic dysfunction is well supported by evidence from clinical trials and includes angiotensin-converting enzyme inhibitors, beta-receptor antagonists, aldosterone receptor antagonists and newer agents such as ivabradine and neprolysin inhibitors. In addition, device therapy especially pacemaker therapy; principally implantable cardioverter defibrillators (ICD) and cardiac resynchronisation therapy (CRT), has become a key part of the armamentarium used to control the condition.

Implantable electronic cardiac devices have revolutionised therapy within cardiology and are recommended in both national[1] and international[2,3] guidelines to treat bradycardia, tachy-arrhythmia and chronic heart failure secondary to left ventricular systolic dysfunction (CHF). The therapeutic use of cardiac pacing traditionally falls within the field of electrophysiology, but increasingly, heart failure physicians are taking the lead on implant decisions and the monitoring of CHF patients with these devices. Over time, through observational, preclinical and clinical studies, the pacemaker has developed from an externally powered device, to a fully implantable, automated device with battery longevity of more than 8 years capable of transmitting data wirelessly for remote follow-up. Whilst early pacemakers were electronic metronomes, modern iterations have added complex hardware and software around that basic function to allow for extremely complex and sophisticated programmability.

Pacemakers are associated with improved quality of life for individuals with sick sinus syndrome [3,4] and improved longevity and symptomatic benefit in patients with atrio-ventricular (A-V) block.[5] In patients with symptomatic CHF, a left ventricular ejection fraction (LVEF) <35% and QRS duration of >120ms, cardiac resynchronisation therapy improves mortality, morbidity and quality of life.[6] In certain subgroups implantable cardioverter defibrillators can improve mortality over a finite period in those with/at risk of ventricular tachy-arrhythmias.[7]

Here we provide an overview of current practice in device management with a focus on CHF, areas of controversy, emerging technology and areas ready for research.

Chronic heart failure and pacemakers

Despite proven mortality and quality of life benefits of pacemaker implantation,[4,5] long-term pacing in the right ventricle may be detrimental to left ventricular function in some individuals. Pacing the heart using a lead situated in the right ventricular apex has been standard practice for many years, but it is now clear that right ventricular pacing should be limited where possible.[8]

Right ventricular pacing for bradycardia a potential substrate for the development of left ventricular systolic dysfunction

The detrimental effects of right ventricular pacing have been appreciated for almost 100 years.[9] Wiggers observed right ventricular pacing-induced adverse changes in LV intra-ventricular pressure curves in canine experiments, and preclinical experiments of rapid chronic right ventricular pacing have been used for decades to induce heart failure,[10] but it was in the late 1980's and early 1990's that the clinical

association between persistent right ventricular pacing and heart failure was documented.[11] Observational cohort studies comparing atrial to ventricular pacing confirmed an association with right ventricular pacing and the increased incidence of CHF and atrial fibrillation.[12,13] The disorganised ventricular activation through right ventricular pacing,[11,14] causes adverse cardiac structural, haemodynamic and neuro-hormonal changes and is associated with adverse clinical outcomes.[12,14,15] In response, pacemaker manufacturers have developed algorithms designed to reduce unnecessary right ventricular pacing.

In patients in whom right ventricular pacing is unavoidable, alternative pacing sites of the right ventricular septum, right ventricular outflow tract and His bundle have been proposed as options to offset the potential negative effects of right ventricular apical pacing. However, although a meta-analysis published by Shimony et al. [16] including 754 patients from 14 randomized studies, comparing right ventricular apical pacing vs non-apical pacing suggested beneficial effects on LVEF in patients with impaired left ventricular function (LVEF≤45%), there were no differences in any measure of quality of life, functional test (walk distance and peak oxygen uptake) and morbidity or mortality rates. Hence, in the absence of clinical benefit, septal and direct His bundle pacing are not widely used due to concerns around long term lead function; since stability and sensing of intrinsic rhythm are less reliable when compared with right ventricular apical pacing.[3]

Pacing for chronic heart failure

Almost 50% of patients with CHF and left ventricular systolic dysfunction have ventricular conduction delays, such as left bundle branch block (LBBB),[17] and the

dyssynchronous contraction that occurs as a result creates a significant increase in myocardial work.[18] The effect is particularly relevant in the presence of left ventricular systolic dysfunction, where dyssynchrony compounds the situation, worsening morbidity and mortality.[19] An appreciation of this led to the concept that pacing might be able to improve conduction delay, reduce dyssynchrony and improve patient outcomes. Ground-breaking studies by Cazeau et al., Auricchio et al., and Kass et al.[20-22] demonstrated the beneficial effects of multisite pacing in patients, leading to the development of cardiac resynchronization therapy, credited as being the first method of improving cardiac function via the use of artificial electrical stimulation.[23] Since then, larger randomised studies have proven that cardiac resynchronisation therapy improves cardiac function, heart failure symptoms, quality of life and mortality and morbidity in specific individuals.[24]

Cardiac resynchronisation therapy involves electrically stimulating the right and left ventricles simultaneously using a pacemaker lead positioned in the right ventricular apex and a pacemaker lead positioned on the left ventricular free wall via the coronary sinus.[23] Although the treatment reduces morbidity and mortality from CHF,[6] around 35% of implanted patients do not improve either symptoms or beneficial remodelling – frequently and unfortunately termed ‘non-response’. Although this is not different to response rates for medical therapy,[25] the upfront approach in terms of cost and complications required for device therapy has led to a focus on de-selecting those less likely to ‘respond’ with considerable efforts to predict response prior to implant, all of which beyond the combination of left bundle branch block and impaired left ventricular function have been neutral.[26] Although mechanical dyssynchrony in the absence of electrical dyssynchrony (broad QRS)

does exist, all studies of cardiac resynchronisation therapy in this situation,[27] have been at best neutral.[28, 29]

Cardiac resynchronisation therapy in patients with existing right ventricular pacemakers

Patients with permanent right ventricular pacemakers are frequently found to have left ventricular dysfunction and heart failure thought to be due to long-term dyssynchrony induced through right ventricular apical pacing on a background of increased risk. Internationally, 'upgrades' from right ventricular devices represent between 23–28% of all cardiac resynchronisation therapy implants,[30] despite the fact that this approach has been tested only in small, mostly non-randomised studies. Three small randomized crossover trials,[30-32] and one randomised, placebo controlled trial,[33] have shown promising results with short term (2-6 months) follow-up periods. All participants in these studies had conventional right ventricular pacing indications for bradycardia (mainly A-V block), CHF symptoms (NYHA class II-IV) and LVEF <50%. When compared with right ventricular pacing, upgraded patients experienced fewer hospitalisations, improved left ventricular function and improved symptoms. Despite the lack of definitive data from large randomised control trials, there is accumulating observational evidence that patients with high volumes of right ventricular pacing, reduced LVEF and CHF symptoms benefit from upgrade to cardiac resynchronisation therapy.

Implantable cardioverter defibrillators

Despite a significant reduction in mortality rates in high income countries,[34] cardiovascular disease remains responsible for approximately 17 million deaths each

year worldwide, of which around 25% are sudden cardiac deaths.[34] In the past, around 40% of patients with CHF suffered sudden or unexplained death,[35] usually assumed to be due to either brady or tachyarrhythmias. Antiarrhythmic medications do not reduce (and may worsen) overall mortality especially in the setting of CHF with reduced ejection fraction.[36] Hence, following landmark trials published in 2002 and 2005 (Multicenter Automatic Defibrillator Implantation Trial II (MADIT-2) and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)) which both described the mortality benefit of ICD therapy in patients with left ventricular systolic dysfunction, primary prevention ICD implantation (in a patient with risk factors for but no proven ventricular arrhythmia) has become commonplace in patients with CHF due to left ventricular systolic dysfunction and is recommended in all major guidelines when optimal medical therapy has failed to increase the LVEF above 35%.[36]

However, new challenges are developing in ICD eligibility. Modern medical therapy and cardiac resynchronisation therapy can significantly reduce the incidence of sudden death,[37] whilst it is also becoming clear that in patients with more severe heart failure and co-morbidities, arrhythmia forms a much smaller proportion of total mortality compared with the incidence of death due to deteriorating CHF.[38] The appreciation of this in the immediate post-myocardial infarction setting has led to guidelines not recommending ICDs within 40 days of a myocardial infarction since a reduction in sudden death is offset by increases in heart failure death, demonstrating that treating arrhythmia in this setting converts only the mode of death.[39] The same pattern is seen in patients with severe symptoms (New York Heart Association class IV heart failure) resistant to standard and unsuitable for advanced CHF therapies since mortality in these patients is overwhelmingly due to heart failure.[36] Finally, ICD

therapy is unlikely to provide any benefit in those with significant co-morbidities with an overall prognosis of less than one year.[40] Controversy remains whether patients with an improvement of LVEF to >35% who have not required their device to deliver a shock should receive a replacement device when the original generator has depleted.[41]

ICDs should be considered in survivors of cardiac arrest, and in those with symptomatic sustained ventricular arrhythmia,[36] although even in this situation, the patient should be counselled, and their quality of life, LVEF (survival benefit is unproven with LVEF >35%) and existing life-limiting co-morbidities should be considered.[42]

Recent data have suggested that the benefit of ICD implantation is greatest in those with CHF and ischaemic aetiology, rather than those with non ischaemic aetiology, due to a greater risk of arrhythmia in those with IHD.[43] Patients with CHF, left ventricular systolic dysfunction and a long QRS duration are also at increased risk, although these patients are also usually offered cardiac resynchronisation therapy.[7, 38] It is possible that the clinical and cost-effectiveness of ICDs in CHF patients without ischaemic heart disease, those with and without important co-morbidities and the incremental benefit in patients receiving cardiac resynchronisation therapy should be re-evaluated.

Subcutaneous implantable cardioverter defibrillators

By avoiding trans-venous leads and the intravascular complications associated with them, subcutaneous ICDs have some advantages over standard trans-venous

systems and may be as effective at treating shockable ventricular arrhythmias.[44] They can be used in patients with difficult or absent venous access, but patient selection is important due to their inability to treat brady-arrhythmia, provide cardiac resynchronisation therapy or anti-tachycardia pacing. More robust evidence from clinical trials, around the performance of these devices, is still required.[45]

Areas of controversy – cardiac resynchronisation therapy

What is response?

Despite the evidence around the success of cardiac resynchronisation therapy, only around 65% of patients 'respond' in terms of standard measures.[46] Efforts to predict 'response' have been made, but no reliable feature has been found.[26] Crucially, although 'response' however measured is associated with a better long-term outcome in both randomised and observational studies, it is unclear whether 'non-responders' do less well in terms of prognosis than those that do not receive an implant at all. This issue is impossible to explore in observational studies. The CARE-HF study steering committee and investigators group performed an analysis with the aim of developing a prognostic model, based on prospectively defined patient characteristics and treatment, on the trial primary outcome of death from any cause or unplanned hospitalization for a major cardiovascular event. They found that those with echocardiographic evidence of marked dyssynchrony and low systolic blood pressure gained superior benefit from implantation, however considerable benefits were found across the range of subjects enrolled.[47] What is clear is that non-LBBB conduction delay does not benefit from cardiac resynchronisation therapy, possibly due to differences in substrate. Straus et al. found that in those with

LVEF≤35%, undergoing ICD implantation, RBBB was associated with more scar on cardiac magnetic resonance than LBBB, whilst LBBB was more commonly associated with magnetic resonance-defined non-ischemic aetiology.[48]

Improving response rates rather than de-selection

The alternative approach, possibly more acceptable than excluding potential non-responders prior to implant, is to improve 'response' rates by optimising electrical therapy delivery. Two optimisation technologies have recently emerged.

One option receiving much attention is multi-point pacing (MPP). The introduction of left ventricular leads with four electrodes capable of pacing from two sites at once, has allowed the opportunity to pace the lateral wall of the left ventricle from several points at once using a single lead. Although it seems logical that electrical activation beginning at several points on the left ventricular wall should improve coordination of the heart, there is no consistent evidence of increased response in terms of improved remodelling or composite scores of patient-related status. The largest study of multi-point pacing, randomly assigned 506 cardiac resynchronisation patients to 6 months of MPP or standard programming. An equal number of patients improved as were worsened by MPP.[49] Rather than improving response across the board, this suggests that careful patient selection might identify a subgroup of patients for whom MPP is of benefit and in whom one might choose to accept the additional battery drain in exchange for greater clinical effect, but there is little evidence that non-responders can be converted to responders in a general cardiac resynchronisation therapy population. On the other hand, since the technology leads to accelerated battery drain, with on average one year less longevity over the lifetime

of the device, in patients with no appreciable benefit from MPP, it should be left de-activated sparing the device battery.

The other approach to improve post-implant response is to optimise atrio-ventricular (A-V) timing - the timing by which ventricular electrical stimulation is offset following atrial activity - and ventricular-ventricular (V-V) timing – the timing of stimulation between the two ventricular leads. A protocol where these variables are adjusted to optimise filling and cardiac output measured by echocardiography can improve left ventricular remodelling, although studies are small and short-term. In addition to the need for repeated scans of limited reproducibility, the major disadvantage of an imaging-based optimisation is that resting haemodynamics might not reflect improved timings during exercise.[50] Hence a novel technology which uses a sensor located in the atrial lead that measures cardiac contractility during rest and exercise might be more reliable and logical. Cardiac contraction generates vibrations that transmit through the heart, the magnitude of these can measured by the atrial sensor, translated into a reproducible measure of cardiac contractility and used to optimise A-V and V-V timings at rest and exercise.[51] In a landmark clinical trial, the use of this system improved response rates and over 24 months reduced all-cause hospitalisation.[52]

Areas of controversy

Implantable cardioverter-defibrillators for all?

We have described the two large trials that demonstrated the benefit of ICD over medical therapy in heart failure due to left ventricular systolic dysfunction. These were published before the widespread use of cardiac resynchronisation therapy.

There has therefore long been controversy over whether a combined device including an ICD (known as CRT-D) is better than cardiac resynchronisation therapy alone (known as CRT-P) since this comparison has never been tested. This discussion, which is especially pertinent in patients with non-ischaemic cardiomyopathy in whom the sudden death risk is lower, has been heightened by recent trials. In 2016, Køber et al.[53] randomised 1116 patients with non-ischaemic, symptomatic systolic heart failure (left ventricular ejection fraction ≤35%) to receive an ICD (n=556), or usual care (no ICD)(n=560). More than half (58%) received cardiac resynchronisation therapy in each group, with a primary outcome of all-cause mortality, and secondary outcomes of sudden cardiac death and cardiovascular death. There was no all-cause survival benefit in individuals receiving ICD although ICD implantation did reduce the risk of sudden cardiac death (by 50%), and younger patients in particular had a survival benefit associated with ICD implantation. There was no influence of concurrent cardiac resynchronisation therapy.

Further information about sudden death in heart failure comes from Shen et al. who explored sudden death rates in a pooled analysis of 40,195 patients with heart failure with reduced ejection fractions (but without an ICD), enrolled in 12 clinical trials from 1995 to 2014.[54] They demonstrated a consistent reduction in sudden death over the period in question of 44% (p=0.03) across the trials. The 90 day sudden death rate was 2.4% in the earliest trial and 1.0% in the most recent trial. Importantly, the rate of sudden death was no different in those with a recent heart failure diagnosis than those with ongoing heart failure.

Both studies attributed their results to improved medical management of patients with heart failure, and will no doubt fuel intense debate amongst heart failure physicians, electrophysiologists and purchasers of healthcare around ICD implantation in CHF.

Cardiac resynchronisation therapy for complete heart block

CHF or asymptomatic left ventricular systolic dysfunction is seen in up to 40% of patients with permanent pacemakers, and relates to right ventricular pacing percentage and cardiovascular co-morbidities of the patient.[55] Whether those at risk of exposure to high volumes of right ventricular pacing should receive a cardiac resynchronisation therapy device at the time of the initial implant rather than a standard pacemaker is unknown. The BLOCK-HF study set out to examine this in 2003.[56] Patients with an LVEF≤50% and evidence of possible future high volumes of right ventricular pacing were implanted with cardiac resynchronisation therapy devices and randomly allocated to biventricular pacing (n=349) or right ventricular pacing (n=342). The primary endpoint was a composite of all-cause mortality, urgent heart failure care requiring intravenous diuretic therapy or increase in left ventricular end systolic volume index of >15% from baseline. The primary endpoint (driven by the remodelling component) was observed less frequently (53%) in the biventricular paced group than in the right ventricular pacing group (64%); equating to a 26% lower relative risk in those randomised to biventricular pacing (HR 0.74 (0.60–0.90)). The BIOPACE study, presented at the European Society of Cardiology conference in 2014, but not yet published, also failed to show a difference in outcomes between these two approaches to heart rate support. Whether cardiac resynchronisation therapy is the treatment of choice for complete heart block is therefore unproven not

least since an indication of ‘CHB’ does not closely predict high volumes of right ventricular pacing,[55] whilst the baseline risk factors predisposing to left ventricular dysfunction, it’s natural history and response to medical therapy are underexplored.

Remote management of heart failure using implantable devices

The majority of modern day devices implanted for heart failure have the ability to transmit diagnostic data remotely, offering the potential to adjust therapy remotely either by a central management service or by local services interpreting the data. Although widely accepted, some caution is required prior to adjusting current services in the hope that workloads will be reduced.[57] As the largest study of remote monitoring using implantable devices, the Remote Monitoring of Heart Failure (REM-HF) study described no benefit of weekly home monitoring vs usual care in 1650 patients (mean age 70 (range 23-98) years) with heart failure due to left ventricular systolic dysfunction on optimal medical therapy and a cardiac resynchronisation or ICD device.[58] The primary endpoint of death from any cause or unplanned hospitalization for cardiovascular reasons was not different after a mean follow-up time of 2.8 years between groups [HR 1.01; 95% CI: 0.87 to 1.18; p = 0.87](Figure 1). There were no significant differences between the two groups in any of the secondary endpoints or time to primary endpoint components.

Areas timely for developing research

Personalisation of programming

Cardiac devices offer many programmable settings, yet standard pacemakers and cardiac resynchronisation devices are often implanted ‘out of the box’ with very little personalisation.

The benefits of personalisation of right ventricular pacemakers to avoid unnecessary pacing is underestimated, with potential to lengthen battery longevity and avoid deteriorating left ventricular function. No independent clinical trials have been performed to explore these potential benefits, although we have previously described an approach that improved left ventricular function in patients with high amounts of right ventricular pacing and left ventricular dysfunction (Figure 2).[8] A randomised controlled trial to test our approach in a larger group of patients is now underway. Careful programming to try to avoid right ventricular pacing should be considered prior to upgrade in patients with right ventricular pacemakers, even those with A-V block.

Using echocardiography to define optimal cardiac resynchronisation settings may also be of benefit but is not widely used. In addition, it is during physical exertion that symptoms occur in heart failure, yet most imaging functional assessments and optimisation are performed at rest. Rather than aiming for de-selection of people currently eligible, optimisation based on individual physiology, whether determined by a device-based measure or imaging should be the target to improve response and thereby cost-effectiveness. Bradycardia and a poor heart rate rise in response to exercise (known as chronotropic incompetence), whether iatrogenic or pathological, are common in CHF failure and little is known about how these affect exercise capacity. Using pacemaker algorithms to counter bradycardia in patients with CHF is not evidence based. Neither a minimal, or aggressive, increase in heart rate rise has been shown to improve exercise capacity in those with CHF and devices,[59] but some degree of heart rate rise has been shown to improve outcomes,[60] and

exercise capacity.[61] Since exercise intolerance is the cardinal feature of heart failure, it is appropriate that research that targets this continues and is focussed on individual physiology rather than assuming that standard programming is the best that we can offer.

Do implantable cardioverter defibrillator guidelines in heart failure need re-examining?

Current implant guidance is largely based on MADIT-2 (2002) and SCD-HeFT (2005). Since these studies were completed, medical therapy has advanced and cardiac resynchronisation therapy is commonly offered, resulting in a decline in sudden cardiac death.[54] Moreover, the most recent NICE guidance,[62] omits diabetes mellitus as a risk factor for sudden cardiac death,[63] despite this co-morbidity being a powerful predictor of increased risk in patients with heart failure,[64] whilst including non-ischaemic cardiomyopathy which is associated with a low sudden cardiac death risk when optimally medically treated. All of this leads to the question of whether the impact of ICDs in heart failure need re-examining in the modern medical environment.

The implantable cardioverter defibrillator box change dilemma

Selection criteria for ICD implantation have been widely studied, but insufficient attention has been paid to the utility of generator replacements. Changes in the clinical circumstances including ongoing risks of arrhythmia and co-morbidities should influence decision making around replacement. Despite the critical nature of this decision for patients, their families and their physicians, there are no studies describing the risks and benefits of ICD generator replacement.[65]

Conclusions

Treatment advances have substantially improved outcomes in heart failure and implantable cardiac devices have played a critical role in this. Robust evidence shows that cardiac devices complement medical therapy to reduce mortality in chronic heart failure. A range of established and emerging device therapies have been reviewed in this article, along with some thoughts to provoke debate. Cardiac resynchronisation therapy is an established and potent therapy for people with symptomatic heart failure and a broad QRS. Work in this area should be based on improving an already successful therapy by personalising settings based on targeting individual physiology. ICDs are also a successful therapy for some, but not all, individuals with heart failure. Work in this area should focus on identifying who is at significant risk of sudden cardiac death and will therefore gain the most benefit from an ICD. The implantation of any cardiac device remains an invasive and potentially complex procedure with upfront cost and at a small but appreciable risk to the patient. Every effort should be made to ensure maximum benefit to individuals and society.

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