The haemodynamic effects of intraaortic versus intravenous administration of protamine for reversal of heparin in man

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A recent report suggests that there may be advantages of intraaortic (IA) versus intravenous (IV) administration of protamine for reversal of heparin at the end of cardiopulmonary bypass. Because complete haemodynamic measurements were not performed in that study, we prospectively and randomly assessed the effects of protamine sulphate administered via either route. Patients were studied in the period immediately following cardiopulmonary bypass. Heparin, 300 units·Kg⁻¹, plus 150 units·Kg⁻¹ when required, was administered to keep the activated clotting time > 400 sec. Protamine 3 mg·Kg⁻¹ was injected over 30 sec. intravenously in the IV group (n = 5) and into the ascending aorta in the IA group (n = 5). There was a significant decrease in arterial blood pressure (28.6 per cent) from 109.2 ± 5.6 mmHg (S.E.) systolic to 78.0 ± 9.0 mmHg observed in the IA group one minute post protamine, which returned to baseline by

2.5 min (analysis of variance $p < 0.05$). No significant hypotension was observed in the IV group. There was no significant change in heart rate, left atrial pressure, central venous pressure, systemic vascular resistance or cardiac index with either IA or IV protamine. In contrast to our recent study in pigs there was no significant change in pulmonary artery pressure, pulmonary vascular resistance or cardiac output with protamine. Results indicate that there are no haemodynamic benefits of IA vs IV injection of protamine.

Key words

BLOOD COAGULATION: heparin, protamine; BLOOD PRESSURE: drug effects.

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Recently it has been reported that the intraaortic (IA) administration of protamine sulphate for reversal of heparin post-cardiopulmonary bypass (CPB) is not accompanied by significant hypotension.¹ However, no other haemodynamic parameters were measured, and no comparison was made between IA versus IV administration of protamine. A recent study from our laboratory² demonstrated that there were no significant differences between IA and IV injection of protamine. Transient decreases in cardiac output (CO) and marked increases in pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) occurred when protamine was administered via either route in pigs. The objective of this study was to assess the haemodynamic effects of IV versus IA administration of protamine in man, and to determine whether one route of administration was safer than the other.

Methods

Ten patients were randomly selected for IA or IV

TABLE I Profile of patients (mean $\pm$ standard deviation)

	Number of patients	Age	Weight (kg)	Number of patients		
				β -blockers	Nitrates	Ca ant
Intravenous Group	5M	58.8 $\pm$ 6.4	78.2 $\pm$ 16.3	2	4	0
NYHA Class III	4					
NYHA Class IV	1					
Intraaortic Group	4M 1F	50.6 $\pm$ 7.9	86.4 $\pm$ 9.9	2	4	1
NYHA Class III	3					
NYHA Class IV	2					

	LVEDP (mmHg)	Coronary artery bypass	Mitral valve replacement	Pump time (min)
Intravenous Group	11.4 $\pm$ 4.3	4 (range 3–5 grafts)	1	78.4 $\pm$ 16
NYHA Class III				
NYHA Class IV				
Intraaortic Group	8.4 $\pm$ 1.1	4 (range 4–5 graft)	1	91.8 $\pm$ 25
NYHA Class III				
NYHA Class IV				

Legend: Ca ant, calcium antagonist, LVEDP, left ventricular end-diastolic pressure (mmHg). NYHA, New York Heart Association. M, Male. F, female.

administration of protamine sulphate and were studied during the period following CPB. Following the published report by Aris *et al.*¹ we elected to adopt the clinical procedure of administering protamine by the intraaortic route, and had been doing this for several months without difficulty. It was then decided to do this comparative study, and it was felt that informed consent was not required. Four patients in each group had severe coronary artery disease requiring coronary artery bypass grafting and one patient in each group had mitral regurgitation necessitating mitral valve replacement (Table I). All patients were reported to have good myocardial function preoperatively as determined by cardiac catheterization and angiography.

Prior to induction of anaesthesia a 20-gauge cannula was inserted into the radial artery for continuous blood pressure monitoring. A thermidilution triple-lumen catheter 7F (Edwards Laboratories) was placed via the right internal jugular vein into the pulmonary artery and was used for determination of PAP (systolic, diastolic, mean and wedge) and CO. Heart rate (HR) and electrocardiogram were continuously recorded. Anaesthesia was induced with fentanyl, diazepam, pancuronium and oxygen and maintained with fentanyl and oxygen.

The left atrial pressure (LAP) was recorded by a cannula inserted via a right superior pulmonary vein. Sodium heparin, all from the same lot, was given in an initial dose of 300 units·Kg⁻¹, followed by increments of 150 units·Kg⁻¹ to keep the activated clotting time greater than 400 sec. Following CPB and after stabilization with replacement of blood volume by intraaortic transfusion of the pump perfusate, control measurements of HR, arterial pressure (AP), PAP, central venous pressure (CVP), LAP and CO (mean of 2 injections of 10 ml cold five per cent dextrose, computed with an Edwards Laboratories Computer) were recorded.

During the study period no crystalloid, blood or vasoactive drugs were given and there was no manipulation of the heart. Protamine sulphate (3 mg·Kg⁻¹) was injected either by a peripheral vein (IV) or directly into the ascending aorta (IA) over 30 sec. Haemodynamics were then recorded at 1.0, 2.5, 5.0 and 10 min following injection.

PVR, systemic vascular resistance (SVR) and cardiac index (CI) were calculated using standard formulae. Control measurements between the IA and IV groups were compared for statistical significance using the Student's *t* test for unpaired data. Data within each group were analyzed using analy-

TABLE II Haemodynamic data for all patients pre- and post-protamine infusion (mean $\pm$ S.E.)

			Post-protamine injection				
	Group	Baseline	1.0 min	2.5 min	5.0 min	10 min	
HR	IA	90.6 $\pm$ 5.3	93.4 $\pm$ 5.6	89.6 $\pm$ 6.7	88.8 $\pm$ 5.7	91.2 $\pm$ 5.6	
	IV	88.8 $\pm$ 1.9	89.8 $\pm$ 2.3	89.0 $\pm$ 3.2	90.6 $\pm$ 3.6	97.0 $\pm$ 3.9	
Systolic AP	IA	109.2 $\pm$ 5.6	78.0 $\pm$ 9.0*	105.8 $\pm$ 5.9	113.2 $\pm$ 7.1	114.4 $\pm$ 9.2	
	IV	108.6 $\pm$ 3.1	110.6 $\pm$ 8.7	117.6 $\pm$ 8.1	121.0 $\pm$ 6.2	126.3 $\pm$ 10.0	
Diastolic AP	IA	69.6 $\pm$ 5.4	51.2 $\pm$ 5.9*	67.0 $\pm$ 4.8	73.2 $\pm$ 4.6	74.6 $\pm$ 4.7	
	IV	62.8 $\pm$ 3.5	66.2 $\pm$ 4.9	67.4 $\pm$ 5.2	69.6 $\pm$ 4.7	78.8 $\pm$ 4.3	
Mean AP	IA	83.0 $\pm$ 5.2	60.2 $\pm$ 6.8*	79.8 $\pm$ 4.6	86.6 $\pm$ 5.1	87.8 $\pm$ 5.4	
	IV	78.4 $\pm$ 2.9	80.8 $\pm$ 6.1	84.2 $\pm$ 5.9	87.2 $\pm$ 4.8	94.5 $\pm$ 6.2	
Systolic PAP	IA	25.6 $\pm$ 3.4	23.4 $\pm$ 0.5	24.6 $\pm$ 1.9	22.0 $\pm$ 2.3	22.4 $\pm$ 2.4	
	IV	30.6 $\pm$ 3.5	30.0 $\pm$ 1.8	34.6 $\pm$ 4.9	31.6 $\pm$ 4.2	29.0 $\pm$ 2.4	
Diastolic PAP	IA	14.6 $\pm$ 2.0	15.0 $\pm$ 1.4	15.8 $\pm$ 2.1	12.4 $\pm$ 1.7	13.8 $\pm$ 2.2	
	IV	18.2 $\pm$ 1.6	20.0 $\pm$ 1.9	20.7 $\pm$ 2.7	17.4 $\pm$ 2.2	18.0 $\pm$ 2.0	
Mean PAP	IA	18.2 $\pm$ 2.4	17.8 $\pm$ 1.1	18.6 $\pm$ 1.9	15.6 $\pm$ 1.8	16.6 $\pm$ 2.2	
	IV	22.0 $\pm$ 2.0	23.4 $\pm$ 1.6	24.6 $\pm$ 2.7	22.2 $\pm$ 2.4	21.8 $\pm$ 4.0	
LA	IA	11.8 $\pm$ 1.2	11.4 $\pm$ 1.2	12.8 $\pm$ 1.2	11.6 $\pm$ 0.9	11.6 $\pm$ 1.2	
	IV	10.2 $\pm$ 1.4	10.6 $\pm$ 1.7	10.8 $\pm$ 1.8	10.2 $\pm$ 2.0	9.5 $\pm$ 1.7	
CVP	IA	10.4 $\pm$ 1.9	10.4 $\pm$ 1.7	10.8 $\pm$ 2.1	11.6 $\pm$ 2.5	13.4 $\pm$ 2.5	
	IV	12.4 $\pm$ 1.0	14.3 $\pm$ 2.4	13.5 $\pm$ 1.2	14.0 $\pm$ 1.8	15.3 $\pm$ 1.0	
CI	IA	2.79 $\pm$ 0.29	2.47 $\pm$ 0.30	2.73 $\pm$ 0.23	2.62 $\pm$ 0.34	2.29 $\pm$ 0.25	
	IV	3.20 $\pm$ 0.27	3.33 $\pm$ 0.20	3.29 $\pm$ 0.30	2.92 $\pm$ 0.36	2.82 $\pm$ 0.34	
PVR	IA	112.8 $\pm$ 24.0	112.8 $\pm$ 22.15	116.4 $\pm$ 32.0	72.2 $\pm$ 23.71	115.4 $\pm$ 25.02	
	IV	174.4 $\pm$ 53.26	116.2 $\pm$ 30.24	189.8 $\pm$ 56.11	178.0 $\pm$ 41.16	206.8 $\pm$ 50.47	
SVR	IA	1230 $\pm$ 193.87	810 $\pm$ 122.52	1068 $\pm$ 182.41	1327 $\pm$ 216.80	1374 $\pm$ 220.0	
	IV	821 $\pm$ 149.99	773 $\pm$ 143.00	870 $\pm$ 175.00	1018 $\pm$ 185.00	1214 $\pm$ 167.0	

* = significant difference from baseline ($p < 0.05$).Legend: HR, heart rate (beats/min). IA, intraaortic. IV, intravenous. AP, arterial pressure (mmHg). LA, left atrial pressure. CVP, central venous pressure. CI, cardiac index ($\text{l}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$). PVR, pulmonary vascular resistance ($\text{dyne}\cdot\text{sec}\cdot\text{cm}^{-5}$). SVR, systemic vascular resistance ($\text{dyne}\cdot\text{sec}\cdot\text{cm}^{-5}$). Systolic and diastolic pressure, mmHg.

sis of variance. Significance was assessed at the $p < 0.05$ level.

Results

Table II summarizes the results. There was no difference between the IA and IV groups in control haemodynamic measurements. There was a significant decrease in arterial blood pressure (28.6 per cent) from 109.2 ± 5.6 (S.E.) mmHg to 78.0 ± 9.0 mmHg observed in the IA group at 1.0 minute, which returned to baseline by 2.5 minutes. No significant hypotension was observed in the IV group. There was no significant change in HR, LAP, SVR, CVP or CI with either route of administration of protamine. In contrast to the study in pigs there was no change in PAP, PVR or CO.

Discussion

Injection of protamine for reversal of heparin at the

end of CPB is not without hazards, and profound hypotension has been known to occur.³ Measures to counteract this haemodynamic effect include the slow administration of the drug,⁴ volume expansion, calcium and/or vasopressor agents.⁵ A recent clinical report indicated that the administration of protamine into the ascending aorta did not result in significant hypotension.¹ Investigation in our laboratory comparing IA versus IV administration of protamine in pigs failed to confirm that observation.² In pigs, there was a decrease in CO and a marked increase in PAP and PVR with both IA and IV injection of protamine. Also, there was considerable individual variation in the arterial blood pressure response to protamine. When protamine alone was administered to the animal, without prior heparinization, no change in haemodynamics was observed.

This present clinical study failed to confirm that

one route of administration (IA vs IV) is superior to the other in establishing stable haemodynamics. In fact there was a significant decrease in arterial blood pressure at 1.0 minute post IA infusion whereas no hypotension was observed in the IV group. Aris *et al.*¹ observed hypotension with the IA injection of protamine which resolved by 2.2 minutes on the average. Unfortunately there was no comparison with the IV route of administration. However, there have been conflicting reports as to the haemodynamic effects of protamine. Some state that the drug has insignificant effects;^{1,6,7} others have observed a decrease in AP and an increase in PAP.³ Postulated causes for the hypotension induced by protamine include a decrease in myocardial contractility, SVR, ionized calcium or release of vasoactive substances from the lung or platelets.^{5,8-12}

In contrast to the study in pigs,² the present study demonstrated no significant change in CO, PAP, or PVR. Since the response of the pulmonary circulation to protamine in pigs was so predictable and dramatic it would appear that species difference is probably the most important reason for its different effects in man. Thus, the rapid IA administration of protamine for reversal of heparin in man causes transient hypotension lasting less than 2.5 minutes. It may be prudent therefore to temporarily delay any therapeutic intervention such as vasopressors or volume replacement as recovery may be imminent. Intravenous injection of protamine appeared to have little effect on the circulation in the dose used in this study and reports of hypotension may be a result of individual sensitivity to the drug or different dosages.

Species difference is very important when assessing the effects of protamine. Further studies are necessary in order to fully understand the mechanism of action of the protamine-heparin complex, its effects on the circulation, and possible pharmacological manipulations that might make its use safer during open-heart surgery.

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Résumé

Une étude récente a suggéré qu'il pourrait être avantageux d'administrer la protamine par voie intra-aortique à la fin de la circulation extra-corporelle. Cependant, cette étude ne comporte pas de mesures précises des conséquences hémodynamiques d'un tel procédé. Nous avons donc décidé d'étudier les effets cardiovasculaires du sulfate de protamine selon qu'il est administré par voie intra-veineuse (IV) ou intra-aortique (IA) et ceci de façon prospective et aléatoire.

Dix patients ont été étudiés immédiatement après le sevrage de la circulation extra-corporelle. Les patients avaient reçu de l'héparine $300 \text{ unités} \cdot \text{Kg}^{-1}$ plus $150 \text{ unités} \cdot \text{Kg}^{-1}$ au besoin pour maintenir un temps de coagulation activé (ACT) plus grand que 400 sec. La protamine, $3 \text{ mg} \cdot \text{Kg}^{-1}$, a été injectée en 30 sec. par voie intra-veineuse ($N = 5$) ou intra-aortique ($N = 5$). On a noté une minute après l'injection intra-aortique, une diminution significative de la pression artérielle (28.6 pour cent), la systolique passant de $109.2 \pm 5.6 \text{ mmHg}$ (ET) à $78 \pm 9 \text{ mmHg}$ et un retour aux valeurs de contrôle à 2.5 min. (analyse de variance $p < 0.05$). Par contre, il n'y a pas eu d'hypotension significative dans le groupe IV. Dans les deux groupes, il n'y a pas eu de changement significatif de la fréquence cardiaque, des pressions auriculaire gauche et veineuse centrale, de la résistance périphérique ou de l'index cardiaque.

Contrairement à notre étude récente chez le porc, il n'y a pas eu, associé à la protamine, de changement significatif dans la pression artérielle, la résistance vasculaire pulmonaire ou le débit cardiaque. Les résultats obtenus indiquent qu'il n'est pas avantageux d'administrer la protamine par voie intra-aortique plutôt que par voie intra-veineuse.