■ CASE REPORTS

Successful Use of a 20% Lipid Emulsion to Resuscitate a Patient after a Presumed Bupivacaine-related Cardiac Arrest

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THE infusion of a lipid emulsion has been shown to increase the survival rates of both rats and dogs that have been resuscitated after an overdose of bupivacaine.[1–3] We report the first successful use of a 20% lipid infusion to resuscitate a patient from a prolonged cardiac arrest that immediately followed the placement of an interscalene block with bupivacaine and mepivacaine.

Case Report

The patient was a 58-yr-old, 82-kg, 170-cm male who presented for arthroscopic repair of a torn rotator cuff in the right shoulder. His medical history was significant for coronary artery bypass graft surgery at age 43 yr. He gave a history of angina upon exertion and occasionally at rest. He declined further preoperative cardiac workup but was considered by his cardiologist to be stable on medical therapy. This included nitroglycerine as needed, lisinopril, atenolol isosorbide mononitrate, and clopidogrel and enteric-coated aspirin, both of which had been discontinued 1 week previously. His preoperative electrocardiogram revealed a right bundle-branch block, a left anterior hemiblock, and evidence of an old anterior wall myocardial infarction.

The patient arrived at the operating room holding area, where standard monitors were applied. Blood pressure was 120/80 mmHg, room air oxygen saturation measured by pulse oximetry was 98%, and heart rate was 60 beats/min. Supplemental oxygen was delivered at 3 l/min *via* a nasal cannula. A 20-gauge intravenous catheter was placed in the dorsum of his left hand, through which 2 mg midazolam and 50 µg fentanyl were administered. A 50-mm, 22-gauge Stimuplex® insulated needle was connected to a Stimuplex®-DIG nerve stimulator (both B. Braun, Inc., Bethlehem, PA), and the interscalene groove was identified at the level of C6. The brachial plexus was identified by eliciting biceps stimulation (0.1-ms duration, 2 Hz) at 0.34 mA, following which 40 ml local anesthetic solution (20 ml bupivacaine, 0.5%, and 20 ml mepivacaine, 1.5%) were injected slowly (over approximately 2.5 min) in 5-ml increments with gentle aspiration between doses. The patient was awake and conversant during the performance of the block. At no time was any blood aspirated, nor did he report pain or paresthesias.

Approximately 30 s after removal of the block needle, the patient became incoherent and then developed a tonic–clonic seizure. Oxy-

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gen was delivered by a facemask attached to a self-inflating resuscitation bag while 50 mg propofol was injected intravenously. The seizure stopped, and spontaneous respirations resumed. Approximately 90 s later, the patient began to seize again; this time, 100 mg intravenous propofol was administered. The electrocardiogram showed asystole, and no pulse, by carotid or femoral palpation, or blood pressure was detectable. Advanced cardiac life support was immediately started. The trachea was intubated, and end-tidal carbon dioxide was detected with an EasyCap®II (Nellcor Inc., Hayward, CA). Tube position was confirmed by auscultation, after which chest compressions were immediately resumed. During the first 20 min of advanced cardiac life support, a total of 3 mg epinephrine, given in divided doses, 2 mg atropine, 300 mg amiodarone, and 40 U arginine vasopressin were administered. In addition, monophasic defibrillation was used at escalating energy levels—200, 300, 360, and 360 J, according to the advanced cardiac life support protocol. Cardiac rhythms included ventricular tachycardia with a pulse, pulseless ventricular tachycardia that momentarily became ventricular fibrillation, and eventually asystole. The arrhythmias observed during most of the resuscitation period were pulseless ventricular tachycardia and asystole.

After 20 min, at which time plans were being made to institute cardiopulmonary bypass, the administration of a lipid emulsion was suggested, and 100 ml of 20% Intralipid (for Baxter Pharmaceuticals by Fresenius Kabi, Uppsala, Sweden) was given through the peripheral intravenous catheter. Cardiac compressions continued, and a defibrillation shock at 360 J was given. Within seconds, a single sinus beat appeared on the electrocardiogram, and 1 mg atropine and 1 mg epinephrine were administered. Within 15 s, while external chest compressions were continued, the cardiac rhythm returned to sinus at a rate of 90 beats/min. The blood pressure and pulse became detectable. An infusion of lipid emulsion was started and continued at 0.5 ml · kg^{-1} · min^{-1} over the following 2 h and then discontinued. The patient remained in sinus rhythm. He was weaned from mechanical ventilation, and his trachea was extubated, approximately 2.5 h later. He was awake and responsive, and had right upper extremity weakness consistent with a brachial plexus block. No neurologic sequelae were sustained, and he was subsequently transferred to a monitored setting for overnight observation. There was no evidence of complications secondary to the administration of intralipid (*i.e.*, pancreatitis) during the following 2 weeks.

Because the patient had a cardiac arrest after which he had increased levels of cardiac enzymes, he agreed to undergo cardiac catheterization. This revealed total occlusion of the right coronary artery and a left ventricular ejection fraction of 32%. As a consequence, an automatic implantable cardiac defibrillator was inserted without any complications, and the patient was discharged home.

Discussion

Bupivacaine was first synthesized in 1963 and since that time has had many applications, including infiltration anesthesia, regional nerve blocks, and neuraxial anesthesia. In addition to its local anesthetic effects, it is a potent depressant of electrical conduction, which predisposes the heart to reentry types of arrhythmias.[4] Weinberg *et al.*[1] made the observation that intravenous

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lipid infusions not only increase the dose of bupivacaine required to produce asystole in rats but also improve survival in rats resuscitated after receiving intravenous bolus doses of bupivacaine. They then applied this observation to dogs, as a model of a species closer in size to humans, and found that lipid infusions during resuscitation from bupivacaine-induced cardiac arrests improved survival. Specifically, 12 dogs were given 10 mg/kg bupivacaine. All of the dogs developed circulatory collapse, and internal cardiac massage was delivered. Six of these dogs received 20% lipid infusion and 6 received saline as a 4-ml/kg bolus given over 2 min, followed by a continuous infusion of $0.5 \; ml \cdot kg^{-1} \cdot min^{-1}$. All of the dogs treated with the intralipid solution were successfully resuscitated, whereas none of the saline-treated animals survived.[2] Weinberg et al. offered two possible hypotheses for their findings. Either the lipid emulsion creates a lipid phase that extracts the lipid-soluble bupivacaine molecules from the aqueous plasma phase (and therefore out of the tissue), or alternatively, the lipid infusion diffuses directly into tissue and interacts with bupivacaine at that level.[2] Although the potential utility of lipid emulsions for cardiac resuscitation after a bupivacaine-induced cardiac arrest in humans has been discussed in the literature, its actual use has not been previously described.

When conventional algorithms for cardiopulmonary resuscitation were unsuccessful, a member of the code team suggested the use of a lipid emulsion, and arranged for the pharmacy to immediately dispatch a dose, through the pneumatic tube system at our institution. While it would have been preferable to infuse the lipid via a central venous catheter, the initial absence of such access necessitated the use of the peripheral intravenous line. Although recommendations for specific doses of intralipid have been suggested, we chose to administer 100 ml of a 20% lipid emulsion. While this is in excess of the suggested initial bolus of 1 ml/kg,[5] we wanted to ensure that an adequate volume of lipid would reach the central circulation during cardiac compressions. Immediately after this administration, 1 mg each of atropine and epinephrine were administered, and sinus rhythm returned, where similar efforts had been unsuccessful before infusion of the lipid emulsion. Our maintenance infusion of $0.5 \; ml \cdot kg^{-1} \cdot min^{-1}$ was consistent with those used in the canine experiments but likely excessive. The specific recommendations of Weinberg et al. entail the use of a bolus infusion of 20% lipid emulsion, 1 ml/kg over 1 min while continuing chest compressions. This dose could be repeated every 3–5 min to a maximum of 3 ml/kg. At the point of conversion to sinus rhythm, Weinberg[6] recommends that an infusion of 20%

intralipid, at a rate of $0.25 \; ml \cdot kg^{-1} \cdot min^{-1}$, should be continued until hemodynamic recovery. Fortunately, there was no deleterious effect from this dose of intralipid. Since this event, a 100-ml bag of 20% lipid emulsion has been made immediately available in all areas in which peripheral nerve blocks are performed at our institution.

Levsky and Miller[7] recently reported cardiovascular collapse from a bupivacaine dose of less than 1.1 mg/kg administered during a lumbar sympathetic ganglion radiofrequency ablation in a patient who previously sustained non–Q-wave myocardial infarction and whose preoperative electrocardiogram showed first-degree atrioventricular block. Although our patient had significant cardiac risk factors, he had been evaluated preoperatively by his cardiologist, who deemed him to be medically optimized to undergo this surgical procedure. His preoperative electrocardiogram revealed both a right bundle-branch block and a left anterior hemiblock. A significant preoperative conduction deficit may predispose to the development of local anesthetic induced cardiac toxicity at lower mg/kg basis than expected, and although no recommendations currently exist, in this group of patients, the use of levo-isomeric local anesthetics may offer some advantage. We have added ropivacaine to our hospital formulary specifically for the use in patients with significant cardiac histories who are undergoing peripheral plexus blockade.

We report the first use of a lipid emulsion as part of the successful resuscitation efforts in a patient who most likely sustained a local anesthetic–induced cardiac arrest. We concur with Picard,[8] who considers a lipid emulsion, like dantrolene, a "crucial antidote" (which is both inexpensive and has a long shelf life) that should be routinely kept in areas in which peripheral nerve blocks are being performed.

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A Case of Severe Diffuse Venous Thromboembolism Associated with Aprotinin and Hypothermic Circulatory Arrest in a Cardiac Surgical Patient with Factor V Leiden

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COMPLEX cardiac operations and reoperative cardiac surgery have a documented risk of excessive perioperative bleeding and increased transfusion requirements. To minimize hemorrhagic complications associated with complex surgical procedures, the literature supports the use of prophylactic antifibrinolytic therapy.[1,2]

Massive intravascular thrombosis in cardiac surgery is a rare but catastrophic occurrence. We previously reported two cases of massive thrombosis in the left ventricle and arterial circulation[3] in two patients undergoing thoracic aortic surgery requiring hypothermic circulatory arrest. Both of these patients had received ε-aminocaproic acid therapy. Blood from one of these patients was retained for postmortem testing, revealing a heterozygous factor V Leiden genotype. We now report a separate case of massive thrombosis involving the venous system and right heart in a patient with unsuspected factor V Leiden mutation.

Case Report

A 61-yr-old man presented for aortic valve replacement for severe calcific aortic stenosis with mild aortic insufficiency. He had undergone myocardial revascularization 10 yr previously and had bilateral patent internal mammary artery grafts. The surgical plan was aortic valve replacement through a limited sternotomy using cardiopulmonary bypass. Immediately preoperatively, his vital signs were normal; his coagulation, hematology, and biochemical profiles were all normal; and he was taking the following medications: ramipril, aspirin, atenolol, hydrochlorothiazide, and amlodipine. He had a history of minor allergic reactions to penicillin and sulfa drugs. Anesthesia and neuromuscular blockade were achieved using 100% oxygen, etomidate, midazolam, sufentanil, and vecuronium and maintained using inhalational isoflurane and infusions of midazolam, sufentanil, and vecuronium. Clindamycin, 600 mg, was administered for antibiotic prophylaxis. Monitoring included standard anesthesia monitors, a radial intraarterial line, a pulmonary artery catheter, and a transesophageal echocardiography probe. The transesophageal echocardiography examination confirmed the severe nature of the aortic stenosis with a peak instantaneous transvalvular gradient of 102 mmHg and a calcu-

lated aortic valve area of 0.47 cm². The examination results were also notable for diffuse atherosclerosis of the ascending aorta, transverse arch, and descending thoracic aorta. Before skin incision, a test dose of 10,000 kallikrein inhibiting units aprotinin was well tolerated; a 2,000,000-kallikrein inhibiting unit loading dose was infused, followed by an infusion of 500,000 kallikrein inhibiting units per hour. Aprotinin, 2,000,000 kallikrein inhibiting units, was also added to the cardiopulmonary bypass priming solution (full-dose Hammersmith regimen).[4]

Kaolin-activated clotting time was maintained at greater than 500 s with bovine lung heparin, and heparin concentration was maintained at greater than 2.7 U/ml. The initial dose of heparin was calculated using an *in vitro* heparin dose–response curve generated using the patient's own blood. Kaolin-activated clotting time testing was performed at least every 30 min thereafter.

Because of the high risk of disrupting the bilateral internal mammary arterial grafts with sternotomy, femoral arterial and venous cannulation was performed, and cardiopulmonary bypass was instituted before limited median sternotomy. The limited median sternotomy and the initial mediastinal dissection were conducted without difficulty during a 37-min period of normothermic cardiopulmonary bypass. The patient was weaned from cardiopulmonary bypass for several minutes for relocation of the arterial cannula to a region of the ascending aorta with minimal atherosclerosis under epiaortic ultrasonic guidance. Cardiopulmonary bypass was reinstituted, the aortic cross clamp was placed with epiaortic ultrasonic guidance, cardioplegia was administered, and aortic valve replacement was performed using a Hewlett-Packard St. Jude (St. Paul, MN) prosthesis. At the completion of the valve replacement, the aortic cross clamp was removed, the endothelial surface of the aorta was inspected, and the aortotomy was closed during a 13-min interval of deep hypothermic circulatory arrest (esophageal temperature 19.2°C.) After aortic valve prosthesis insertion, rewarming and resuscitation of the heart were remarkable for ventricular arrhythmias controlled with amiodarone and ventricular pacing.

The patient was weaned from cardiopulmonary bypass using moderate doses of epinephrine and norepinephrine by continuous infusion. A vasopressin infusion was added. Moderate pulmonary hypertension was treated with inhaled nitric oxide, 40 parts per million. The venous cannula was removed from the right femoral vein, and a slow protamine infusion was begun. Hypotension and worsening pulmonary hypertension required discontinuation of the protamine infusion after administration of 120 mg—approximately 50% of the calculated dose. Large reticular thrombi that nearly filled the inferior vena cava and extended into the right atrium, right ventricle, and pulmonary arteries were noted on transesophageal echocardiography. The patient was reheparinized, aprotinin was discontinued, and cardiopulmonary bypass was reinstituted.

The thrombosis extended inferiorly into the left femoral vein and was evacuated upon replacement of the femoral venous cannula. Using moderately hypothermic perfusion, the right atrium and pulmonary artery were opened, and massive quantities of friable thromboembolic material were removed. After rewarming, the patient did not wean from cardiopulmonary bypass due to severe biventricular failure. He could not be adequately oxygenated despite a fractional inspired oxygen concentration of 1.0, high levels of positive end-expiratory pressure, and inhaled nitric oxide therapy, presumably because of distal

pulmonary embolization of the friable thromboembolic material. Extracorporeal membrane oxygenation was instituted, but severe hemorrhage from the aortic cannulation site was present. The ascending aorta was replaced using a Hemashield (Medi-Tech, Natick, MA) graft during a second period of hypothermic circulatory arrest.

Massive bleeding ensued intraoperatively. The patient developed a consumptive coagulopathy that was diagnosed by persistent increase of the Kaolin-activated clotting time to greater than 1,000 s, despite heparin concentrations less than 2.0 U/ml in the face of continued heparin administration. The patient received further extracorporeal membrane oxygenation support and massive transfusion of packed cells, platelets, fresh frozen plasma, and cryoprecipitate. He died in the operating room.

The family underwent counseling and testing for hypercoagulable states. The patient's two sons both tested positive as heterozygotes for the Leiden mutation of factor V (FV:R506Q), and their biologic mother (the patient's wife) tested negative for this mutation. We conclude that the patient was a carrier of the factor V Leiden mutation.

Discussion

Reoperative cardiac surgery is associated with a more complex and prolonged surgical intervention that results in a higher incidence of pathologic bleeding and perioperative requirement for allogeneic transfusions. The inflammatory, coagulation, and fibrinolytic cascades are activated to a greater degree than in primary cardiac surgery due to incision through the thromboplastin-rich mediastinal scar, extensive tissue dissection, and prolonged cardiopulmonary bypass duration. To minimize hemorrhagic complications associated with complex surgical procedures, data support the use of prophylactic antifibrinolytic therapy.[5-8] The risks of hypercoagulability or overt thrombosis in association with antifibrinolytic therapy are theoretical, at best. The mechanisms of activity of these agents are not "procoagulant," but are "antifibrinolytic," in a population of patients who are hypocoagulable and have active fibrinolysis. However, a small subset of patients experience thrombosis after cardiopulmonary bypass despite standard care. We previously reported two cases of complete aortic thrombosis after aortic repair and deep hypothermic circulatory arrest in which ε-aminocaproic acid was used.[3] Perimortem blood samples were drawn, and one patient was found to have a factor V Leiden gene mutation (FV:R506Q). It seems reasonable to propose that patients with known predispositions to thrombotic disease should not receive prophylactic antifibrinolytic therapy, even in association with cardiopulmonary bypass. However, in patients with a heterozygous mutation or a subclinical presentation of such an illness, preoperative recognition would be impossible to detect by clinical history and examination.

In operations requiring deep hypothermic circulatory arrest, antifibrinolytic therapy is frequently used, although its efficacy in this population has not yet been demonstrated. There are early reports of renal failure and thrombosis when using antifibrinolytic therapy in

deep hypothermic circulatory arrest, but many of these reports are retrospective, anecdotal, or both.[9-14] Aortic surgery is itself associated with a risk of renal dysfunction, and this is not increased by the concomitant use of aprotinin.[15] The retrospective nature of these studies cannot identify those patients with thrombosis who had presumed inadequate heparin levels during cardiopulmonary bypass because the threshold diatomaceous earth (Celite) kaolin-activated clotting time was maintained at only 480 s. Nor can retrospective reporting identify which patients may have received two different antifibrinolytic agents in combination.[9] The risks of thrombosis in deep hypothermic circulatory arrest have prompted some investigators to avoid the use of aprotinin. Others recommend using the drug *after* deep hypothermia and circulatory arrest have been completed.[16] Most other clinicians continue to use the drug without a change in practice.[17]

High concentrations of aprotinin inhibit many serine proteases, including kallikrein and protein C.[18] Factor V Leiden mutations, which occur in 3–5% of the population, yield a resistance to activated protein C, which results in impaired signaling for anticoagulation and fibrinolysis. Using a clot-based assay, *in vitro* analyses evaluating the response to activated protein C in cardiac surgical patients indicate that aprotinin does induce a factor V Leiden–like defect in normal plasma. *In vitro* analyses from factor V Leiden patients suggest that aprotinin further exacerbates this defect in the plasma.[19] Corroborating clinical data demonstrate that factor V Leiden patients have lesser amounts of mediastinal tube drainage and allogeneic transfusions.[20,21] A case report describes a patient with factor V Leiden who experienced thrombosis of coronary artery revascularization grafts within a month of surgery.[22]

In the current case, the patient experienced a thrombotic event before the overt consumptive coagulopathy to which he succumbed was diagnosed. The inherited factor V Leiden mutation and abnormality of the protein C anticoagulant pathway predisposed this patient to hypercoagulability, which became evident when the protective effects of heparin were reversed with protamine. After the consumptive coagulopathy ensued, the patient would certainly have been at high risk for further thrombotic and bleeding complications. The thrombus in the inferior vena cava at the same anatomical site occupied by the venous cannula (from the femoral vein to the right atrium) is rare and suggests that endothelial integrity disruption provided a nidus for thrombus formation. Therefore, the possible etiologies for this thrombotic event include endothelial injury, disseminated intravascular coagulation after hypothermic cardiopulmonary bypass and deep hypothermic circulatory arrest, factor V Leiden mutation, and the use of an antifibrinolytic agent. Elimination of just one of these risk factors might have avoided this outcome.

Factor V Leiden mutation has been associated with an increased risk for *venous* thrombosis, although large-scale observational studies have not demonstrated the presence of factor V Leiden as an independent risk factor for the development of *arterial* atherosclerotic cardiovascular disease.[23–25] In population-based studies, the elderly seem to have no increased risk of arterial thrombosis due to factor V Leiden, whereas women and, specifically, obstetric patients do have significant thrombotic risks.[26] Although no direct link between factor V Leiden and atherosclerosis has been shown, resistance to activated protein C has been identified as a laboratory marker that is linked to an increased risk of advanced atherosclerosis.[27,28]

Screening for subclinical procoagulant states such as factor V Leiden abnormality may be considered in patients undergoing deep hypothermic circulatory arrest in which the use of antifibrinolytic therapy is planned. The benefits of reduced blood loss due to pharmacologic therapy need to be carefully weighed against the cost of testing in any population.[29] Because no causative agents or clinical conditions have been definitively identified, the potential risk of intravascular thrombosis is not currently known.

At our institution, we have had four fatal thrombotic events in cardiothoracic surgical patients in a 3-yr span. The common factors include antifibrinolytic therapy (aprotinin or ε-aminocaproic acid), a period of hypothermic circulatory arrest, and documented predisposition to hypercoagulable state (factor V Leiden mutation in two cases and antiphospholipid antibody in one). Based on this experience, we have begun screening elective surgical procedures requiring hypothermic circulatory arrest for factor V Leiden mutation at a cost of $175 per patient. We plan to withhold antifibrinolytic therapy in any patient testing positive for factor V Leiden mutation despite the absence of scientific evidence of a causal relation between antifibrinolytic therapy and adverse outcomes, in patients with this genetic trait.

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