

Cardiorespiratory effects of protamine after cardiopulmonary bypass in man

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Jastrzebski, J., Sykes, M. K., and Woods, D. G. (1974). *Thorax*, 29, 534–538. **Cardiorespiratory effects of protamine after cardiopulmonary bypass in man.** The cardiorespiratory changes following the injection of protamine sulphate (6 mg/kg) were studied in 15 patients who had undergone cardiopulmonary bypass. There was a transient fall in arterial pressure and a more prolonged increase in pulmonary artery pressure. There was a significant fall in arterial oxygen tension which was mainly due to a reduction in mixed venous oxygen tension resulting from a fall in cardiac output. Dead space/tidal volume ratio and percentage shunt did not change significantly.

There is commonly a marked fall in arterial blood pressure when protamine is administered after cardiopulmonary bypass. This is but one manifestation of a series of changes which appear to result from the release of vasoactive substances from the platelet in response to the injection of protamine. In dogs, Rådegran and McAslan (1972) found that protamine infusion produced a fall in platelet count and a fall in aortic blood pressure and systemic vascular resistance while pulmonary artery pressure and resistance increased. Lung compliance decreased, airway resistance increased, and there was a fall in arterial oxygen tension. Although some of the cardiovascular changes have been documented in man, we have been unable to find any report detailing changes in lung function after the injection of protamine. This paper describes the effects of protamine on gas exchange in the lung after open-heart surgery.

METHODS

Fifteen patients were studied during the period immediately following cardiopulmonary bypass. Details of the patients and heparin and protamine dosages are given in Table I. Heparin was given in an initial dose of 3 mg/kg followed by 1.5 mg/kg every hour. Protamine was given in a dose of 6 mg/kg when major surgical haemorrhage had been controlled. All the patients were premedicated with omnopon and scopolamine and anaesthetized with thiopentone, pancuronium, nitrous oxide, and phenoperidine. A cuffed oral tube was inserted and mechanical ventilation was provided by an Engström ventilator set at 20 breaths per minute, the tidal volume

being adjusted to provide an arterial PCO_2 of 30–40 mmHg. Inspired gases were humidified with a hot water humidifier except during the period of study. An end-expiratory pressure of 5–10 cmH₂O was applied as soon as the chest was open and maintained until the chest was closed.

Just before perfusion was discontinued, a further dose of phenoperidine was given and a collect valve was interposed between the patient Y-piece and the endotracheal tube (Sykes, 1969a). The lungs were then hyperinflated several times to +40 cmH₂O by occluding the expiratory port of the collect valve, and the plateau of airway pressure was observed to ensure that no leaks were present. The expiratory port on the valve was then connected to a Wright's respirometer, a weight-operated end-expiratory pressure valve, a gas-mixing unit (Sykes, 1968), and a calibrated dry gas meter. The collect valve separated gas compressed in the ventilator tubing from true expired gas, while the Wright's respirometer was used to check that there was no leakage of inspired gas through the expiratory port during inspiration.

When perfusion was discontinued the inspired gas mixture was changed to 30% oxygen in nitrogen and the expired volume was adjusted to a value which was approximately 1 l/min more than that required to maintain a normal PCO_2 before bypass (Pauca and Sykes, 1966). The aortic perfusion cannula was removed as soon as cardiovascular stability had been achieved, and the first set of measurements was made when major surgical haemorrhage had been controlled. Protamine (6 mg/kg) was then injected over a period of about 5 minutes and the second set of measurements was made 5 minutes after the end of the injection. The third set of measurements was made 15 minutes after the end of the injection.

Arterial samples were obtained from the radial artery line and pulmonary arterial samples were obtained by

TABLE I

Age (yr)	Weight (kg)	Height (cm)	Body Surface Area (m ²)	Diagnosis	Operation	Heparin (mg)	Protamine (mg)	Duration of Bypass	PEEP (cmH ₂ O)	Result
9	38	100	0.96	Fallot's tetralogy	Complete repair	115	150	1 hr 10 min	0	S
41	63	165	1.72	MI and MS	MVR	332	380	2 hr 4 min	10	S
31	67	158	1.70	AI	AVR	250	400	1 hr 19 min	10	S
44	53	165	1.60	MI and TI	MVR and TVR	308	312	2 hr 14 min	8	S
62	75	134	1.47	AI	AVR	225	300	1 hr 20 min	8	S
58	71	163	1.75	Coronary ischaemia	Vein graft	330	440	51 min	5	S
53	43	150	1.30	MI	MVR	132	260	1 hr 25 min	8	S
61	54	167	1.60	MI	MVR	243	324	1 hr 50 min	7	S
46	58	160	1.56	MI	MVR	252	340	1 hr 16 min	8	S
64	53	154	1.49	AI	AVR	150	300	1 hr 27 min	7	S
32	45	149	1.35	AI and MI	MVR and AVR	260	280	2 hr 42 min	9	D
18	58	183	1.76	Marfan's syndrome	AVR	360	360	4 hr 25 min	10	S
42	46	163	1.42	MI and MS	MVR and tricuspid annuloplasty	250	280	1 hr 50 min	10	S
41	57	160	1.58	MI	MVR	265	340	2 hr 10 min	8	S
14	65	158	1.65	ASD	ASD closure	195	390	45 min	8	S

MS, MI, MVR = mitral valve stenosis, incompetence, valve replacement.
 AI, AVR = aortic valve incompetence, valve replacement.
 TI, TVR = tricuspid valve incompetence, valve replacement.
 ASD = atrial septal defect.
 S = survived; D = died.

TABLE II
 CARDIORESPIRATORY CHANGES 5 TO 15 MIN AFTER INJECTION OF PROTAMINE

	Before		After 5 min			After 15 min		
	Mean	SD	Mean	SD	P	Mean	SD	P
Mean pulmonary artery pressure (mmHg)	25.6	9.5	28.8	11.4	NS	35.1	11.7	<0.05
Cardiac index (l./m ²)	2.41	0.90	1.78	0.88	NS	1.87	0.71	NS
Q _{va} /Q _t	6.5	3.2	9.1	5.4	NS	8.9	5.8	NS
P(A-a)O ₂ (mmHg)	89.0	60.4	109.4	68.7	NS	120.1	70.9	NS
PaO ₂ (mmHg)	128.8	34.7	111.6	38.1	NS	95.6	26.8	<0.03
Paco ₂ (mmHg)	39.7	7.4	41.3	7.3	NS	39.7	7.5	NS
pH	7.387	0.057	7.377	0.067	NS	7.378	0.071	NS
P \bar{v} O ₂ (mmHg)	35.2	8.0	30.5	8.4	NS	26.2	4.4	<0.01
V _D /V _T	41.2	10.8	43.0	9.7	NS	45.5	6.5	NS
P(a-A)CO ₂ (mmHg)	6.4	4.8	8.4	4.9	NS	8.3	4.4	NS
V _O (ml/min)	181.4	34.4	169.0	43.4	NS	195.4	62.7	NS
V \bar{c} O ₂ (ml/min)	157.1	30.4	156.1	35.2	NS	154.9	36.1	NS
No. of observations	13		13			9		

direct puncture of the artery by the surgeon. Simultaneous pulmonary artery and arterial pressures were recorded immediately after blood sampling. Inspired and mixed expired oxygen concentrations were measured on a Servomex 101A paramagnetic oxygen analyser while end-tidal and mixed expired CO₂ concentrations were determined with a Hartmann-Braun URAS 4 infrared analyser. Blood samples were analysed for Po₂, Pco₂, and pH on a Radiometer system and inspired, and mixed expired gas samples were also checked on this apparatus. The O₂ content of arterial and mixed venous blood was also measured on a Lex-O₂-Con apparatus which had been previously calibrated against a van Slyke apparatus. This arteriovenous O₂ content difference (CaO₂-C \bar{v} O₂) was used for calculation of cardiac output by the Fick method and for the calculation of venous admixture (Q_{va}/Q_t) from the equation:

$$\frac{Q_{va}}{Q_t} \% = \frac{Cc'O_2 - CaO_2}{(Cc'O_2 - CaO_2) + (CaO_2 - C\bar{v}O_2)}$$

The end-pulmonary capillary-to-arterial O₂ content difference (Cc'o₂-CaO₂) was calculated from the ideal alveolar Po₂ and arterial Po₂, Pco₂, pH, and Hb using the

Severinghaus (1966) dissociation curve. All the other calculations were based on standard equations and incorporated in a computer program described by Adams (1970).

RESULTS

These are summarized in Table II.

Femoral artery pressure fell in most patients during the injection but usually returned to pre-injection levels before the second sample was taken. No significant changes were therefore recorded. Pulmonary artery pressure began to increase either immediately or when the systemic pressure returned to normal levels. In some patients the increase in pressure lasted only a few minutes (Figure) but in the majority the rise in pressure outlasted the period of observations. As a result there was a significant increase in pulmonary artery pressure 15 minutes after the end of the protamine injection. Cardiac index fell but the changes did not reach significant levels. There was a significant fall in arterial oxygen

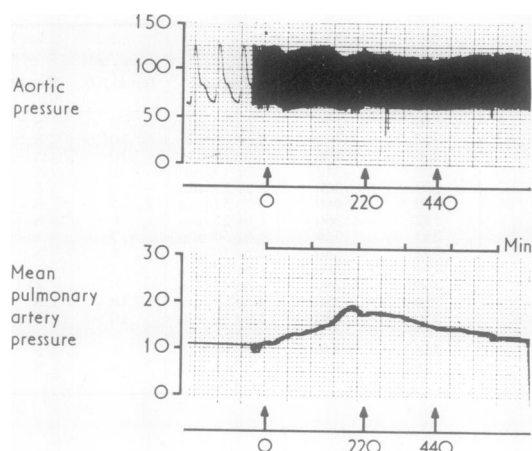


FIGURE Aortic pressure and mean pulmonary artery pressure during protamine injection. Injection started at 0; 220 and 440 represent milligrams of protamine injected.

tension (P_{aO_2}) after the injection of protamine but this was mainly due to the fall in mixed venous oxygen tension ($P\bar{v}O_2$) since there was little change in venous admixture (\dot{Q}_{va}/\dot{Q}_t). There was no statistically significant change in any of the other measurements.

DISCUSSION

These results confirm previous observations that protamine produces a marked fall in cardiac output and a brief fall in systemic arterial pressure. However, it is also apparent that there is a progressive increase in pulmonary arterial pressure and that the fall in cardiac output is the main cause of the fall in arterial PO_2 .

It is not yet clear why cardiac output falls after protamine. Goldman, Joison, and Austen (1969) observed a depression of myocardial contractility as measured by a strain gauge sutured across the right ventricle of both heparinized and non-heparinized dogs. They also observed a decrease in the rate of rise of left ventricular pressure (dp/dt) but conditions were poorly controlled and there is therefore some doubt as to whether these changes represented a true decrease in contractility. Gourin, Streisand, and Stuckey (1971), however, measured left ventricular dp/dt under more controlled conditions and claimed that protamine, 10 mg/kg, produced, if anything, a slight positive inotropic effect. Both of these groups of authors, Jacques (1949) and Rådegran and McAslan (1972) noted that protamine produced systemic vasodilatation and portal venous congestion. Gourin *et al.* (1971) supported the concept

that the hypotension is partly due to peripheral pooling of blood by infusing fluid during the administration of protamine. They claimed that this prevented the occurrence of hypotension in the majority of animals.

The increase in pulmonary artery pressure in the presence of a reduced cardiac output suggests either left ventricular failure or an increase in pulmonary vascular resistance. Although left atrial pressure was not specially measured during the present observations a left atrial pressure line was commonly in place and no obvious elevations of left atrial pressure were seen during the administration of protamine. This suggests that the pulmonary hypertension was due to an increase in pulmonary vascular resistance.

One possible cause of an increase in pulmonary vascular resistance is obstruction of the pulmonary vascular bed by microthrombi. Protamine produces a marked fall in platelet count both *in vitro* (Grøttum, 1969; Zbinden, Mehrishi, and Tomlin, 1970) and *in vivo* (Perkins *et al.*, 1961; Woods *et al.*, 1967; Rådegran, 1971; Rådegran and McAslan, 1972). Rådegran (1971) labelled platelets with chromium-51 and showed that the decrease in circulating platelets following protamine injection was accompanied by an increase in platelets in the lung but not in skeletal muscle. It is therefore reasonable to suggest that the pulmonary hypertension might have been due to obstruction of the pulmonary vascular bed with microthrombi. This should have led to an increase in alveolar dead space or a- $APCO_2$ and to an increase in dead space/tidal volume ratio. However, there were no significant changes in the present studies although there must have been a marked increase in pulmonary vascular resistance. The lack of change in dead space/tidal volume ratio does not necessarily rule out obstruction of the pulmonary vascular bed, for the increase in pulmonary artery pressure may have improved perfusion to previously non-perfused alveoli in the superior parts of the lung. This would have decreased alveolar dead space in these areas at a time when dead space was increasing in other parts of the lung because of obstruction by microthrombi.

A second possible cause of the increase in pulmonary artery pressure is pulmonary vasoconstriction. There is now a great deal of evidence to suggest that this is the main cause of the increase in resistance and that it is due to the release of vasoconstrictor substances from the blood or lung tissue. An increase in pulmonary vascular resistance occurs whenever platelet aggregation is induced, whether this is due to infusion of protamine, thrombin, endotoxin or to any of the other causes of disseminated intravascular coagulation (Rådegran, 1971; Swedenborg, 1971).

Disseminated intravascular coagulation (DIC) produces an increase in respiratory rate and minute volume, pulmonary vasoconstriction, systemic vasodilatation, a low cardiac output, an increase in airway resistance, a decrease in lung compliance, and a fall in arterial oxygen tension. The magnitude of these changes is related to the fall in circulating platelets (Whitaker and McKay, 1969; Rådegran, Taylor, and Olsson, 1971) and the changes seem to be minimal in the absence of platelets (Jacques, 1949). The previous administration of acetyl salicylic acid does not affect the decrease in circulating platelets or the systemic hypotension but minimizes the changes in pulmonary artery pressure, airway resistance, lung compliance, and arterial P_{O_2} after protamine injection (Rådegran and McAslan, 1972). Vagotomy or the previous injection of methysergide, a serotonin antagonist, does not prevent the changes induced by protamine. In view of these observations there is now some doubt as to the validity of the earlier suggestion that the pulmonary changes were mainly due to the release of serotonin while the systemic vasodilatation was due to the release of ADP and ATP from the platelets when the release reaction was initiated (Rådegran, 1971; Swedenborg, 1971). Furthermore, Jastrzebski, Hilgard, and Sykes (1974) demonstrated pulmonary vasoconstriction when protamine, protamine-heparin complex or the supernatant from this mixture was injected into the pulmonary artery of an isolated cat lung perfused with a blood-free prime. This would suggest either that protamine has a direct effect on pulmonary blood vessels or that it is capable of releasing vasoconstrictor substances from the lung itself.

Measurements of lung mechanics were not made in the present studies but the increase in venous admixture was minimal. Patterson (1972) states that measurements in man have occasionally revealed a decrease in lung compliance and an increase in airway resistance after protamine injection; similar findings have been recorded in animal experiments (Jacques, 1949; Stein, Hirose, Yasutake, and Khan, 1970; Rådegran and McAslan, 1972). Patterson showed in the dog that there was a close correlation between the changes in mechanics and the reduction in CO_2 elimination following the reduction in cardiac output. He also showed that the changes could be abolished by keeping the end-tidal PCO_2 constant. Rådegran and McAslan (1972) showed that intermittent hyperinflation of the lung or the application of a positive end-expiratory pressure (PEEP) abolished the changes in lung mechanics and increased arterial oxygen tension in dogs. It is possible that the application of PEEP during the present observations had similar effects, thereby

minimizing changes in lung mechanics or venous admixture. It is also possible that the PEEP accentuated the fall in cardiac output after protamine. However, Seed, Sykes, and Finlay (1970) showed that there was little change in cardiac output when an end-expiratory positive pressure of +10 cmH_2O was applied after cardiopulmonary bypass, and Sykes *et al.* (1970) showed in dogs that the application of similar pressures caused little change in cardiac output when venous pressure was high. Since the central venous pressure during the present observations was in the range 10–18 mmHg and little change was recorded after the injection of protamine, this possibility seems unlikely.

Although the effects of protamine seem to be relatively transient in man there may be other long-term effects. It has been suggested that DIC initiated by shock may be a cause of the later pulmonary complication known as the 'shock lung' (Blaisdell, Lim, and Stallone, 1970) and it is equally possible that DIC initiated by protamine injection may lead to the later development of the post-perfusion lung syndrome (Sykes, 1969b). DIC has been shown to occur in low output states two to 10 days after open-heart surgery (Boyd, Engelman, Beaudet, and Lackner, 1972) but there is as yet no evidence that the injection of protamine is associated with delayed damage to the lung. Castaneda (1966) and Castaneda, Gans, Weber, and Fox (1967) reported that cardiopulmonary bypass could be carried out without the use of protamine and found little increase in post-operative bleeding. If lung damage is shown to occur as a result of protamine administration such a policy may have to be reconsidered.

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