Anesthesiology
69:609–614, 1988

Treatment of Non-cardiogenic Pulmonary Edema following Cardiopulmonary Bypass with Veno-venous Extracorporeal Membrane Oxygenation

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Pulmonary edema following cardiopulmonary bypass (CPB) is an infrequent event, occurring in less than 1% of all cases.[1] Pulmonary edema can be differentiated into cardiogenic and noncardiogenic etiologies. The causes of non-cardiogenic pulmonary edema (NCPE) following CPB are diverse and include sepsis, anaphylactic reactions to drugs, reactions to blood products, and complement activation.[2] The treatment for NCPE, regardless of etiology, is similar. The syndrome usually resolves rapidly. Supportive measures including positive pressure ventilation with high inspired oxygen concentrations, and high levels of positive end-expiratory pressure (PEEP) are required to maintain oxygenation and allow recovery of the normal pulmonary vascular integrity.[2,3] We report a case in which conventional treatment was inadequate and veno-venous extracorporeal membrane oxygenation (ECMO) was therapeutic.

CASE REPORT

The patient was a 71-yr-old woman with a history of coronary artery disease (CAD) and New York Heart Association Class IV angina. In addition, she had atherosclerotic peripheral vascular disease, hypertension, and non-insulin-dependent diabetes mellitus. Her angina persisted despite maximal medical management with diltiazem, metoprolol, and nitroglycerin. She was hospitalized for further evaluation of her coronary artery disease. Additional medications at the time of admission included glyburide, dipyridamole, and aspirin. Cardiac catheterization revealed three vessel CAD with normal ventricular function. Following catheterization, the patient developed persistent chest pain that required intravenous nitroglycerin therapy. Upon review of her angiograms and past medical history, the decision was made to proceed with an emergency coronary artery bypass operation. The preoperative laboratory values were normal except for the arterial blood gas analysis. While breathing 2.0 l/min of oxygen *via* nasal cannula, pH_a was 7.43, Pa_{O_2} 62 mmHg, and Pa_{CO_2} 30 mmHg. Her preoperative chest radiograph was normal and on physical examination her lungs were clear to auscultation. No previous arterial blood gas analysis was available for comparison. Her preoperative ASA status was IIIE.

Upon arrival in the operating room, and while breathing 100% O_2 *via* a mask, the standard monitors were placed, including a flow-directed, pulmonary artery catheter with mixed venous oxygen saturation ($S\bar{v}O_2$) monitoring capabilities. Anesthesia was induced with an iv infusion of sufentanil (5 μg/kg), and maintained with additional iv sufentanil (30 μg/kg), pancuronium (1 mg/kg), and diazepam (0.5 mg/kg) while breathing 100% O_2. Induction of anesthesia and pre-bypass hemodynamics were stable (table 1). Methyprednisolone (2 gm) was given iv prior to the initiation of CPB as per the surgeon's protocol. During cardiopulmonary bypass, a left internal mammary artery graft to the left anterior descending coronary artery and two saphenous vein grafts from the aorta to the posterior descending artery and to the second obtuse marginal artery were created. Aortic cross clamp time was 60 min, and cardiopulmonary bypass time was 90 min. Bypass was terminated without difficulty. The patient was receiving dopamine ($7.0\ \mu g \cdot kg^{-1} \cdot min^{-1}$) at this time (table 1). Heparin-induced anticoagulation was reversed with an iv infusion of protamine (300 mg). Following protamine, the patient continued to bleed from multiple sites despite adequate surgical hemostasis. Diffuse bleeding continued after the administration of an additional 200 mg of protamine. At this time, the activated clotting time had returned to its control value; the prothrombin time and partial thromboplastin time were 16.1 s and 59.2 s, respectively; thrombin time was 25.0 s (control 24.0 s), and the fibrinogen level was 91.5 mg/100 ml (normal > 150 mg/100 ml). The patient was given a transfusion of 2 units of fresh frozen plasma (FFP) and 14 units of platelets. Good hemostasis was then present and the chest was closed. Approximately 15 min after blood product infusion, a sharp decline in $S\bar{v}O_2$ from 82% to 50% was noted. The pulmonary artery pressures increased from 24/10 to 60/30 mmHg. The CVP increased from 12 to 24 mmHg, but directly measured left atrial pressure was unchanged at 14 mmHg. pH_a was 7.34, Pa_{O_2} 130 mmHg, and Pa_{CO_2} 35 mmHg. The electrocardiogram was unchanged. To decrease pulmonary artery pressures, intravenous nitroglycerin (190 μg/min) was started. Norepinephrine (8 μg/min) and dopamine ($3.0\ \mu g \cdot kg^{-1} \cdot min^{-1}$) were used to treat systemic hypotension. In addition, copious amounts of straw-colored, frothy secretions were suctioned from the endotracheal tube. The chest was reopened and the grafts were inspected and appeared patent. The heart was not distended. Methyprednisolone (1 gm) and furosemide (50 mg) were given intravenously, and PEEP (7.5 cm H_2O) was added to the respiratory circuit. Pulmonary artery pressures decreased slightly to 50/27 mmHg; the hemodynamic profile stabilized; the chest was closed; and the patient was transported to the intensive care unit (ICU). A chest radiograph obtained prior to transfer showed diffuse, bilateral pulmonary infiltrates. Medications at the time of transfer to the ICU included intravenous nitroglycerin, norepinephrine, dopamine, and lidocaine (2 mg/min) (table 1). Following arrival in the ICU, oxygenation and hemodynamic function continued to deteriorate in spite of the addition of high levels of PEEP, iv infusion of prostaglandin E_1 (PGE_1), and intensive iv vasopressor therapy. Her medications eventually included

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Received from the Departments of Anesthesia and Surgery, Georgetown University Hospital, 3800 Reservoir Road, N.W., Washington, D.C. 20007. Accepted for publication May 12, 1988.

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Key words: Complications: non-cardiogenic pulmonary edema; transfusion reaction. Lung: extracorporeal membrane oxygenation.

TABLE 1. Hemodynamic Measurements and Blood Gas Values

Stage of Surgery	BP (mmHg)	HR	CVP (mmHg)	PAP (mmHg)	LA (mmHg)	CI (L/M^2)	$S\bar{v}O_2$ (%)	PVR ($dyn \cdot s \cdot cm^{-5}$)	SVR ($dyn \cdot s \cdot cm^{-5}$)	$pH/Pa_{O_2}/Pa_{CO_2}$ (units/mmHg/mmHg)	FI_{O_2} (%)	PEEP (cm H_2O)
Pre-bypass	110/50	62	7	23/12	—	2.4	93	—	1235	7.46/384/24.5	100	0
Post-bypass	120/60	105	9	20/10	9	2.7	86	76	1237	7.45/254/27.6	100	0
R_x: DA 7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ 15 min after FFP and platelets	140/60	95	18	60/30	14	—	60	—	—	7.34/130/35	100	0
One hour after transfusion	110/64	101	18	42/17	15	2.0	66	130	853	7.23/94/42.5	100	10
R_x: NE 8 μg/min DA 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ NTG 200 μg/min												
Prior to IABP	103/61	113	17	33/24	16	2.3	53	100	1175	7.32/50.7/34.9	100	15
R_x: NE 35 μg/min DA 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ NTG 200 μg/min EPI 2 μg/min PGE_1 90 $\mu g \cdot kg^{-1} \cdot min^{-1}$												
Following IABP placement	123/36	106	16	35/21	16	2.0	57	143	1229	7.38/46.5/39.2	100	20
R_x: as above												
After ECMO	129/31	98	18	37/23	17	2.6	80	133	1489	7.45/238/30.2	100	20
R_x: NE 10 μg/min DA 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ NTG 60 μg/min EPI 0.5 μg/min												

BP = systemic blood pressure; HR = heart rate; CVP = central venous pressure; PAP = pulmonary artery pressure; LA = left atrial pressure; CI = cardiac index; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; $S\bar{v}O_2$ = mixed venous oxygen saturation; ABG = arterial blood gas; FI_{O_2} = inspired oxygen concentration; PEEP = positive end-expiratory pressure; NE = norepinephrine; EPI = epinephrine; DA = dopamine; NTG = nitroglycerin; PGE_1 = prostaglandin E_1.

norepinephrine, epinephrine, dopamine, prostaglandin E_1, nitroglycerin, and lidocaine (table 1). At this time, 4 h following the onset of these events, the electrocardiogram developed changes that were consistent with global ischemia. Because of the increasing requirements for inotropic support and evidence of ischemia, an intra-aortic balloon (IABP) was inserted. Despite the use of intra-aortic balloon counterpulsation, the patient's clinical condition continued to deteriorate (table 1). Because of her hemodynamic instability, attempts to improve oxygenation by increasing PEEP, tidal volume, or respiratory rate resulted in further compromise of her cardiovascular function. Previous experience at this institution with NCPE following CPB is that the syndrome is frequently lethal. At least one patient within the last year died rapidly following the development of a similar clinical presentation. Therefore, because the function of this patients' cardiovascular and respiratory systems continued to deteriorate as demonstrated by the development of severe hypoxia, myocardial ischemia, low cardiac output, and persistent metabolic acidosis despite maximal medical management, veno-venous extracorporeal membrane oxygenation (ECMO) was initiated.

Cut-downs were performed bilaterally to expose the saphenous veins which were cannulated with 16 French pediatric chest tubes. The ECMO circuit consisted of a 50 ml collapsible venous reservoir, a 5-inch roller pump, and a 2.5 m^2 SCI-MED II® membrane oxygenator with integral heat exchanger. Blood was drained by gravity from the right common iliac vein to the venous reservoir. From the reservoir blood was circulated by the roller pump through the membrane oxygenator and returned to the patient through the venous return catheter advanced *via* the left saphenous vein to the infrarenal level of the inferior vena cava. Blood flows of 450–500 ml/min (15–20% of cardiac output) were achieved. The roller pump was servo controlled by a pressure switch against the venous reservoir, which stopped the pump if venous return was inadequate. In addition, an ultrasonic air detector was located around the vena caval return line. When activated, this sensor was also capable of stopping the ECMO pump. Additional monitoring of the ECMO circuit included measurement of the pressure differential across the blood path of the oxygenator, serial platelet counts, and activated clotting time (ACT) determinations. Measurement of the pressure differential is recommended by the manufacturer during use of the oxygenator for prolonged support as an early screen for thrombus formation on the membrane surface. Platelet transfusions were required to maintain a platelet count between 80,000 and 100,000 cells/mm^3. A heparin infusion was titrated to maintain the ACT between 200 and 250 s.

ECMO was instituted with an initial blood flow of 500 ml/min. Mechanical ventilation was continued without any change (Tidal Volume 600 ml, IMV rate of 10, PEEP of 20 cm H_2O, FI_{O_2} 1.0). Arterial oxygenation improved dramatically to pH_a 7.45, Pa_{O_2} 238 mmHg, and Pa_{CO_2} 30 mmHg (table 2). This was accompanied by an improvement in the hemodynamic profile as well (table 1). During postoperative day 1, the hemodynamic profile stabilized and inotropic and ventilatory support could be reduced slightly. Approximately 12 h after beginning ECMO, the need for continued support was re-evaluated by decreasing the oxygen concentration delivered to the membrane oxygenator from 100% to 50% (table 2). The result was a rapid decline in arterial oxygenation and a concurrent deterioration of the hemodynamic profile. Both changes quickly reversed when the ECMO FI_{O_2} was returned to 1.0. Early on postoperative day 2, the PEEP was decreased to 10 cm H_2O without any deterioration of pulmonary function. It was then possible to rapidly decrease the inotropic support to dopamine (6 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and dobutamine (5 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Shortly thereafter, a second attempt was made to wean from ECMO support. The patient was able to tolerate a decrease in the oxygen concentration delivered to the membrane to 60%. Further weaning was then attempted by slowly decreasing the blood flow through the ECMO circuit. The result was a deterioration of both arterial oxygenation and cardiovascular function presenting as hypoxemia and a rising central venous pressure. Again, the patient was returned to full ECMO support. Late on postoperative day 2, a third attempt was made to wean the

TABLE 2. Effects of Extracorporeal Membrane Oxygenation on Systemic Oxygenation

Event	Ventilator Settings				ECMO Settings		Arterial Blood Gas		
	FI_{O_2} %	V_T (ml)	Rate (Per Min)	PEEP (cm H_2O)	O_2 (%)	Flow (ml/min)	pH (units)	P_{O_2} (mmHg)	P_{CO_2} (mmHg)
Before ECMO	100	600	14	20	—	—	7.38	47	39
After ECMO	100	600	10	20	100	500	7.45	238	30
Postoperative day 1 wean attempt									
Pre	70	600	8	17	100	400	7.41	123	39
Post (10 min)	70	600	8	17	50	400	7.40	78	40
Postoperative day 2 wean attempt									
Pre	70	600	8	10	100	300	7.54	76	32
Post (4 h)	80	600	8	10	—	—	7.44	79	43
12 h off ECMO	50	700	8	10	—	—	7.50	150	39

patient from ECMO support (table 2). The venous oxygenator was gradually clamped out of the system and the respiratory and hemodynamic profile remained stable for 4 h. The venous ECMO cannulae were removed early on postoperative day 3. The patient continued to make steady improvement. The IABP was removed on postoperative day 4. On day 6, the trachea was extubated, and on day 10 the patient was transferred from the ICU. She continues to do well without recurrance of respiratory failure or angina 10 weeks later.

DISCUSSION

The incidence of non-cardiogenic pulmonary edema (NCPE) following cardiopulmonary bypass (CPB) is extremely low. Despite multiple reports of this syndrome in the literature, the exact incidence and mortality of NCPE remains uncertain. In a study of 1000 patients with various predisposing conditions for adult respiratory distress syndrome (ARDS), Fowler *et al.*[1] reported a 1% incidence of ARDS following CPB and an overall mortality attributable to ARDS in all patient groups of 50%. It is unclear what percentage of the CPB patients had a syndrome consistent with NCPE. Hashim *et al.*[4] reviewed their experience with NCPE following CPB at their institution. They do not calculate an incidence, but over a 5-yr period they report nine cases of NCPE with a mortality of 30%. All of their cases were temporally associated with the infusion of fresh frozen plasma. Popovsky[5] has estimated that the incidence of blood product associated NCPE is at least 1 in 5000 transfusions, but it has been suggested that this low incidence might be secondary to underreporting.[6] Other reports indicate a similar low incidence but high mortality of NCPE following CPB.[7,8]

Following CPB, NCPE presents in its most dramatic form as an acute onset of a massive outpouring of proteinaceous edema fluid from the endotracheal tube. This is accompanied by an increase in pulmonary vascular resistance. Hypoxia results from intrapulmonary shunting and accumulation of intraalveolar fluid. Pulmonary compliance is markedly decreased and diffuse bilateral infiltrates are seen on the chest radiograph. All of these symptoms are similar to those seen with cardiogenic pulmonary edema. Distinguishing factors for NCPE are a low left atrial filling pressure and a high protein concentration in the edema fluid.[2]

During open heart surgery, patients are potentially exposed to many adverse events that may trigger NCPE. These include: white blood cell reactions during blood product transfusions, protamine reactions, complement activation by the pump oxygenator, drug reactions, aspiration, endotoxin release, and neurogenic phenomena.[2,3]

NCPE has been associated with the transfusion of packed red blood cells, but is more commonly seen following administration of whole blood or plasma products.[5,9] Although the etiology of this reaction is unclear, antileukocyte antibodies have been isolated from both donors and recipients and are most frequently suggested to be the cause.[5,6,9,10] Antibody binding to the leukocyte may activate the cells to release proteolytic enzymes with subsequent endothelial damage. Alternatively, the antigen-antibody complexes may directly activate complement and initiate a complement mediated injury of the pulmonary capillary endothelium.[11]

Protamine has been associated with many adverse effects, including NCPE.[2,7,12,13] It had been suggested that protamine may produce NCPE by means of an immune mediated hypersensitivity reaction (Type I), by directly activating complement pathways, or by enhancing heparin's ability to activate complement.[2,14]

The pump oxygenator has also been suggested as a cause for NCPE following CPB.[2] Again, this has been attributed to activation of either classic or alternate complement pathways. It has been shown that membrane oxygenators, like bubble oxygenators, can initiate the complement cascade.[15]

In the case presented, protamine or infusion of blood products was the most likely cause of the pulmonary edema. There is no firm evidence to support either cause. Analysis of both donor and recipient serum for the pres-

ence of antileukocyte antibodies or leukoagglutinins would help in determination of the etiology of this case. The treatment, regardless of etiology, is similar.[2,3,6] Suggested therapy includes high inspired oxygen concentration, positive pressure ventilation, high levels of PEEP, the administration of diuretics, and high-dose corticosteroids. Although the efficacy of many of these therapeutic interventions can be debated,[16,6] they were all employed in our treatment of this patient but were insufficient.

Following the first report of adult ECMO by Hill in 1972,[17] the procedure was subsequently attempted with variable success by multiple groups.[18] In 1979, an NIH sponsored randomized, prospective, multicenter study was unable to demonstrate any improvement in survival rates of patients with ARDS who were treated with arteriovenous ECMO in comparison with patients treated conventionally using continuous positive pressure ventilation.[19] After publication of this study, the use of ECMO as a therapeutic option rapidly decreased. Recently, there has been renewed interest in a modified form of ECMO, utilizing a low flow veno-venous bypass circuit and low frequency positive pressure ventilation.[20,21] In normal respiration, both oxygen uptake and carbon dioxide removal are performed by the lungs. With veno-venous ECMO, the uptake of oxygen is dissociated from the removal of carbon dioxide. Oxygen uptake occurs largely by apneic oxygenation in the patient's lung, while carbon dioxide is removed by the extra corporeal membrane lung.[20] Blood flow through the membrane oxygenator of only 20–30% of the cardiac output is necessary for removal of carbon dioxide by the extracorporeal circuit.[20] An added benefit is that the blood returned from the extracorporeal lung is fully oxygenated. Gattinoni *et al.*,[21] in an uncontrolled retrospective study, reported improved survival (50% *versus* 10%) in patients with ARDS treated with ECMO and low-frequency, positive pressure ventilation. The patients discussed in the Gattinoni *et al.* study had long-standing acute respiratory failure with a mean duration of ventilation of 9 days prior to initiation of ECMO. Since improved survival was demonstrated in chronic patients, improved survival is conceivable in the acute setting as well. There have been recent reports in the literature demonstrating the efficacy of ECMO in a variety of acute settings, including removal of an intratracheal foreign body,[22] therapeutic lavage for alveolar proteinosis,[23] fat embolism,[24] viral pneumonia,[25] and pulmonary-renal syndrome.[26]

As a result of the limited experience with ECMO in this clinical setting guidelines for patient management must be extrapolated from other related situations. In this instance, ECMO was instituted as a temporizing measure to allow recovery of pulmonary function following an injury that is known to resolve relatively rapidly. Objective criteria for institution of ECMO in patients with ARDS have been described.[20] These include a Pa_{O_2} less than 50 mmHg for more than 2 h, despite an FI_{O_2} of 1.0 and a PEEP of 5 cm H_2O or more (fast entry), or a Pa_{O_2} less than 50 mmHg for more than 12 h with an FI_{O_2} of 0.6, PEEP of 5 cm H_2O or more, and a right-to-left shunt greater than 30% of the cardiac output despite 48 h of maximal medical therapy (slow entry). In addition, Gattinoni *et al.* required a static lung compliance of less than 30 ml/cm H_2O.[20] It is difficult to extrapolate these criteria to the acute setting of NCPE. Despite maximal therapy, the clinical condition of this patient continued to deteriorate with respect to both oxygenation and hemodynamic function. This was largely as a result of the compromised state of the cardiovascular system immediately following cardiopulmonary bypass, which limited her ability to compensate for the hypoxemia and pulmonary vascular changes. Veno-venous ECMO was instituted as a last resort based on the clinical condition of this patient and previous experience with the syndrome of NCPE at our institution.

Guidelines for maintenance of ECMO are more easily extrapolated from previously published reports. Patients must be heparinized while on ECMO. Maintenance of the activated clotting time (ACT) between 200 s and 300 s is sufficient to prevent significant thrombus formation. In addition, experience at our institution suggests that the silicone type membrane oxygenator is best suited for long-term use, but that it does produce a significant thrombocytopenia that must be monitored and corrected with platelet transfusions during the first 24–48 h. Guidelines for optimizing ECMO support are best drawn from the study of Gattinoni *et al.*[20,21] Their studies of patients with ARDS consistently demonstrate that an ECMO flow of 20–30% of the cardiac output is sufficient to provide the gas exchange support necessary to allow the lungs to recover. The ECMO flow in this case was limited by the access catheter size. We were able to achieve a flow of only 10–15% of the cardiac output. Subsequent work has demonstrated that ECMO flows can be easily maximized with an increase in access cannula size. Once optimal ECMO flow is obtained, guidelines for mechanical ventilatory support were again drawn from the work of Gattinoni *et al.*[20,21] Goals were to decrease the inspired oxygen concentration to minimize the risks of oxygen toxicity and then to decrease the levels of PEEP to minimize effects on hemodynamic function. Our ability to manipulate ventilatory support may have been limited by the low ECMO circuit flow. It was not until the PEEP was significantly decreased that we were able to demonstrate significant improvements in the patient's condition. Despite the common use of PEEP in the treatment of pulmonary edema, this therapy is not without limitations. The use of PEEP has significant effects on the incidence of barotrauma induced by mechanical ventilation.[27] The cardio-

vascular effects of PEEP are well known.[16] In addition, in the setting of NCPE, PEEP may actually exacerbate the capillary leak by increasing the hydrostatic pressure in the pulmonary microvasculature and increasing the surface area of extra-alveolar vessels.[16] In addition, high levels of PEEP may delay the resolution of the pulmonary edema by inhibiting the epithelial solute flux[28] and by decreasing the rate of pulmonary lymphatic drainage.[29] However, PEEP is crucial to the treatment of ARDS where oxygenation is dependent on recruitment of collapsed alveoli and stabilizing alveolar units.[20] It is apparent that, in a patient whose clinical condition is rapidly changing, selection of the level of PEEP which produces the most improvement in pulmonary function with the fewest side effects requires frequent re-evaluation.

Re-evaluation of the continuing need for veno-venous ECMO can be done either of two ways. The amount of ECMO support can be reduced by either decreasing the $F_{I_{O_2}}$ and gas flow to the oxygenator or by decreasing blood flow through the ECMO circuit. Both methods were utilized for this case. Initial re-evaluation after 10 h of ECMO was done by decreasing the $F_{I_{O_2}}$ to the oxygenator and resulted in a rapid clinical deterioration. Final weaning from the ECMO circuit was accomplished late on postoperative day 2 by slowly decreasing the flow through the ECMO circuit to zero. The clinical condition of the patient remained stable over the following 4 h and the bypass was disconnected shortly thereafter.

In summary, we report an additional acute indication for ECMO. This patient had cardiovascular disease that was complicated by pulmonary failure following cardiopulmonary bypass. Because of the compromised cardiac function, and the deteriorating pulmonary function, the patient could not tolerate maximal conventional ventilator therapy without further compromise of her cardiovascular system. We postulate that the addition of ECMO improved oxygenation sufficiently that we were able to decrease the ventilator support and consequently increase cardiac output by minimizing the effects of mechanical ventilation on ventricular function. This improved cardiac output decreased the intra-pulmonary shunting that is a major cause of the hypoxia[30] associated with NCPE, and the result was a dramatic improvement in oxygenation. We present veno-venous ECMO as an addition to the armamentarium of suggested therapy for the treatment of NCPE in the post-bypass patient whose compromised cardiovascular system cannot compensate for the demands of maximal ventilator therapy.

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Anesthesiology
69:614–615, 1988

Cetacaine-induced Acute Methemoglobinemia

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Cetacaine spray (cetacaine: 14% benzocaine, butyl aminobenzoate 2.0%, tetracaine HCL 2.0%, cetyl dimethyl ethyl ammonium bromide 0.005%, benzalkonium chloride 0.5%) is a topical anesthetic used by various types of medical practitioners, including gastroenterologists, bronchoscopists, and anesthesiologists. We present a case of acute cyanosis requiring tracheal intubation and mechanical ventilation secondary to cetacaine-induced methemoglobinemia.

CASE REPORT

A 73-yr-old man with unresectable esophageal carcinoma was seen in our outpatient clinic for esophagoscopy. The patient had an esophagoscopy 4 weeks ago for local radiation implants. Past medical history was significant for renal insufficiency and anemia. Previous esophagoscopies using topical lidocaine were performed without incident.

Topical cetacaine was sprayed for approximately 10 s to the posterior pharynx and esophagus. No other medication was administered. Within 5 min after spraying the area, during which time esophagoscopy was attempted, the patient became cyanotic and hypotensive. While breathing oxygen via a nasal cannula at 4 l/min, pH_a was 7.34, Pa_{CO_2} 28 mmHg, Pa_{O_2} 179 mmHg, HCO_3 15 mEq/l, SaO_2 saturation 100%. Prior to receiving the arterial blood gas results, the trachea was intubated and the patient was admitted to the Intensive Care Unit. He was on Assist/Control ventilation, tidal volume 800 ml/breath, respirations 16 breaths/min, FI_{O_2} 1.0. Arterial blood pressure 120/60 mmHg, heart rate 122 bpm, temperature 37° C. Except for marked cyanosis, the remainder of the physical examination was unremarkable. Arterial blood sample obtained through an indwelling radial artery catheter was dark and "chocolate brown" in color. Chest radiograph was clear. Electrocardiogram revealed a sinus tachycardia. Co-oximetry of the arterial blood (Corning 2500 co-oximeter) revealed a hemoglobin of 7.8 g/dl, SaO_2 51%, methemoglobin level 48.5%. Arterial blood gas analysis of same blood revealed a Pa_{O_2} of 573 mmHg and SaO_2 of 100%.

Methylene blue, 2 mg/kg in a 1% solution was administered over 20 min. Complete resolution of cyanosis occurred within 15 min. Repeat co-oximetry revealed a methemoglobin level of 4.7%, SaO_2 94%. The trachea was extubated, and he was discharged from the Intensive Care Unit on the following day. The remainder of his hospital course was uneventful.

DISCUSSION

Acute methemoglobinemia has been observed following the use of several local anesthetics.[1,2] First reported in 1956, methemoglobinemia occurred following the use of lidocaine for a dental extraction.[3] Other commonly used local anesthetics such as prilocaine[1,2] and benzocaine can also cause methemoglobinemia.[1,2,4–10] Cetacaine aerosol spray contains benzocaine 14.0%. Additionally, methemoglobinemia can be caused by exposure to oxidant drugs such as amines, phenols, nitrates, and aniline dyes.[5,11]

The diagnosis of acute methemoglobin should be suspected in any patient who has received topical anesthesia

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Key words: Anesthetics, local: cetacaine. Blood: methemoglobinemia.