Effect of inspired oxygen on the cardiovascular effects of protamine after cardiopulmonary bypass

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Summary
We have performed a randomized prospective study of the effects of inspired oxygen fraction (FIO2) on the haemodynamic changes after protamine infusion. Thirty-four patients undergoing first time coronary artery bypass surgery were allocated randomly to receive either an FIO2 of 1.0 (group O) or 0.35 (group A) after cardiopulmonary bypass. Before, and after infusion of protamine, haemodynamic measurements were obtained, including mean arterial pressure (MAP), mean pulmonary artery pressure, central venous pressure, pulmonary capillary wedge pressure (PCWP), cardiac index (CI), pulmonary vascular resistance index (PVRI) and systemic vascular resistance index (SVRI). In group O, there were increases in mean MAP (8 %), PVRI (48 %) and SVRI (18 %), and decreases in mean CI (10 %) and PCWP (15 %). Group A showed changes of 0 %, −8 %, −6 %, +3 % and +32 %, respectively. We found a significant difference between groups in changes in PVRI (P < 0.0001), SVRI (P < 0.01), CI (P < 0.05) and PCWP (P < 0.001). During infusion of protamine, 31 % of patients in group O and 6 % of patients in group A had a decrease in systolic arterial pressure to less than 80 mm Hg (ns, chi-square test). These observations suggest that FIO2 alters the haemodynamic effects of protamine. (Br. J. Anaesth. 1995; 75: 413–416)

Key words

Protamine is a polycationic peptide obtained from fish that is used to reverse the anticoagulation induced by heparin. It is a highly alkaline compound and many side effects have been attributed to its use, including anaphylaxis [1], histamine release [2] and hypocalcaemia [3]. Its most common haemodynamic effect, especially if given rapidly, is a decrease in systemic arterial pressure. This may result from systemic vasodilatation and pulmonary vasoconstriction, which may be catastrophic in some patients [4]. These effects have been attributed to mediator release [5] and various agents that attenuate them have been investigated, including thromboxane receptor antagonists [6] and histamine receptor blockers [2].

Kim and colleagues showed that protamine interferes with the hypoxic pulmonary vasoconstriction reflex [7]. This animal study showed that protamine, when given into a pulmonary artery of a normoxic lung, produced an increase in pulmonary vascular resistance of nearly twice the value as that when given into a hypoxic lung. Their comparison of normoxia and hypoxia cannot be performed in the clinical setting, so we devised our study to compare superoxia and relative normoxia on the cardiovascular effects of protamine.

The aim of this study, therefore, was to see if the fraction of inspired oxygen (FIO2) delivered to the lungs after cardiopulmonary bypass (CPB) alters the haemodynamic changes associated with protamine.

Patients and methods
The study was approved by the local Hospital Ethics Committee and informed consent obtained. We studied 34 patients, ASA III, undergoing first time coronary artery bypass graft surgery. Only patients with good ventricular function (angiogram) were studied. Patients were excluded if they had a history of diabetes mellitus and were receiving protamine-containing insulin and if they had respiratory disease. Patients were allocated randomly to one of two groups. In group O (n = 17) the lungs were ventilated with 100 % oxygen (FIO2 1.0) at termination of CPB and in group A (n = 17) with an air-oxygen mixture (FIO2 0.35). All patients were premedicated with lorazepam 2 mg, morphine 0.15 mg kg−1 and droperidol 2.5 mg. Anaesthesia was induced with fentanyl 15–20 g kg−1 and pancuronium 12 mg, and maintained with nitrous oxide and enflurane. The ECG was monitored with continuous ST segment analysis and pressures were measured via a radial artery cannula and a thermidilution pulmonary artery catheter (Abbott). Cardiac outputs were measured in triplicate and calculations made using a cardiac output computer (Siemens Sirecust 1281). The gases delivered to the patient were analysed using a Datex (Capnomac Ultima) monitor and arterial oxygenation was measured using oximetry and arterial blood-gas analysis. All patients received...
heparin 4 mg kg\(^{-1}\) before bypass, during which anaesthesia was maintained with enflurane.

The bypass prime consisted of Hartmann’s solution and heparin. We used non-pulsatile bypass flow using membrane oxygenators and 20 m arterial line filters. Arterial pump flows of 2.4 litre min\(^{-1}\) m\(^{-2}\) were used during normothermia and reduced to 1.5 litre min\(^{-1}\) m\(^{-2}\) when nasopharyngeal temperature was less than 30 °C. Haemoglobin concentration was maintained at greater than 60 g litre\(^{-1}\). Vasocostricitors and vasodilators were given as required to maintain a mean arterial pressure of 50–80 mm Hg, and alpha-stat management of arterial blood-gas tensions was used. Separation from bypass occurred after achieving a temperature greater than 37 °C.

The study period was the duration of infusion of protamine which was started only when transfusion from the pump had finished and when arterial pressure and pulmonary capillary wedge pressure (PCWP) had not fluctuated by more than 5% over a 2-min period. The atria and ventricles were paced sequentially at a rate of 90 min\(^{-1}\) and the lungs were ventilated with a tidal volume of 10 ml kg\(^{-1}\) and a minute volume to maintain an end-tidal carbon dioxide partial pressure of 4.5–5.0 kPa. Anaesthesia was maintained with 1% enflurane, and GTN 1 g kg\(^{-1}\) min\(^{-1}\) was infused when discontinuing bypass in all patients. During the study period, the rate of this infusion was not altered and no fluids were given. If inotropes were needed when discontinuing bypass, the patient was excluded from the study. Nitrous oxide was not used after CPB in any patient. The dose of protamine given was equal to the total dose of heparin that had been used for anticoagulation and was infused at a rate of 1.5 mg kg\(^{-1}\) min\(^{-1}\) via a central venous cannula. If systolic arterial pressure decreased to less than 80 mm Hg, protamine was stopped, and if the pressure continued to decrease, colloid or boluses of phenylephrine were given as required. The protamine infusion was recommenced when pressure was restored to greater than 80 mm Hg.

We obtained a set of haemodynamic data comprising mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), central venous pressure (CVP), PCWP, cardiac index (CI), systemic vascular resistance index (SVRI) and pulmonary vascular resistance index (PVI) immediately before and after infusion of protamine.

Student’s \(t\) test was used to study the haemodynamic changes in both groups before and after infusion of protamine and the chi-square test was used to compare the incidence of hypotension. Differences between groups were compared by analysis of variance (ANOVA). The SPSS PC+ program was used for statistical evaluation of the data. \(P < 0.05\) was considered statistically significant.

### Results

We studied 34 patients. One patient in group O required inotropes to permit discontinuation of bypass and one in group A required an increase in \(P_{O_2}\) because of an oxygen saturation of 94% caused by a collapsed left, lower lobe. Both were excluded from the study. There were no patient or surgical differences between the groups (table 1).

Conditions in each group before infusion of protamine did not differ significantly (table 2). In group O there were significant increases in mean MAP, MPAP, PVRI and SVRI, and significant decreases in CI and PCWP after protamine. In group A there was a significant increase in mean PCWP. During the infusion, five patients (31 %) in the \(P_{O_2}\), 1.0 group and one patient (6 %) in the \(P_{O_2}\), 0.35 group had a decrease in systolic arterial pressure to less than 80 mm Hg, requiring the infusion to be stopped (ns, chi-square test). Four of these patients, all in the 100 % oxygen group, required intervention to restore arterial pressure, three needing volume (100–150 ml of colloid) and one needing volume and phenylephrine (0.1 mg).

Comparison between the groups showed significant differences in changes in PVRI, SVRI, CI and

### Table 1  Patient data (mean (range or sd) or number)

<table>
<thead>
<tr>
<th></th>
<th>Group O</th>
<th>Group A</th>
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<tbody>
<tr>
<td>(n)</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>11/5</td>
<td>12/4</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>64.3 (56–72)</td>
<td>67.2 (51–79)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73 (15.5)</td>
<td>78.5 (11.9)</td>
</tr>
<tr>
<td>Protamine dose (mg)</td>
<td>390 (40)</td>
<td>415 (45)</td>
</tr>
<tr>
<td>Bypass time (min)</td>
<td>91 (45–135)</td>
<td>88 (53–121)</td>
</tr>
<tr>
<td>Cross-clamp time (min)</td>
<td>50 (28–85)</td>
<td>48 (30–69)</td>
</tr>
<tr>
<td>Patients given vasopressors during CPB</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Patients given vasodilators during CPB</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

### Table 2  Mean (sd) haemodynamic measurements before and after administration of protamine in patients whose lungs were ventilated with an \(P_{O_2}\) of 1.0 (group O) or \(P_{O_2}\) of 0.35 (group A). *\(P < 0.05\), **\(P < 0.001\) compared with value before protamine

<table>
<thead>
<tr>
<th></th>
<th>Group O ((n = 16))</th>
<th>Group A ((n = 16))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>65 (9)</td>
<td>70 (8)*</td>
</tr>
<tr>
<td>MPAP (mm Hg)</td>
<td>18 (4)</td>
<td>21 (6)*</td>
</tr>
<tr>
<td>CI (litre min(^{-1}) m(^{-2}))</td>
<td>2.9 (0.7)</td>
<td>2.6 (0.6)*</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>10.5 (5)</td>
<td>8.9 (5)*</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>7.8 (3)</td>
<td>8.4 (3)</td>
</tr>
<tr>
<td>PVRI (dyn s cm(^{-5}) m(^{-2}))</td>
<td>265 (121)</td>
<td>392 (183)**</td>
</tr>
<tr>
<td>SVRI (dyn s cm(^{-5}) m(^{-2}))</td>
<td>1645 (385)</td>
<td>1937 (537)*</td>
</tr>
</tbody>
</table>
The effects of protamine given after CPB are unpredictable. The most common effect is a decrease in arterial pressure, especially if protamine is given rapidly to patients with poor ventricular function [8]. However, the actual cause of the decrease in arterial pressure remains controversial.

In some animal studies, protamine has been shown to have a negative inotropic effect [9] but a positive inotropic effect in others [10]. There appears to be a negative inotropic effect [9] but a positive arterial pressure remains controversial.

PCWP (Table 3). Arterial saturations were maintained greater than 97 % in all patients. Mean $P_{O_2}$ was 41 (range 32–61) kPa in group O and 15.2 (9.8–19.5) kPa in group A, measured after completion of protamine infusion.

### Discussion

The effects of protamine given after CPB are unpredictable. The most common effect is a decrease in arterial pressure, especially if protamine is given rapidly to patients with poor ventricular function [8]. However, the actual cause of the decrease in arterial pressure remains controversial.

In some animal studies, protamine has been shown to have a negative inotropic effect [9] but a positive inotropic effect in others [10]. There appears to be no direct action on the human heart [11]. Most animal studies have shown that protamine produces an increase in pulmonary arterial pressure (PAP) and PVR [12] and a reduction in SVR [10,12], but human studies have shown more variable effects. Some have shown an increase in PAP [13], and some a decrease in PVR [14], while others have shown no change in pulmonary haemodynamics following protamine [15]. None of these studies stated what $P_{O_2}$ was being delivered. Michaels and Barash [8] found no significant haemodynamic response when protamine was given slowly to patients with good ventricular function, although in patients with poor ventricles they found a significant decrease in SVRI. Conversely, when they gave protamine at a faster rate they found an increase in SVRI of 35 %, although this was not significant.

There are probably two main reasons for these conflicting results. First, it is difficult to attribute any haemodynamic changes as solely caused by protamine at a time when the cardiovascular system is recovering from CPB. Second, all of these studies have different experimental methods, including variations in dosage of protamine, route of injection, route of administration, anaesthetic conditions and the time at which haemodynamic responses were measured. The effects of protamine are maximal at 1 min and have completely worn off by 4 min [16]. Thus we gave our protamine comparatively rapidly and measured variables immediately after infusion, making it more likely that the changes seen were caused solely by protamine.

It is probable that the hypoxic insult that the lungs were subjected to during CPB alters their response to subsequent drugs and therapies. However, this effect would have been the same in both groups.

We found a significant difference between the groups in changes in PVRI, SVRI, CI and PCWP, with the group receiving 100 % oxygen having an increase in mean PVRI and SVRI and a decrease in mean CI and PCWP. These effects may be as a result of pulmonary vasoconstriction leading to decreased pulmonary blood flow and consequently a reduction in venous return to the left side of the heart. Hypotension was deemed to have occurred if systolic arterial pressure decreased to less than 80 mm Hg during infusion of protamine. This occurred in one patient in the 35 % oxygen group with spontaneous recovery, and five patients in the 100 % oxygen group, of which four required intervention. This would suggest that in the 100 % oxygen group there was a greater chance of a decrease in arterial pressure. The increase in SVRI that we found could be in response to this, via the baroreceptor reflex, exaggerated because of the fixed, paced heart rate, and leading to an over compensated increase in MAP.

The pulmonary vascular effects of protamine have been attributed to the heparin–protamine complex causing release of thromboxane, a powerful vasoconstrictor [16]. The results of our study suggest that a hyperoxic lung is more sensitive to the effects of protamine, an effect that has been described previously in animals [7]. The explanation for this was that a hyperoxic lung is more vasodilated and thus able to constrict more than a lung receiving less oxygen in response to protamine. If we found this effect in our study we would have expected to see a lower PVRI in the 100 % oxygen group before protamine was given, and although this was the case, it was not significant. If the $P_{O_2}$ delivered does affect the pulmonary effects of protamine then there must be other complex factors involved.

Oxygen metabolites can stimulate thromboxane production also leading to pulmonary vasoconstriction by interfering with arachidonic acid metabolism in the cell membrane [17] and it has been shown that these metabolites are released after ischaemic events such as aortic cross-clamping during CPB [18]. It may be that the presence of oxygen metabolites enhances mediator release by the heparin–protamine complex, but it is not known if the concentration of oxygen being delivered affects the levels of oxygen metabolites in the post-bypass period.

None of the patients studied had any ischaemic cardiac events in the post-bypass period and all patients maintained an arterial saturation greater than 97 %. Supplying a high $P_{O_2}$ may be indicated in some circumstances but our results suggest that by avoiding 100 % oxygen whenever possible, there may be less haemodynamic upset during protamine infusion after CPB.

### References


