Dual-site Right Ventricular Pacing in Patients Undergoing Cardiac Resynchronization Therapy: Results of a Multicentre Propensity Matched Analysis.

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Abstract **Words:** 242

Background: Dual RV has been proposed as an alternative for patients with heart failure undergoing cardiac resynchronization therapy (CRT) with a failure to deliver a coronary sinus (CS) lead. Only short-term haemodynamic and echocardiographic results of Dual RV are available. We aimed to assess the long-term results of Dual-site right ventricular pacing (Dual RV) and its impact on survival.

Methods: Multicentre retrospective assessment of all CRT implants during a 12-year period. Patients with failed CS lead implantation, treated with Dual RV were followed and assessed for the primary end point of all-cause mortality and/or heart transplant. A control group was obtained from contemporary patients using propensity matching for all available baseline variables.

Results: 93 patients were implanted with Dual RV devices and compared with 93 matched controls. During a median of 1,273 days (IQR 557-2,218), intention-to-treat analysis showed that all-cause mortality and/or heart transplant was higher in the Dual-RV group (adjusted HR=1.66, 95%CI 1.12-2.47, P=0.012). As-treated analysis yielded similar results (HR=1.97, 95%CI 1.31-2.96; P=0.001). Cardiac device related infections occurred 7-times more frequently in the Dual RV site group (HR=7.60, 95%CI 1.51-38.33; P=0.014). Among Dual RV non-responders, 4 had their apical leads switched off, 5 required and epicardial LV lead insertion, a transseptal LV lead was implanted in 2, and in 9 patients, after reviewing the CS venogram, a new CS-lead insertion was successfully attempted.

Conclusion: Dual RV pacing is associated with worse clinical outcomes and higher complication rates than conventional CRT.

Key-words: heart failure; electrical dyssynchrony; cardiac resynchronization therapy; endocardial pacing.

Abbreviations: CRT – cardiac resynchronization therapy; CS – coronary sinus; Bi-V – biventricular pacing; Dual RV – Dual right ventricular pacing; RV – right ventricular; LV – left ventricular; LVEF – left ventricular ejection fraction; AF – atrial fibrillation; VT – ventricular tachycardia; VF – ventricular fibrillation; ATP – anti-tachycardia pacing; ICD – implantable cardioverter defibrillator.

Background

Cardiac resynchronization therapy (CRT) has emerged as one of the major developments in the treatment of patients with advanced heart failure and electrical dyssynchrony, providing symptom relief, decreasing hospitalizations for heart failure and leading to improved survival [1-3].

Standard CRT consists of Bi-Ventricular pacing (Bi-V) from the right ventricle (RV) and coronary sinus (CS) aiming to correct electrical dyssynchrony and delayed activation of the lateral left ventricular (LV) wall [4]. Unfortunately, due to technical or anatomical difficulties, failure to implant a functioning LV lead occurs in <5% of cases (95%CI 3.1 to 4.3) [5].

Alternative approaches for failed CS lead implants have been suggested, with dual RV pacing (Dual RV), also known as bifocal RV pacing, being an attractive option due to its technical simplicity (characterised by a short learning curve, lack of need for special delivery tools and a high success rate) [6, 7]. This approach aims to restore the origin of depolarization to the high ventricular septum. It is based on the assumption that the high septum is thinnest, and impulses travelling to the septum achieve an earlier depolarization of the LV [7]. *Lane* and colleagues have also suggested it causes LV activation to spread from two widely spaced RV sites adjacent to the anteroseptal and inferior LV walls, potentially facilitating more coordinated LV contraction [8].

Despite the promising results presented in early studies [7, 8], no long-term data on this resynchronization approach, namely with assessment of its impact on survival, has been published so far.

Methods

This was a multi-centre; propensity-matched comparison to compare the long-term clinical outcomes of patients implanted with Dual RV and standard CRT devices. Permission to

retrospectively review medical records for this analysis was obtained from the local ethics committees.

Setting and Study Population

Between February 2005 and June 2016, 2,548 consecutive patients implanted with CRT devices in three centers were assessed for potential inclusion in this analysis. Patients implanted with Dual RV and patients implanted with conventional bi-ventricular devices (with or without a defibrillator) within the next month were considered potentially eligible.

Patients were implanted with CRTs if they had symptomatic heart failure (New York Heart Association class II to IV) despite maximally tolerated medical therapy, had LV ejection fraction (LVEF) < 35%, and QRS duration ≥ 120ms.

Patients were not considered for the purpose of this analysis if they were aged < 18, if they required intravenous inotropic drug therapy, or had an estimated life expectancy of < 12 months due to a cause other than heart failure. Patients with failed CS lead implants and referred for epicardial or endocardial LV insertion, and patients treated with multisite pacing were also excluded to preserve homogeneity while comparing groups.

Propensity score matching with a 1:1 ratio was used to obtain a control group of standard CRT patients (Bi-V group) and assure that Dual RV and their contemporary Bi-V controls were similar in all baseline variables. Probabilities in the Dual RV group were matched 1:1 to the best Bi-V corresponding patient.

Sample Characterization

All variables at the time of the procedure and during follow-up were defined and categorized. Information was collected regarding demographics, anthropometric data, baseline cardiac disease, echocardiographic data and medication.

The following variables were used for creating the propensity score, which was used for creating a well matched-control group: device type (CRT with or without a defibrillator), age at time of implant, gender, presence of atrial fibrillation (AF), estimated glomerular filtration rate (calculated using the Modified Diet in Renal Disease – MDRD - formula), chronic obstructive pulmonary disease, previous stroke or cancer, New York Heart Association functional class, primary or secondary prevention of sudden cardiac death, QRS width, bundle branch or QRS pattern, ischemic or non-ischemic cardiomyopathy, LVEF and medication (use of oral anticoagulants, antiplatelet agents, beta-blockers, other anti-arrhythmic agents, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, spironolactone and loop diuretics).

Dual RV Site Pacing Implant Procedure

While attempting to implant a standard CRT device (with a right atrial, RV and CS lead), if lead positioning inside the CS leading to effective LV capture was not possible, the operator was allowed to opt for Dual RV pacing. This consisted of positioning one lead into the RV apex and another one into the high RV septum or outflow tract (Figure 1). These were then plugged into the device header, usually the high RV septum/outflow tract lead into the CS port.

Choice of a CRT-P or CRT-D was based in the patient's clinical history, risk profile, and past arrhythmic events.

Device Programming

As some of the patients were implanted prior to the MADIT-RIT trial [9], devices were programmed with two ventricular tachycardia zones *ab initium*, based on patient's age and presence of previous ventricular arrhythmia events. The ventricular tachycardia (VT) zone was routinely programmed starting at 170bpm in all devices, unless there was previous documentation of slower VTs occurring. The nominal number of intervals for initial detection was used and detection was set to 2.5s–9.0s (depending on manufacturer) in the VT zone and 1.0s–5.0s in the VF zone. Supraventricular tachycardia discriminators were switched on and high-rate timeout turned off. Anti-tachycardia pacing (ATP) and shocks were programmed in the VT and VF zone. Subsequent adjustments to therapies and detection zones were performed during follow-up, or following the occurrence of any arrhythmic events.

From 2012 onwards some patients were implanted with quadripolar LV leads. However, the multisite pacing option was not switched on. Different dipoles were used for reduced capture thresholds and to avoid phrenic nerve capture.

Follow-up and Outcomes

Safety data and the presence of complications including lead dislodgement, lead failure (defined as lead performing inappropriately and requiring replacement), device-related infection (whether pocket or lead infection), phrenic nerve capture refractory to electronic programming (requiring temporarily switching off the LV lead and repositioning or insertion of a new lead), and haematoma requiring drainage or bleeding requiring red blood cell transfusion was recorded.

Presence of CRT response, defined as a ≥5% increase in LVEF and/or improvement ≥1 of NYHA class was assessed within the first 6 months.

Mortality data (all-cause mortality) and information on patients accepted for heart transplant were collected through hospital reports. In patients who transferred their follow-up to another hospital,

long-term follow-up data was retrieved. When patients were lost to hospital follow-up, data was collected through patients' registered general practitioners.

Data from our local device clinic follow-up records and stored device electrograms (EGMs) during episodes of detected VT, VF, any therapy deliveries, and inappropriate shocks were analysed by a cardiac physiologists specialized in electrophysiogy and a Consultant Electrophysiologist or Senior Electrophysiology Fellow. The occurrence of sustained ventricular tachycardia episodes terminated with implantable cardioverter defibrillator (ICD) intervention (shock or anti-tachycardia pacing) was logged. Patients were then classified as having had appropriate shocks, if a shock was delivered during a VT or VF event. An effective ATP therapy was defined as overdrive ventricular pacing able to restore sinus rhythm following a VT or VF episode. An appropriate ICD intervention was classified as the presence of either an appropriate shock or an effective ATP.

The incidence of inappropriate shocks delivered due to misdetection of tachycardia (either supra-ventricular tachycardia, sinus tachycardia, fast AF or artefact) was also compared between the two treatment groups. Presence of arrhythmic storm, defined as ≥3 sustained episodes of VT, VF, or appropriate ICD therapies during a 24-hour period, and need for ventricular tachycardia ablation was also documented.

From 2011 onwards, home-monitoring systems became available and were widely used for follow-up purposes.

Statistical analysis

A propensity score was obtained for all participants undergoing a transvenous CRT implantation through binary logistic regression: CRT modality (Dual RV or Bi-V) was the binary outcome and all baseline variables (mentioned above) were used as covariates for estimating a probability (the propensity score). Then, probabilities in the Dual RV group were matched 1:1 to the closest Bi-V

patient fulfilling inclusion criteria using the nearest neighbour matching approach. The propensity score was matched to 5 decimals whenever possible. If this was not possible, we subsequently attempted 4, 3 and then 2 decimal matching. If a treated subject could not be matched to any untreated subject on the second digit of the propensity score, then the treated subject was discarded from the matched analysis. Histograms and comparison of means were used for assessing distribution and matching success.

Comparisons between Dual RV and Bi-V were performed. Based on Stuart [10], analyses were performed using the groups as a whole, rather than using the individual matched pairs. Chi-square was used for the comparison of nominal variables. The student t-test, or its non-parametric equivalent, Mann-Whitney when appropriate, was used for comparison of continuous variables; the *Levene's* test was used in order to check the homogeneity of variance. Results with $P < 0.05$ were regarded as significant.

Kaplan-Meier curves were traced for comparing survival (freedom from all-cause mortality or heart transplant) among the two intervention groups. Hazard ratio was used for assessing the existence of differences. For the endpoint of all-cause mortality or heart transplant, both an as-treated analysis (where patients were censored if they lost biventricular pacing or if their dual RV devices were upgraded with an epicardial LV lead) and an intention-to-treat analysis (including all 93 patients implanted with Dual RV devices and their matched controls in spite of subsequent upgrade/downgrade) were performed. For the purpose of time to event analysis only time to first event was considered (and analysed using Kaplan-Meier curves and Cox Regression). For every specific assessed endpoint, the patients were censored after their first event.

PASW Statistics (SPSS Inc, Chicago, IL) version 18.0 was used for descriptive and inferential statistical analysis.

Results

During the specified time interval 93 out of a total of 2,548 (3.65%) patients were implanted with Dual RV site pacing. The reasons for this were: unsuccessful cannulation of the CS (n=10), no suitable target veins (small or not lateral enough; n= 15), unacceptably high threshold/phrenic nerve capture in the only existing target veins (n=21), inability to pass the guide sheath beyond a proximal corkscrew morphology CS or to position the lead in the target vein due to severe anatomical difficulties (n=26), lead not stable after cutting with dislodgment (n=14), and dissection of the CS with lead positioning no longer possible (n=7).

591 patients were successfully implanted with CRT devices within the same month as patients implanted with Dual RV devices. Three of such CRTs had epicardial leads and 44 were triventricular pacing devices, and therefore excluded from analysis.

Among the remaining 544 patients, 93 were selected through propensity matching to act as controls.

Propensity matching was adequate with a similar distribution of probabilities (Figure 2) and no significant differences in baselines or medication were observed between the two treatment groups (Tables 1 and 2).

Safety data

Two patients in the Dual RV group developed a cardiac tamponade during their implant procedure and required insertion of a percutaneous cardiac drain. One patient in the standard CRT group had a severe pocket haematoma requiring drainage. No cases of pneumothorax were observed. All patients were alive at discharge.

During a median follow-up of 1,273 days (IQR 557-2,218), the incidence of lead-related complications (lead dislodgement and lead failure) was low and comparable between the two groups (Table 3).

Cardiac device related infections occurred 7-times more frequently in the Dual RV site group.

Phrenic nerve capture was not controllable with device programming and required a new CS lead insertion in 2 patients of the Bi-V group.

The incidence of inappropriate shocks was less than 1 per 100 patient-years and occurred as a result of AF or tachycardia in 4 cases, lead failure / noise in 2, and T-wave over-sensing in one patient.

Arrhythmic Events

Only 30 patients (16.1%) experienced appropriate ICD interventions (19.4% in the standard Bi-V group vs. 12.9% in the Dual RV CRTs; P=0.232), resulting in a similar occurrence of appropriate ICD shocks or ATPs in both groups (4.55 per 100 patient-years in the Dual RV group vs. 4.66 in the standard CRT-group; P=0.619).

Only 5 patients (5.4%) in the standard CRT and 4 (4.3%) in the bifocal RV pacing group (P=0.733) experienced arrhythmia storms, and only one patient in each group underwent catheter ablation of ventricular tachycardia as a result of this.

CRT Response and Survival Free from Transplant

The Bi-V group displayed more favourable post-procedure NYHA and LVEF results (2.1±0.9 vs. 2.5±0.9; P=0.002; and 36±13% vs. 30±12%; P=0.008; respectively), and presence of CRT response also occurred more frequently (Bi-V 73.0% vs. Dual RV 40.2%; P<0.001). During follow-up the incidence of heart transplant was numerically, but non-significantly, higher and all-cause mortality was significantly higher in Dual RV patients. In the intention-to-treat analysis, the combined composite endpoint of all-cause mortality and/or heart transplant occurred more frequently in Dual RV patients (Table 3).

Four Bifocal RV pacing patients had their apical leads switched off as their symptoms worsened after the implant procedure. Five patients in this group required a surgical epicardial LV lead insertion, and a transseptal LV lead was implanted in two. In 9 patients, after reviewing the CS venogram, a new CS lead insertion was successfully attempted. Two patients in the Bi-V group developed refractory phrenic nerve pacing and required a new CS lead insertion. After excluding these patients, a new as-treated analysis confirmed the presence of a significant difference in the incidence of all-cause mortality or heart transplant, which now became even more pronounced (HR = 1.97; P =0.001) (Figure 3). Similar results were obtained when comparing all Dual RV patients with the whole cohort of non-matched CRT patients (HR=2.02, 95%CI 1.50-2.71, P<0.001).

Discussion

This data shows a higher incidence of all-cause mortality and heart transplant in advanced heart failure patients treated with bifocal RV pacing for standard CRT indications, in the setting of a failed CS lead implant. Furthermore, presence of CRT response was less frequent in the Dual RV group, and in some patients bifocal RV pacing aggravated their symptoms and had to be switched off. A higher incidence of cardiac device-related infection was observed in the dual RV pacing group of patients, possibly occurring as a result of prolonged procedure times, and the use of more catheters, wires and sheaths, before abandoning the possibility of a CS lead implant. No impact was observed in the burden of ventricular arrhythmia or other lead-related complications.

This data would strongly discourage the use of Dual RV site pacing in CRT candidates. However, a small select group of patients theoretically may still derive a benefit from this pacing approach: patients with right bundle branch block and compromised RV systolic function are potential candidates for this treatment option. In right bundle branch block the latest activation in the RV occurs in the basolateral portion [11], and routinely we positioned our leads in right ventricular apex and high ventricular septum. Another option would be positioning a single lead in the septum below

the level of block or delayed conduction, similarly to what is done in direct His-bundle pacing. However, more studies are needed to assess its role in this group of patients.

Previous studies with Dual RV have suggested that it might lead to an improvement in LV ejection fraction [8, 12-14], improvement of electrical [8, 15] and global mechanical dyssynchrony [8], NYHA class [14-16], reduction of hospitalizations [15], increase in walked distance in the six-minute walk test [14-16], improvement of B-type natriuretic peptide levels [15], reduction of mitral regurgitation severity [6, 14-16], and improvement of quality of life [15, 16]. However, preliminary evidence of worse results with Dual RV when compared to Bi-V was also available. *Lane et al.* suggested that superior electrical and mechanical resynchronization in patients with heart failure might be achieved with biventricular pacing when compared to Dual RV [8]. *Rocha et al.* in a small cohort study comparing Bi-V with Dual RV observed superior electrical resynchronization as assessed by change in QRS width post CRT, and a numerical but non-significant, 5% difference in the improvement of LV ejection fraction in the Bi-V group [17], like we have observed in our cohort. Furthermore, the authors observed a significantly higher incidence of clinical and echocardiographic non-responders in the Dual RV groups and trend for less heart failure admissions in the Bi-V group of patients [17].

As Dual RV appears to be inferior to Bi-V, other options may be considered for patients with failed CS implants. The classical and most used alternative is surgical epicardial LV lead placement (via thoracotomy or video-assisted thoracoscopy). This is more invasive than transvenous techniques, causes more surgical trauma and results in a longer recovery time [18], which is associated with higher risk in severe heart failure patients. Additionally, it requires general anaesthesia and the presence of epicardial fat and adhesions can make even a limited open approach challenging [19]. Although this approach has obtained good results [20], lead failure rate is generally higher [21]. Video-assisted thoracoscopy requires smaller incisions and causes less post-operative pain [22], but requires a skilled surgeon [23].

LV endocardial pacing seems to have a better haemodynamic profile than LV epicardial pacing [24-26], and may be less pro-arrhythmic as it reduces the dispersion of ventricular repolarization [27]. Therefore, alternative strategies developed in recent years for unsuccessful CS lead implants may be worth considering. Transseptal LV lead insertion through the atrial [28, 29] or ventricular [30] septum has recently been suggested. However, these are complex procedures, with a long learning curve, higher risk of lead dislodgement and are associated with more frequent thromboembolic complications than standard CS leads (even when patients are on anticoagulants). Even though the initial results are promising, long-term outcome with these techniques has not yet been compared with conventional CS lead implants. Transapical LV lead implantation is a minimally invasive surgical option for LV endocardial pacing [31]. However, it requires general anaesthesia and it shares the above-mentioned safety concerns that are associated with LV endocardial lead pacing.

Bundle branch block may occur as a result of proximal block or delay in the specialised conduction system [32] and can be normalized through direct His-bundle pacing [33]. In patients who are candidates for CRT, this was shown to be possible in 72% of cases [34]. *Lustgarten* and colleagues have observed that results with this approach were comparable to Bi-V with regard to quality of life, NYHA, 6-minute walk test, and LV ejection fraction improvement. Participants were randomized in a patient-blind fashion to direct-His bundle pacing or conventional Bi-V, and cross-over occurred at 6 months, with similar benefit being observed irrespectively of pacing modality [34]. Advantages of this approach include lack of need for intravenous contrast, very specific endpoint at the time of implant (QRS normalization), and no leads in the LV endocardium.

Study Limitations

We acknowledge some limitations in our work. “First, the results of this multicenter propensity matched study should be interpreted with caution in view of the absence of randomization. The use of propensity-score matching provided an appropriately matched control group, thus attempting to

minimize this limitation. However, as most patients implanted with Dual RV had no possibility for conventional BiV pacing, we reinforce that instead of assessing Dual RV as an alternative to CRT, we have assessed its role in patients where implant of a standard CRT was not possible, which has been shown to provide significantly adverse outcome. Second, even though both groups were matched for baseline variables and medication, we cannot entirely rule out that unaccounted aspects can have contributed in part to the observed differences in events. Third, it is known that sometimes reverse remodelling and LVEF improvements may take longer to occur [35], and therefore data on LVEF after the first year in initial echocardiographic non-responders would have been of interest. Unfortunately we did not have data collected systematically for most of echocardiographic non-responders who were still alive after the first year, and the small number of patients in question would likely lead to underpowered comparisons. Finally, as we collected no data on procedure times, and number of used catheters, wires or sheaths used, we can only hypothesize regarding the potential causes of the increased infection rate in the bifocal RV pacing group.

Conclusion

Our data indicate that Dual RV pacing may not be the best alternative for patients with a conventional CRT indication and a failed CS lead insertion. The increase in mortality and lower responder rate suggests that alternatives to this approach should be considered in these patients.

Author Contributions: RP and AWC were involved in the design, RP coordinated data collection for this investigation helped by NP, AI, TW, DF, SB, DR, RD, MC, GB, who were also involved in the final assembly of the database. GB, VE, SAh, DR, OS, ER, SS, MD, ML, PL, ML, SAg, SB, AWC were involved in patient care and data analysis (tracings, etc). RP performed the statistical analysis and wrote the first version of the current manuscript, which was thoroughly revised by AWC. All authors contributed to the final version of the manuscript, through careful and critical revision. The final version of the manuscript was revised by all authors, and approved before submission.

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Figure 1 – Lead positioning in Dual RV site implants.

Note: AP view. Active fixation leads positioned in the RV apex and high septum. Contrast retention can be seen, and signals the presence of CS dissection.

Figure 2 – Propensity Matching Assessment.

Legend: Bi-V – bi-ventricular devices; Dual RV – Dual RV site pacing.

Note: Mean probabilities of both groups were matched to the 5th decimal: 0.20797±0.10035 vs. Bi-V 0.20796±0.10021; P=0.999.

Figure 3 – All-cause mortality and heart transplant during follow-up (As Treated Analysis).

Legend: HR – hazard ration; CI – confidence interval; Bi-V – bi-ventricular devices; Dual RV – Dual RV site pacing.