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APPENDIX 1

Pain analog scale		
No pain	———	Worst pain
Sedation analog scales		
Almost asleep	———	Wide awake
Tired	———	Energetic
Clumsy	———	Well-coordinated
Fuzzy	———	Clear-headed
Drowsy	———	Alert

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Pulmonary Hypertension and Noncardiogenic Pulmonary Edema Following Cardiopulmonary Bypass Associated with an Antigranulocyte Antibody

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The syndrome of fulminating noncardiogenic pulmonary edema (NCPE) following cardiopulmonary bypass (CPB) has been described many times. The proposed causes are an anaphylactic or idiosyncratic reaction to protamine or some undefined reaction to blood products. Yet a specific mechanism was not established in the previously reported cases.[1,2] The following is a case report of a patient in whom severe NCPE likewise developed with marked pulmonary hypertension following CPB. Follow-up investigations revealed the presence of an antigranulocyte antibody in the serum of one of the donors that specifically reacted with the recipient's granulocytes.

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REPORT OF A CASE

A 50-year-old man with persistent exertional angina was scheduled for elective coronary artery bypass grafting. Medical history was significant for a 40 pack-year smoking history, but the patient denied any wheezing, chronic sputum production, or prior treatment for pulmonary disease. Aside from localized edema following a prior penicillin injection, he had no other known allergies to medications. He had previously received protamine 5 mg iv during cardiac catheterization without sequela. There was no history of prior blood transfusions or adverse reactions to general anesthetics.

Preoperative physical examination revealed clear lung fields and an S4 gallop. Chest roentgenogram showed slight cardiomegaly, but lung fields were clear and without evidence of pulmonary vascular engorgement.

On the morning of surgery, the patient began to complain of angina shortly after arriving in the operating room area; these symptoms quickly resolved with the administration of nitroglycerin (sublingual, followed by 75 μg/min, iv) and propranolol, 2 mg, iv. Uneventful induction of general anesthesia with fentanyl, 50 μg/kg, iv and metocurine, 26 mg, iv, ensued. Baseline and subsequent hemodynamics, arterial blood gasses, ventilator settings, and concomitant medications

are listed in table 1. (The baseline Pa_{O_2} of 218 mmHg with an $F_{I_{O_2}}$ of 1.0 presumably reflects some preexisting small airways disease complicating the increased ventilation–perfusion mismatching seen with general anesthesia, muscle relaxation, and mechanical ventilation without PEEP; there was no evidence of aspiration during induction, and breath sounds were clear bilaterally.) Following chest opening, new T-wave invasion was noted in lead V5, prompting an increase in nitroglycerin, 150 μg/min iv, with intermittent use of neosynephrine (up to 20 μg/min) to keep the systolic blood pressure above 100 mmHg. Hemodynamics remained stable with a cardiac output (CO) of 4.5–5.1 $l \cdot min^{-1}$ and a pulmonary capillary wedge pressure (PCW) of 10–15 mmHg (all pressures measured by Statham® transducers calibrated with mercury).

Cardiopulmonary bypass proceeded without difficulty. Aortic cross-clamp time was 63 min and total bypass time 106 min. Routine separation from bypass ensued with stable hemodynamics (entry #2, table 1). Continuing T-wave inversion in lead V5 prompted resumption of nitroglycerin infusion, 125 μg/min iv. Protamine, 200 mg, was slowly administered via a central line over 12 min without any immediate adverse effects.

Approximately 25 min later (#3, table 1), the calculated pulmonary vascular resistance (PVR) increased along with the appearance of a 5 mmHg gradient between the pulmonary artery diastolic pressure (PAD) and the PCW. A unit of whole blood, subsequently found to contain leukoagglutinins, had been infused over 10 min beginning 20 min before these observations. Over the next 30 min, the PVR gradually increased to fivefold over baseline, and the PAD-PCW gradient increased to 14 mmHg (#4, table 1 and fig. 1). The possibility of artifact in the PCW giving a factitiously low reading was considered, but observation of the heart revealed an adequately contracting left ventricle without overdistension. Analysis of arterial blood gasses at this time showed no evidence of hypoxia or hypercarbia, although a small metabolic acidosis was present (base deficit of −8.0 mEq/l). Both lungs ventilated easily, and breath sounds were clear. There was no discoloration of the urine, unexplained bleeding diathesis, wheezing, hives, significant decrease in systemic vascular resistance, or elevation in temperature (rectal temperature was 36° C upon discontinuation of CPB).

Cardiac output and urine production decreased further with chest closure. Increased intravascular volume supplementation (Ringer's lactate 700 ml and Hespan® 500 ml) resulted in minimal hemodynamic improvement. Low-dose dopamine infusion (3 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was begun with a subsequent increase in cardiac output, decrease in pulmonary vascular resistance, and improvement in urine output (#5, table 1).

Approximately 1 h after the specified transfusion, rales were auscultated through the esophageal stethoscope. This was followed shortly by the appearance of copious amounts of frothy fluid in the endotracheal tube. Forty milligrams of furosemide and 250 mg of hydrocortisone were administered iv. With stable hemodynamics, the patient was quickly transferred to the surgical intensive care unit. Subsequent analysis of arterial blood gasses now revealed marked deterioration in oxygenation (#6, table 1) with an $F_{I_{O_2}}$ of 1.0 and 10 mmHg of positive end-expiratory pressure (PEEP). Chest x-ray revealed diffuse alveolar infiltrates without pulmonary vascular engorgement (fig. 2). Subsequent therapy included maintenance of PEEP and high inspired oxygen concentration, inotropic and vasodilator support with dopamine and nitroprusside (later changed to dobutamine), and continued induced diuresis along with restriction of iv fluid administration to the minimum tolerated for adequate cardiac output and urine production. The elevated PVR and PAD-PCW gradient gradually returned to normal levels over the next 12 h (#7 and #8, table 1) along with concomitant improvements in oxygenation and clinical and radiologic evidence of resolving pulmonary edema. The trachea was extubated successfully in the early morning of the second postoperative day. The patient was discharged 5 days later, and the remainder of his recovery period was uneventful.

Immunologic Methods

The patient's pretransfusion serum sample was screened for abnormal antibodies and serum IgA levels. No lymphocytotoxic or antigranulocyte antibodies were detected. The latter were tested for using both leukoagglutination[5] and radiolabeled antiglobulin techniques.[6] Serum IgA levels were normal.

Samples taken at the time of reaction (within approximately 1 h of the involved transfusion) showed no red blood cell incompatibility. Levels of the third and fourth components of complement in these serum samples were within normal limits when assayed by a nephelometric assay (total intact C3 was 150 mg/dl, with the normal range being 101–198 mg/dl; total intact C4 was 40 mg/dl, with the normal range being 16–39 mg/dl). Total hemolytic complement was not measured (insufficient blood sample).

Serologic studies of all involved blood donors revealed an antigranulocyte antibody in the donor of the unit of whole blood mentioned earlier. When tested against the recipient's neutrophils, serum from this multiparous female donor showed a leukoagglutinin titer of 1:16 (normally undetectable). Quantitative radiolabeled testing revealed that the donor's plasma bound 260 fg. of IgG per neutrophil (normal less than 121 ± 29 [mean ± SD]). A granulocytotoxicity assay was negative, indicating that the antibody was not complement fixing *in vitro*.[7] When screened against the neutrophils of normal donors, this serum gave a positive immunofluorescence reaction with two out of five samples and a positive agglutination reaction in five out of 10 samples (Dr. P. Lalezari, Albert Einstein College of Medicine, New York).

No lymphocytoxic antibodies were detected in any of the sera tested.

Discussion

More than 20 cases of transfusion-related NCPE associated with leukocyte antibodies have been described. Recent reports suggest that the offending antibody is more often in the sera of the donors (especially multiparous female donors)[8,9] than in the recipient, but the latter has also been reported. Although whole blood or plasma products usually are involved, two cases have been reported that followed transfusion of packed red blood cells.[8] Respiratory distress along with clinical and/or radiologic evidence of NCPE usually occurs within 30 min to 2 h following transfusion, but delays up to 4 h have been reported.[8] Accompanying fever, tachycardia, hypotension, urticaria, and hives have been variably described. If the patient does not succumb early on, the pulmonary lesion usually resolves over the next 24–48 h.

TABLE 1. Hemodynamic Measurements and Blood Gases

	BP	HR	CO	CVP	PAP	PCWP	PVR	ABGs	$F_{I_{O_2}}$	PEEP
1. Baseline Rx: Nitroglycerin 85 μg/min	95/52	66	5.0	8	25/15	13	112	218/35/7.35	1.0	0
2. Off CPB	95/55	92	6.0	6	21/11	10	93	207/35/7.35	1.0	0
3. Twenty minutes after transfusion Rx: Nitroglycerin 125 μg/min	88/55	80	4.3	7	32/16	11	225		1.0	0
4. One hour after transfusion Rx: Nitroglycerin 125 μg/min	90/58	84	2.8	9	37/24	10	537	379/34/7.32	1.0	0
5. Dopamine infusion Rx: Dopamine 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ Nitroglycerin 125 μg/min	90/55	90	3.8	9	36/20	10	356		1.0	0
6. Three hours after transfusion Rx: Nitroglycerin 200 μg/min Dopamine 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ Nitroprusside 50 μg/min	94/60	118	3.5	8	23/15	10	251	69/34/7.49	1.0	10
7. Nine hours after transfusion Rx: Nitroglycerin 85 μg/min Dobutamine 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$	88/50	120	6.1	13	30/18	16	144	78/30/7.46	0.6	7.5
8. Nineteen hours after transfusion Rx: Nitroglycerin 85 μg/min Dobutamine 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$	110/70	98	7.9	13	25/15	15	81	88/31/7.49	0.5	7.5

BP = systemic blood pressure (mmHg); HR = heart rate (beats/min); CO = cardiac output (l/min) CVP = central venous pressure (mmHg); PAP = pulmonary artery pressure (mmHg); PCWP = pulmonary capillary wedge pressure (mmHg); PVR = pulmonary vascular resistance ($dyn \cdot s \cdot cm^{-5}$; normal 67 ± 23); ABG = arterial blood gases; $F_{I_{O_2}}$ = inspired oxygen concentration; PEEP = positive end-expiratory pressure (cmH_2O).

The course of NCPE in our patient was clearly similar to this pattern. Recognition of such similarities has led other authors to look for evidence of transfusion reactions as an etiologic factor in the syndrome of NCPE following CPB. Olinger *et al.*[1] stated that no evidence of blood reactions could be identified in the sera of one of their recipients. No mention was made, however, regarding testing of *donor* sera for possible leukoagglutinins. Specific testing for donor leukoagglutinins was described in a case by Culliford *et al.*[2] in which respiratory and circulatory difficulties began 15 min after beginning a fresh-frozen plasma infusion. Examination of this plasma "failed to reveal any unusual or potent antibodies." The immunologic methods used were not discussed. Also no mention is made of other blood products administered over the preceding 1–4 h and of testing all donor sera if such had been administered.

Whether other concomitant factors may have played an additive, synergistic, or even predominant role in this case warrants consideration. Complement activation is known to occur during routine CPB,[11] and heparin and protamine *in vitro* form complexes that can activate complement.[12] In experimental animals, activated complement (specifically C5a) may interact with circulating granulocytes and cause measurable leukoagglutination, pulmonary sequestration of leukocytes, pulmonary hypertension with elevated PVR, increased pulmonary ventilation-perfusion mismatching, increased pulmonary lymph flow, and pulmonary interstitial edema.[3,4,13–15] Whether this mechanism alone is capable of producing severe pulmonary dysfunction in the clinical setting is uncertain.

Perhaps some degree of complement activation, and resultant sequela, occur to a variable degree following all operative procedures that use CPB and/or protamine administration. However, the occurrence of NCPE following such procedures is extremely uncommon. Thus, such complement activation is either usually insufficient in magnitude or duration or insufficient in the absence of other etiologic factors to result in fulminating pulmonary edema. Complement activation by other factors may be an important variable, however, in the clinical expression of a leukoagglutination reaction and thus may contribute to the severity of pulmonary edema.[10] In our patient, this possibility cannot be proven. Although total C3 and C4 levels were within normal limits, low levels of complement activation may not be detected by the assays used. In future cases, a systematic study of these potential interactions of systemic complement activation with the presence of an antigranulocyte antibody needs to be undertaken.

Significant pulmonary artery hypertension or elevated PVR during the initial stages of leukoagglutinin reactions in patients has not been described previously. Hemodynamic monitoring in this case documented a fivefold increase in PVR prior to the onset of clinical pulmonary edema or marked deterioration in oxygenation. Since these reactions may involve leukostasis with pulmonary leukocyte sequestration, these hemodynamic changes would not be unexpected. Prior work in experimental animals has demonstrated large increases in PVR occurring very early following complement-induced granulocyte aggregation and subsequent pulmonary sequestration of granulocytes.[3,4] The possibility exists that prior complement activation by CPB and/or protamine also may have played a role in the pulmonary hypertension we ob-

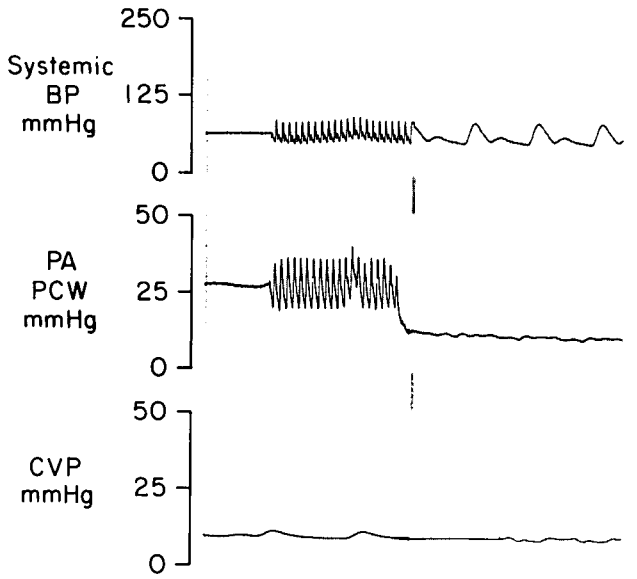

FIG. 1. Hemodynamic tracings during period of maximal elevation in pulmonary vascular resistance. The PAD-PCW gradient has increased to 14 mmHg. BP = systemic blood pressure; PA = pulmonary artery pressure; PCW = pulmonary capillary wedge pressure; CVP = central venous pressure.

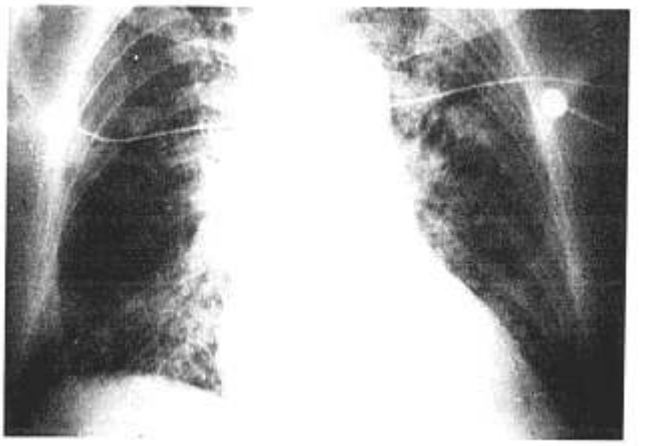

FIG. 2. Chest radiograph upon arrival in the intensive care unit showing diffuse alveolar infiltrates (approximately 2 h following transfusion).

served. Morel *et al.*[16] demonstrated a "transient (less than 3 min) transpulmonary gradient of white blood cells" across the pulmonary vascular bed following bolus administration of protamine (100 mg over 15 s) into the right atrium, suggesting that protamine may induce transient pulmonary sequestration of leukocytes. Jastrzebski *et al.*[29] demonstrated a 10 mmHg increase in mean pulmonary pressure 15 min following protamine administration (6 mg/kg over 5 min). Both of these studies, however, involved administration of protamine at much more rapid rates and/or larger doses than used in this patient (2.5 mg/kg over 12 min). The 15 subjects described by Jastrzebski *et al.* included eight with mitral valve disease and two with congenital heart anomalies. Possible underlying pulmonary vascular disease in such patients may predispose to protamine-induced elevations in PVR.[18] With slower rates of administration in patients without preexisting pulmonary vascular disease, it is unusual to see protamine-induced elevations in the PVR and PAD-PCW gradient of the magnitude and duration observed in this patient. The type of sudden, catastrophic pulmonary artery hypertension following protamine infusion described by Lowenstein *et al.*[18] appears distinctly different than the gradually developing hypertension reported herein.

Systemic vasodilation appears as an inconsistent but sometimes prominent feature in other reported cases of NCPE following CPB.[1,2] Whether this relates to different etiologic factors remains speculative, as vasodilation has also been a variable finding in documented cases of leukoagglutinin reactions.

Although protamine has multiple effects that in theory could be related to the development of NCPE, a causative relationship has never been established definitively. Cases of true anaphylactic reactions to protamine have been reported, yet these have differed considerably from NCPE following CPB in terms of speed of onset, time course of resolution, and severity of induced pulmonary compromise.[19–21]

In summary, we report a case of NCPE following CPB associated with the finding of an antigranulocyte antibody in the plasma of one of the involved blood donors that specifically interacted with the recipient's granulocytes. With aggressive supportive therapy, the pulmonary changes resolved over 36 h without apparent residual. Hemodynamic monitoring revealed a marked increase in calculated PVR (up to fivefold over baseline), which preceded any deterioration in oxygenation. This early increase in PVR may be similar to that observed in experimental animals during complement-induced pulmonary sequestration of leukocytes. Since systemic complement activation may be an important variable in the clinical response to transfusion of an antigranulocyte antibody,[10] prior complement activation by CPB and/or protamine may have contributed to the fulminant picture of NCPE described. Whether such antibodies may have been detectable in other reported cases of NCPE following CPB if the sera of all blood donors had been thoroughly investigated remains uncertain, as the described syndrome may be multifactorial in origin. Until further understanding of such possible etiologies is obtained, however, we suggest that, in subsequent cases of NCPE following CPB, thorough testing of all involved blood donors should be performed. If leukoagglutinins are detected, the dangerous donor should be deferred permanently as a blood donor in the future.

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Single *versus* Divided Doses of Atracurium: Does 0.05 + 0.10 Equal 0.15?

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Other authors have reported that pretreatment with a small subparalyzing dose of atracurium may expedite the onset of neuromuscular block resulting from a second, larger dose of atracurium.[1,2] This strategy also may diminish the total muscle relaxant dose required to achieve conditions suitable for endotracheal intubation.[2,3] In apparent contrast to these studies,[2,3] 0.25 mg/kg of atracurium given by single bolus injection produces more intense neuromuscular blockade than does the same dose given incrementally.[4] All these studies,[1–4] however, employed total muscle relaxant doses in excess of the ED_{95} for atracurium[5] and therefore were not ideally suited to detect subtle alterations in drug effect. However, a total dose of atracurium that corresponds to the steep portion of its dose–response curve will render perceptible the drug effects obscured by large ("off-scale") doses. This study was designed specifically to determine, using the ED_{75} of atracurium, if the combined effect of pretreatment with a small (subclinical) dose of atracurium followed by a second (therapeutic) dose produces a degree of neuromuscular blockade that differs from that resulting from a single bolus injection.

MATERIALS AND METHODS

The study protocol was approved by the institution's Human Investigation Committee, and written informed consent was obtained from all patients. The subjects were 20 adult patients, ASA physical status 1 or 2. No premedication was given. After placement of a blood pressure cuff and electrocardiographic electrodes, anesthesia was induced with thiopental 4–6 mg/kg iv and maintained with fentanyl 3–5 μg/kg iv and N_2O, 67% in O_2.

Neuromuscular blockade was monitored with a force-displacement transducer (Grass FT-10®), which measured adductor pollicus twitch tension in response to supramaximal ulnar nerve stimulation at 0.15 Hz, delivered for a duration of 0.15 ms via 25-gauge needles placed subcutaneously. A strip chart continuously recorded the force transducer measurements from 10 min before to 50 min after atracurium administration.

Patients were allocated randomly by blinded lottery to receive either a single dose of atracurium, 0.15 mg/kg, or divided doses of atracurium, 0.05 mg/kg, followed 5 min later by 0.10 mg/kg. The time to initial twitch depression, the magnitude of neuromuscular block, and time to maximal neuromuscular block were measured, as were times to 25, 50, and 95% recovery of initial twitch height. Student's t test was used to test statistical significance between groups, with $P < 0.05$ considered significant.

RESULTS

Maximal neuromuscular block (twitch height depression) and the times to initial and maximal twitch depression are shown in table 1. The small pretreatment dose of atracurium provoked no discernible change in twitch height over 5 min. Atracurium 0.10 mg/kg after the pretreatment dose resulted in a more rapid onset of initial twitch height depression than did the same total dose delivered as a single injection. However, maximal neuromuscular block and the time required to achieve maximal neuromuscular block were unaltered by pretreatment. The profiles of twitch height recovery following atracurium 0.15 mg/kg in single and divided doses, shown in table 1, were similar for both treatment protocols. Thus, pretreatment with a subparalyzing dose of atracurium de-

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