Quadripolar Leads in Cardiac Resynchronization Therapy

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ABSTRACT

Despite the benefit of cardiac resynchronization therapy (CRT) in patients with heart failure and conduction delay, a considerable number of patients do not respond substantially. Left ventricular lead position is an important factor in response, restricted by the patient’s specific anatomy and local pathophysiology. Quadripolar leads could enhance response to CRT, offering 4 pacing locations along the distal end of the lead. Several quadripolar leads are available, all with different shapes and electrode spacing. Electrodes can be positioned in an ideal pacing location, determined by delayed mechanical or electrical activation, and away from phrenic nerve stimulation, high pacing thresholds, and fibrosis. Implantation is safe, with comparable or even lower complication rates compared with standard bipolar leads. Studies on biventricular pacing with quadripolar leads show apparent variations in acute hemodynamic response between pacing configurations, implying a patient-specific response. Pacing with an optimal pacing vector of a quadripolar lead benefits acute hemodynamic response. Multipoint pacing, pacing the left ventricle with 2 of 4 electrodes, could further enhance response. However, larger trials are needed to confirm these results, and results on long-term outcome of CRT with quadripolar leads and the benefit of multipoint pacing are warranted. We conclude that quadripolar leads are an important improvement in the treatment of heart failure patients with CRT. (J Am Coll Cardiol EP 2015;1:225–37) © 2015 by the American College of Cardiology Foundation.

Cardiac resynchronization therapy (CRT) has proven its benefit for a selection of heart failure patients by reducing mortality and morbidity, according to renewed guidelines (1,2). CRT improves prognosis in patients with dilated cardiomyopathy by inducing reverse remodeling through electromechanical resynchronization. Unfortunately, a considerable proportion of patients (approximately 30% to 40%) show no significant response to CRT (1). Suboptimal left ventricular (LV) lead position is an important factor for diminished CRT response (3). Besides targeting of the posterolateral wall and avoiding apical segments, the optimal position depends on several patient-specific factors (4,5). Even if the ideal pacing location is known, lead placement in or near this location is difficult.

Formerly, only unipolar and bipolar leads were available for transvenous epicardial LV pacing, with 2 electrodes placed at the tip of the lead. These leads need to be wedged in a distal vessel or actively fixed by dedicated systems. The anatomy of the coronary sinus and its side branches, lead instability, local pacing parameters, and phrenic nerve stimulation (PNS) could restrict lead placement. Options to overcome suboptimal positioning are available (thoracoscopic placement) or emerging, such as endocardial pacing, implantation of multiple LV leads, and quadripolar leads.

Quadripolar LV leads have 4 electrodes along the distal end. These leads can pace the LV wall, via transvenous access, at several locations and multiple vectors along the lead. Optimal pacing sites (i.e., the latest mechanical or electrical activated region) could...
AABBREVIATIONS
AND ACRONYMS

AHR = acute hemodynamic response
AV = atrioventricular
BIG = biventricular pacing with a quadripolar lead
CONV = conventional biventricular pacing with a bipolar lead or distal pacing vector of a quadripolar lead (i.e., tip electrodes)
CRT = cardiac resynchronization therapy
EAM = electroanatomic map
MPP = multipoint pacing (i.e., multiple points on a quadripolar lead)
PNS = phrenic nerve stimulation
QLV = Q-wave (on electrocardiogram) to left ventricular depolarization (on intracardiac electrogram)
VTI = velocity time integral
VV = interventricular

more easily be reached during and even after implantation. Suboptimal sites can be avoided, such as areas with fibrosis due to myocardial infarction or areas with PNS (Central Illustration). These properties come without compromising lead stability, as the tip can be wedged in a distal part of the vein while other electrodes are placed near the optimal pacing site. Moreover, quadripolar LV leads have the ability of multipoint pacing (MPP), pacing the LV with 2 of 4 available electrodes. Quadripolar leads therefore reinforce the discussion about optimal pacing sites, multisite pacing, and timing optimization, because a single quadripolar lead can offer multiple pacing options. This paper reviews background information, recent developments, and future implications about optimizing CRT with a quadripolar lead.

Based on a systematic search in BioMed Central, Cochrane Library, and PubMed, all relevant papers in English about CRT and quadripolar leads published between December 2000 and May 2015 were selected. Further studies were sought through a manual search of secondary sources, including references from primary papers. All studies and trials on multipolar and quadripolar leads regarding acute, short-term, and long-term results were regarded as relevant. Furthermore, technical specifications of current quadripolar leads and delivery systems were sought on manufacturers’ web sites or by communication with their representatives.

DESIGN OF QUADRIPOLAR LEADS

Several quadripolar leads have been developed with various shapes (Figure 1) and electrode spacing (Figure 2). Boston Scientific (St. Paul, Minnesota) offers 3 different leads with different curvature and different electrode spacing. Biotronik (Berlin, Germany) and Medtronic Inc. (Minneapolis, Minnesota) offer leads with different curvatures but similar electrode spacing. St. Jude Medical (St. Paul, Minnesota) has 1 option available. Straight leads are designed for smaller distal veins, whereas curved leads are meant to be fixed in larger veins. Positioned in a target vessel, practical electrode spacing of these leads may be smaller. Total and effective interelectrode distance can be of importance. Although never documented, the total electrode spacing may overextend the target vessel, resulting in proximal electrodes positioned in the coronary sinus or great cardiac vein instead of 1 of the tributary veins. Moreover, a pre-shaped lead design may improve positioning of proximal electrodes (Figure 1). Pre-shaped leads therefore improve functionality, as an unstable position in the larger cardiac veins could increase the distance to the myocardium, resulting in high pacing thresholds. Moreover, a pre-shaped lead design may improve positioning of proximal electrodes, which is offered by all manufacturers (Figure 1). A short (interelectrode) distance diminishes the benefit of extra electrodes, as electrodes could still cause PNS or be placed on scar tissue. However, the position of the second and third electrode of the Attain Performa leads of Medtronic (1.3 mm apart) were chosen because of lower PNS thresholds at small interelectrode distances (6). Although there are 4 pacing sites, electromechanically only 3 separate spots can be stimulated with this lead. Moreover, in case of high pacing thresholds of the proximal electrode (e.g., due to vessel diameter), only 2 functionally different bipolar vectors can be used. Two leads of Boston Scientific have the same limitation, as 3 proximal electrodes are positioned close together. Due to the spiral shape, at least 1 electrode should be placed close to the myocardium, whereas others may become unusable.

The manufacturers also differ in the location of corticosteroid on quadripolar leads. The leads of Medtronic have steroid reservoirs near all 4 electrodes. Both Biotronik leads have a corticosteroid coating on the entire lead with a steroid reservoir at the tip. Boston Scientific and St. Jude Medical supply leads with steroid reservoirs at the tip of the lead. Besides small and clinically irrelevant differences found in a small animal study (7), the effect of steroids on the long-term performance of transvenous LV leads is unknown. Steroids are especially beneficial for the long-term impedance of screw-in leads.

All leads should fit through a 7-F introducer; however, not all leads are compatible with a 5-F inner guide, as most are wider (maximal width: Biotronik: 4.8-F, St. Jude Medical: 5.1-F, Medtronic: 5.3-F, and Boston Scientific: 5.2-F). Although leads are coated and therefore compatible with the inner guide for smooth introduction, the electrodes are not coated and may cause friction.

As all manufacturers have IS-4 compatible devices, all combinations of quadripolar leads and dedicated devices can be used. However, 2 cases have shown that problems may arise when using quadripolar leads and CRT defibrillator devices of different manufacturers, resulting in unacceptable high impedance levels at the 3 proximal quadripolar electrodes (8). The high impedance is probably a result of misalignment of these electrodes within the spring...
A quadripolar lead is wedged in a distal cardiac vein. The distal electrode (1) is positioned close to an area of myocardial infarction and an area of phrenic nerve stimulation, whereas 2, 3, and 4 are positioned near the optimal pacing site. The latter is possibly defined by electroanatomical mapping or speckle tracking echocardiography. IVC = inferior vena cava; LV = left ventricle; PNS = phrenic nerve stimulation; RV = right ventricle.

Photographic overview of current quadripolar leads, with respect to curvature. Boston Scientific: (A) Acuity X4 Spiral L, (B) Spiral S, and (C) Straight; Medtronic: Attain Performa (D) 4298, (E) S 4598, and (F) S 4398; St. Jude Medical: (G) Quartet; Biotronik: (H) Sentus, (I) Sentus (straight).
contacts in the connector block of the device (8). This issue needs to be resolved so that operators can select the preferred (quadripolar) lead for the target vessel and optimal pacing location, independent of the chosen device.

**IMPLANTATION AND LONG-TERM USE**

Implantation and long-term use of quadripolar leads seems safe (9). Quadripolar leads have a lower complication rate compared with conventional bipolar leads (Table 1) (9,10). Even in cases of minor dislocation, alternative pacing vectors may be selected, circumventing the need for a secondary invasive procedure and thereby reducing complications (11). Although Behar et al. (9) even found a lower all-cause mortality rate in patients with quadripolar leads compared with bipolar leads, their results are on the basis of a registry: a comparison of non-randomized cohorts. Selection bias could have driven results, as baseline characteristics show that the percentage of patients with ischemic cardiomyopathy and patients not in sinus rhythm were higher in the group with bipolar leads. Both are associated with a reduced response to CRT (12,13). Moreover, simple baseline and follow-up characteristics, such as ejection fraction, end-systolic volumes, New York Heart Association functional class, and QRS width and morphology, are unknown. Comparison of both groups is, therefore, difficult. Nevertheless, the results are interesting (Table 1), as a reduced mortality rate is compelling for full implementation in clinical practice. Unfortunately, most studies focus solely on the quadripolar leads, without comparison to bipolar leads. Moreover, most used the quadripolar lead of either St. Jude Medical or Medtronic, whereas performance of other leads has received little attention (9–11,14–16). Results of the MORE-CRT (MORE RESPONSE on Cardiac Resynchronization Therapy With MultiPoint Pacing) trial (17), a randomized comparison of quadripolar versus bipolar leads on performance and outcome, are therefore warranted.

**OPTIMIZING LEAD PLACEMENT**

The benefit of quadripolar leads lies in the additional pacing options. More pacing options facilitate placement in a stable position, while avoiding areas with fibrosis or PNS (Central Illustration). Several studies have demonstrated the benefit of finding the optimal site for LV lead positioning, in terms of acute hemodynamic benefit, echocardiographic reverse remodeling, and long-term clinical outcome (Table 2) (3,18–20).

**AVOIDING PNS**

As the left phrenic nerve is located close to the posterolateral side of the pericardium, PNS in the conventionally targeted midposterior and lateral positions is a common finding (21). PNS due to LV pacing is seen in 13% to 33% of patients during CRT implantation with bipolar LV leads, with 10% requiring lead revision (22,23). Although programming of the pacing stimulus may overcome PNS, lead placement can be restricted (22). Phrenic nerve involvement can also occur after implantation, due to lead dislodgement or intrathoracic displacement of the heart due to patient positioning (22). Hypothetically, PNS may occur due to a changed anatomic position of the heart after reverse remodeling. As summarized in Table 1, the percentage of PNS requiring lead revision is between 0.0% to 0.3% among quadripolar leads. A large, multicenter, prospective study showed a lower prevalence of PNS requiring lead revision among quadripolar leads compared with bipolar leads (11). A lower amount of lead revisions means even fewer possible complications due to a second intervention, which is an important clinical benefit.
Patients with ischemic cardiomyopathy are more frequent nonresponders to CRT (22). Both scar tissue near the LV lead and total scar burden influence the response to CRT (12). Pacing in a region of scar tissue can even deteriorate LV function, as proven by acute hemodynamic experiments and by long-term follow-up (24,25). Pacing in scarred regions results in slow or even absent electrical wave front propagation and reduces the effect of biventricular pacing. Avoiding lead placement in scarred regions is, therefore, an important determinant of response that is directly related to the implantation procedure (26). The quadripolar lead can aid in this process; whenever a successful lead position is limited by venous anatomy and results in the tip placed near scar tissue, the additional electrodes may offer important alternatives. Forleo et al. (27) found no differences in long-term volumetric and clinical response between ischemic and nonischemic patients with quadripolar leads. Their results could indicate that the increase of pacing options benefits response rate in ischemic patients. There was even a trend toward a higher decrease of end-systolic volume in nonischemic patients. Larger trials are needed to prove these results.

**IMAGING-GUIDED LEAD PLACEMENT**

Two recent trials (i.e., TARGET [Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy] and STARTER [Speckle Tracking Assisted Resynchronization Therapy for Electrode Region]) proved the benefit of LV lead positioning of a bipolar lead while knowing the latest contracting segment (on the basis of peak radial strain derived by speckle tracking echocardiography) (3,18). Both studies found an increased benefit of the echocardiographic strategy on survival and echocardiographic response. Even in the control group, a large proportion of leads were placed concordant or adjacent. When lead positioning in both groups was compared to response, optimal placement was strongly associated with survival and response. Nevertheless, reaching the pre-defined target with bipolar leads can be difficult, as these trials showed that 10% to 15% of leads were placed remote from the intended area. Moreover, 7% to 23% of leads were placed apically, which was not part of the echocardiographic protocol. Quadripolar leads could facilitate imaging-guided lead placement, increasing the chance to reach the intended target.
TABLE 2  Studies on Comparison of Response to CRT With a Quadripolar LV Lead (Alternative Vector or Multipoint Pacing) to Conventional Biventricular Pacing

<table>
<thead>
<tr>
<th>First Author (Ref. #)</th>
<th>Design</th>
<th>N</th>
<th>Pacing Configuration</th>
<th>Parameter(s)</th>
<th>Main Result</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones et al. (37)</td>
<td>Intraoperative</td>
<td>22</td>
<td>BiQ</td>
<td>Bioreactance measurement: CI</td>
<td>Large variations between BiQ electrodes within veins</td>
<td>Fixed AV delay</td>
</tr>
<tr>
<td>Asbach et al. (38)</td>
<td>Intraoperative</td>
<td>16</td>
<td>BiQ vs. CONV</td>
<td>dP/dt_{max}</td>
<td>BiQ improves AHR: 31.3% vs. 28.2%; p &lt; 0.001</td>
<td>1 optimized AV delay per patient</td>
</tr>
<tr>
<td>Thibault et al. (40)</td>
<td>Intraoperative</td>
<td>19</td>
<td>MPP vs. CONV</td>
<td>dP/dt_{max}</td>
<td>MPP with proximal and distal electrode: greatest benefit</td>
<td>1 optimized AV delay per patient</td>
</tr>
<tr>
<td>Pappone et al. (42)</td>
<td>Intraoperative</td>
<td>42</td>
<td>MPP vs. BiQ</td>
<td>SW (pressure-volume loops) and dP/dt_{max}</td>
<td>MPP improves AHR: SW: 27.2% vs. 19.4%; p &lt; 0.018 dP/dt: 15.9% vs. 13.5%; p &lt; 0.001</td>
<td>2 BiQ vs. 7 MPP settings, Fixed AV delay</td>
</tr>
<tr>
<td>Osca et al. (36)</td>
<td>Post-implantation</td>
<td>27</td>
<td>BiQ vs. CONV</td>
<td>Transthoracic impedance electrocardiography: CI, CO, and SV</td>
<td>No significant difference BiQ and CONV</td>
<td>Optimized AV and VV delay for each setting</td>
</tr>
<tr>
<td>Cabrera Bueno et al. (59)</td>
<td>Post-implantation</td>
<td>51</td>
<td>BiQ vs. CONV</td>
<td>Echo: CO</td>
<td>BiQ improves CO: 4.33 vs. 4.16 L/min; p = 0.058</td>
<td>10 patients best CO with BiQ vector, Optimized AV delay for each setting</td>
</tr>
<tr>
<td>Thibault et al. (40)</td>
<td>Post-implantation</td>
<td>40</td>
<td>MPP vs. CONV</td>
<td>Echo, STE: peak radial strain CW-Doppler: VTI of LVOT</td>
<td>MPP increases peak strain and VTI Strain: 18.3% vs. 9.3%; p &lt; 0.001 VTI: 13.5 cm vs. 10.9 cm; p &lt; 0.01</td>
<td>VTI: 13 patients Fixed AV delay</td>
</tr>
<tr>
<td>Rinaldi et al. (46)</td>
<td>Post-implantation</td>
<td>41</td>
<td>MPP vs. CONV</td>
<td>Echo, TDI: Ts-SD</td>
<td>MPP decreases Ts-SD: 33.3 ± 36.4 ms vs. 50.2 ± 29.1 ms; p &lt; 0.001</td>
<td>Fixed AV delay</td>
</tr>
<tr>
<td>Rinaldi et al. (46)</td>
<td>Post-implantation</td>
<td>41</td>
<td>MPP vs. CONV</td>
<td>ECG: QRS duration Echo: VTI, MPI, MR, EF, ESV, EDV, and NYHA functional class at 6-month follow-up</td>
<td>BiQ higher VTI, MPI, less MR, and shorter QRS-duration compared with CONV. No effect on long-term outcome</td>
<td>7 BiQ vs. 3 CONV setting, fixed AV delay</td>
</tr>
<tr>
<td>Calo et al. (35)</td>
<td>Post-implantation and long-term outcome</td>
<td>22</td>
<td>BiQ vs. CONV</td>
<td>ECG: QRS duration Echo: VTI, MPI, MR, EF, ESV, EDV, and NYHA functional class at 3-month follow-up</td>
<td>MPP improves response: ΔESV: −21.0 vs. −12.6; p = 0.03; ΔEF: +9.8% vs. −2.0%; p &lt; 0.001; ΔNYHA: −1.05 vs. −0.72; p = 0.006</td>
<td>Optimal MPP configuration determined by SW CONV: distal or proximal electrode</td>
</tr>
<tr>
<td>Pappone et al. (47)</td>
<td>Short-term outcome</td>
<td>43</td>
<td>MPP vs. CONV</td>
<td>Echo, EF, ESV, EDV, and NYHA functional class at 6-month follow-up</td>
<td>MPP improves response: ΔESV: −21.0 vs. −12.6; p = 0.03; ΔEF: +9.8% vs. −2.0%; p &lt; 0.001; ΔNYHA: −1.05 vs. −0.72; p = 0.006</td>
<td>Optimal MPP configuration determined by SW CONV: distal or proximal electrode</td>
</tr>
</tbody>
</table>

AHR = acute hemodynamic response; BiQ = biventricular pacing with a quadripolar lead; CI = cardiac index; CO = cardiac output; CONV = conventional biventricular pacing with a quadripolar lead; CW = continuous wave; dP/dt_{max} = maximal rate of left ventricular pressure rise; ECG = electrocardiogram; Echo = echocardiogram; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; LVOT = left ventricular outflow tract; MPI = myocardial performance index; MPP = multipoint pacing; MR = mitral regurgitation; NYHA = New York Heart Association; STE = speckle tracking echocardiography; SW = stroke volume; TDI = tissue Doppler imaging; Ts-SD = standard deviation of time to peak contraction; VTI = velocity time integral.

ELECTROANATOMICAL-GUIDED PLACEMENT

Delayed activated segments can also be found by determining the delay in electrical depolarization. The Q-wave to left ventricular depolarization (QLV) interval is used for this purpose, by determining the recorded timing of onset of the QRS complex ("Q") on the electrocardiogram and the local depolarization at the LV lead electrode ("LV"). As an interindividual parameter, QLV is related to acute response, reverse remodeling, and long-term outcome (28-30). Long QLV intervals (>95 ms) were associated with an increase in reverse remodeling and quality of life (28). Longer QLV intervals also result in higher maximal rate of left ventricular pressure rise (dP/dt_{max}), with a 10-ms increase in QLV leading to a 1.7% to 2.0% increase in dP/dt_{max} (29,31). Zanon et al. (30) confirmed the strong positive correlation of QLV and dP/dt_{max} within individual patients. QLV could therefore be used in combination with quadripolar leads, as the electrode with the highest QLV can be selected for biventricular pacing. Although the difference in QLV within a single vein can be relatively small, the differences in dP/dt_{max} are significant (32). Figure 3 illustrates QLV within a vein for 2 separate patients using 2 different quadripolar leads.

Latest activated regions can also be mapped using electroanatomic mapping (EAM) systems. Existing EAM systems have been used to find the latest activated regions, using dedicated catheters within the coronary sinus and its side branches (Figure 4) (33). Areas with PNS can also be detected and therefore avoided during lead placement. The (acute) hemodynamic and clinical benefit of this method is unknown, but would be promising on the basis of the results of studies on QLV and acute hemodynamic...
response (30). Figure 4 is an excellent example of the benefits of quadripolar leads in combination with EAM, as the lead is wedged apically while the proximal electrode is positioned in the area with latest depolarization. However, accessibility by a thin guidewire used for EAM does not guarantee successful lead placement.

Whether QLV or a similar parameter is the ideal tool for (quadripolar) lead positioning can be discussed. For a homogenous activation of the LV, the (very) last activated region is hypothetically suboptimal. Pacing the latest activated region will require more time to depolarize the entire LV. Nevertheless, pacing in a “late” activated region is beneficial to acute and long-term response, as proven by QLV (28,30). Moreover, CRT depends on biventricular pacing, with fusion between right ventricular (RV) and LV pacing. Mafi Rad et al. (34) have shown that the order of activated regions due to RV pacing can differ from intrinsic activation. Therefore, the delay between RV pacing and LV capture may be more important than QLV.

**OPTIMIZING PACING CONFIGURATION OF A QUADRIPOlar LEAD**

Several studies have assessed the effects of optimizing pacing configurations of a quadripolar lead (Table 2). Most studies focus on parameters for acute hemodynamic response, whereas only 1 reports results on short- or long-term response.

Calo et al. (35) compared echocardiographic findings (e.g., velocity time integral [VTI] of the LV outflow tract) and QRS duration, and found significant improvements of all parameters with optimized biventricular pacing using a quadripolar lead (BiQ).
compared with conventional biventricular pacing using distal pacing vectors (CONV). Conventional vectors were distal pacing vectors of the quadripolar lead, using a combination of electrode D1, M2, or the RV coil, thus mimicking a standard bipolar lead. Two studies used noninvasive measurement of cardiac index to evaluate CRT with a quadripolar lead and found a widespread response to tested pacing settings, but no significant differences between BiQ and CONV pacing (36,37).

Studies on invasively measured hemodynamic response of CRT with quadripolar leads report apparent differences between pacing vectors. Asbach et al. (38) found a significant increase of dP/dt\textsubscript{max} in 12 of 16 patients with BiQ versus CONV. Shetty et al. (39) used quadripolar leads to test differences in dP/dt\textsubscript{max} within a coronary vein and between veins. For individual patients, acute hemodynamic response (AHR) within a vein varied between pacing electrodes. When patient data was combined, the overall difference between vectors was nonsignificant.

Only 1 small study reported short-term response of biventricular pacing using CRT with a quadripolar lead. Calo et al. (35) optimized quadripolar pacing configurations using echocardiography in 22 patients. They found no differences in New York Heart Association functional class or reverse remodeling (>15% decrease in LV end-systolic volume) after
6 months between 11 patients with optimized BiQ pacing and 11 patients with optimized CONV pacing.

**OPTIMIZING MPP**

Currently, 1 manufacturer has a CRT defibrillator device with MPP capability (Unify Quadra MP, St. Jude Medical). MPP is programmable as “simultaneously” (minimal delay of 5 ms) or with programmable inter left ventricular electrode delays. Compared with implanting multiple LV leads, implanting a single quadripolar lead will not increase procedure duration and fluoroscopy time.

Several smaller studies recently published favorable results on the hemodynamic, electrical, and mechanical response of MPP (Table 2) (40–43). Rinaldi et al. (41) used echocardiographic-derived VTI of continuous wave Doppler of the LV outflow tract. VTI has a low signal-to-noise ratio and requires numerous iterations to make reliable estimations of LV function (44). Also, a short and nonphysiological atrioventricular (AV) delay (25 ms) was used, and some settings with long inter left ventricular electrode delays were compared (up to 80 ms). This may have led to pacing in already depolarized myocardium, as the maximal spacing between 2 electrodes (47 mm) combined with the conduction velocity (0.84 m/s) of patients with dilated cardiomyopathy would lead to a theoretical maximum delay of 56 ms (45). However, myocardial fibrosis in between electrode positions may result in longer delays. Besides VTI, Rinaldi et al. (41) compared peak radial strain derived by speckle tracking echocardiography and found higher values for MPP compared with CONV pacing (18.3 ± 7.4% vs. 9.3 ± 5.3%; p < 0.001). The same group published results of reduced dyssynchrony assessed with tissue Doppler imaging with MPP compared with conventional biventricular pacing (46). However, 8 nonrandomized MPP settings were compared to only 1 conventional setting in both studies. Thereby, the chance of defining outlying results of MPP as an optimum increased.

MPP has been compared with conventional pacing with a quadripolar lead. However, in most cases MPP was compared to only 1 or 2 unifocal pacing vectors (40,42). Pappone et al. (42) compared pressure-volume loops obtained with MPP to CONV pacing and found significant increase with MPP. However, they compared a large number of MPP configurations (7) to a limited amount of conventional configurations (2). Thibault et al. (40) reported heterogeneous effects of MPP, ranging from detrimental to beneficial, compared to conventional CRT. Zanon et al. (43) used quadripolar LV leads and found a slight but significant increase in dP/dt_max with MPP, compared to unifocal proximal and distal pacing. Although they repeated measurements, there was no comparison to baseline and physiological variation over time could therefore have influenced results.

Only one follow-up study focused on the effects of MPP on echocardiographic response. Pappone et al. randomized 41 patients to conventional biventricular pacing or MPP (47). The group receiving MPP had a higher percentage of echocardiographic responders after 3 months (76% vs. 50%). Ejection fraction improved and end-systolic volume was reduced compared with the conventional pacing group (Table 2). The authors suggested that the favorable response could be attributed to the patients with ischemic cardiomyopathy, as MPP may have led to more homogenous electrical depolarization in ventricles with fibrotic tissue in these patients.

**REMARKS ON REPORTED RESULTS**

As can be appreciated from Table 2, only a few studies directly compared BiQ to CONV. The added benefit of quadripolar leads to standard bipolar leads on AHR needs further study. Recent studies do show that AHR varies significantly between pacing vectors of a quadripolar lead, implying a patient-specific approach to vector selection (37,38). A quadripolar lead can therefore be beneficial, if stimulation at the additional electrodes is at least feasible. Both pacing and PNS thresholds are as important as the benefit in AHR. Reports on available pacing vectors are variable. Asbach et al. (38) reported an average of 9 of 10 possible vectors, tested in 16 patients. Unfortunately, they did not report specific cut-offs. Surprisingly, Sperzel et al. (14) found that only 20% of patients had at least 9 possible pacing vectors without PNS and with good pacing threshold. A total of 89% of patients had at least 3 (of 10) possible vectors compared with 53% with 3 or more conventional vectors, with a cutoff for pacing threshold ≥2.5 V and PNS ≥7.5 V.

Anodal capture is a confounder in results on pacing with quadripolar leads. Stimulation on an electrode pair (i.e., cathode and anode) is meant to depolarize myocardium at the cathodal electrode. However, with substantial output, the anodal site could also be depolarized. Trolese et al. (48) reported changes in QRS width and morphology using pacing vectors with a similar cathode and different anodes of the quadripolar lead. The changes could be ascribed to anodal capture (49). If anodal electrodes have low thresholds, intended bipolar stimulation could lead to dual site stimulation. This affects QRS width as well as
AHR and makes comparison between vectors problematic. Comparison of vectors with the RV coil as anode could be a solution.

The absence of AV and interventricular (VV) delay optimization is an important limitation of results on AHR. As AV and VV delay optimization significantly influence AHR, published studies on hemodynamic assessment without optimization are difficult to interpret (50). As can be appreciated from Table 2, a large proportion of studies use a fixed AV and/or VV delay. The increase of the hemodynamic improvement of the optimal pacing vector may be underestimated because a longer VV delay (with LV pre-activation) will be beneficial during LV pacing with the more basal electrodes of the quadripolar lead. Using different electrodes of a quadripolar lead or even MPP with a quadripolar lead would require intensive study protocols, with multiple AV and/or VV delays for each vector. Protocols become even more time consuming when the comparison of a larger range of configurations requires iterations or curve fitting to reduce the risk of bias (44).

Most studies on quadripolar leads primarily focus on MPP, neglecting optimal single-site LV pacing. Animal experiments show that AHR of an optimal single pacing position could only be matched by adding a total of 6 pacing sites to a suboptimal pacing position (51). So, 1 optimally placed (quadripolar) lead is better than adding a pacing site. If the ideal pacing site is reached, which is even more likely with quadripolar leads, thoracoscopic epicardial placement, or the emerging endocardial approach, an extra pacing site may be obsolete. Shetty et al. (52) confirmed this hypothesis, as they found a significant increase of AHR while pacing a single endocardial site compared with MPP. Perhaps only a subset of patients would be eligible to respond to MPP. Unfortunately, none of the currently published studies were designed to identify markers for response to MPP. MPP is thought to depolarize the myocardium with a more homogenous electrical wave front, and could be beneficial in ventricles with heterogeneous conduction delays, for example due to fibrosis. This was confirmed in a group of CRT patients with posterolateral scar (53). Another small study showed that 2 of (only) 3 patients converted to responders with MPP, compared with conventional CRT (54). Patient selection for MPP could be of interest, as MPP can also have detrimental effects on LV function (40). Whether patients with heterogeneous conduction delays and/or previous myocardial infarction or simply nonresponders are eligible for MPP is of interest.

The benefit of MPP depends on the location of the extra pacing site. The ideal location for an extra stimulus for MPP is unknown. Ploux et al. (51) showed that pacing the latest activated site (during pacing with the previous implanted leads) is of incremental hemodynamic benefit. Implanting an additional lead at the latest electrical activated region during conventional biventricular pacing would be an interesting method for future patient trials. This concept is not feasible for quadripolar leads, as the electrode spacing and location is limited to 1 vein. Shetty et al. (52) found no significant differences in AHR between MPP (with quadripolar leads) or multisite pacing (with multiple LV leads), although their sample size was small (n = 15). As shown by Figure 3 and by Mafi Rad et al. (34), the electrical delays along the optimal vein can be quite similar. Stimulating 2 spots with relatively comparable electrical delays is probably not beneficial. It is therefore interesting to define the relation between the electrical delays between quadripolar electrodes and the benefit to MPP. Pappone et al. (42) found that the electrode pair with the largest anatomical spacing was optimal in 71% of patients, compared with the pair with the largest interelectrode delay. An expected overlap between both strategies was not reported. Nevertheless, it is an interesting result, as anatomical spacing merely resembles position, whereas the electrical delay is a functional parameter.

**ONGOING STUDIES**

Two ongoing studies on MPP are the MultiPoint Pacing IDE study and the MORE-CRT trial (17,55). The first trial is designed to include 506 patients with a CRT indication (55), comparing the effects on response and complications of CRT with a quadripolar lead to CRT with a standard bipolar lead. The MORE-CRT trial is even larger, enrolling 1,250 patients (17). This multicenter study will investigate the clinical effects of CRT with a quadripolar lead compared with a bipolar lead. The effect of MPP on nonresponders at 6-month follow-up will also be investigated.

**FUTURE DIRECTIONS**

Multipolar leads are currently restricted to 4 electrodes, possibly due to limitations in maximal lead diameter and device header size. Future developments could overcome these restrictions and open the door for hexapolar or even octapolar leads. Additional electrodes increase the number of pacing options and will only increase the success rate of CRT
implantation. Several short distanced dipoles for example (like the 2 middle electrodes in Medtronic quadripolar leads), could reduce the chance of PNS. Optimization however, becomes even more time consuming without a proper surrogate parameter (beside QLV). Whether multisite pacing on more than 2 sites could be beneficial for a selection of patients is controversial. First, the benefit of 1 extra pacing site should be investigated thoroughly. The extra pacing sites can also be positioned in the coronary sinus for left atrial sensing (56). Left atrial sensing could cause the right atrial electrode to become obsolete in patients without atrial arrhythmia.

Lead positioning strategies could be optimized by incorporating results of imaging and electroanatomic modalities. If scar tissue, delayed activation (either mechanical or electrical), PNS, and pacing thresholds are incorporated in the venogram during implantation, an implanting physician could choose the optimal position and lead for the patient’s specific anatomy (33,57). The quadripolar lead with a specific shape and distance between electrodes could then be selected to achieve an optimal mid or basal position with more proximal electrodes, whereas distal electrodes are wedged near the apex. A heterogeneous choice of leads, as currently available, is therefore practical. Figure 4 displays a possible strategy using EAM to guide the operator in choosing a lead with electrodes placed in the area with maximal electrical delay.

Optimization of CRT configuration is complicated by the additional electrodes and pacing options (e.g., MPP) of a quadripolar lead. Automated optimization algorithms based on electrical delays could incorporate the electrode with longest QLV and acceptable pacing threshold without PNS for optimal quadripolar pacing configuration. However, the benefit of AV and VV delay optimization is debatable, as a meta-analysis of several optimization techniques found no apparent benefit (58).

**CONCLUSIONS**

The benefit of quadripolar leads over conventional bipolar leads has been underlined by recent trials. Quadripolar LV leads have lower complication rates and more pacing options, thereby reducing the frequency of PNS, circumventing fibrosis, and facilitating reaching a pre-defined optimal position. Leads are available in various models and different electrode spacing, with an expected heterogeneity in use. On the basis of acute hemodynamic studies and a small randomized trial, quadripolar leads can improve acute and short-term response to CRT. Currently, 1 manufacturer offers MPP, a pacing modality that can have benefit in certain cases. Its application is unclear due to methodological shortcomings and contradictory results of recent studies, besides the unknown ideal substrate for MPP. Results of ongoing and future comparative studies on quadripolar leads regarding both acute hemodynamic response and long-term outcome are warranted.

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