New developments in cardiac resynchronization therapy

Cardiac resynchronization therapy significantly reduces mortality and morbidity in patients with heart failure and ventricular dyssynchrony. This is a dynamic field with some exciting recent advances, and these future directions are discussed in this review.

Pacemaker technology started nearly five decades ago when the first human pacemaker implant was performed in 1958 by Ake Senning. This lasted a mere 3 hours necessitating a further implant which in turn lasted 2 days. Following these rather humble beginnings, pacemaker technology has made astonishing progress in the last few decades to where we stand now, perhaps on the cusp of another revolution. The early 1990s heralded the advent of cardiac resynchronization therapy and several landmark trials in the last decade have incontrovertibly demonstrated that cardiac resynchronization therapy leads to improvement in mortality as well as morbidity in patients with significant systolic heart failure and dyssynchronous ventricular contraction. Cardiac resynchronization therapy has thus become firmly established in the multipronged strategy to manage heart failure.

In addition we have witnessed miniaturization of generators, with more complex functions and monitoring capabilities, improvements in longevity of battery life, major advances in lead design and technology and more recently seen the increasing use of remote monitoring. These developments have helped to reduce implant procedure times, improved pacemaker performance and follow up.

Current status and future directions

Despite these developments, the success of cardiac resynchronization therapy remains hindered by the significant problem of 'non-response', which can affect up to 30% of patients who have had cardiac resynchronization therapy (Auricchio and Prinzen, 2011; Zaca et al, 2011). In addition, left ventricular lead implant can be unsuccessful in one out of 10 patients who undergo cardiac resynchronization therapy implant, mainly as a result of procedural difficulties related to abnormal coronary sinus anatomy (Daubert et al, 2012).

The latest international (American and European) guidelines for cardiac resynchronization therapy implant issued in 2012 (McMurray et al, 2012; Tracy et al, 2012) have expanded the indications, and thus with more heart failure patients now eligible for this therapy, the number of non-responders could also possibly increase. Non-response is likely to have a substantial economic impact on health-care resources as both the implant procedure and the post-implant follow-up need for revisions and generators change could skew the overall cost–benefit ratio of this therapy.

Other problems include pacemaker system infection requiring device and lead extraction, a procedure associated with significant morbidity and mortality. Lead-related issues include diaphragmatic twitching, lead displacement, conductor fracture and insulation breaks causing inadequate pacing, which necessitates further procedures, system revisions and lead re-positioning, which again increases the risk of infection.

These weaknesses related to the lead are the Achilles' heel of pacemaker technology and pose a significant challenge to cardiologists as well as the device industry. These issues have therefore spurred interest in research into novel techniques to assist left ventricular lead implant using imaging or mapping techniques, alternative routes for left ventricle pacing such as trans-septal or trans-apical endocardial left ventricle pacing, minimally invasive techniques for epicardial lead placement and multi-site left ventricle pacing. Another promising area includes research into leadless technology using ultrasound or magnetic field-delivered electrical energy and biological pacemakers may also herald a new revolution. These novel strategies will be discussed in this article.

Novel left ventricular lead implant techniques

The main difficulty with cardiac resynchronization therapy implantation is that posed by the left ventricular lead. The ideal left ventricular lead position is in the lateral or postero-lateral vein to achieve optimum resynchronization, although this can be easier said than done. Cannulating the coronary sinus can be challenging and

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the operator is often limited by coronary venous anatomy. There may not be a suitable branch in which to place the left ventricular lead, or the branch may be so tortuous, small and degenerate or stenosed that it does not allow the lead into it. Equally pacing may be hampered by the lead being in an area of posterolateral scar giving unsatisfactory thresholds, or cause troublesome diaphragmatic twitching requiring it to be placed at an alternative albeit less suitable location.

Use of new imaging techniques during cardiac resynchronization therapy implant

A variety of imaging techniques are being investigated to both aid implant of the left ventricular lead as well as to assess the optimal implant site. Use of a magnetic navigation system for left ventricular lead implant such as the Niobe system (Stereotaxis Inc., St. Louis, USA) incorporates two permanent magnets on either side of the fluoroscopy table to create a steerable magnetic field. The magnetic guidewire also has a small magnet at the tip and can be remotely navigated enabling precision to allow engagement of angulated target veins and also leads to reduced fluoroscopy time (Rivero-Ayerza et al, 2006, 2007, 2008; Gallagher et al, 2007). Similarly, use of electro-anatomic mapping with the Ensite NavX system (St Jude Medical, Endocardial Solutions Inc., St. Paul, MN, USA) (Del Greco et al, 2012) has also been shown to improve accuracy of left ventricular lead placement and to reduce fluoroscopy time.

Use of pre-implant imaging

Increased scar burden, especially in the posterolateral area in patients with ischaemic heart disease, has been shown to predict non-response to cardiac resynchronization therapy (Bleeker et al, 2006; Ypenburg et al, 2007). Scar in this region limits optimal positioning of the left ventricular lead, causing high thresholds and inadequate resynchronization (Ypenburg et al, 2007). A variety of techniques can be used to effectively map the left ventricular myocardium beforehand in order to help assess the amount of scar, regions of scar and transmurality of scar. This can indicate optimal pacing sites to best improve resynchronization, and also inform the implanter which areas of the left ventricle need to be avoided. Certainly the most contemporary modality in imaging with respect to this is cardiac magnetic resonance. Prior imaging with cardiac magnetic resonance seems to predict clinical response and long-term prognosis following cardiac resynchronization therapy (Leyva, 2010; Taylor et al, 2010). Despite this the operator is still limited by coronary venous anatomy – even with prior imaging, the left ventricular lead can only be placed down whichever branch is available.

Perhaps prior imaging with cardiac magnetic resonance could be used to predict which patients may be non-responders and in this group of patients alternatives such as endocardial or multisite pacing (described below) could be considered. Certainly there needs to be better patient selection, criteria need to be refined and parameters that best define response and non-response clarified in order to address the issue of non-response. Other imaging modalities that have also shown promise in identifying scar and predicting non-response to cardiac resynchronization therapy include single photon emission computed tomography myocardial perfusion imaging (Adelstein and Saba, 2007). Further studies could help improve our understanding of non-response and provide better prediction criteria for the cardiologist in the future in appropriately selecting and assessing the patient for cardiac resynchronization therapy.

The significant non-response rate has also spurred a huge interest in several imaging studies in order to improve the selection of appropriate patients for cardiac resynchronization therapy implant. Prominent among these is the large, prospective, multicentre trial (PROSPECT; Predictors of Response to CRT) which assessed the utility of twelve different echocardiographic measures of ventricular dyssynchrony in improving patient selection (Chung et al, 2008) but rather disappointingly showed that no single echocardiographic measure is either sensitive or specific enough to predict cardiac resynchronization therapy response. Currently QRS duration remains the mainstay in assessing eligibility for cardiac resynchronization therapy; imaging predictors of dyssynchrony are yet to significantly influence clinical decision-making as a result of inter- and intra-observer variability. However, echocardiography using speckle tracking can play a useful role in guiding left ventricular lead implant away from myocardial scar as suggested by the TARGET trial (Khan et al, 2012).

New routes for left ventricular lead implant

While epicardial left ventricular lead placement is well established as an alternative means of accessing the lateral wall of the left ventricle, it has the disadvantage that it involves surgery on an already frail, sick group of patients and there is also variation in the long-term outcome from epicardial lead placement for optimum resynchronization.

Endocardial left ventricular lead implant

Endocardial lead implantation by means of trans-septal puncture at the atrial level offers several potential advantages. It allows access to all left ventricular regions, overcoming the limitations of coronary venous anatomy, and endocardial ventricular layers offer faster impulse propagation than epicardial layers which might result in improved haemodynamics (Mischke and Knackstedt, 2011). Combined with prior imaging or mapping techniques this could allow the left ventricular lead to be placed in the ideal area of ventricle that is not scarred, and also the latest area to be activated, offering good pacing thresholds and optimum resynchronization.

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Superior electrical resynchronization and haemodynamic improvement, assessed by means of the maximum rate of pressure change in the ventricle (dP/dt_{max}), has been shown with endocardial left ventricle pacing in an acute canine model compared with epicardial stimulation, which resulted in transmural dispersion of repolarization and less effective improvement (van Deursen et al, 2009). Further studies in humans have shown mixed results. Spragg et al (2010) evaluated the haemodynamic effects of left ventricle endocardial pacing in patients with ischaemic cardiomyopathy. In this study, left ventricle endocardial *vs* epicardial pacing at transmural sites yielded equivalent dP/dt_{max} values, suggesting no differences in haemodynamics, although superior haemodynamic results were seen in patients when endocardial pacing was performed from extreme basal sites at positions adjacent to the mitral ring (>85% increase in dP/dt_{max}).

In a study by Derval et al (2010) pacing at the best left ventricle site in 35 patients with non-ischaemic cardiomyopathy was associated with twice the improvement in dP/dt_{max} compared to coronary sinus pacing. Bracke et al (2010) also showed that left ventricular endocardial pacing improves clinical efficacy in a cardiac resynchronization therapy non-responder. Several articles suggest that endocardial left ventricle pacing may be a realistic consideration for the cardiac resynchronization therapy non-responder with unfavourable coronary sinus anatomy as an alternative to epicardial pacing, offering better haemodynamic benefit, particularly when the left ventricular lead is placed in the basal postero-lateral region (Bordachar et al, 2010; van Gelder et al, 2011; Bracke et al, 2012). There are problems, however; the procedure is technically challenging, there is increased risk of thromboembolism as a result of leads in the left ventricle cavity (and therefore requires lifelong anticoagulation), and as the lead crosses the mitral valve there is risk of mitral regurgitation and endocarditis if there is pacemaker system infection (Mischke and Knackstedt, 2011). To avoid this, a trans-apical approach to endocardial left ventricular lead placement has also been described in a limited number of patients (Kassai et al, 2008).

Advances in epicardial left ventricular lead implant

An alternative to transvenous left ventricular lead implant is the surgical epicardial left ventricular lead implant which was first described in 1994 (Cazeau et al, 1994). While this approach can offer benefits such as direct visualization of the implanting segment, lack of need for fluoroscopy or contrast or the lack of difficulties posed by atypical coronary sinus anatomy, there are also disadvantages such as need for general anaesthesia, longer post-operative recovery time and inferior long-term pacing parameters leading to a 5-year lead failure rate of 15% (Lau, 2009). However surgical left ventricular lead implant techniques have also evolved to now include less invasive techniques requiring reduced procedural times such as using the lateral mini-thoracotomy technique, video-assisted thoracoscopic approaches and robotically-assisted procedures (Kamath et al, 2011; Singh and Gras, 2012).

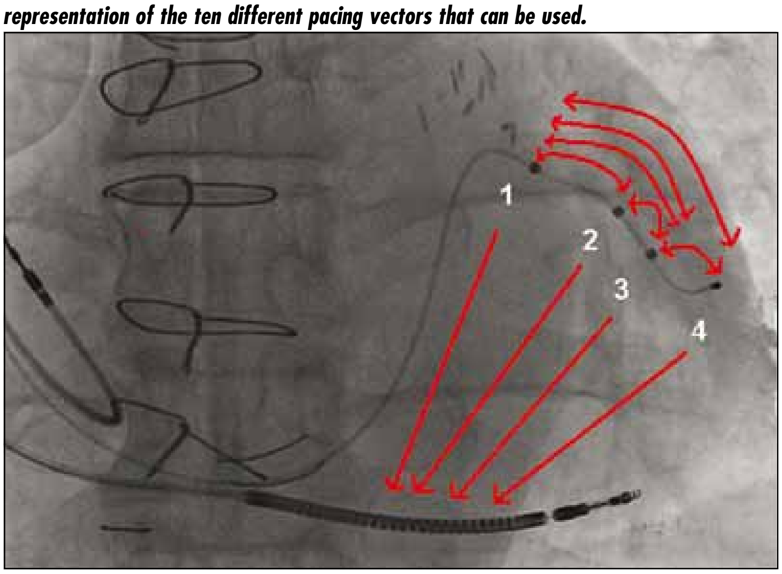
New left ventricular lead technology

Quadripolar left ventricular lead

The problems with cardiac resynchronization therapy are primarily related to the left ventricular lead, which can cause phrenic nerve stimulation, diaphragmatic twitch and high capture thresholds which often results in further procedures and attempts to reposition the lead. Clinically relevant phrenic nerve stimulation occurs in about 22% of patients at cardiac resynchronization therapy implant or follow up, with its occurrence highest in those patients where the left ventricular lead is at the sites most associated with reverse remodelling (Biffi et al, 2009; Shetty et al, 2011).

A quadripolar left ventricular lead, the St Jude Quartet model 1458Q, has been developed to help overcome these problems. The Quartet lead allows ten different pacing vectors which lets the cardiologist 'electronically reposition' and change the electrode configuration to help avoid phrenic nerve stimulation and optimize pacing thresholds without having to adjust lead position. A chest X-ray (*Figure 1*) from a patient in whom a cardiac resynchronization therapy device with a quadripolar left ventricular lead has been implanted is shown along with a diagrammatic representation of the ten possible pacing vectors. This flexibility reduces the need for procedural, manual lead repositioning, which is difficult and time consuming, with further, longer procedures being associated with higher chance of infection and need for extraction. This quadripolar lead therefore not only allows programming flexibility but also offers more options to achieve effective and safe cardiac resynchronization therapy. These findings have also been confirmed in the lit-

Figure 1. The quadripolar left ventricle lead (poles 1–4) with a diagrammatic representation of the ten different pacing vectors that can be used.



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erature (Thibault et al, 2010; Burger et al, 2011; Shetty et al, 2011), and the Quartet lead has started to be used in clinical practice and forms a useful tool in the cardiologist's armamentarium in enhancing cardiac resynchronization therapy success and reducing phrenic nerve stimulation. It appears likely that the Quartet will become a more widely used, and established piece of kit in cardiac resynchronization therapy implantation, at least for the near future.

Multi-site left ventricle pacing

Apart from endocardial left ventricle lead pacing there has also been interest in various types of multisite pacing to see if this might help in the issue of non-response, the theory being that placing multiple pacing leads at different sites could create multiple waves of electrical activation, further reducing dyssynchrony in the case of ventricular conduction delay (Auricchio and Prinzen, 2008). Following case reports and small observational studies (Yoshida et al, 2008; Hof and Maass, 2012), it seemed that triple ventricular pacing or triangle ventricular pacing (so-called 'Tri V' pacing), whether it be with an extra right ventricular or left ventricular lead, seemed to result in larger haemodynamic improvement compared with traditional biventricular pacing (Leclercq et al, 2008).

This led on to the TRIP-HF (Triple Resynchronization in Paced Heart Failure Patients) study, the first randomized prospective multicentre trial comparing triple-site stimulation (two transvenous left ventricular leads placed on the anterior and lateral or posterolateral left ventricle wall, and one right ventricular lead) with conventional biventricular pacing. *Figure 2* shows a sample X-ray view of the lead positions used in this study. *Figure 3* is a diagrammatic representation of triple ventricular stimulation. These can be compared to the lead positions used in the 'typical' biventricular cardiac resynchronization therapy from one of the authors' patients (illustrated in *Figure 4*). The study enrolled patients with heart failure presenting with slow atrial fibrillation and showed that, compared with standard biventricular pacing, triple site ventricular stimulation promoted further left ventricle reverse remodelling as assessed by end-systolic and end-diastolic volumes and ejection fraction at 3-month follow up. However, long-term difference in clinical outcome was not shown and this question remains to be answered. While multisite and endocardial pacing offer a possible alternative to improve biventricular pacing in cardiac resynchronization therapy non-responders, there has not been enough large scale evidence yet to bring this into routine clinical practice, and how far this changes the face of future cardiac resynchronization therapy remains to be assessed.

Optimizing device programming in non-responders

In some non-responders, optimizing device programming by adjusting ventricle-to-ventricle (V–V) or atria-to-ventricle (A–V) timing delays in order to optimize ventricular function may be of benefit. Often during cardiac resynchronization therapy implant, the atrioventricular delay is programmed at a nominal low value of around 100–120 ms to ensure maximum biventricular pacing although this may excessively reduce atrial contribution to left ventricle filling. Some studies suggest maintaining intrinsic atrioventricular conduction in non-responders to avoid this (Wang et al, 2009). Similarly, output and timing of right and left ventricular stimulation can be programmed to optimize inter-ventricular delay. While some patients respond well to simultaneous biventricular pacing, others do better with pre-activation of the right ventricle before the left. In this respect there is considerable inter-individual variability, and fine tun-

Figure 2. Chest X-ray showing lead positions in tri-ventricular pacing. RV = right ventricular lead; LV1 = left ventricular lead 1; LV2 = left ventricular lead 2.

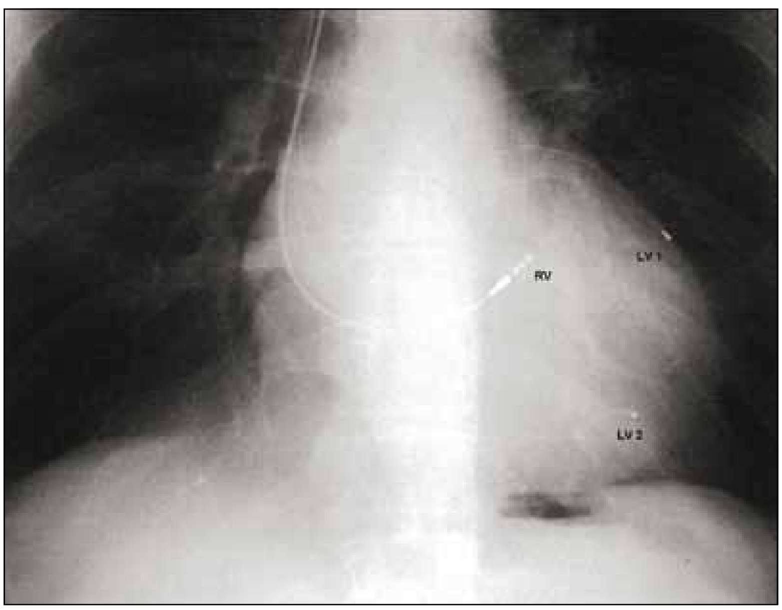
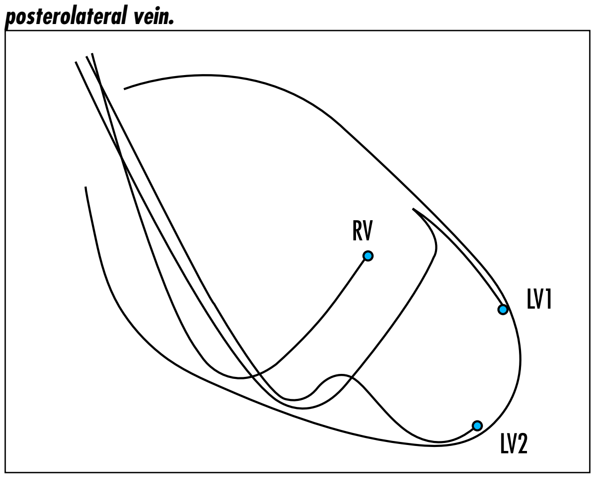


Figure 3. Diagrammatic representation of triple ventricular stimulation showing right ventricular (RV) lead positioned on the septum, left ventricular (LV1) lead positioned in the anterolateral vein of the coronary sinus, and LV2 lead positioned in the posterolateral vein.



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ing of the V–V interval has to be tailored to the individual to gain maximum benefit. While large inter-ventricular delays (up to 100 ms) can be programmed, optimal settings for V–V delay seem to be in a relatively narrow range (12–20 ms) (Fox et al, 2005). Several methods can be used to achieve optimization, most involve use of echocardiography. These include Doppler measures of mitral inflow velocity and left ventricle outflow velocity as markers for left ventricle filling and ejection (Gorcsan, 2011), aortic valve velocity time integral optimization, and M-mode with septal to posterior wall times. In addition to this, electrocardiographic-based QRS duration measures and, more recently, intra-cardiac electrogram-based optimization, can be used.

Leadless technology

Ultrasound or magnetic field-mediated energy

Problems related to the pacing lead include infection, fracture and dislodgement (necessitating further procedures such as lead repositioning), system revisions and extractions (with their associated risks). Substitution of the lead with an alternative means of energy transfer seems a rational solution to avoid these problems. Perhaps one of the most exciting advances to achieve this objective is that of leadless pacemakers, which may help to dramatically change the face of pacing technology in the not too distant future.

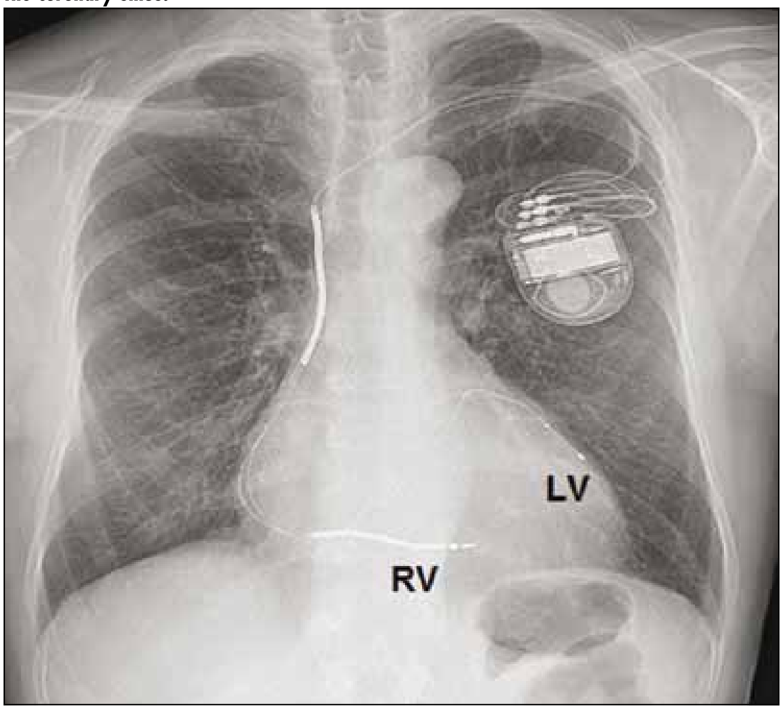
Studies have assessed ultrasound or magnetic field-mediated energy as an alternative to the flow of electricity down a conductor in a pacing lead (Lee et al, 2007; Kapa et al, 2010). A leadless pacing system includes an ultrasound generator implanted subcutaneously in the acoustic window of the chest wall and an endocardial receiver electrode which is delivered to the target heart chamber and implanted into the endocardium directly using a steerable trans-vascular catheter. This uses the mechanical to electrical properties of piezoelectric materials for the transformation of acoustic to electrical energy to capture and pace the heart muscle. The safety and acute efficacy of this ultrasound-mediated leadless technology has been evaluated successfully in animal models for biventricular pacing (Echt et al, 2006). The efficacy and safety of the Wireless Cardiac Stimulation LV System (WiCS, EBR Systems Inc., Sunnyvale, CA) are being evaluated in human implants in the ongoing WISE CRT trial (DeFaria et al, 2011).

For leadless cardiac resynchronization therapy a further receiver electrode will have to be implanted in the left ventricle endocardium following trans-septal puncture. A leadless pacing system has the advantages that it is less invasive, making implants potentially simpler, less time-consuming and technically less challenging, exposing the patient to less radiation, with fewer acute and chronic complications such as infection and skin erosion. It also has better patient aesthetics, should allow lower cost and reduced length of hospital stay, and overcomes problems related to the lead such as fracture and dislodgement. While the reliability of this technique to provide sustained energy over a prolonged period of time is currently unproven, other disadvantages include larger diameter catheters that are needed for implantation. It is also difficult to explant or reposition, and therefore must be abandoned at end of service. It also potentially has the adverse event of device dislodgement and embolization, although theoretically it should become endothelialized after a certain period of time. All these will have to be taken account of and technology further developed and refined, but certainly leadless pacing systems appear a very real and attractive prospect for the future of pacing and cardiac resynchronization therapy, and its arrival on the clinical scene is much anticipated.

Biological pacemakers

The next logical step to leadless systems would be to eliminate all pacing hardware altogether. Biological pacemakers could help to achieve this and in principle bio-pacemaker generation can be achieved by either inducing pacemaker activity in normally quiescent ('working') myocardium or implanting exogenous cells engineered to sustain pacemaker activity ('cell based' approach), once electrically connected to the host myocardium (de Bakker and Zaza, 2007). This could theoretically be performed by injecting cells (perhaps stem cells, or gene therapy to deliver recombinant genes that activate specific ion channels or currents) via a catheter positioned from the femoral vein into the appropriate region of the heart (e.g. the sinus node) to activate or stimulate the patient's own

Figure 4. Chest X-ray posterior anterior view showing right ventricular (RV) lead positioned at apex and left ventricular (LV) lead positioned in the anterolateral branch of the coronary sinus.



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conduction system. While still perhaps just a researcher's dream, this may provide a vision of the future to come, where medical technology advances to a point where we can simply restore normal physiology, where treatment is simple and effective, with little in the way of side effects and complications.

Conclusions

Cardiac resynchronization therapy has undergone several advances over the last decade to become one of the crucial components of modern heart failure therapy. Despite adherence to guidelines in selecting eligible patients, there is a significant non-response rate and current efforts are focussed on improving patient selection and thus cardiac resynchronization therapy response. There have been several exciting advances in implant techniques and lead technology as well as imaging which could herald the onset of a new generation in this dynamic field. While it remains to be seen if most of these novel ideas and developments will fully blossom from their embryonic stages to see the full light of day in our lifetimes, certainly these are exciting times in the story of cardiac resynchronization therapy. These novel techniques in the field of cardiac resynchronization therapy could offer cardiologists a variety of options that can be tailored to each individualized patient thus enabling more personalized device therapy in the near future. **BJHM**

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KEY POINTS

- Cardiac resynchronization therapy is a dynamic field in device technology with several ongoing advances.
- These include new developments in lead technology, imaging as well as research into leadless technology and bio-pacemakers.
- These novel techniques may help to increase successful response to cardiac resynchronization therapy.

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