

MULTIPOINT™ PACING WITH THE SJM™ QUADRA CRT SYSTEM

The first-to-market Quartet™ left ventricular (LV) lead from St. Jude Medical, is uniquely designed with four electrodes. The Quartet LV lead is capable of delivering two pulses per pacing cycle with MultiPoint™ Pacing, providing more options to allow them to capture more cardiac tissue and tailor therapy to each patient's need. The goal of MultiPoint Pacing is to provide potential benefits to patients not responding to traditional bi-ventricular (BiV) therapy or incremental benefits in patients responding to traditional BiV therapy. MultiPoint Pacing has demonstrated safety and efficacy and is approved by the FDA. Additional supporting data from international clinical experience demonstrate that MultiPoint Pacing can improve cardiac function, hemodynamics and reverse remodeling.

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Clinical Advancements in CRT: Key Highlights

The following clinical highlights were enabled by revolutionary technology introduced by St. Jude Medical.

Quadripolar Pacing

Quadra Assura™ CRT-D has demonstrated improvement in cost, quality and outcomes when compared to bipolar CRT

- 18% relative reduction in mortality¹
- 53% reduction in risk of hospitalization²
- 87% reduction in hospital costs³

Quartet™ LV Leads demonstrated improved procedural and clinical success as compared to bipolar leads

- 28% faster implant times with 55% lower fluoroscopic exposure^{4,5}
- 100% of phrenic nerve stimulation was resolved at implant or post-operatively without a surgical revision or lead manipulation^{6,7}
- 100% of patients demonstrated improved cardiac synchrony at 12-months⁸

The Burden of Non-Response

Despite these advancements, individual patient response to CRT is unpredictable and too often inadequate.⁹ Historical CRT studies have measured patient response using various methods and the published non-response rates often exceed 30% and 40%.¹⁰ The patients who do not respond adequately often require additional hospital readmissions that can be costly. In a retrospective analysis of CRT-D patients classified as responders and non-responders:¹¹

- 135 patients were followed for 17 ± 9 months.
- 103 (76%) were CRT responders and 32 (24%) were CRT non-responders.
- The relative risk of HF hospitalization was 55% lower in the CRT responder group.
- Annual costs for management of HF hospitalizations were \$7,205 and \$13,861/patient-year in the CRT responder and CRT non-responder groups respectively.
- Annual costs for management of HF hospitalizations were 48% lower (\$6,656) for CRT responders compared to the non-responder group (p = 0.035).

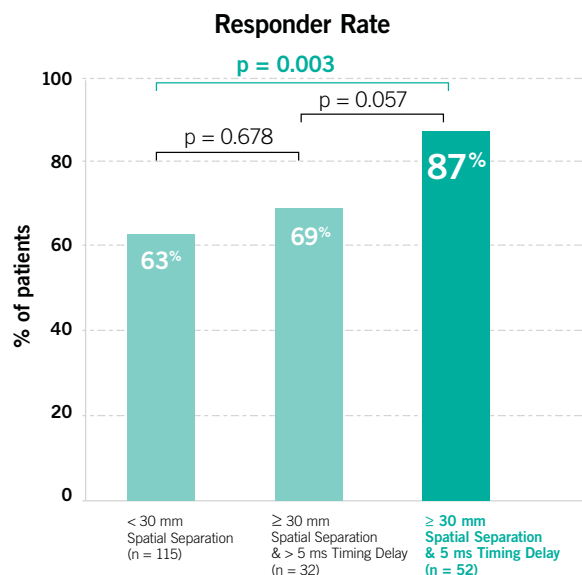
MultiPoint™ Pacing

MultiPoint Pacing has been deemed safe and effective by the FDA.

- Safety endpoint: 93.2% freedom from system-related complications.¹²
- Efficacy endpoint: MultiPoint Pacing was demonstrated to be non-inferior to quadripolar BiV with respect to non-responder rate.¹²

In addition to these primary endpoints, the MultiPoint Pacing IDE Study also demonstrated that wider cathode spacing and near-simultaneous intraventricular timing delays are best. When MPP™ technology was programmed with cathode spacing ≥ 30 mm and 5 ms LV delay:

- CRT response was greatest at 87% and the super-responder rate was greatest at 54% (n = 52)¹²
- Non-responders were converted to responders (8 of 8 patients)¹²



Clinical Advancements in CRT: Key Highlights

The following clinical highlights were enabled by revolutionary technology introduced by St. Jude Medical.

A Growing Body of Clinical Evidence

MultiPoint™ Pacing enables more tissue capture for better intraventricular conduction. Several studies have demonstrated the potential to improve patient response to CRT with MultiPoint Pacing as compared to single-site pacing.

Findings from International Studies

Zanon et al. compared 20 patients optimized with MultiPoint Pacing to 36 patients optimized with traditional BiV pacing and 54 non-optimized BiV patients.¹³ The results indicate a clear progression in response from non-optimized BiV to optimized BiV to optimized with MultiPoint Pacing at 12 months:

- 90% response rate with MultiPoint Pacing measured by ESV decrease > 15%.
- 95% response rate with MultiPoint Pacing measured by ≥ 1 decrease in NYHA class.
- 90% response rate with MultiPoint Pacing measured by Packer's score.

Figure 1

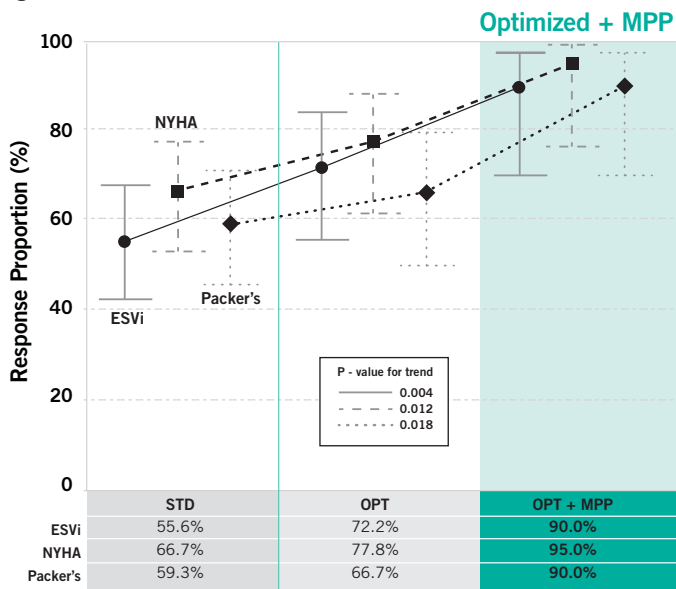
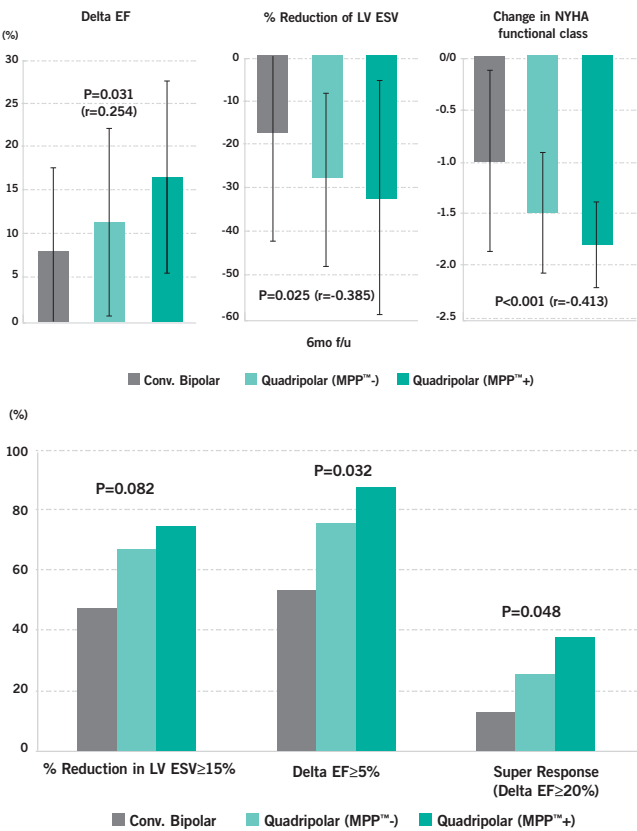


Figure: ΔESVi, ΔNYHA, and PACKER'S response rates. Response indicates ΔESVi ≥ 15%, ΔNYHA Class > 0, or PACKER'S score = 0 at follow-up relative to baseline. The vertical segments represent the 95% CI of the estimated proportions.

- Electrical Benefit:** MultiPoint Pacing was able to recruit a greater portion of the LV than traditional BiV pacing, resulting in reduced activation times and QRS duration.¹⁴
- Mechanical Benefit:** MultiPoint Pacing reduced mechanical dyssynchrony by more than 20% as measured with tissue Doppler imaging in 63% of 41 patients tested.¹⁵
- Hemodynamic Benefit:** MultiPoint Pacing improved acute LV contractility assessed with pressure wire in 84% of patients compared to Bi-V pacing.¹⁶
- Multiple studies have shown improvement in QRS duration, EF and ESV at six months.¹⁷⁻¹⁹



Summary of MultiPoint™ Pacing Clinical Studies

Improved CRT Response: Results of Long-Term Follow-Up

The Quartet™ left ventricular (LV) lead with MultiPoint™ Pacing (MPP™) provides more pacing options and has the ability to deliver two LV pacing pulses simultaneously in order to recruit more myocardium. The following studies provide support that MultiPoint Pacing safely delivers two separate LV pacing pulses and improves cardiac function and hemodynamics.

Safety and Efficacy of MultiPoint Pacing in Cardiac Resynchronization Therapy: The MultiPoint Pacing (MPP) IDE Study

Tomassoni G, et al. *Heart Rhythm*, 2016.¹²

- The MPP IDE Trial was a prospective, multi-center, randomized, double-blinded clinical trial in which 506 patients were enrolled in 49 centers. All devices implanted in the trial were St. Jude Medical™ Quadripolar CRT-D systems using 1458Q Quartet™ LV Leads. The objective of the study was to assess the safety and efficacy of the MPP feature in heart failure (HF) patients indicated for a CRT-D device in order to receive FDA approval.
- Patients' responder status was assessed at three and nine months using the Clinical Composite Score (CCS), which includes: NYHA class, Patient Global Assessment (PGA), HF events, and cardiovascular death. At the three month mark, both responders and non-responders were randomized (1:1) to either continue to receive BiV (single-site) therapy or to receive MPP therapy. The study endpoints were then evaluated at the nine month follow-up visit.
- The primary safety endpoint was freedom from system-related complications > 75% at nine months. The safety endpoint was met, with a result of 93.2% freedom from system-related complications.
- The primary efficacy endpoint was non-inferiority of the proportion of non-responders in the MPP arm compared with the Bi-V arm between three and nine months. The efficacy endpoint was met, with a result that MPP technology was demonstrated to be non-inferior to quadripolar BiV with respect to non-responder rate ($p = 0.0131$).
- In addition to the primary endpoints, sub-analysis of the MPP IDE study also provided important insights for the programming of MPP technology. The study demonstrated that wider cathode spacing and near-simultaneous intraventricular timing delays achieved the best response rate compared to other programmed settings. When MPP technology was programmed with cathode spacing > 30 mm (D1 to M3 or D1 to P4) and 5 ms LV delay, CRT response was greatest at 87% ($n = 52$) and non-responders were converted to responders (8 of 8 patients).

Key Takeaways:

- Based on meeting the primary endpoints, safety and efficacy, of the IDE study and the overall body of clinical evidence, FDA approved MultiPoint Pacing in two new devices: Quadra Assura MP™ CRT-D and Quadra Allure MP™ RF CRT-P.
- When MPP™ technology was programmed with cathode spacing ≥ 30 mm and 5 ms LV delay ($n = 52$), the CRT response was greatest at 87% (Figure 1) including a super-responder* rate of 54% and non-responders were converted to responders.

Acute Optimization of Left Ventricular Pacing Site Plus MultiPoint Pacing Improve Remodeling and Clinical Response of CRT at One Year Follow Up

Zanon, F. et al. *American College of Cardiology*, 2016.¹³

- This study evaluated the long-term one-year clinical outcomes of CRT patients treated with either conventional CRT (STD), CRT optimized (OPT) or CRT optimized plus MPP (OPT+MPP). Improved clinical outcomes or response was measured in terms of a reduction in end-systolic volume of $\geq 15\%$, reduction in NYHA class ≥ 1 and PACKER score variation (NYHA response with no HF-related hospitalization or death).
- A total of 110 patients were treated with either conventional CRT (STD, $n = 54$), CRT optimized (OPT, $n = 36$) or CRT optimized plus the MPP™ feature (OPT+MPP, $n = 20$).
- Conventional CRT (STD) utilized bipolar LV leads; CRT optimized (OPT) used a combination of bipolar and quadripolar and the CRT optimized with MPP (OPT+MPP) used the Quadra Assura MP™ CRT device with the Quartet™ LV lead.
- CRT optimization (OPT) included hemodynamic and electrical optimization of the LV pacing site.
- Response rates at one year were:
 - Reduction in end-systolic volume $\geq 15\%$: 90.0% OPT+MPP; 72.2% OPT; 55.6% STD
 - Reduction in NYHA class ≥ 1 : 95.0% OPT+MPP; 77.8% OPT; 66.7% STD
 - PACKER score of 0: 90.0% OPT+MPP; 66.7% OPT; 59.3% STD
- Response proportion for end-systolic volume, NYHA class and PACKER score all demonstrated a statistically significant trend from STD to OPT+MPP of $p = 0.004$, $p = 0.012$ and $p = 0.018$ respectively.

Key takeaways:

- The study showed that patients treated with MultiPoint Pacing had the highest response rate (response proportion %) in all clinical outcome measures from baseline to one year. Evaluation of by all three methods showed a minimum of 90% responder rate when utilizing MultiPoint Pacing. See Figure 1.

Improved CRT Response: Results of Long-Term Follow-Up

Improving Cardiac Resynchronization Response with MultiPoint Left Ventricular Pacing: Twelve-month Follow-up Study.

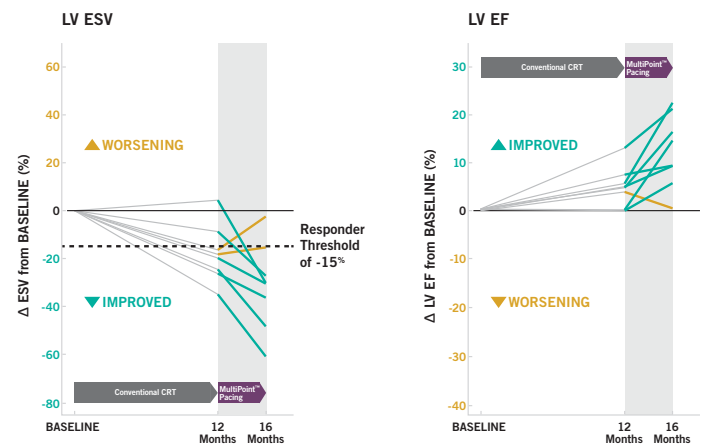
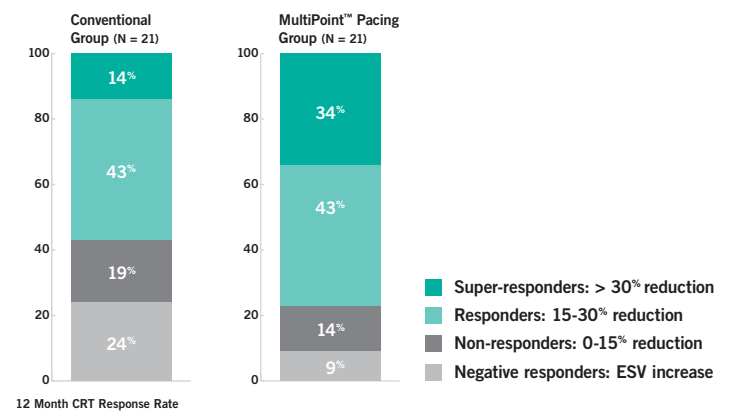
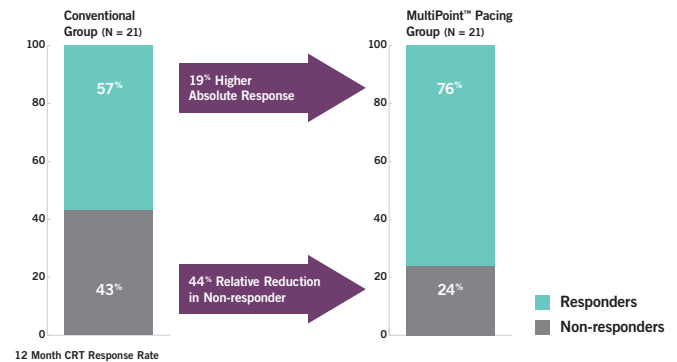
Pappone C, et al. *Heart Rhythm*, 2015.²⁰

- The purpose of this study was to determine whether the benefits of MultiPoint™ Pacing (MPP™) previously observed at three months follow-up vs. conventional biventricular (BiV) pacing also improved left ventricular function at 12 months.
- A total of 44 consecutive patients were randomized to receive pressure-volume (PV) loop optimized MPP or BiV pacing at a single center in Italy. The primary endpoint was the change in end systolic volume (ESV) and ejection fraction (EF) from baseline to 12 months in the MPP group vs. the BiV group. Response to CRT was defined as alive status and $\geq 15\%$ decrease in ESV relative to the baseline.
- ESV and EF increase relative to baseline were significantly greater with MPP than with BiV (ESV: median -25% vs. median -18% , $P = 0.03$; EF: median $+15\%$ vs. median $+5\%$, $P < 0.001$).
- At 12 months, 76% (16/21) of patients in MPP group were classified as CRT responders compared with 57% (12/21) in the BiV group, $P = 0.33$. The CRT response rate in the MPP group remained consistent at 76% from 3-month to 12-month follow-up. In addition fewer patients became non-responders in the MPP group than in the BiV group.

Key takeaways:

- The findings of this study confirm that benefits of MPP™ technology vs. conventional BiV previously observed acutely at three-months are sustained out to 12 months. PV loop-guided MPP technology resulted in greater LV reverse remodeling and increased LV function at 12 months compared with similar optimized BiV.
- A 44% relative reduction in non-responders over a 12-month period, as measured by reduction in ESV.
- A 19% higher absolute response over a 12-month period, as measured by reduction in ESV.

Response definition:
ESV reduction $\geq 15\%$ and Alive Status



Improved CRT Response: Hemodynamic and Cardiac Function Benefits

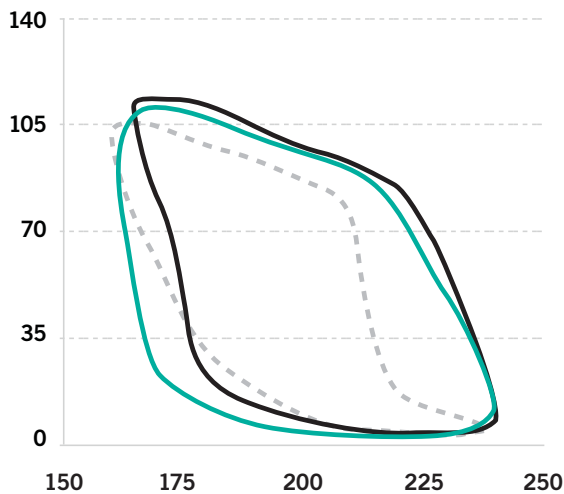
MultiPoint Left Ventricular Pacing Improves Acute Hemodynamic Response Assessed with Pressure-Volume Loops in Cardiac Resynchronization Therapy Patients.

Pappone C, et al. *Heart Rhythm*, 2014.²¹

- This study evaluated the acute impact of MultiPoint™ Pacing (MPP™) on hemodynamic response in CRT-D patients (n = 44).
- The best MPP™ technology intervention significantly increased the rate of pressure change (dp/dt_{max}), stroke work, stroke volume, and ejection fraction as compared to the best conventional pacing intervention.
- The best MPP technology intervention improved acute diastolic function, significantly decreasing $-dp/dt_{min}$, relaxation time constant, and end-diastolic pressure as compared to the best conventional intervention.

Key takeaways:

- Results showed that CRT with MPP technology can significantly improve acute LV hemodynamic parameters compared to conventional pacing.



Acute Effects of Multisite Left Ventricular Pacing on Mechanical Dyssynchrony in Patients Receiving Cardiac Resynchronization Therapy.

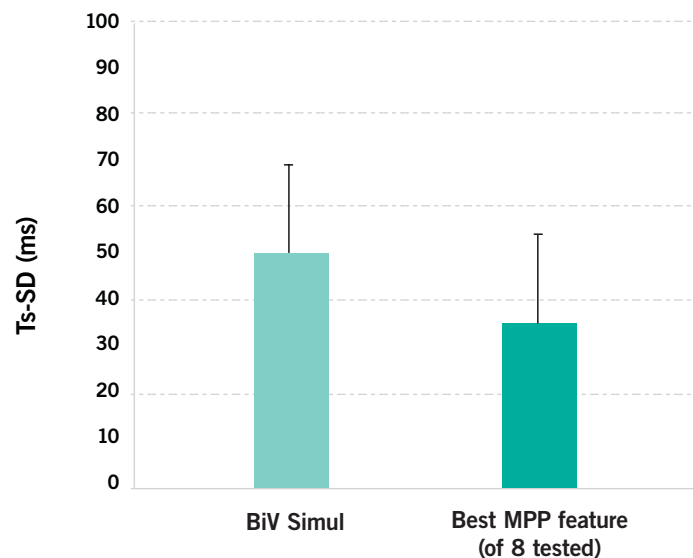
Rinaldi CA, et al. *Journal of Cardiac Failure*, 2013.¹⁵

- This study evaluated the effect of acute MultiPoint™ pacing (MPP™) on mechanical dyssynchrony in 52 CRT patients.
- Mechanical dyssynchrony was measured as the standard deviation of time to peak contractions of 12 LV segments (Ts-SD) using transthoracic tissue Doppler imaging (TDI).
- Compared with baseline the mean Ts-SD was significantly lower for the optimal MPP technology configuration (of eight tested).
- At least one MPP technology configuration exhibited a significant dyssynchrony improvement in 63% of patients.
- The mean number of LV segments with delayed longitudinal contractions was significantly reduced with the optimal MPP technology configuration.

Key takeaways:

- MPP technology in the acute setting was safe and resulted in a significant reduction in echocardiographic dyssynchrony compared with conventional CRT.

Reduced Mean Dyssynchrony with MPP™ technology



Improved CRT Response: Hemodynamic and Cardiac Function Benefits

MultiPoint Left Ventricular Pacing Provide Additional Echocardiographic Benefit to Responders and Non-responders to Conventional Cardiac Resynchronization Therapy.

Pappone C, et al. *European Heart Journal*, 2015.²²

- The aim of this study was to evaluate if patients receiving conventional CRT (CONV) would receive additional benefit by switching CRT programming to MPP (n = 8).
- Patients implanted with a CRT 12 months post-implant had their CRT programming switched to MPP after echo and NYHA class assessment and classified as responders (6/8) or non-responders (2/8) based on echo comparison to baseline. Responder was defined as ESV \geq 15% relative to baseline.
- At 16 months post-implant “echo” exam and NYHA class assessments were done to determine the outcome of switching from CONV to MPP.
- Results showed that the two non-responders to CONV became responders with MPP with reduction in ESV and improvement in EF relative to the 12 month exam and the remaining six patients classified as responders to CONV also experienced additional reduction in ESV and improvements in EF.

Key takeaways:

- MultiPoint LV pacing may provide additional improvement to LV function in responders and non-responders to conventional CRT.
- The study results suggest that activating MPP feature may be a potential strategy to convert non-responders to responders or further improve response in patients already responding to conventional therapy.

MultiPoint Pacing by a Left Ventricular Quadripolar Lead Improves the Acute Hemodynamic Response to CRT Compared with Conventional Biventricular Pacing at Any Site.

Zanon F, et al. *Heart Rhythm*, 2015.⁹

- This prospective study systematically compared the acute hemodynamic effects of MultiPoint™ Pacing (MPP™) with conventional biventricular (BiV) pacing in 29 consecutive patients at a single center.
- A total of 3.2 ± 1.2 different veins and 6.3 ± 2.4 pacing sites were tested in each patient. The LV electrical delay (Q-LV) as well as the paced QRS width and LV dP/dt_{max} (maximum rate of increase in LV pressure) during MPP and BiV were assessed.

- A total of 90% (26/29) patients had a higher LV dP/dt_{max} with MPP than with conventional BiV at the LV pacing site with the best results (increase from baseline of 942 ± 202 mm Hg/s to 1231 ± 267 mm Hg/s with MPP compared with increase to 1200 ± 267 mm Hg/s with conventional BiV). The improved response with MPP was observed for all measurements, including those taken at the worst sites.
- The mean QRS duration was significantly narrower during MPP compared with conventional BiV (171 ± 18 ms vs. 175 ± 16 ms, $P = 0.003$).

Key takeaways:

- As demonstrated in this study, MPP therapy results in a consistent increase in acute hemodynamic response compared with conventional BiV. MPP–induced improvement in contractility was also associated with significantly greater QRS narrowing.

Characterization of Ventricular Activation Pattern and Acute Hemodynamics during MultiPoint Left Ventricular Pacing.

Menardi E, et al. *Heart Rhythm*, 2015.¹⁴

- This study evaluated the effect of MultiPoint™ Pacing (MPP) on the left ventricular (LV) activation pattern and hemodynamics in the same patient population.
- A total of 10 patients with non-ischemic cardiomyopathy underwent an acute pacing protocol that included 2 biventricular (BiV) and up to 9 MPP interventions. Electroanatomic mapping of the LV was performed using the EnSite™ Velocity™ cardiac mapping system to assess the percentage of the LV endocardium activated during various pacing interventions.
- Compared with BiV, MPP significantly increased LV dP/dt_{max} ($30 \pm 13\%$ vs. $25 \pm 11\%$, $P = 0.041$); reduced QRS duration ($22 \pm 11\%$ vs. $11 \pm 11\%$, $P = 0.01$) and decreased total endocardial activation time ($25 \pm 15\%$ vs. $10 \pm 20\%$, $P = 0.01$).
- MPP also captured significantly greater LV mass during the first 25 ms and first 50 s of pacing, suggesting faster wavefront propagation throughout the LV.

Key takeaways:

- MPP therapy improved acute hemodynamic parameters, QRS duration and activation patterns in comparison to BiV.

Improved CRT Response: Hemodynamic and Cardiac Function Benefits

The Use of Multisite Left Ventricular Pacing via Quadripolar Lead Improves Acute Haemodynamics and Mechanical Dyssynchrony Assessed by Radial Strain Speckling Tracing: Initial Results.

Osca J, et al. *Europace*, 2015.²³

- The objective of this prospective study was to evaluate the effect of MultiPoint™ Pacing (MPP) on acute hemodynamics, cardiac contractility and LVEF in comparison to conventional biventricular (BiV) pacing.
- A total of 27 consecutive patients implanted with a CRT device were enrolled in this prospective, single-center, non-randomized study. Transthoracic echocardiography was used to obtain hemodynamic and dyssynchrony parameters. Hemodynamic evaluation was performed at 3-month follow-up.
- The increase in mean LVEF was significantly higher with MPP technology compared with baseline ($38.4 \pm 1.8\%$ vs. 26.1 ± 2.2 , $P < 0.001$). The increase in the cardiac index (CI) was also significantly higher with MPP compared with conventional BiV ($34.7\% \pm 5.1\%$ vs. $21.8 \pm 5.4\%$, $P = 0.19$). The percentage of CRT responders ($\geq 10\%$ increase in CI) was significantly higher with MPP than with conventional BiV (85.2% vs. 62.9% , $P < 0.001$).
- MPP also resulted in significant decreases in the anteroapical-to-posterior wall time delay and the standard deviation of the time-to-peak radial strain of the 6 LV basal segments compared with conventional BiV. There was a positive correlation ($r = 0.69$) between a reduction in dyssynchrony and an increase in CI, $P < 0.0001$.

Key takeaways:

- The MPP™ feature resulted in further decreases in LV dyssynchrony compared with conventional BiV as well as additional improvement in LVEF and in CI. This was translated into a higher number of acute responders to CRT.
- There was also an association between higher reduction in mechanical dyssynchrony and further improvement in hemodynamics with MPP technology.

MultiPoint Pacing Acutely Induces Better Hemodynamics and QRS Narrowing Compared to Conventional Pacing.

Zanon F, et al. *European Society of Cardiology*, 2015.²⁴

- The objective of this study was to systematically compare the acute hemodynamic effects of MultiPoint Pacing (MPP) with conventional biventricular (BiV) pacing in 39 patients
- The left ventricular (LV) electrical delay (LV-Q) was measured at each pacing site tested as well as the increase in the LV dp/dt_{max} obtained with MPP and conventional BiV.
- Overall, a total of 3.2 ± 0.7 different MPP measurements were collected per patient. LV dp/dt_{max} increase from baseline (962 ± 194 mmHg/s) was greater with MPP than with BiV (1194 ± 253 mmHg/s with MPP vs. 1157 ± 252 mmHg/s with BiV). On considering the best site, LV dp/dt_{max} increased from a baseline value of 964 ± 207 mmHg/s to 1262 ± 258 mmHg/s (MPP) compared with 1230 ± 260 mmHg/s (BiV).
- The mean values of QRS duration at any site was significantly shorter with MPP technology (171 ± 18 ms) compared with conventional CRT (177 ± 20 ms), $P = 0.0002$.

Key takeaways:

- MPP technology at any LV site resulted in consistent improvement in hemodynamic response compared with conventional BiV. A correlation between improved hemodynamics and Q-LV was observed with MPP technology for all measurements.
- MPP technology-induced improvement in contractility was associated with significantly greater QRS narrowing compared with conventional BiV.

Improved CRT Response: Hemodynamic and Cardiac Function Benefits

Acute Hemodynamic Comparison of Biventricular, LV Only and MultiPoint Pacing in CRT patients.

Zanon F, et al. *European Society of Cardiology*, 2015.²⁵

- The objective of this study was to evaluate the acute effects of different pacing configurations with and without the adjunctive contribution of MultiPoint™ Pacing (MPP™) on left ventricular (LV) dP/dt_{max} and QRS narrowing in 31 patients who underwent implantation of a cardiac resynchronization therapy (CRT) device.
- The hemodynamic effects of pacing at different sites and during various pacing protocols (LV only, biventricular (BiV), MPP LV only and MPP BiV) were evaluated by means of invasive measurement of LV dP/dt_{max} . MPP LV only refers to dual bipolar LV pacing. One-way analysis of variance and Bonferroni post-hoc testing were used to evaluate differences between the pacing protocols.
- The baseline LV dP/dt_{max} was 985 ± 189 mmHg/s and steadily increased during all four of the pacing protocols. Values during LV MPP were higher than LV-only and values during BiV MPP were higher than during BiV.
- While QRS duration was considerably higher during LV than during BiV pacing, MPP reduced QRS duration during both LV and BiV pacing.

Key takeaways:

- MPP technology increased the hemodynamic benefits of CRT during both LV only and BiV pacing. The improvement was associated with reduced QRS duration.

Impact of MultiPoint Left Ventricular Pacing on QRS Duration and Left Ventricular Ejection Fraction. Preliminary Results from a Multicenter Prospective Study.

Santini L, et al. *European Society of Cardiology*, 2015.²⁶

- The aim of this study was to evaluate the effect of MultiPoint™ pacing (MPP™) on the QRS duration and left ventricular ejection fraction (LVEF) on 386 patients implanted with cardiac resynchronization therapy (CRT) devices at 67 hospitals in Italy. Patients with an EF increase of at least 5% were considered CRT responders. This abstract reported baseline and follow-up results in a subset of patients with available data. QRS and EF data were available at follow-up in 88 patients.
- The implant procedural was 114 ± 47 min. MPP technology was programmable in 96% of patients with a cardiac threshold < 5 V for both cathodes and without phrenic nerve stimulation issues.
- In 86 patients optimized by QRS, the percentage change in QRS from baseline was significantly greater for patients in optimized MPP compared with the best conventional biventricular (BiV) mode.
- The relative percentage change from baseline QRS was significantly greater for patients with optimized MPP ($17\% \pm 21\%$) compared with best conventional biventricular mode (BIV) ($12\% \pm 20\%$), $P < 0.001$. At follow-up, the percentage change in QRS was greater in MPP mode ($20\% \pm 21\%$) than in BiV mode ($13\% \pm 24\%$), $P = 0.16$. Baseline EF was not significantly different between the two groups. However, after 6 months, EF increased significantly in the MPP group ($12\% \pm 10\%$) vs the BiV group ($7\% \pm 9\%$) $P = 0.01$. Only 62% of patients programmed in BIV were responders compared with 76% in the MPP group.

Key takeaways:

- MPP technology was programmable in 96% of the patients; it could provide greater QRS shortening and EF improvement, compared to conventional BiV.

Improved CRT Response: Hemodynamic and Cardiac Function Benefits

Acute Haemodynamics and Left Ventricular Mechanical Dyssynchrony Improving with Multisite Left Ventricular Pacing via Quadripolar Lead.

Fernandez PA, et al. *CardioStim*, 2015.²⁷

- The purpose of this study was to evaluate the effect of MultiPoint™ pacing (MPP) on acute hemodynamics Cardiac index (CI), cardiac contractility and left ventricular (LV) dyssynchrony in comparison with conventional cardiac resynchronization therapy (CRT).
- Consecutive patients implanted with a CRT device were included in the study. Echocardiographic evaluation was performed at follow-up. Patients were evaluated using conventional pacing vs. MPP, each presented in a randomized order. MPP technology was delivered using an anatomic strategy with the D1 and P4 electrodes as cathodes to capture as large an area of the LV as possible.
- A total of 25 patients were analyzed. All of the patients had left bundle branch block or a paced QRS with a mean width of 165 ± 6 ms.
- Left ventricular ejection fraction (LVEF) was significantly higher with MPP technology ($38.2\% \pm 1.8\%$) compared to baseline ($26.9\% \pm 1.9\%$), $P < 0.001$ and also with conventional biventricular pacing (BiV) ($33.8\% \pm 1.6\%$) compared with baseline ($26.9\% \pm 1.9\%$), $P = 0.026$. When comparing the increase in LVEF of each patient in the MPP and conventional BiV configurations with regard to baseline, there was an increase of $51.4\% \pm 9\%$, $P < 0.0001$ (MPP) and $33.2\% \pm 8\%$ (BiV), $P = 0.034$.
- CI was increased by 22.3% and 37.9% in conventional and MPP technology configurations ($p = 0.19$). Percentage of acute responders (CI increase $\geq 10\%$) was 47% with conventional BiV and 80% with MPP, $P = 0.014$. The baseline AS-P delay and time to peak radial strain of the 6 LV basal segment (RS-SD6) were also significantly reduced with MPP technology compared with baseline. A positive correlation ($r = 0.79$) between reduction in dyssynchrony and an increment in CI was also observed, $P < 0.0001$.

Key takeaways:

- MPP technology showed a greater reduction in LV dyssynchrony compared with conventional (BiV). An association between a greater reduction in mechanical dyssynchrony and further improvement in hemodynamics was also observed.
- MPP technology resulted in an additional improvement in LVEF and in CI, which was translated into a higher number of acute responders to CRT.

MultiPoint Pacing in Cardiac Resynchronization Therapy: Optimization and Effect on QRS.

Di Stolfo G, et al. *CardioStim*, 2015.²⁸

- The objective of this multicenter study was to evaluate different types of cardiac resynchronization therapy (CRT) optimization and the influence of MultiPoint™ pacing (MPP™) on QRS duration.
- Data from 372 patients who underwent CRT implantation at 66 hospitals in Italy was collected. After device implantation, programming was optimized per the standard practice at the center and electrical measurements were performed.
- Device optimization was performed in 76% of cases. In 38% of the patients, only QRS width was measured; in 30% the electrical delays between the electrodes were calculated through automatic device algorithms; in 5% different echocardiographic techniques were considered, in 4%, only a pressure guidewire was used to measure dp/dt_{max} and in 23% different joint optimization criteria were used.
- The effects of MPP and conventional biventricular (BiV) pacing were compared in 86 of 108 patients optimized with QRS width. The QRS width during MPP was significantly shorter than the baseline and the percentage decrease in QRS width was significantly greater in the optimized MPP configuration compared with the best conventional BiV ($16\% \pm 21\%$ vs. $12\% \pm 20\%$, $P < 0.000$).

Key takeaways:

- A total of 76% of devices were optimized after implant, primarily with quick automatic algorithms and reduction in QRS duration. MPP technology resulted in greater QRS shortening compared with conventional BiV.

Improved CRT Response: Hemodynamic and Cardiac Function Benefits

A New Algorithm for MultiPoint Pacing in Cardiac Resynchronization Therapy: Feasibility from a Multicenter Experience.

Giammaria M, et al. *CardioStim*, 2015.²⁹

- The objective of this prospective study was to verify the feasibility of MultiPoint™ Pacing (MPP™) in real life clinical practice at 66 centers in Italy.
- Cardiac thresholds (CTs) and the presence of phrenic nerve stimulation (PNS) were determined in different left ventricular (LV) pacing configurations. Device programming was optimized per standard practice at each center.
- Data were collected from 325 patients. Procedural time was 114 ± 47 min and fluoroscopy time was 21 ± 15 min. The LV lead was implanted in a lateral vein in 49% of patients, a posterior vein in 5%, an anterior vein in 3%, an anterior-lateral vein in 14% and a posterior-lateral vein in 29%. LV CTs were measured in at least 2 out of 10 available configurations (vectors) with different cathodes. The mean of CT (at 0.5 ms) was ≤ 3 V in all pacing configurations and ≤ 2 V in 8/10 patients.
- MPP technology was programmable in 98% of patients. PNS was reported in 67 patients in at least one configuration. MPP was not programmable in seven patients due to PNS.
- No adverse events or arrhythmias were reported during implant or pre-discharge.

Key takeaways:

- MultiPoint Pacing algorithm was programmable in 96% of patients without issues regarding thresholds or PNS.

MultiPoint Left Ventricular Pacing Improves Pre-Ejection Period and Ejection Duration Assessed with Non-Invasive Radial Artery Tonometry Measurements in Cardiac Resynchronization Therapy Patients.

Pappone C, et al. *CardioStim*, 2015.³⁰

- The purpose of this study was to evaluate the feasibility of using non-invasive radial arm tonometry to characterize arterial pressure morphology changes during the pre-ejection period (PEP) and ejection duration (ED) in both MultiPoint™ pacing (MPP) and conventional biventricular (BiV) pacing in CRT patients.
- A total of 19 patients implanted with a CRT device at one center in Italy underwent non-invasive radial arm tonometry 3 to 6 months post-implant. A pacing protocol was performed in a randomized order to include one QuickOpt™ optimization conventional BiV configuration and 4 to 5 MPP configurations. Right ventricular pacing (baseline) was repeated after every test configuration. PEP, ED and PEP/ED ratio were determined for each intervention from the radial artery pressure waveform and the simultaneously recorded 3-lead ECG.
- In 17/19 (89%) of patients, at least one MPP technology intervention resulted in improved PEP, ED, and PEP/ED compared with conventional BiV pacing.
- MPP technology significantly improved PEP/ED compared with BiV (-0.07 ± 0.14 vs. -0.04 ± 0.13), $P = 0.02$.

Key takeaways:

- Non-invasive radial artery tonometry was used to characterize changes in the PEP and ED between MPP and conventional BiV pacing interventions. MPP technology was shown to significantly reduce the PEP/ED relative to conventional BiV.

Improved CRT Response: Hemodynamic and Cardiac Function Benefits

Biventricular, Left Ventricular Only and MultiPoint Pacing in CRT Patients: An Acute Hemodynamic Comparison.

Zanon F, et al. *CardioStim*, 2015.³¹

- The objective of this prospective multicenter study was to evaluate the acute effects of different pacing configurations, with and without the adjunctive contribution of MultiPoint™ Pacing (MPP™) on left ventricular (LV) dP/dt_{max} and QRS narrowing.
- The hemodynamic effects of pacing at different sites was evaluated in 31 patients. A total of 98 measurements (3.2 ± 0.8) and pacing sites were analyzed. MPP LV only refers to dual bipolar LV pacing. One-way analysis of variance with repeated measures and Bonferroni post-hoc testing were used to evaluate differences in the pacing protocols.
- Baseline LV dP/dt_{max} was 985 ± 189 mmHg/s. LV dP/dt_{max} increased steadily during LV only, conventional biventricular (BiV), MPP LV only, and MPP BiV. The values during LV-MPP were higher than LV only and the values during MPP BiV were higher than during BiV.
- QRS duration was considerably wider during LV than during BiV pacing. MPP reduced QRS duration during both LV and BiV pacing.

Key takeaways:

- MPP technology increased the hemodynamic benefit during both LV only and BiV pacing. The improvement was associated with a reduction in QRS duration.

Optimizing the LV Pacing Site by Means of Electrical Delay and LV dP/dt_{max} May Predict the Clinical Outcome in CRT Patients: Results of One Year Follow-up.

Zanon et al. *CardioStim*, 2015.³²

- The aim of this multicenter study was to assess the clinical response to cardiac resynchronization therapy (CRT) in 41 patients whose left ventricular lead was positioned after optimization for the maximum electrical delay (Q-LV) and highest LV dP/dt_{max} .
- A mean number of 3.4 ± 0.7 veins and 7.8 ± 1.5 pacing sites were tested. In 40/41 (98%) of patients, the site of highest dP/dt_{max} and maximum Q-LV interval coincided and was selected as the target site for LV lead placement.
- The heart failure Packer score was evaluated at 12-month follow-up. A total of 31/40 patients (78%) demonstrated improvement in their New York Heart Association functional class.

- Mean QRS decreased from 189 ± 21 ms at baseline to 147 ± 30 ms at 12-month follow-up. Mean LV EF increased significantly from $29 \pm 7\%$ at baseline to $40 \pm 11\%$ at follow up, $P < 0.001$. Mean end systolic volume decreased from 150 ± 59 mL (81 ± 29 mL/m²) at baseline to 113 ± 60 mL (60 ± 31 mL/m²) at 12-month follow-up, $P < 0.001$.

Key takeaways:

- Acute optimization of the targeted LV lead site by systematically screening the local electrical delay and LV dP/dt_{max} resulted in a 78% response to CRT.

A New Algorithm for MultiPoint Pacing in Cardiac Resynchronization Therapy: Feasibility from a Multicenter Experience.

Forleo GB, et al. *HRS*, 2015.¹⁷

- The aim of this study was to evaluate the feasibility of MultiPoint™ Pacing (MPP) in real clinical practice and to present acute results.
- In 313 patients at 57 hospitals in Italy, implant procedure time was 114 ± 47 min and fluoroscopy time was 21 ± 15 min. The left ventricular (LV) lead was implanted in the following locations: anterior vein (2%), antero-lateral vein (14%), lateral vein (50%), posterior vein (5%) and postero-lateral 29%.
- LV cardiac threshold (CT) data (at least 2 of 10 available configurations with different cathodes) was available in 279 patients. The mean CT was ≤ 3 V in all configurations. MPP technology was programmable in 97% of patients with CT for both cathodes < 5 V and without phrenic nerve stimulation (PNS) issues. In 86.2% of patients, both vectors had CT < 3 V. PNS was reported in 62 patients but was resolved in all but two patients due to other pacing choices.
- No adverse events or provoked arrhythmias were reported during implant or pre-discharge.

Key takeaways:

- MPP technology was programmable in 97% of patients without issues regarding thresholds or PNS.

Improved CRT Response: Hemodynamic and Cardiac Function Benefits

Impact of MultiPoint Left Ventricular Pacing on QRS Duration and Left Ventricular Ejection Fraction: Preliminary Results from a Multicenter Prospective Study.

Forleo GB, et al. *HRS*, 2015.¹⁸

- This prospective study compared the impact of MultiPoint™ Pacing (MPP™) on QRS duration and left ventricular ejection fraction (LVEF) compared to conventional biventricular pacing (BiV) at 57 centers in Italy.
- QRS width during MPP was significantly shorter than baseline in 82 patients optimized via QRS, $P < 0.001$. Additionally, the relative percentage change in QRS width was significantly greater in the optimized MPP group compared with the conventional BiV group ($17 \pm 21\%$ vs. $12 \pm 20\%$), $P < 0.001$.
- At follow-up, QRS duration was significantly shorter in the MPP group than in the conventional BiV group (130 ± 26 ms vs. 136 ± 25 ms).
- LVEF at baseline did not differ between groups. However, at 6-month follow-up, LVEF in the MPP group increased significantly compared with both conventional BiV ($42 \pm 8\%$ vs. $35 \pm 10\%$, $P < 0.001$) and baseline ($P < 0.001$).

Key takeaways:

- Preliminary analysis suggests that MPP technology may provide options for QRS shortening and improvement in LVEF compared with conventional BiV.

Cardiac Resynchronization Therapy Response at 12 Months Is Associated with Decreases in Interventricular Electrical Conduction Delay.

Pappone C, et al. *HRS*, 2015.³³

- The purpose of this study was to evaluate whether echocardiographic response to cardiac resynchronization therapy (CRT) is associated with a decrease in the interventricular electrical conduction delay (IECD) from right ventricular (RV) pacing to left ventricular (LV) sensing.
- A total of 44 patients were randomized to receive conventional biventricular (BiV) or MultiPoint™ Pacing (MPP) at a single center in Italy. IECDs were measured at each of the four LV electrodes at baseline and at 12 months. Patients with a $\geq 15\%$ reduction in end systolic volume (ESV) were defined as responders. Complete data was available for 35 patients.

- At 12 months, 71% (25/35) of patients were responders and 29% (10/25) were non-responders. Responders demonstrated a greater reduction in IECDs at 12 months compared to baseline than non-responders.
- Responders with longer baseline IECDs had an increased reduction in IECDs at 12 months compared with non-responders, according to a least squares fit analysis.

Key takeaways:

- CRT responders experienced decreases in IECD more frequently than non-responders. Automated IECD measurements may be valuable in trending or predicting CRT response.

Acute Hemodynamic Comparison of Left Ventricular, Biventricular and Multipoint Pacing in CRT.

Zanon F, et al. *HRS*, 2015.³⁴

- The objective of this study was to evaluate the acute effects of different pacing configurations with and without MultiPoint™ Pacing (MPP) on left ventricular (LV) dP/dt_{max} and QRS narrowing.
- The hemodynamic effects of LV only, biventricular, MPP LV only and MPP biventricular (BiV) were evaluated in 31 patients. MPP LV only refers to dual bipolar LV pacing. Analysis of variance with repeated measures and with Bonferroni post-hoc testing was used to evaluate the differences in pacing protocols.
- The baseline LV dP/dt_{max} was 985 ± 189 mmHg/s and steadily increased during all four of the pacing protocols. However, LV dP/dt_{max} was higher during LV MPP than during LV only pacing and values during BiV MPP were higher than during BiV.
- QRS duration was considerably higher during LV only than during BiV pacing. The addition of MPP reduced the QRS value during both LV only and BiV pacing.

Key takeaways:

- MPP technology increased the hemodynamic benefit during both LV only and BiV pacing and the improvement was associated with a reduction in QRS duration.

Improved CRT Response: Hemodynamic and Cardiac Function Benefits

Improvement in Acute Contractility and Hemodynamics with MultiPoint Pacing via a Left Ventricular Quadripolar Pacing Lead.

Rinaldi CA, et al. *Journal of Interventional Cardiac Electrophysiology*, 2014.³⁵

- This study evaluated the impact of MultiPoint™ Pacing (MPP™) on acute cardiac contractility and hemodynamics compared to conventional CRT (n = 40).
- Compared to conventional CRT, the mean peak radial strain was significantly higher for the optimal MPP configuration, and at least one MPP configuration (of 8 tested) was significantly superior (> 20%) in 63% of patients.
- The mean LV outflow VTI was significantly higher for optimal MPP compared to conventional CRT (n = 13).

Key takeaways:

- MultiPoint Pacing delivered via a quadripolar LV lead resulted in a significant improvement in acute cardiac contractility and hemodynamics compared to conventional CRT in the majority of patients studied.

Multipoint Left Ventricular Pacing in Cardiac Resynchronization Therapy Patients Provides Similar Acute Hemodynamic Improvement Regardless of QRS Duration or Lead Location.

Pappone C, et al. *Heart Rhythm*, 2014.³⁶

- The aim of this study was to evaluate acute hemodynamic performance while using MultiPoint Pacing (MPP) in patients with varying QRS duration and lead location (n = 44). Measurements evaluated were dP/dt_{max} , stroke work, stroke volume and ejection fraction.
- No significant difference was seen in hemodynamic improvement for patients with QRS duration < 150 ms versus ≥ 150 ms.
- Hemodynamic improvement was also not significantly different for lateral versus non-lateral LV lead positions.

Key takeaways:

- MultiPoint Pacing can significantly improve LV acute hemodynamic properties relative to traditional CRT and can achieve similar improvement regardless of QRS duration or LV lead position.

Multisite Left Ventricular Pacing is Safe and Improves Cardiac Hemodynamic in Heart Failure Patients – Results from a 1-month Follow-up Study.

Gutleben, K-J, et al. *CardioStim*, 2012.³⁷

- This study evaluated the safety and hemodynamic effect of MultiPoint™ Pacing (MPP™) on CRT patients at one month postimplantation (n = 59).
- Patients implanted with a St. Jude Medical™ (SJM) CRT-D and Quartet™ LV lead were tested at pre-discharge (PD) and at one month visits. Seventeen of the 59 patients were included in the hemodynamic analysis. Aortic velocity time integral (AoVTI) was computed using a mean of three consecutive beats at each selected MPP interventions and conventional BiV with QuickOpt™ optimization (QO BiV).
- For all 59 patients, there were no adverse events attributable to MPP for the duration of 1 month.
- MPP increased or did not change the AoVTI at pre-discharge and one month in 94% (16/17) and 76% (13/17) of patients, respectively, when compared to QO BiV at predischage.
- When comparing MPP at one month versus predischage, MPP increased or did not change AoVTI in 71% (12/17) of patients (mean increase of $16.8 \pm 26.9\%$).

Key takeaways:

- MPP improved hemodynamic performance compared to conventional BiV with QuickOpt optimization at predischage.
- For patients receiving MPP, hemodynamic improvement continued for one month during the course of the study.

Improved CRT Response: Hemodynamic and Cardiac Function Benefits

Acute Hemodynamic Comparison of Multisite and Biventricular Pacing with a Quadripolar Left Ventricular Lead.

Thibault B, et al. *Europace*, 2013.¹⁶

- This study evaluated the acute hemodynamic effects of multisite pacing configurations using the Quartet™ lead (n = 21).
- Using an acute pacing protocol, four configurations of multisite LV and simultaneous RV pacing were tested. Each was conducted three times in randomized order for 30 seconds, with baseline recording of standard BiV between each test.
- At implant, 16 of the 19 analyzed patients (84%) had at least two of the four multisite configurations tested produce an increase in LV dP/dt_{max} when compared to pacing from a single BiV vector.

Key takeaways:

- 72% of all tested configurations of multisite pacing produced greater LV dP/dt_{max} than obtained with BiV pacing.

Vector Co-Viability Supports Suitability of Quadripolar Coronary Sinus Lead for the Purposes of Multisite LV Pacing in Patients Undergoing Cardiac Resynchronization Therapy.

Banga S, et al. *Heart Rhythm*, 2014.³⁸

- This study of 218 patients evaluated the availability of at least two viable pacing vectors with pacing threshold ≤ 3 V and phrenic nerve stimulation safety margin ≥ 3 V.
- For any individual viable vector, at least one other co-viable vector was found 64–89% of the time, while all possible co-viable vectors were found 42–53% of the time.
- Vectors with M2 as a cathode were most likely to have a co-viable vector option.

Key takeaways:

- This analysis shows the likely availability of suitable vectors for multisite pacing with a quadripolar lead.

More favorable electrical and mechanical reverse remodeling after cardiac resynchronization therapy with quadripolar versus conventional bipolar lead.

Park SJ, et al. *HRS*, 2015.¹⁹

- This study compared N = 51 patients with conventional bipolar CRT vs. N = 12 patients with Quad without MultiPoint™ Pacing vs. N = 8 patients with Quad with MultiPoint™ Pacing.
- Comparisons were made of acute changes in QRS duration and six-month changes in echocardiographic parameters between groups.
- Paced QRS duration was less than 120 ms in significantly more MPP patients than in conventional bipolar or Quad without MPP patients (P = 0.023).
- At six months follow-up there was greater EF improvement (P = 0.031), ESV reduction (P = 0.025), and NYHA class improvement (P < 0.001) among the MPP patients.
- The response rate with MultiPoint Pacing was 75% (definition: % ESV reduction $\geq 15\%$).

Key takeaways:

- This study provides evidence that MultiPoint Pacing improved LV function and reverse remodeling at long-term follow-up.

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