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A 17-Year-Old Female With Respiratory Depression as a Result of Opioid Overdose

A 17-year-old female was found by her boyfriend unresponsive after a party at a friend's house. She was last seen normal at 03:00 hours; she had been seen drinking vodka and taking hydrocodone/acetaminophen (Vicodin; Abbott Laboratories, Abbott Park, IL). Her boyfriend found her 7 hours later unresponsive lying in bed. She was taken via private vehicle to a local emergency department. Upon arrival, she was noted to have pinpoint pupils with agonal respirations. She was administered naloxone (Narcan; Amphastar Pharmaceuticals, Inc, Rancho Cucamonga, CA) 2 mg intravenously with no improvement in respirations. Because of her unchanged respiratory status, she was subsequently intubated using rapid sequence intubation techniques. The patient was previously healthy but per her family did have a social history significant for illicit drug and alcohol abuse. She was not on any home medications and had no allergies noted.

Her initial vital signs showed a rectal temp of 86°F, systolic blood pressure in the 60s to 80s, and agonal respirations with a rate of 6 breaths per minute. Her oxygen saturation was 78%. When hemodynamic monitoring was initiated, staff noted that her heart rate was 130 beats per minute in rapid atrial fibrillation. The outlying facility was able to obtain intravenous access, and they administered 4 L normal saline for her hypotension. Her physical examination was notable for a Glasgow Coma Score of 5 (verbal = 1, eye = 1, and motor = 3), cyanotic mucous membranes, and pupils that were 3 mm and sluggish to light bilaterally. Periorbital edema was also noted. Her respiratory examination was notable for bilateral crackles with diminished breath sounds globally. She occasionally flexed her arms and legs without purpose, but the remainder of her muscle tone was normal. No tremors were noted. Capillary refill was delayed at 4 seconds distally, but peripheral pulses in the upper and lower extremities were faint but present.

After gaining peripheral access, laboratory values were drawn, and vasopressors (including norepinephrine) were initiated to treat her noted hypotension that was refractory to crystalloid therapy. She was placed on a lorazepam (Ativan; West-Ward Pharmaceuticals, Eatontown, NJ) drip for sedation. Initial blood gases showed significant acidosis, and, therefore, she was administered multiple bolus doses of sodium bicarbonate.

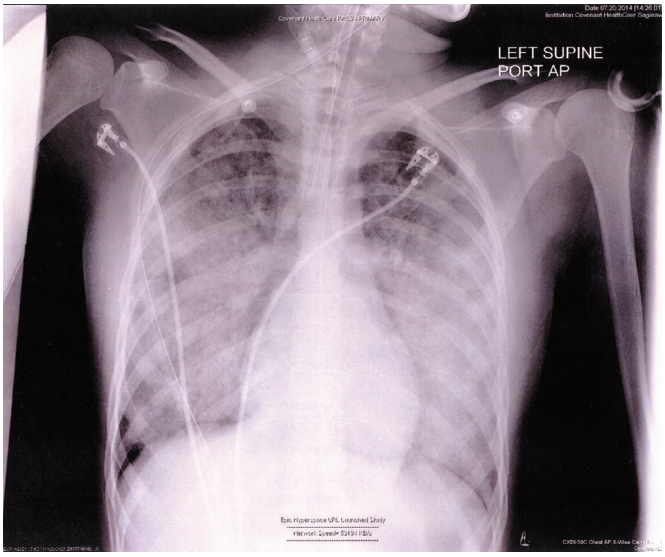
She was then transferred by a local air medical helicopter service for a higher level of care because she would require pediatric intensive care support, which was not available at the outlying facility. Upon flight crew arrival, there was concern for flash pulmonary edema given the rales and the pink frothy sputum being copiously suctioned from the endotracheal tube. Fluids were discontinued, and she was administered 20 mg furosemide intravenously (Lasix; Sanofi-Aventis US LLC, Bridgewater, NJ). The initial mechanical ventilation settings consisted of a rate of 10, a volume of 800, fraction of inspired oxygen of 100, and positive end-expiratory pressure (PEEP) of 5. However, the patient was noted to be hypoxic en route, and thus multiple changes to the ventilation settings were made by flight crew staff after discussion with medical control, including a gradual increase in PEEP to 15 and a decrease in tidal volume to 450 mL.

Upon arrival to the receiving facility, the patient continued to have difficulty maintaining appropriate oxygen saturations. She was taken off mechanical ventilation and was manually ventilated by a bag mask in the emergency department. Central access was obtained, and a bedside ultrasound was performed. It was evident that there was decreased cardiac contractility, which was contributing to the rapidly developing pulmonary edema that was noted on a chest x-ray (Fig. 1). The pediatric intensivist was at the bedside and recommended initiating an epinephrine drip to help improve contractility and subsequently hypotension.

At the tertiary center, a repeat laboratory evaluation was completed. The patient had an elevated troponin of 4.65 ng/mL, lactate of 8.8 mmol/L, elevated d-dimer, and decreased fibrinogen. A urine drug screen was positive for opiates. Acetaminophen and salicylate levels were negative. Her blood alcohol level was 0.11 g/dL. Imaging was completed including a computed tomographic scan of the head, which did not show any acute intracranial abnormalities. An electrocardiogram showed sinus tachycardia (Fig. 2).

The patient was then admitted to the pediatric intensive care unit where she was placed on high-frequency oscillatory ventilation (HFOV) and administered nitric oxide. Unfortunately, the patient did not tolerate these adjuncts and needed to be ventilated with a bag mask. Because of her persistent hypotension and hypoxia, the decision was made to transfer this patient to a facility that had the capability of performing extracorporeal membrane oxygenation (ECMO). At this time, transfer protocols were initiated, but in the meantime the patient continued to receive immediate resuscitation. In light of her continued profound hypotension that was associated with decreased contractility, a milrinone (Primacor, West-Ward Pharmaceuticals) drip was initiated. A formal echocardiogram performed at bedside did show a noticeable improvement in contractility. Still, the patient remained in physiologic extremis so she was further resuscitated by optimizing all other parameters including the

Figure 1. A portable chest x-ray of a 17-year-old female presenting with an acute polypharmacy overdose.



administration of 2 g 25% albumin and the administration of 1 g calcium chloride for her hypocalcemia.

Her pulmonary edema began to improve, and she tolerated being placed on mechanical ventilation with a PEEP of 16 to assist with oxygenation. Finally, the patient was given 2 g ceftriaxone (Rocephin; Roche Laboratories, Pleasanton, CA) to empirically cover for respiratory pathogens as well as 2 g methylprednisolone (Solu-Medrol; Pfizer, Kalamazoo MI). The patient was transferred to an ECMO facility.

Discussion

The pathophysiology of respiratory depression caused by opioid use is clearly identified well in the emergency medical services community and is a commonly seen and treated condition. However, the subsequent link between opioids and cardiogenic shock is seen less frequently and is not well established. The pathophysiology is very likely multifactorial and is without a single mechanism of action.

The state of hemodynamic "shock" has been defined as any condition that results in inadequate tissue perfusion and is classified into many subcategories. To be considered cardiogenic in etiology, there must be evidence of tissue hypoxia with decreased cardiac output with adequate intravascular volume.[1,2] Irrespective of the etiology, cardiogenic shock occurs when the heart fails to act as a forward pump; the consequences of which are numerous and, if severe enough, can be irreversible.

In the absence of structural heart abnormalities, cardiogenic shock in the pediatric population has 2 major etiologies, myocarditis and toxic ingestion.[2] Toxic ingestion includes a multitude of agents, but in this case alcohol and prescription opioids were implicated. Central nervous system depression is a documented effect of both alcohol and opioids and was likely the largest contributing factor. This event incited a cascade of effects leading to cardiac failure.

Opioids bind to receptors in the brainstem triggering suppression of leading basic physiologic functions including respiration, heart rate, and mentation.[3] This effect is amplified by the concomitant ingestion of alcohol.[4] Additionally, once ingested, it can bind directly to cardiac myocytes, leading to an alteration of cardiac contractility. The toxic effects of opiates are dose dependent, with an initial increase in cardiac contractility at low doses. However, as the dose increases, there is an overall decrease in contractility and heart rate.[5-7,9,10] Dilation of venous and arterial vasculature can lead to decreased blood pressure, which is also mediated by the effect of opioids. The mechanism of this effect is less clear and likely multifactorial. In healthy individuals at appropriately prescribed doses, the combined central and direct effects of opioids on cardiovascular function are unlikely to cause overt pump failure leading to cardiogenic shock. However, as the dosages increase, side effect effects are more pronounced. Unless reversed immediately, a cascade of sequelae can lead to irreversible devastating effects.

As cardiac contractility declines, the ability of the heart to eject blood forward into the arterial vasculature will decrease, leading to an increase in end-systolic ventricular volumes. This in turn will produce an increase in ventricular end-diastolic volume and pressure because of the fact that there is a larger amount of volume in the ventricle that is not "pumped forward." By virtue of the increase in this volume, this too will lead to an increase in stretching of the myocardium. In healthy individuals, an increase in contractility via Frank-Starling forces would occur to rectify this issue; however, in the setting of opioid overdose, the physiological response is inhibited because of a variety of factors including hypoxia.

In order for the compensatory mechanism to correct the loss of contractility, there must be an adequate oxygen supply. Unless corrected, the decreased contractility will lead to an increase in vascular back pressure, resulting in cardiogenic pulmonary edema (left-sided heart failure) and eventually anasarca (right-sided heart failure). As pressure increases, intravascular pressure alters fluid dynamics and leads to extravasation of fluid from the vascular space to the intercellular space often referred to as "third spacing."

Mixed venous blood returning to the heart typically has an oxygen saturation of about 75%. As cardiac output falls, blood flow to tissues also slows. This subsequently causes a fractional increase in oxygen extraction, which in turn decreases mixed venous oxygen saturation (even more pronounced lower oxygen saturations). With lower venous saturations, there is an additional need to reoxygenate the venous blood. However, because of the pulmonary edema, the ability of blood to be oxygenated is limited. A pulmonary shunt has been noted to lead to additional hypoxemia, thus worsening the physiologic situation.

As the lack of available oxygen worsens and tissue hypoxia ensues, sympathetic stimulation is triggered. This leads to an increase in cardiac contractility and rate, renal compensation,