

## Use of Colforsin Dalopate following Cardiac Surgery in a Neonate

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THE authors report a case of a neonate with congenital complex heart anomaly who underwent total repair with a successful outcome, with the use of a forskolin-derived, adenylyl cyclase stimulator, colforsin dalopate hydrogen chloride [HCl].

### Case Report

A FEMALE neonate, weighing 2,690 g, developed severe cyanosis immediately after birth, and was diagnosed as having complex heart anomaly (truncus arteriosus, interruption of aortic arch, aortopulmonary septal defect, patent ducts arteriosus, and persistent foramen ovale). Despite support with dopamine, dobutamine, and epinephrine, congestive heart failure developed. Therefore, total correction surgery was scheduled to take place on the patient's twenty-first day of life.

Anaesthesia was induced and maintained with fentanyl (25 µg/kg) and midazolam (0.3 mg/kg). Surgery was performed under the moderately hypothermic (25°C) cardiopulmonary bypass (CPB) with a total flow of 2.8 l·min<sup>-1</sup>·m<sup>-2</sup>. CPB was started 55 min after the anesthetic induction. The interval from the start of CPB to the initial attempt to wean the patient from CPB with sufficient body temperature recovery (36.2°C) was 5 h and 20 min. The attempt was made to discontinue CPB with the aid of dopamine (4–8 µg·kg<sup>-1</sup>·min<sup>-1</sup>) and dobutamine (5–8 µg·kg<sup>-1</sup>·min<sup>-1</sup>). However, decreasing the bypass flow to less than 1.5 l·min<sup>-1</sup>·m<sup>-2</sup> resulted in sustained hypotension. Adding epinephrine (0.5 µg/kg/min) and isoproterenol (0.1 µg·kg<sup>-1</sup>·min<sup>-1</sup>) did not improve the patient's hemodynamics; her systemic mean arterial pressure while still on partial bypass was ≤ 30 mmHg, while her central venous pressure (CVP) was approximately 17 mmHg. The addition of an infusion of milrinone (0.5 µg·kg<sup>-1</sup>·min<sup>-1</sup>) for approximately 40 min also had no significant effect. Echocardiography (using an epicardial probe) showed an adequate surgical repair.

At this point, with the patient back on full bypass support, all inotropic agents were discontinued. We next administered a combination of colforsin dalopate HCl (0.25 µg·kg<sup>-1</sup>·min<sup>-1</sup>) and dopamine (5 µg·kg<sup>-1</sup>·min<sup>-1</sup>). The patient's CPB flow rate decreased to 1.0 l·min<sup>-1</sup>·m<sup>-2</sup> and CVP was controlled at 8–11 mmHg. Over the next 30 min, the patient's mean arterial pressure increased from 35 to 65 mmHg, and her heart rate increased from 140 to 170 beats/min. After approximately 20 min of stable conditions, CPB was successfully discontinued. Her postweaning hemodynamic parameters showed heart rate, mean systemic arterial pressure, and CVP levels in the ranges of 170–180 beats/min, 55–65 mmHg, and 11–13 mmHg, respectively. Arterial blood gas analysis did not show metabolic acidosis, hypercarbia, or hypoxemia. The surgery terminated 2 h after the CPB

weaning. Hemodynamic parameters recorded after each attempt to discontinue bypass are summarized in table 1.

After being transferred to the intensive care unit, the patient's heart rate continued to increase, reaching 190 beats/min. Her colforsin infusion was discontinued while dopamine was maintained. Two hours later, her mean arterial pressure decreased to 35 mmHg from 60 mmHg, her heart rate decreased to 140 beats/min from 170 beats/min, and CVP increased from 11 mmHg to 17 mmHg. An infusion of epinephrine was added, but without success. Therefore, approximately 1 h later, colforsin dalopate HCl infusion (0.25 µg·kg<sup>-1</sup>·min<sup>-1</sup>) was restarted. Mean arterial pressure and heart rate quickly increased to 65 mmHg and 178 beats/min, respectively. Colforsin was discontinued without difficulty 5 h later.

### Discussion

This case demonstrates the successful use of colforsin dalopate for cardiovascular support during and after CPB, even when treatment with multiple other drugs had failed.

This patient's apparent insensitiveness to exogenous catecholamines suggests that there was some degree of preoperative adrenoceptor down-regulation, either caused by her chronic congestive heart failure or related to the prolonged preoperative use of adrenergic drugs. This phenomenon has been seen both in adults with chronic heart failure<sup>1,2</sup> and in neonates with congenital heart disease and severe cardiac dysfunction.<sup>3</sup>

Colforsin dalopate HCl (Adehl®Inj., Nihon Kayaku Ltd., Tokyo, Japan) is a newly available forskolin derivative in Japan. It exerts its cardiovascular effect through the direct activation of adenylyl cyclase of cardiomyocytes.<sup>4,5</sup> Doses in the range of 0.25–0.75 µg·kg<sup>-1</sup>·min<sup>-1</sup> are recommended. The major adverse effect is tachyarrhythmia (supraventricular and ventricular ectopic beats). However, all of the existing clinical data has been derived from studies of adults, and little information is available regarding its use in children.

The activation of adenylyl cyclase, which is closely linked to β-adrenoceptors, induces the generation of cellular cyclic adenosine monophosphate (cAMP). When the activation of β-adrenoceptors is severely affected, accumulation of cellular cAMP is diminished through the catalysis of it by the responsible phosphodiesterase.<sup>6,7</sup> In this case, we administered milrinone, phosphodiesterase inhibitor [PDEI], in combination with epinephrine and isoproterenol in large doses, but we were not able to normalize the patient's cardiac function. The fact that colforsin dalopate HCl was successful after the failure of milrinone suggests that cAMP formation, presumably caused by the down-regulated state, was of greater importance than cAMP metabolism.

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**Table 1. Changes in Hemodynamic Parameters**

Weaning Trial from CPB	1st		2nd		3rd		4th	
Attempts ( $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ )								
Dopamine	3		5		8		5	
Dobutamine	5		5		8			
Epinephrine			0.5		0.5			
Isoproterenol		0.1		0.1				
Milrinone					0.5			
Colforsin dalopate								0.25
Heart rate (beats/min)	145	150	140	140	155	150	140	170
Systemic blood pressure (mmHg)	65/25	60/15	45/25	50/20	65/15	60/15	60/20	90/45
Central venous pressure (mmHg)	17	18	17	17	16	17	17	10

Table depicts the changes in systemic, central venous pressures, and heart rate after each of the attempts to discontinue from the bypass. Parameters are depicted as pre- and after 30 min attempt values under assisted flow of  $1.0 \text{ l} \cdot \text{kg}^{-1} \cdot \text{m}_2$ .

In conclusion, we report a case in which the continuous infusion of colforsin dalopate HCl successfully permitted the weaning of a neonate from CPB after correction of a complex congenital cardiac defect, under conditions in which better known inotropic agents had failed.

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## Successful Treatment of Delayed Onset Paraplegia after Suprarenal Abdominal Aortic Aneurysm Repair

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PARAPLEGIA is a well-recognized complication of thoracic aortic aneurysm (TAA) repair, but rarely occurs after abdominal aortic aneurysm (AAA) repair.<sup>1,2</sup> In most reported cases of postoperative paraplegia, it is difficult to identify the exact time of onset for the event, the factors that may have contributed to the development of spinal cord ischemia, or whether therapeutic interven-

tions were effective. In the case described in this article, the delayed onset of paraplegia in the postoperative period after repair of a suprarenal AAA temporally followed an episode of hypotension, suggesting that the neurologic deficit was caused by hypoperfusion. Acute diagnosis and interventions directed to increase spinal cord perfusion by increasing arterial pressure and decreasing lumbar cerebrospinal fluid (CSF) pressure were immediately effective in reversing paraplegia, and led subsequently to full neurologic recovery.

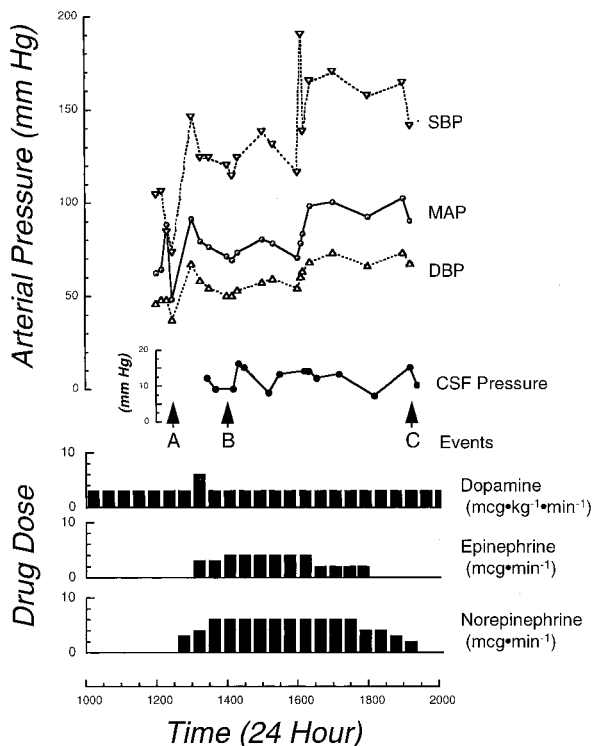
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## Case Report

A 76-yr-old, 58-kg man was hospitalized for elective repair of a  $5.5 \times 7$  cm suprarenal AAA. The patient's medical history was notable for hypertension, mesenteric artery stenosis, and infrarenal aortobifemoral bypass graft repair with right nephrectomy 12 yr ago. Aortic angiography demonstrated absence of the inferior mesenteric artery, occlu-



**Fig. 1.** Systolic (SBP), diastolic (DBP), and mean arterial pressures (MAP) in the immediate postoperative period in relation to postoperative events and intravenous vasopressor infusion doses are shown. After arrival to the surgical intensive care unit at 11:45 AM, the patient became hypotensive at 12:30 PM (event A), and developed paraplegia at 12:45 PM. A lumbar cerebrospinal fluid drain was inserted and functioning at 1:25 PM. Bilateral lower extremity motor strength and sensation returned at 2:00 PM (event B) and neurologic examination demonstrated normal symmetrical motor strength and sensation in the lower extremities at 7:30 PM (event C). The hemoglobin concentration was 13.8 g/dl at 1:15 PM.

sion of the celiac and superior mesenteric arteries, and ostial stenosis of the left renal artery.

An epidural catheter was inserted into the T7-T8 thoracic vertebral interspace. General anesthesia was induced by thiopental, fentanyl, and cisatracurium. Anesthesia was maintained with inhaled isoflurane, cisatracurium, and a continuous infusion of bupivacaine 0.05% and fentanyl 2  $\mu\text{g}/\text{ml}$  at a rate of 6 ml/h *via* the epidural catheter. The right radial artery and pulmonary artery pressures were monitored. The aneurysm was approached through a left retroperitoneal incision. After the intravenous administration of heparin 5,000 USP units and mannitol 25 g, the aorta was cross-clamped at the level of the diaphragm. A 20 mm Dacron graft (Sulzer Vascutek Gelweave™, Sulzer Vascutek, Austin TX) was interposed between the proximal end of the previous infrarenal aortic bifurcation graft and the aorta at the level of celiac artery. A 6 mm Dacron graft was used to bypass the superior mesenteric artery. The aorta was cross-clamped for 40 min. At the end of surgery, protamine 25 mg was administered intravenously. The hemoglobin concentration of the patient was 10.5 g/dl. His trachea was extubated in the operating room, and the patient had normal motor strength in all four extremities.

Neurologic assessment performed upon admission to the intensive care unit (ICU) verified intact motor and sensory function in all extremities. Forty-five minutes after arrival to the intensive care unit the patient's mean arterial pressure (MAP) decreased from 78 mmHg to 48 mmHg (fig. 1). Shortly thereafter, the patient reported weakness and loss of sensation in the lower extremities. Examination by a

neurologist demonstrated flaccid paralysis and paraplegia extending to the T10 thoracic dermatome. MAP was increased to 75 mmHg by discontinuing the epidural infusion and increasing dopamine to 6  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  intravenously. In addition, phenylephrine 50  $\mu\text{g}$  intravenous bolus, 250 ml of packed red blood cells, and 5.5 l of normal saline were administered. After the arterial pressure increased, the patient was able to move his left leg weakly. Intravenous norepinephrine 3–6  $\mu\text{g}/\text{min}$  and intravenous epinephrine 3–4  $\mu\text{g}/\text{min}^{-1}$  were then started in an effort to keep the MAP in the range of 95–105 mmHg. A 0.7 mm ID lumbar CSF drainage catheter (Moni-Torr ICP™, Clinical Neuro Systems, Exton, PA) inserted 7 cm into the subarachnoid space *via* a 14-gauge Tuohy needle at the L3-L4 vertebral interspace measured a lumbar CSF pressure of 12 mmHg (fig. 1). Clear CSF, 15 ml was immediately drained, and 10 ml of CSF was drained every hour for a lumbar CSF pressure greater than 10 mmHg. Bilateral lower extremity motor strength and sensation gradually recovered and returned to normal over the next 60 min. The arterial pressure improved, permitting the discontinuation of norepinephrine, epinephrine, and a reduction of the dopamine dose to 3  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . Neurologic examination 7 h later demonstrated normal symmetrical motor strength in the lower extremities, no sensory deficits, and hyperreflexia. The lumbar CSF catheter was occluded 48 h later and then removed at 72 h after surgery. There were no further episodes of paraplegia, and the patient was discharged 23 days after the operation with no neurologic deficits.

## Discussion

Postoperative paraplegia after AAA repair has an estimated incidence between 0.15–0.3%.<sup>2</sup> Although the precise mechanism of paraplegia after aortic reconstruction remains to be established, factors that increased the risk in the case described were the presence of extensive peripheral vascular disease, previous replacement of the infrarenal aorta with a bifurcated graft, suprarenal position of the aneurysm, need for a supraceliac aortic cross clamp, and onset of hypotension in the immediate postoperative period. Investigators have suggested that the lumbar, iliolumbar, and lateral sacral arteries of the hypogastric and pelvic circulation are important sources of blood flow to vessels supplying the caudal portion of the spinal cord.<sup>2–3</sup> In the presence of occlusive disease of the aortoiliac arteries, the hypogastric and pelvic circulation may be supplied by collaterals from the hypogastric, inferior mesenteric, or superior mesenteric arteries.<sup>4</sup> Previous aortobifemoral bypass grafting with prior sacrifice of the inferior mesenteric artery and severe occlusive atherosclerotic disease of the mesenteric vessels in this patient were likely to have severely compromised the collateral blood supply to the spinal cord arising from the hypogastric and pelvic circulation. In this situation, it was likely that the further decrease in spinal cord perfusion as a consequence of hypotension was a primary event that contributed to the development of spinal cord ischemia in a watershed distribution. In previous reports, hypotension has also been implicated as a factor that contributed to ischemic infarction of the spinal cord.<sup>5–8</sup>

Combined general anesthesia and epidural analgesia with a very dilute concentration of local anesthetic per-

mitted early neurologic evaluation and the immediate diagnosis of paraplegia caused by spinal cord ischemia. Clinical experience has indicated that continuous epidural infusion of bupivacaine 0.05% and fentanyl 2  $\mu\text{g}/\text{ml}$  started during surgery produces satisfactory analgesia without impairment of motor function.<sup>9</sup> Although epidural hematoma or local anesthetic-induced motor blockade were considered, the acute onset of paraplegia and complete sensory loss in the early postoperative period was most consistent with spinal cord ischemia.

Emergency treatment of paraplegia with vasopressor therapy to augment the arterial pressure and lumbar CSF drainage to decrease the lumbar CSF pressure was immediately initiated to increase the net spinal cord perfusion pressure. Lumbar CSF drainage to prevent postoperative paraplegia after aortic surgery has been advocated, but its effectiveness for the treatment of delayed onset postoperative paraplegia remains controversial.<sup>2,10-15</sup> The specific use of vasopressor therapy for the treatment of spinal cord ischemia has not been studied, but the presumed ischemic etiology of the complication prompted its use. Norepinephrine and epinephrine were chosen in an effort to increase both the arterial pressure and cardiac output. Multiple vasopressor agents at relatively high doses were required initially to generate a MAP greater than 90 mmHg. Recovery of neurologic function coincided with the increased arterial pressure. It was possible that hypotension at the onset of spinal cord ischemia may have also been caused by ischemia-induced autonomic dysfunction as in the syndrome of spinal or neurogenic shock. Ischemia-induced autonomic dysfunction would explain also the need for vasopressor therapy during the event and the spontaneous recovery of arterial pressure after the return of neurologic function.

Cases of delayed onset of paraplegia in the postoperative period after AAA have been reported, but their frequency has been difficult to determine because not all patients have neurologic assessments immediately after surgery.<sup>5,16-17</sup> In contrast to paraplegia detected upon emergence from general anesthesia, delayed onset of paraplegia indicates that the vascular supply to the spinal cord was not irreversibly damaged as a consequence of surgery.<sup>15</sup> Delayed onset of paraplegia suggests that postoperative events such as hypotension, increased CSF pressure, or embolization, may have triggered the onset of neurologic dysfunction in patients at risk for spinal cord ischemia.<sup>14-15</sup> Based on this pathophysiology, it is reasonable to predict that delayed onset paraplegia is reversible and will respond to treatment with interventions directed at increasing spinal cord perfusion. Full or

partial recovery from delayed onset paraplegia after AAA or TAA repair has been reported, but standard treatment algorithms for this complication have not yet been developed or tested.

The events of this case challenge earlier presumptions that postoperative paraplegia is an unavoidable, unpredictable, and untreatable complication of aortic reconstruction.<sup>2,10,14</sup> Although it was not possible to determine with certainty the precise mechanism of postoperative paraplegia and the relative contribution of individual treatment interventions, the additive effect of the treatment strategy to increase spinal cord perfusion pressure was temporally followed by the recovery of neurologic function. Considering the severity of this complication and its associated morbidity, early implementation of this treatment algorithm can be justified while awaiting additional evidence to support its clinical effectiveness.

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## Atypical Presentation of Malignant Hyperthermia

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**MALIGNANT** hyperthermia (MH) is a potentially fatal hypermetabolic response to volatile inhalation agents and succinylcholine that may have variable presentations. The authors describe an unusual presentation with late onset of malignant hyperthermia after laparoscopic cholecystectomy, with rhabdomyolysis as the principal sign.

### Case Report

A 52-year-old white male (height, 170 cm; weight 100 kg) with chronic biliary colic presented for laparoscopic cholecystectomy. The patient's medical history consisted of hypertension, obstructive sleep apnea with use of a nocturnal continuous positive airway pressure device, gastric esophageal reflux disease, gastritis, osteoarthritis, and gout. Past surgeries were a right toe repair using local anesthesia in 1968 and a thoracocentesis for pleurisy in 1983, both uneventful. The anesthetic for the thoracocentesis was unknown to the patient. Current medications included lisinopril, atenolol, hydrochlorothiazide, omeprazole, and cholicine. The patient denied any personal or family history of anesthetic complications. Routine preoperative laboratory blood analysis (complete blood count and liver function tests) and electrocardiogram were unremarkable. The patient took his usual medications the day of surgery.

After premedication with 2g cefoxitin, 10 mg metoclopramide, 0.2 mg glycopyrrolate, and 1 mg midazolam, anesthesia was induced at 7:38 AM with 100 µg fentanyl, 50 mg lidocaine, 200 mg propofol, and 160 mg succinylcholine. A rapid sequence intubation was performed. After fasciculation, we noted what was thought to be masseter muscle rigidity. However, this resolved in approximately 10 s and uneventful laryngoscopy and intubation was performed. Transient diaphoresis was also noted. The temperature from the liquid crystal skin strip placed on the patient's forehead read 37.0°C. There was no peripheral rigidity or skin discoloration. The patient's heart rate remained at 70-75 beats/min. The initial end-tidal carbon dioxide was 48 mmHg, but slowly decreased with normal tidal volumes. Because of the initial episode of jaw rigidity and diaphoresis, there was an index of suspicion for MH and a possible course of action was discussed in the operating room. However, there were no other signs or symptoms to further increase our index of suspicion, and it was decided to continue with the surgery and anesthesia without altering our plan. In addition, since this was a rapid sequence induction, we questioned if we had attempted to open the jaw before complete relaxation. Anesthesia was maintained with desflurane and oxygen, and mivacurium was used for muscle relaxation. A total of 250 µg of fentanyl was administered. The intraoperative course was uneventful. Minute ventilation was set at

approximately 9 l/min. Heart rate ranged 65-85 beats/min, and skin temperature read 37.0-37.2°C. End-tidal carbon dioxide remained 38-40 mmHg. Operative and anesthesia time totaled 80 min. Ketorolac 30 mg was given before extubation. The patient was admitted to the Postanesthesia Care Unit and observed for 30 min. The patient was afebrile and vital signs remained stable with heart rate ranging from 78-88 beats/min. He was subsequently discharged to the ward in stable condition.

The patient arrived on the ward at 9:15 AM, with a recorded oral temperature of 36.6°C, heart rate of 78 beats/min, respiratory rate of 16, and blood pressure of 157/88. At 1:00 PM, the patient noticed cola colored urine upon urination. He immediately notified the nursing personnel. There was no dysuria, but the patient now complained of muscle aches in the jaw, neck, triceps, and lower back. The last recorded oral temperature at 12:20 PM was 37.3°C. Both the surgery and anesthesia departments were notified, and the initial impression was myoglobinuria secondary to rhabdomyolysis. Aggressive intravenous hydration was ordered. An arterial blood gas was essentially normal (pH 7.41, CO<sub>2</sub> 36 mmHg, O<sub>2</sub> 72 mmHg, HCO<sub>3</sub> 24 mEq/l). The family history was reinvestigated, but the patient and his wife denied any usual events. The Malignant Hyperthermia Hotline was contacted at approximately 3:30 PM and following discussion with the consultant, a late MH reaction was suspected. A complete work-up was begun and the patient was transferred to the intensive care unit. The initial creatine kinase (CK) was 100,030 U/l (table 1), sodium 141 mEq/l, potassium 4.5 mEq/l, chloride 104 mEq/l, CO<sub>2</sub> 23 mEq/l, BUN 17 mg/dl, creatinine 1.0 mg/dl, and glucose 88 mg/dl. The urinalysis was reported as red, turbid, 2+ bilirubin, 3+ protein, and 3+ occult blood. The urine myoglobin was 796,000 mg/l. Subsequent complete blood counts and coagulation studies were normal. The patient's oral temperature at 3:20 PM was 38.5°C, and at 5:30 PM peaked to 38.8°C. Cooling measures were initiated. Once again, the patient and his wife were questioned, and the history of a teenage nephew (patient's side) who died years ago from "anesthesia" during surgery was disclosed, with the qualification that "it is not talked about in our family." The specifics were unknown. In addition, the patient admitted to self-administration of testosterone intramuscularly, herbal supplements, and also to a history of muscle cramps. Furthermore, the patient stated he was recently prescribed simvastatin (Zocor® Merck & Co., Inc. Whitehouse Station, NJ). None of this information had been disclosed before surgery.

Treatment included dantrolene, aggressive hydration with normal saline, diuresis supported with furosemide, sedation, and antiemetics. Dantrolene 100 mg (1 mg/kg) was given intravenously every 4-6 h, a total of five times, then changed to 100 mg orally every 6 h for three doses. Intravenous labetalol and hydralazine were required for control of a hyperdynamic state consisting of tachycardia and hypertension, most likely brought on by a positive fluid balance and preexisting hypertension. During the course of treatment, the patient's complaints included weakness, fatigue, and nausea, and were attributed to the dantrolene, as they would exacerbate immediately after each dose. He also experienced shortness of breath, most likely caused by the positive fluid balance, as evidenced by chest radiograph. However, aggressive hydration and diuresis was initially necessary to prevent the possibility of acute tubular necrosis from myoglobinuria. By instituting his usual antihypertensive medication, hemodynamics was better controlled.

The patient spent approximately 48 h in the intensive care unit, and was subsequently transferred to the surgical ward in satisfactory condition. Appropriate counseling of the patient and family was completed, and the patient was registered in the North American Malignant Hyperthermia Registry. The patient spent approximately 24 h on the

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**Table 1. Creatine Kinase Levels**

Day 1		Day 2		Day 3		Day 4	
Time	CK	Time	CK	Time	CK	Time	CK
3:00 PM	100,030	5:30 AM	104,270	8:30 AM	50,547	6:00 AM	16,438
5:30 PM	103,000	11:30 AM	94,483				
7:00 PM	133,270	6:00 PM	81,240				
10:30 PM	153,170	11:30 PM	69,160				

CK = creatine kinase levels U/l.

surgical ward tolerating a regular diet, with pain well managed with oral analgesics, and was subsequently discharged. The patient had a full recovery with no evidence of renal failure.

Five months later, the patient underwent muscle biopsy for evaluation of susceptibility to malignant hyperthermia at University of California Medical Center, Davis, CA. The *in vitro* contracture test (IVCT) was performed using a muscle sample excised from the left vastus lateralis. Six viable muscle bundles were mounted and supramaximal voltage optimal length was determined. Three bundles exposed to 3% halothane responded with contractures of 1.9, 3.2, and 5.7 g of tension (greater than 0.7 g represents MH susceptible). The remaining three bundles exposed to incremental doses of caffeine exhibited thresholds of 1, 1, and 2 mM (less than 4 mM caffeine specific concentration represents MH susceptible). These results were abnormal and indicated that the patient was susceptible to malignant hyperthermia. Histology and histochemical examinations found no evidence of a metabolic or degenerative disorder. It is unknown if any other first-degree relatives have been tested.

## Discussion

Malignant hyperthermia can have a highly variable clinical presentation and delayed onset, potentially making a definitive diagnosis challenging. This case was characterized by mild masseter muscle rigidity and sweating after administration of succinylcholine, and then rhabdomyolysis, myoglobinuria, and temperature elevation several hours later. In the typical presentation of MH, elevations of temperature can be delayed; therefore, the earliest signs of MH include tachycardia, tachypnea, and increased end-tidal carbon dioxide levels. However, in this patient, many early signs of MH were not apparent or possibly masked by the medication regime.

Without more definitive signs, it was initially assumed that this was a purely succinylcholine induced myoglobinuria. The patient's later disclosure of unconventional medications and recent addition of simvastatin further clouded the picture. Inhibitors of hepatic hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase, including simvastatin, can occasionally cause myopathy and elevated CK. According to the makers of simvastatin (Zocor®, Merck & Co., Inc. Whitehouse Station, NJ), there have been reports of rhabdomyolysis with or without acute renal failure.<sup>1</sup> However, upon advice from the Malignant Hyperthermia Hotline consultant, the patient was treated as MH susceptible and biopsy testing was recommended.

Until the report from the muscle biopsy was received, it was unclear as to the exact etiology of the rhabdomyo-

lysis. Was it purely from the succinylcholine or was it MH? Although mild masseter muscle rigidity in adults is not usually associated with signs of an overt MH episode, these patients should be observed for hypermetabolism, CK elevation, as well as rhabdomyolysis and myoglobinuria. When the CK elevation exceeds 20,000 U/l, there is a high correlation with positive muscle contracture testing.<sup>2</sup> In this case, both the masseter muscle rigidity and elevated CK predicted the subsequent diagnosis of MH. Protocol after an episode of adult masseter muscle rigidity varies considerably among clinicians, ranging from close observation and continuation of the anesthetic, to termination of anesthesia and surgery, administration of dantrolene, and monitoring for 24 h. Our decision was the former, and with no further signs or symptoms, the patient was treated routinely. Fortunately, the nursing staff quickly alerted the medical staff of the myoglobinuria, and appropriate treatment was begun.

Certainly there are several lessons learned. From the onset of the MMR, a high index of suspicion for MH and subsequent rhabdomyolysis should be followed, and immediate diagnostic testing begun, such as urinary catheterization to observe and test urine, CK analysis, accurate temperature monitoring, and an arterial blood gas. Changing the anesthetic plan to nontriggering agents should be considered. Also, it is inappropriate to rely on a skin temperature for accurate readings, and a central core temperature device should be inserted. Finally, it is probably not uncommon for patients to conceal their use of unconventional medications or herbal remedies, and to discount family histories as trivial. Stressing the significance of this information during a preanesthetic interview may facilitate disclosure. In conclusion, this unusual clinical appearance of malignant hyperthermia demonstrates the variability of the disease and has heightened the awareness of atypical presentation in our department. Any future episodes of masseter muscle spasm, adult or pediatric, will certainly be aggressively investigated and treated as an indicator of malignant hyperthermia until proven otherwise.

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## Monitoring Hirudin Anticoagulation in Two Patients Undergoing Cardiac Surgery with a Plasma-modified Act Method

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HEPARIN-INDUCED thrombocytopenia (HIT) is an immunologically-mediated reaction to unfractionated heparin that can result in life-threatening thrombotic complications. When patients with a history of HIT present for cardiac surgery, anticoagulation for cardiopulmonary bypass (CPB) can be challenging. Recombinant hirudin (r-hirudin) has been reported as a feasible alternative for anticoagulation.<sup>1-8</sup> R-hirudin is a potent direct thrombin inhibitor that works independently of antithrombin-III, offers a rapid onset of anticoagulation, and has a relatively short half-life (60-90 min) in patients with normal renal function.<sup>9</sup>

The ability to rapidly and reliably monitor intraoperative levels of r-hirudin anticoagulation, however, has been problematic. The levels of r-hirudin recommended for anticoagulation during CPB (3.5-4.5  $\mu\text{g/ml}$ )<sup>10</sup> exceed those that can be effectively monitored with either the partial thromboplastin time or activated clotting time.<sup>11</sup> The authors described a plasma-modified kaolin-activated clotting time (PM-ACT) assay as a new point-of-care monitoring tool for r-hirudin anticoagulation has been previously described.<sup>12</sup> This assay, accomplished by mixing patient whole blood samples with an equal volume of citrated commercial normal plasma, extends the ACT monitoring range by correcting for hemodilution of coagulation factors and diluting r-hirudin plasma concentrations. The authors present two cases where the PM-ACT was used to monitor r-hirudin anticoagulation during cardiac surgery, and describe the potential for significant perioperative bleeding complications.

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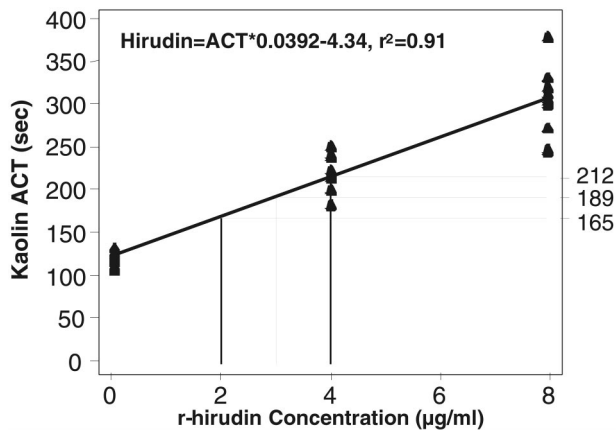
### Case Reports

#### Case 1

An 80-yr-old, 58-kg woman presented for repeat coronary artery bypass graft surgery and closure of patent foramen ovale. After her coronary artery bypass grafting 3 yr earlier, HIT was suspected as the cause of two bypass graft occlusions on postoperative day 6 and subsequent inferior vena cava thrombosis, pulmonary embolism, and paradoxical cerebral embolism. She was treated initially with low molecular weight heparin and then, when platelet count continued to remain low, with danaparoid. Heparin- and low molecular weight heparin-reactive platelet antibodies were detected by an ELISA assay. Preoperatively, she presented with an estimated ejection fraction of 25%, atrial fibrillation, and adult-onset diabetes mellitus but with normal renal function (creatinine 0.9 mg/dl).

Upon presentation, the patient no longer had detectable HIT-antibodies by ELISA. Given her previously significant thrombotic complications, the decision was made by consensus of the hematology, anesthesiology, and surgical services to avoid heparin administration. R-hirudin was selected as the alternative anticoagulant for CPB.

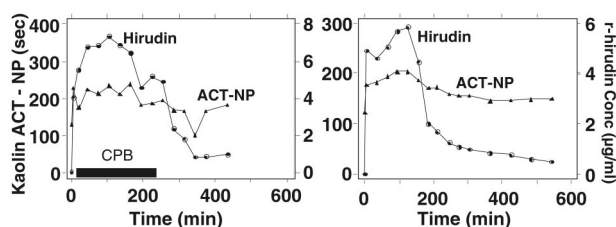
On the day of surgery, intravenous and arterial lines were placed, along with a nonheparin-coated pulmonary artery catheter, using saline flushes only. Anesthesia was fentanyl-based, with midazolam, isoflurane, and pancuronium supplementation. Aprotinin was administered using a weight-adjusted modification of the full-Hammersmith regimen, based on evidence that weight adjustment results in less variability in plasma aprotinin concentrations.<sup>13</sup> The weight-adjusted full-dose Hammersmith regimen consisted of 2 million units (or 280 mg) for a patient with an ideal body weight of 80 kg, and for patients whose ideal body weight was more or less than 80 kg, the dose was increased or decreased using the following formula: 280 mg  $\times$  ideal body weight in kilograms (kg) per 80 kg for bolus and pump prime, and 70 mg  $\times$  ideal body weight in kg per 80 kg. Adjunctive platelet inhibition therapy was employed with oral aspirin and dipyridamole preoperatively and prostaglandin E<sub>1</sub> infusion (0.01-1.0  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) intraoperatively. The r-hirudin anticoagulation strategy was adapted from previously published recommendations and consisted of 0.25 mg/kg intravenous bolus plus 0.25 mg/kg to CPB circuit prime followed by 0.5 mg/min intravenous infusion to continue until approximately 30 min before discontinuing CPB.<sup>10</sup> Using the previously established *in vitro* relationship between PM-ACT and hirudin concentrations (fig. 1),<sup>12</sup> a target PM-ACT value of 212 s would correspond to a r-hirudin concentration of 4  $\mu\text{g/ml}$ . Therefore, in following the patient's PM-ACT every 30 min, an additional four 5-mg boluses were given during CPB to maintain this PM-ACT minimum of 212 s. The r-hirudin infusion lasted 2.5 h. In an effort to later validate the PM-ACT *in vitro* relationship shown in figure 1, additional patient whole blood samples were obtained with each PM-ACT sample for measurements of *ex-vivo* r-hirudin concentrations using a chromogenic method (fig. 2). Time on CPB was 3 h, 32 min with an aortic cross-clamp time of 1 h, 56 min. Eight minutes after initial CPB discontinuation, CPB was urgently reinitiated for significant hemodynamic instability, and an additional 5 mg r-hirudin was given intravenously to ensure adequate anticoagulation. An intraaortic balloon pump was placed, and the patient was weaned from CPB with significant inotropic support. Major bleeding further complicated the



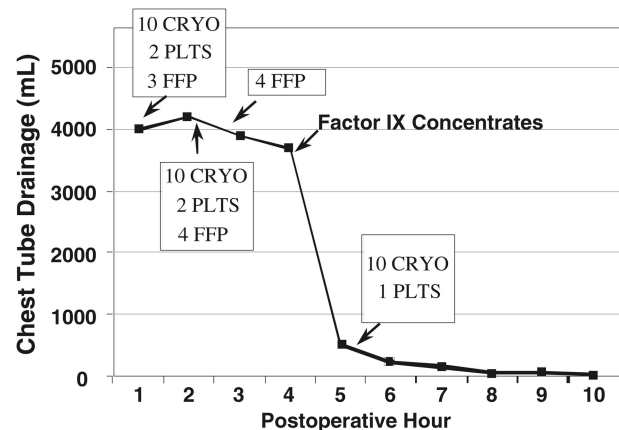
**Fig. 1.** Kaolin activated clotting time (ACT) values *versus* r-hirudin concentrations in plasma-supplemented patient blood samples after cardiopulmonary bypass, obtained previously from an *in vitro* study.<sup>12</sup> The addition of plasma provides additional coagulation proteins, dilutes the platelet effect, and dilutes the hirudin concentration, resulting in a linear and reproducible relationship ( $r^2 = 0.94$ ). Target plasma-modified kaolin-activated clotting time (PM-ACT) values are extrapolated to the right for estimated necessary r-hirudin plasma concentrations for carotid endarterectomy (2  $\mu\text{g}/\text{ml}$ ), coronary artery bypass graft without cardiopulmonary bypass (3  $\mu\text{g}/\text{ml}$ ), and coronary artery bypass graft with cardiopulmonary bypass (4  $\mu\text{g}/\text{ml}$ ). Reprinted with permission from Despotis GJ *et al.*<sup>12</sup>

post-CPB period. Initially managed by retransfusing salvaged blood *via* the CPB circuit, this was discontinued when right atrial thrombus was detected *via* transesophageal echocardiography, necessitating right atrial thrombectomy. In addition to the 8 units packed red blood cells and 3 units of fresh frozen plasma that were given during CPB, the patient was transfused with 5 units packed red blood cells, 10 units of fresh frozen plasma, 3 six-packs of platelets, and 20 units of cryoprecipitate plus 24  $\mu\text{g}$  l-deamino-8-D-arginine vasopressin (DDAVP). Subsequent laboratory evaluation showed a hematocrit 24.1%, platelet count 281,000/ml, International Normalized Ratio 1.4, and activated partial thromboplastin time 117.4 s. Good urine output was maintained throughout the intraoperative course (average 4.5  $\text{ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ). The patient was taken directly to the intensive care unit with the sternum open and sterilely covered.

The massive blood loss continued in the immediate postoperative period (fig. 3). Within the first 6 h, the patient lost approximately 18 l of blood through her chest tubes. This blood loss required the transfusion of an additional 18 units packed red blood cells, 11 units fresh frozen plasma, 8 six-packs platelets, and 30 units cryoprecipitate. The international normalized ratio rose as high as 3.01 and activated partial



**Fig. 2.** Kaolin activated clotting time (ACT) values modified with normal plasma (NP) and corresponding *in vivo* r-hirudin concentrations over time for patient 1 (*left*). Cardiopulmonary bypass bar indicates time spent on cardiopulmonary bypass.  $r^2 = 0.66$ . (*Right*) kaolin ACT values modified with normal plasma (NP) and corresponding *in vivo* r-hirudin concentrations over time for patient 2.  $r^2 = 0.87$ .



**Fig. 3.** Postoperative chest-tube drainage in patient 1 over time, indicating significant blood loss. Coagulation factor and platelet transfusions are noted per hour. CRYO = cryoprecipitate; PLTS = platelets; FFP = fresh frozen plasma. Blood loss is dramatically reduced after transfusion of Factor IX concentrate.

thromboplastin time  $> 150$ . Because of persistent severe coagulopathy, Factor IX concentrate (6,068 international units) was administered 4 h postoperatively (chosen primarily because it was the only factor concentrate immediately available) resulting in a considerable decrease in bleeding (fig. 3). Two hours later, the following laboratory values were noted: hematocrit 28%; platelet count 158,000; international normalized ratio 1.29; activated partial thromboplastin time 52.6; Creatinine 1.4 mg/dl. The patient remained in the intensive care unit for approximately 3 weeks and was discharged from the hospital on postoperative day 29.

### Case 2

A 58-yr-old, 100-kg man was admitted for a left carotid endarterectomy and single-vessel coronary artery bypass grafting without CPB. His past medical history was significant for left ventricular ejection fraction 23%, atrial fibrillation, adult-onset diabetes mellitus, chronic renal insufficiency (Cr 1.7 mg/dl), and history of right femoral-popliteal bypass 15 yr earlier complicated by HIT during unfractionated heparin treatment of postoperative deep venous thrombosis and pulmonary embolism. During this episode, he suffered three cerebral vascular embolic infarcts; diagnosis of HIT was confirmed with serotonin-release assay.

Upon presentation, his HIT-antibodies were negative by ELISA. Given his previously significant thrombotic complications, the decision was made by consensus of the hematology, anesthesiology, and surgical services to avoid heparin administration. R-hirudin was selected as the alternative anticoagulant.

On the day of surgery, intravenous and arterial lines were placed, along with a nonheparin-coated pulmonary artery catheter, using saline flushes only. Anesthesia was fentanyl-based, with midazolam, isoflurane, and rocuronium supplementation. Aprotinin was not administered to this patient. Because of his preexisting renal insufficiency, mannitol, renal-dose dopamine (2  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) and furosemide (0.5  $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ) infusions were administered to maintain adequate clearance of r-hirudin through forced diuresis. Hirudin dosing and adjunctive therapies were identical to those administered to patient 1, except that the infusion was stopped just before completing the last anastomosis (total 2.25 h). Additional 5 mg boluses were given on two occasions after the surgeon noted clots on the surgical field. Therefore, although the target r-hirudin plasma concentration was 3  $\mu\text{g}/\text{ml}$ ,<sup>10</sup> which, based on *in vitro* data, would correspond to an estimated PM-ACT value of 200 (fig. 1), the additional doses resulted in a PM-ACT value of 225, or a projected



concentration of greater than  $4 \mu\text{g}/\text{ml}$ . In an effort to later validate the PM-ACT *in vitro* relationship shown in figure 1, additional patient whole blood samples were obtained with each PM-ACT sample for measurements of *ex-vivo* r-hirudin concentrations (fig. 2). The total amount of fluid administered was 1 l of 6% hetastarch, 9 l crystalloid, 2 units of packed red blood cells, and 400 ml cell saver blood to correct for intraoperative blood loss and forced diuresis (urine output of  $6.5 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ).

Upon arrival to the intensive care unit, laboratory values were: hematocrit 33.3%, platelet count 126,000/ml, prothrombin time 16.2 s, and activated partial thromboplastin time 68.2 s. The patient was extubated in stable condition 5 h later. During the first 12 h postoperatively, the patient received 4 more units of fresh frozen plasma for a transient chest tube output of 300 ml in 1 h; cumulative chest tube output was 1,300 ml over 18 h. He was transferred to the telemetry floor on postoperative day 1 and discharged a few days later.

## Discussion

The optimal strategy for managing patients with current or past history of HIT during cardiac surgery is a matter of controversy and continued investigation. This report describes two cardiac surgical scenarios where r-hirudin was used for anticoagulation. They demonstrate that (1) r-hirudin can be used as an alternative to unfractionated heparin, (2) a PM-ACT system can be used to monitor the concentration of anticoagulation, and (3) bleeding may or may not be a serious complication in certain high-risk patients (e.g., repeat cardiac surgical procedures, patients who require reinitiation of CPB, patients with significant renal insufficiency).

Anticoagulation for cardiac surgery was successfully performed in both patients. The r-hirudin dosing schedule was derived from previously published experiences using r-hirudin for cardiac surgery, in an effort to achieve the recommended plasma concentrations of  $4 \mu\text{g}/\text{ml}$  for CPB,  $3 \mu\text{g}/\text{ml}$  for coronary artery bypass grafting without CPB, and  $2 \mu\text{g}/\text{ml}$  for carotid endarterectomy.<sup>4,10</sup> Using previously obtained *in vitro* correlation between PM-ACT values and *ex-vivo* r-hirudin concentrations,<sup>12</sup> additional doses were administered to these patients in an effort to maintain these plasma concentrations. In contrast to unfractionated heparin, r-hirudin does not inhibit platelet activity, therefore prostaglandin  $E_1$ , aspirin, and dipyridamole were administered. The right atrial clot formation that occurred in the first patient may have been related to inadequate anticoagulation of the retransfused blood from the CPB circuit. In the second case, the clots noted on the field were found in static pools of blood outside the patient's body; therefore, the clinical significance of this finding is uncertain. Although the clots were not observed after higher concentrations of r-hirudin were achieved with additional doses, this does not necessarily imply that higher concentrations are needed for cardiac surgery without CPB.

Previous studies have described the ecarin clotting time assay as a reliable method for monitoring r-hirudin doses during CPB.<sup>8,11</sup> However, the ecarin reagents and

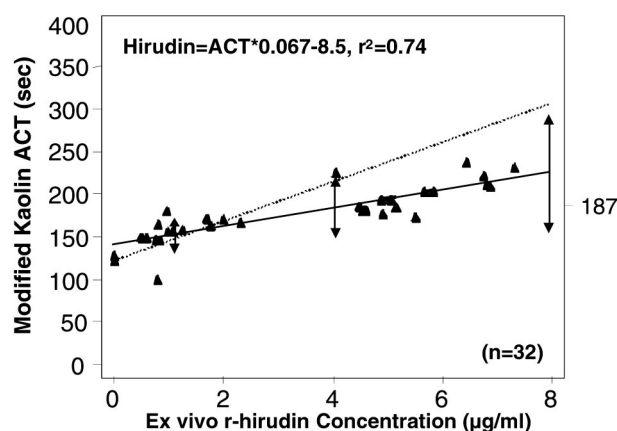


Fig. 4. Plasma-supplemented kaolin activated clotting time (ACT) values versus *ex vivo* r-hirudin concentrations in two patients. The linear relationship is represented with the following linear equation: hirudin concentration = PM-ACT \* 0.067–8.5,  $r^2=0.74$ . The solid horizontal line represents predicted regression line from the *ex vivo* analysis (two patients) whereas the dotted horizontal line represents the predicted line from the *in vitro* analysis. Vertical arrows depict 95% confidence intervals at three concentrations (e.g., 0, 2, 4  $\mu\text{g}/\text{ml}$ ) of hirudin as obtained from the previously published *in vitro* analysis.<sup>12</sup> Although the slope and intercept have changed when *ex-vivo* hirudin concentrations are compared with the calculated *in vitro* concentrations, nearly all PM-ACT data points fall within these confidence intervals.

test system are currently not approved for clinical use in the United States. PM-ACT system uses a currently approved ACT method (Hepcon instrument, Medtronic Perfusion Systems, Minneapolis, MN).<sup>12</sup> By supplementing patient blood specimens with normal plasma in a 1:1 ratio, the PM-ACT corrects for the prolongation in ACT measurements caused by CPB-induced hemodilution of coagulation proteins.<sup>12</sup> In addition, plasma supplementation leads to dilution of circulating plasma r-hirudin and platelet concentrations thus extending the ACT monitoring range, reducing the effect of platelets on the ACT, and facilitating the monitoring of higher hirudin concentrations.

These initial cases have confirmed a linear relationship between r-hirudin plasma concentrations and PM-ACT values (fig. 4). However, in at least these two patients, the PM-ACT values seem to underestimate the *ex-vivo* hirudin plasma concentration as detected by the chromogenic method. This result may be caused by interpatient variability, a limitation of the plasma-supplemented ACT method, or perhaps inaccuracies in measuring hirudin concentrations using the chromogenic method. No standardized method has been currently accepted for measurement of hirudin concentrations, and in the *in vitro* study the concentrations were calculated by dose and not actually measured. Nevertheless, it seems that one can conclude that a reasonable ( $r^2 = 0.74$ ) relationship exists between these two methods, although the relationship (slope and y-intercept) may need adjustment based on this new *ex-vivo* information. Based on the revised

current linear relationship ( $y$ -intercept at  $4 \mu\text{g/ml}$ ), a PM-ACT of 187 s should be used to maintain hirudin concentrations at  $4 \mu\text{g/ml}$ ). Further studies are needed to evaluate the reproducibility of the PM-ACT technique in monitoring r-hirudin concentrations and to determine the optimal therapeutic range of r-hirudin in cardiac surgery patients.

The first patient had significant, life-threatening blood loss in the postoperative period. It is likely that a number of factors contributed to this bleeding, including the repeat operative status and the urgent reinitiation of CPB that resulted in more extensive hemodilution of coagulation factors and platelets. It is unknown whether the residual concentration of r-hirudin contributed to the bleeding. The decline in r-hirudin concentration after cessation of CPB (fig. 2) demonstrates its expectedly short half-life in a patient with normal renal function (approximately 60 min). It is possible, however, that its duration of action, or context sensitive half-time, exceeded the pharmacokinetic half-time and thus contributed to the bleeding. This experience prompted the use of forced diuresis in the second patient who had mild renal insufficiency, on the basis that the risk of bleeding increases as renal function decreases.<sup>9</sup>

The severe bleeding of patient 1 must be recognized as a potential problem for all patients when using r-hirudin as an alternative coagulant, given the lack of an antidote for this agent. While minimal blood loss has been described in several relatively small series of cardiac surgical patients treated with r-hirudin during CPB,<sup>4</sup> other reports also indicate that blood loss may be considerable. None have described blood loss as severe as that described with our patient.<sup>6,8</sup> Other newer therapies, like bivalirudin, which have a shorter biologic half-life (*i.e.*, 30 min) may be advantageous with respect to minimizing bleeding in this clinical setting. On the other hand, inadequate anticoagulation in cardiac surgical patients could lead to potentially fatal thrombosis. These potential complications highlight the critical importance of point-of-care monitoring, such as

with PM-ACT or ecarin clotting time testing, to achieve and maintain therapeutic r-hirudin concentrations and yet avoid overdose.

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## Doxorubicin-induced Cardiomyopathy during Pregnancy: Three Case Reports of Anesthetic Management for Cesarean and Vaginal Delivery in Two Kyphoscoliotic Patients

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WITH childhood cancer survival rates on the rise, increasing numbers of female pediatric cancer patients are reaching childbearing age. The long-range effects of childhood chemotherapy can have significant clinical implications for these women. The toxicity of an anti-neoplastic drug given to the pediatric patient may not be fully apparent until other physical conditions in adulthood, such as pregnancy, force the issue. Pregnancy imposes significant physiologic changes and cardiovascular stress. The cardiotoxicity of one chemotherapeutic agent in particular, doxorubicin, is frequent in young females, potentially severely limiting myocardial growth in childhood, leading to a lifelong reduction in myocardial mass, which may result in a significantly decreased cardiac reserve in the child as she grows.<sup>1,2</sup> Pregnancy can unmask the cardiovascular damages caused by doxorubicin even from the remote past in otherwise asymptomatic patients. When these women require an anesthetic for vaginal or cesarean delivery, anesthesiologists should be aware of the possibility of cardiac failure, even in asymptomatic pregnant patients, if they have previously been treated with doxorubicin.

The interaction of the long-term cardiotoxic effect of doxorubicin with pregnancy and anesthetic management has not been well described. We present two cases in which regional anesthesia, particularly combined spinal-epidural (CSE) technique, was used successfully for cesarean delivery and vaginal delivery in kyphoscoliotic patients with doxorubicin-induced cardiomyopathy. To our knowledge, this is the first report of the successful use of epidural and combined spinal-epidural technique in kyphoscoliotic pregnant patients with doxorubicin-induced cardiomyopathy presenting during pregnancy.

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### Case Reports

#### Case 1

A 35-yr-old kyphoscoliotic woman, primigravida, at 36 weeks of gestation with fetal breech presentation was admitted to the intensive care unit (ICU) for pulmonary edema and congestive heart failure. Her medical history was significant for osteosarcoma, which was treated with left hemipelvectomy and intravenous doxorubicin 20 yr earlier. She was active and asymptomatic with good exercise tolerance until 28 weeks of gestation, when she developed shortness of breath and dyspnea. Echocardiography revealed moderate mitral regurgitation and a 30% ejection fraction, which was improved with digoxin 0.25 mg/day. By 36 weeks of gestation, her clinical status deteriorated and led to this ICU admission. Repeated echocardiography revealed an ejection fraction of 10%, mild mitral and moderate tricuspid regurgitation, dilated ventricles with systolic dysfunction, and mild pulmonary hypertension. She improved clinically with diuresis, but required maximum doses of milrinone ( $0.75 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) and dobutamine ( $15 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) to maintain her hemodynamic stability. She later required the switching of dobutamine to dopamine infusion ( $10\text{--}15 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) and the addition of lidocaine infusion (1 mg/min) to control ventricular dysrhythmias. To prevent cardiovascular deterioration, a semiurgent cesarean section was planned. In the ICU, her pulmonary artery catheter revealed CO of  $3.5\text{--}4.2$  l/min, systemic vascular resistance of  $950\text{--}1550$  dynes $\cdot\text{s}\cdot\text{cm}^{-5}$ , central venous pressure of 13-16 mmHg, PAS of 40 to 50 mmHg, PAD of 20 to 36 mmHg, and pulmonary capillary wedge pressure of 16-18 mmHg. Her blood pressure was 115/60 with a sinus tachycardia rate of 130, and her oxygen saturation was 96-98% while on 6 l/min of oxygen by nasal cannula. A low dose combined spinal epidural technique was performed (intrathecal 0.8 ml of hyperbaric 0.75% bupivacaine, 25  $\mu\text{g}$  fentanyl, and 50  $\mu\text{g}$  epinephrine, then followed by titrating epidurally 9 ml of 2% lidocaine with epinephrine). With a bilateral sensory anesthesia level of T5, she was maintained in a semiupright position of 30° throughout the epidural dosing and the surgical procedure to allow better spontaneous ventilation and to limit the upper cephalad spread of the intrathecal local anesthetic. She received 150 ml of 25% albumin during and after the placement of the combined spinal-epidural anesthetic. In addition to inotropes, she also required small amounts of phenylephrine (20  $\mu\text{g}$  increments, total of 120  $\mu\text{g}$ ) after the delivery of the fetus to correct hypotension. The patient and the fetus tolerated the anesthetic and surgical procedure with no complications and with an estimated blood loss of 1,400 ml. The patient was delivered of a live infant of 2,840 g with 1 and 5 min APGAR scores of 9. She received epidural patient-controlled analgesia with fentanyl for postoperative pain management. She was weaned off inotropes in 24-48 h and discharged without complications on the third postpartum day with oral digoxin and captopril. At her 6-week postpartum visit, she remained asymptomatic and had no other complications.

#### Case 2

A 31-yr-old kyphoscoliotic woman, G2P1, at 35 weeks of gestation was admitted to our hospital with progressive shortness of breath. Her

medical history was significant for Ewing's sarcoma at age 16, which was treated with intravenous doxorubicin and resection of her right clavicle. She had been active and asymptomatic until the fifth postpartum day after her first vaginal delivery at age 24, at which time she developed pulmonary edema with an ejection fraction of 35%. She recovered uneventfully with ejection fraction improved to 40–45% after receiving diuresis and vasodilator. She remained asymptomatic for 4 yr until the thirty-fifth week of gestation of her second pregnancy when she developed pulmonary edema. Echocardiography showed a decreased ejection fraction of 35%, mild pulmonary hypertension, mild tricuspid and mitral regurgitation, biatrial enlargement, a dilated right ventricle, and a hypokinetic left ventricle. She responded well and improved upon diuresis. An epidural catheter was placed with moderate technical difficulty during her labor induction. A low concentration epidural local anesthetic (0.125% bupivacaine) with fentanyl (1.5  $\mu\text{g}/\text{ml}$ ) was administered successfully for early labor analgesia. A significantly higher volume and concentration of a local epidural anesthetic and narcotic was required for the later stage of labor. A healthy infant with APGAR scores of 9 was delivered uneventfully. The patient remained asymptomatic until her third pregnancy 4 yr later.

### Case 3

The above patient, at age 35, G3P2, (19 yr from doxorubicin chemotherapy) at 35 weeks of gestation was admitted to our hospital with the diagnosis of pulmonary edema and ejection fraction of 25%. She responded well and improved upon diuresis, and induction of labor was initiated. Based on her positive fluid balance, no preload was administered before anesthetic. A combined spinal-epidural (CSE) technique was used to administer intrathecal sufentanil 7.5  $\mu\text{g}$ , 1.25 mg bupivacaine, and 50  $\mu\text{g}$  epinephrine. She did not develop hypotension. A healthy infant was delivered uneventfully with normal APGAR scores. At her 6-week postpartum visit, she remained asymptomatic without complications.

## Discussion

The anthracycline chemotherapeutic agents, doxorubicin (Adriamycin) and daunorubicin (Cerubidine) intercalate with DNA, affecting DNA and RNA synthesis. The anthracyclines react with cytochrome P450 reductase in the presence of reduced nicotinamide adenine dinucleotide phosphate (NADPH) to form semiquinone radical intermediates, which in turn react with oxygen to produce superoxide anion radicals (OH). These radicals are highly destructive to cells, including myocytes. Several clinical presentations of doxorubicin-induced cardiotoxicity, including atrial and ventricular dysrhythmias, a pericarditis-myocarditis syndrome, acute hypertensive reactions, cardiovascular collapse, and death during and after administration of anesthetics, have been described in nonpregnant patients.<sup>3,4,5</sup>

Pregnancy is accompanied by a significant blood-volume expansion, an increase in metabolic demands, dilution anemia, and alterations in vascular resistance that are associated with ventricular dilatation and increases in cardiac output.<sup>6</sup> A patient treated with doxorubicin in childhood may have a significantly reduced myocardial mass and decreased cardiac reserve, but may remain asymptomatic, developing heart failure for the first time

during pregnancy, especially during the third trimester and the immediate postpartum period when the cardiac output requirement and demand are highest. Both patients reported here had been asymptomatic and active with good exercise tolerance for many years after doxorubicin therapy. Only in their third trimesters of pregnancy did they experience any cardiac symptoms.

In pregnant patients with cardiomyopathy alone, the optimum anesthetic technique for cesarean section is controversial, and both general and regional anesthesia techniques have been described.<sup>7–10</sup> Even more challenging, however, is performing a rapid sequence induction on a pregnant kyphoscoliotic patient with severely compromised cardiac function. It can be potentially detrimental to both mother and fetus. Several authors have reported perioperative cardiovascular collapse, and complications, and even death in nonpregnant patients who previously received doxorubicin who are administered general anesthesia.<sup>3–5</sup> McIncoe reported a case of peripartum cardiomyopathy presenting as a cardiac arrest at induction of general anesthesia for cesarean section.<sup>11</sup> A retrospective analysis carried out in the United States from 1979–1990, showed that most maternal deaths resulting from anesthesia-related complications occurred during general anesthesia for cesarean section.<sup>12</sup> Furthermore, the risk ratio for general anesthesia had increased to 16.7 times that for regional anesthesia. A controlled afterload reduction by regional anesthesia may be beneficial for patients with low cardiac output.

Our first patient presented an unusual combination of anesthetic considerations: severe doxorubicin-induced cardiomyopathy, thoracolumbar kyphoscoliosis, and previous hemipelvectomy, in addition to the physiologic changes of pregnancy. We chose combined spinal-epidural (CSE) technique for the cesarean delivery because (1) CSE avoids the risk of general anesthesia, particularly its cardiac depressive effects in this patient with doxorubicin-induced cardiomyopathy; (2) CSE allows the use of a lower initial dose of intrathecal local anesthetic and a gradual setup of the final desired anesthetic level by titrating a small amount of epidural drug, thereby minimizing hypotension or hemodynamic changes and lowering the maternal and umbilical cord blood concentration of local anesthetics,<sup>13</sup> all of which are critical for a patient with severe cardiomyopathy; (3) CSE allows flexibility for the duration of anesthesia, especially in potentially difficult surgical cases, such as this patient with a previous hemipelvectomy; (4) CSE allows postoperative use of epidural patient-controlled narcotics for postoperative pain management to minimize hemodynamic changes, postoperative stress, and respiratory depression of systemic narcotics; (5) CSE provides a denser quality of sensory block than epidural anesthetic alone and it has a lower failure rate *versus* epidural alone,<sup>13,14,15,16</sup> especially in kyphoscoliotic patients, by the clear identification and confirmation of the intrathecal space and possibly the epidural space as well.

For this patient, we chose a low initial dose (6 mg) of intrathecal bupivacaine administered in the sitting position to minimize rapid cephalad spread and hypotension, and to provide dense anesthesia for the lower dermatomal level to approximately T10 sensory level, where the predominate part of the surgery took place. No vasopressor was needed during the establishment of the anesthetic block, and only a small amount of vasopressor was needed at the latter part of the surgery after the delivery of the fetus.

When the second patient presented for her third delivery, we also performed a CSE technique for many of the same reasons discussed above, especially because of the potential for diminished efficacy of the epidural during the later stage of her first labor anesthetic. Continuous spinal technique is also a possible option for these patients.<sup>17</sup> The major disadvantage, particularly in the obstetric population, is the high potential for post-dural puncture headache and difficulty in performing an epidural blood patch if subsequently required.

It is important for anesthesiologists to be aware of the possibility of cardiac failure in asymptomatic pregnant patients previously treated with doxorubicin even in the remote past. We believe that the administration of epidural and combined spinal-epidural anesthesia to patients with doxorubicin-induced cardiomyopathy for cesarean or vaginal delivery can be done safely with excellent outcomes and stable hemodynamics if it is performed with precision and meticulous attention to details in intravascular volume, anesthetic block level, drug dose, and hemodynamics.

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## Weaning from Mechanical Ventilation in a Neurologic Disease: An Unusual Application for Tracheal Gas Insufflation

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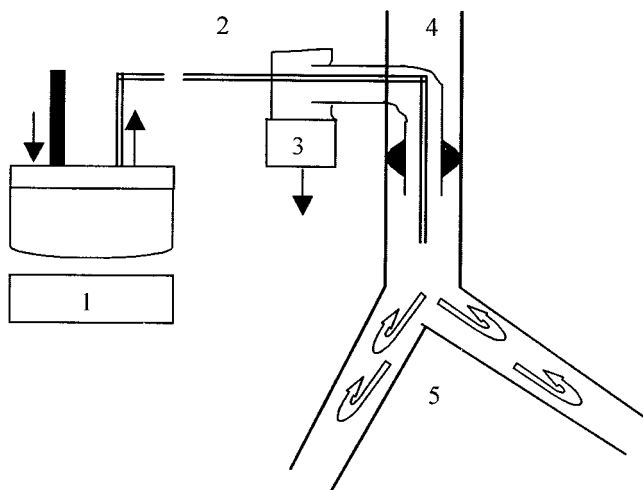
RESPIRATORY failure caused by central nervous system (CNS) disease necessitates prolonged mechanical ventilation. Some patients with neurologic conditions requiring mechanical ventilation (*i.e.*, Guillain Barré syndrome, myasthenia gravis) show spontaneous recovery or adequate response to therapy, so that the

patient can be successfully weaned off from mechanical ventilation.<sup>1,2</sup> However, a small number of patients with degenerative CNS diseases are difficult to wean from mechanical ventilation, and as a result occupy intensive care beds or require home ventilation, both of which are expensive.<sup>3</sup> In most of these patients, the respiratory effort is at least partly preserved, but is insufficient to maintain adequate carbon dioxide elimination. Measures that augment elimination of carbon dioxide from the anatomic dead space might be helpful. Tracheal gas insufflation (TGI) has been used in acute respiratory distress syndrome to facilitate carbon dioxide elimination.<sup>4</sup> The authors used the principle of TGI to wean a patient with very feeble spontaneous respiratory efforts caused by se-

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**Fig. 1.** A schematic diagram of the tracheal gas insufflation system used for weaning: (1) humidifier; (2) gas insufflation catheter; (3) short catheter mount open to atmosphere; (4) tracheostomy tube; (5) carina.

vere central nervous system disease from mechanical ventilation.

### Case Report

A 10-yr-old girl weighing 24-kg was admitted to our hospital with an 8-day history of fever, headache, and vomiting, and a 3-day history of depressed consciousness and convulsions. Her Glasgow Coma Score (GCS) was 6. A diagnosis of Japanese encephalitis was made on the basis of a computed tomographic (CT) scan and serologic examinations. Her neurologic and respiratory function deteriorated over 12 h, necessitating tracheal intubation and mechanical ventilation. At the time of her admission to the intensive care unit (ICU), her respiratory efforts were minimal. She had a heart rate of 100 beats/min and a blood pressure of 110/60 mmHg. Her lungs were ventilated using a Dräger Evita II-Dura<sup>®</sup> ventilator (Dräger Medizintechnik GmbH, Lübeck, Germany) in a BIPAP mode. Her arterial blood gases during ventilation at an  $F_{iO_2}$  of 0.5, and a minute volume of 5.6 l/min showed a  $P_{aO_2}$  of 150 mmHg and a  $P_{aCO_2}$  of 32 mmHg. By day 25, her spontaneous respiratory effort improved marginally to the extent that she could consistently initiate spontaneous breaths at a frequency of 15–20 breaths/min and a minute volume of 5.3–6.0 l/min, while being ventilated in a continuous positive airway pressure mode with an end-expiratory pressure of 10 cm  $H_2O$ , a pressure support of 12 cm  $H_2O$ , an  $F_{iO_2}$  of 0.5, and a flow trigger of 3 l/min. An attempt at weaning by T-piece trial at this point was aborted as her respiratory rate increased to

greater than 60 breaths/min and her  $Sp_{O_2}$  decreased to less than 90% in 5 min. T-piece weaning trials were conducted and aborted on four different occasions over the next 5 weeks.

After 2 months of ICU stay, the patient's spontaneous respiratory effort continued to be very feeble with tidal volumes unrecordable by a spirometer because of very low flows. During T-piece trials, her arterial oxygenation could be maintained with increased  $F_{iO_2}$ , but arterial  $P_{CO_2}$  increased rapidly. At this stage, tracheal gas insufflation (TGI) was considered an option to decrease her  $P_{aCO_2}$  values so that she could be weaned from mechanical ventilation. A schematic representation of the system used for TGI is shown in figure 1. A 2-mm ID polyvinyl chloride catheter was passed through the suction port of the tracheostomy tube catheter mount (open to atmosphere) so that its tip was just above the carina. Oxygen was administered through this catheter at a rate of 3 l/min after humidification using a heated humidifier (MR 428<sup>®</sup>, Fisher and Paykel, Auckland, New Zealand) maintained at 35–37°C. Her respiratory rate was 15–20 breaths/min while she was on the ventilator with a CPAP of 10 cm  $H_2O$  and a pressure support of 12 cm  $H_2O$ . It increased to 50–60 breaths/min while she was on spontaneous breathing without TGI but decreased to 30–35 breaths/min on spontaneous respiration with TGI. Arterial blood gases on the TGI system were found to be acceptable at 30 and 90 min when compared with those on a 30-min T-piece trial just before the TGI trial (table 1). Over the next 11 days, weaning trials with this system were continued during the day with progressively longer periods of TGI. Chest physiotherapy and tracheal suctioning were carried out frequently to prevent retention of secretions and development of atelectasis. Her arterial oxygen saturation was greater than 95% throughout her course. There was no evidence of drying of tracheobronchial secretions or formation of mucus plugs. The TGI system was removed during tracheal suction to avoid its interference with clearance of secretions. On day 72, the patient was weaned off from mechanical ventilation totally. On day 75, she was transferred out of the ICU on TGI with an airflow of 3 l/min.

### Discussion

Tracheal gas insufflation has been used to promote carbon dioxide elimination in severe acute respiratory distress syndrome requiring mechanical ventilation with high airway pressures.<sup>4,5</sup> A recent study reported a decrease of  $P_{aCO_2}$  by  $28 \pm 11\%$  when TGI was used during mechanical ventilation at low-tidal volumes that would have increased the  $P_{aCO_2}$  at a rate of 0.5–1.5 mmHg/min.<sup>6</sup> In the current patient with minimal respiratory effort, in whom  $P_{aCO_2}$  increased at a similar rate during spontaneous breathing (table 1), we used the principle of TGI to facilitate weaning from mechanical ventilation.

**Table 1.** Arterial Blood Gas Values before and during Different Phases of Weaning

	At the Beginning of TGI*				Day 15 of TGI‡
	On Ventilator (baseline)†	30 min of T Piece Trial	30 min of TGI Weaning	90 min of TGI Weaning	
pH	7.42	7.29	7.33	7.39	7.35
$P_{aO_2}$ (mmHg)	149	247	72	81	82.7
$P_{aCO_2}$ (mmHg)	32.5	53.6	43.8	38	32.4
$HCO_3^-$ (mm)	21	25	22.5	22.7	18.3
ABE (mm)	-2.1	-2.1	-3.2	-1.6	-4.6
$Sa_{O_2}$ (%)	99	99.6	93	95	95

\* Blood gas on TGI with oxygen; †  $F_{iO_2}$  0.5 and min volume 5.6 l/min; ‡ blood gas with TGI on air.

TGI = tracheal gas insufflation; ABE = actual base excess.

Functionally, the system used in the current case is similar to that of continuous flow TGI. The mechanism of carbon dioxide elimination by TGI mainly involves washout of carbon dioxide from the anatomic and apparatus dead space during the expiratory phase.<sup>7,8</sup> In continuous flow TGI systems used in combination with mechanical ventilators, the insufflation flow occurring during the inspiratory phase of the ventilator also augments the inspired tidal volume. However, in our patient, the contribution of the insufflation flow to the inspired tidal volume may not be significant, because she was breathing spontaneously through a tracheostomy tube open to atmosphere without any valves. Therefore, we propose expiratory washout as the major mechanism of carbon dioxide washout in her, even though gas insufflation was provided both during inspiratory and expiratory phases. Limiting the insufflation to expiratory phase during TGI with mechanical ventilation decreases peak inspiratory pressures and the need for humidification of insufflation gases.<sup>9</sup> We could not restrict the insufflation to expiratory phase, as there is no device that provides expiratory washout in a spontaneously breathing patient.

The effect of various flows of insufflation and various positions for catheter tip on the efficacy of carbon dioxide elimination has been investigated earlier.<sup>10,11</sup> Gas exchange was found to be best when the catheter tip was at 1 cm above the carina and the insufflation flow was 6 l/min.<sup>10</sup> In our patient, a fresh gas flow of 3 l/min washed out the carbon dioxide adequately so that the patient's PaCO<sub>2</sub> normalized even though her spontaneous respiratory efforts continued to be feeble. Insufflation flows ranging from 2–15 l/min have been used in various TGI trials.<sup>12</sup> The majority of these studies pertain to the adult population. A flow rate of 0.5 l/min was used in studies in neonates.<sup>13</sup> The drawbacks of high flow TGI used in combination with mechanical ventilation are high peak airway pressures and adverse effects on hemodynamics. These complications, however, are not applicable to our patient who received TGI without a mechanical ventilator through a tracheostomy tube open to the atmosphere. The fact that the patient's PaCO<sub>2</sub> was 32.4 mmHg on D15 of weaning suggests that adequate carbon dioxide elimination probably could have been achieved with lower insufflation flows with appropriate positioning of the catheter tip.

The flow used in the current study is likely to have increased the patient's resistance to spontaneous expiratory flow, as has been documented in earlier studies.<sup>6,7,11</sup> However, we cannot comment on the extent of its influence on the patient's spontaneous respiration, because we did not measure the inspiratory and expiratory flows with or without TGI during spontaneous breathing.

Humidification is a major concern during TGI. High flows of dry gases impinging directly on the tracheo-

bronchial mucosa may cause drying of secretions leading to formation of mucus plugs. In the current case, we prevented this complication by humidifying the insufflation gases by using a heated humidifier.

Patients with severe irreversible neurologic diseases may pose problems of weaning from mechanical ventilation because of decreased respiratory drive or decreased neural and neuromuscular transmission.<sup>14,15</sup> The success of the TGI technique with our patient suggests that it may be useful in patients with neuromuscular diseases on permanent tracheostomy requiring mechanical ventilation during a part of the day. Conventionally, these patients are managed by home ventilation, which is expensive and technically difficult to manage. In a hospital setting, the current technique helps to mobilize patients with severe irreversible neuromuscular diseases out of the ICU. Maintenance of sterility of the catheter and good chest physiotherapy to clear the secretions are important requirements of this technique.

In conclusion, we report a patient with severe respiratory insufficiency caused by central nervous system disease who was successfully weaned from mechanical ventilation using the principle of TGI.

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