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ABSTRACT

Cardiac resynchronization therapy (CRT) improves mortality, morbidity and quality of life in selected heart failure patients with severe left ventricular ejection fraction impairment**.** However, between 20% and 40% of device recipients do not benefit clinically from CRT. Indeed, some anatomical and technical difficulties are related to the coronary venous implantation site via the coronary sinus (CS). Additionally, electrical constraints have been described and CS does not always correspond to the optimal LV lead position. In the last decade, engineers and physicians work together to overcome the challenging LV lead implantation and various bi-ventricular pacing alternatives have been developed to improve CRT response. In this review, we discuss the evolution from the CS pacing to wireless LV stimulation and His bundle pacing.

KEW WORDS: Cardiac resynchronization therapy, non-responder, optimal left ventricular lead location, endocardial stimulation, leadless stimulation

INTRODUCTION

Cardiac resynchronization therapy (CRT) improves mortality, morbidity and quality of life in selected heart failure (HF) patients with severe left ventricular ejection fraction (LVEF) impairment (1-7). Left ventricular (LV) pacing is conventionally achieved with an epicardial LV lead, placed into one of the branches of the CS, mainly lateral or postero-lateral in location. However, between 20% and 40% of device recipients do not benefit clinically from CRT (7). In addition, some patients eligible do not receive CRT due to anatomical and technical difficulties, such as an unsuitable CS anatomy, chronic occlusion of venous access, phrenic nerve stimulation or high pacing threshold in areas of extensive myocardial scar (8-9).

To overcome these challenges, bi-ventricular pacing alternatives have been described, such as surgical epicardial leads or transeptal LV endocardial leads (10-12). However, these strategies expose the patient to high surgical risks for the epicardial approach or ischemic stroke for endocardial approach (13). Furthermore, the lead remains the Achilles heel of these strategies. Nevertheless, LV endocardial (LVendo) pacing has shown promising results and may allow a higher number of site implantation locations compared to conventional CRT. These encouraging effects are counterbalanced by the relative complexity of the lead implantation and the risk of stroke. Currently, LVendo leadless stimulation has been developed and demonstrated clinical feasibility and benefits in patients with failed CRT implantation or non-response to conventional CRT (14-15).

In current practice, placing the LV lead via the CS is the dominant strategy with sometimes anatomical limitations and thus conventional approach may not be sufficient. From the CS epicardial stimulation to the leadless endocardial pacing, engineers and physicians have been developing alternative LV pacing approaches to improve CRT. This review aims to describe these different approaches and the evolution that has been taking place from LV epicardial to LVendo techniques.

THE BENEFIT AND LIMITS OF CARDIAC RESYNCHRONIZATION THERAPY IN PATIENTS WITH HEART FAILURE

There are now numerous landmark trials establishing the efficacy of CRT therapy in patients with HF. MUSTIC (Multisite Stimulation in Cardiomyopathies) trial was the first to evaluate the benefit of CRT in severe HF patient (NYHA III). Biventricular pacing significantly improved patients' exercise tolerance, quality of life and risk of hospitalization (decreased by 2/3) (1). Similarly, MIRACLE (Multicenter Insync Randomized Clinical Evaluation) trial assessed the benefit of CRT in 453 patients with advanced HF (NYHA III/IV) (2). Indeed, CRT was associated with LV chronic reverse remodeling, improvement of the quality of life and a 40% decrease of death or HF hospitalization. Similar results were reported in the CARE-HF (Cardiac Resynchronization on Morbidity and Mortality in Heart Failure) trial among patients with NYHA III/IV status (3). The benefit of CRT in patients with mildly symptomatic HF was assessed in the REVERSE-HF, MADIT-CRT and RAFT trials, including mostly patients with NYHA I/II. In this population, CRT was associated with LV reverse remodeling and a reduction in HF hospitalizations of between 25% and 50% (4-6). Among these studies of mild-HF CRT recipients, the RAFT trial was the only one to show a positive impact on mortality with a 25% risk reduction (6). Currently, CRT is highly recommended for symptomatic HF patients in sinus rhythm with severe LVEF (<35%) and large left bundle branch block (>150ms) (7) but also at a lower level in patients with LBBB and QRS duration between 120 to 150 ms. For patients without LBBB the class of recommendation is lower. Unfortunately, not all patients respond favorably to CRT with a non-responders rate between 20% and 40% (8-10). Therefore, research related to the mechanism underlying response (and failure to respond) has been performed and some factors specific to each patient have been associated with a lower response rate to this therapy (e.g. narrower QRS, QRS morphology, underlying cardiomyopathy).

CORONARY SINUS VEIN: A CONVENTIONAL APPROACH WITH HIGH BENEFIT BUT ALSO WITH LIMITS

Coronary sinus vein provides an optimal lead location in a majority of CRT patients

Early CRT Systems took advantage of the CS anatomy to place the LV lead due to the straightforward accessibility from the venous side and reasonable ability to establish and maintain capture in this location. In time, this has been improved upon but remains the first line approach. A crucial determinant of successful CRT is the position of the LV pacing lead. Initial hemodynamic studies have recommended that targeting the lateral or posterolateral wall by way of an appropriate CS branch can improve clinical outcomes after CRT. Indeed, CRT with lateral free wall stimulation produced improvements in LV systolic performance with a significant increase of LV+dP/dt (max) (16). Similarly, the influence of the LV lead position was assessed among 346 patients of the REVERSE cohort, revealing that the lateral position was associated with a significantly lower risk of HF hospitalization or death from any cause compared to the non-lateral placement (17). In addition, LV apical pacing has been associated with poor outcomes for CRT and this placement should be avoided. Indeed, a sub analysis of the MADIT-CRT trial showed that, compared to mid-ventricular or basal pacing, LV apical pacing was associated with worse clinical outcomes (18). Consequently, based on the hypothesis that lateral or posterolateral sites have the latest activation in a majority of patients, these implant sites are commonly preferred in patients eligible for CRT (19).

Through the CS vein, CRT with LV-only pacing has also been described (20). Indeed, Medtronic's *AdaptiveCRT* algorithm has been developed and used the patient's intrinsic conduction by pre-pacing the LV to synchronize with intrinsic right ventricular (RV) activation and establish fusion. Of note, when the patient's heart rate increases > 100 bpm or atrio-ventricular conduction is prolonged, the pacing mode switches automatically to bi-ventricular pacing. This interesting approach aims to avoid unnecessary RV pacing and has been associated with reduction in death, AF and HF hospitalization (20).

However several reports describe a considerable variability in the LV activation pattern and distribution of mechanical dyssynchrony in case of typical LBBB. Consequently, there is inter-individual inconsistency regarding the most optimal pacing site (21). Furthermore, some CRT candidates do not have a typical LBBB morphology or present ischemic cardiomyopathy, and thus likely have variable and heterogeneous LV activation sequences (22). As a result, the optimal LV pacing site to restore LV synchrony does not always correspond to the lateral or posterolateral branch of the CS vein and conventional approach sometimes fails to improve HF patients. In addition, electrical constraints, such as phrenic nerve stimulation, and occluded CS anatomy or other anatomical constraints can limit procedure success.

Coronary sinus: electrical and/or mechanical constraints

Discordance between the CS and the optimal position for LV stimulation has been described by Derval *et al.* (23). In this study, a cohort of 35 non-ischemic patients who received CRT, LV hemodynamic (dP/dTmax) response was optimized by pacing 11 LV sites. None of these positions were consistently associated with the best hemodynamic improvement and the distribution of the best pacing site for each individual patient was uniformly spread among the tested sites. Furthermore, CS pacing was the best pacing site in only 3 patients (9%) and had no or detrimental effect in 8 patients (23%). These results are consistent with results previously described by Dekker *et al.* who found that the hemodynamic response to biventricular pacing varied widely based on LV site (24). According to these results, the best site is not a predetermined area of the LV but rather specific to each patient.

Whether there is any benefit in targeting the area of maximal mechanical delay was studied in the prospective TARGET (Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy) study (25). In a cohort of 220 patients, the impact of targeting the LV lead at the most delayed viable segment defined by speckle-tracking echocardiography was compared the standard clinical practice. After 6 months of CRT, there was a significantly higher rate of responders in the TARGET group compared to the control group (70% vs. 55% respectively) and a lower rate of death and HF hospitalization. Although imaging technique improves CRT response and avoids the LV lead placement in scar areas, it is time-consuming, suffers from reproducibility and may be hard to correlate with fluoroscopic imaging at the time of device implantation.

A more practical intra-operative measurement is the delay between QRS onset on the surface ECG and the LV electrograms (i.e. so called “Q-LV” interval). As previously described, pacing at the longest delay site was strongly associated with LV reverse remodeling and the alleviation of symptoms. In addition, multivariable analysis shows that longer Q-LV interval of ≥95ms predicts better CRT response (26). However, the anatomy of the CS vein limits the number of Q-LV measurement sites and can contribute to suboptimal LV lead location.

Coronary sinus related anatomical constraints

Several lead-related issues complicate conventional CRT, such as the absence of appropriate CS vein, a challenging CS venous anatomy, lead displacement and high pacing threshold in an area of scar (27). Due to these difficulties, up to 30% of transvenous LV lead placements fail or result in limited or no clinical response, a challenge which may be overcome with the development of new technology (28). Indeed, new quadripolar LV leads, which enable a greater number of pacing configurations, have recently been introduced and were associated with a very low rate of phrenic nerve stimulation and an overall improvement in therapeutic performance (29). Recently, multipoint pacing (MPP) has been developed using a unique quadripolar LV lead and a dedicated algorithm enabling two LV stimulations from two separate dipoles located in the same CS branch (**Figure 1, Panel A**). In early testing, MPP led to more homogeneous electromechanical activation and had significantly better acute hemodynamic response (AHR), functional improvement and reverse remodeling than was achieved through conventional biventricular pacing (30). Currently, the MORE-CRT MPP (MOre REsponse on Cardiac Resynchronization Therapy With MultiPoint Pacing) trial is evaluating the impact of MPP in the treatment of non-responder patients to standard CRT <NCT02006069>.

Multisite pacing has also been proposed as another LV stimulation configuration (**Figure 1, Panel B**). Indeed, this stimulation scheme uses two leads implanted in two separate CS tributaries aiming to obtain a more rapid and homogeneous LV activation pattern. The approach has been evaluated in a randomized study and appears to be feasible (31) but is associated with a high rate of adverse events and to this point has not shown significant long-term clinical benefits (32).

ALTERNATIVE LEAD PLACEMENT FOR LEFT VENTRICULAR STIMULATION IN CASE OF FAILED CORONARY SINUS APPROACH

Despite the development of multipolar LV electrodes and multipoint pacing, clinical non response due to suboptimal lead positioning remains a critically relevant problem. Additionally, unsuitable CS vein anatomy leads to failed procedures, causing physicians have to propose alternative solutions. Surgical LV epicardial lead, LVendo lead placement or more recently His bundle pacing (HBP) have been described as options to overcome the challenging CS approach.

Surgical left ventricular epicardial stimulation

Epicardial LV lead placement through a small lateral thoracotomy or using thoracoscopic techniques has been evaluated to overcome these obstacles and has been shown to be feasible (11) (**Figure 1, Panel C**). Furthermore, surgical epicardial LV lead placement can provide the flexibility for lead placement at a position anticipated to have maximal dyssynchrony. However, such an approach is appropriate only if a cardiac surgical service is available in the implanting center. Additionally, previous study showed that epicardial LV lead placement did not result in significant improvement of LVEF or cardiac perfusion (33). Lastly, access to the basal posterolateral aspect of the LV with a surgical lead can be relatively difficult and may not always be achieved in clinical practice (34). Currently, epicardial LV lead indication is mainly limited to re-implantation after device infection or for children with congenital heart disease who need to be permanently paced (35).

Endocardial left ventricular stimulation

In some cases of unsuccessful transvenous implantation or non-response to CRT, operators have developed an alternative technique and implanted the LV lead in the LV endocardium through a transseptal atrial or ventricular approach (12) (**Figure 1, Panel D**). The placement of a transseptal LVendo lead was first described in 1998 and has undergone multiple modifications with a superior, inferior, or mixed approach (14). Though this technique is familiar to electrophysiologists, atrial transseptal puncture performed through a superior venous access (subclavian/axillary vein) remains challenging and peri-procedure transoesophageal echocardiography is often necessary to guide operators. Currently, atrial septum is punctured with a needle and ventricular septum puncture is performed using radiofrequency energy (12; 36). Then a balloon/dilatator may be used to dilate the orifice. A wire is placed in the left cavity (atria or ventricular), serving as a guide for the introduction of the stimulation lead through a deflectable sheath. Although complex, the reported procedural success rates are high. The ALSYNC (ALternate Site Cardiac ResYNChronization) study reported an atrial transseptal success rate of 89.4% among the 138 patients treated (37). The steps of the atrial transseptal approach are illustrated in the **Figure 2**. In addition, Gamble *et al* described a successful ventricular transseptal approach performed in all the 20 patients recruited with mean time from venous access to passage of the sheath into the LV of 25 minutes (12).

Despite more complex implant procedure, LVendo pacing may bring several advantages compared to the CS approach: 1) operators theoretically have access to all regions of the LV, 2) potentially faster LV depolarization resulting from faster impulse propagation in the endocardial ventricular layers than the epicardial ones, 3) more physiologic LV stimulation, preserving the transmural activation and repolarization sequence, and 4) elimination of phrenic nerve stimulation as a concern (14;15). Indeed, Derval *et al.* tested endocardial and epicardial pacing at the exact same location in human subjects and showed that LVendo pacing provided a significant benefit in diastolic, but not systolic function (22). In addition, the study showed that the best sites were frequently accessible only via the endocardial approach. LVendo pacing has also been evaluated in ischemic cardiomyopathy with poor response to conventional CRT (38). In this study, 8 patients underwent cardiac magnetic resonance mapping which was compared to extensive invasive electroanatomic mapping to target optimal LVendo pacing sites and avoid the scar areas. A total of 135 epicardial and endocardial sites were evaluated during this study. LVendo pacing showed superior AHR as well as shorter stimulation-QRS duration and paced QRS compared to CS pacing. Of note, in 6 of 8 patients, there was no correlation between the optimal LVendo site and the site of latest electrical activation on electroanatomic mapping due to slow conduction areas inside islands of scar.

Concretely, the efficacy of LVendo lead has been evaluated in the ALSYNC study that enrolled a population who had previously failed to conventional CRT implantation or classified as non-responder to CRT (37). The study showed that 55% and 59% of patients had a reduction in LV end-systolic volume of at least 15%, and achieved an improvement by ≥1 NYHA class, respectively. Of note, 33% of the patients showed 'super-response' at 6 months. Recently, a meta-analysis estimated the clinical response rate as 82% using this approach (39).

Despite these advantages, there are some drawbacks of this strategy. The main and most serious concern is the risk of thrombo-embolic events that requires long-term anticoagulation. In the ALYNSC study, 6-month after implantation, 17.8% patients had at least one endocardial LV lead-related complication, with an incidence of thrombo-embolic and transient ischemic attack events at 2.6 and 7.4 per 100 patient-years; respectively (37). Similar results were found in a meta-analysis with an incidence of stroke and transient ischemic attack of 2.5 and 2.6 events per 100 patient-years (39). In addition, this procedure necessitates a transseptal puncture to reach the LV, which holds inherent risks.

In the light of these results and associated complications, endocardial pacing shows promise with a more physiological LV stimulation compare to CS pacing. However, the endocardial lead remains a critical shortcoming of this approach, given the associated risk of stroke, the need for long-term of vitamin K antagonist therapy and drug monitoring. In addition, atrial or ventricular transseptal approaches add difficulty to the CRT implantation procedure (12).

Resynchronization using His bundle pacing

Permanent HBP has recently emerged as a more physiological form of ventricular pacing and viable alternative to CRT. Indeed, previous study demonstrated that His resynchronization is achieved by recruiting LV conduction fibers (40). Briefly, the dedicated *SelectSecure* HB pacing lead (Medtronic Inc, Minneapolis, MN) is delivered through a fixed curve sheath or a deflectable sheath. During procedure, HB electrograms are carefully mapped and paced with the dedicated lead until pacing recruited the diseased bundle and narrowed the QRS duration by at least 20%. The lead is then screwed into position by means of 4–5 clockwise rotations. Of note, the HB is surrounded by fibrous tissue and the average capture thresholds tend to be higher than routine RV pacing but capture thresholds above 2.5V/1ms would must make the operator consider re-implantation lead (41).

Feasibility and safety of HBP CRT eligible patients have been demonstrated among 106 CRT candidates or patients with failed conventional approach. In this cohort, HBP was successful in 90% and both groups experienced significant QRS duration narrowing (from 157±33ms to 117±18ms). Additionally, HBP patients exhibited clinical and echocardiographic improvement during follow-up but with 7% of loss of bundle branch recruitment (42). Similarly, hemodynamic performance and electrical activation mapping have been compared using HBP and conventional biventricular pacing (43). Authors demonstrated that acute hemodynamic response was higher when delivered using HBP than bi-ventricular pacing. Furthermore, activation map obtained during HBP showed resolution of the LBBB and provided more homogeneous LV resynchronization than bi-ventricular pacing. Lastly, current study highlighted the promising results of CRT using HBP in patients with right BBB and reduced LVEF (44). Currently, the HIS-SYNC (His Bundle Pacing versus Coronary Sinus Pacing for Cardiac Synchronization Therapy) trial is comparing HBP to bi-ventricular pacing and should provide important information regarding the impact of resynchronization using HBP <NCT02700425>.

In the light of these data, HBP seems hopeful for CRT and when compared to LVendo lead, this techniques avoids the thrombo-embolic and transseptal puncture risks. However, the biggest limitation of permanent HBP is the inability to map the HB and perform implantation of the lead at the HB in 10% of cases. Additionally, the need for higher pacing output might result in shorter battery longevity of devices. Lastly, endocardial lead remains the Achilles heel of HBP.

LEADLESS LEFT VENTRICULAR PACING: THE NEXT ADVANCE FOR PATIENTS WITH A FAILED CORONARY SINUS APPROACH?

Evidence of left ventricular leadless pacing benefit

Despite significant advances, transvenous leads have remained the greatest weakness of pacing devices. In an attempt to address these lead-related acute and chronic complications, leadless cardiac pacing has been developed. The last technological prowess is probably the development of CRT using a leadless endocardial LV electrode (**Figure1, Panel E**) (WiSE-CRT, EBR Systems, Sunnyvale, California). Recently, a case of an entirely leadless CRT was published, providing a tantalizing view of the potential future of CRT (45) (**Figure 1, Panel F**).

Briefly, the WiSE-CRT system provides wireless pacing by transmitting acoustic energy from a pulse generator transmitter, implanted subcutaneously above an intercostal space, to a receiver electrode implanted in the LV wall, which converts the acoustic energy to electrical pacing energy. The WiSE-CRT System is co-implanted with any pacemaker, ICD, or CRT device, which provides RV pacing. Biventricular pacing is achieved by sensing the RV pacing signal of the co-implant device, and using it as a trigger for LV stimulation. Implanting the WiSE-CRT System typically requires a 2-step process. First, the pulse generator system is surgically implanted in one of the left subcutaneous intercostal spaces (4^{th} to 6^{th}) adjacent to the parasternal border. Second, the wireless electrode is implanted in the LV wall with anchor barbs via a transaortic retrograde or transseptal approach. In addition to the leadless pacing advantages, LV electrode could offer the opportunity for congenital heart disease and a uni-ventricular heart to receive minimally invasive non thoracotomy pacing systems.

The feasibility and safety of the WiSE system was evaluated in the WiSE-CRT (Wireless Stimulation Endocardially for CRT) study (46). Seventeen patients were enrolled and at 6-month follow-up, all the implanted patients (n=13) were alive, though 7 serious adverse events occurred in 6 patients (35%). The system performance was also assessed with biventricular pacing recorded in 92% of the patients at 6 months. In addition, two-thirds of the patients had at least one functional class change and a significant 6-point increase in LVEF. However, because of a very high incidence of pericardial tamponade (18%), the study was stopped after 17 patients. A new generation device was developed with the addition of a balloon to facilitate atraumatic engagement with the LV endocardium. Recently, the SELECT-LV study evaluated the performance of the new version of the wireless electrode (47). A total of 39 patients were enrolled and 35 underwent the procedure, which was successful in 34 patients. Of note no pericardial effusions occurred. At 6-month follow-up, bi-ventricular pacing was achieved in 93.9% of patients and 84.8% had improvement in the clinical composite score. During follow-up, one pocket hematoma and two confirmed subcutaneous device-related infections occurred and device extraction was performed in one patient. Future planned enhancements, such as a smaller pulse generator and different delivery catheter designs are in development, which may reduce the risk of complications. Currently, the SOLVE-CRT (Stimulation Of the Left Ventricular Endocardium for Cardiac Resynchronization Therapy in Non-Responders and Previously Untreatable Patients) study was recently launched to evaluate the safety and efficacy in a cohort of 350 patients and will probably provide stronger benefit information < NCT02922036>.

How to achieve the optimal LV electrode placement site

The optimal LVendo pacing location exhibits marked variability in ischemic and non-ischemic cardiomyopathy and physicians may use a combination of either preprocedural or periprocedural imaging and/or electrophysiology mapping criteria to identify the best pacing sites. Recently, a multicenter study hypothesized that guided the placement of the wireless pacing electrode would achieve greater improvements in CRT response (48). Different strategies were used: 1) echocardiography to identify the latest mechanical activated LV segment, 2) cardiac magnetic resonance determined the latest activation area and scar, 3) electro-anatomical mapping to identify areas with late electrical activation and low voltages or 4) electrical latency parameters (i.e. Q-LV duration and Q-LV/QRS ratio) (49). In the 4th approach, Q-LV interval <100ms were excluded and the viability was assessed by excluding any sites with a pacing capture threshold >2V. During each procedure, AHR was measured to assess the immediate response to LVendo pacing. The target site identified with pre-procedural imaging was reached in 92% of patients and a strong linear relationship between AHR and both Q-LV and Q-LV/QRS ratio was observed, especially in the case where the Q-LV/QRS ratio was >0.5 at the pacing site. This suggests that patients will be more prone to a reverse remodeling if a site with a LV/QRS ratio of >0.5 is selected. Results showed that guidance for the optimal site selection of a wireless LV electrode improves chronic reverse remodeling at a rate of 71% and thus may increase the rate of responders to CRT. **Figure 3** synthesizes the main strategies used to guide LVendo lead implantation and proposes concrete clinical application.

*Limits of the wireless left ventricular electrod*e

There are several potential limitations to the wireless LV electrode approach. First, for optimal LVendo pacing, the transmitter must target the electrode to efficiently focus acoustic energy. A severe angulation or a large distance (>10cm) between the transmitter and electrode reduces the system efficiency. To address this, the location, distance, and angle of the electrode are tracked in real time during implantation by the transmitter's tracking algorithm. Moreover, the system requires an acoustic window in order to transmit ultra-sound effectively. Second, in case of large dilated cardiomyopathy, it may be difficult to reach some areas of left lateral free wall, since the current delivery sheath has one unique curve, which could limit implantation in the basal area. Lastly, similarly to LVendo lead complication, thromboembolic events could occur in patients implanted with a WiSE electrode.

Future direction

Recently, two novel resynchronization techniques seem promising: HBP and LV wireless electrode. However, trans-venous lead implantation are still required for both techniques (HB stimulation for the first one and RV pacing detection for the second one). The future of the CRT might be written in the combination of these two systems and the development of leadless HBP leading to an entirely leadless resynchronization using a mono-electrode.

CONCLUSION

Several methods have been proposed to improve CRT and decrease unsuccessful procedures, each with advantages and disadvantages (**Figure 4**). While current alternatives to optimize LV stimulation using surgical epicardial leads or LV endocardial leads have shown promise, none have proved to be ideal. Recently, HBP has demonstrated interesting results and represents promising alternative to conventional bi-ventricular pacing. Lastly, leadless endocardial strategy provides an individualized optimized LV lead location coupled with more physiological endocardial activation. Future clinical use and randomized clinical trials will help us to evaluate the safety and efficacy of this invasive technique and clarify the place of LV leadless stimulation in our current clinical practice.

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FIGURE TITLES AND LEGENDS

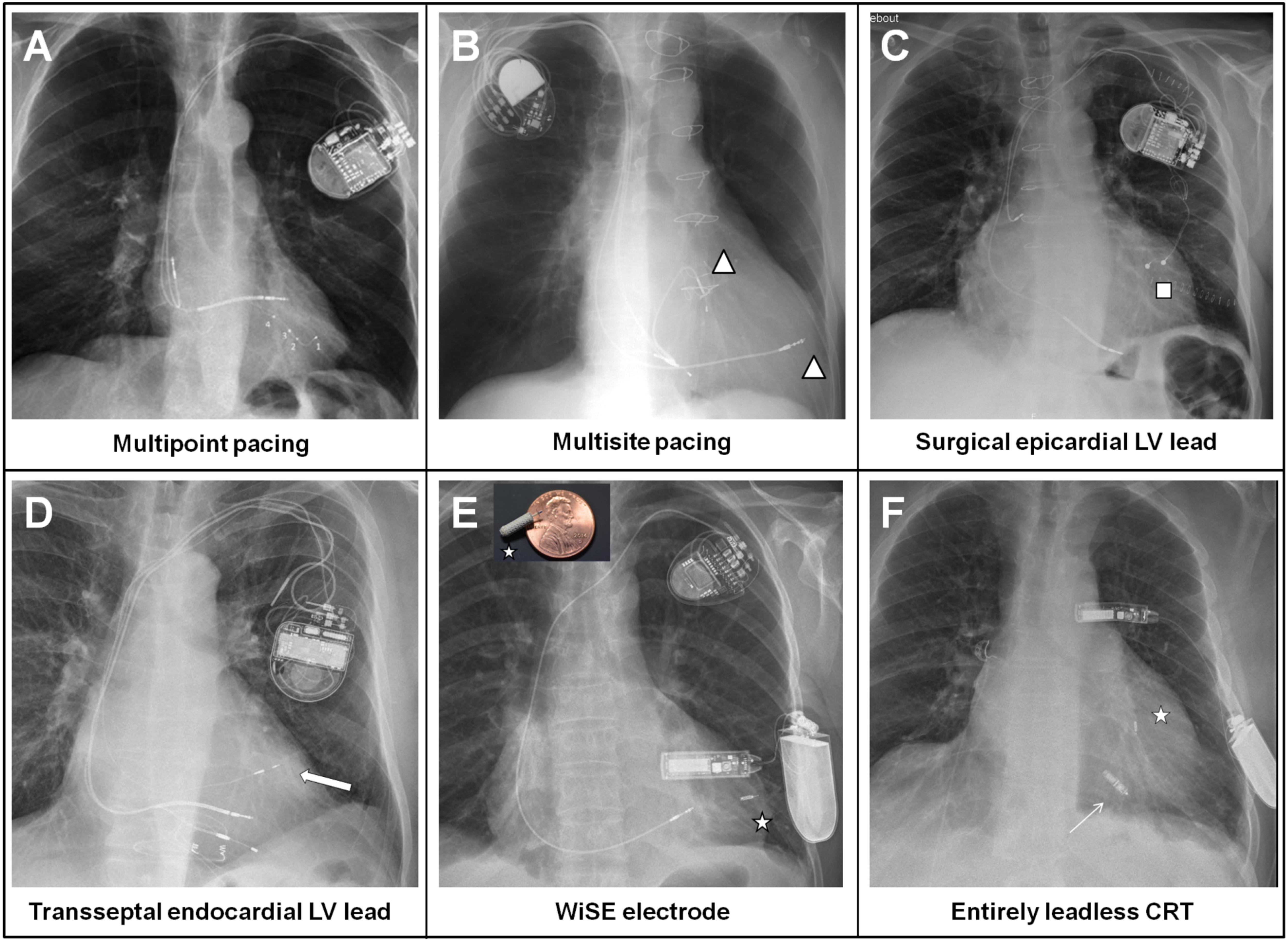
FIGURE 1:Evolution of the LV pacing sites. Panel A=Multipoint pacing, Panel B=Multisite pacing with two LV lead in the CS (triangles), Panel C=Surgical epicardial lead (square), Panel D=LV endocardial lead using an atrial transseptal approach (arrow), Panel E=LV endocardial leadless with the WiSE electrode (star), Panel F=Entirely leadless CRT with a Micra pacemaker (arrow) and WiSE electrode (star).

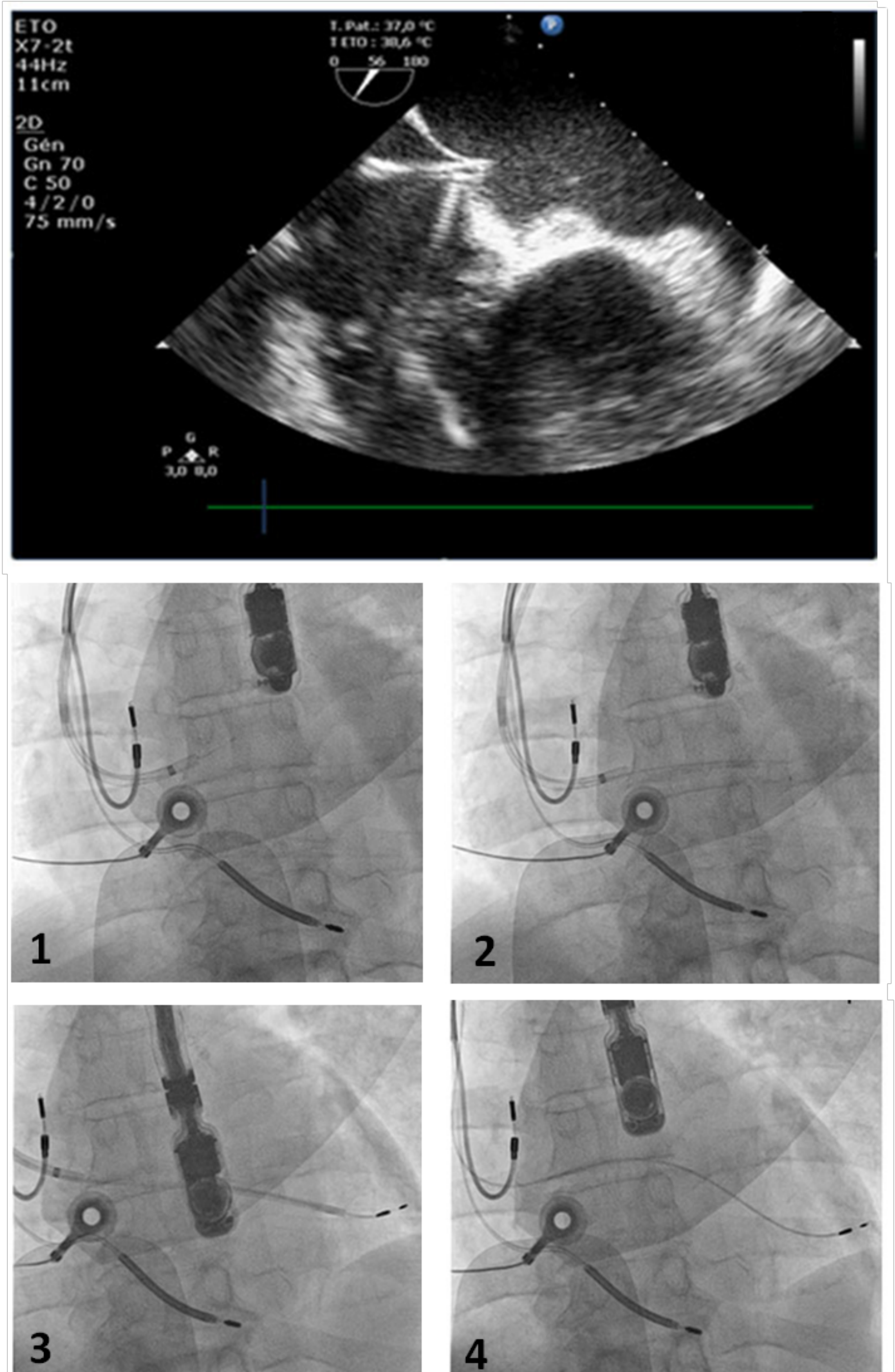
CRT=Cardiac resynchronization therapy; LV=Left ventricular

FIGURE 2:Illustration of atrial transseptal approach. Panels 1 to 4 represent the different steps from transseptal puncture to LV lead placement. Adapted from Morgan *et al* (38). Reproduced with permission from the European Heart Journal.

FIGURE 3:Main strategies described to guide LV electrode implantation and suggested clinical practice application. CMR=Cardiac magnetic resonance; LV=Left ventricular.

FIGURE 4:Advantages/disadvantages of current approaches, alternative and future directions for LV pacing. LV=Left ventricular.


A
Multipoint pacing
B
Multisite pacing
C
Surgical epicardial LV lead
D
Transseptal endocardial LV lead
E
WiSE electrode
F
Entirely leadless CRT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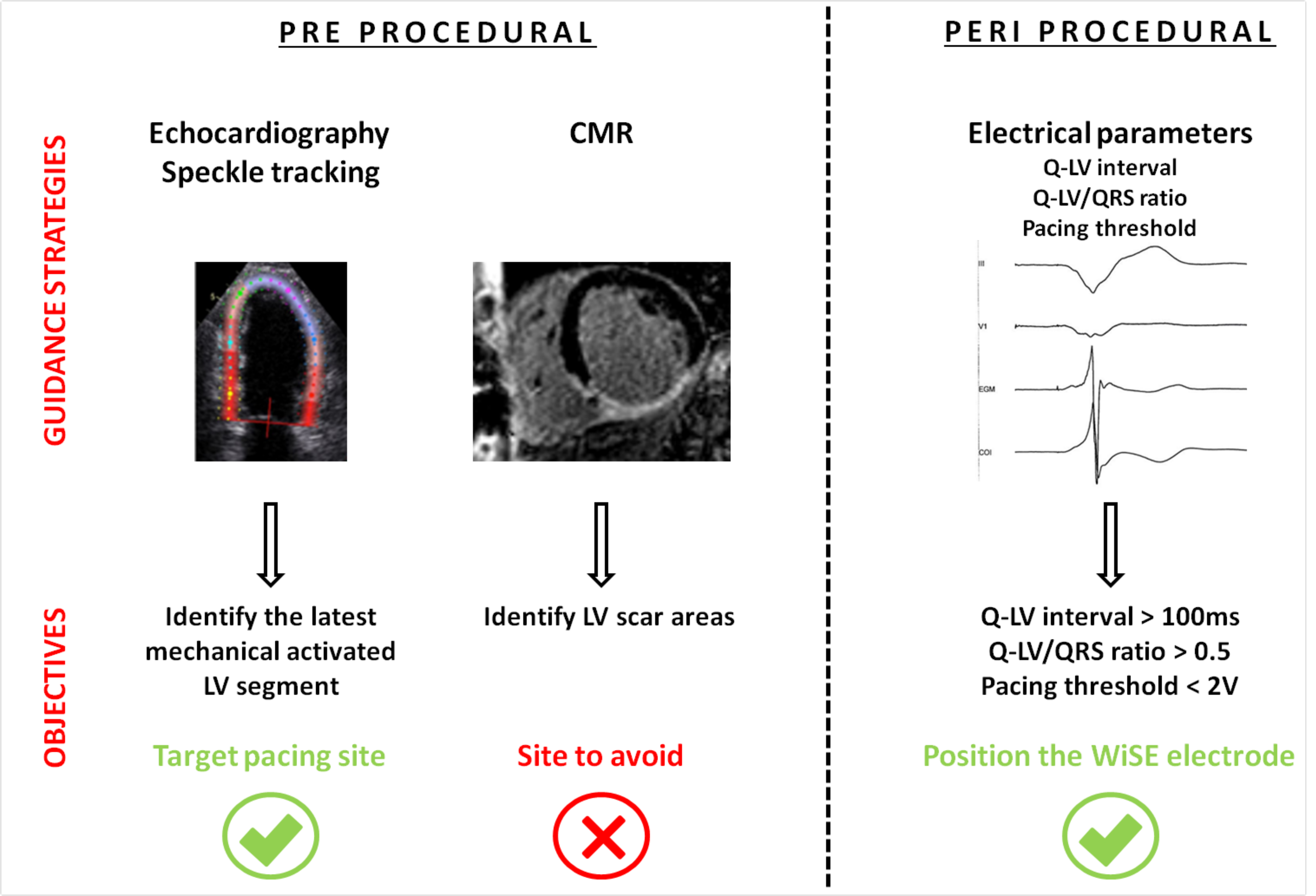
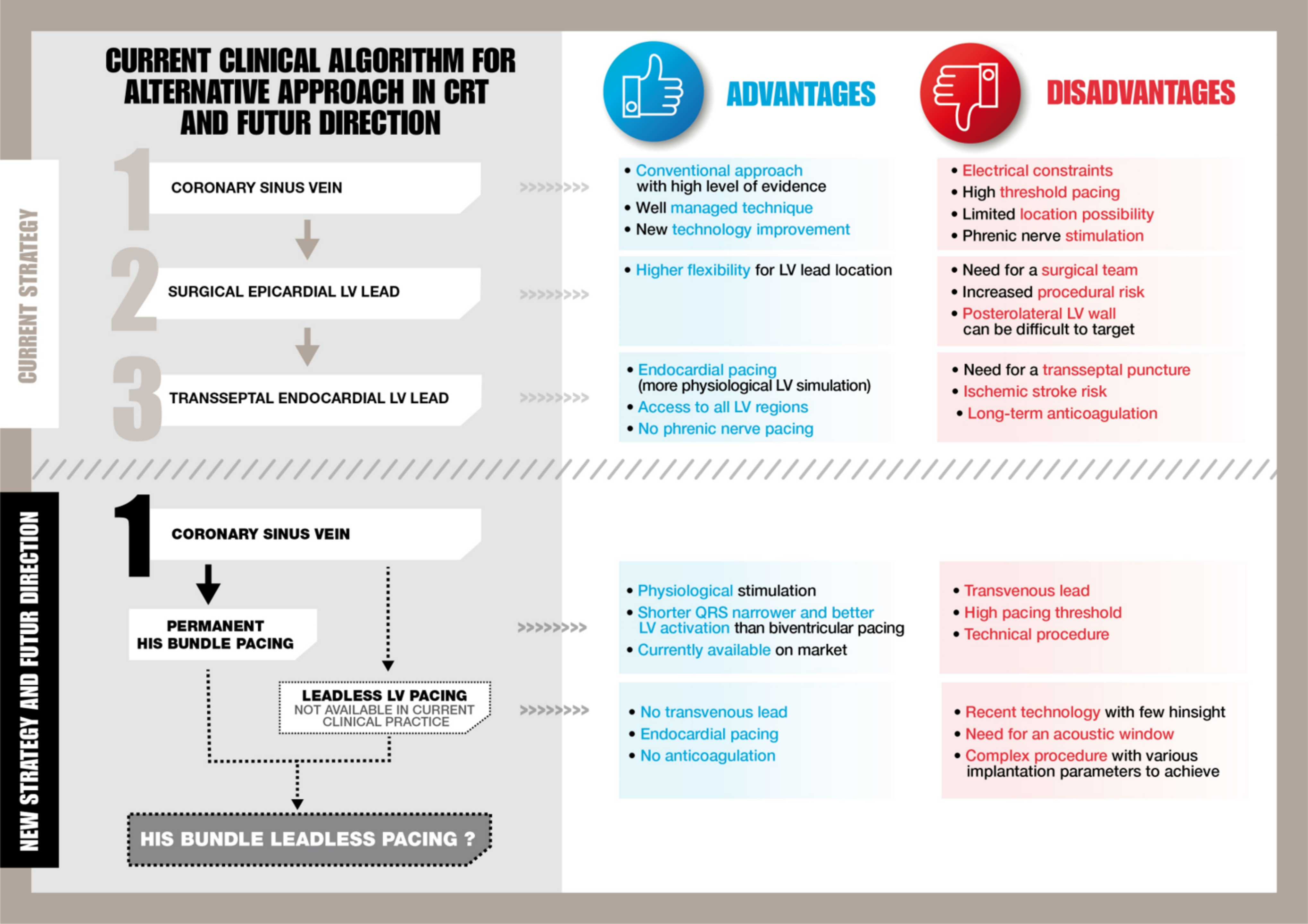


PRE PROCEDURAL
PERI PROCEDURAL
GUIDANCE STRATEGIES
OBJECTIVES
Echocardiography
Speckle tracking
CMR
Electrical parameters
Q-LV interval
Q-LV/QRS ratio
Pacing threshold
III
V1
EGM
Identify the latest
mechanical activated
LV segment
Identify LV scar areas
Q-LV interval > 100ms
Q-LV/QRS ratio > 0.5
Pacing threshold < 2V
Target pacing site
Site to avoid
Position the WiSE electrode


CURRENT CLINICAL ALGORITHM FOR ALTERNATIVE APPROACH IN CRT AND FUTUR DIRECTION
ADVANTAGES
DISADVANTAGES
CURRENT STRATEGY
1
CORONARY SINUS VEIN
• Conventional approach with high level of evidence
• Well managed technique
• New technology improvement
• Electrical constraints
• High threshold pacing
• Limited location possibility
• Phrenic nerve stimulation
2
SURGICAL EPICARDIAL LV LEAD
• Higher flexibility for LV lead location
• Need for a surgical team
• Increased procedural risk
• Posterolateral LV wall can be difficult to target
3
TRANSSEPTAL ENDOCARDIAL LV LEAD
• Endocardial pacing (more physiological LV simulation)
• Access to all LV regions
• No phrenic nerve pacing
• Need for a transseptal puncture
• Ischemic stroke risk
• Long-term anticoagulation
NEW STRATEGY AND FUTUR DIRECTION
1
CORONARY SINUS VEIN
PERMANENT HIS BUNDLE PACING
• Physiological stimulation
• Shorter QRS narrower and better LV activation than biventricular pacing
• Currently available on market
• Transvenous lead
• High pacing threshold
• Technical procedure
LEADLESS LV PACING
NOT AVAILABLE IN CURRENT CLINICAL PRACTICE
• No transvenous lead
• Endocardial pacing
• No anticoagulation
• Recent technology with few hinsight
• Need for an acoustic window
• Complex procedure with various implantation parameters to achieve
HIS BUNDLE LEADLESS PACING ?