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# Angiotensin II for Near Drowning: A Case Series

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**OBJECTIVE:** This case series describes the effect of angiotensin II administration on hemodynamics in patients with parenchymal lung injury due to submersion injury.

**CASE SUMMARY:** A 33-year-old female and a 72-year-old female were both brought to the emergency department after incidents of near drowning. Upon arrival to the emergency department, both patients were hemodynamically unstable and were eventually intubated for airway protection. Imaging done by conventional chest radiograph for both patients revealed bilateral pulmonary edema. Due to their hemodynamic status, vasopressors were initiated for both patients and were quickly titrated, leading to the initiation of angiotensin II. In one patient, angiotensin II was initiated early in shock and resulted in rapid improvement of hemodynamics. In the other patient, angiotensin II was initiated later and a more muted response was observed.

**CONCLUSIONS:** In patients with near drowning, angiotensin II appeared to improve hemodynamic status rapidly. This is the first case series to report the use of this new vasoactive agent in this population and poses noteworthy mechanistic considerations.

**KEY WORDS:** angiotensin II; case series; hemodynamics; near drowning; parenchymal lung injury; submersion injury

Hemodynamic compromise following near-drowning events leads to significant morbidity and mortality (1). Drowning accounts for over 4,000 deaths in the United States each year with near-drowning submersion injuries affecting up to 400,000 individuals (2–4). Drowning is often described in five stages including surprise, breath holding, hypoxic convulsion, unconsciousness, and clinical death (5). Reflex inspiratory efforts lead to aspiration and reflex laryngospasm, causing hypoxemia, hemodynamic instability, and multiorgan failure (4, 6–8). Cold water submersion results in "cold diuresis," wherein blood shifts to the core via increased venous return from peripheral vasoconstriction. As a result, central volume receptors detect fluid overload and signal for the decreased production of antidiuretic hormone, leading to hypovolemia, hypotension, and shock, thus worsening instability (9).

The renin-angiotensin-aldosterone system (RAAS) plays an important role in the physiologic regulation of blood pressure and fluid balance and may be altered in submersion injuries due to its role in pulmonary tissues and acute lung injury (10). Local renin-angiotensin systems (RASs) have been described in most organ systems with angiotensin II (ATII) having a different effect on each system (11). In the pulmonary RAS, levels of the angiotensin-converting enzyme 2 enzyme, which converts ATII into angiotensin 1-7, and the angiotensin 2 receptor have been found to be protective against acute lung injury



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induced by aspiration or sepsis, which may have important ramifications in near-drowning. Angiotensin-converting enzyme (ACE), ATII, and the angiotensin 1 receptor, on the other hand, have been associated with pulmonary edema (11, 12).

In 2017, the U.S. Food and Drug Administration approved the use of synthetic ATII to treat hypotension resulting from distributive shock (13). Given the potential interaction between submersion injury and the RAAS and pulmonary RAS systems, exogenous ATII therapy may benefit patients suffering from nonfatal drowning. In this case series, we describe ATII use in two patients with acute respiratory failure and shock secondary to submersion injuries. The McLaren Northern Michigan institutional review board (IRB) was consulted on August 28, 2020, and it was determined that IRB policy does not require written consent for this report.

## Patient Case 1

A 33-year-old Caucasian female (weight 54.7 kg, height 150 cm) with a history of nonverbal autism and seizure disorder was found by her father in 6 feet of water at the end of a dock. The father believed she was under water for less than 5 minutes. After retrieving her from the water, she was coughing up sputum and appeared to be in distress. A Heimlich-type maneuver was performed, which resulted in expulsion of a significant amount of water. The patient was transported by her father to the hospital where she walked into the emergency department (ED) independently.

Upon arrival, the patient's vital signs were: blood pressure 98/62 mm Hg (mean arterial pressure [MAP] 74 mm Hg), pulse oximetry 55% on room air, heart rate 79 beats/min, respiratory rate 41 breaths/min, and temperature 36.4°C. Arterial blood gas (ABG) showed pH 7.32, $P_{CO_2}$ 51 mm Hg, and $P_{O_2}$ 17 mm Hg on 100% nonrebreather mask. Chest radiography showed bilateral patchy airspace opacities indicative of pulmonary edema. She was placed on bilevel positive airway pressure and exhibited further deterioration over the next 30 minutes, with oxygen saturation in the 80s. A repeat ABG revealed a $Pao_2$:$FIO_2$ ratio of 85, suggestive of severe acute respiratory distress syndrome (ARDS). The intensivist service was notified, and the patient was intubated in the ED. Bronchoscopy was performed, and she was transferred to the ICU for further management.

After admission to the ICU, the patient quickly became hypotensive with a MAP of 46 mm Hg (decreased from 93 mm Hg 15 min prior), and she was initiated on IV fluids at 200 mL/hr at 23:00 and on norepinephrine at 0.01 μg/kg/min at 23:30 on hospital day 1 (2 hr 28 min after presentation to the ED). Ampicillin/sulbactam 3 g every 6 hours was initiated for suspected aspiration pneumonia. Increasing doses of norepinephrine were required, and the patient was briefly trialed on dobutamine due to a central venous oxygen saturation ($Scvo_2$) of 59%, which was quickly stopped due to tachycardia. Vasopressin 0.04 units/min was added at 4:04 AM on hospital day 2, as was hydrocortisone 50 mg intravenously every 6 hours. A few hours later, hypotension persisted. An echocardiogram was performed due to the patient's low $Scvo_2$ and revealed a left ventricular ejection fraction of 65%; thus, the decision was made to initiate ATII at 20 ng/kg/min. The time course of vasopressor infusions is detailed in **Figure 1**. The patient received a continuous infusion of propofol for sedation; however, this was initiated after hypotension had developed. No other blood pressure-lowering medications were administered.

The institution's protocol for management of vasopressors in septic shock includes norepinephrine as the first-line agent. Vasopressin is initiated if norepinephrine greater than or equal to 0.1 μg/kg/min is required for 4 hours or more. If the patient is on vasopressin for 1 hour, the intensivist should be notified for consideration of ATII. If the patient has a low $Scvo_2$, then an echocardiogram is performed prior to initiation of ATII.

The first MAP meeting the goal of 65 mm Hg was documented at 9:36 AM on hospital day 2, 32 min after initiation of ATII and 10 hours after initiation of norepinephrine. At 21:30, approximately 24 hours after hospital admission, the patient remained on norepinephrine 0.25 μg/kg/min, vasopressin 0.04 units/min, and ATII 50 ng/kg/min to maintain an MAP of 70–80 mm Hg and was transferred to an outside facility for initiation of extracorporeal membrane oxygenation.

## Patient Case 2

A 72-year-old Caucasian female (weight 93 kg, height 162.5 cm) who was river rafting in high water levels was ejected from the raft. She had a past medical history of hypertension and some degree of heart failure

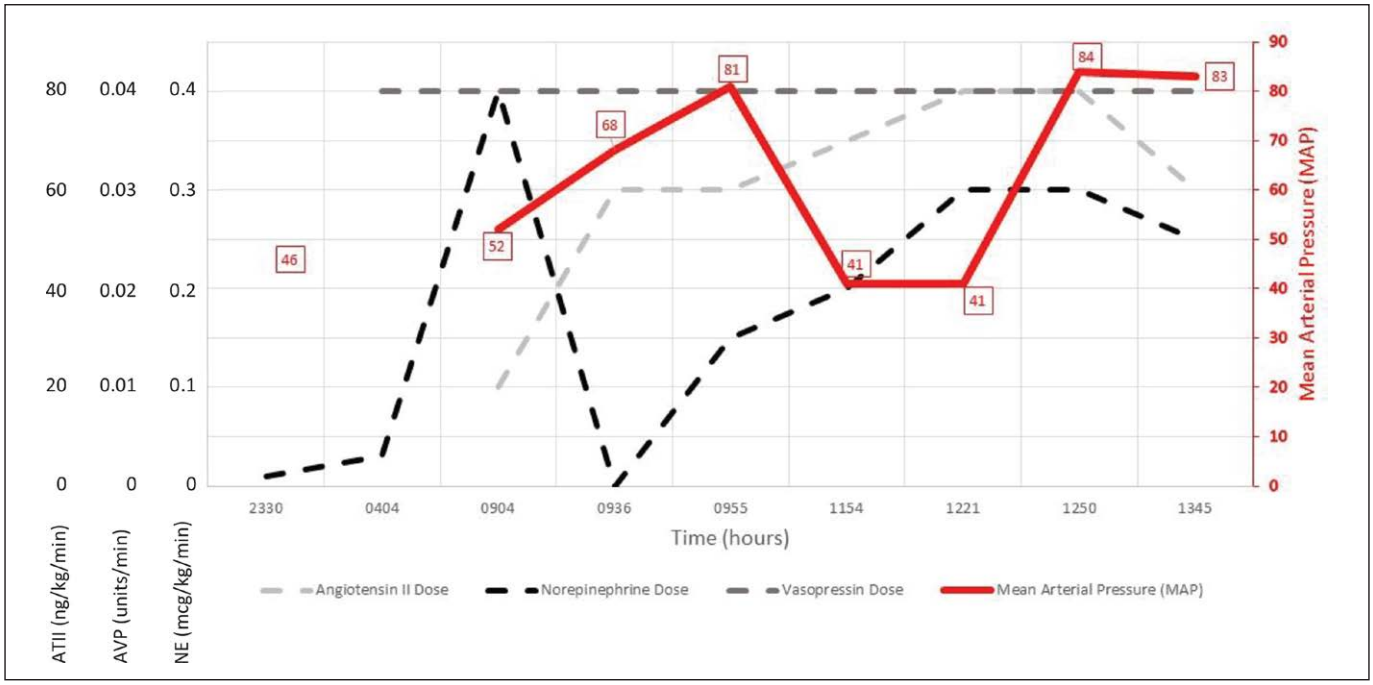


**Figure 1.** Time course of hemodynamic parameters and vasopressor infusion rates for patient 1. ATII = angiotensin II, AVP = vasopressin, MAP = mean arterial pressure, NE = norepinephrine.

that had been treated 8 years prior with no recurrence. Home medications were significant for lisinopril 30 mg daily. Initially, she was able to hold on to a nearby tree until the raft went over her and pinned her underneath logs. Family members estimated that the patient was submerged for approximately 5 minutes. Rescue breathing was initiated in the water, although it is unknown how effective this may have been. Upon arrival on shore, the family members stated the patient was notably ashen and dusky with emesis on her face. Rescue breathing was continued by family members on shore, and her family members noted that her color dramatically improved prior to the initiation of cardiopulmonary resuscitation, which was started by the family. Emergency medical services (EMS) arrived on scene 14 minutes after the initial call.

The total duration that the patient was submerged is unclear; however, the records indicate it was anywhere from 1 to 10 minutes with the additional 14 minutes until EMS arrived. The patient was estimated to have a total downtime of 25–30 minutes.

Upon EMS arrival, the patient had a pulse with oxygen saturation in the 80s. The decision was made by EMS to intubate in the field. On arrival to the ED, the patient's vital signs were: blood pressure 117/101 mm Hg (MAP, 107 mm Hg), heart rate 79 beats/min, temperature 35.1°C , and oxygen saturation greater than 94% on mechanical ventilation with 100% $FIO_2$. Laboratory values at admission were notable for serum creatinine 1.74 mg/dL, lactate 9.3 mmol/L, and high-sensitivity cardiac troponin 912 pg/mL.

A CT scan of the chest revealed bilateral infiltrates, notably worse on the right, likely representative of pulmonary edema. A superimposed multifocal pneumonia could not be excluded. The patient was initiated on ampicillin/sulbactam, and bronchoscopy was performed with culture of bronchoalveolar lavage (BAL) fluid significant for rare Gram-positive cocci and rare yeast. A repeat BAL culture 7 days later was significant for *Klebsiella pneumoniae*, *Proteus mirabilis*, *Serratia marcescens*, and a nonlactose fermenting Gram-negative rod. The patient received 2 days of ampicillin/sulbactam followed by 8 days of piperacillin/tazobactam.

Within 20 minutes of presentation, the patient's MAP had decreased to 54 mm Hg. She received initial resuscitation with 2,800 mL (30 mL/kg) of lactated Ringer's solution and was initiated on norepinephrine 0.04 μg/kg/min at 21:47 on hospital day 1. ATII was added at 22:54, just over 1 hour after initiation of norepinephrine, with rapid attainment of the MAP goal. Norepinephrine was initially titrated off over the next 16 minutes, and ATII was weaned over the next 24 hours. **Figure 2** displays the time course of vasopressor

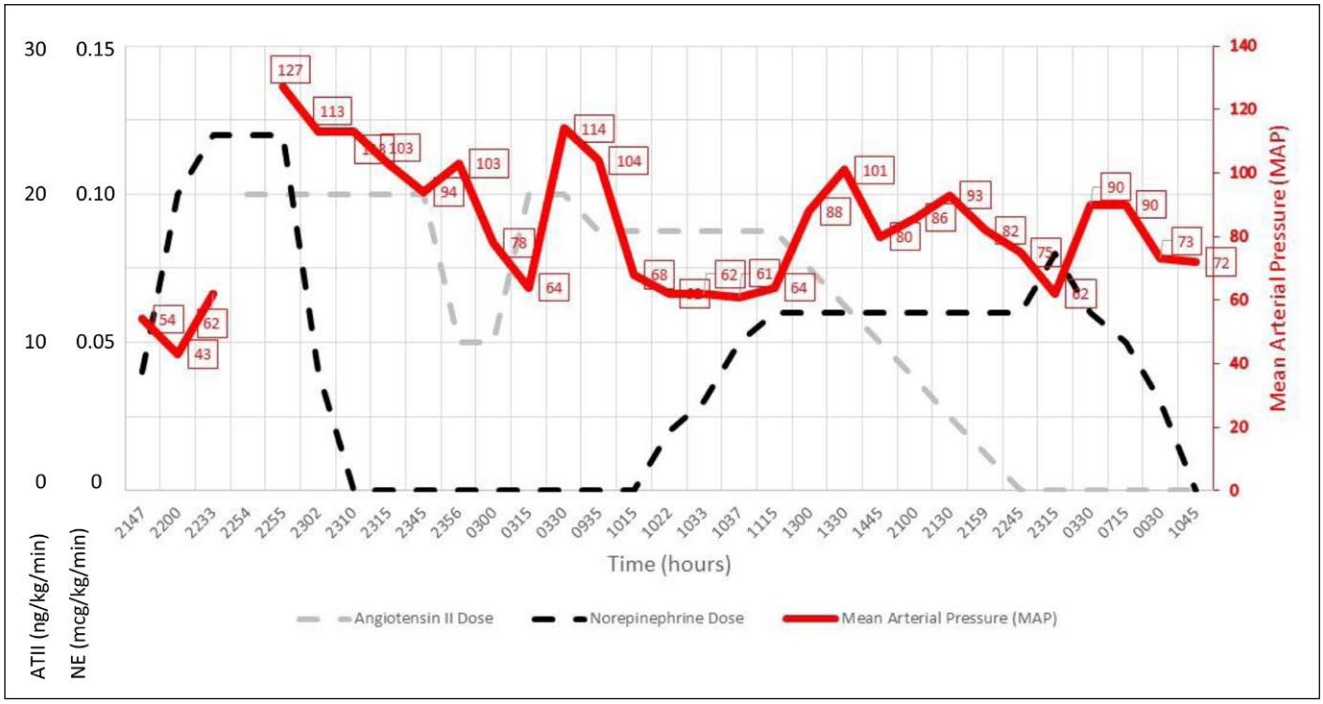


**Figure 2.** Time course of hemodynamic parameters and vasopressor infusion rates for patient 2. ATII = angiotensin II, MAP = mean arterial pressure, NE = norepinephrine.

infusion. The patient was mechanically ventilated for 11 days and spent 12 days in the ICU. After an 18-day hospitalization, she was transferred to an inpatient rehabilitation facility and was subsequently discharged home 2 weeks later with normal neurologic function.

## DISCUSSION

These two cases present the first time ATII has been successfully used for the treatment of shock following submersion injuries. Both cases were characterized by refractory shock that was rapidly reversed upon initiation of ATII. In the first case, ATII was initiated approximately 10 hours after the onset of shock, and the patient reached a MAP above 65 mm Hg within 30 minutes, though she required escalating doses of vasopressors for the next 5 hours until transfer to an outside facility. In the second case, ATII was initiated approximately 1 hour after the onset of shock, and the patient experienced immediate and significant increase in blood pressure that allowed for initial discontinuation of norepinephrine within 15 minutes.

Submersion injuries pose complex clinical challenges characterized by pulmonary edema, cerebral hypoxia, and multiorgan failure (14–16). With no approved treatments to target drowning-related pathophysiology, treatment is largely supportive in nature. Traditionally, hemodynamics are supported by IV fluids, catecholamines, and vasopressin, but these do not have mechanisms specific to the pathophysiology of submersion injuries. As such, ATII poses a unique therapeutic option.

In victims of submersion injuries, initiation of ATII for suspected ACE inhibition due to parenchymal lung injury appears to decrease catecholamine use and promote hemodynamic stabilization. The pulmonary RAS plays a key role in the injury/repair response of lung tissue. ACE is present in high concentrations in lung tissue and is elevated in a number of interstitial lung diseases, suggesting that ATII could play a role in mediating the response to lung injury. Activation of a local RAS within the pulmonary circulation and lung parenchyma could influence the pathogenesis of lung injury via several mechanisms, including an increase in vascular permeability, vascular tone, and fibroblast activity, and by reducing alveolar epithelial cell survival (12). In conditions of significant lung injury, reduced expression of ACE may result in decreased levels of ATII, leading to the potential benefit of exogenous ATII in supporting hemodynamics in patients with ARDS (14–17). This is demonstrated in acute hypoxia, during which decreased levels of pulmonary ACE and the ability of

the lung to convert ATI into ATII occurs, leading to an observed decrease in ATII activity (18).

## CONCLUSIONS

In two victims of submersion injuries, we observed rapid improvement in hemodynamic parameters after initiation of ATII. Notably, hemodynamic stability was sustained when ATII was initiated within 1 hour of shock onset, but additional catecholamine support was needed when ATII was initiated at a later time point. Exogenous ATII is a possible form of treatment for shock following submersion injury. Future research should examine the place and timing for ATII in the treatment of hemodynamically compromised victims of submersion injury.

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