Effects of angiotensin converting enzyme inhibition on systemic vascular resistance and vasoconstrictor requirements during hypothermic cardiopulmonary bypass

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Abstract

Objective: We proposed that angiotensin converting enzyme (ACE) inhibitor therapy would alter systemic vascular resistance (SVR) during rewarming and increase the requirement for vasoactive drugs in the immediate post-bypass period. Methods: Sixty-five sequential adult patients undergoing cardiac surgical procedures requiring hypothermic (28°C) cardiopulmonary bypass (CPB) were recruited. Sixty-two fitted the inclusion criteria of which 21 were receiving ACE inhibitors prior to surgery. SVR was calculated at 1 min intervals during the rewarming phase of hypothermic CPB. The use of vasoactive drugs during and immediately after termination of CPB was recorded. The doctor administering these drugs was unaware of the nature of the study. Results: Mean SVR in the ACE group was 978 dyne/s per cm$^5$ and in the control group was 1194 dyne/s per cm$^5$ ($P = 0.006$). Mean arterial pressure was 48.8 mmHg in the ACE group and 56.3 mmHg in the control group ($P = 0.004$). There was a significant difference in vasoactive drug requirements between the groups ($P < 0.01$). There was no statistically significant difference in age, weight, body mass index, body surface area, theatre temperature, core temperature at which rewarming started, rate and time of rewarming, haematocrit on bypass or preoperative left ventricular function. Conclusion: Preoperative ACE inhibitor therapy decreases SVR during the rewarming phase of CPB and increases post-bypass vasoactive drug requirements. © 1998 Elsevier Science B.V. All rights reserved

Keywords: ACE inhibitor; Systemic vascular resistance; Cardiopulmonary bypass

1. Introduction

The renin–angiotensin system is a major determinant of vascular tone. Activation of this system in the rewarming phase of hypothermic cardiopulmonary bypass (CPB) increases systemic vascular resistance (SVR) [1,2]. Blockade of this system by angiotensin converting enzyme (ACE) inhibition reduces SVR [3,4]. Preoperative therapy with ACE inhibitors is associated with hypotension immediately following CPB and increased vasoconstrictor requirements [5,6].

We proposed patients on preoperative oral ACE inhibitors would have lower systemic vascular resistance during cardiopulmonary bypass. For the first time, measurements of SVR during the rewarming phase of CPB have been made in these patients. Vasoconstrictor requirements in the immediate post-bypass period are also documented.

2. Materials and methods

Sixty-five patients undergoing elective coronary artery bypass grafting and/or valve replacement were studied in sequence. This number was calculated from a pilot study examining SVR in ACE and control patients, aiming to give the final study a power >0.80. Three patients in whom ACE
Rewarming aimed to restore the patient’s core temperature to 37.0°C before termination of CPB. The use of vasoconstrictor drugs during weaning from cardiopulmonary bypass or in the immediate post-bypass period prior to arrival in the intensive care unit (ICU) was recorded. The decision to use vasoconstrictor drugs was made by a consultant anaesthetist unaware of the nature of the study. A vasoconstrictor or inotrope infusion was commenced during weaning from bypass or in the immediate post-bypass period in the presence of a low systolic blood pressure (<80 mmHg) despite adequate left (if measured) or right atrial filling pressures. Vasoconstrictor drugs included phenylephrine 100–500 μg boluses, dopamine 10–15 μg/kg per min, noradrenaline 1–20 μg/kg per min and adrenaline 0.1–1.0 μg/kg per min. For analysis of data, patients were classified as requiring or not requiring vasoconstrictor drug support during weaning from, or immediately after, termination of CPB.

2.1. Statistical analysis

Patient age, weight, body mass index (BMI), body surface area (BSA), volume of cold cardioplegia administered, rewarming time on bypass, ischaemic aortic cross clamp time and duration of CPB were compared between the two groups with non-paired t-tests. SVR and MAP were compared using non-parametric t-tests. The relationship between preoperative and operative variables and vasoconstrictor use was tested using logistic regression. Significance was taken as P < 0.05.

3. Results

A total of 62 patients were studied, 21 of which were on ACE inhibitors; seven on captopril, four on enalapril, five on lisinopril, four on ramipril, one on trandolapril. There was no significant difference between groups in patient characteristics, temperature parameters or duration of surgery (Table 1). There was no significant difference in anaesthetic or perfusion technique between the groups.

Significant differences were demonstrated between groups in MAP (control 56.3 mmHg; ACE 48.8 mmHg; P = 0.004) and SVR (control 1194 dyne/s per cm²; ACE 978 dyne/s per cm²; P = 0.006) during rewarming from hypothermic CPB (Table 2). The standardised difference of SVR was 0.758 giving the study a power of 0.85 [7]. CPB pump flow rates did not differ between the two groups during rewarming (control 3.91 l/min; ACE 4.05 l/min; P = 0.26).

Rewarming time on bypass (P = 0.03), left ventricular function (P = 0.01), and preoperative ACE therapy (P = 0.0001) were significantly associated with vasoconstrictor use during weaning from CPB (logistic regression). On multiple logistic regression, rewarming time on bypass (P = 0.02), and ACE inhibitor therapy (P = 0.002) remained sig-
significant. Relative risk for vasoconstrictor drug support in patients treated with ACE inhibitors was 3.32 (95% confidence interval 1.43–7.71). Preoperative therapy with nitrates, β-blockers or calcium channel antagonists was not a significant predictor for inotrope requirements.

### 4. Discussion

This is the first study to demonstrate that preoperative oral ACE inhibitor therapy significantly lowers SVR during the rewarming phase of hypothermic CPB. Licker et al. investigated the effects of oral administration of ACE inhibitors on SVR during CPB and reported no difference in MAP and SVR between ACE and control groups. Further analysis revealed that only patients with well preserved left ventricular function were studied, an unusual distribution in modern day practice [10]. Furthermore the number of patients they recruited did not confer enough power in the study to draw meaningful conclusions [7]. Other studies have documented the haemodynamic effects of intravenously administered ACE inhibitors. Boldt et al. described significantly lower SVR and MAP when intravenous enalapril, following induction of anaesthesia was administered before CPB, a difference which no longer existed following termination of CPB. In a separate study [8] they did not show any difference in SVR and MAP between groups when measured 20 min after the start of CPB. Boldt et al. also investigated the effects of intravenous enalapril administered during CPB and found that bolus administration of this drug significantly reduced both SVR and MAP within 10 min [9]. In all three studies, ACE inhibitors were administered intravenously and thus cannot be used to describe the effect in patients taking preoperative oral ACE inhibitors.

There was no significant difference in preoperative medication between the two groups other than ACE inhibitors. The same cardiopulmonary bypass parameters and anaesthetic drugs were administered perioperatively in the two groups. Differences in SVR during the rewarming phase can therefore be attributed to the ACE inhibitors. Conversely vasoconstrictor/inotrope requirements cannot be directly correlated to any change in SVR because cardiac output was not measured when the requirement for the vasoconstrictor/inotrope occurred.

SVR is determined by non-vascular and vascular factors [5]. The main non-vascular factors include plasma haematocrit, plasma viscosity, temperature and pump flow rates on bypass. Principle vascular factors are vessel diameter and length, the number of vessels through which blood is flowing and the degree of pre-capillary shunting. The renin-angiotensin system is a major determinant of SVR, controlling vessel diameter and pre-capillary shunting. After commencing CPB, SVR initially falls due to a sudden reduction in plasma viscosity caused by haemodilution. As CPB progresses, SVR increases due to an increase in plasma angiotensin II, a change that appears particularly marked during the rewarming phase of CPB [2,11]. Bailey et al. [1] have described increases in plasma renin activity during CPB and a 4-fold increase in aldosterone levels by the end of CPB. Similar findings were reported by De Leeuws et al. [12] who documented a marked increase in angiotensin II and aldosterone levels during CPB, a change continuing into the post-operative period. Weinstein et al. [13] noted a non-

### Table 1

<table>
<thead>
<tr>
<th>Patient characteristics and temperature comparisons between the groups</th>
<th>Control (±SD)</th>
<th>ACE inhibitor (±SD)</th>
<th>Mean difference (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.8 (±12.3)</td>
<td>63.9 (±27.3)</td>
<td>1.9 (~4.0 to 7.8)</td>
<td>0.52</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.5 (±16.2)</td>
<td>73.5 (±10.9)</td>
<td>0.0 (~7.9 to 7.9)</td>
<td>1.00</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.9 (±4.6)</td>
<td>24.9 (±3.0)</td>
<td>0.99 (~124 to 3.21)</td>
<td>0.38</td>
</tr>
<tr>
<td>Core temperature at start of rewarming (°C)</td>
<td>29.5 (±15.5)</td>
<td>30.0 (±21.6)</td>
<td>0.5 (~1.5 to 0.4)</td>
<td>0.25</td>
</tr>
<tr>
<td>Rewarming time (min)</td>
<td>30.7 (±15.5)</td>
<td>33.1 (±21.5)</td>
<td>2.4 (~1.1 to 3.2)</td>
<td>0.39</td>
</tr>
<tr>
<td>Rate of rewarming (°C/min)</td>
<td>0.30 (±0.11)</td>
<td>0.25 (±0.08)</td>
<td>0.05 (~0.1 to 0.11)</td>
<td>0.10</td>
</tr>
<tr>
<td>Core temperature at end of CPB (°C)</td>
<td>37.8 (±10.8)</td>
<td>37.9 (±21.1)</td>
<td>0.1 (~4.6 to 0.5)</td>
<td>0.74</td>
</tr>
<tr>
<td>Cross clamp time (min)</td>
<td>51.8 (±151.1)</td>
<td>54.7 (±240.0)</td>
<td>2.9 (~12.9 to 7.0)</td>
<td>0.56</td>
</tr>
<tr>
<td>Total CPB time (min)</td>
<td>74.1 (±21.6)</td>
<td>76.8 (±31.8)</td>
<td>2.7 (~16.4 to 10.9)</td>
<td>0.69</td>
</tr>
<tr>
<td>Haemotocrit on bypass</td>
<td>25.4 (±24.3)</td>
<td>26.0 (±24.1)</td>
<td>0.6 (~2.9 to 1.1)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Results shown as mean ± SD.

### Table 2

<table>
<thead>
<tr>
<th>Haemodynamic variables</th>
<th>Control (±SD)</th>
<th>ACE inhibitor (±SD)</th>
<th>Mean difference (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR (dyne/s per cm²)</td>
<td>1194 (±329)</td>
<td>978 (±329)</td>
<td>216 (63–370)</td>
<td>0.006</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>56.3 (±10.0)</td>
<td>48.8 (±7.4)</td>
<td>7.4 (25.2–12.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>CPB flow (l/min)</td>
<td>3.91 (±0.49)</td>
<td>4.05 (±0.36)</td>
<td>0.14 (~0.38–0.10)</td>
<td>0.26</td>
</tr>
</tbody>
</table>
significant trend toward elevation of these variables during CPB and studies in dogs have shown an increase in angiotensin II associated with a increased SVR following a period of CPB [14]. The increase in renin and angiotensin II levels have not been found in all studies [15,16] but this has been attributed to differences in pump flow and degree of induced hypothermia [17]. The activation of the renin–angiotensin system is thought to be of sufficient intensity to account for the postoperative hypertension seen in some patients following cardiac surgery [18–20].

Angiotensin converting enzyme inhibitors block the vasoconstrictive effects of angiotensin II, thereby reducing SVR throughout the vascular tree [3]. They have a vasodilating effect on large arteries such as the brachial artery [21] where they act to decrease forearm vascular resistance and increase forearm blood flow [3]. They also however affect smaller arteries, increasing blood flow in the kidney, skeletal muscle, limbs and skin [3,4]. These effects have been observed with all ACE inhibitors and continue with long-term ACE administration [22]. We have demonstrated for the first time that preoperative ingestion of ACE inhibitors has a significant effect on vascular tone throughout cardiopulmonary bypass.

We also demonstrated a significant association between preoperative ACE inhibitor therapy and the requirement for vasoconstrictors/inotropes in the immediate post-bypass period. We did not distinguish whether the observed hypotension was a result of low SVR or low cardiac output. These results are therefore limited in their interpretation. They are consistent however with previous studies showing that preoperative administration of ACE inhibitors increases postoperative requirements for vasoconstrictor therapy immediately following termination of CPB [6].

5. Conclusion

The longer half-life of many of the newer ACE inhibitors and clinical considerations may make it impractical to stop ACE therapy in sufficient time before surgery. These medications alter SVR during the rewarming phase of CPB. Clinicians need to be aware of the haemodynamic changes caused by these drugs in the perioperative period and anticipate management accordingly.

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References

[20] Colson P, Ribstein J, Minnan A. Effect of angiotensin converting enzyme inhibitors...


Appendix A. Conference discussion

Dr P. Sergeant (Leuven, Belgium): How severe have been the consequences? Do you think this might have been detrimental to the immediate follow-up of the patient, or have they all been fairly well controlled, in both situations?

Dr Deakin: Generally speaking, it appears that the vasoconstrictors that we have needed to give have only been for the immediate post-bypass period, and there have been no long-term detrimental effects. We have not specifically looked at this, but there are two other papers that have looked at vasoconstrictor requirements in intensive care over the first 48 h and neither paper has shown any difference in vasoconstrictor requirements once the patient has actually reached the intensive care unit.

Dr A.P. Kappetein (Leiden, The Netherlands): As you noted, the systemic vascular resistance is measured by an equation: the filling pressure divided by the cardiac output. How sure are you that the decrease in systemic vascular resistance is not the result of an underfilling of the patient?

Dr Deakin: The systemic vascular resistance was measured on cardio-pulmonary bypass itself. We did not actually measure it once the patients were off bypass.

Dr Kappetein: What you do is, when you measure the systemic vascular resistance, it’s an equation which gives you the systemic vascular resistance. It’s an equation: the filling pressure divided by the cardiac output.

So it reflects two other stages of the patients: first, the filling stage of the patient and second, the cardiac output of the patient. And so one of these two influences the systemic vascular resistance you measure. So if the patient is underfilled, you will also measure a low systemic vascular resistance. That might be the case in patients with ACE inhibitors.

Dr Deakin: The patients were, in terms of the bypass flows, managed by the perfusionists and were treated exactly the same in both groups. So we have no reason to think that any of that actually accounts for the difference between the two groups.

Dr Mohl (Wien, Austria): Based on your experience, do you think you could recommend that we should not use ACE inhibitors before bypass, that we should discontinue it for 2 or 3 days?

Dr Deakin: I think in ideal circumstances it would be sensible to stop ACE inhibitors 2 or 3 days before surgery. However, for many of the patients that we see at our unit, surgery is arranged at short notice and it’s not always possible to actually stop the ACE inhibitors as we have discussed. There does not seem to be any long-term detrimental effects, that we are aware of. I think it is useful for the anaesthetist managing the patient to be aware of the possible problems with an ACE inhibitor, but I do not think, certainly in the patients we have looked at, that ACE inhibitors have caused any particular long-term problems.