

## Case Reports

# Seizures Following Cardiopulmonary Bypass

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**Abstract:** Seizures following cardiopulmonary bypass are an immediate and alarming indication that a neurologic event has occurred. A case report of a 67-year-old man undergoing aortic valve surgery who unexpectedly experiences seizures following cardiopulmonary bypass is outlined. Possible contributing fac-

tors including atheromatous disease in the aorta, low cerebral perfusion pressures, an open-chamber procedure, and the use of tranexamic acid are identified. **Keywords:** seizures, cardiopulmonary bypass, tranexamic acid. *J Extra Corpor Technol. 2016; 48:137–140*

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A 67-year-old man with a previous history of coronary artery bypass surgery presented with aortic stenosis for aortic valve replacement. He had a history of rheumatic fever, hypertension, and cigarette abuse. He was known to have a single kidney; however, his creatinine level remained in the normal range. He had no prior history of neurologic dysfunction or seizures.

The patient was prepared for surgery with the insertion of a 16-gauge peripheral venous line, a 20-gauge right radial arterial line and a 4-lumen central venous catheter. Standard intraoperative monitoring included a two-channel electrocardiogram, direct arterial and central venous pressure monitoring, end-tidal capnography, cerebral entropy, nasopharyngeal temperature measurements, and transesophageal echocardiography (TEE). Anesthetic induction agents included fentanyl 500 mcg, midazolam 2.5 mg, thiopentone 75 mg, and pancuronium 8 mg. A propofol infusion at 100 mg/h was commenced and continued for the duration of the operative procedure. Cephazolin 1gm was given intravenously (IV) prior to bypass. Sevoflurane served as the inhalation agent of choice during anesthesia and cardiopulmonary bypass.

An intraoperative TEE revealed grade 3 atheromatous disease of the descending aorta, however, the ascending aorta was free from significant atheroma. A milrinone infusion together with low-dose noradrenaline was commenced at the start of cardiopulmonary bypass and continued throughout the operative period. These inotropic infusions were commenced in anticipation of a prolonged bypass time and the likely presence of diastolic dysfunction in a patient with known aortic stenosis and left ventricular (LV) hypertrophy.

The patient's ascending aorta was cannulated using a 22-Fr arterial cannula (EOPA 3D<sup>®</sup>, Medtronic, Minneapolis, MN) and a 36/46-Fr two-stage venous cannula (Thin-Flex<sup>®</sup>, Edwards Lifesciences, Irvine, CA) was inserted via the right atrium. The heart was vented with a 20-Fr LV vent catheter (DLP<sup>®</sup>, Medtronic) inserted through the right superior pulmonary vein. Cardiopulmonary bypass was instituted using a hard-shell cardiotomy reservoir with a membrane oxygenator (RX25<sup>®</sup>, Terumo, Tokyo, Japan) and a 20-micron arterial filter (AL20<sup>®</sup>, Pall, Port Washington, NY). A roller pump provided non-pulsatile blood flow with a target flow rate of 2.4 L/min<sup>1</sup>/m<sup>2</sup> and venous oxygen saturations >70%. The patient was slowly cooled to 31°C nasopharyngeal.

The operative field blood was scavenged with the cardiotomy sucker and returned to the cardiotomy reservoir. A cell saver was not used.

A patent left internal mammary artery graft to the left anterior descending artery was untouched during the procedure due to the potential for damage through surgical

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manipulation. The unclamped mammary graft caused continuous flooding of the surgical field with blood and compromised the surgeon's view. This was despite the use of the LV vent and cardiotomy suction. Repeated requests for reduced arterial blood flow to facilitate the suturing of the valve to the annulus were of short duration (1.2 minutes longest time). Three episodes occurred where the mean arterial blood pressure (MAP) remained less than 40 mmHg despite a return to high blood flow rates (3.3, 2.5, and 2.3 minutes in duration). Incremental doses of metaraminol and increases in the noradrenaline infusion were strategies used in an effort to restore MAP. The total aggregate time with a MAP less than 40 mmHg was 11 minutes. An in-line oxygen saturation/hematocrit monitor (CDI 100<sup>®</sup>, Terumo) recorded venous saturations less than 60% for 1 minute 34 seconds during the total bypass period of 117 minutes and cross-clamp time of 90 minutes. Cerebral oximetry was not available for use.

A nadir hematocrit of 29% was recorded with a blood sugar range between 7.6 and 12.4 mmol/L. No blood product transfusions were given. Activated clotting time (ACT Plus<sup>®</sup>, Medtronic) remained >600 seconds during bypass. Entropy monitoring (GE Healthcare, Little Chalfont, United Kingdom) was used to measure the depth of anesthesia. Entropy readings remained within the normal range for an anesthetized patient.

A 23-Fr tissue valve (PERIMOUNT Magna Ease<sup>®</sup>, Edwards Lifesciences) was inserted to replace the patient's stenotic aortic valve. Following replacement, standard de-airing procedures included placing the patient in the Trendelenburg position, infusion of warm blood into the coronary sinus, inflating the lungs, filling the heart, and applying gentle suction to the aortic root, prior to cross-clamp removal. Despite these manoeuvres a large amount of air was seen on TEE in the left ventricle. Venting of the ascending aorta continued until the LV air had cleared entirely. The heart required defibrillation with a single 10 J shock to return to sinus rhythm. The patient was slowly rewarmed to 36.5°C nasopharyngeal before bypass was discontinued. Temperature gradients (arterial outlet and venous inflow) did not exceed 4°C with arterial outlet blood temperature not exceeding 37°C.

Tranexamic acid was given to prevent fibrinolysis. The patient weighed 78 kg and was given a bolus dose of 2 g IV tranexamic acid following induction of anesthesia and 1 g was given in the pump prime (total 3 gm or 38.5 mg/kg).

On arrival to the intensive care unit the patient was stable with pupils equal and reactive. "Generalized body movement/shaking" was noted 20 minutes following his arrival. Initial treatment with propofol 50 mg IV arrested the seizures. Pupils were pinpoint with normal corneal reflexes. Three more episodes of seizure-like activity were noted over the ensuing 5 hours. He was treated with 5 mg midazolam and commenced on both midazolam and pro-

pofol infusions. Phenytoin 300 mg was given IV for 2 days. The anticonvulsant, levetiracetam 1 gm IV was given for 2 days then continued orally 500 mg twice daily until and following discharge.

Only one further dose of 1 gm IV cephazolin was given.

The patient's serum creatinine was never above normal range in the postoperative period and his electrolyte levels remained normal. There was no evidence of acute kidney injury. Two postoperative computed tomography (CT) head scans were performed and neither showed any recent intracranial event. The first CT (day 0) showed calcified atheromatous plaque in the carotid arteries with <25% narrowing of the right internal carotid, 25–50% narrowing of the left internal carotid, 50–75% narrowing of the right vertebral artery, and occlusion of the distal 1.5–2 cm of the left vertebral artery. The patient remained ventilated for 3 days postoperatively and was confused for 5 days. He was discharged home day 12 with generalized weakness but alert and oriented.

## OVERVIEW

Seizures following cardiopulmonary bypass are an immediate and alarming indication that a neurologic event has occurred. Convulsive seizures, whether generalized or focal, are easily discerned and reported. Non-convulsive seizures, however, may easily be missed and lead to under-reporting. With this in mind, the incidence of seizures following cardiac surgery has been reported to be approximately .4–1.3% (1–5). Two significant publications using multivariate regression analysis have identified factors associated with postoperative seizures (3,4). Sharma et al. identified age, female gender, redo cardiac surgery, ascending aortic disease, congestive heart failure, deep hypothermic circulatory arrest, duration of aortic cross-clamp, and tranexamic acid as independent predictors of seizures (3). Although Manji et al. identified tranexamic acid exposure, an APACHE II score >20, preoperative cardiac arrest, preoperative neurological disease, open-chamber surgery, bypass time >150 minutes, and previous cardiac surgery as factors significantly associated with seizures (4). In a study by Kalavrouziotis et al., 90% of patients with an early documented seizure had undergone an operation involving the opening of the left side of the heart with only 10% having had coronary artery bypass (5). In Sharma's paper, 94% of patients having a postoperative seizure underwent open-chamber surgery (3).

Stroke is indicative of a focal brain injury and it has been postulated that atherosclerotic emboli released through the surgical manipulation of the aorta is the primary cause (1). Large emboli often cause infarcts to the entire territory of a cerebral artery (6). The pathophysiology of generalized seizures or encephalopathy, however,

is more suggestive of a multifocal injury and small emboli and/or inadequate cerebral blood flow are implicated (1,7). Micro-emboli may enter smaller vessels with particles less than 200 microns traveling into watershed territories (6). Arterial gas emboli cause a reduction in blood flow distal to the obstruction as well as a local inflammatory response at the site of the bubble (8). Reduced cerebral blood flow due to hypotension (before/after or during bypass) may cause ischemic brain injury to vulnerable territories in the brain or hypotension may simply prevent the clearance of micro-emboli within the smaller vessels (9,10).

Micro-emboli may be introduced into the bloodstream through surgical or perfusion manoeuvres. The positioning of a LV vent or incomplete de-airing following open-heart procedures have been recognized as possible sources of surgical air that may travel up the cerebral carotid arteries (9). As well, air may enter the bypass circuit entrained into the venous line due to holes in the right atrium or incomplete snaring of the vena cava. Inadequate reservoir volume and poor design have been shown to potentiate this effect (11,12). Membrane oxygenators as well as arterial filters are not enough to rid the circuit entirely of micro-emboli (13,14). Lipid emboli may enter the bypass circuit from pericardial suction blood and has been implicated as a source of particulate emboli despite the use of venous and arterial filtration (15).

Hypotension is a well-known cause of cerebral ischemia and stroke. Healthy individuals maintain cerebral blood flow through auto regulatory mechanisms that may be affected by changes in their cerebral metabolic rate for oxygen, partial pressure of carbon dioxide, hematocrit, and MAP. In patients with severe aortic atheromatous disease higher mean arterial pressures, closer to their own individual auto regulatory range, have been associated with reduced stroke rates (16,17). Low MAP during cardiac surgery affects cerebral blood flow and, again, can result in poor clearance of micro-emboli particularly in the watershed regions of the brain (10).

Hypothermia reduces the oxygen requirement of the brain and may provide protection from cerebral ischemia. During the rewarming phase of cardiopulmonary bypass, however, the patient may be exposed to hyperthermia if the arterial blood outlet temperature is not limited to 37°C. Recommendations suggest that hyperthermia should be avoided to protect the patient from neurologic injury (18).

Tranexamic acid is a synthetic antifibrinolytic often given routinely during cardiac surgery to reduce blood loss and limit transfusion requirements (19). It is largely cleared by the glomeruli and therefore patients with renal failure are at an increased risk of drug accumulation. Patients having a smaller body surface area and the use of a tranexamic acid infusion, during long surgical procedures, also increase the risk of drug accumulation (3). Investigators have observed that tranexamic acid doses approaching or more

than 100 mg/kg in total are associated with postoperative seizures (5,20). Reducing the dose of tranexamic acid is associated with a drop in seizure rates, exhibiting a dose-response relationship (4,5). Recently, there has been some focus on the drug's pro-convulsant effect even in the presence of moderate dosing regimens (21). Tranexamic acid crosses the blood brain barrier (22). It is structurally similar to the inhibitory neurotransmitter glycine and has been shown to block its effect (23). Tranexamic acid is also a competitive antagonist to  $\gamma$ -aminobutyric acid<sub>A</sub> receptors in both cortical and spinal cord neurons which may lead to increased excitability (24). Micro-emboli and long bypass times (increased inflammatory response) have been suggested as possible contributing factors to the loss of integrity of the blood brain barrier allowing tranexamic acid to enter the cerebral tissue and cause seizures (4,20,21).

## COMMENT

Unavoidable, episodic periods of low flow were required to complete this patient's valve replacement. These low flow episodes were due to blood flooding the operative field and could have been managed in several ways other than the intermittent low flow technique documented in this case. To control the internal mammary artery the graft could have been dissected out from the mediastinum and clamped. Alternately, the left coronary ostia could have been sewn closed during valve placement. The surgeon made his decision based on his experience and the immediate needs of this particular patient.

Hypotension was a concern and may have contributed to his neurologic outcome. A high MAP may have improved cerebral blood flow and also enhanced the clearance of micro-emboli within the cerebral vessels. Reducing this patient's blood temperature further, in an effort to decrease cerebral metabolism, may have been beneficial.

The dose of tranexamic acid did not immediately warrant concern; however, a redo open-heart procedure requiring 2 hours of bypass increased this patient's exposure to gaseous micro-emboli and the activation of his inflammatory system. Remembering air could be seen, on the transesophageal echocardiogram, in the LV following the removal of the cross-clamp and took some time to clear. It is possible that an alteration in the blood brain barrier's permeability has left this patient more susceptible to the pro-convulsant effects of tranexamic acid. Several studies have found that open-heart chamber procedures and tranexamic acid exposure are associated with seizure activity following cardiopulmonary bypass (4,5,20).

The etiology of seizures in this patient was most probably multifactorial. There are several factors at play including the presence of significant atheromatous change in the aorta, periods of low cerebral perfusion, an open-chamber

cardiac procedure, and the use of tranexamic acid. A review of the literature helps to highlight these contributing factors and how they might inter-play in the larger setting of cardiopulmonary bypass.

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