Leadless endocardial left ventricular resynchronization: is it ready for prime time?

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This editorial refers to ‘Feasibility, safety and short-term outcome of leadless ultrasound-based endocardial left ventricular resynchronization in heart failure patients. Results of the Wireless Stimulation Endocardially for CRT (WiSE-CRT) study’ by A. Auricchio et al., on page 681.

Cardiac resynchronization therapy (CRT) entails placement of a left ventricular (LV) lead in patients with heart failure, systolic dysfunction, and dysynchrony in order to coordinate electrical and mechanical ventricular activation to improve ventricular function. Cardiac resynchronization therapy improves functional capacity, reduces heart failure hospitalization, and prolongs survival in recipients. However, 30–35% of patients fail to respond to CRT. Mechanisms proposed to account for non-response have included poor patient selection, suboptimal LV lead position with regard to LV segment, and more recently, epicardial as opposed to endocardial electrical activation of the LV. To overcome these limitations, a leadless endocardial LV pacing system (WiCs-LV system) has been developed. In the WiCs system, a small, bullet-like, wireless LV endocardial bipolar electrode is deployed that transduces ultrasound energy into electrical pacing pulses. A subcutaneous pulse generator is implanted alongside a standard pacemaker or defibrillator (the ‘co-implant’). The subcutaneous pulse generator detects the co-implant’s right ventricular (RV) pacing pulse, triggering generation of an ultrasound pulse that the LV endocardial plug converts to a near-synchronous LV pacing waveform. In this issue of the Journal, Auricchio et al. report on the feasibility and safety of the wireless endocardial LV pacing system.

Why endocardial left ventricular pacing?

Left ventricular pacing via a lead in the epicardial coronary venous system introduces many potential mechanisms of non-response. Coronary venous valves, tortuosity, or absence of branches (particularly in the setting of ischaemic disease or previous surgery) may preclude pacing the site of latest activation. Epicardial LV leads have higher pacing thresholds than endocardial leads, dislodge in 6% of patients, and result in phrenic nerve capture in 12%. Moreover, epicardial pacing may be inherently inferior to endocardial pacing. Epicardial pacing is non-physiological, and leads to slow transmyocardial conduction, often seen as a pseudo-delta wave on the surface electrocardiogram. In contrast, endocardial pacing results in more rapid activation of the LV myocardium due to physiological activation from the endocardium to the epicardium and by recruiting the sub-endocardial Purkinje network. It may also improve the timing of papillary muscle contraction. It is possible that endocardial, M-cell, and epicardial myocyte activation in physiological sequence may reduce arrhythmic risk. Endocardial LV pacing has been shown to result in shorter QRS duration and more favourable Doppler indices of LV function compared with epicardial pacing. Thus, due to the greater flexibility in LV pacing site selection, absence of phrenic nerve stimulation, better haemodynamic response, and potentially lower dislodgment rate, endocardial LV pacing may be the preferred method of delivering CRT. However, clinically acceptable methods of delivering safe, long-term, endocardial LV pacing have been lacking.

Endocardial LV lead implantation using conventional pacing leads placed transapically or through the inter-atrial or inter-ventricular septum has been described in small case series. While these techniques are limited by the lack of appropriate tools for trans-septal implantation, a far more significant concern is the risk of thromboembolism related to systemic lead implantation. Currently available pacemaker leads are inherently thrombogenic, with mobile thrombi present in 30% of patients examined by intracardiac echocardiography. Anticoagulation may not fully mitigate this risk. A 3-fold increased risk of cardioembolic stroke has been reported in cardiac device recipients with a patent foramen ovale (PFO) compared with similar patients without a PFO, attributed to paradoxical embolus of lead thrombi through the PFO. The risk persisted in patients treated with warfarin. Exposure of a long segment of lead to the systemic circulation increases stroke risk. The largest study of thromboembolic risk related to endocardial LV leads to date reported an alarming stroke or transient ischaemic attack rate of 14% in patients with a mean follow-up limited to 2 years, despite high intensity anticoagulation. In the majority, thrombus was seen...
on the pacing lead body with ultrasound imaging. Trans-septal placement of a lead across the mitral valve also carries the risk of worsening mitral regurgitation. In patients with standard CRT systems, tricuspid regurgitation develops or worsens in ~15% of patients, limiting their response to CRT and increasing mortality. It is possible that up to 50% of non-response may be due to tricuspid regurgitation created by the RV lead of CRT systems (unpublished observation). Placing a lead across the mitral valve, with its greater pressure gradients, may pose greater longer-term risk than the currently available studies of ~50 patients with limited follow-up can detect. Thus, a small leadless device that can be reliably implanted in the LV endocardium with a low risk of procedural complications is a highly desirable tool for the treatment of refractory heart failure. 

**Leadless left ventricular pacing: are we there yet?**

Auricchio et al. report on the feasibility and safety of LV endocardial lead implantation in 17 patients in the prospective observational WiSE-CRT study. Over half of these patients had failed earlier attempts at coronary sinus lead implantation or were CRT non-responders. The device was successfully implanted in 75% of subjects. The authors report a mean reduction in QRS duration of 41 ms compared with RV pacing and modest improvement in ejection fraction on the pacing lead body with ultrasound imaging. Trans-septal placement of a lead across the mitral valve also carries the risk of worsening mitral regurgitation. In patients with standard CRT systems, tricuspid regurgitation develops or worsens in ~15% of patients, limiting their response to CRT and increasing mortality. It is possible that up to 50% of non-response may be due to tricuspid regurgitation created by the RV lead of CRT systems (unpublished observation). Placing a lead across the mitral valve, with its greater pressure gradients, may pose greater longer-term risk than the currently available studies of ~50 patients with limited follow-up can detect. Thus, a small leadless device that can be reliably implanted in the LV endocardium with a low risk of procedural complications is a highly desirable tool for the treatment of refractory heart failure. 

(i) A number of serious adverse events resulted in premature termination of the study. The most significant complication was tamponade due to perforation of LV in 3 of 17 patients. The procedure was abandoned in all three and death occurred in one patient. Perforation was thought to be related to sheath manipulation in the LV, although maneuvers related to deployment of the lead including the use of anchor barbs may also increase the risk of myocardial injury and perforation. Further technical advances including redesigning of the delivery system may reduce the risk in the future, but not eliminate it.

(ii) The Achilles heel of leadless LV pacing may be the need for an acoustic window free of intervening lung and bone tissue to efficiently transmit the ultrasound pulses from the subcutaneous transmitter to the intracardiac receiver. While an appropriate window was present in all patients prior to implantation, this window can vary with posture and shift with chronic implantation. Three patients in the study required repositioning of the transmitter device in the immediate post-implantation period due to loss of capture. Long-term follow-up is required to confirm the stability of the acoustic window. Furthermore, while the LV lead can theoretically be positioned at any optimal endocardial site identified by mapping, the suitability of a site is also limited by the ability to align the receiver device with the transmitter.

(iii) Monitoring of device performance using conventional parameters such as electrical pacing threshold and lead impedance is not possible. While the ultrasound threshold for capture can be measured, the efficiency of energy transfer can vary and its clinical significance is unknown. As a corollary, automated algorithms used to confirm capture in conventional leads cannot be utilized and observation of the paced QRS morphology is required. The automatic determination of percentage of true bi-ventricular pacing crucial to the management of CRT non-responders is also not available.

(iv) Left ventricular lead pacing is triggered by sensing the RV lead pacing output, which means that LV pacing cannot be performed before RV pacing. While programmability of the interventricular delay with LV first offset may improve outcomes in selected patients, the clinical importance of the feature has not been consistently confirmed, making this limitation likely insignificant. Moreover, it is possible that the benefits of endocardial pacing will outweigh the modest benefit of LV first pacing when present.

(v) The potential for electromagnetic and ultrasonic interference to cause inappropriate or withheld pacing is not well understood. Further data regarding the potential for external electrical interference and algorithms to prevent it are needed.

These serious concerns—predominantly the effusion rate—have led to an appropriate pause in the trial. New technologies often require refinements as they are introduced, and this is particularly true for a complex system that involves several implanted components that must inter-communicate. Nonetheless, the advent of a means of leadless endocardial LV resynchronization is an exciting advance in pacing technology with the potential to improve the quality of life and survival in patients with heart failure. In the near term, it represents an important option for selected patients with refractory heart failure who have failed epicardial LV lead placement or who are non-responders. The widespread adoption of the device, however, will require improvement in the technology to address safety and reliability issues. Finally, long-term studies comparing the efficacy of conventional epicardial resynchronization with the endocardial device will be needed.

**Towards the future**

Other strategies may enhance CRT response and avoid current limitations. In canine studies, a lead with totally intramyocardial electrodes (anode and cathode) placed endocardially at the atrioventricular septum pre-excites the LV, decreases dyssynchrony without the presence of a lead in the LV and with no lead-systemic circulation contact. Percutaneous epicardial advancement of such a lead into the mid-myocardium of the LV may also be attractive, avoiding any contact with the systemic circulation while permitting subendocardial stimulation. Percutaneously placed epicardial leads with specially insulated electrodes permit myocardial capture while avoiding phrenic stimulation, in early animal tests (unpublished data).

Cardiac resynchronization therapy improves the quality and quantity of life in most recipients. Further advances in technology hold great promise for it broader applicability and greater effectiveness. While care must be taken to address the current limitations, the wireless LV endocardial system holds promise as an important innovation.

**Conflict of interest:** M.M.—none; P.A.F.—co-inventor of the intramyocardial electrode and insulated epicardial electrode.
References

-- Removal of a chronically implanted active-fixation coronary sinus pacing lead using the Cook Evolution® lead extraction sheath --

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In this case, a unipolar active-fixation coronary sinus lead (Star Fix®) had to be removed because of severe infection. For lead removal, a venous lead entry site approach with a transvenous mechanical dilator technique was used. However, the lead could not be extracted, as its polyurethane lobes, expanded in the lateral coronary vein, could not be relaxed. A 9F mechanical dilator sheath (Evolution®), was then advanced through the coronary sinus into the lateral coronary vein. It was possible to reach the tip of the StarFix® and to extract the entire lead. Immediately after the procedure, a discrete pericardial effusion was seen. This effusion disappeared without the need for pericardiocentesis within 3 days.

Extraction of chronically implanted active-fixation coronary sinus leads can be extremely challenging. Within the coronary sinus or coronary veins, mechanical dilator sheaths like the Evolution® should only be used by experienced operators because of potential risks for severe complications. Thus, active-fixation coronary sinus leads should only be implanted, if there are no other options.