The hemodynamic effects of different pacing modalities after cardiopulmonary bypass in patients with reduced left ventricular function

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The Hemodynamic Effects of Different Pacing Modalities After Cardiopulmonary Bypass in Patients With Reduced Left Ventricular Function

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Objectives: Patients with decreased left ventricular function undergoing cardiac surgery have a greater chance of difficult weaning from cardiopulmonary bypass and a poorer clinical outcome. Directly after weaning, interventricular dyssynchrony, paradoxical septal motion, and even temporary bundle-branch block might be observed. In this study, the authors measured arterial dP/dtmax, mean arterial pressure (MAP), and cardiac index using transpulmonary thermodilution, pulse contour analysis, and femoral artery catheter and compared the effects between right ventricular (A-RV) and biventricular (A-BiV) pacing on these parameters.

Design: Prospective study.

Setting: Single-center study.

Participants: The study comprised 17 patients with a normal or prolonged QRS duration and a left ventricular ejection fraction < 35% who underwent coronary artery bypass grafting with or without valve replacement.

Interventions: Temporary pacing wires were placed on the right atrium and both ventricles. Different pacing modalities were used in a standardized order.

Measurements and Main Results: A-BiV pacing compared with A-RV pacing demonstrated higher arterial dP/dtmax values (846 ± 646 mmHg/s v 800 ± 587 mmHg/s, p = 0.023) and higher MAP values (77 ± 19 mmHg v 71 ± 18 mmHg, p = 0.036).

Conclusion: In patients with preoperative decreased left ventricular function undergoing coronary artery bypass grafting, A-BiV pacing improve the arterial dP/dtmax and MAP in patients with both normal and prolonged QRS duration compared with standard A-RV pacing. In addition, arterial dP/dtmax and MAP can be used to evaluate the effect of intraoperative pacing. In contrast to previous studies using more invasive techniques, transpulmonary thermodilution is easy to apply in the perioperative clinical setting.

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Key Words: artificial cardiac pacing; left ventricular dysfunction; coronary artery bypass graft; resynchronization therapy; hemodynamic effect

CARDIAC RESYNCHRONIZATION THERAPY (CRT) is used frequently for patients with heart failure associated with abnormal ventricular conduction, indicated by a wide QRS complex, resulting in cardiac dyssynchrony. An increase of left ventricular (LV) contractility is observed in the majority of these patients.1,2
Patients with decreased LV function undergoing cardiac surgery are at an increased risk of difficult separation from cardiopulmonary bypass (CPB) and a poor clinical outcome despite revascularization. Directly after weaning, interventricular dyssynchrony, paradoxical septal motion, and even temporary bundle-branch block are frequently observed, which could compromise optimal contractility and output of the left ventricle. Furthermore, atrioventricular blockade after CPB is observed in coronary artery bypass grafting (CABG) patients, which also can be effectively treated with a temporary atrioventricular (A-RV) pacemaker. In patients with interventricular dyssynchrony caused by RV pacing, this could diminish contractility and efficiency of the left ventricle. The presence of severe LV dyssynchrony in patients undergoing CABG was associated with high in-hospital and long-term mortality in patients with ischemic heart failure undergoing myocardial revascularization. It has been demonstrated that the use of CRT in these patients has a positive effect on hemodynamics, both postoperatively and directly after weaning from CPB. LV or biventricular (A-BiV) pacing in patients with a prolonged QRS duration has been demonstrated to improve systolic function and decrease the energy cost and use of inotropic support.

These previous observations were derived from LV dP/dt max measurements via invasive transmurally RADI (Radiwire, St Jude Medical Inc, St. Paul, MN, USA) pressure-tip guidewires placed directly into the left ventricle or via a pressure-volume catheter. The less-invasive transpulmonary thermodilution (TPTD) and pulse contour analysis have been shown to measure femoral dP/dt max accurately and correlate with changes in LV dP/dt max and volumetric preload parameters, including intrathoracic blood volume and global end-diastolic volume. The arterial pressure waveform was obtained using arterial waveform analysis. The arterial pressure waveform describes the change in pressure over time. The upslope of the arterial pressure curve represents the rise in LV pressure; therefore, the dP/dt max gives a representation of the contractility of the left ventricle.

Patients with a low left ventricular ejection fraction (LVEF) and intraventricular conduction delay could benefit from A-BiV pacing during cardiac surgery through a decreased need for inotropic medication, easier separation from CPB, and shorter intensive care unit stay.

The objective of this prospective, single-center study was to compare the effects of atrial right ventricular (A-RV) or A-LV pacing with A-BiV simultaneous pacing on the arterial dP/dt max, mean arterial pressure (MAP), and cardiac index (CI) via minimally invasive TPTD measurements. The secondary objective was to evaluate whether there exists a difference in the effect of A-BiV pacing on patients with normal QRS duration (< 120 ms) and prolonged QRS duration (> 120 ms).

Methods

Ethics

This prospective, single-center study was approved by the local medical ethical review board. All patients provided written, informed consent. This study is registered in the ISRCTN registry under trial number 90330260.

Patients

Because this study was a subanalysis of the authors’ previous work, some patient data also were used in a previous study on pulmonary blood volume measurement using contrast-enhanced ultrasound. All eligible patients were 18 years or older, had an LVEF < 35%, and signs of dyssynchrony with and without prolonged QRS duration and were scheduled for CABG surgery and/or valve surgery. Patients who experienced a myocardial infarction within 3 months before the study were excluded. Because this study was a subanalysis of the authors’ previous study on pulmonary blood volume measurement using contrast-enhanced ultrasound, patients with a contraindication for transesophageal echocardiography also were excluded.

Preoperative procedures

All patients received standard preoperative care, which included a physical examination, 12-lead electrocardiogram, and preoperative laboratory data. All patients underwent a preoperative echocardiogram to assess the LVEF, LV end-diastolic diameter, LV dyssynchrony, and the presence of concomitant valvular disease.

Surgical procedures

Surgical procedures were equal to those of the authors’ previous study. Per local protocol, every patient received the following medication at the induction of anesthesia: cefazolin 2 g, tranexamic acid 1 g, etomidate 0.2 mg/kg, fentanyl 5 to 7 µg/kg, and rocuronium 0.6 mg/kg. If indicated and deemed necessary by the attending anesthesiologist, patients received midazolam 5 mg and dexmedetomidine 1 mg/kg. General anesthesia was maintained with propofol 5 mg/kg/h and alfentanil 0.05 mg/kg/h via a perfusor. The decision whether to use inotropic/vasoactive drugs and dosage were made by the attending anesthesiologist. After induction, patients’ airways were intubated, and an 8.5 F central venous catheter (DM-12853; Arrow, Reading, PA) was placed in the right jugular vein. The medial lumen was connected to the injectate temperature sensor (PV-4046; Pulsion Medical Systems, Munich, Germany). A PulsioCath 5 F thermistor-tipped catheter (PV2015L20A; Pulsion) was placed in the femoral artery. Both the injectate sensor and the PulsioCath were connected to the pulse contour cardiac output (PiCCO) monitor (Pulsion Medical Systems, Munich, Germany).

The effect of the different pacing modalities was monitored continuously with a sample every 12 seconds after CPB during hemostasis of the thorax in a period with minor hemodynamic fluctuations and no change in inotropes and vasopressor doses. The pacemaker technician and anesthesiologist (B.G. and I.H., respectively) performed the different pacing modalities once, and the values of arterial dP/dt max,
MAP, and CI were registered by the PiCCO monitor automatically. Times were registered by the attending anesthetic nurse.

The dP/dt\text{max}, MAP, and CI parameters were collected using pulse contour analysis of the arterial pressure wave. Therefore, a calibration measurement was performed via injection of 20 mL of cold saline as an indicator in the central venous catheter.\textsuperscript{23} At the tip of the femoral artery PiCCO catheter, a thermistor registered the temperature change in time. The CI was estimated from the thermodilution curve using the Stewart-Hamilton equation.

The injection of this indicator automatically started the measurement on the PiCCO monitor. All TPTD data were stored via PiCCO-Win software (Pulsion Medical Systems, Munich, Germany) on a computer that was linked to the PiCCO monitor.

Volume replacement was standardized. Before surgery, no volume was added, and volume status was evaluated before and after bypass via transesophageal echocardiography. The CPB machine was primed with 1 L of saline and 0.5 L of colloid (Voluven; Fresenius Kabi Norge, Halden, Norway). After weaning the patient from CPB, the aim was to empty the reservoir completely; otherwise, the reservoir volume was concentrated and returned to the patient. Other blood loss was cell-saved and returned to the patient. The preload and contractility of the left ventricle were estimated visually using echocardiography before and after bypass.\textsuperscript{24}

For pacing, temporary wires were sutured to the right atrium and right ventricular (RV) free wall, according to standard procedures. Similar to the right ventricle, additional temporary LV leads were sutured to the basal obtuse marginal part of the left ventricle. Pacing leads were connected to a standard external dual-chamber pacemaker (Medtronic Temporary Pacemaker Model 5388; Medtronic, Minneapolis, MN). To connect the RV and LV leads to this device, a splitter was placed in the ventricular channel, thus enabling simultaneous A-BiV pacing (Fig 1).

**Pacing Protocol**

After confirmation of an adequate pacing and sensing threshold, the different pacing modalities were used in standardized order. Atrial pacing 5-to-10 beats above the intrinsic atrial rhythm was used for patients with normal atrioventricular (AV) conduction. By using this minimal overdrive pacing, the heart rate is kept constant during the hemodynamic measurements to avoid changes in hemodynamics due to unpredictable changes in heart rate. For patients with prolonged AV conduction, RV pacing was used as a backup, with an AV interval of 120 ms.

In patients with intact AV conduction, A-RV pacing was performed with an AV interval equal to 75% of the intrinsic PQ time. The pacing protocols for A-LV pacing and simultaneous A-BiV pacing were identical to A-RV pacing, as previously described. A-RV pacing is considered to be baseline conditions. Simultaneous A-BiV pacing was obtained using a splitter in the ventricular channel for simultaneous RV and LV pacing (Fig 1).

Determination of the pacemaker stimulation threshold was performed for each pacemaker lead by slowly turning the output (mA) to a higher range until capture was obtained on the electrocardiogram, which is the stimulation threshold. The output of the pacemaker was subsequently set at 2 times the stimulation threshold.

Baseline was defined as the average A-RV pacing before and after each pacing mode, depending on the status of AV conduction. To minimize the effect of drift over time, all data were obtained for a minimal period of 45 seconds per pacing modality to reach a steady state, and a baseline pacing mode was performed between the different pacing modalities, both as recommended by Thibault et al.\textsuperscript{25}

The authors have observed that after changing pacing conditions, positive and negative LV dP-dt are stabilized within these 45 seconds.\textsuperscript{8}
The effect of the different pacing modalities was monitored continuously after CPB during hemostasis of the thoracotomy wound and closure of the thorax.

Statistical Analyses

All data were analyzed using SPSS Statistics, Version 21, (IBM, Armonk, NY). Because the total number of included patients was fewer than 20, nonparametrical testing was performed. Therefore, continuous variables were described in terms of medians and interquartile range. Differences in the arterial dP/dtmax values between settings of the pacing modalities were tested using Wilcoxon’s test. Differences in arterial dP/dtmax values between normal and prolonged QRS duration were determined using the Mann-Whitney test. QRS duration < 120 ms was defined as normal, and a QRS duration ≥ 120 ms was defined as prolonged. A p value < 0.05 was considered to be significant.

Results

A total of 17 patients undergoing cardiac surgery between January 2010 and July 2013 met the inclusion criteria of this study. Two patients were excluded; in 1 patient, use of an intra-aortic balloon pump, and in another patient, the PiCCO catheter malfunctioned. Preoperative patient characteristics, subdivided into the QRS duration among the different pacing modalities.

Arterial dP/dtmax

No difference was found regarding dP/dtmax when comparing RV pacing with LV pacing (800 ± 587 mmHg/s v 810 ± 597 mmHg/s, p = 0.382). However, simultaneous A-BiV pacing showed significantly higher dP/dtmax values compared with RV pacing (846 ± 646 mmHg/s v 800 ± 587 mmHg/s, p = 0.023) (Fig 2A).

When comparing the dP/dtmax between patients with a normal and a prolonged QRS duration, significant differences were observed in RV pacing (629 mmHg/s v 956 mmHg/s, p = 0.028), LV pacing (562 mmHg/s v 994 mmHg/s, p = 0.04), and simultaneous A-BiV pacing (663 mmHg/s v 966 mmHg/s, p = 0.049) (Fig 3). Within the intrinsic and baseline groups, the dP/dtmax values between the normal and prolonged QRS times were not significantly different.

MAP

MAP was not different when comparing RV pacing with LV pacing (70.8 ± 18 mmHg v 71.0 ± 18 mmHg, p = 0.650). However, simultaneous A-BiV pacing showed greater MAP values compared with RV pacing (70.8 ± 18 mmHg v 77 ± 19 mmHg, p = 0.036) (Fig 2B).

Discussion

This study demonstrated that simultaneous A-BiV pacing improve hemodynamics (arterial dP/dtmax and MAP) in patients with reduced LV function undergoing cardiac surgery compared with standard RV pacing. Furthermore, patients with a prolonged QRS duration demonstrated a significantly higher
arterial dP/dt\textsubscript{max} compared with patients with a normal QRS duration for RV, LV, and simultaneous A-BiV pacing. Moreover, these results indicated that arterial dP/dt\textsubscript{max} and pressure measurements are feasible for evaluating the effect of intraoperative pacing.

The effect of simultaneous A-BiV pacing on cardiac function has been well established, and simultaneous A-BiV pacing has become the gold standard for treating heart failure patients with an LVEF \( < 35\% \), a QRS complex \( > 130 \) ms, and sinus rhythm.\textsuperscript{26} Multiple studies have shown the acute beneficial effect of CRT on pulse pressure, LV dP/dt\textsubscript{max}, and cardiac output (CO).\textsuperscript{2,13,27}

Only recently has A-BiV pacing after coronary surgery with CPB gained research interest. One of the first studies to focus on the hemodynamic effects after elective CABG was performed by Foster et al.\textsuperscript{9} They investigated 18 patients without atroventricular and intraventricular conduction delay, including 14 patients with an LVEF \( > 40\% \), and found that atrioventricular pacing increased the CI significantly 12-to-36 hours after coronary artery revascularization compared with AAI pacing.

In 54 patients with a mean QRS duration of 124 ms and a mean LVEF of 25\%, Dzemali et al found that simultaneous A-BiV pacing improved CO and that this improvement lasted 12-to-36 hours postoperatively.\textsuperscript{10} Flynn et al found similar results for CI 1 hour postoperatively, but their study mainly included patients without conduction delay.\textsuperscript{11} These studies are in agreement with the findings of the study presented here, which demonstrated that the difference in response between normal and prolonged QRS is not significant. However, the absolute values were greater in the prolonged QRS groups for all pacing modes.

CRT is indicated in patients with decreased ejection fraction (\( < 35\% \)) with signs of dyssynchrony between the left and right ventricles. As reported earlier, the response to CRT is limited to 60\% to 70\%.\textsuperscript{28}

A positive response to CRT is defined using different criteria, such as a decrease in N-terminal pro-brain natriuretic peptide, improvement in ejection fraction, or an increase in functionality. The most frequently used criterion is a decrease in LV end-systolic volume \( > 15\% \).\textsuperscript{29–31} Contrary to the aforementioned criteria, the present study evaluated response using changes in dP/dt, MAP, and CI perioperatively.

Predictors for response to CRT are defined within different diagnoses. Ischemic cardiomyopathy is known to respond less than non ischemic origin of LV dysfunction, as are patients with a severely decreased functional capacity as described by New York Heart Association classification and low quality-of-life scores (Minnesota Living with Heart Failure score).\textsuperscript{29,32,33} Furthermore, extremely dilated LV volume, body mass index \( < 30 \) kg/m\(^2\), smaller left atrial size, and male sex also are factors associated with nonresponse.

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**Fig 2.** Perioperative (A) arterial dP/dt\textsubscript{max} and (B) MAP measurements during different pacing modes compared with RV pacing as a baseline for both. *NS; \( \spadesuit p = 0.023 \); and \( \diamondsuit p = 0.036 \). VV0 = pacing of left and right ventricles with 0 ms of delay.

**Fig 3.** Boxplots displaying the difference in arterial dP/dt\textsubscript{max} between patients with a normal or prolonged QRS duration for (A) RV (\( p = 0.028 \)), (B) LV (\( p = 0.040 \)), and (C) A-BiV (\( p = 0.049 \)) pacing modalities.
It appears that there is a limit to which response seems possible to expect. This study’s patient population was mainly ischemic and therefore was less prone to respond; however, the study included a group of patients with left bundle-branch block (n = 7), which is known to demonstrate a higher response rate when the QRS duration is > 150 ms. However, the mean QRS duration in the prolonged QRS duration group was just below this margin at 148 seconds.

Multiple studies have focused on the effect of CRT directly after weaning from CPB. A recent study performed by Russell et al included 38 patients with an LVEF < 35% undergoing on-pump surgical revascularization with or without associated valve surgery. They reported an increased CO of 7% and 9% for A-Biv pacing compared with AAI and RV pacing, respectively. The study by Hanke et al found that both CI and LV dP/dtmax improved when comparing A-Biv pacing with RV pacing. Although both studies did not exclude patients with a QRS duration > 130 ms, the average QRS duration in the A-Biv group was lower than the average QRS duration in the study presented here, 113.3 ms and 98 ms, respectively, versus 126.8 ms in the present study.

Hamad et al also studied the effects of A-Biv CRT in patients with poor LV function and focused on patients who had a QRS duration > 130 ms with a left bundle-branch pattern. Mean LV dP/dtmax was measured transmurally using a RADI sensor-tipped pressure guidewire. Although only 11 patients were included, they also found a significant increase in mean LV dP/dtmax when comparing simultaneous A-Biv pacing with RV pacing.

Whereas this study focused on measuring the effect of CRT directly after weaning from CPB using a minimally invasive approach, previous studies on the same subject were performed with more invasive measurement methods. Hanke et al, Hamad et al, and Russell et al used a pressure-volume catheter, a transmurally placed RADI sensor-tipped pressure-guided wire, and a pulmonary artery catheter, respectively. The articles by De Hert et al and Morimont et al both concluded that femoral dP/dtmax underestimates LV dP/dtmax but accurately reflects changes in LV dP/dtmax during various interventions. Because femoral artery dP/dtmax measurement is less invasive than the methods used in previous research on this subject, it also is easier to incorporate it into clinical routine and it is less time consuming. An additional advantage of the femoral artery catheter over the more invasive measurement methods is that it can be used during and after surgery. Adequate vascular filling is the only essential condition for accurate assessment of hemodynamics via PiCCO.

Limitations

The relatively small number of included patients may limit interpretation of the present results because the number of patients was not large enough to stratify for QRS duration and compare the effect of the different pacing modalities.

This study focused on the effect of simultaneous A-Biv resynchronization and LV pacing versus standard RV pacing. The authors did not incorporate sequential A-Biv resynchronization, which is pacing both ventricles with different intraventricular conduction delays, in their research. However, earlier research on patients with severe heart failure showed that when simultaneous A-Biv resynchronization is compared with sequential A-Biv resynchronization, the latter improves the LV systolic and diastolic performance even more. Recent studies on the effect of sequential A-Biv resynchronization in patients with LV dysfunction undergoing CABG seem to confirm that sequential biventricular resynchronization also improves cardiac function peripheratively.

As previously stated, other studies found an improved CO or CI up to 32 hours postoperatively with A-Biv pacing compared with AAI pacing. However, the presented results did not demonstrate such improvement, which may be related to the variability in the CO measurements and the subtlety of change in hemodynamic parameters. Therefore, subtle changes in CO/CI may have remained undetected in this relatively small sample size study.

In this study, the authors found no significant difference in CI, which could be due to the relatively small number of included patients. The studies by Hanke et al and Garcia-Bengochea et al both found relatively small differences in CI among pacing modalities (0.53 L/m², p < 0.01, n = 21 and 0.27 L/m², p < 0.05, n = 50, respectively). These expected subtle changes in hemodynamic parameters combined with the variability of CO measurements may explain the lack of increase of CI. Moreover, different studies have shown a high agreement between the measured CO using pulse contour analysis but a less reliable trending compared with TPTD CO. On the other hand, a recent study in dogs showed a high accuracy of the pulse contour analysis in measuring CO during large volume shifts.

Due to these hemodynamic changes, the authors of the present study did not perform different sequential A-Biv pacing modalities. Another limitation of this study was that no stratification was performed for the use of inotropic drugs. Inotropic drugs could influence the effect on arterial dP/dtmax and MAP. However, as shown in Table 2, only 7 patients received inotropic drugs. The dosage and the decision to use inotropic/vasopressor drugs were determined by the attending anesthesiologist. All measurements per patient were performed with the same dosage of inotropic/vasopressor drugs. Pacing protocol was performed in a relatively stable post-bypass phase in which no extra fluids needed to be administered. If the dP/dtmax and/or MAP would have been altered by the use of inotropic/vasopressor drugs, this effect would be (roughly) the same for each pacing modality because the dosage did not change during the different pacing modalities. Therefore, the

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<th>Type</th>
<th>n (%)</th>
<th>Mean dose (range)</th>
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<tr>
<td>Any inotropic drug</td>
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<td></td>
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<tr>
<td>Dobutamine, μg/kg/min</td>
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<td>Milrinone, μg/kg/min</td>
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<tr>
<td>Norepinephrine, μg/kg/min</td>
<td>3 (20%)</td>
<td>0.04 (0.03-0.07)</td>
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authors presume that the effect of inotropic drugs on the arterial dP/dt\textsubscript{max} and MAP was limited in this study.

**Future Studies**

As previously stated, the authors found a significantly higher arterial dP/dt\textsubscript{max} in the groups with the prolonged QRS duration for the RV, LV, and simultaneous A-BiV pacing modalities, which can be explained by the presence of dyssynchrony in the patients with a prolonged QRS duration. Stratification for this variable could be interesting for future studies with larger patient groups.

The present study focused only on the acute improvement of cardiac function after CPB and did not examine the possible long-term benefits of the improvement of cardiac function. According to Steendijk et al., the long-term hemodynamic effects of simultaneous A-BiV pacing in patients with heart failure showed that the acute hemodynamic improvements of CRT are maintained and that ventricular-atrial coupling, mechanical efficiency, and chronotropic response are improved after 6 months of CRT. The study by Cleland et al., which included 813 patients with heart failure who were randomly assigned to receive either medical therapy only or medical therapy with CRT, found that CRT improved the quality of life and symptoms and reduced complications and the risk of death. To the authors’ knowledge, no other studies have focused on the long-term outcome of CRT in patients with reduced LV function who are undergoing cardiac surgery. This might be a focus for upcoming studies.

**Conclusion**

In conclusion, in patients with preoperative decreased LV function undergoing CABG, A-BiV pacing improved the arterial dP/dt\textsubscript{max} and MAP in patients with both a normal and a prolonged QRS duration compared with standard RV pacing. Patients with a prolonged QRS duration seem to benefit more from RV, LV, and A-BiV pacing than do patients with a normal QRS duration, as shown by the larger effect of A-BiV on the arterial dP/dt\textsubscript{max}; there were no differences in MAP and CI among the groups.

Because it was feasible to evaluate for the effect of pacing on cardiovascular function using a clinical measurement technique, the authors believe that CRT strategies in the intraoperative setting after CPB warrant further exploration in different patient populations with regard to QRS duration and ventricular function.

**References**


