Abstract

OBJECTIVES: We have previously demonstrated that left ventricular pacing improves coronary vascular resistance (CVR) in the CABG patient with atrial fibrillation (AF) [1]. The aim of the present study was to determine the mechanism of this improved coronary conduit and, in addition, to explore the possible benefits with biventricular pacing in patients with and without severe left ventricular dysfunction.

METHODS: In 43 CABG patients (mean age 69.5 ± 1.3 years; ejection fraction (EF) 49 ± 2%) with AF, we analysed coronary vascular resistances (CVRs) and the contemporary changes in the BGF obtained during right ventricular outflow tract (RVOT), right- (RV), left- (LV) and right-left ventricular pacing (biventricular pacing, BiVP) using the ultrasonic transit-time methodology.

RESULTS: BiVP resulted in the highest percentage decrease of CVR in the overall study group by 17.5 ± 3.0% (P < 0.001), followed by RVOT pacing with 13.9 ± 3.9%. Accordingly, the highest mean BGF was achieved during BiVP, resulting in a 21.6 ± 2.6% increase when compared with no pacing and 16 ± 3.7% when compared with RV pacing. Analysis of patients according to their preoperative LV function (EF ≥50%, n = 26; EF <50%, n = 17) showed significantly lower CVR (P < 0.037) and higher BGF during BiVP in patients with lower EF.

CONCLUSIONS: Placement of an additional LV pacing wire offered a significant improvement in BGF by minimizing CVR in patients with AF and poor EF.

Keywords: Atrial fibrillation • Coronary vascular resistance • Pacing • Coronary artery disease

INTRODUCTION

Atrial fibrillation (AF) and poor left ventricular function (EF) are frequent co-morbidities in patients undergoing cardiac surgery. A perioperative increase in coronary vascular resistance (CVR) is associated with increased coronary vascular resistance (CVR) and reduced coronary blood flow. Hence, the choice of the pacing site is very important for acute haemodynamic effects. Whereas numerous studies have been performed to investigate the haemodynamic effects of cardiac pacing [2–4], the choice of the optimal pacing site in patients with chronic AF and its impact on coronary vascular bed and myocardial blood flow are less extensively investigated. The high prevalence of AF in patients undergoing cardiac surgery underscores the importance of identifying the optimal pacing site to improve postoperative haemodynamics and myocardial perfusion that may benefit early clinical outcome of this high-risk patient cohort.

We have previously demonstrated the role of univentricular pacing modalities in influencing bypass graft flows (BGFs) in the immediate postoperative period in the CABG patient with AF, but we had not demonstrated the mechanism by which this is achieved [5]. We hypothesized that changes in the coronary vascular bed occur, and that these result in alterations in the coronary conduit flow. Therefore, we wished to determine the mechanism of this improved coronary conduit and, in addition,
to explore the possible benefits with biventricular pacing (BiVP). The present study examined the acute effects of mono- and BiVP sites on coronary vascular resistance (CVR) assessed by bypass graft transit-time flow measurements in patients with and without severe left ventricular dysfunction and AF following CABG.

**PATIENTS AND METHODS**

Enrolment criteria for this study included any adult patient with chronic AF undergoing first-time coronary artery bypass grafting who required intraoperative pacing due to bradycardia. Exclusion criteria included tachycardia (>100 beats/min) or the presence of a permanent pacing system. Preoperative ECG details were noted, including rhythm, QRS duration and aberrant conduction. Perioperative risk was predicted by EuroSCORE. Left ventricular ejection fraction (LVEF) was measured by ventriculography.

**Surgical technique**

The technique of operation was similar in all patients. Cardiopulmonary bypass was performed with standard equipments and techniques using routine cannulation (right atrial cannulation and ascending aortic cannulation) under systemic normothermia and cardiac arrest achieved using antegrade warm hyperkalaemic blood cardioplegia. Cardioplegia was repeated every 20 min or whenever electrical activity resumed. All distal anastomoses were carried out during a single interval of aortic cross-clamping, and the aortic anastomoses were performed with partial aortic cross-clamping while the heart was kept in the beating, empty state. The site of the proximal anastomosis was chosen in order to achieve an optimal bypass course without kinking or tension.

**Epicardial pacing modalities**

Prior to weaning from cardiopulmonary bypass, standard temporary bipolar pacing wires (Osypka TME 66 ZL bipolar, Germany) were placed on the right ventricular outflow tract (RVOT), on the mid paraseptal region of the right (RV) and the left anterolateral wall (LV) close to the left atrial appendage. The following monoventricular pacing modes were studied: RV pacing, RVOT pacing and LV pacing. To achieve biventricular stimulation (RV–LV pacing), the RV and LV pacing wires were connected to the negative pole of the external pacemaker. Another pacing wire was placed subcutaneously and attached to the positive pole of the pacemaker. PACing was performed using a commercially available external dual-chamber pacemaker 5388 Medtronic (Medtronic, Inc., Minneapolis, MN, USA). Sensing and pacing functions of the leads were tested and confirmed. The pacing rate was set at 100 beats/min. Systemic haemodynamics and graft flow parameters were collected simultaneously before pacing and during ventricular stimulation after weaning from cardiopulmonary bypass and before the sternum was closed. All recordings were acquired after AF was confirmed through ECG and under stable haemodynamic conditions. Each patient underwent 2 min periods of RV, RVOT, LV and BiVP followed by a 1-min period for recovery. During the pacing period, no changes were made in inotropic medications, sedation or mechanical ventilation, and no surgical interventions were performed. At the end of each pacing mode, the following haemodynamic variables were recorded: arterial blood pressure (systolic, diastolic and mean), central venous pressure and left atrial pressure.

**Measurement of graft flow**

Transit-time flow measurement is a well-established method for intraoperative quality control during coronary artery bypass grafting [6, 7]. ECG-triggered blood flow measurements were performed using a transit-time flowmeter (CardioMed CM2005, MediStem AS, Oslo, Norway) under stable haemodynamic conditions. The same transit flow measurement set-up was used in all cases. Probes measuring 2, 3 and 4 mm in size were available to avoid distortion or compression of grafts. The flexible perivascular flow probes were placed 2 cm from the proximal anastomosis and chosen to fit perfectly around the grafts using a small amount of sterile gel. Only saphenous vein grafts with a single distal anastomosis were used for measurement. For demonstration technical reasons, arterial grafts (i.e. left internal mammary artery (LIMA)) were not included in the study. The target vessel differed among patients, but all patient measurements were performed within the same graft, which served as an internal control. Flow measurements included mean flow (ml/min) and the pulsatility index (PI). The PI, expressed as an absolute number, is an index related to the resistance to flow distal to the measurement site in the graft. Clinical studies have shown that a PI of <5 indicates a well-functioning graft [8, 9]. The PI was automatically calculated by the flowmeter according to the following formula:

\[
\text{PI} = \frac{\text{maximum volumetric peak flow} - \text{minimum volumetric peak flow}}{\text{mean volumetric flow}}.
\]

**Graft flow reserve**

The graft flow reserve (GFR) was calculated from the mean flow occurring during pacing divided by the mean flow during temporary cessation.

\[
\text{GFR} = \frac{\text{mean graft flow (pacing on)}}{\text{mean graft flow (pacing off)}}.
\]

**Coronary vascular resistance**

The resistance was calculated using the Poiseuille–Hagen equation \( R = (P_1 - P_2)/Q \), where \( R \) is the peripheral resistance, \( P_1 - P_2 \) is the pressure drop across the perfused segment of the coronary vascular bed (mmHg) and \( Q \) is the blood flow (ml/min). Since the CVR depends on the pressure gradient over the vascular bed and the flow through it, CVR at the end of operation could be determined from the mean arterial pressure, right atrial pressure and the flow through the graft to that area by applying the same formula:

\[
\text{CVR (mmHg/ml/min)} = \frac{\text{mean systemic arterial pressure} - \text{mean right atrial pressure}}{\text{mean coronary bypass flow}}.
\]
Statistical analysis

All values were expressed as mean ± standard error of mean (SEM) in the text and tables. Statistical analysis was performed on absolute values. To avoid intraoperative biases and to further achieve a sufficient statistical power, each patient served as his or her own control. Comparison between paired data was tested with a t-test with a Bonferroni correction for multiple comparisons. Results were analysed as an overall group (n = 43), the LVEF ≥50% subgroup (n = 26) and the LVEF < 50% subgroup (n = 17). A value of P < 0.05 was considered statistically significant. All authors have read and agreed to the manuscript as written.

RESULTS

Table 1 demonstrates the preoperative patient demographics and patient operative details. A total of 43 adult patients with AF were prospectively enrolled in the study. All the patients were elective cases. In the overall group, the mean age was 69.5 ± 1.3 years (range, 48–89 years) and the mean EuroSCORE was 5.9 ± 0.4 (range, 2–13). The majority of patients were males (72%, n = 31). The preoperative mean left ventricular function was 49.2 ± 2.3%, as assessed by left ventriculography. The QRS duration on preoperative ECG was greater than 120 ms in 8 patients (119.5 ± 6.4 ms, range from 75 to 172 ms) in the EF <50% group and in 3 patients in the EF ≥50% group (96.8 ± 4.0 ms, range from 59 to 135 ms; P < 0.0029). No statistical differences were observed between groups.

In the overall study group of 43 patients, the mean arterial pressure recorded prior to ventricular pacing was 68.8 ± 1.5 mmHg. BiVP resulted in a significant increase in the mean arterial pressure when compared with no pacing (72.7 ± 1.5 vs 68.8 ± 1.5 mmHg; P < 0.05). No significant differences in the mean arterial pressure was noted between various ventricular pacing modes. Analysis of patients divided according to their preoperative LV function revealed that in patients with EF ≥50%, BiVP resulted in significantly higher mean arterial pressure when compared with RVOT pacing (P < 0.05). In patients with EF < 50%, a statistically significant increase was observed during BiVP and RV pacing relative to RVOT pacing.

The average CVR as measured in the 43 patients was 53.0 ± 11 mmHg/ml/min without pacing, 145 ± 11 mmHg/ml/min during RV pacing, 1.3 ± 0.1 mmHg/ml/min during RVOT pacing, 1.34 ± 0.1 mmHg/ml/min during LV pacing and 1.25 ± 0.09 mmHg/ml/min during BiVP (Fig. 1A). BiVP resulted in the highest percentage decrease of CVR in the overall study group by 17.5 ± 3.0% (P < 0.001), followed by RVOT pacing with a 13.9 ± 3.9% decrease. Accordingly, highest mean BGFs (Fig. 1B) were achieved during BiVP, resulting in a 21.6 ± 2.6% increase when compared with no pacing and 16 ± 3.7% when compared with RV pacing (no pacing: 48.2 ± 3.7; RV: 56.0 ± 4.3; RVOT: 60.6 ± 4.4; LV: 59.2 ± 4.3; BiVP: 63.5 ± 4.5 ml/min). No significant differences in PIs were recorded during the four different pacing modalities.

Analysis of patients divided according to their preoperative left ventricular function (EF ≥50%, n = 26; EF < 50%, n = 17) reported statistically significant differences. Considering CVR (Fig. 2A), in patients with lower EF (EF < 50%) with BiVP, a significant higher decrease was achieved (P < 0.037). Accordingly, highest mean BGFs were found in patients with lower EF during BiVP (Fig. 2B). However, no significant differences in graft flow and systemic haemodynamics were observed between groups.

GFR was recruited during all ventricular pacing modes in all grafts (GFR > 1). Comparing different pacing sites, BiVP followed by RVOT pacing showed greater recruitment of GFR both in the overall study group and subgroups (Fig. 3).

<table>
<thead>
<tr>
<th>Table 1: Patient characteristics and intraoperative details</th>
<th>All (n = 43)</th>
<th>Subgroups</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EF ≥50 (n = 26)</td>
<td>EF &lt;50 (n = 17)</td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>31/12</td>
<td>19/7</td>
<td>12/5</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69.5 ± 1.3</td>
<td>66.8 ± 1.7</td>
<td>73.6 ± 1.6</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>5.9 ± 0.4</td>
<td>4.7 ± 0.3</td>
<td>7.6 ± 0.6</td>
</tr>
<tr>
<td>2-vessel disease</td>
<td>28% (n = 12)</td>
<td>35% (n = 9)</td>
<td>18% (n = 3)</td>
</tr>
<tr>
<td>3-vessel disease</td>
<td>72% (n = 31)</td>
<td>65% (n = 17)</td>
<td>82% (n = 14)</td>
</tr>
<tr>
<td>Mean LVEF</td>
<td>49.2 ± 2%</td>
<td>60 ± 1%</td>
<td>34 ± 3%</td>
</tr>
<tr>
<td>HR prior to pacing (bpm)</td>
<td>84 ± 1.4</td>
<td>80 ± 2.2</td>
<td>81 ± 3.6</td>
</tr>
<tr>
<td>QRS duration &gt;120 ms</td>
<td>25% (n = 11)</td>
<td>11% (n = 3)</td>
<td>47% (n = 8)</td>
</tr>
<tr>
<td>Mean QRS duration (ms)</td>
<td>105.8 ± 3.9</td>
<td>96.8 ± 4</td>
<td>119.5 ± 6.4</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>81.5 ± 2.7</td>
<td>81.6 ± 3.3</td>
<td>81.5 ± 4.8</td>
</tr>
<tr>
<td>Cross-clamping time (min)</td>
<td>46.6 ± 2.3</td>
<td>45.7 ± 2.6</td>
<td>48.1 ± 4.2</td>
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<tr>
<td>Total number of used grafts</td>
<td>134</td>
<td>83</td>
<td>51</td>
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<tr>
<td>Total number of pedicled LITAs</td>
<td>40</td>
<td>24</td>
<td>16</td>
</tr>
<tr>
<td>Mean number of used grafts</td>
<td>3.1 ± 0.1</td>
<td>3.2 ± 0.1</td>
<td>3 ± 0.2</td>
</tr>
</tbody>
</table>

Results are reported as the mean ± SEM. A value of P < 0.05 was considered significant.

CPB: cardiopulmonary bypass; HR: heart rate; LITA: left internal thoracic artery; LVEF: left ventricular ejection fraction; EF: ejection fraction.
DISCUSSION

Over the last decade, several studies have indicated that chronic long-term right ventricular apical pacing is associated with left ventricular dysfunction, regional wall motion abnormalities and AF, and leads to increased mortality and morbidity [10–13]. Therefore, alternative ventricular pacing sites have been investigated to prevent these potential deleterious effects [1, 14, 15].

In cardiac surgical procedures, it has become standard practice to position pacing leads on the right atrial and right ventricular surface for temporary pacing in patients with sinus rhythm. In the critical ill cardiac surgery patient, the loss of sinus rhythm and atrial contribution to cardiac output can lead to significant haemodynamic instability. In these instances, if pacing is required, patients with AF receive only right ventricular pacing wires. Although the anterior wall of the right ventricle is traditionally the most commonly used location (due to the ease of application), there is no agreement on optimal wire position. Over the last decade, the alternative ventricular pacing sites have been abundantly debated. Yet, there is much controversy regarding the optimal site for lead placement. We have previously demonstrated improved coronary conduit flows during VVI pacing (ventricular demand pacing (ventricle paced, ventricle sensed, pacemaker inhibited in response to a sensed beat)) with ventricular wires placed on the RVOT in patients with AF [5], but we had not demonstrated the mechanism by which this was achieved.

The data of our study indicate that simple LV pacing is less effective than RVOT pacing with regard to mean BGF and mean CVR. This finding may be explained by the proximity of the RVOT pacing lead to the native ventricular conduction system. Consistent with our results, other investigators attribute the favourable effect of RVOT pacing to its more physiological activation pattern that results in less LV dyssynchrony [5, 12, 16–18]. We assume that the proximity to the normal conduction system in RVOT pacing compared with LV or RV pacing mimics the physiological ventricular activation sequence, results in less dyssynchrony and produces less deterioration in left ventricular performance. Hence, an improvement in the mean BGF and the mean CVR can be observed.

The benefit of cardiac re-synchronization therapy in cardiac surgery patients with sinus rhythm has already been demonstrated [3, 19, 20]. BIVP at optimum atrio-ventricular delay is associated
ventricle; RVOT: right ventricular outflow tract; LV: left ventricle; BV: biventricular; EF: ejection fraction.

The main limitation of this study is that the cardiac output is not measured. Graft flow reserve was defined as the mean bypass graft flow during pacing divided by the mean bypass graft flow without pacing. RV: right ventricle; RVOT: right ventricular outflow tract; LV: left ventricle; BV: biventricular; EF: ejection fraction.

Figure 3: Graft flow reserve during different ventricular pacing modes relative to no pacing. Graft flow reserve was defined as the mean bypass graft flow during pacing divided by the mean bypass graft flow without pacing. RV: right ventricle; RVOT: right ventricular outflow tract; LV: left ventricle; BV: biventricular; EF: ejection fraction.

with improved cardiac performance, cardiac output, coronary blood flow and decreased systemic vascular resistance compared with atrio-ventricular or AAI pacing (atrial demand pacing (atrium paced, atrium sensed, pacemaker inhibited in response to a sensed beat)). BiVP narrows the QRS complex duration in patients with heart block, which may have consequent beneficial effects on the coronary conduit flow by prolonging the duration of diastole, and reducing global LV strain.

Nevertheless, recent investigations by Evonich et al. and Eberhardt et al. did not show improved postoperative hemodynamics or clinical outcome with regard to BiVP [21, 22]. In contrast to our study, they evaluated the effects of BiVP in postoperative patients, whereas we focused on the direct intraoperative weaning process after myocardial ischaemia and reperfusion injury. Several investigators describe a mechanical dysynchrony that occurs after weaning from CPB as a result of regional myocardial oedema despite normal preoperative QRS complexes [21, 23]. Hence, improvement and acute haemodynamic effects of BiVP apply to the immediate perioperative period after weaning from CPB [21]. Eberhardt et al. [21] showed that the positive effect of BiVP disappears with restoration of myocardial function. Therefore, the perioperative setting in our study is not comparable with long-term effects in postoperative investigations.

Whereas numerous studies have been performed to investigate the haemodynamic effects of atrio-biventricular pacing, minimal data exist regarding BiVP in surgical patients with AF and its impact on CVR and coronary conduit flow. In the present study, we showed that BiVP significantly improved BGFs. In addition, we have now demonstrated that this is the result of decreased CVR generated by the site of ventricular pacing. Interestingly, although systemic haemodynamics did not seem to be influenced by BiVP in comparison with RV pacing, BGFs achieve an optimal level by BiVP.

**Limitations of the study**

The main limitation of this study is that the cardiac output is not included in the model. The number of patients who received a pulmonary catheter or whose cardiac outputs were measured at the time of measuring the graft flow was too small to include cardiac output in the statistical model. Furthermore, this study did not control for inotropic support. Nevertheless, the flows were measured in all patients during comparable haemodynamic conditions. We did not study the long-term effects of the different pacing modes in our patients. In this study, we chose to place the left-sided lead on the anterolateral aspect of the left ventricle. However, there is much controversy regarding the optimal site for left ventricular lead placement. Alternative sites may still demonstrate some benefits [24]. However, there appears to be great individual variability in the optimal site for left ventricular pacing. Some factors that are involved with the coronary flow, such as the flow competition and vasomotoricity, the phenomenon of coronary autoregulation, as well as factors such as age, gender or medical conditions, among others were not considered in this study because the aim was to determine the CVR related exclusively to the coronary bed, accepting it as persistent to the physiological or pathological changes. For demonstrative technical reasons, arterial grafts (i.e. LIMA) were not included in the study. Different mean flows of arterial and venous graft conduits according to different pacing modalities were not recorded. Finally, graft flow variations concerning grafts to different myocardial areas (vein grafts to the left or right side) were not analysed.

**CONCLUSION**

We conclude that BiVP is associated with significantly higher mean bypass graft flows by lowering CVR in patients with reduced left ventricular function and AF following cardiopulmonary bypass. Although the results of all patients regardless of their LV function did not reach significance, a clear trend towards higher graft flows was observed in BiVP. Hence, BiVP may improve blood flow to the ischaemic myocardium by providing more optimal myocardial oxygen conditions. Therefore, the placement of biventricular leads appears to be the optimal pacing strategy in these patients. However, further studies are necessary in order to examine whether the acute graft flow improvement is sustained, and whether these changes are translated into an improved outcome.

**Conflict of interest:** none declared.

**REFERENCES**


