

## CASE REPORTS

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## Administration of Protamine Rather Than Heparin in a Patient Undergoing Normothermic Cardiopulmonary Bypass

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INADEQUATE anticoagulation may occur during cardiopulmonary bypass (CPB) if heparin is inadvertently omitted or otherwise does not reach the vascular system. Because most protocols for CPB include addition of heparin to the priming solution, highly unusual circumstances are required for a patient to undergo CPB completely without heparin.

This report describes a case in which a patient underwent CPB completely without heparin because protamine was erroneously administered instead of heparin.

### Case Report

An 81-yr-old, 61-kg woman with coronary artery disease was scheduled for elective coronary artery bypass grafting. Coronary arteriography showed three-vessel coronary disease, a normal left main coronary artery, and an ejection fraction greater than 50%. Medications included dipyridamole, diltiazem, nitroglycerin, and ranitidine. Pre-catheterization laboratory values were as follows: hemoglobin 12.9 g · dl<sup>-1</sup>, creatinine 1.4 mg · dl<sup>-1</sup>, blood urea nitrogen 32 mg · dl<sup>-2</sup>, prothrombin time 11.8 s, and partial thromboplastin time 25 s. No neurologic abnormalities were noted on routine preoperative history-taking and physical examination. The patient was alert and appropriate during a preoperative visit by the anesthesiologist.

Anesthesia was induced with fentanyl, thiopental, and pancuronium and maintained with isoflurane in oxygen. The extracorporeal circuit included a Harvey 1700 bubble oxygenator with a 40-μm Bard H645 heparinized filter in the arterial tubing. The priming solution consisted of 1,000 ml 5% dextrose in lactated Ringer's solution and 2 U designated donor red blood cells (added because of a postinduction hemoglobin value of 8.4 g · dl<sup>-1</sup>). One thousand units of heparin was added to each unit of red blood cells and 2,500 U to the liter of 5%

dextrose in lactated Ringer's solution to a total of 5,500 U heparin in 1,400 ml blood-crystalloid prime. The calculated dose of heparin to be administered intravenously before bypass was an additional 19,000 U (300 U · kg<sup>-1</sup>). This was drawn into a 20-ml syringe labeled "heparin" and before aortic cannulation was injected into the peripheral intravenous tubing through the stopcock closest to the patient. To ensure that the contents reached the vascular system, the site and tubing were directly inspected to confirm that the catheter had not infiltrated, that the catheter and tubing had not separated, and that intravenous fluid ran freely through the tubing before and after injection. No hematologic tests are routinely performed at any time during surgery at this institution, and none was performed in this case.

The patient participated in a study requiring active warming during CPB to maintain a nasopharyngeal temperature of 37°C. At the start of CPB, full flow (50 ml · kg<sup>-1</sup> · min<sup>-1</sup>) was established immediately, the aortic cross clamp applied, and cardioplegia solution injected into the aortic root. The surgeon constructed three distal saphenous vein anastomoses while the heart was asystolic. After 25 min of normothermic CPB, the surgeon observed fresh clot in the pericardial sac. The anesthesiologist gave 6,000 U heparin. The perfusionist then noted clot in the cardiomy reservoir of the CPB circuit; the question of whether heparin had been administered was raised. Inspection of the wastebasket revealed four empty vials of protamine and none of heparin. An additional 14,000 U heparin was then administered so that a full planned dose (300 U · kg<sup>-1</sup>) of heparin had been given after the discovery of clot and approximately 30 min after the administration of protamine. The first of several blood samples was then taken for laboratory analysis of coagulation (table 1). The cardiomy reservoir was changed. No further clot was seen in the field or in the new cardiomy reservoir.

Proximal anastomoses were constructed after removal of the aortic cross clamp using a side-biting clamp. Several minutes after removal of the aortic cross clamp the heart spontaneously resumed normal sinus rhythm. The patient was separated from CPB without the need for inotropic drugs. When the venous tubing was clamped, blood from the oxygenator was rapidly transfused until the minimal safe reservoir level had been reached. Venous and aortic cannulas were removed and blood remaining in the CPB circuit discarded. Inspection of the empty circuit revealed a 15-cm clot in the arterial reservoir beneath the defoaming chamber, fibrin strands in the coronary suction tubing, and a small clot in the arterial filter. No clot was seen in the arterial or venous tubing or in the second cardiomy reservoir.

Protamine 300 mg was given after decannulation, and clot promptly appeared in the surgical field. Hemostasis was easily achieved, and the sternum was closed uneventfully. Aortic cross-clamp and CPB times were 36 and 54 min, respectively. The patient received no inotropic or vasoconstrictor drugs at any time during surgery. Estimated intraoperative blood loss was 1,600 ml, including blood discarded in the CPB circuit.

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Table 1. Laboratory Values from This Patient and from Other Studies of Patients Anticoagulated with Heparin

Report	Patients (n)	Before CPB	Early CPB	Late CPB	End of Operation	ICU
Plt ct (1,000/ml)						
This patient		—	84	87	88	160
Bick <sup>1</sup>	30	200	—	153	140	—
Gravelee <sup>2</sup>	10	263	—	—	147	—
Holloway <sup>3</sup>	9	200	—	125	100	—
Milam <sup>4</sup>	75	194	119	—	—	144
Fibrinogen (mg · dl <sup>-1</sup> )						
This patient		—	110	145	110	230
Bick <sup>1</sup>	30	234	—	151	—	169
Gravelee <sup>2</sup>	10	308	—	—	166	—
Milam <sup>4</sup>	75	282	176	—	—	237
FDP (μg · ml <sup>-1</sup> except dilutions and ratios; see text)						
This patient		—	1:40	1:40	—	1:80
Bick <sup>1</sup>	30	4/30	—	30/30	—	11/30
Blauhut <sup>5</sup>	13	0.3	—	1.0	—	1.6
Dietrich <sup>6</sup>	20	2	6	11	10	—
Gravelee <sup>2</sup>	10	—	—	—	13	—
Paramo <sup>7</sup>	100	0.9	—	1.6	1.5	—
Sundaram <sup>8</sup>	5	0.08	1.2	0.4	—	0.4
D-dimer (μg · ml <sup>-1</sup> except dilutions; see text)						
This patient		—	1:16	1:16	1:16	—
Dietrich <sup>6</sup>	20	0.8	1.1	1.2	1.0	—
Paramo <sup>7</sup>	100	0.8	—	—	4.1	3.9
PT (s)						
This patient		11.8	17.2	16.4	15.8	13.4
Bick <sup>1</sup>	30	11.9	—	—	—	14.6
Gravelee <sup>2</sup>	10	11.9	—	—	15.2	—
Milam <sup>4</sup>	75	12	—	—	—	14
PTT (s)						
This patient		25	52	>150	37	31
Bick <sup>1</sup>	30	43	—	—	—	48
Gravelee <sup>2</sup>	10	25	—	—	33	—
Milam <sup>4</sup>	75	35	—	—	—	33

Please see text for explanations of sample times, abbreviations, and units.

CPB = cardiopulmonary bypass; PT = prothrombin time; PTT = partial thromboplastin time; Plt ct = platelet count; FDP = fibrin degradation products; SFM = soluble fibrin monomer; neg = negative; pos = positive; NA = not available.

In anticipation of coagulopathy the patient was given 2 additional U red blood cells, 2 U fresh frozen plasma, and 10 U platelets during the 1st h in the intensive care unit (ICU). She subsequently became mildly hypertensive, to 190/80 mmHg, and was treated with nifedipine and nitroglycerin ointment. Mediastinal tube drainage was 350 ml during the first 4 h in the ICU; 200 ml in the second 4 h; and none in the following 12 h. Her total 24-h ICU blood loss, 750 ml, was less than the average of 900 ml at this institution.

The patient made an otherwise uneventful recovery. The trachea was extubated without difficulty 8 h after arrival in the ICU. The next morning she was appropriately oriented and alert. No other neurologic testing was performed. Urine output was adequate without diuretic agents. Blood urea nitrogen and creatine values on postoperative day 4 were 30 and 1.4 mg · dl<sup>-1</sup>, respectively. The postoperative electrocardiogram was unchanged from the electrocardiogram before the operation. The patient was discharged from the ICU after 2 days and from the hospital after 10 days.

## Discussion

CPB protocols commonly require addition of heparin to the priming solution, reducing the chance of catastrophic clot formation during CPB if intravenous heparin is inadvertently omitted or does not reach the central circulation. Our patient received no intravenous heparin; furthermore, the heparin in the priming solution was neutralized by protamine. The probable dose of protamine administered (190 mg, presuming a comparable 19-ml volume of protamine [10 mg · ml<sup>-1</sup>] instead of heparin [100 U · ml<sup>-1</sup>]) is more than sufficient to neutralize the 5,500 U heparin in the priming solution.

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Results of our limited coagulation tests and comparable values from patients undergoing CPB with clinically adequate heparin<sup>1-8</sup> are listed in table 1. No pre-CPB laboratory studies were performed in this patient except for prothrombin time and partial thromboplastin time, performed the night before operation. The "early CPB" sample in this patient was drawn after 30 min of CPB without anticoagulation and 5 min after administration of heparin. The "late CPB" sample was drawn 20 min later, just before termination of CPB. The "end-operation" sample was drawn after administration of post-CPB protamine and before transport to the ICU. The "ICU" sample was drawn in the ICU after transfusion with 2 U red blood cells, 2 U fresh frozen plasma, and 10 U platelets.

For other investigators, sampling times have varied. "Pre-CPB" values were drawn either the evening before operation, before the induction of anesthesia, or before administration of heparin during operation. Early CPB values were uniformly taken within 30 min after the start of CPB. Late CPB samples were taken at the conclusion of CPB, the duration of which ranged from 1 to 3 h or was not stated. End-operation values were uniformly drawn after administration of protamine and before transport from the operating room. ICU values were drawn within 1 h after arrival in the ICU.

Fibrin degradation products and D-dimer are reported as dilutions by the laboratory at this institution. A fibrin degradation product dilution of 1:40 represents a value of approximately  $40 \mu\text{g} \cdot \text{ml}^{-1}$ , with a range of 20–80  $\mu\text{g} \cdot \text{ml}^{-1}$ . A D-dimer value of 1:16 represents 8  $\mu\text{g} \cdot \text{ml}^{-1}$  with a range of 4–32  $\mu\text{g} \cdot \text{ml}^{-1}$ . Fibrin degradation products are reported by Bick *et al.*<sup>1</sup> as the ratio of patients with positive results to total patients.

The laboratory results from this patient differ from reported values of patients whose blood is anticoagulated with heparin only in that measurements of fibrin formation, fibrinolysis, and platelet consumption were increased. If laboratory tests of fibrin formation and fibrinolysis are proposed as determinants of adequate anticoagulation during CPB, then results from this case suggest that the difference between "safe" and "dangerous" values appears slight. Had these tests been used in this patient, the results could easily have been interpreted as "within normal limits." The small difference between coagulation studies in this patient and those in previous reports was associated with potentially dangerous clot in this patient and with clinically adequate anticoagulation in other patients.

This patient did not suffer a consumptive coagulopathy. Prolonged extracorporeal circulation with mem-

brane oxygenators has been performed in dogs without heparin and without clinically apparent clot or post-CPB bleeding.<sup>9,10</sup> High flows were maintained in these studies. The appearance of clot only in areas of low flow of this patient's circuit (*e.g.*, cardiectomy reservoir, arterial reservoir, and surgical field) suggests that prevention of stasis within most sections of the extracorporeal circuit and within the patient's vascular system avoided serious consumption of coagulation factors.

The perfusion protocol at this institution relies on vigilance rather than laboratory testing to determine that administered heparin reaches the patient's vascular system. In this case, the anesthesiologist demonstrated vigilance during administration by determining patency of the intravenous tubing as described above, but not when the syringe was filled. Although many institutions use hematologic testing (most commonly an activated coagulation time [ACT] or heparin assay) to detect mistakes in heparin administration, it is not clear if such tests would have prevented this problem.

Failure of the ACT to increase after the presumed administration of heparin suggests failure of heparin to reach the vascular system. However, this patient received protamine, which is also capable of altering coagulation tests. There have been no studies of the effect of protamine administered during anesthesia on the ACT in humans. Ellison *et al.*<sup>11</sup> administered 200  $\text{mg} \cdot 70 \text{ kg}^{-1}$  protamine to awake volunteers and noted a clinically inconsequential increase (from 6.7 to 7.1 min.) in the Lee-White whole-blood clotting time. ACT was not measured. Kresowick *et al.*<sup>12</sup> administered 3  $\text{mg} \cdot \text{kg}^{-1}$  protamine to anesthetized dogs and reported an increase in ACT from 94 to 134 s, a 40% increase. It is noteworthy that a larger dose of protamine, 6  $\text{mg} \cdot \text{kg}^{-1}$ , increased the ACT to 313 s, similar to the ACT of 343 s after 150  $\text{U} \cdot \text{kg}^{-1}$  of heparin.

Based on these few results, an ACT performed in this case after unintentional protamine administration may not have been sufficiently different from a baseline ACT to allay suspicions that heparin had not been given. On the other hand, a heparin assay properly performed in this case after protamine administration would have detected the failure of heparin to reach the vascular system and thus would have prevented the problem. It seems prudent, then, to perform a heparin assay rather than measure ACT if laboratory confirmation that administered heparin has reached the vascular system is desired. Use of hematologic testing does not render vigilance unnecessary, however; results consistent with successful administration of heparin are still possible in a patient receiving no heparin if blood samples are

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drawn from a heparinized catheter or into a heparinized syringe.

This incident altered our practice. Protamine is no longer stored in our operating room drug drawer. Unopened bottles are received in a sealed plastic pouch from the pharmacist and the pouch not opened until protamine is requested by the surgeon. Because neither this practice nor laboratory testing renders a repeat of this incident impossible, we continue to emphasize a high level of vigilance at all points of heparin administration.

In summary, the administration of protamine instead of heparin before CPB resulted in this patient's undergoing normothermic CPB for 25 min with the heparin in the priming solution neutralized by protamine and with no heparin received from the anesthesiologist. Laboratory values reflecting fibrin formation drawn immediately after this discovery were not greatly different from those expected from patients whose blood is successfully anticoagulated with heparin; nonetheless, clot formed in sequestered and turbulent portions of the CPB circuit and surgical field, including sites that could be sources of systemic emboli. It is emphasized that vigilance includes reading of the label on the heparin bottle.

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## Autonomic Imbalance of the Heart during Total Spinal Anesthesia Evaluated by Spectral Analysis of Heart Rate Variability

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TOTAL spinal anesthesia after the presumed injection of local anesthetics into the subarachnoid space during

epidural anesthesia is not rare.<sup>1-4</sup> The incidence of unrecognized dural puncture with subsequent total spinal anesthesia is 0.01-0.2%.<sup>5,6</sup> Total spinal anesthesia anesthetizes cranial nerves as well as peripheral nerves,

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