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The relationship between extravascular lung water and oxygenation in three patients with influenza A (H1N1)-induced respiratory failure

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Der Zusammenhang zwischen extravaskulärem Lungenwasser und der Oxygenation bei drei Patienten mit Influenza A (H1N1)-induziertem Lungenversagen

Zusammenfassung. Diese Fallsammlung berichtet über die Korrelation zwischen extravaskulärem Lungenwasser (EVLW) und dem arteriellen Sauerstoffpartialdruck/fraktionierten inspiratorischen Sauerstoffkonzentration (PaO_2/FiO_2) Quotienten bei drei Patienten mit schwerem Influenza A (H1N1)-induziertem Lungenversagen. Alle Patienten erlitten eine ausgeprägte Hypoxie (PaO_2, 26–42 mmHg), mussten mit dem Biphasic Airway Pressure Mode (PEEP, 12–15 mmHg; FiO_2, 0,8–1) mechanisch beatmet werden und wurden in 12 stündlichen Intervallen in die Bauchlage gedreht. Alle Patienten waren während 8–11 Tagen mit dem PICCO® System monitorisiert. Während der mechanischen Beatmung wurden insgesamt 62 simultane Bestimmungen des PaO_2/FiO_2 Quotienten und des EVLW durchgeführt. Es zeigte sich ein signifikanter Zusammenhang zwischen dem EVLW und dem PaO_2/FiO_2 Quotienten (Spearman-rho Korrelationskoeffizient, –0,852; $p < 0{,}001$). Bei allen Patienten war eine Abnahme des EVLW von einer Verbesserung der Oxygenation begleitet. Die Serumkonzentrationen der Laktatdehydrogenase waren bei allen Patienten erhöht und korrelierten signifikant mit dem EVLW während des Intensivaufenthaltes (Spearman-rho Korrelationskoeffizient, 0,786; $p < 0{,}001$). Zusammenfassend erscheint es, dass das EVLW bei Patienten mit schwerem H1N1-induziertem Lungenversagen erhöht ist und dabei eng mit Einschränkungen der Oxygenationsfunktion korreliert.

Summary. This case series reports the correlation between extravascular lung water (EVLW) and the partial arterial oxygen pressure/fractional inspiratory oxygen (PaO_2/FiO_2) ratio in three patients with severe influenza A (H1N1)-induced respiratory failure. All patients suffered from grave hypoxia (PaO_2, 26–42 mmHg) and were mechanically ventilated using biphasic airway pressure (PEEP, 12–15 mmHg; FiO_2, 0.8–1) in combination with prone positioning at 12 hourly intervals. All patients were monitored using the PICCO® system for 8–11 days. During mechanical ventilation, a total of 62 simultaneous determinations of the PaO_2/FiO_2 ratio and EVLW were performed. A significant correlation between EVLW and the PaO_2/FiO_2 ratio (Spearman-rho correlation coefficient, –0.852; $p < 0.001$) was observed. In all patients, a decrease in EVLW was accompanied by an improvement in oxygenation. Serum lactate dehydrogenase levels were elevated in all patients and significantly correlated with EVLW during the intensive care unit stay (Spearman-rho correlation coefficient, 0.786; $p < 0.001$). In conclusion, EVLW seems increased in patients with severe H1N1-induced respiratory failure and appears to be closely correlated with impairments of oxygenatory function.

Key words: Influenza A (H1N1), respiratory failure, extravascular lung water, oxygenation.

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Introduction

In April 2009, a novel influenza A virus of swine-origin (H1N1) virus was identified in two separate patients in the United States [1]. Since then, influenza A (H1N1) infection has rapidly spread over Central/South America, the United States, Australia and Europe [2–4]. The clinical spectrum of the disease is highly variable ranging from mild self-limited flu-like symptoms to severe respiratory failure and death. By August 10, 2010, the World Health Organization stated that the influenza A (H1N1) outbreak has moved into the post-pandemic period [5]. As of August 1, 2010, at least 18,449 deaths due to infections with H1N1 virus had been reported from 214 countries [6].

Because of the recent emergence of the disease, pathophysiology of H1N1-associated respiratory failure remains incompletely understood. In this case series, we report on the relationship of extravascular lung water (EVLW) and oxygenation failure in three patients with severe respiratory failure due to influenza A (H1N1) infection. All patients or their next of kins gave written informed consent that the course of their disease is published anonymously.

Material and methods

Between Nov. 2009 and Feb. 2010, 37 patients with complicated influenza A (H1N1) disease were admitted to our hospital. H1N1 infection was confirmed by nasopharyngeal swabs analyzed with a real-time reverse-transcriptase polymerase chain reaction assay (Artus Influenza/H1®; Quiagen, Hilden, Germany). Three patients (2 females, 1 male) entered the intensive care unit because of severe hypoxia and were intubated and mechanically ventilated (Table 1). Further diagnostic work-up included blood, tracheobronchial and urine bacterial cultures, chest X-ray, chest computertomography-scan as well as determination of antinuclear antibodies and antineutrophil cytoplasmatic antibodies. Oseltamivir (Tamiflu®; Hoffmann-La Roche AG; Grenzach-Wyhlen, Germany) was administered at 150 mg *bid via* a nasogastric tube. Haemodynamic monitoring included an arterial and central venous line. In all patients, cardiac output, intrathoracic blood volume and EVLW were determined using the transpulmonary thermodilution method (PICCO®; PULSION Medical Systems; Munich, Germany). Haemodynamic therapy was guided by an institutional protocol [7]. In all patients, EVLW measurements and blood gas analyses were performed at least 2–4 times daily. Fluid balances were calculated between EVLW measurements. Laboratory investigations including blood cell count, determination of C-reactive protein, procalcitonin, lactate dehydrogenase, liver enzymes, serum creatinine, troponin I were documented once daily.

To evaluate the correlation between EVLW and the partial arterial oxygen pressure/fractional inspiratory oxygen concentration (PaO_2/FiO_2) ratio, bivariate correlation analyses applying the Spearman-rho correlation coefficient were calculated (SPSS 12.0 Software; SPSS Inc. Chicago, Illinois). Furthermore, correlations between EVLW and lactate dehydrogenase levels, fluid balance as well as the positive endexpiratory pressure (PEEP) were calculated. *P*-values <0.05 were considered to indicate statistical significance.

Table 1. Characteristics and clinical data of patients

	Reference	Patient 1	Patient 2	Patient 3
Age (years)		39	46	54
Sex		Female	Female	Male
Body weight (kg)		89	81	90
PaO_2 (mmHg)*	(70–100)	27	26	42
$PaCO_2$ (mmHg)*	(32–43)	37	25	31
pH	(7.37–7.45)	7.47	7.53	7.4
Ventilator mode**		BiPAP	BiPAP	BiPAP
PEEP (mbar)**		15	12	14
Plateau pressure (mbar)**		30	25	26
Minute volume (L/min)**		6.5	7.5	9
Dyn compliance (mL/mbar)**		22	31	41
I:E ratio**		2:1	2:1.2	2:1.3
FiO_2 (%)**		100	100	100
Temperature (°C)*	(36–37)	38.8	37.8	38
Heart rate (bpm)*	(60–100)	125	155	85
Systolic BP (mmHg)*	(100–140)	100	100	130
Diastolic BP (mmHg)*	(60–90)	60	50	65
Creatinine (mg/dL)*	(0.5–0.9)	0.8	1.3	3.4
LDH (IU/L)	(100–250)	353	1276	838
ASAT (IU/L)	(3–31)	32	101	111
ALAT (IU/L)	(<34)	29	30	42
Leucocytes (cells/µL)	(4500–8000)	4001	1410	3920
CRP (mg/dL)	(0–0.5)	10.8	39	24.5
PCT (ng/mL)	(<0.5)	<0.5	>10	2
Neutrophiles (%)	(40–70)	47.5	84.7	84.2
Lymphocytes (%)	(20–45)	48.3	12.1	9.6
Lactate (mmol/L)	(0.4–2)	1.7	5.1	0.8
Troponin I (ng/mL)	(0–0.15)	0.1	1.5	0
Outcome ICU		Alive	Died	Alive
Outcome hospital		Alive	Died	Alive

PaO_2 Partial arterial oxygen tension; *$PaCO_2$* partial arterial carbon dioxide tension; *BiPAP* biphasic positive airway pressure; *PEEP* positive endexpiratory pressure; *dyn* dynamic; *I:E* inspiratory:expiratory; *FiO_2* fracitonal inspiratory oxygen concentration; *BP* blood pressure; *LDH* lactate dehydrogenase; *ASAT* asparate aminotransferase; *ALAT* alanine aminotransferase; *CRP* C-reactive protein; *PCT* procalcitonin; *ICU*, intensive care unit.
*At hospital admission; **Initial ventilator settings.

Results

Before hospital admission all patients reported high fever, dry cough and sore throat for one week or longer. Patient 2 complained about upper abdominal pain and diarrhoea finally leading to dehydration and shock. Two patients were treated with broad spectrum antibiotics, and all patients took non-steroidal antirheumatic medications. None demonstrated particular risk factors suggesting a severe course of H1N1 infection. In all patients, chest radiographs showed bilateral infiltrates consistent with multilobar pneumonia or the acute respiratory distress syndrome. Chest computertomography displayed diffuse interstitial and patchy alveolar infiltrates involving both lungs with accentuation in dependent regions (Fig. 1). Patient characteristics, clinical and laboratory parameters at hospital admission are summarized in Table 1. At ICU admission, all patients were severely hypoxic with PaO_2 values in the range of 26–42 mmHg. Patient 2 presented with shock, leucopenia, elevated serum procalcitonin and troponin I levels. Patient 3 was in oliguric renal failure necessitating renal replacement therapy.

EVLW was increased in all patients (Fig. 2) and significantly correlated with the PaO_2/FiO_2 ratio during the intensive care unit stay (Fig. 2). Clinical signs of lung oedema were present in all patients at intensive care unit admission. While EVLW gradually decreased in patients 1 and 3, it initially decreased in patient 2 but escalated again on day 5. Simultaneously, the PaO_2/FiO_2 ratio deteriorated and refractory multiple organ failure developed in this patient. Serum lactate dehydrogenase levels were elevated in all patients and significantly correlated with EVLW during the intensive care unit stay ($r = 0.786$, $p < 0.001$). No correlations between EVLW and PEEP ($r = 0.332$, $p = 0.07$) or fluid balance ($r = 0.308$, $p = 0.12$) were observed.

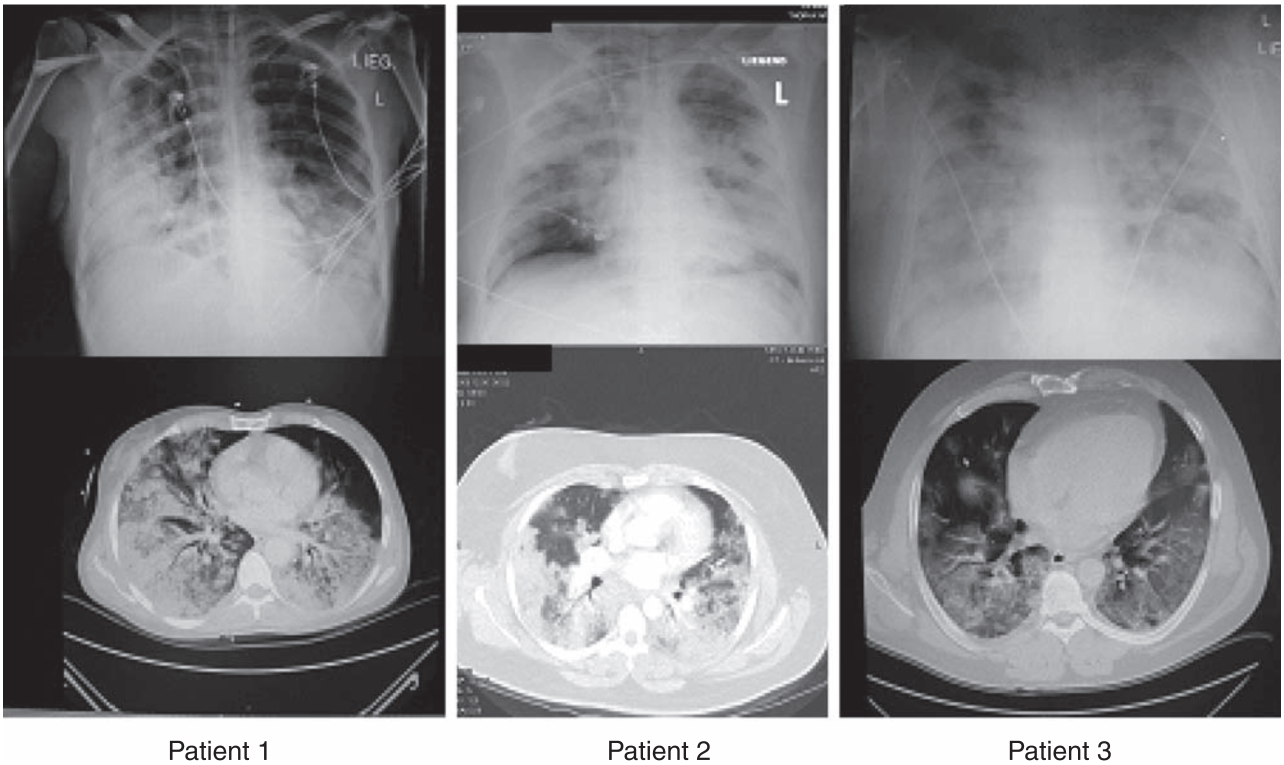

Fig. 1. Chest radiographs and computertomography images of presented patients during the first 24 h after hospital admission

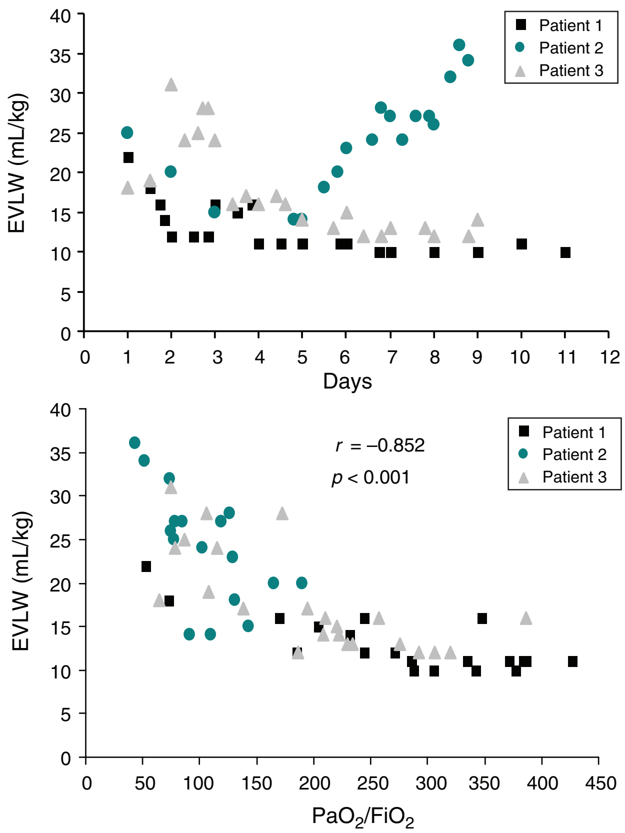

Fig. 2. Course of EVLW data in the presented patients (upper panel) and correlation between EVLW and the PaO_2/FiO_2 ratio (lower panel). EVLW, extravascular lung water; PaO_2/FiO_2 ratio, partial arterial oxygen tension/fractional inspiratory oxygen concentration ratio

Discussion

EVLW was relevantly increased in all presented patients with influenza A (H1N1)-induced respiratory failure. A recent publication by Li et al. reported similar high EVLW measurements (28 and 33 mL/kg) in two patients with acute respiratory distress syndrome induced by probable 2009 pandemic influenza A (H1N1) infection [8]. Since our report included only three patients, no conclusions can be made whether EVLW in H1N1-induced respiratory failure is disproportionally higher than in lung failure from other aetiologies. Studies in different critically ill patient populations reported EVLW measurements in the ranges as observed in our patients during the intensive care unit stay [9]. However, EVLW measurements recorded at intensive care unit admission in our patients were higher than those, for example, reported in patients with sepsis-induced acute lung injury or acute respiratory distress syndrome [10, 11]. Considering that PEEP can effectively reduce EVLW [12, 13], one may speculate that the comparably low PEEP values applied in our patients may have contributed to EVLW accumulation in the patients presented.

In our patients, EVLW was closely correlated with simultaneous measurements of the PaO_2/FiO_2 ratio suggesting a potential key role in the impairment of oxygenatory function in patients with acute respiratory failure due to H1N1 infection. A similar though weaker correlation between EVLW and the PaO_2/FiO_2 ratio was reported in septic shock patients with acute lung injury or acute respiratory distress syndrome [14]. In addition, EVLW was shown to correlate well with survival and independently predicted outcome in a general critically ill patient population [15]. In line with this report, patient 2 in our report exhibited the highest EVLW values (36 mL/kg) and subsequently died.

Several main mechanisms might be responsible for high EVLW values and the development of lung oedema in our patients: First, high virus loads in the lower respiratory tract were shown to induce excessive pulmonary inflammation [16]. A virus-induced "cytokine storm" has been reported for acute respiratory failure due to the influenza A (H5N1) virus [17]. Second, influenza virus-induced inhibition of amiloride-sensitive sodium channels in respiratory epithelia has specifically been reported to impair lung fluid clearance and promote the formation of lung oedema [18, 19]. Third, we observed a close correlation between EVLW and serum levels of lactate dehydrogenase. Elevated lactate dehydrogenase levels have been reported in patients infected with influenza A (H1N1) and may reflect pathogen-induced tissue break-down in the lungs or other tissues such as the musculature [2, 20, 21]. Our results indicate that influenza A (H1N1) infection may cause relevant lung tissue destruction thus contributing to lung oedema formation and impaired oxygenation.

EVLW in patients with H1N1-induced respiratory failure may serve as a useful surrogate marker of the severity of lung damage. Evolution of EVLW during the clinical course of the disease may guide intensivists in their therapeutic decisions including ventilator settings [9] and lung recruitment [22], fluid balance [9, 23] and prone positioning [24].

In conclusion, EVLW seems increased in patients with severe H1N1-induced respiratory failure and appears to be closely correlated with impairments of oxygenatory function.

Conflict of interest

This work was supported by institutional funds. No author has a potential conflict of interest in regards of drugs or techniques discussed in this manuscript.

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