Editorial

Leadless left ventricular endocardial pacing: a real alternative or a luxury for a few?

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The WiSE-CRT system and the SELECT-LV study

In the May 2017 issue of *JACC* Reddy *et al.* (1) reported the results of a prospective multicenter non-randomized study (SELECT-LV), assessing the safety and the performance of biventricular pacing obtained with a wireless, ultrasound (US) based, left ventricular (LV) endocardial system (WiSE-CRT; EBR system, Sunnyvale, California, USA).

The WiSE-CRT consists of a LV endocardial leadless pacemaker and two subcutaneous components (battery and transmitter) in conjunction with a co-implanted right ventricular (RV) pacing system. The implantation is a quite complex 2-step process and takes place over consecutive days: the first step is surgical subcutaneous implant of the pulse generator system (2 incisions required, 1 for the battery and 1 for the ultrasound transmitter); the second step is the catheter-based placement of a leadless endocardial LV electrode via femoral artery approach.

The battery pocket is created at the mid-axillary line, while the ultrasound transmitter pocket requires an acoustic parasternal window of at least 3 cm^2. This window is a lung- and bone-free acoustic line of sight from the pocket to the LV, usually located between the 4^{th} and 6^{th} intercostal spaces, lateral to the left parasternal border and is identified before the procedure using transthoracic echocardiography that represents a fundamental screening tool (5–10% of candidates are excluded for inadequate acoustic windows). Additionally, a subcutaneous channel is needed between the 2 pockets to pass a 30 cm cable connecting battery and transmitter.

The placement of the LV endocardial electrode is obtained through a 12-F steerable delivery system and a 8-F retractable delivery catheter pre-mounted with the receiver electrode and inserted in the femoral artery (to date, even if it's still considered off label, there are some experiences that demonstrated safety and efficacy with the transseptal approach). Under fluoroscopic guidance the electrode is advanced to the LV via a transaortic retrograde approach. The pacing site is chosen with a combination of echo evaluation (essentially for the acoustic window), electrical timing and pacing thresholds; location, angle and distance of the electrode are tracked in real time with the help of a dedicated transmitter's algorithm. The next generation of the transmitters will be probably thinner with an easier placement and a wider angle of US. The implanted LV endocardial electrode is an ultrasound receiver and energy converter.

The system requires co-implantation of a standard right-sided transvenous device to trigger biventricular pacing. RV pacing pulses are sensed by dedicated electrodes placed on the outside surface of the transmitter. Immediately after sensing, the WiSE-CRT triggers an US pulse that is received and transformed in electrical energy to pace LV endocardium, almost simultaneously to RV pace.

Following implantation aspirin and clopidogrel are

prescribed for 3–6 months, while anticoagulation is not mandatory, unless other indications exist. Actually, after 3–4 weeks there is a complete endothelization of the LV electrode, with a consequent reduction of stroke and infection risks, which could be close to zero.

The complexity and the risks of the procedure are not negligible. Which kind of patients can benefit?

LV endocardial pacing could be an option for all that patients that failed a "conventional" transvenous resynchronization or in which the target pacing site (evaluated before the implant and defined as the latest site of contraction) does not match with a coronary vein. These two groups of patients are not more than 15% of CRT candidates.

The SELECT-LV study enrolled 35 very challenging patients, for whom a "conventional" strategy to achieve resynchronization had previously failed. These patients were implanted in 6 USA and European "excellence" academic centers with a great expertise in interventional electrophysiology. The indications for WiSE-CRT were: (I) coronary sinus lead implantation failed due to anatomical constraints, high pacing threshold or phrenic capture (about 55% of cases); (II) coronary sinus lead implantation not advisable/feasible due to high infection risk or upper body vein obstruction (about 15%); (III) non-response to previously implanted "conventional" CRT device (worsening/unchanged symptoms and no positive remodeling after 6 months of resynchronization) (about 30%).

Of the 39 patients initially enrolled, 3 were excluded because of inadequate acoustic window and 1 retired before the planned intervention. The procedure was successful in 34/35 patients with documented biventricular stimulation on the ECG (97%); the only patient with failed attempt had serious ventricular arrhythmias during the implantation. After 6 months of follow-up 94% of patients continued to correctly receive biventricular pacing, 88% experienced and improvement in the clinical composite HF score, 66% demonstrated a positive echocardiographic remodeling (>5% absolute increase in LV ejection fraction). Serious adverse events occurred in 3 patients (8.6%) within 24 hours (ventricular fibrillation and prolonged cardiac arrest; electrode embolization to left tibial artery; femoral artery fistula) and in 8 patients (22.9%) in the first month (1 death after lead-induced VF; 1 stroke; 3 infections; 1 pocket hematoma; 2 femoral pseudoaneurysms).

The authors concluded that WiSE-CRT system implant was clinically feasible and provided a clinical benefit to a majority of very challenging patients with an otherwise failed "traditional" CRT approach. They also claimed that additional studies are needed to improve the technique and reduce complications, select the optimal LV pacing site and explore long-term outcome.

WiSE-CRT: is it worth?

There is no doubt that LV endocardial leadless pacing offers an alternative to "traditional" CRT achieved by implanting a transvenous lead in a venous branch of the coronary sinus. The WiSE-CRT system has several advantages: it makes possible to pace the LV from the endocardium (while in traditional CRT the epicardium is paced first), without phrenic nerve stimulation and with better pacing threshold compared to epicardial sites; it avoids the need for a transvenous lead; target pacing site will not depend on the coronary veins anatomy.

It has been demonstrated that endocardial pacing is better than epicardial pacing because it results in more physiological myocardial activation, improved hemodynamic function and narrower paced QRS complexes (2); moreover, endocardial pacing reduces the dispersion of ventricular repolarization proving to be less arrhythmogenic (3). It is not surprising, since in normal hearts ventricular depolarization starts from the endocardium of the basal portion of the interventricular septum, the epicardium being the last to be activated.

On the other side, the possibility to implant a wireless electrode in the LV endocardium makes the doctor free from the anatomical constraints of coronary sinus branches, and the patient free from acute and long term issues associated with a transvenous lead (failure, displacement, endocarditis).

However, this new CRT approach is so new and "young" and at the moment it has several limitations. First of all, the system requires at least a co-implanted transvenous RV pacing/defibrillation for initiating left work. Second, not all patients are suitable, since a pre-procedure screening is required to identify an adequate parasternal acoustic window to allow the transmitter to have a good sight of LV. In the SELECT-LV study about 10% of screened patients failed the test and were discarded. Third, the procedure is surgically quite complex: it requires two chest wall incisions and a retrograde femoral artery access; it is carried out over consecutive days, increasing patient's discomfort and risk of pocket infection and vascular complications. Fourth, for transmitter and battery placement a deep sedation is required (needing anesthesiologic assistance). So it seems "wise" to leave the work in the hands of highly experienced

operators in high volume centers, with expertise in leadless pacing. Last but not least, despite the overall safety profile in the SELECT-LV study, complication rates and type were not negligible. Acute and short term serious adverse effects were significant (8.6% and 22.9% respectively), including (among others): 1 death, 1 stroke, 1 electrode embolization to lower extremities, 2 pocket infections. The initial evaluation of WiSE-CRT in 2013 (4) was stopped for safety reasons: 18% of implanted patients developed pericardial tamponade after LV electrode delivery, which was fatal in 1 case. The delivery system used in the SELECT-LV study was improved by equipping the distal portion of the sheath with a balloon to facilitate less traumatic contact with LV endocardium; indeed, no pericardial effusion occurred thereafter, but it is reasonable to speculate that also operator experience played a role in reducing this serious complication.

Specific technological issues regarding US-based leadless LV pacing system remain to be addressed: (I) as outlined before, about 1 of 10 patients did not have and adequate acoustic window for the transmitter; (II) 3 of 35 patients (8.5%) experienced defective transmitter circuitry within the first months after implant; (III) US-mediated pacing is poorly efficient from an electrical point of view and could result in a short battery lifespan; (IV) it is not clear how exercise or pulmonary pathology can affect the electrode-transducer interaction; (V) an optimal LV site selection—in order to obtain the greatest benefit in term of resynchronization—is limited by the need of a correct alignment between the electrode and the transmitter within a narrow thoracic acoustic window; (VI) the risks and difficulties of retrieving a long-term implanted electrode in the LV endocardium remain largely unknown.

According to the authors, the population enrolled in the SELECT-LV study did gain a significant benefit from the implant of the WiSE-CRT system, considering that patients were very complex due to failed coronary sinus lead implantation or non-response to "traditional" CRT. The favorable outcomes included an improvement in HF clinical composite score at 6 months (85%) and a positive echocardiographic reverse remodeling at 6 months (52%). These outcomes are comparable with those observed in "conventional" CRT trials. Data are clear and encouraging, but some additional considerations should be made regarding non-response or failed CRT. Response to CRT is a complex issue and several clinical, functional and remodeling definitions have been proposed (5). With current technological advancements "conventional" CRT (achieved via coronary sinus lead implantation) has considerably improved over years. New tools and refined implanting and imaging techniques have been developed and studied; new generation quadripolar LV transvenous leads are now available. Several studies demonstrated the importance of preventing non-response to CRT in different moments: before implant (patient selection); during implant (targeting the latest activated LV sites); after implant (optimization of care, up-titration of drugs, correct device programming). "Historically" 30% to 40% of CRT patient are considered non-responders and an additional 8–10% of eligible patients fail to receive CRT due to anatomical constraints (6). A fundamental question arises: are these percentages obsolete? In our opinion the response is "*probably yes*, *they are!*". With current improvements in "conventional" CRT technology the rate of non-response or failed CRT is gradually declining and could be further reduced over time.

Medical and technological efforts to improve outcome of patients with heart failure must be encouraged. Going in this direction, the authors of the SELECT-LV study (and the manufacturers of the WiSE CRT system) have to be greatly congratulated for their huge work. However, at the moment, this approach to CRT should be considered a niche indication for highly selected patients in highly selected centers. …making it a luxury for a few.

Which other options do we have today? What does the future hold?

Other approaches for non-responders or failed CRT include surgical epicardial LV lead implant and transseptal endocardial LV lead placement.

Surgical technique is more invasive than percutaneous one, as it requires a minithoracotomy and can be challenging in patients with prior cardiac surgery with consequent pericardial adhesions. Moreover, the long term performance of surgically placed epicardial leads seems to be poorer and optimal LV pacing sites are limited to basal segments (7). Recently a new minimally invasive technique has been described using a video-assisted thoracoscopic approach (8), which appears promising with an excellent tolerability, a low surgical risk and a good pacing performance.

Another possible alternative is transseptal (interatrial or interventricular) implantation of a transvenous pacing lead in the LV endocardium. This technique allows for a more physiological pacing (like WiSE-CRT) and has proved to be

beneficial in a population of patients who had failed or were unsuitable for "conventional" CRT in the ALSYNC study and in a recent subanalysis (9,10), which demonstrated clinical and echocardiographic improvements similar to those observed in the SELECT-LV study. However, this latter approach is associated with a high thromboembolic risk requiring life-long oral anticoagulation and carries the risk of adverse effects of the mitral valve.

Available data indicate that LV endocardial pacing has several advantages over epicardial pacing, and it is reasonable to postulate that in the near future it could eventually become a first-line option in patients requiring CRT. However, currently, both LV endocardial approaches (WiSE-CRT system and transvenous/transseptal pacing lead implant) are limited by technical, technological and safety issues. The future of cardiac pacing is going in the direction of leadless technology, and it is foreseeable that other wireless pacing systems (Nanostim by St. Jude Medical and Micra by Medtronic) could be further developed to pace LV endocardium. The combination of a subcutaneous defibrillator with a completely leadless single-component pacing system, eliminating the need for a pocket and allowing anti bradycardia and antitachycardia pacing, is currently under investigation (11).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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