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Simultaneous Presentation of Swimming-Induced Pulmonary Edema in a Set of Monozygotic Twin Elite Maritime Warfare Candidates: A Novel Case Report

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ABSTRACT Swimming-induced pulmonary edema (SIPE) is an incompletely understood condition that is often seen in U.S. special operations candidates participating in maritime qualification training courses. We present a case of two monozygotic twins with the simultaneous onset of acute respiratory distress during a crucible event of a maritime assessment and selection course. Subsequent pulmonary ultrasonography in both candidates showed wedge-shaped hyperechoic lines (B-lines) extending from the pleural interface into the interstitium. Chest radiography of both candidates revealed bilateral asymmetric hazy opacities consistent with SIPE. Both candidates recovered with supportive measures but were medically removed from training. Given the near-identical exposures of the candidates to the same ambient and water temperatures, duration of water submersion, magnitude of physical stressors, and viral colonization, this case study suggests that there may be underlying genetic factors, in addition to environmental factors, that predispose individuals to developing SIPE. Further benchtop and clinical research must be performed to identify potential genetic polymorphisms that contribute to the development of SIPE and to investigate safe interventions that address the underlying etiologies of SIPE pathophysiology.

INTRODUCTION

Swimming-induced pulmonary edema (SIPE) is a condition that has been well described in Naval special operations personnel, particularly during the crucible events of elite maritime warfare qualification training.[1] It has previously been defined as the rapid onset of shortness of breath, cough, and rales in persons competing in water sports or undergoing maritime military training.[2] Prior studies have demonstrated a SIPE incidence between 4.3% and 5.0% in Navy special operations trainees.[3] Swimming-induced pulmonary edema typically resolves with supportive treatment measures; however, documented cases exist in the literature of individuals developing SIPE necessitating invasive ventilatory interventions and Intensive Care Unit admission.[3] The underlying pathogenesis of SIPE is complex and incompletely understood. Here, we present a case study of two monozygotic twin elite maritime warfare candidates participating in the same selection course and exposed to essentially equivalent environmental stressors, who simultaneously developed SIPE-characteristic symptoms during the crucible event of training.

CASE STUDY

Two healthy 21-year-old monozygotic twin candidates participating in the elite maritime qualification training were presented to the medical clinic in acute respiratory distress that began just before arrival. They recently finished a 1 nautical mile ocean swim and were transiting to the next evolution when the symptoms began. Both candidates endorsed the presence of rhinorrhea, dry cough, sore throat, and sinus congestion for 3 to 4 days before their initial presentation but elected not to seek medical attention at that time. Neither candidate was using devices that restrict airflow such as Self Contained Underwater Breathing Apparatus gear or snorkels, nor had prior diagnoses of pulmonary barotrauma. Both candidates had received their SARS-CoV-2 illness (COVID-19) vaccinations (2-dose series), COVID-19 booster, and influenza vaccinations. No vaccinations were administered in the month before their presentation. Neither candidate was ever a smoker.

Both candidates presented with hypoxia and tachypnea with vital signs shown in Table I. Findings on physical examination were similar in both candidates, with audible crackles on auscultation in the posterior middle and lower lung fields. Cardiac examinations were normal with no S3 or S4 gallop, jugular venous distension, or evidence of cyanosis and with distal capillary refill times less than 3 s.

A polymerase chain reaction respiratory panel was collected on both twins, and both tested positive for rhinovirus/enterovirus. A Point of Care Ultrasound was performed on both candidates using a handheld ultrasound system. A linear transducer was used to evaluate the lungs, which demonstrated greater than 3 discreet reverberation artifacts

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TABLE I. Key Characteristics and Clinical Parameters of Two Monozygotic Twins Diagnosed with SIPE during Tactical Maritime Training. The Data Include Initial Measurements upon Initial Presentation and Corresponding Values after 24 h of Observation and Treatment

Metric	Twin A	Twin B
Height (cm)	180	175.26
Weight (kg)	70.7	70.76
Body Mass Inde (BMI) (kg m^{-2})	21.84	23.04
Initial O_2 saturation (%, on room air)	93	82
Initial respiration (respirations per minute)	44	18
Initial heart rate (beats per minute)	98	82
Initial temperature (Celsius)	36.3	36.3
Initial blood pressure (mmHg)	134/74	105/45
Initial chest X-ray read (read by the same radiologist)	"Increased conspicuity of airspace consolidation in the RLL and bilateral perihilar regions. Interlobular septal thickening in the periphery of the lower lobes."	"Right lower lobe and perihilar airspace consolidation and peripheral interlobular and septal thickening."
Initial cardiac silhouette diameter (cm)	12.5	13.8
Initial azygos vein diameter (mm)	8.7	10
24 h O_2 saturation (%, on room air)	97	97
24 h Respiration (respirations per minute)	14	14
24 h Heart rate (beats per minute)	65	69
24 h Temperature (Celsius)	37	36.9
24 h Blood pressure (mmHg)	126/82	118/50
Final Chest X-ray read (read by the same radiologist)	Resolving right lower lobe and perihilar consolidations, consistent with improving SIPE	Resolving right lower lobe and perihilar consolidations, consistent with improving SIPE.
24 h Cardiac silhouette diameter (cm)	12.0	11.9
24 h Azygos vein diameter (mm)	7.1	5.6

(B-lines) in all lung fields bilaterally, suggestive of pulmonary edema. Two-view posterior-anterior (PA) chest radiographs of both twins revealed bilateral perihilar airspace opacities with peripheral interlobular septal thickening (Fig. 1A–D). The cardiac silhouette on PA chest radiography measured 12.0 cm (Twin A) and 13.8 cm (Twin B), which represented a 4% (Twin A) and 13.7% (Twin B) increase in silhouette diameter compared to their baseline chest radiograph measurements, respectively (Table I). The azygos vein diameter on PA chest radiography measured 8.7 mm (Twin A) and 10 mm (Twin B), which represented an 18.3% and 44% increase in diameter compared to their baseline chest radiograph measurements, respectively (Table I). Taken together, this clinical picture and radiographic findings suggested simultaneous diagnoses of SIPE.

Upon presentation to the supporting medical clinic, both candidates were decontaminated from sand and cold ocean water using a shower system and passively rewarmed. Both were placed on high-flow oxygen with rapid correction of their hypoxia. Their oxygen requirements were then titrated downwards over a course of 4 h. Both trainees attempted an internally established cardiopulmonary stress test. Unfortunately, no trainee was able to complete the stress test. Therefore, the recommendation was made to medically remove the candidates from training. After continued demonstration of hemodynamic stability, both candidates were discharged to the post-crucible recovery observation center where their oxygen saturations, heart rates, and clinical status were directly monitored by a medical provider for an additional 24 h.

After an uneventful 24-h observation, both candidates returned to the supporting medical clinic for follow-up. Both patients' sets of vital signs were within normal parameters. Their clinical pulmonary exams showed resolution of crackles and repeat chest radiographs showed resolving perihilar opacities, sharpened costodiaphragmatic angles, and cardiac silhouette and azygos vein measurements that returned to baseline (Fig. 2A–D). Given the candidates' stable vital signs, unremarkable physical exam, and resolution of symptoms, further workup was not performed.

DISCUSSION

Here we present a case of two monozygotic twin elite maritime warfare candidates that both simultaneously developed acute respiratory distress. Though SIPE was highest on the differential, other processes were also considered and included infectious pneumonia, congestive heart failure, inhalation of pulmonary irritants, and asthma exacerbation. Lack of fever, rigors, or cough productive of sputum before the ocean swim made an infectious pneumonia less likely. The resolution of symptoms without traditional inhaled beta-agonists and lack of wheezing on clinical exam made asthma less likely. Radiographically, the transient increase in

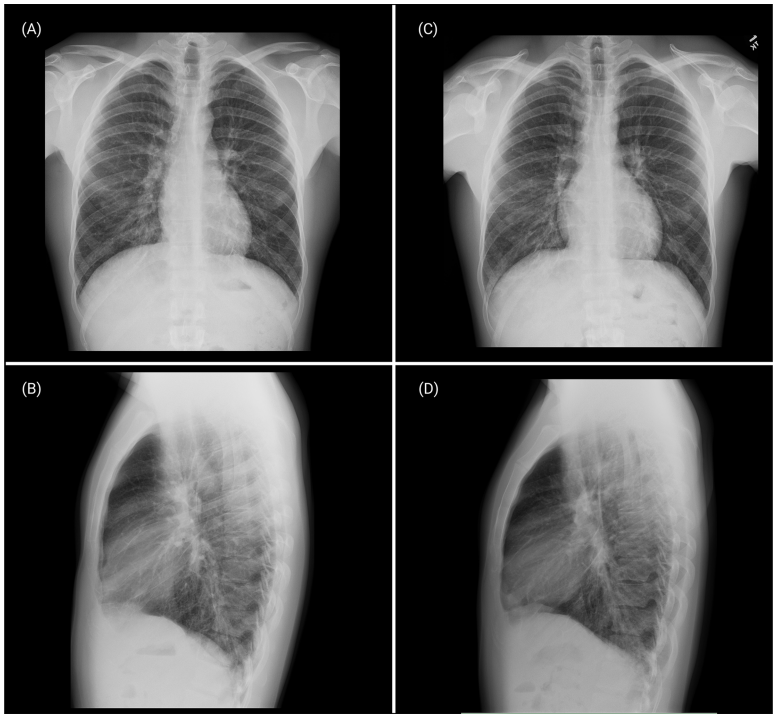

FIGURE 1. Posterior-anterior and standing lateral X-rays of Twin A (A, B) and Twin B (C, D) upon presentation to the Navy Special Warfare clinic endorsing SIPE symptomatology. Characteristic findings included right lower lobe and perihilar airspace consolidation with peripheral interlobular septal thickening. Radiograph formatting performed via licensed Biorender.

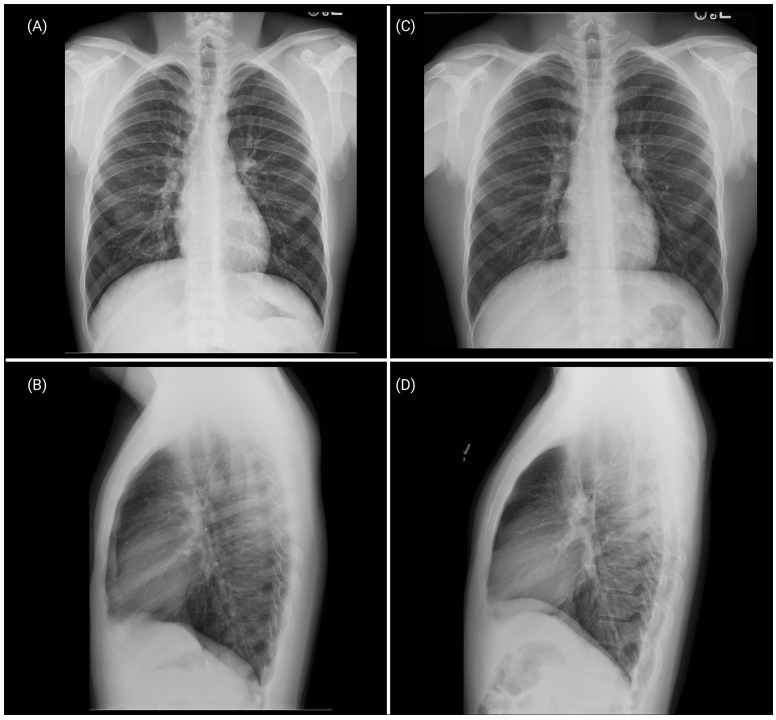

FIGURE 2. Anterior-posterior and standing lateral X-rays of Twin A (A, B) and Twin B (C, D) 24 h following the inciting SIPE event. Findings include resolving perihilar airspace consolidation, resolution of interlobular septal thickening, sharpened costodiaphragmatic angles, and a modest reduction in cardiac size in both twin candidates. Radiograph formatting performed via licensed Biorender.

both azygos vein and cardiac silhouette, which resolved after removal from the training pathway, is a pattern typically seen in SIPE over infectious pneumonia.[3] Although increases in azygos vein and cardiac silhouette can also be seen in congestive heart failure and from increases in right ventricular pressure, this was less likely as both candidates had no medical comorbidities and neither had had evidence of jugular venous distension or lower extremity edema. Additionally, both the lack of large clusters of patients with similar symptoms in the training environment and rapid improvement after removal from the water made inhalation injury less likely. Furthermore, the rapid resolution of the pulmonary edema without treatment is not consistent with infectious pneumonia, acute eosinophilic pneumonia, or other immune-mediated rapidly progressive forms of acute respiratory distress syndrome all of which typically progresses over several days after initial diagnosis, especially without intervention. Thus, SIPE was favored as the likely diagnosis for these monozygotic twins.

Given that all proposed external SIPE risk factors were essentially held constant in this set of monozygotic twins,[4–8] this case study suggests that there are specific underlying genetic factors that predispose individuals to developing SIPE.[9] The theory of a genetic predisposition toward developing SIPE is supported by two prior studies of the Navy Special Warfare population which demonstrated the incidence of SIPE recurrence rates of 9.4% and 22% ($n = 10/45$), respectively.[3,4]

Classic theories suggest that SIPE pathophysiology occurs in susceptible individuals because of the central redistribution of blood volume secondary to immersion in cold water.[10,11] This causes elevations in mean pulmonary artery pressure and pulmonary artery wedge pressure.[11–13] Once a critical threshold has been reached, the hydrostatic pressure fractures the pneumocyte junctions at the capillary-alveolar interface and pulmonary edema ensues resulting in dyspnea, hemoptysis, and hypoxia (Fig. 3).[14–16] Within this pathophysiological process, there are multiple sites that may be potential loci for genetic polymorphisms that contribute to the drivers of SIPE.

Peripheral Vasoreactivity to Cold and Water Immersion (Sympathetic Activation, Mammalian Dive Reflex, Cold Reflex)

Peripheral vasoconstriction is a key mechanistic feature in the development of SIPE.[10,11] Differences in peripheral vascular reactivity have been investigated in multiple twin studies using the Cold Pressor Test, which induces peripheral vasoreactivity via both a thermoregulatory reflex and global sympathetic activation, demonstrated that the degree of vasoconstriction secondary to a stimulus had a significant genetic component.[17,18] Interestingly, multiple polymorphisms in genes that influence the extent of peripheral vascular response have been described in individuals susceptible to high-altitude pulmonary edema. These include the angiotensin-converting-enzyme,[19,20] β-adrenergic receptor,[21] and the aldosterone synthase families of proteins.[22]

The mammalian dive reflex may also play a role in the shunting of blood from peripheral to central circulation. The reflex, characterized by apnea, bradycardia, peripheral vasoconstriction, and selective redistribution of blood flow to vital central organs, is a series of physiological changes shared by all semi-aquatic mammals, including humans.[23,24] Studies have demonstrated that genetic polymorphisms within the renin-angiotensin-aldosterone and kinin-bradykinin systems were correlated with increased peripheral vasoreactivity when the mammalian dive reflex was elicited.[25] Thus, we hypothesize that genetic polymorphisms within various peripheral vasoreactive systems that respond to cold stimuli and water immersion may contribute to the development of SIPE pathophysiology.

Polymorphisms at the Capillary-Alveolar Interface

Prior animal studies have proposed that microscopic breaks in the alveolar-capillary interface result in the development of SIPE.[26] These findings prompt exploration into potential sites within the pulmonary microcirculation that might contribute to an individual's susceptibility to develop SIPE, particularly pulmonary endothelial transient receptor potential cation channel member 4 (TRPV4) channels. Shearing and stretching of the endothelial interface secondary to increased capillary pressure has been shown to activate the TRPV4 Ca^{2+} channel, resulting in calcium-mediated activation of myosin light chain kinase, contraction of the endothelium, and formation of pulmonary edema.[27] Studies have suggested that gain-of-function mutations in the TRPV4 channel have been associated with pathologic states, suggesting a heritability component to TRPV4 expression.[28] Clinical trials have also demonstrated prevention and resolution of hydrostatic pulmonary edema secondary to heart failure with TRPV4 blockade.[28] Given these data, it is plausible that TRPV4 genetic polymorphisms may contribute toward the development of SIPE.[29]

Clearance of Pulmonary Transudate

As shown in Fig. 3, reabsorption of fluid via pulmonary lymphatic channels prevents fluid accumulation in the lungs. This network of vessels begins as blind-ended tubules within the lung parenchyma that drain into collecting vessels within the bronchovascular bundles and interlobular septa.[30,31] Lymphatic vessels are subject to the same starling forces that drive fluid flow along the capillary-alveolar interface.[32] Although the effect of individual differences in lymphatic vessel anatomy and density on the development of SIPE is limited, a small study by Carter et al. shows radiographic evidence of smaller lymphatic networks in SIPE-susceptible individuals compared to SIPE-resistant individuals.[33] Thus, it is possible that SIPE-susceptible individuals could have a smaller pulmonary lymphatic surface area resulting in a reduced rate of fluid clearance.

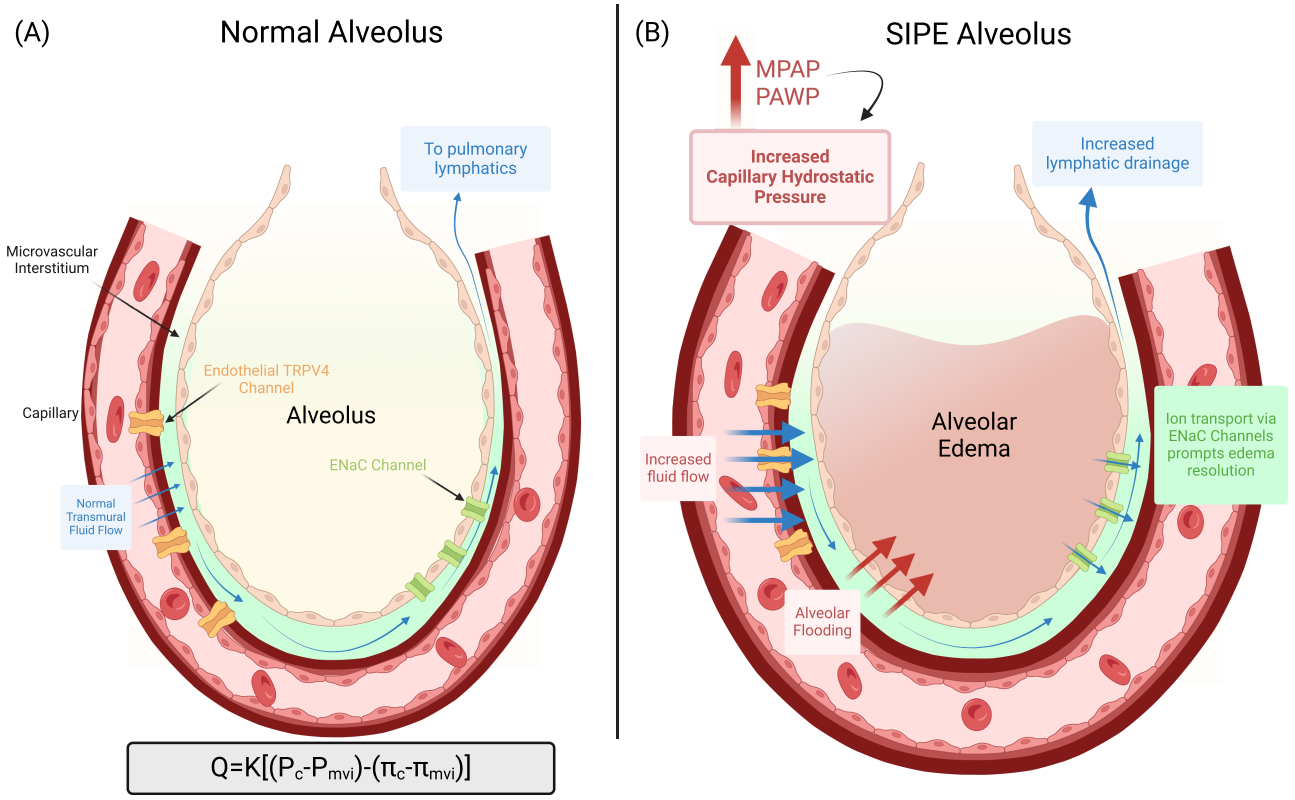

FIGURE 3. Fluid exchange at the capillary-alveolar interface is dictated by the Starling equation, where Q is the net trans-capillary fluid flow, K is a permeability constant, P_c is the hydrostatic pressure of the capillaries, P_{mvi} is the hydrostatic pressure of the microvascular interstitium, π_c is the osmotic pressure of the capillaries, and π_{mvi} is the osmotic pressure of the microvascular interstitium. A physiologically normal capillary-alveolar interface has net flow into the interstitium given the slight differences in osmotic and hydrostatic pressure (A). When capillary hydrostatic pressure increases (such as in SIPE pathophysiology), the rate of fluid leaving the capillary increases, overwhelming the type I pneumocyte barrier of the alveoli, resulting in pulmonary edema. In otherwise healthy alveoli, Na^+/K^+-ATPase in pneumocytes are thought to be responsible for the active extrusion of sodium, and therefore resolution of alveolar edema via secondary diuresis (B). Created via licensed Biorender

Clearance of lung fluid from the pulmonary parenchyma is an active process that includes utilization of the amiloride-sensitive epithelial sodium channel (ENaC).[34] The epithelial sodium channel is expressed in the apical membrane of type I and II alveolar cells, and allows for the passive transport of Na^+ ions, and therefore fluid down its electrochemical gradient.[35] A recent study by Baker et al. demonstrated that subjects with an alanine, threonine amino acid substitution at the amino acid 663 position (A663T) of the ENaC α-subunit resulted in decreased diffusion capacity for carbon monoxide (DL_{CO}) and nitric oxide (DL_{NO}), and therefore likely reduced pulmonary fluid handling during heavy exercise.[34] Further studies by Foxx-Lupo et al. demonstrated that the αA663T ENaC mutation reduced α-adrenergic-driven clearance of sodium from the lungs.[36] Therefore, genetic polymorphisms in the ENaC channel may contribute to impaired clearance of fluid from the alveoli, particularly when concomitantly faced by elevated sympathetic tone and periods of hypoxia.[37] It follows that certain genetic variants of ENaC in SIPE-susceptible individuals could potentially play a role in the initiation of SIPE pathophysiology or augment its effects.

Management, Outcomes, and Impact on Training

Swimming-induced pulmonary edema is typically self-limiting and resolves with rest and avoidance of water exposure within 24 h to 48 h of symptom onset.[38] Diuretics, α_2-agonists, and noninvasive positive pressure ventilation oxygen may be given for persistent or severe cases of SIPE.[38,39] To assess a candidate's suitability to return to training, candidates will frequently undergo a functional cardiopulmonary test involving moderate-intensity exercise on a stationary bicycle. To pass this test, candidates must be able to maintain specified levels of exercise intensity for a sustained period while not developing symptoms of respiratory distress or hypoxia. As demonstrated in this study, candidates not passing the cardiac stress test are recommended for medical removal from the training pipeline.

CONCLUSION

Here we present a case of monozygotic twin elite special operations candidates participating in the crucible event of a maritime assessment and selection course that simultaneously developed clinical and radiographic evidence of SIPE with

similar disease progression and symptom resolution. Given that all environmental factors were held nearly constant, this case highlights the potential role of underlying genetic factors that predispose individuals to the development of SIPE. By further delineating and validating potential genetic variants involved in SIPE pathophysiology, we may be better equipped to predict disease susceptibility and develop interventions for both the prevention and treatment of SIPE.

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CLINICAL TRIAL REGISTRATION

Not Applicable.

INSTITUTIONAL REVIEW BOARD (HUMAN SUBJECTS)

Not Applicable—Case Report.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC)

Not applicable.

INDIVIDUAL AUTHOR CONTRIBUTION STATEMENT

M.A.T. and B.S. conceptualized the study and collected the clinical data. G.B. analyzed the clinical data. All authors discussed the case report in detail and contributed to the final manuscript.

INSTITUTIONAL CLEARANCE

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None declared.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY

The data that support the findings of this study are available on request from the corresponding author. All data are freely accessible.

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