Clinical Workshop

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Post-transfusion Pulmonary Edema in Surgical Patients: Etiology, and Therapeutic Use of Trimethaphan Camphorsulfonate (Arfonad)

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The development of pulmonary edema in surgical patients has been the subject of two reviews [1, 2] and several reports.[2-8] Masson [1] noted that the condition occurs infrequently. Adriani *et al.*[2] reported that it may be precipitated in patients with no evidence of systemic disease. Analysis of these reports reveals that pulmonary edema followed blood transfusion in two patients [2, 5] and that vasodilatation produced by hexamethonium and phenoxybenzamine was used successfully twice.[3, 7] The use of trimethaphan in the treatment of pulmonary edema has been reported for medical patients only.[9-11]

This is a report of the etiology and treatment of pulmonary edema in four young surgical patients, free of cardiovascular disease, in whom the condition followed blood loss and replacement, and in whose treatment trimethaphan was used.

Patient 1. A 12-year-old girl was admitted for surgical correction of marked congenital thoracic scoliosis. There was no evidence of cardiovascular disease.‡ After application of a Risser localizer cast 22 days prior to surgery, the vital capacity fell from 1,060 ml to 600 ml (20 per cent of predicted value).

Prior to anesthesia the patient was extremely frightened, with vasoconstricted extremities. Multiple laminectomies and osteotomies of three fused thoracic vertebrae, and insertion of a Harrington rod, were performed. Anesthesia, which lasted four hours and 43 minutes, was conducted with thiopental sodium, 150 mg, succinylcholine, 40 mg, and halothane, endotracheally given with intermittent positive-pressure breathing (I.P.P.B.) throughout. Blood pressure was unobtainable on three occasions because of bleeding. The volume of blood lost and blood and fluid replacement required to maintain systolic pressure above 75 mm Hg are shown in table 1. Approximately two thirds of the transfused blood was warmed before administration.

On admission to the recovery room at 12:35 p.m. the rectal temperature was 34.3 C. During the next hour, profound cyanosis, marked lower thoracic inspiratory retraction, and expiratory straining developed, and rales became audible throughout both lung fields. The extremities were severely vasoconstricted. In view of the severe pulmonary edema the endotracheal tube was reinserted at 1:55 p.m. Oxygen was administered by I.P.P.B., and trimethaphan, 5 mg, was injected intravenously at 2:20 p.m. There was a transient fall in systolic pressure from 120 to 80 mm Hg, a maintained fall in the central venous pressure from 37 to 24 cm H_2O, and a decrease in the pulmonary edema and vasoconstriction. The bladder was catheterized at 3:00 p.m. and 500 ml of urine were obtained. The pulmonary edema abated steadily with two additional doses of trimethaphan, 2.5 mg, and the endotracheal tube was removed at 5:30 p.m., at which time the lungs were free of rales. At 6:30 p.m., in arterial blood drawn while the patient was breathing humidified oxygen by mask, Pa_{O_2} was 308 mm Hg, Pa_{CO_2} 44 mm Hg, *p*H 7.44.

Because of the low urinary output (table 2) 100 ml of whole blood were administered, but the transfusion was discontinued when the central venous pressure rose from 15 to 19 cm H_2O. At 1:00 a.m. central venous pressure was found to have fallen to 3 cm H_2O, and administration of 300 ml whole blood resulted in a urinary output of 200 ml in one hour. Blood requirements and

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‡ The authors are aware that scoliosis of this severity can cause hemodynamic abnormalities.[12]

TABLE 1. Courses of the Patients before Onset of Pulmonary Edema

Patient	Weight (kg)	Preoperative Hematocrit (per cent)	Blood loss (ml)	Blood transfused (ml)‡	Fluid Administered		
					Dextran (ml)	Saline (ml)	Water (ml)
1	42	41.5	5,225*	7,500 W.B.	—	1,900	—
2	33	38	5,900*	6,000 W.B.	—	—	250
3	—	27	7,500	9,000 W.B.	500	—	2,300
4	—	34	2,500	3,500 W.B.	500	1,250	200

* Measured by weighing the sponges and packs, and by measuring the volume of blood in the suction apparatus; did not include the blood in the wound or on the surgical drapes.

hematocrit values, in the absence of overt hemorrhage, are shown in table 2.

Patient 2. A 13-year-old girl was admitted for surgical correction of moderate paralytic thoracic scoliosis. There was no evidence of cardiovascular disease. The vital capacity was 1,790 ml (76 per cent of predicted value). A Risser localizer cast was applied seven days prior to surgery.

Insertion of a Harrington rod and spinal fusion were performed. Following awake nasotracheal intubation, anesthesia, which lasted five hours and 15 minutes, was conducted with thiopental sodium, 125 mg, halothane and nitrous oxide, with I.P.P.B. throughout. The volume of blood lost and blood and fluid replacement required to maintain systolic arterial pressure above 70 mm Hg are shown in table 1. The transfused blood was cold.

Pulmonary edema developed on the way to the recovery room at 1:00 p.m. Trimethaphan, 5 mg, was injected intravenously at 1:05 p.m. and oxygen was administered by I.P.P.B. via the endotracheal tube. Two additional doses of trimethaphan, 5 mg and 10 mg, were given, and at 1:15 p.m. the systolic arterial pressure had risen from 80 mm Hg to 115 mm Hg. At 1:25 p.m. the lungs were free of rales, and at 3:00 p.m. the rectal temperature was 33.0 C. At 6:00 p.m. the arterial pressure had fallen to 90/60 mm Hg, but rose to 110/60 mm Hg after transfusion of 500 ml whole blood. Blood requirements and hematocrit values, in the absence of overt hemorrhage, are shown in table 2.

Patient 3. A 20-year-old, 32-weeks-pregnant woman was admitted for evaluation 30 minutes after an automobile accident. There was no evidence of cardiovascular disease. A nasal fracture was diagnosed but no evidence of uterine damage, vaginal bleeding or fetal distress was found. Four hours later, the fetal heart was noted to be irregular. Cesarean section and hysterectomy were performed under endotracheal cyclopropane anesthesia which lasted three hours. Premature separation of the placenta was found and a stillborn fetus delivered at 3:04 p.m. The systolic arterial pressure was 105 mm Hg on discharge from the recovery room at 9:25 p.m., but at 6:00 a.m. it had fallen to 80/50 mm Hg and the abdomen was markedly distended. The hematocrit had fallen from 32 per cent to 23 per cent.

A left salpingo-oophorectomy was performed because of bleeding from the area of the left ovary. This anesthesia lasted two hours and 30 minutes and was conducted with cyclopropane, with I.P.P.B. throughout. The volume of blood lost and blood and fluid replacement required after admission are shown in table 1. The transfused blood was cold.

On admission to the recovery room at 10:45 a.m. the patient was plethoric and cyanotic, with rales throughout both lung fields. Radiologic examination at 11:15 a.m. revealed pulmonary edema. Trimethaphan, 5 mg, was given intravenously at 11:40 a.m. The systolic blood pressure rose from 90 mm Hg to 120 mm Hg at 11:45 a.m. At 11:50 a.m. a venesection was performed but was discontinued after only 300 ml blood had been removed. Additional doses of trimetaphan, and a single dose of hexamethonium, 10 mg, injected intravenously at 12:05 p.m. resulted in disappearance of the pulmonary edema. Radiologic examination at 7:00 p.m. revealed mild congestive changes with a decrease in pulmonary edema. There was a high urinary output, and no further blood transfusions were required to maintain the hematocrit (table 2).

Patient 4. An 18-year-old woman was admitted, three hours and 30 minutes after an automobile accident, with severe facial lacerations, a compound comminuted fracture of the nasal bones, a comminuted fracture of the right femur, and a compound comminuted fracture of the right tibia. There was no evidence of cardiovascular disease.

Primary closure of the facial lacerations, open reduction of the nasal fracture, and insertion of a K wire into the right tibial tuberosity were performed. Anesthesia was induced and intubation performed, with divinyl ether and diethyl ether

administered by the open-drop technique, because it was not possible to apply a mask to the face, and because the hysterical condition of the patient would not allow awake intubation. Anesthesia, which lasted two hours and 55 minutes, was maintained with diethyl ether and nitrous oxide, with spontaneous respiration throughout. The volume of blood loss and blood and fluid replacement required after the accident are shown in table 1. The transfused blood was cold.

At 2:12 a.m., during preparation for removal of the endotracheal tube, large amounts of pink frothy fluid were obtained on endotracheal suction, and rales were noted throughout both lung fields. The initial treatment of the pulmonary edema consisted of: oxygen administered by I.P.P.B.; reverse Trendelenberg position; aminophylline, 500 mg, digoxin, 0.5 mg, and mercuhydrin, 2 ml, all given intravenously; and rotating tourniquets. Because the response was only fair, 1,100 ml blood were removed by venesection at 2:45 a.m. This resulted in a fall in the arterial systolic pressure to 75 mm Hg and a dramatic but only temporary improvement in the pulmonary edema. Trimethaphan, 2 mg, was therefore given intravenously at 3:15 a.m., followed by an additional dose of 1 mg. Morphine sulfate, 6 mg, was administered subcutaneously, and a second dose of digoxin, 0.5 mg, intravenously, and at 3:50 a.m. a third dose of trimethaphan, 1 mg, was given. The pulmonary edema abated steadily. Radiologic examination of the lungs at 4:30 a.m. revealed an unusual type of pulmonary edema, the appearance suggesting diffuse fat embolization. At 5:15 a.m. the endotracheal tube was removed. At 6:00 a.m. the lungs were free of rales except at the bases, and by 9:45 a.m. they were completely free of rales. There was a high urinary output, and no further blood transfusions were required to maintain the hematocrit (table 2).

Discussion

Luisada [13] has stated that in the pathogenesis of pulmonary edema three main mechanisms should be considered: decreased colloid osmotic pressure of blood; distention of pulmonary capillaries; and increased permeability of pulmonary capillaries. Distention of pulmonary capillaries is believed to have been of prime importance in each of our patients. Adriani *et al.*[2] stated that pulmonary edema is seldom due to one factor alone, and suggested six precipitating factors: incomplete cardiac emptying; shift of blood from the periphery to the pulmonary vascular bed; circulatory overload; negative pressure on the airway; idiopathic; and injury to the alveolar membrane. Although it is difficult to differentiate clinically among them, either circula-

TABLE 2. Courses of the Patients after Pulmonary Edema

Patient	Initial Urinary Output (ml/hour)	Blood Administered (ml) on Postoperative Day					Hematocrit (per cent) on Postoperative Day						
		0	1	2	3	4	0	1	2	3	4	5	6
1	16.0	400 W.B.* 500 W.B.	300 P.C.† 500 W.B.	300 P.C.	—	—	33 32 45	33 25 34	28 30 28	30	29	31	—
2	not measured	—	—	—	300 P.C.	300 P.C.	40	40	27	23 18	20 32	35	35
3	146.8	—	—	—	—	—	44 40	44	40	—	42	—	—
4	150.0	—	—	—	—	—	40 41	41	37	35	—	30	—

* Whole blood; one unit assumed to be 500 ml.
† Packed cells; one unit assumed to be 300 ml.

TABLE 3. Possible Causes of Systemic Vasoconstriction in the Four Patients

Patient	Hypovolemia		Fear	Cold	Bladder Distention
	Blood Loss	Bed Rest			
1	Yes	Yes	Yes	Yes	Yes
2	Yes	No	Possible	Yes	No
3	Yes	No	Possible	Possible	No
4	Yes	No	Yes	Possible	No

tory overload, or systemic vasoconstriction * leading to a shift of blood from the periphery to the pulmonary vascular bed, or both, were felt to have precipitated the pulmonary edema in the patients presented.

The first patient received 54 ml/kg more blood than the measured loss (table 1). However, the low initial urinary output and hematocrit, the absence of overt hemorrhage, the ultimately low central venous pressure, and subsequent blood requirements (table 2), indicated that this patient was hypovolemic at the time of the pulmonary edema. The second patient received almost exact replacement of the measured blood loss (table 1), and also presented evidence of hypovolemia during the postoperative course (table 2). Because of the problem of evaluating blood loss upon opening the uterus of the third patient, and because of the injuries in the fourth, the blood losses of these patients could only be estimated (table 1). However, both patients had high initial urinary outputs and hematocrit values (table 2) and could maintain satisfactory hematocrit values without further blood transfusion, and following removal of 300 ml blood by venesection from the third patient and 1,100 ml from the fourth. These responses indicate that the latter patient was markedly hypervolemic, the former probably hypervolemic but to a lesser degree, at the time of the pulmonary edema. Therefore, although systemic vasoconstriction was considered a precipitating factor in all four patients, the evidence indicates that it was predominant in the first two only. That all four patients were young adults is of interest because this age group is said to possess increased vasoconstrictor tone.[15] The other possible causes of systemic vasoconstriction [16-19] or hypovolemia [20] leading to compensatory venoconstriction [21] in the patients are listed in table 3.

In laboratory experiments, Sarnoff and his co-workers [22-24] have demonstrated that systemic vasoconstriction leads to a shift of blood from the peripheral to the pulmonary vascular bed, the shift due to systemic venoconstriction and increased arteriolar resistance. During treatment of induced pulmonary edema with trimethaphan, data indicating the importance of the shift of blood back from the pulmonary to the peripheral circulation, owing to both systemic venodilatation and to decrease in left ventricular work, were also obtained.

Evaluation of the four case histories reveals that pulmonary edema was rapidly reversed by trimethaphan and reinstitution of I.P.P.B. in the first two patients, and by trimethaphan and removal of a small volume of blood by venesection in the third. In the fourth patient the pulmonary edema was initially treated by multiple methods, including removal of a large volume of blood by venesection, with slow improvement. Ultimate improvement followed administration of trimethaphan. Finlayson *et al.*[25] have also noted the rapid and dramatic response of pulmonary edema to vasodilatation in comparison to the much slower improvement with intravenous morphine, oxygen, and venous tourniquets.

Although the incidence of pulmonary edema

* The term systemic vasoconstriction is used, throughout this report, to refer to a condition in which there is active contraction of the smooth muscle in the walls of the systemic venous capacitance vessels and the walls of many systemic arteriolar resistance vessels, generally assumed to result from generalized sympathetic nervous system activity. The authors recognize that there is evidence that a vasoconstrictor response may be elicited predominantly in one or other of the two sets of vessels mentioned, not necessarily in both to a similar extent at the same time.[18]

in the operating room and in the recovery room is low,[1] attempts to avoid systemic vasoconstriction and circulatory overload should reduce this complication even further. The sooner blood loss is replaced the better is the chance of avoiding systemic vasoconstriction. The less a patient is emotionally disturbed, the less chance there is of fear-induced systemic vasoconstriction. Egbert *et al.*[26] found that doctor–patient rapport established by the preoperative visit was more likely to cause the patient to be calm on the operative day than the use of pentobarbital without such a visit. The smaller the volume of blood administered cold, the less chance there is of inducing hypothermic systemic vasoconstriction. Morris and Trachtenberg[27] recently obtained data that indicates that transfusion of warmed blood leads to a reduction in peripheral resistance, whereas transfusion of cold blood increases this parameter. Avoidance of overdistention of the bladder will eliminate systemic vasoconstriction from this cause. Situations are going to develop, however, when the ideal cannot be achieved, and post-transfusion pulmonary edema will continue to be a rare but spectacular and serious complication of the operative period.

Sarnoff *et al.*[9] have noted that the advantage of using an intravenous infusion of trimethaphan to achieve systemic vasodilatation is that it provides a qualitative method of diminishing peripheral resistance in a promptly controllable manner. Single injections of the drug were used in the four patients presented partly because of personal preference and partly because it was felt that once the vasoconstriciton had been eliminated it might not recur; a supposition that proved correct. The short duration of action of trimethaphan is considered a significant advantage because it ensures that if excessive hypotension develops it will be short-lived.[28]

Sarnoff and Berglund[24] compared the hemodynamic effects of trimethaphan, 0.04 to 0.05 mg/kg, intravenously with those of removal of 200 ml blood by venesection in the treatment of pulmonary edema in dogs. The two methods resulted in similar reductions in left atrial and vena caval pressures. However, in contrast to the results of venesection, trimethaphan achieved this with an increase in systemic blood flow and a decrease in the external work performed by the left ventricle. In ten patients with low-output congestive failure, Sobol *et al.*[29] found that trimethaphan lowered vascular pressures in all patients while increasing cardiac output, without increasing cardiac work in eight. In one patient reported by Finlayson *et al.*[25] there was a similar hemodynamic response to reversal of pulmonary edema by hexamethonium. These data, the results achieved in the patients presented, and the ready availability in the operating room of the conditions essential for use of a vasodilator suggest that serious consideration should be given to the use of trimethaphan in the treatment of post-transfusion pulmonary edema in surgical patients.

Summary and Conclusions

The experience gained in the treatment of post-transfusion pulmonary edema in four young surgical patients, free of cardiovascular disease, has been reported.

Systemic vasoconstriction was considered a precipitating factor in all four patients, but predominant in only two. Circulatory overload was considered the predominant precipitating factor in one patient. The possible causes of systemic vasoconstriction included blood loss, bed rest, fear, hypothermia, and distention of the bladder.

Data relating to the mechanism whereby systemic vasoconstriction leads to a shift of blood from the peripheral to the pulmonary circulation have been reviewed. Both systemic venoconstriction and increased arteriolar resistance are considered to be factors, and vasodilatation therapy with trimethaphan is considered to reverse both processes.

Pulmonary edema was rapidly reversed by trimethaphan and reinstitution of I.P.P.B. in two patients, and by trimethaphan and removal of a small volume of blood by venesection in another. In the fourth patient it was not possible to be certain to what extent the trimethaphan had been effective.

It is suggested that attempts to avoid systemic vasoconstriction and circulatory overload be made, but when post-transfusion pulmonary edema does develop, serious consideration should be given to the therapeutic use of trimethaphan.

REFERENCES

1. Masson, A. H. B.: Pulmonary edema during or after surgery, Anesth. Analg. 43: 446, 1964.
2. Adriani, J., Zepernick, R., Harmon, W., and Hiern, B.: Iatrogenic pulmonary edema in surgical patients, Surgery 61: 183, 1967.
3. Gigot, A. F., and Holloway, J. L.: Pulmonary edema occurring during anesthesia: Report of a case, Lahey Clin. Bull. 8: 105, 1953.
4. Harrison, B. L., and Seward, E. H.: Pulmonary edema due to latent phaechromocytoma, Brit. Med. J. 1: 1077, 1954.
5. Balagot, R. C., Reyes, R. M., and Sadove, M. S.: Antifoam agents in pulmonary edema, J.A.M.A. 163: 630, 1957.
6. Clinical Anesthesia Conference. Pulmonary Edema. N. Y. State J. Med. 57: 3693, 1957.
7. Eckenhoff, J. E., and Cooperman, L. H.: The clinical application of phenoxybenzamine in shock and vasoconstrictive states, Surg. Gynec. Obstet. 121: 843, 1965.
8. Clinical Anesthesia Conference. Value of Autopsy. N. Y. State J. Med. 68: 950, 1968.
9. Sarnoff, S. J., Goodale, W. T., and Sarnoff, L. C.: Graded reduction of arterial pressure in man by means of a thiophanium derivative (Ro2-2222), Circulation 6: 63, 1952.
10. Danzig, C. E., and Gomez, A. C.: Long-term intravenous use of arfonad in the treatment of pulmonary edema, Amer. J. Med. Sci. 228: 626, 1954.
11. Ellestad, M. H., and Olson, W. H.: Use of intravenously given ganglion blocking agents for acute pulmonary edema, J.A.M.A. 161: 49, 1956.
12. Bergofsky, E. H., Turino, G. M., and Fishman, A. P.: Cardiorespiratory failure in kyphoscoliosis, Medicine 38: 263, 1959.
13. Luisada, A. A.: Therapy and management of paroxysmal pulmonary edema, Clin. Pharmacol. Ther. 5: 629, 1964.
14. Lurie, A. A.: Anesthesia and the systemic venous circulation, ANESTHESIOLOGY 24: 368, 1963.
15. Larson, A. G.: Deliberate hypotension, ANESTHESIOLOGY 25: 682, 1964.
16. Chien, S.: Role of sympathetic nervous system in hemorrhage, Physiol. Rev. 47: 214, 1967.
17. Webb-Peploe, M. M., and Shepherd, J. T.: Veins and their control, New Eng. J. Med. 278: 317, 1968.
18. Glaser, E. M., Berridge, F. R., and Prior, K. M.: Effects of heat and cold on the distribution of blood within the human body, Clin. Sci. 9: 181, 1950.
19. Lapides, J., and Lovegrove, R. H.: Urinary vesicovascular reflex, J. Urol. 94: 397, 1965.
20. Taylor, H. L., Erickson, L., Henschel, A., and Keys, A.: The effect of bed rest on the blood volume of normal young men, Amer. J. Physiol. 144: 227, 1945.
21. Rushmer, R. F.: Cardiovascular Dynamics, second edition. Philadelphia and London, W. B. Saunders Co., 1961, p. 21.
22. Sarnoff, S. J., and Sarnoff, L. C.: Neurohemodynamics of pulmonary edema. I. Autonomic influence on pulmonary vascular pressures and the acute pulmonary edema state, Dis. Chest 22: 685, 1952.
23. Sarnoff, S. J., Berglund, E., and Sarnoff, L. C.: Neurohemodynamics of pulmonary edema. III. Estimated changes in pulmonary blood volume accompanying systemic vasoconstriction and vasodilatation, J. Appl. Physiol. 5: 367, 1952.
24. Sarnoff, S. J., and Berglund, E.: Neurohemodynamics of pulmonary edema. IV. Effect of systemic vasoconstriction and subsequent vasodilatation on flow and pressures in systemic and pulmonary vascular beds, Amer. J. Physiol. 170: 588, 1952.
25. Finlayson, J. K., Luria, M. N., Stanfield, C. A., and Yu, P. N.: Hemodynamic studies in acute pulmonary edema, Ann. Int. Med. 54: 244, 1961.
26. Egbert, L. D., Battit, G. E., Turndorf, H., and Beecher, H. K.: The value of the preoperative visit by an anesthetist, J.A.M.A. 185: 553, 1963.
27. Morris, R. H., and Trachtenberg, H. A.: Physiologic alterations induced by blood warming during light ether anesthesia, ANESTHESIOLOGY 29: 205, 1968.
28. Aviado, D. M.: The Lung Circulation. New York, Pergamon Press, 1965, p. 905.
29. Sobol, B. J., Kessler, R. H., Rader, B., and Eichna, L. W.: Cardiac, hemodynamic and renal functions in congestive heart failure during induced peripheral vasodilatation: Relationship to Starling's law of the heart in man, J. Clin. Invest. 38: 557, 1959.