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Review

Alternative Pathways of Delivering Cardiac Resynchronization Therapy: A Single Center 10 Year Experience on 400 Consecutive Patients

D.A. Radu*, R.G. Vătășescu*, C. Iorgulescu, Ș. Bogdan, E. Ene, A. Năstasă, M. Dorobanțu

Department of Cardiology, Clinical Emergency Hospital, Bucharest

REZUMAT

Introducere: Terapia de resincronizare cardiacă (TRC) este o terapie statuată, bazată pe implantarea unui stimulator cardiac tricameral, rezervată anumitor pacienți cu insuficiență cardiacă (IC). Livrarea clasică a sondei de ventricul stâng (VS) nu este mereu posibilă.
Obiective: Evaluarea numărului de cazuri în care livrarea clasică nu a fost posibilă într-un lot de 400 de pacienți consecutive implantați și definirea abordărilor "alternative".
Metode: Pacienții cu TRC au fost extrași dintr-o bază de date dedicată împreună cu mediile anumitor parametrii demografici, clinici și paraclinici. Au fost examinate imagini flurosocopice stocate ale TRC-urilor implantate între 10.2005 și 06.2014. Am definit abordarea "alternativă" ca fiind o variație de la tehnica standard de implant.
Rezultate: Am identificat un total de 61/400 pacienți (15.25%) care au necesitat TRC "alternativă". Aceștia au fost împărțiți în: abord prin colaterale ± venoplastie (12 cazuri), amplasare endocardică a sondei de VS (4 cazuri), TRC epicardic (2 cazuri), stimulare bifocal de VD (3 cazuri), configurații multi-site (4 cazuri) și sonde VS tetrapolare ± stimulare multi-point (36 cazuri) și le-am discutat utilitatea.
Concluzie: O proporție semnificativă din pacienții referiți spre TRC necesită amplasare alternativă, intervențională sau chirurgicală a sondei de VS.

Cuvinte cheie: TRC, trans-septal, multi-site, quadripolar, multi-point

ABSTRACT
Introduction: Cardiac resynchronization therapy (CRT) is a well-established device-based therapy for specific heart failure (HF) patients. Classical delivery of the left-ventricular (LV) lead is not always feasible.
Objective: To evaluate how often classical LV-lead delivery was not possible during 400 consecutive implants and define "alternative" approaches.
Methods: CRT patients were retrieved from a dedicated database along with averaged demographics, clinical and para-clinical data. Stored fluoroscopies of CRTs implanted between 10.2005 and 06.2014 were examined. We defined the "alternative" approach as a deviation from the straightforward technique.
Results: We identified a total of 61/400 patients (15.25%) that required "alternative" CRT. These were divided into: collateral approach ± balloon venoplasty (12 cases), endocardial LV lead placement (4 cases), genuine epicardial CRT (2 cases), RV bi-focals (3 cases), multi-site configurations (4 cases) and LV quadripolar leads ± multi-point pacing (36 cases) and reviewed their potential uses.

Corresponding author: R.G. Vătășescu, MD
Department of Cardiology, Clinical Emergency Hospital, Bucharest
e-mail: radu_vatasescu@yahoo.com *equal contributions

Conclusion: A significant proportion of patients submitted to CRT require alternative interventional or surgical LV-lead placement.

Key words: CRT, trans-septal, multi-site, quadripolar, multi-point

INTRODUCTION

Heart failure (HF) can be either induced or aggravated by the existence of left ventricular (LV) intraventricular dyssynchrony (IVD). Cardiac resynchronization therapy (CRT) can potentially correct LV-IVD in well-characterized populations (see current Guidelines). CRT has demonstrated clear benefits in both soft (NYHA class, 6MWT, QoL) and hard (all cause mortality, 6 months hospitalizations) randomized control trial (RCT) endpoints. The standard approach is to deliver a unipolar (UP)/bipolar (BP) dedicated LV-lead via the coronary sinus (CS) into a postero-lateral (PL) tributary vein. Suboptimal LV-lead positioning has been long recognized as an important cause of CRT non-response. Optimal, delay-targeted LV-lead placement might sometimes only be possible with non-standard techniques due to various patient particularities. We decided to retrospectively evaluate the frequencies and types of techniques we used in over a decade of CRT experience in our centre. “Alternative CRT” is not yet a coined term. We defined unexpendable variations from the straightforward technique as alternative pathways of delivering CRT.

METHODS

Four-hundred patients with either only pacing (CRT-P) or both pacing and defibrillation (CRT-D) indication (according to ESC guidelines in act at the time of implantation) were reviewed. All procedures were performed within the Clinical Emergency Hospital of Bucharest between October 2005 and June 2014. Upgrades of previously conventional pacing/defibrillation configurations (i.e. AAI, VVI, DDD, mono/dual chamber ICDs) were also included in the review. We derived demographical, clinical, electrocardiogram (ECG) and echocardiogram (EcCG) data from the database in which all CRT patients from our centre are included.

After reviewing the case history and fluoroscopic images at the time of implantation we identified a few “alternative CRT” categories of patients as defined below:

1) Indirect LV venous access

- absence/occlusion of a dedicated vein, disadvantageous take-offs from the CS body, vein of a too small diameter to allow any/sufficient lead advancement, severe kinking along the course, isolated or serial (focal or extended) stenosis etc.

2) Trans-septal lead delivery

- no direct target-vessel access + no suitable navigable collaterals (absent, reduced in diameter or also stenosed), provided that the mitral valve does not exhibit significant[1] disease

3) Genuine epicardial CRT

- unfeasible CS approach (no direct subclavian/CS branch venous approach and/or no suitable collaterals) + significant mitral valve disease

4) RV bifocal stimulation (true CRT failures)

- all previously mentioned conditions concomitantly + inability to withstand general anesthesia with reasonable risk (highly co-morbid)

5) Multi-site pacing using tripod configurations

- either previous RV bifocals with subsequent successful LV-lead delivery by any route (3V/2R) or de novo (usually markedly dilated ventricles)/sequential (usually CRT non-responders with residual dyssynchrony) dual LV-lead delivery (3V/2L)

6) Quadripolar leads/anodal capture/multi-point pacing

- large proximal diameter veins, extensive myocardial scarring, extremely dilated ventricles otherwise suitable for multi-site pacing, phrenic nerve stimulation (PNS)/high pacing thresholds (PT) in BP lead optimal position

RESULTS

The average characteristics of the studied population are listed in the **Table 1**. The population is obviously extremely heterogenous since it includes most types of cadiomyopathies irrespective of etiology, ischaemic status of the patient or timing of implantation (de novo or

[1]Disease of the mitral valve in the sense of either stenosis and/or regurgitation that cannot be expected to improve secondary to correction of dyssynchrony or LV reverse-remodeling (i.e. severe mitral stenosis, extensive calcification, flail etc)

Table 1. General characteristics of patients who underwent de-novo/upgrade to CRT between 10.2005 and 06.2014

No#	400
Implant type	CRT-P/CRT-D
Implant sequence	De novo/Upgrade
Male/Female ratio	´3:2
Mean age	61.63±10.88
Ischaemic/Non-ischaemic ratio	´2:3
Hypertensive (y)	´1/3
Dyslipidemic (y)	´1/2
Diabetic (y)	´1/6
Mean baseline NYHA class	3.18±0.43
Mean baseline QRS width	172.78±24.6 msec
Mean baseline EF	21.27±5.22%
Mean baseline LVEDV	219.29±75.03 ml
Mean baseline LVESV	171.57±68.02 ml
Patients with "alternative" CRT	61/400 (15.25%)
CRT-delivery failures (necessity pure RV bifocals)	3/400 (0.75%)

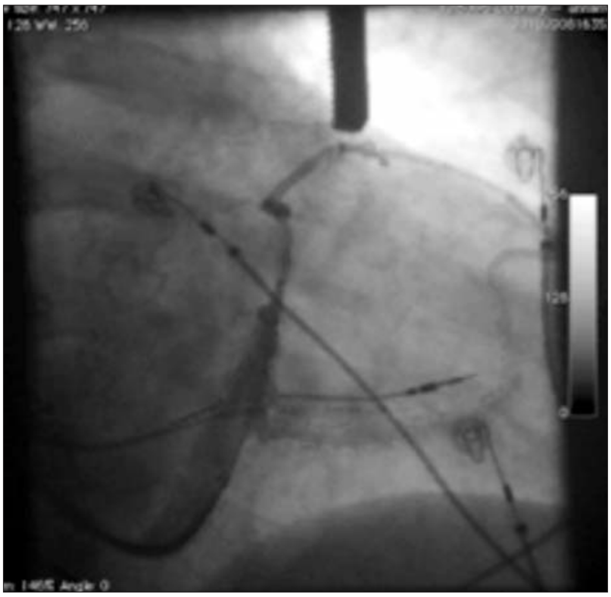

Figure 1. CS venogram showing only indirect, collateral access to the PL target territory

upgrade).

Among the 400 reviewed patients, 61 (´15%) of them required an "alternative" approach to CRT as defined above.

1) Indirect LV venous access

Such situations are rather frequent when implanting in ischaemic and hypertrophic cardiomyopathies. Since all viable myocardium needs proper venous drainage, collaterals usually form and empty within other patent vessels that finally end up in the CS. Thus, the PL territory of the LV can sometimes be reached "retrogradely" (in an opposite direction than the usual approach) after navigating via collaterals (**Fig. 1, Fig. 2, Fig. 3**).

In our experience twelve patients (3%) were implanted after an indirect venous approach; two patients (0.5%) had an apparently complete absence of PL branches, other two (0.5%) had occlusion of good-diameter target branch while other three patients (0.75%) had PL branches of reduced diameters (proximo-distal or only distal). Another three patients (0.75%) had extreme kinking of the PL branch in the proximal part probably due to a very acute take-offs from the CS body. All these 10 patients (2.5%) necessitated a retrograde approach via permeable, good caliber collaterals that was ultimately successful.

The remainder two (0.5%) only had isolated focal stenosis that precluded advancement of the sheath and/or lead distal enough. This was overcome by first guidewire navigation distal to the stenosis and then venoplasty using very small diameter (1.5 mm or even 1.25 mm) regular, preferably non-compliant over-the-wire (OTW) balloons (**Fig. 4, Fig. 5**).

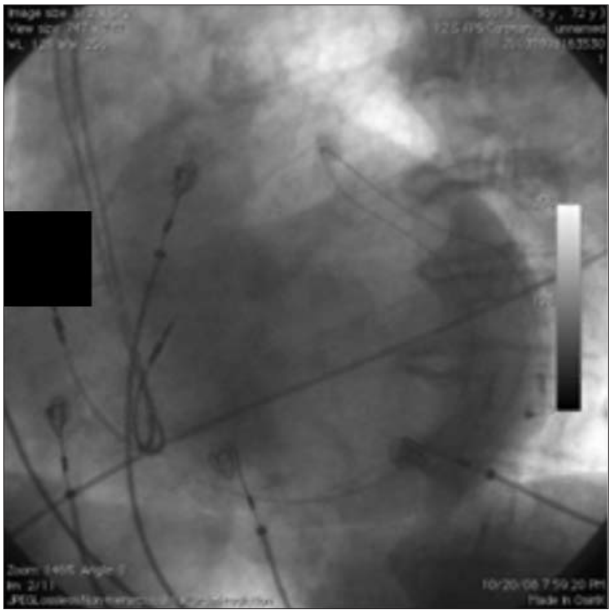

Figure 2. LAO projection with trans-collateral LV-lead finally in place

2) Trans-septal lead delivery

Specifically, a classical trans-septal puncture via right femoral route is first performed. While keeping the femoral sheath in place along with the guidewire trans-septally in the LA (as a radiological landmark), the left/right subclavian is punctured and approached with a special steerable lead introducer and guidewire. These are finally advanced from the RA to the LA, then run trans-mitrally, within the LV. Finally, a dedicated, screw-in, polyurethane-coated, endocardial, BP LV-lead is delivered, usually to the high PL aspect of the LV endo-

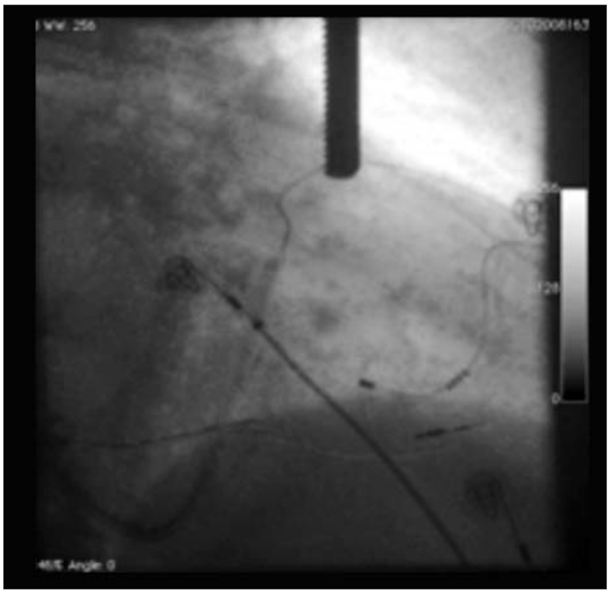

Figure 3. RAO projection with trans-collateral LV-lead finally in place

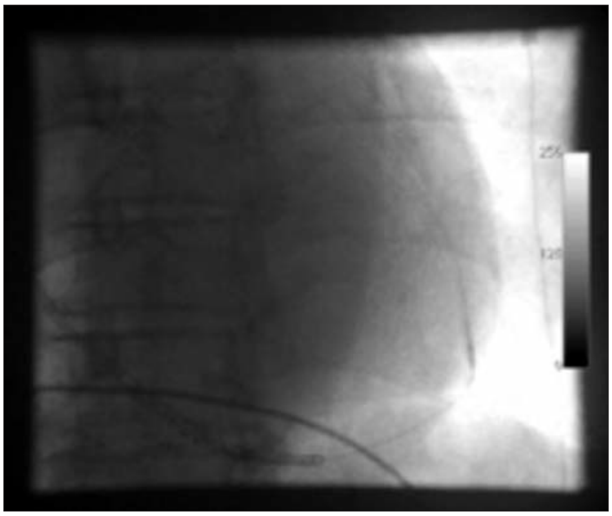

Figure 4. OTW ballon venoplasty of branch finally leading to PL target territory

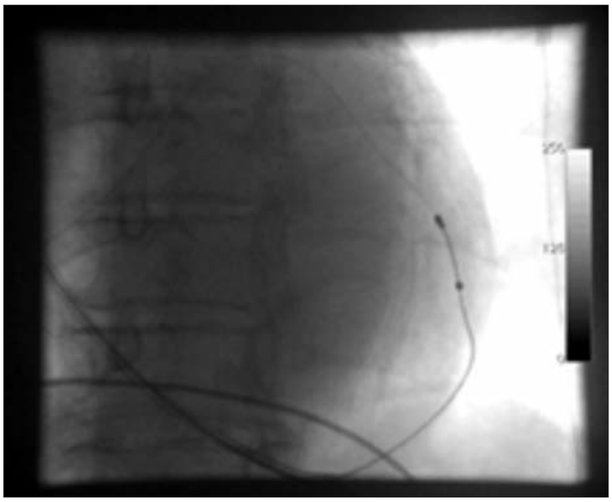

Figure 5. OTW LV-lead delivery after balloon venoplasty

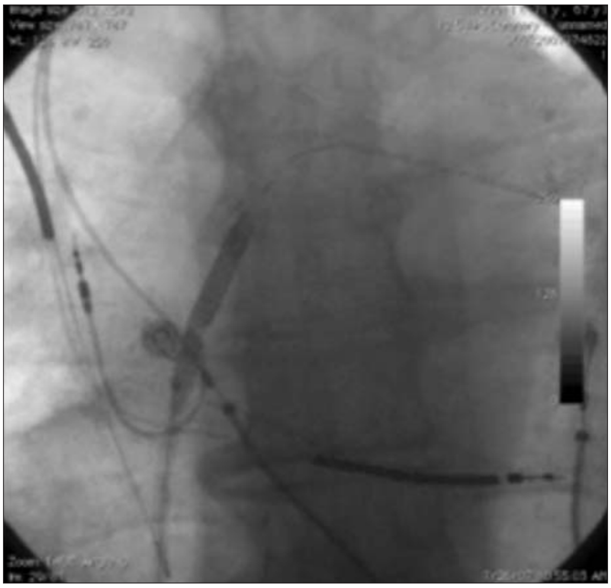

Figure 6. Femoral route IAS dilation with OTW balloon

cardial wall (1) (**Fig. 6, Fig. 7, Fig. 8**).

We observed 4 cases of patients with improper direct venous access whose collaterals were also very reduced in diameter (2 patients – 0.5%) or severely kinked thus producing serial stenoses (2 patients – 0.5%). In all these the mitral valve was free of significant disease and endocardial active fixation of the LV-lead was carried out with successful subsequent CRT.

3) Genuine epicardial leads

This is performed under general anesthesia by a thoracic/cardiovascular surgeon since opening of the pericardial sack is necessary for attachment of the bipolar pacing electrode to the epicardium. Both open surgery and minimally invasive techniques (through video-assisted thoracoscopic surgery – VATS) have been described (2). After epicardial attachment the lead is then tunneled to the final position of the device (**Fig. 9, Fig. 10, Fig. 11**).

Out of the 400 cases in our centre this approach was only employed in 2 cases (0.5%). One of these had no direct suitable CS branch access, unsuitable collaterals and simultaneous significant mitral disease, while the remainder was a 2 year-old CRT with a fractured LV-lead that needed to be changed associating chronic thrombosis of the left subclavian vein.

4) RV bifocal stimulation (true CRT failures)

The impossibility to deliver LV depolarization by any

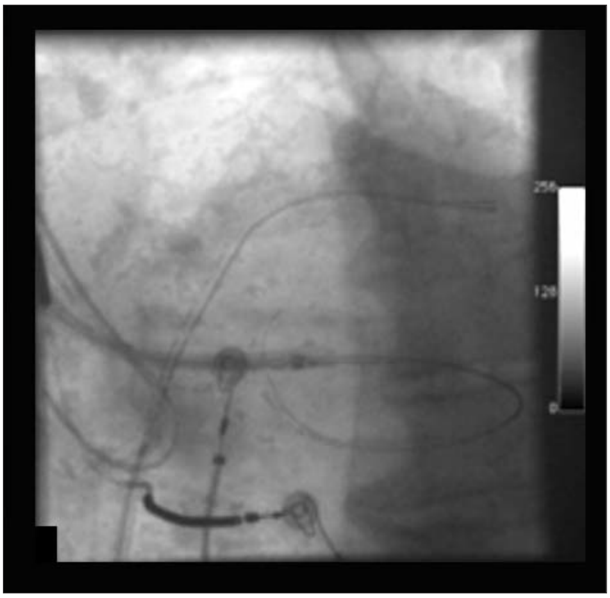

Figure 7. Femoral route guidewire in place (radiological landmark) with trans-IAS sheath and guidewire in the LV

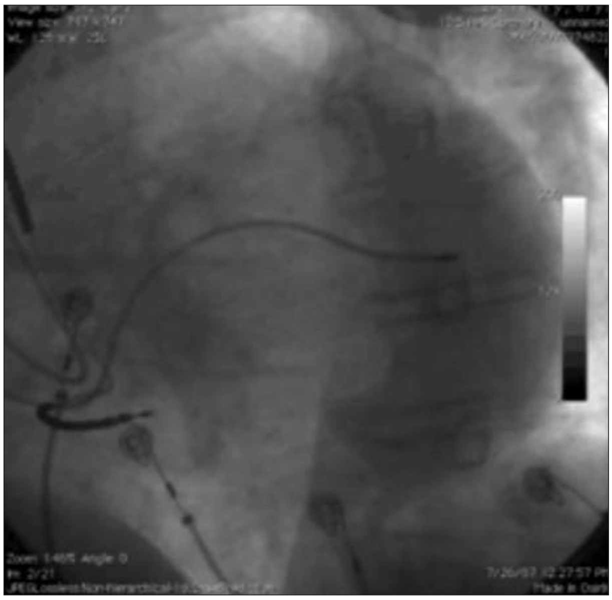

Figure 8. Trans-IAS, trans-mitral endocardial BP LV-lead in place

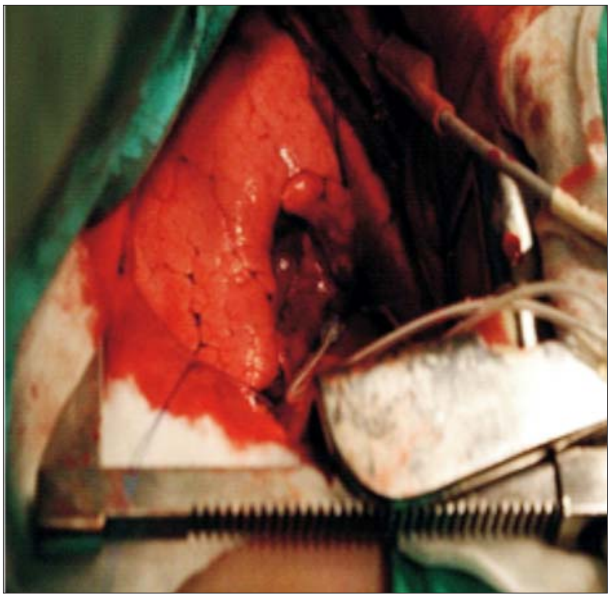

Figure 9. Surgical placement of the epicardial LV lead

Figure 10. Intra-procedural delay-targeted optimal positioning during of an epicardial LV-lead electrode

of the above mentioned routes was only encountered in 3/400 patients (0.75%) in our centre. In all of these, a "salvage" RV bi-focal configuration was employed. One RV lead was placed in the apex and the second either in the midseptum or in the lower right ventricular ejection tract (RVOT). Depolarization fronts were simultaneous by means of a Y-connector inserted in the RV-socket of a conventional DDD pacemaker (**Fig. 12**).

5) Multi-site pacing using tripod configurations

Four of our patients (1%) had different forms of multi-site (MS) pacing. One patient was an RV bi-focal from another centre in who we managed to deliver the LV-lead classically, thus turning him into a tri-ventricular paced, 2 leads in the RV configuration (3V/2R) (**Fig. 13**).

Tripod configurations with two LV-leads (3V/2L) refer to dual CS approach (although mixed approaches are probably also possible). We found 3 such patients (0.75%) within our database.

Either in the same session or later in time the CS needs to be searched for another permeable branch to fit the second lead (preferably distant from the first) and correct residual dyssynchrony. For example, in cases of a preexistent AL lead (unsuccessful previous PL approach)

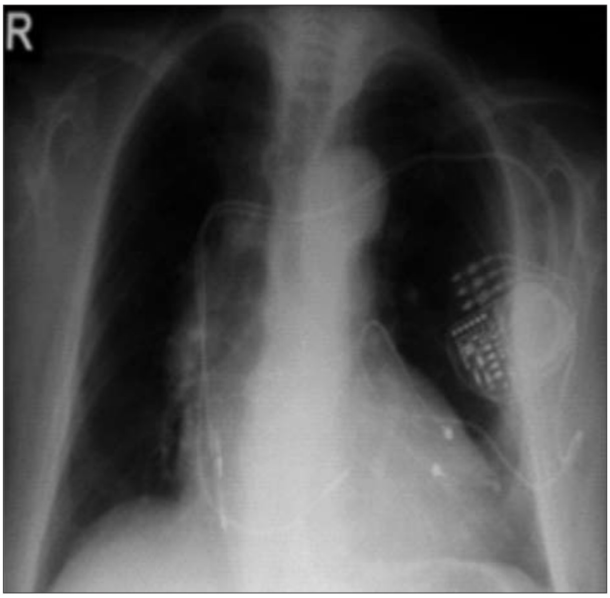

Figure 11. Final aspect of genuine epicardial CRT

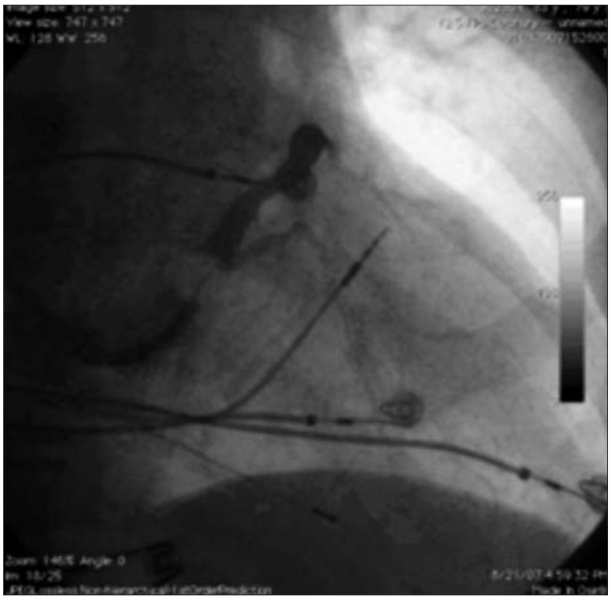

Figure 12. Apical and RVOT RV-leads in place; concomitant CS venogram with no suitable available target branch

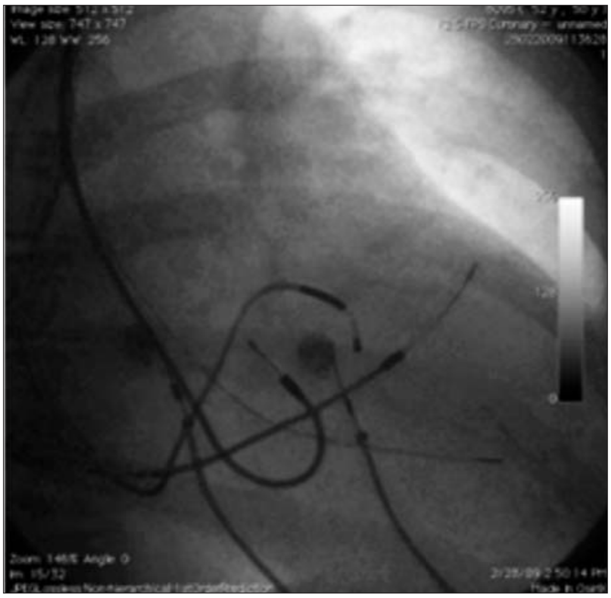

Figure 13. Succesful LV-lead addition in case of a previous RV bifocal. Final 3V/2R configuration in place

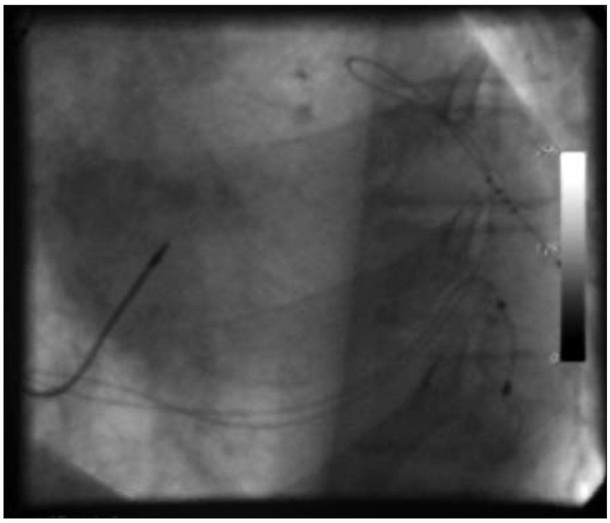

Figure 14. Final aspect of a 3V-2L configuration; observe the extreme LV-dilation and very large RV-LV leads distance

we managed successful PL delivery. As in the case of RV-bifocals, the LV-leads converge into a Y-connector that makes their wave fronts simultaneous, this in turn being inserted in the LV-socket (**Fig. 14**).

6) Quadripolar leads/anodal capture/multi-point pacing

Out of 400 patients, 36 (9%) patients were paced using either single-point (Sp) or Mp QP (SpQP/ MpQP) configurations (**Fig. 15**). All these patients were included in the review since this modality was considered a necessity in each individual case (various reasons).

DISCUSSION

Contact mapping of endocardial activation proved the basal or mid-ventricular, PL area of the LV myocardium to be the maximally delayed. Slight variations were observed more to the posterior or lateral aspects. Current CRT guidelines admit that LV lead placement may be targeted at the latest activated segment. At the same time avoidance of apical positions is warranted due to additional induced dyssynchrony, higher chances of phrenic nerve stimulation and precluding of CRT by reduced RV-LV inter-lead distance3. In our experience

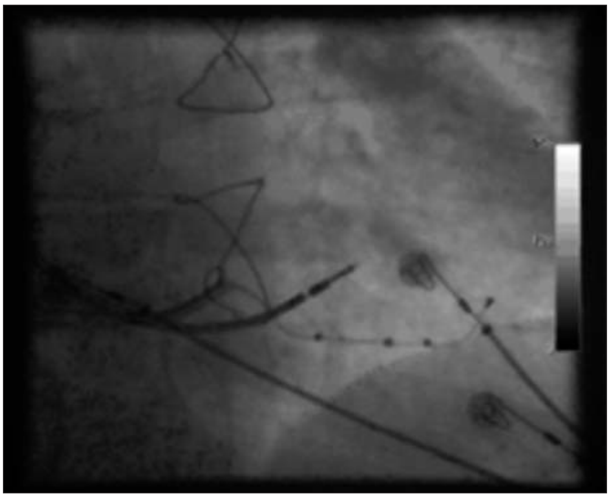

Figure 15. Aspect of a QP LV-lead in place (part of a CRT-D)

in both classical and alternative approach the targeted territory was always PL (>90%), posterior or lateral. During each procedure (including endocardial and genuine epicardial CRT) adequate delays were confirmed by QRS-end to local EGM delta measurement as a standard of care.

In the case of trans-septal CRTs, a troublesome inter-atrial septum puncture (IAS) can yield life-threatening complications (i.e. aortic root puncture). All patients will require life-long oral anticoagulation to avoid embolic events associated with a lead inside the left-sided heart (4). A minimal degree of mechanically induced MR is possible [ALSYNC study, (4)]. This is most likely very reasonable since CRT potentially corrects the dyssynchrony-dependent component of MR. If reverse-remodeling occurs CRT will favorably impact the functional component of MR. Although small-publications have not observed a significant risk of associated endocarditis so far (ALSYNC study), the long-term effect of a trans-mitral lead upon valve quality is unknown. Emphasizing the superior haemodynamic effect of endocardial vs. epicardial pacing (4) (physiological depolarization/repolarization sequence) a trans-apical LV-lead delivery technique under general aneshesia was developed (5). It is appealing since it by-passes the mitral valve and also has a minimally-invasive version (just as genuine epicardial CRT). This is currently still evaluated (4,5).

Probably owing to shared experience of IAS puncture from a large volume of atrial fibrillation procedures we observed no such complications in our centre. Notably, all our endocardial patients have reverse-remodeled and have had stable HF during >5 years of follow-up. MR had a biphasic improvement with immediate (resynchronized papillary muscles) and late (6 months of ventricular remodeling) components. None of these patients had endocarditis so far.

In epicardial CRT it is advisable for an electrophysiologist to assist the surgeon out of various reasons. In our two cases we performed multiple intra-operative measurements to ensure proper delay-targeted LV electrode surface alignment. The corresponding lead needs to be of sufficient length to be tunneled from the pericardial sack right up to the final device location and be loose enough to prevent downward traction of the device or tension within the conductors. We observed no significant bleeding, infection, lead dislodgement or fracture and both patients are sustained CRT responders over >5 years of follow-up. To undergo this procedure a patient must have an acceptable risk of general anesthesia which may not always be the case of CRT candidates. Patients with CRT who empirically received an epicardial electrode at the time of surgery for cardiac pathology with associated LV-dysfunction in the event of future pacemaker-dependency were not accounted for. In their case the prerogative of "alternative" as described above were not met.

We considered RV bi-focal stimulation to be actually a failure of CRT as a concept. Some data derived from small series of patients with unsuccessful LV-lead delivery shows that RV bi-focal stimulation alone does have positive, even statistically significant effects in the same direction as CRT, both clinical and paraclinical (NYHA class, 6 month hospitalizations, 6MWT, QRS, B-natriuretic peptide, EF, MR). These are however of clear lower amplitude than in the LV-lead successful delivery counterparts6. In our limited experience all three patiens had important ischaemic heart disease and were severely co-morbid. Two of them were attempted upgrades from conventional DDDs while the last was a de-novo CRT attempt. Because of a limited myocardial reserve expectations were not high. A post-implant clinical response was observed. Placebo effect could be an explanation in the previously pacemaker-naive patient and probably much less in the other two. Dyssynchrony and associated MR persisted in the LV afterwards and structural remodeling was modest compared to our matched LV-successful candidates.

The so-called tripod configurations refer to variants of tri-ventricular pacing. The 3V/2R configuration was previously rare, occurring usually after a bi-focal RV stimulation with failed LV approach. The patient would finally be referred to a more experienced centre that would then manage placement of the LV-lead. We described one such case who became a super-responder to CRT at 6 months. Initial LV-lead delivery failure was due to atypical location of the CS ostium, with no possibility of trans-septal/epicardial CRT in the referring centre.

At the same time 3V/2R configurations with apical RV and RVOT leads were proven superior to standard BiV pacing in acutely improving mechanical dyssynchrony and are sometimes indicated in some non-responders to classical CRT7. The discussion to be made however is that in such cases it is very likely for the LV lead to be sub-optimally positioned. Some case reports also mention the usefulness of 3V/2R in dyssynchronous LVs with concomitant RBBB and left anterior hemiblock QRS morphologies (8).

For a good mechanical performance LV depolarization must be quasi-synchronous. In normal volume healthy hearts this mainly depends on conduction velocity. In case of diseased myocardium conduction velocity decreases both longitudinally and from endocardium to epicardium (or reverse) in spite of possibly decreased wall-thickness by dilation. In this case distance starts to matter. The 3V/2L configuration was initially considered as an alternative for non-responders to previously successful one LV-lead CRT supposedly because of extremely dilated ventricles (residual dyssynchrony).

As a consequence, an additional LV-lead was to be placed generally in an antero-lateral CS branch (on condition that the first one was PL) or vice-versa. Results were rather inconclusive after a significant number of small-volume trials, with inconstant increases of dP/dt observed9; some showed that if the initial LV-lead was optimally placed, adding a secondary LV-lead was of no beneficial effect10. If we were to consider the randomized trials, they showed not only a superior response of patients to 3V/2L when compared to standard BiV pacing but also a strange potential antiarrhythmic effect. Other randomized trials are still on-going.

We decided to use 3V/2L in three of our cases, all of them sequential (second LV-lead added after initial CRT non-response with demonstrated persistent dyssynchrony). Secondary LV-leads were added in PL branches since in all patients the preexisting leads were in AL positions. Clinical and structural improvement was observed at 6 months and there were no detected complications (although literature expects a higher rate because of procedural complexity). We believe that response after initial non-response is an argument against dual LV-lead from the start approach, especially in the era of SpQP/MpQP pacing. Perhaps establishing a certain cutoff beyond which dual LV-lead should be done from the start seems more practical. Still, the utility of the second lead is likely to be more dependent on myocardial conduction velocity than on total LV volume. These parameters are certainly non-linearly correlated.

Feasibility of implanting more than one lead via the CS is generally high (>90% success rate in large volume centers)11. The question to be asked however is: is 3V/2L multi-site still necessary in the era of Mp? The acute hemodynamic response seems to be superior in case of 3V/2L when compared to MpP12 although randomized comparisons have not been made. All 3V/2Ls in our centre were performed long ahead MpP was commercially available.

The initial idea behind QP leads was overcoming the necessity to re-operate on a patient whose BP LV-lead would not offer any suitable pacing configuration in case of post-implant PNS/high PT. Although PNS is systematically searched for at the time of implant, minor spontaneous advancement/stabilization of the LV-lead within the CS branch can sometimes induce phrenic capture or alter the PT. Simply reprogramming the vector on a standard BP very frequently failed to solve the problem since the two possible cathodes were spatially close, no matter the anodal position. Along with more electrodes, devices enhanced their programmability with multiple variants of stimulations vectors, drastically lowering the chances of no PNS-avoidant/no acceptable PT configuration. In order to maximize this effect, spacing between the four electrodes is much larger than in case of conventional tip-to-ring distances11. QP leads electrodes are coded P4-M3-M2-D1 where P stands for proximal, M for mid and D for distal.

Later on it was observed that QP leads could also aid under many other circumstances. For example, in case of large diameter branches of the CS that would not allow sufficient stabilization of a standard BP LV-lead, a QP lead can be advanced much further until narrowing of the vein. Even if stimulation from de distal part of the lead will never be feasible, due to either PNS or apical location, the P4 and M3 electrodes will ensure pacing availability. At the same time, in ischaemic hearts, it might be possible to have significant PL scar. The chance of finding a reasonable PT along 4 spaced electrodes is higher. Also, should a subsequent infarction occur in a myocardial area spatially close to the LV-lead, there is a better chance of still capturing the LV with a changed configuration.

Eight of our patients had different such issues that were successfully resolved by QP leads. Apart from that we employed QPs in other 12 highly dilated LVs with an empirically chosen cutoff for left ventricular end-diastolic volume (LVEDV) above 250 ml. As we did this, MpP was not available. Post-procedural device programming was performed with designation of the most distal electrode as a cathode, using a high energy pulse (if the phrenic nerve threshold allowed it). By this we hoped to create a current density strong enough (relative to the small size of QP lead electrodes) to induce anodal-capture preferably of P4 or M3. If anodal capture would be sustainable, the LV would be paced at two different sites each beat (rendering this a one-lead pseudo-MpP). Such patients showed very good clinical and structural response at 6 months and sustained it over the recurring follow-ups.

Device programmability recently allowed introduction of Mp pacing (MpP) along the same QP lead which we also employed above 250 ml of LVEDV. Specifically, along the same four electrode lead there is the possibility to program two different depolarization vectors designated LV1 and LV2 (two different cathodes with different/ shared anodes). Their actual configuration and the time sequence between them as well as between left- and right-sided vectors is highly customizable (in case of 3V/2L vectors are invariably simultaneous). This is aimed at replacing (if possible) the need for multi-site 3V/2L configurations in case of extremely dilated LVs. The reasons for this would be: a) delivering only one LV-lead is technically easier and safer (less fluoroscopy, less complications), b) some initial highly dilated LV non-responders to CRT had significant improvement with an additional LV-lead and c) the feasibility of implanting >1 LV-leads is certainly not 100% (˜90-95%). At the same time the anodal capture on P4/M3 described above for simple QP LV leads with no MpP does not always succeed while other times it cannot be sustained.

In our 16 cases we always tried to program devices with D1 and P4 as cathodes and M2/M3 as differing/shared anode(s) thus making the two wave fronts as far away as possible from one another (mimicking 3V/2L configuration). We configured the slightest possible interval (5 msec) between the two LV wave fronts in order to ensure their efficiency (larger time gaps would allow vicinity-depolarization from the other vector). These patients also showed good and sustained clinical and structural response.

A thing to be also noted is that although there are both CRT-P and CRT-D commercially available devices employing QP leads, for the moment only some CRT-Ds have MpP capability, though such CRT-P configurations are expected to soon emerge.

CONCLUSION

According to the definition employed the percentage of so-called "alternative" approaches can be lower or higher. We hereby obtained an overall considerable percentage slightly over 15% (61/400). The decision to go for "alternative" needs to be taken by an experienced CRT-team (preferably with surgical and sometimes intensive care back-up) in order to allow for optimally tailored solutions. Irrespective of the technique implied efficient and complication-free capture of the LV is the desired effect.

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Disclosures

None.

Authors' contributions

The first two authors contributed equally to this paper.

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