

## Case Report of Acute Pulmonary Edema and Sudden Death After Heart Surgery

Joshua M. Thigpen, DNP, CRNA

**Affiliation:**

*Dr Thigpen was a student at Texas Christian University at the time of writing this article.*

**Funding/Conflict of Interest Disclosure:**

*None*

**KEYWORDS:** Cardiac surgery, cardiopulmonary bypass, transfusion-related acute lung injury, protamine reaction, noncardiogenic pulmonary edema

### Abstract

A 47-year-old man underwent aortic valve replacement surgery. After cessation of cardiopulmonary bypass, the patient exhibited refractory hypoxia, fulminant pulmonary edema, and hypotension and ultimately died less than 1 hour after his arrival to the intensive care unit. The patient may have experienced either a severe type III reaction to protamine sulfate or a transfusion-related acute lung injury. Both of these conditions can produce hypoxia, pulmonary edema, and hypotension. Anesthesia professionals must be able to identify patients at risk for both conditions, recognize their presentations, and respond quickly and appropriately when presented with these deadly reactions.

### INTRODUCTION

Aside from the inherent risks of heart surgery and individual morbidities, unforeseen risks are sometimes overlooked and can be devastating. These covert problems in the time period of coronary artery bypass graft surgery usually manifest after cardiopulmonary bypass (CPB), after hemodynamic stabilization, when complications are less likely. The post-CPB period is when protamine sulfate and blood products are commonly administered. Protamine sulfate reverses the effects of the heparin that was administered before and during CPB to prevent coagulation.

In this case, a 47-year-old man undergoing several procedures on his heart and requiring CPB experienced fulminant pulmonary edema after the administration of protamine and blood products. It is unclear whether the protamine or the blood products were responsible, because transfusion-related acute lung injury (TRALI) and severe reactions to protamine have similar presentations. Unfortunately, the severity of the resulting pulmonary edema led to this patient's death. Anesthesia professionals should be familiar with the risk factors, presentation, and treatment for each.

## CASE SUMMARY

A 47-year-old man with a weight of 101 kg and height of 182.9 cm was scheduled for a modified left atrial maze procedure, coronary bypass of the posterior descending artery, and aortic root replacement with a mechanical aortic valve conduit. The patient had a recently diagnosed history of hypertension, atrial fibrillation, coronary artery disease, nonruptured ascending aortic aneurysm, aortoannular ectasia with severe aortic insufficiency, and hyperlipidemia. The patient was taking metoprolol, furosemide, hydrochlorothiazide, lovastatin, and dabigatran (which had been discontinued for at least 3 days). The results of the patient's chemistry panel and complete blood count were unremarkable, but hemoglobin and hematocrit values of 11.8 mg/dL and 35%, respectively, were noted. Upon assessment in the preoperative holding area, the patient appeared alert with no signs of distress and a supportive family was present. The results of a physical examination were normal except for an obvious heart murmur and a continuous electrocardiogram displaying atrial fibrillation.

After the patient was administered fentanyl 100 mcg intravenous (IV) and midazolam 2 mg IV, a right radial arterial line was placed in the preoperative holding area. The patient was then transported to the operating room, standard monitors were applied, and the arterial line was connected for blood pressure (BP) monitoring. Induction of anesthesia was performed with a combination of the inhalational agent sevoflurane and additional administration of midazolam 5 mg, sufentanil 25 mcg, propofol 50 mg, and vecuronium 10 mg IV. The patient was orally intubated with an 8.0-mm endotracheal tube via direct laryngoscopy and the tube was secured at 22 cm at the teeth following confirmation of placement. Anesthesia was maintained with sevoflurane at variable end-tidal concentrations along with sufentanil and propofol boluses to maintain a bispectral index monitor reading of 40 to 60 while maintaining systolic BP (SBP) at a desirable value of 90 to 110 mm Hg for the indicated procedures. After induction, a right subclavian central line and right internal jugular pulmonary artery catheter with a sheath introducer were placed. The pulmonary artery catheter revealed a pulmonary artery pressure of 32/22 mm Hg, central venous pressure of 16 mm Hg, cardiac output of 5.5 L/min, cardiac index of 2.5 L/min/m<sup>2</sup>, and a mixed venous oxygen saturation (SvO<sub>2</sub>) of 68%. Cefuroxime 1.5 g IV was administered for infection prophylaxis. Aminocaproic acid 10 g IV bolus was given prior to incision and an additional 5 g was administered over 5 hours during the procedure. The other medication infusions administered were dexmedetomidine 0.3 mcg/kg/h and milrinone 0.375 mcg/kg/min.

The procedure proceeded in the usual fashion for patients undergoing coronary artery bypass with endoscopic vein harvest, save for the time taken to perform the maze procedure. The pre-CPB period was uneventful. Minimal boluses of phenylephrine 100 mcg and ephedrine 5 mg IV were given to maintain SBP at 90 to 110 mm Hg. CPB was initiated approximately 60 min after incision. Total CPB time was 4 hours. The aortic valve and root were replaced along with the graft bypassing the posterior descending coronary artery. The patient received 4 units of packed red blood cells while on CPB. As rewarming began, norepinephrine was started at 0.04 mcg/kg/min. When

the primary aortic cross-clamp was removed, lidocaine 100 mg IV was given along with calcium chloride (CaCl) 500 mg IV. Albumin 5% 500 mL was given prior to cessation of CPB. After successful weaning from CPB and transesophageal echocardiography revealed satisfactory improvement of forward flow of blood through the mitral and aortic valves, protamine sulfate 500 mg IV was infused over 10 min with close hemodynamic monitoring. After the protamine had finished infusing, 2 units of fresh frozen plasma and 1 unit of platelets were infused. During the time of CPB weaning, crystalloids were given more liberally owing to inadequate filling of the heart. The total volume of crystalloid was approximately 2.3 L at 5 hours from the start of the case. The patient was hemodynamically stable after complete weaning from CPB and in sinus rhythm with a heart rate of 83, BP in the 90s/60s mm Hg, cardiac output of 5.1 L/min, cardiac index of 2.3 L/min/m<sup>2</sup>, pulmonary artery pressure of 48/34 mm Hg, central venous pressure of 30 mm Hg, and SvO<sub>2</sub> of 63%.

Forty-five minutes after weaning from CPB and 30 minutes after infusion of the platelets and fresh frozen plasma, the patient's oxygen saturation as measured by pulse oximetry (SpO<sub>2</sub>) was trending into the low 90s and upper 80s but responded to large manual breaths and was initially thought to be due to atelectasis. As time progressed, however, the patient's SpO<sub>2</sub> continued to decrease with a concomitant decrease in end-tidal CO<sub>2</sub> to approximately 20 mm Hg. The initial diagnosis included a possible pulmonary embolus or clot resulting in obstructed gas exchange. An arterial blood gas sample revealed a partial pressure of oxygen (PaO<sub>2</sub>) of 53 mm Hg (despite 100% FiO<sub>2</sub> [fraction of inspired oxygen]), pH 7.24, and arterial oxygen saturation (SaO<sub>2</sub>) of 83%. It was almost accepted that an embolus was the precipitating factor owing to adequate tidal volumes, normal airway pressures, and transesophageal echocardiography (TEE) revealing significant improvement in cardiac function. A chest x-ray revealed pulmonary infiltrates versus effusion on the right side. The sternum was reopened for inspection and a pleural chest tube was placed. At 80 minutes post-CPB time, mucus was present in the heat and moisture exchange filter where the endotracheal tube (ETT) connects to the breathing circuit. In-line suctioning of the ETT produced copious amounts of fluid that totaled a volume of 400 mL plus the large amount that spilled onto the floor and onto towels. Fiberoptic bronchoscopy revealed a lake of fluid. Suctioning with the bronchoscope was performed and an additional 600 mL was removed. However, the lungs filled back up with fluid almost as fast as the fluid was aspirated. Furosemide 20 mg IV was given but failed to improve the situation.

The patient's BP began to wane despite a high number of phenylephrine boluses equalling 5 mg over about 1 hour, a norepinephrine infusion at 0.5 mcg/kg/min, plus the addition of epinephrine at 0.02 mcg/kg/min. Dexmedetomidine was discontinued. The surgeon, anesthesia team, and intensivist all agreed that all resuscitation measures had been taken; there was nothing more to do. The patient was transported to the intensive care unit 8 hours after the surgery began and was pronounced dead 30 minutes after arrival. Postoperative laboratory values were unremarkable aside from the arterial blood gas and slightly elevated coagulation values, prothrombin time of 22.2, partial thromboplastin time of 44, and international normalized ratio

of 1.9. The patient received a total of 3500 mL of crystalloids, 4 units of packed red blood cells, 2 units of fresh frozen plasma, 500 mL of 5% albumin, and 1 unit of platelets. Urinary output was 1400 mL and estimated blood loss was 795 mL.

## DISCUSSION

The initial consideration was that the patient had developed a pulmonary embolus. The patient was in atrial fibrillation before the case and up to the time of the maze procedure. Dabigatran had been discontinued for at least 3 days before surgery, leading to the possibility of clot formation. The physician's assistant noted the presence of clots during the endoscopic vein harvest of both legs. The low SpO<sub>2</sub>, low end-tidal carbon dioxide (ETCO<sub>2</sub>), and hemodynamics requiring vasopressor support lent credence to a diagnosis of a pulmonary embolus. However, no pulmonary embolus was detected by TEE. A pulmonary embolus was ruled out after manifestation of fulminant pulmonary edema. Other possibilities considered were TRALI or a severe reaction to protamine sulfate. Furosemide was administered, although it did little, if anything, to relieve the pulmonary edema. Despite almost continuous suctioning of the airway via the fiberoptic bronchoscope, fluid continued to fill the lungs. The only viable option at this point for resuscitation was extra-corporeal membrane oxygenation (ECMO). Unfortunately, ECMO was not available at the facility or in the local community. The exact cause of the devastating event was unknown. The presentation supported TRALI and a severe reaction to protamine as the culprit. Further investigation was required to identify the cause. An acute lung injury occurring during or within 6 hours of the administration of blood products defines the rare and often deadly TRALI.<sup>1</sup> Several signs may be observed as this process occurs, such as dyspnea, hypoxia, hypotension, pulmonary hypertension, pulmonary edema, pulmonary infiltrates on chest x-ray, and decreased lung compliance.<sup>2</sup> The ALI is noncardiogenic in nature and occurs without the presence of circulatory overload.<sup>3</sup> All of the aforementioned signs were part of the clinical picture for the patient in this case except for the decrease in lung compliance. However, it has been suggested that there is a time gap between the development of pulmonary hypertension and a decrease in lung compliance.<sup>2</sup> The length of that time gap may be patient-dependent. Because this patient died about 3 hours after the administration of the blood products, the decreased compliance may not have manifested before transport from the operating room. The complete pathophysiology of TRALI is unknown but is likely precipitated by leukocyte antibodies or the activation of inflammatory mediators that can result in increased pulmonary capillary permeability and ultimately poor pulmonary function.<sup>1</sup> The treatment for TRALI is primarily supportive with the primary goal of discontinuing administration of the insulting blood products if possible. Some evidence suggests that the use of steroids may be of benefit.<sup>1</sup> In

the case of this patient, the devastating toll that the pulmonary edema caused could only be treated with ECMO. Unfortunately, ECMO was not available at this facility or within the local community. Some studies have presented evidence for increased risk factors linked to TRALI, such as higher interleukin-8 levels, elevated peak airway pressures during mechanical ventilation, smoking, and a positive fluid balance.<sup>3</sup>

A severe reaction to protamine sulfate is a second possible cause of the fulminant pulmonary edema and cardiovascular collapse. There are 3 types of reactions to protamine classified as type I, type II, and type III. The type III reaction is the most severe and exerts its profound effects by the formation of large heparin-protamine complexes that accumulate in the pulmonary circulation. This leads to the release of chemical mediators, a profound decrease in BP, and an elevation in pulmonary artery pressures that can ultimately lead to right ventricular failure.<sup>4</sup> Documented cases of noncardiogenic, fulminant pulmonary edema after the administration of protamine are published.<sup>5,6</sup> One case report describes a reduction in oxygen saturation and pink, frothy sputum suctioned from the ETT immediately after the administration of protamine.<sup>6</sup> A second case report describes the same presentation but was unable to state with confidence whether the triggering agent was blood products or protamine.<sup>5</sup> The release of endothelial nitric oxide and histamine with mast cell degranulation due to rapid infusion of protamine has been suggested as the process for protamine reactions.<sup>4</sup> Primary risk factors for protamine reactions include rapid infusion, prior exposure, history of vasectomy, impaired left ventricular function, and hemodynamic instability.<sup>7</sup> During the slow administration of protamine to the patient in the present case, no hemodynamic instability was noted. The evidence suggests that slowing the infusion rate of protamine when hypotension is encountered is often enough to eliminate symptoms. However, in the case of severe type III reactions, it may be necessary to re-heparinize and resume CPB until stable by reducing the heparin-protamine complex size.<sup>4</sup> Furthermore, if a patient has a known sensitivity to protamine or has had prior exposure, an alternative anticoagulant agent may be necessary.<sup>4</sup>

## CONCLUSION

Noncardiogenic pulmonary edema after CPB can be deadly. Treatment to restore effective gas exchange and restore hemodynamic stability is difficult and multifaceted. In retrospect, prompt determination of differential diagnoses and treatment involving the surgical, anesthesia, and perfusion teams to resume CPB may have changed the outcome in the present case. There was no definitive diagnosis of TRALI vs type III protamine reaction for this patient. Anesthesia professionals must know the risk factors for TRALI and protamine reactions, identify onset promptly, and initiate treatment immediately.

## REFERENCES

1. Bitargil M, Arslan C, Basbug HS, et al. Transfusion-related acute lung injury following coronary artery bypass graft surgery. *Perfusion*. 2015;30(8):626-628. PMID:25575703.
2. Kojima T, Nishisako R, Sato H. A patient with possible TRALI who developed pulmonary hypertensive crisis and acute pulmonary edema during cardiac surgery. *J Anesth*. 2012;26:460-463. PMID:22249282.
3. Miller RD. Patient blood management: transfusion therapy. In: Miller RD, ed. *Miller's Anesthesia*. 8th ed. Philadelphia, PA: Elsevier; 2015:1830-1867.
4. Nussmeier NA, Sarwar MF, Searles BE, et al. Anesthesia for cardiac surgical procedures. In: Miller RD, ed. *Miller's Anesthesia*. 8th ed. Philadelphia, PA: Elsevier; 2015:2007-2095.
5. Kindler C, Bircher A, Stulz P. Protamine-induced fulminating non-cardiogenic pulmonary edema following cardiopulmonary bypass. *Eur J Cardiothorac Surg*. 1996;10(6):463-466. PMID:8817145.
6. Brooks JC. Noncardiogenic pulmonary edema immediately following rapid protamine administration. *Ann Pharmacother*. 1999;33(9):927-930. PMID:10492491.
7. Kimmel SE, Sekeres MA, Berlin JA, et al. Risk factors for clinically important adverse events after protamine administration following cardiopulmonary bypass. *J Am Coll Cardiol*. 1998;32(7):1916-1922. PMID:9857872.