CASE REPORTS

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Probable Carbon Dioxide Embolism during Endoscopically Assisted Varicose Vein Stripping

Mladen I. Vidovich, M.D., Edwin W. Lojeski, D.O.†*

SUBFASCIAL endoscopic perforator vein surgery is a minimally invasive method of ligating perforating veins in the lower leg and correcting lower-extremity varicosities. It has recently gained popularity in the hope of decreasing patient morbidity associated with the traditional surgical approach to perforator ligation.[1] A similar procedure, endoscopic saphenous vein harvesting, is used to obtain vein grafts in cardiac surgery.[2,3] Analogous to laparoscopic procedures, carbon dioxide is insufflated to facilitate visualization. Although carbon dioxide embolism is a rare yet well-recognized complication of laparoscopic procedures, it has not been described with endoscopically assisted lower-extremity procedures. We describe a case of probable carbon dioxide embolism during endoscopically assisted lower-extremity vein stripping.

Case Report

A 67-yr-old man with chronic nonhealing venous stasis ulcers was scheduled for bilateral endoscopically assisted stripping of lower-extremity varicose veins. His medical history included severe peripheral vascular disease for which he had undergone several lower-extremity revascularization procedures without any complications. Physical examination was unremarkable.

Anesthesia was induced with propofol and fentanyl, and muscle relaxation was attained with cisatracurium. American Society of Anesthesiologists standard monitors were used, along with a neuromuscular blockade monitor. Intubation was easily accomplished, and proper positioning of the oral endotracheal tube was confirmed by auscultation and the presence of end-tidal carbon dioxide. Anesthesia was maintained with sevoflurane (0.85–1.4% end-tidal concentration) in 66% N_2O and 33% O_2. Mechanical ventilation was adjusted to maintain end-tidal carbon dioxide between 30 and 36 mmHg. The patient was in the supine position.

The patient's hemodynamics and respiratory parameters remained stable for the first 2 h of the surgical procedure, during which classic vein stripping was performed. For the endoscopic part of the operation, a 5-mm port (Stryker Endoscopy, Santa Clara, CA) was inserted through the superficial fascia of the medial aspect of the right calf. Blunt dissection was used to develop a potential space in the superficial posterior compartment of the calf (Spacemaker, General Surgical Innovations, Palo Alto, CA), which was then insufflated with carbon dioxide at 6 l/min (Electronic Endoflator; Karl Storz, Culver City, CA). Insufflation pressure and total amount of carbon dioxide used during the procedure were not documented. A second port was then placed to allow identification and ligation of venous perforators located between the superficial and deep venous systems. Total insufflation time was approximately 90 min.

Approximately 7 min after beginning the endoscopic dissection, spontaneous ventilatory efforts were noted on the capnogram (curare clefts). At this time, the patient was mechanically ventilated, not paralyzed, and end-tidal carbon dioxide was 32 mmHg. Approximately 15 s later, end-tidal carbon dioxide abruptly decreased to 13 mmHg (fig. 1), and severe bradycardia with frequent ventricular escape beats was noted on electrocardiogram. Oxygen saturation by pulse oximetry remained unchanged at 99%. Noninvasive blood pressure measurements were unobtainable, but weak carotid and femoral pulses were palpated. The surgeons were notified, insufflation was stopped immediately, and the patient was placed in a head-down position. Inspired oxygen concentration was increased to 100%, anesthetics were discontinued, and the patient was manually ventilated. Ephedrine (25 mg intravenously) was administered. Anterior chest auscultation confirmed the presence of bilateral, equal breath sounds. With these maneuvers, the blood pressure increased to 160/80 mmHg within 3 min of the initial decrease in end-tidal carbon dioxide, and end-tidal carbon dioxide returned to 30 mmHg.

Anesthesia was continued with sevoflurane in 66% N_2O and 33% O_2. Carbon dioxide insufflation was reinstituted, and surgery was completed endoscopically without further complications. At the end of the 5-h procedure, the patient awoke easily, and the trachea was extubated. Subsequent hospital course and recovery were unremarkable. The patient suffered no neurologic sequelae.

Discussion

Endoscopic subfascial ligation of perforating veins offers many advantages over traditional surgical approach to venous ligation. It allows more precise localization of perforating veins and the use of smaller incisions placed

* Instructor.

† Assistant Professor.

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Address reprint requests to Dr. Vidovich: Department of Anesthesiology, Northwestern University Medical School, Passavant Pavilion, 303 East Superior Street, Chicago, Illinois 60611. Address electronic mail to: miv909@nwu.edu

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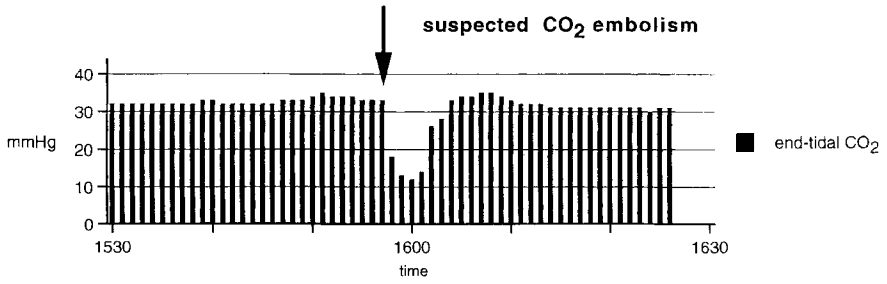

Fig. 1. End-tidal carbon dioxide trend tracing. Arrow indicates onset of suspected carbon dioxide embolism.

in relatively healthy skin, improving wound healing. Immediate postoperative mobilization is possible, and surgical results are comparable to classic vein stripping.[1-3]

Carbon dioxide embolism is a potentially lethal complication of laparoscopic procedures, although its incidence is low (15 of 113,253 gynecologic laparoscopies).[4] Diagnostic criteria for gas emboli vary considerably in the literature, with the only absolute criterion being visualization of gas bubbles in the vasculature. Most cases are diagnosed based on clinical signs.[5-12] The volume of gas and its rate of entry into the blood determines the clinical presentation of a gas embolism. Cardiovascular collapse, hypotension, and dysrhythmias have all been reported to occur with carbon dioxide embolism. The median lethal dose of carbon dioxide embolism in dogs is 25 ml/kg.[13] In pigs, the volume of carbon dioxide required to change end-tidal carbon dioxide is approximately 0.66 ml/kg.[14] Because carbon dioxide is highly soluble in blood, it is rapidly absorbed from the bloodstream, and if embolization does occur, it is less likely to be fatal than if air or oxygen is used for insufflation.[13]

In our case, the initial presentation of presumed carbon dioxide embolism was spontaneous ventilatory efforts in a nonparalyzed mechanically ventilated patient. This most likely occurred because of an increase in arterial carbon dioxide above the apneic threshold as a result of absorption of carbon dioxide into the blood stream. A sudden decrease in end-tidal carbon dioxide and profound hypotension were then noted. Massive carbon dioxide embolism can obstruct pulmonary outflow, dramatically decreasing cardiac output and possibly resulting in right heart failure. The abrupt decrease in end-tidal carbon dioxide was likely a result of decreased cardiac output and increased dead space.

The diagnosis of carbon dioxide embolism under these clinical circumstances is a diagnosis by exclusion. Unless gas is aspirated from the right side of the heart, detected by precordial Doppler or transesophageal echocardiography, the diagnosis of venous carbon dioxide embolism can only be presumptive. Transesophageal echocardiography is the most sensitive method of detection of carbon dioxide embolism, whereas changes in end-tidal carbon dioxide, pulmonary artery pressure, and precordial Doppler are less sensitive.[14]

Two previous reports of carbon dioxide embolism describe an initial increase in end-tidal carbon dioxide followed by an acute decrease.[5,6] In this case, we did not observe this pattern. However, the sudden appearance of spontaneous ventilatory efforts suggests that arterial carbon dioxide was increased before the decrease in end-tidal carbon dioxide. The absence of increased end-tidal carbon dioxide may represent the inability of capnography to reflect accurately arterial carbon dioxide in the face of rapid, massive changes in arterial carbon dioxide.

Other causes of hemodynamic collapse that need to be considered included hemorrhage, tension pneumothorax, pulmonary thromboembolism, and anaphylactic shock. In this patient, the entry of carbon dioxide into the circulation was presumably through the perforating veins into the deep venous system. Rapid recovery of systemic circulation after minimal drug therapy without other manipulations helped to refute the other differential diagnoses. The solubility of carbon dioxide contributed to the rapid reversal of the clinical signs with treatment.

In conclusion, we present a patient with probable carbon dioxide venous embolism who developed profound hypotension and dysrhythmias with carbon dioxide insufflation during endoscopically assisted lower-extremity vein stripping. He was successfully treated with intravenous ephedrine with complete resolution of symptoms and excellent outcome.

Because endoscopically assisted lower-extremity procedures may gain popularity in the future, anesthesiologists should be aware of this possible complication. To identify potential factors that contribute to carbon diox-

ide embolism, carbon dioxide insufflation pressure, carbon dioxide insufflation time, and the amount of carbon dioxide used should be documented.

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Transfusion-related Lung Injury with Leukopenic Reaction Caused by Fresh Frozen Plasma Containing Anti-NB1

Roland Leger, M.D., Sebastian Palm, M.D.,† Hinnerk Wulf, M.D.,‡ Axel Vosberg, M.D.,§ Jürgen Neppert, M.D.‖*

TRANSFUSION-related acute lung injury (TRALI) is the cause of 15% of all fatal complications of blood transfusion.[1] The pathophysiologic mechanism is a specific antigen-antibody reaction involving donor antibodies specific for leukocyte antigens of the recipient in most cases. Neutrophils are activated and aggregation in small pulmonary vessels occurs, initiating the complement and cytokine cascade that leads to capillary leakage.[2-5] Clinically, TRALI is characterized by hypoxia, respiratory failure, and a noncardiogenic pulmonary edema occurring during or shortly after transfusion. Because TRALI is clinically indistinguishable from acute respiratory distress syndrome, we present a case report in which a severe leukopenic reaction after the infusion of fresh frozen plasma (FFP) could be documented.

* Resident in Anesthesia, Clinic for Anesthesiology and Critical Care, Christian-Albrechts-University, Kiel, Germany.

† Staff Anesthesiologist, Clinic for Anesthesiology and Critical Care, Christian-Albrechts-University, Kiel, Germany.

‡ Professor and Senior Lecturer, Clinic for Anesthesiology and Critical Care, Christian-Albrechts-University, Kiel, Germany.

§ Head, Red Cross Blood Transfusion Service, Hamburg and Schleswig Holstein, Germany.

‖ Professor, Institute of Transfusion Medicine, Christian-Albrechts-University, Kiel, Germany.

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Address reprint requests to Dr. Leger: Clinic for Anesthesiology and Critical Care, Christian-Albrechts-University Kiel, Schwanenweg 21, D-24105 Kiel, Germany. Address electronic mail to: wulf@anaesthesie.uni-kiel.de

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Case Report

A 58-yr-old man with carcinoma of the stomach was admitted to our hospital for gastrectomy. The patient had a 20-yr history of heavy smoking with chronic obstructive pulmonary disease, emphysema, and mild hypertension. Long-term medication consisted of β_2-sympathomimetics and nifedipine. Preoperative laboratory values, including white blood cell (WBC) count, were within the normal range.

Table 1. Clinical Parameters before, during, and after Transfusion-related Acute Lung Injury due to Transfusion of the Leukocyte Antibody Containing Fresh Frozen Plasma

Time	Before	Transfusion Period: Beginning TRALI	Transfusion Period: After Intubation	+ 1 h	+ 5 h
FI_{O_2}	—	—	1	1	0.5
O_2 (l/min per mask)	2	6	—	—	—
Sa_{O_2} (%)	97	90	84	92	97
Pa_{O_2} (mmHg)	—	85	60	—	—
HR (bpm)	90	120	100	100	100
BP (mmHg; S/D)	150/90	200/70	80/60	140/60	160/80
MAP (mmHg)	110	112	66	86	107
MPAP (mmHg)	—	—	—	22	22
CVP (mmHg)	10	14	—	14	12
PCWP (mmHg)	—	—	—	16	16
CI ($l \cdot min^{-1} \cdot m^{-2}$)	—	—	—	3.5	3.32
SVR ($dyne \cdot s^{-1} \cdot cm^{-5}$)	—	—	—	929	1,003
PVR ($dyne \cdot s^{-1} \cdot cm^{-5}$)	—	—	—	77	80

FI_{O_2} = inspired oxygen fraction; Sa_{O_2} = oxygen saturation; Pa_{O_2} = arterial oxygen partial pressure; HR = heart rate; BP = blood pressure (S/D = systolic/diastolic); MAP = mean arterial blood pressure; MPAP = mean pulmonary artery pressure; CVP = central venous pressure; PCWP = pulmonary capillary wedge pressure; CI = cardiac index; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; TRAL = transfusion-related acute lung injury.

After premedication with dipotassiumclorazepat (long-acting benzodiazepin) and ranitidine, a balanced anesthesia was administered with isoflurane, nitrous oxide, and oxygen supplemented by sufentanil and pancuronium after induction with etomidate and succinylcholine. Anesthesia and surgery were uneventful. Volume replacement consisted of hydroxyethylstarch (6%; 1.5 l) and albumin (5%; 3 l), transfusion of 2 U packed red blood cells and 4 U FFP, and 2 l Ringer's solution.

The patient was easily extubated postoperatively. Two units packed red blood cells and 4 U FFP were transfused within the first 2 h in the intensive care unit. Thirty hours after admission to the intensive care unit, an additional 2 U FFP was transfused, as drainage losses continued and coagulation parameters showed an International Normalized Ratio value of 1.78 (tables 1 and 2). Immediately after starting the second infusion of FFP, the patient complained of severe dyspnea that was initially treated with inhalation of β_2-sympathomimetics. Shortly afterward, the patient coughed up yellowish frothy fluid. He then described chills but had no rigor. The infusion of FFP was stopped immediately. On clinical examination there were no signs of urticaria and no peripheral edema. Auscultation of the lung showed bilateral rales. Despite supplemental oxygen and furosemide (80 mg), prednisolone (500 mg), and the H_1-receptor-antagonist clemastine (2 mg) intravenously, the patient's condition deteriorated rapidly, requiring endotracheal intubation and mechanical ventilation with a positive end-expiratory pressure of 7 mmHg and a fraction of inspired oxygen of 1.0. To maintain adequate blood pressure, a continuous infusion of dopamine (6 $\mu g \cdot kg$ body $weight^{-1} \cdot min^{-1}$) was started. Measurements with a pulmonary artery catheter, echocardiography, 12-lead electrocardiogram, and serial measurements of creatine phosphate kinase levels were within the normal range. A chest radiograph showed a normal heart size and discrete bilateral infiltrates consistent with pulmonary edema. Fiberoptic bronchoscopy showed no abnormalities. Infection was ruled out by negative blood and sputum cultures. The WBC count within the time of the incident went through a severe neutropenic nadir (800 cells/μl; before, 9,400 cells/μl; 16 h later, 6,700 cells/μl).

Within the next 12 h the patient recovered rapidly, oxygenation improved, and he was extubated 16 h later. A chest radiograph 48 h later was normal. The patient was discharged from the intensive care unit in good clinical condition the 10th day after admission.

Because TRALI was the most likely diagnosis, the last 2 U FFP transfused was investigated for leukocyte antibodies (table 3).[6-8] The recipient's serum was negative for any antibody analyzed by granulocyte immune fluorescence test, granulocyte agglutination test, complement-dependent cytotoxic microassay using lymphocytes, immune phagocytosis (Fcγ receptor) inhibition test using monocytes, and monoclonal antibody-specific immobilization of granulocyte antigens assay using panels of the appropriate cell samples from selected and

Table 2. Laboratory Parameters before, during, and after Transfusion-related Acute Lung Injury due to Transfusion of the Leukocyte Antibody Containing Fresh Frozen Plasma

Time	Before	Transfusion Time	+ 2 h	>+ 5 h
Hemoglobin (g/dl)	11.2	9.8	9.2	10.8
WBC (n/μl)	9,400	800	1,300	6,700
Granulocytes (%)	85	—	—	95
Lymphocytes (%)	6.4	—	—	2.5
Monocytes (%)	6.7	—	—	2.4
Eosinophils (%)	0.8	—	—	0.2
Basophils (%)	0.2	—	—	0
Platelets (n × 10^3/μl)	175	143	—	113
Quick's test (%)	43	46	—	48
INR	1.78	1.69	—	1.64
aPTT (s)	47	43	—	51
Fibrinogen (mg/dl)	505	—	—	—
Clotting factor II (%)	70	—	—	56
Clotting factor V (%)	38	—	—	55

WBC = white blood cell count; aPTT = activated partial thromboplastin time; INR = international normalized ratio.

Table 3. Serological Results Investigating Recipient and Donor's Blood after Transfusion-related Acute Lung Injury

Serum	GIFT	GAT	LCT*	IPI*	MAIGA†
Leukocyte antibody tests					
Patient	—	—	—	—	—
Donor	+++‡	+++‡	—	—	Not tested
Serological typing of leukocyte antigens					
Patient: NA2,§ NA2§					
Donor: NA1,§ NA2§, Fcγ receptor III,					
5b positive; NB1 negative‖					

GIFT = granulocyte immune fluorescence test; GAT = granulocyte agglutination test; LCT = complement dependent cytotoxic microassay using lymphocytes; IPI = immune phagocytosis (Fc γ receptor) inhibition test using monocytes; MAIGA = monoclonal antibody-specific immobilization of granulocyte antigens assay.

* Antibodies to HLA A, B, C (LCT and IPI), and DR (IPI).

† MAIGA using monoclonal antibodies to NB1 (MEM 166, 7D8); controls were NB1 specific sera (B.w. and XVI, M.v.V.z.).

‡ The donor's serum reacted in GIFT and GAT strongly with cells from all of 25 unselected healthy individuals.

§ Confirmed by genotyping with PCR-SSP.

‖ Confirmed by NB1-specific sera, monoclonal antibodies separately and combined by MAIGA with M.v.V.z.

neutrophil-typed individuals. The second unit of FFP, given to the patient immediately before the lung reaction, contained a neutrophil-specific antibody that reacted strongly in the granulocyte immune fluorescence and granulocyte agglutination tests. The granulocyte immune fluorescence test showed that the antibody only bound to subpopulations of approximately 40–80% of the neutrophils in each sample of the panel, typical for expression of the neutrophil antigen NB1. The serum from the donor (a 33-yr-old female with no history of pregnancy and transfusions) of the second FFP unit showed negative granulocyte agglutination test reactions with cells of a Fcγ receptor III–deficient and 5b- and NB1-negative donor. Taking this and all serologic tests into account, we conclude that the antibody of the donor is specific for the neutrophil antigen NB1.

Discussion

The patient presented with symptoms of respiratory failure caused by pulmonary edema. Even though the suspicion of a TRALI was discussed at the bedside, invasive and noninvasive methods were applied to rule out cardiogenic and various other causes (aspiration, pulmonary infection, septic shock, *etc.*) of this incident. Mechanical ventilation and low catecholamine support allowed the patient to recover within 24 h.

Occurrence of a pulmonary edema without hypervolemia associated with blood transfusion is defined as TRALI.[3] The incidence of TRALI varies from 0.16–0.24% per transfusion of blood products.[3,9] Although pulmonary reactions are rare, they are the second most common cause (5%) of transfusion-related deaths.[1] All patients with TRALI require oxygen supplementation, and 72% require mechanical ventilation, which reflects the severity of these complications.[10] Perioperative mortality rates between 0% and 5% have been reported.[3,11] The onset of the reaction varies from direct initiation to 8 h.[2,9]

For TRALI, as one cause of noncardiogenic pulmonary edema, our focus was on the 2 U FFP given in close relation to the reaction. Although TRALI associated with transfusion of red blood cells is not uncommon, cases with FFP have hardly been reported.[12] In a series of 36 patients, the implicated blood products were whole blood (n = 21), red blood cells (n = 10), and FFP (n = 5).[10]

Immunodiagnosis must include testing the donor's and the recipient's blood. In contrast to the erythrocyte antibody–mediated transfusion reactions, TRALI can be caused by antibodies specific for neutrophil antigens in the donor's plasma.[3,10] In 89% of cases, these antibodies are specific for neutrophil antigens. Antibodies to HLA A, B, C, and DR are seldomly found. However, a number of factors are likely to be relevant, including the specificity, titer, immunoglobulin subclasses, complement or cell-activating ability of the antibody, and the neutrophil priming activity of lipids in stored blood.[2,4,13] In the present case, we detected an NB1-specific alloantibody in one of the FFP units. NB1 has a phenotype frequency of 97% and was first described in a case of alloimmune neutropenia of a newborn caused by the corresponding antibody.[14] To our knowledge, there are only two published cases in which this antibody was involved.[4,14]

During the initial phase of the presented case, the laboratory findings showed severe leukopenia, which was confirmed by manual count. A hemogram demonstrated a normal distribution pattern, and WBC count normalized 16 h later. Thus, this neutropenic reaction was most probably a result of massive sequestration of neutrophils in the pulmonary capillary system after antigenic contact. Neutropenic reactions caused by bone

marrow damage, infection, drugs, and other immunologic diseases could be ruled out because of the short time course of the reaction. With regard to the available literature, only a single case of TRALI-associated leukopenia has been documented thus far.[14] Bux *et al.*[15] reported a course of TRALI with a discrete decrease of WBCs (6,500 to 2,600 cells/μl) that recovered within 72 h.

Although a neutropenic reaction connected with TRALI, as in the present case, has been reported rarely thus far, close monitoring of WBC count might be of help in the evaluation of the clinical symptoms.

Fresh frozen plasma, as any other blood product, can cause severe transfusion-related reactions. To reduce the amount of such transfusion-associated incidents, the indications for the use of FFP should be restricted, and international guidelines should be followed.[16] Blood donors whose donations have given rise to transfusion-associated reactions should be eliminated from the donor pool.

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