Protamine induced arterial hypoxaemia: the relationship to hypoxic pulmonary vasoconstriction

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Protamine administration may induce arterial hypoxaemia in dogs and humans. However, the responsible mechanism has not been established. Protamine, as it is a pulmonary vasoactive substance, may interfere with normal hypoxic pulmonary vasoconstriction (HPV) and cause arterial hypoxaemia. This possibility was tested in dogs utilizing a one lung hypoxic model. One lung hypoxic ventilation decreased pulmonary blood flow in the hypoxic lung from 1022 ± 96 ml·min^{-1} (mean ± SEM) to 846 ± 39 ml·min^{-1} ($p < 0.05$) while increasing blood flow from 833 ± 85 ml·min^{-1} to 1109 ± 101 ml·min^{-1} ($p < 0.05$) in the normoxic lung, resulting in 24 per cent effective diversion of blood flow. Protamine infusion, after heparinization, markedly elevated pulmonary vascular resistance in both lungs but preferentially in the normoxic lung (102 ± 27 per cent increase in normoxic lung, 60 ± 6.4 per cent increase in hypoxic lung) and significantly reversed the pulmonary blood flow shift induced by one lung hypoxic ventilation (effective diversion of blood flow was reduced to four per cent). Concurrently, arterial PO_2 further decreased. Our results demonstrate that protamine interferes with effectiveness of pre-existing HPV and suggest that this mechanism, at least in part, may be responsible for arterial hypoxaemia observed after protamine infusion. The marked generalized pulmonary vasoconstriction with protamine appears to be the direct force that interferes with pre-existing auto-regulatory HPV. In addition to the well known haemodynamic effects of protamine, protamine infusion may also cause arterial hypoxaemia in those patients in whom HPV plays a significant role in maintaining arterial oxygenation.

Key words

BLOOD, COAGULATION: protamine; OXYGEN: hypoxaemia; LUNG: hypoxic pulmonary vasoconstriction.

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Protamine infusion often decreases systemic arterial pressure and vascular resistance while pulmonary arterial pressure and resistance increase; concurrently, arterial oxygen tension (PaO_2) may fall.[1-3] Most of these changes are thought to be mediated by the release of endogenous vasoactive substances or direct action on pulmonary vasculature.[3,4] However, the exact mechanisms for the arterial hypoxaemia have not been explained.

Administration of various pulmonary vasoactive drugs results in arterial hypoxaemia, which has been attributed to the inhibition of hypoxic pulmonary vasoconstriction (HPV) with subsequent ventilation–perfusion mismatches.[5-8] Decrease in PaO_2 after protamine administration, therefore, may result from the alteration of normal HPV. This possibility was tested in six foxhound dogs utilizing the one lung hypoxic ventilation model.[8]

Methods

Six foxhound dogs of either sex, weighing 25–30 kg, were anaesthetized with intravenous pentobarbitone (25–30 mg·kg^{-1}). After tracheal intubation was accomplished, the animal was secured on the operating table in the supine position and ventilated with a Harvard animal ventilator. Catheters were placed in the femoral artery and vein.

A median sternotomy was then performed so as to leave the mediastinal ligaments intact. The pericardium was opened along its ventral aspect from the apex to its reflection on the ascending aorta. Traction sutures were placed along the cut edges of the pericardium and carried up to the edges of the sternum. This in conjunction with the mediastinal ligaments maintained the heart in a midline position, preventing torsion about the great vessels. The right and left main pulmonary arteries were then dissected from their origins to their bifurcations with care taken to remove as much adventitia as possible and to free the vessel circumferentially. An appropriately sized Statham SP-7500 series perivascular implantable flow probe was then placed on each pulmonary artery and adequate grounding was established individually for each probe. The probes were then connected to two Statham SP-2202 flowmeters. The proper calibration factors were set for the probes and null and electrical zero adjustments were made. The two flowmeters were then synchronized in the manner prescribed by the manufacturer to prevent either from interfering with determination made by the other.

A catheter was introduced into the left atrium through a stab wound in the appendage and secured with a ligature. A balloon tipped double lumen catheter was also introduced into the right atrium and advanced until the tip could be palpated in the distal main pulmonary artery. The femoral arterial and left atrial catheters and the proximal (pulmonary arterial) lumen of the balloon tipped catheter were connected to Statham transducers and these were subsequently connected to Brush transducer couplers with associated universal preamplifiers. Output signals from the flowmeter were directed to Brush universal couplers with associated preamplifiers. The outputs from these units were displayed as ink recordings on a multichannel general purpose recorder.

A tracheostomy was performed and the single lumen endotracheal tube was replaced with a double lumen endobronchial tube (National Catheter Company, Broncho-Cath) and, after the proper positioning of tube, the cuffs were inflated. The separation of the ventilation to each lung was checked by pressurizing each limb of the tube to 40 cmH_2O while the individual lung inflation or air leak around the cuff was directly observed.

The mass spectrometer (MEDSPECT II) had been aligned for ion sources and then calibrated with the known gas compositions. The compensation was also adjusted to eliminate non-specific gas interferences. Two six foot connecting cannulas were attached, one to each inlet of the Mass Spectrometer. The female end of each connecting cannula was then attached to a 16 gauge metal needle whose tip was inserted into each limb of endobronchial tube so that each needle sampled its respiratory gas samples from right and left lung separately. Each lung gas was sequentially sampled for a preset time (50 seconds). The respiratory gas (N_2, O_2 and CO_2) concentrations were then continuously monitored and the analog outputs were also continuously recorded.

After all monitoring devices were arranged, each lung was then separately ventilated utilizing two Harvard animal ventilators at the each lung tidal volume of 10 $ml \cdot kg^{-1}$ (total 20 $ml \cdot kg^{-1}$). The ventilatory frequency (f) was then adjusted to obtain 4(+0.2) per cent end-tidal CO_2 ($ET-CO_2$) from the right lung. The same f was synchronously applied for the left lung ventilator regardless of the resulting $ET-CO_2$ from the left lung. With this ventilatory setting, arterial carbon dioxide tension was maintained within normal range (36 ± 3.2 torr). The experimental conditions are schematically shown in Figure 1.

Once a stable condition was reached, blood gas analysis was done utilizing Instrumentation Laboratory Blood Gas Analyzer (#513), and, if necessary, metabolic acidosis was corrected with sodium bicarbonate. While continuously monitoring pressures (airway, left atrial, systemic and pulmonary arterial blood pressures), respiratory gases (O_2, CO_2 and N_2), and pulmonary arterial blood flows, the experiments were carried on stepwise; both lungs were initially ventilated with 100 per cent O_2 for 30 minutes and heparin (3 $mg \cdot kg^{-1}$) was given IV (control period). Without changes in tidal volumes and f, the right lung was ventilated with 100 per cent N_2 while the left was with 100 per cent O_2 until the peak steady state of right lung hypoxia (plateaued N_2 washin curve from the right lung monitored by Medspect) and plateaued pulmonary blood flow were reached (right lung hypoxic period, before protamine infusion). At this point, protamine (3 $mg \cdot kg^{-1}$) was infused through the catheter in the femoral vein over 30–40 seconds (right lung

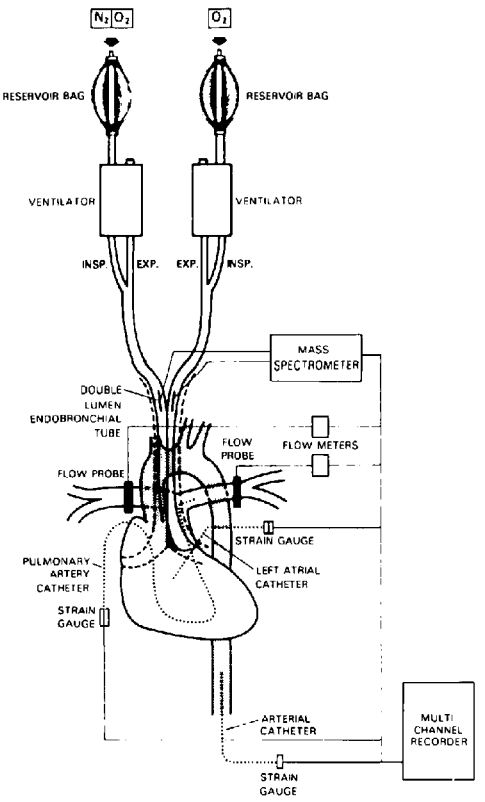

FIGURE 1 Diagram of ventilator sources of inspiratory gases, locations of pressure catheters and blood flow probes, gas sampling sites for mass spectrometer and arrangement for multi-channel recorder.

hypoxic period, after protamine infusion). Arterial and mixed venous blood gases were analyzed during control period, just before and four minutes after protamine when plateaued pulmonary blood flow change was observed. Statistical differences were tested using analysis of variance for repeated measures. The Bonferroni t-test was then used to isolate differences. A p-value less than 0.05 was considered statistically significant. All reported values are mean ± SEM.

Results

During the control period, right pulmonary blood flow (RPA_Q) was slightly higher then the left pulmonary blood flow (LPA_Q), which was also

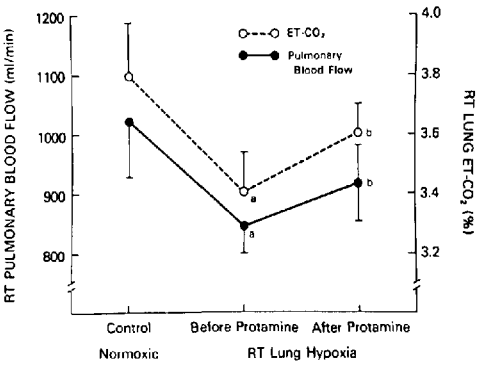

FIGURE 2 Pulmonary blood flow and end tidal CO_2 (ET–CO_2) of right lung. Parallel changes in blood flow and ET–CO_2 were observed after right lung hypoxic ventilation and protamine infusion. $^{a}p < 0.05$ compared to control normoxic values, $^{b}p < 0.05$ compared to values of before protamine (Bonferroni t-test).

reflected in end tidal carbon dioxide (ET–CO_2) levels (Table I). Right lung hypoxic ventilation reduced RPA_Q (17 per cent decrease) while LPA_Q increased (31 per cent increase) resulting in 24 per cent effective diversion (LPA_Q–RPA_Q/LPA_Q). The blood flow changes had plateaued within eight minutes from the beginning of hypoxic ventilation.

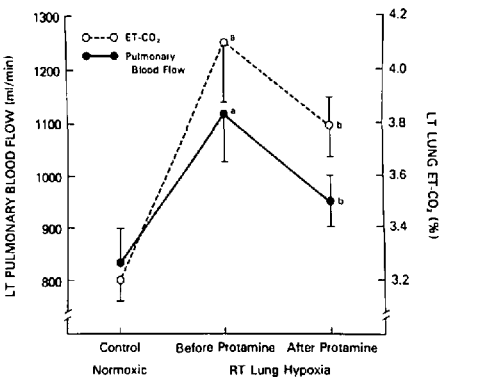

FIGURE 3 Pulmonary blood flow and end tidal CO_2 (ET–CO_2) of left lung. ET–CO_2 changes after right lung hypoxic ventilation and protamine infusion were nearly parallel with the changes in pulmonary blood flow. $^{a}p < 0.05$ compared to control normoxic values, $^{b}p < 0.05$ compared to before protamine infusion (Bon ferroni t-test).

TABLE I Haemodynamics, blood gases and end tidal carbon dioxide during hypoxic ventilation and after protamine infusion (mean ± SEM)

	Right lung hypoxia		
	Control period	*Before protamine*	*(4 minutes) after protamine*
RPA_Q ($ml \cdot min^{-1}$)	1022 ± 96	846 ± 39[a]	914 ± 53[b]
LPA_Q ($ml \cdot min^{-1}$)	833 ± 85	1109 ± 101[a]	955 ± 52[b]
Rt. ET–CO_2 (%)	3.8 ± 0.20	3.4 ± 0.14[a]	3.6 ± 0.10[b]
Lt. ET–CO_2 (%)	3.2 ± 0.16	4.1 ±0.25[a]	3.8 ± 0.15[b]
MAP (torr)	128 ± 5.5	135 ± 10	123 ± 12
PAM (torr)	17 ± 3.2	23 ± 4.1[a]	36 ± 4.1[ab]
LAM (torr)	7 ± 0.6	8 ± 2.3	10 ± 3.4
PaO_2 (torr)	408 ± 25	59 ± 5.2[a]	48 ± 4.3[ab]
$P\bar{v}O_2$ (torr)	52 ± 4.4	43 ± 5.5	36 ± 5.7
$PaCO_2$ (torr)	36 ± 3.2	37 ± 3.6	38 ± 3.9

[a] $p < 0.05$ compared with control, [b] $p < 0.05$ compared with values of before protamine.
PaO_2, $P\bar{v}O_2$: O_2 tension of arterial blood and mixed venous blood.
MAP, PAM, LAM: Mean pressures of aorta, pulmonary artery and left atrium.
RPA_Q, LPA_Q: Right and left pulmonary arterial blood flow.
ET–CO_2: End tidal CO_2.
$PaCO_2$: Arterial CO_2 tension.

PaO_2 markedly decreased from mean of 408 torr to 59 torr. After protamine infusion, pulmonary blood flow diversion induced by HPV was significantly reversed (four per cent effective diversion of blood flow) and PaO_2 further dropped to 48 torr. ET–CO_2 from each lung was also changed proportionally to the pulmonary blood flow changes (Figures 2 and 3). Total pulmonary blood flow (cardiac output) and airway pressures were not significantly altered during study periods. During right lung hypoxia but before protamine infusion, mean systemic blood pressure (MAP) and left atrial pressure (LAM) were not elevated significantly above control levels; whereas, mean pulmonary arterial pressure (PAM) increases significantly (Table I and Figure 4).

After protamine administration, MAP reduced and LAM rose for a brief period and rather quickly (within 3–4 minutes) recovered to the levels of before protamine infusion. PAM, on the other hand, increased further with protamine infusion and slowly recovered to the baseline values (5–10 minutes) (Figure 4). The changes in calculated pulmonary vascular resistances (PVR) of individual lung are summarized in Table II. Hypoxic ventilation increased PVR of right lung only. Protamine infusion increased PVR in both lungs but preferentially in normoxic lung.

Discussion

Our findings of systemic and pulmonary haemodynamics, and subsequent arterial blood gas changes after protamine infusion agree in general with the findings of previous studies in both dogs[1,2] and man[3] ventilated with normoxic gases.

The common observations after protamine infusion of marked fall in systemic blood pressure and resistance while the pulmonary arterial pressure and resistance increase, have been attributed to the release of endogenous vasoactive substances or the direct effect on vascular smooth muscles.[1–4] In dogs, Radegran and McAslan[2] found that protamine infusion reduces platelet counts concurrent with the haemodynamic alterations and a decrease in PaO_2. Acetylsalycylic acid, injected before protamine infusion in their study, did not prevent the fall in platelet counts but significantly inhibited the changes in pulmonary haemodynamics and arterial hypoxaemia, suggesting smooth muscle contracting substances released from platelet aggregates play a major role rather than mechanical obstruction of pulmonary capillary bed by the platelet aggregates. Jastrzebski and Sykes,[4] in the isolated cat lung study, found the increase in pulmonary arterial pressure after infusion of protamine–heparin complex occurred with both blood

TABLE II Pulmonary vascular resistance with one lung hypoxic ventilation and protamine infusion

		Right lung hypoxia	
	Normoxic control	*Before protamine*	*After protamine*
Right – PVR (dynes·sec·cm^{-5})	782.7 ± 73	1418.4 ± 65[a]	2275.8 ± 132[a,b]
Left – PVR (dynes·sec·cm^{-5})	906.0 ± 92	1082.1 ± 98	2178.0 ± 114[a,b]

Results are mean ± SEM.
[a]$p < 0.05$: compared to values of control normoxic period, [b]$p < 0.05$: compared to values of before protamine infusion.

and dextran perfusate although the response was attenuated in the lung perfused with dextran, suggesting that pulmonary vasoconstriction with protamine may be in part due to the direct action on pulmonary vasculature.

The exact mechanisms for protamine induced arterial hypoxaemia, however, have not been clearly explained in the previous studies. Radegran and McAslan[2] postulated alveolar atelectasis as responsible mechanism based on the observation that the fall in PaO_2 was partially prevented by adding positive end expiratory pressure (PEEP) or hyperinflation of the lung. However, atelectasis was not demonstrated in their study. A marked decrease in pulmonary arterial pressure upon lung hyperinflation was observed in their study, implicating the role of reduction of pulmonary arterial pressure in the improvement of PaO_2 could not be ruled out.

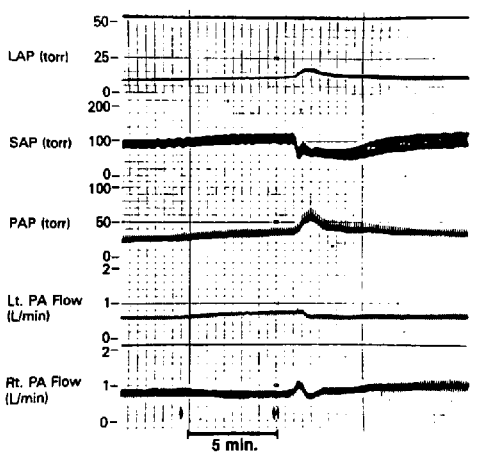

FIGURE 4 Multi-channel recording of left atrial pressure (LAP), systemic arterial pressure (SAP), pulmonary arterial pressure (PAP) and blood flow of right and left main pulmonary arteries (Rt. & Lt. PA flow). (↑) indicates beginning of right lung hypoxic ventilation, (↑ ↑) indicates infusion of protamine at the steady state of right lung hypoxia.

Jastrzebski *et al.*,[3] in a human study, explained the protamine-induced arterial hypoxaemia as a result of decreased cardiac output (CO). In their study, however, CO reductions were not significant; in addition, the patients were receiving PEEP of various degree. Therefore, the changes in shunt fraction and thereby the blood gas changes may have been altered by PEEP.

Since von Euler advanced the idea of hypoxic pulmonary vasoconstriction (HPV),[9] HPV is generally believed to be part of the self-regulatory mechanism by which pulmonary capillary blood flow is automatically adjusted to alveolar ventilation and thereby ventilation–perfusion ratio is favourably adjusted to protect arterial oxygen tension.[7,10] The mechanism of HPV may be either a direct action of alveolar hypoxia on pulmonary vasculature or indirectly through the release of vasoactive substances.[7,10]

Pulmonary vasoactive drugs such as isoproterenol, nitroglycerin and nitroprusside cause decrease in PaO_2 and the mechanism is thought to be the inhibition of pre-existing HPV.[5–8] Since protamine is a pulmonary vasoactive substance, the question as to whether the decrease in arterial PO_2 with protamine is a result of the interference with normal HPV is a logical extension.

During the control period, the left lung likely

received a relative overventilation since equal ventilation was applied in both lungs without considering the differences in pulmonary blood flow partitioning between two lungs. This resulted in the lower ET–CO_2 from the left lung (Table I). This overventilation should have reduced hypoxic pulmonary vasoconstriction in the left lung. In our study, however, hypoxic challenge was in the right lung while left lung was ventilated with 100 per cent oxygen, thus minimizing the potential implication of left lung overventilation on the results of our study. The effective diversion of blood flow (24 per cent) in response to one lung hypoxic ventilation is significantly smaller than the previously reported 27–37 per cent diversion.[11] This smaller response, however, was expected because of the following reasons. First, as RPA_Q decreased in response to hypoxic ventilation, right lung alveolar carbon dioxide (CO_2) was allowed to decrease, resulting in right lung respiratory alkalosis since there was neither concomitant decrease in ventilation nor inspiratory CO_2 supplementation. This selective right lung respiratory alkalosis may have affected responsiveness of pulmonary vessels to hypoxia.[12,13] Second, the extent of right lung hypoxia is self-limited by the reverse diffusion of oxygen from mixed venous blood to right lung alveoli.[14] Third, this weak response in our experiment may have originated from one time short exposure to hypoxia. It has been shown that several intermittent exposures to hypoxia increase HPV responses.[15]

Despite the small response to hypoxia, our experimental model appears to have certain advantages. First, pulmonary blood flow partitioning between two lungs can be additionally indexed by ET–CO_2 monitoring from each lung to confirm pulmonary blood flow diversion.[8] In a previous study, we observed a close relationship between ET–CO_2 and pulmonary blood flow changes.[16] Second, our experimental model may closely simulate certain clinical conditions where inspired gas contains no CO_2 and yet ventilation is constant, such as in the case of controlled ventilation. Although the observed responses were small, HPV induced in our study was significant and was substantially reversed upon protamine infusion supporting the notion that protamine may have inhibited HPV and thereby decreased arterial PO_2. Protamine, however, induces pulmonary vasoconstriction and cannot counteract directly the pre-existing HPV as is the case of other pulmonary vasodilators.[5–8] Thus, it appears that protamine is different in its mechanism of action in interfering with HPV from most of drugs that causing pulmonary vasodilation.

Benumof *et al.*[13] observed the proportional obtundation of HPV as pulmonary vascular pressure was raised by occluding the left atrium or infusion of dextrose, thus suggesting that protamine-induced pulmonary hypertension may have been a direct cause for HPV obtundation. The elevation of PAM in our study, however, was not the result of increased pulmonary vascular volume or pulmonary congestion but was the result of active vasoconstriction. After right lung hypoxia, pulmonary vascular resistance (PVR) rose in hypoxic lung (80 per cent increase) while no change was noted in normoxic lung (Table II). Protamine infusion raised PVR in both lungs, more in the right lung (193 per cent in the right lung, 128 per cent in the left). However, if the values were compared with values of right lung hypoxic stage but before the protamine infusion, the increase in pulmonary resistance was more prominent in the left normoxic lung (102 per cent increase vs. 60 per cent increase). These results, therefore, indicate that protamine evoked generalized pulmonary vasoconstriction in both lungs, but more in normoxic lung than hypoxic lung. It is probable that in hypoxic lung, vascular tone has already been raised above normal, the potential for further increase upon protamine infusion would have reduced while relatively relaxed vasculature of normoxic lung was able to constrict more effectively.

Marshall, *et al.*,[11] based on analysis of published data from a variety of animals, confirmed Benumof's findings[13] by showing a progressive depression of blood flow diversion response to hypoxia as transmural pulmonary arterial pressure increases. our findings, therefore, are compatible with that of Marshall *et al.*; the effective force of HPV to divert blood flow to normoxic lung was counteracted with protamine induced non-selective pulmonary vasoconstriction and PaO_2 subsequently declined. If this is the case, arterial hypoxaemia after protamine infusion appears to be transient and self-limited in nature since protamine-induced pulmonary hypertension was resolved in about ten minutes.

Clinically, protamine administration was well cautioned mainly because of adversarial haemo-

dynamic effects.[4,17] The results of our study indicate that an additional caution must be paid when protamine is administered in the patients with certain pulmonary diseases wherein HPV plays a significant role for maintaining arterial oxygenation.

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Résumé

L'administration de protamine peut provoquer de l'hypoxémie artérielle chez le chien et chez les humains par un mécanisme qu'on n'a pas encore élucidé. La protamine qui possède une activité sur la circulation pulmonaire peut interférer avec le réflexe vasoconstricteur hypoxique (HPV) et ainsi causer de l'hypoxémie. Cette hypothèse a été vérifiée chez des chiens grâce au modèle expérimental à un seul poumon hypoxique. Le poumon à ventilation hypoxique a vu sa circulation sanguine diminuer de 1022 ± 96 ml·min^{-1} (± SEM) à 846 ± 39 ml·min^{-1} ($p < 0.05$) pendant que la circulation dans le poumon normal a augmenté de 833 ± 85 ml·min^{-1} à 1109 ± 101 ml·min^{-1} ($p < 0.05$) ce qui représente une dérivation du flux sanguin de l'ordre de 24 pour cent. L'infusion de protamine après héparinisation a élevé la résistance pulmonaire dans les deux poumons mais surtout dans le poumon à ventilation normale (102 ± 27 pour cent d'augmentation contre 60 ± 6.4 pour cent). Ces modifications de résistance ont réduit à quatre pour cent la partie du flux sanguin dérivée par la ventilation hypoxique. Une nouvelle baisse de la PO_2 artérielle a accompagné le phénomène. Ce résultat montre donc que la protamine interfère avec le réflexe vasoconstricteur hypoxique ce qui explique, en partie du moins, l'hypoxémie artérielle qu'on observe après l'infusion de protamine. C'est par l'entremise d'une vasoconstriction pulmonaire généralisée que la protamine semble exercer son action sur le HPV. En conclusion, en plus de ces effets hémodynamiques bien connus, la protamine peut donc causer de l'hypoxémie artérielle chez un patient qui compte sur le réflexe vasoconstricteur hypoxique pour maintenir son oxygénation artérielle.