Chapter 33
Unusual Case of Acute Pulmonary Edema Treated by Non Invasive Ventilation: A 30 Years Ago "Cold Case"!

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Abbreviations

ABG	Arterial blood gas
ADH	Anti-diuretic hormone
AFC	Alveolar fluid clearance
AG	Anion gap
APACHE II	Acute physiology and chronic health evaluation
APE	Acute pulmonary edema
ARDS	Acute respiratory distress syndrome
CPAP	Continuous positive airway pressure
CRX	Chest radiograph
CVP	Central venous pressure
ED	Emergency department
EVLW	Extra-vascular lung water
FiO_2	Inspiratory oxygen fraction

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A. M. Esquinas (ed.), *Teaching Pearls in Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-030-71298-3_33

GCs	Glasgow Coma score
HR	Heart rate
ICU	Intensive care unit
MV	Mechanical ventilation
NIV	Noninvasive ventilation
O_2T	Oxygen therapy
P/F	PaO_2/FiO_2 ratio
$PaCO_2$	Carbon dioxide arterial pressure
PaO_2	Oxygen arterial pressure
PAWP	Pulmonary arterial wedge pressure
PEEP	Positive end-expiratory pressure
PSV	Pressure support ventilation
pts	Patient/s
RHDCU	Respiratory high-dependency care unit
RR	Respiratory rate
SB	Spontaneous breathing
SID	Strong ion difference
SpO_2	Trans-cutaneous pulse oximetry saturation
Va/Q	Ratio of ventilation to perfusion
VPW	Vascular pedicle width

33.1 Introduction

As shown by Bone and Balk 1988 [1], a non-invasive respiratory care unit is a cost-effective solution in acute respiratory failure treatment of patients whose primary need consists in monitoring or assistance with weaning, and are hemodynamically stable.

In Italy, respiratory high dependency care units (RHDCUs) provide an intermediate level of care between the intensive care unit (ICU) and the general ward for patients with single organ respiratory failure, who do not need ICU admission. Although Italian RHDCUs are mainly devoted to the monitoring and treatment of acute and chronic respiratory failure by non-invasive ventilation (NIV), they also help weaning from invasive mechanical ventilation. In 1984, an 8 beds RHDCU at the S. Camillo-Forlanini Hospital, Rome (Italy) was instituted. In this short paper, we report the arguments that were discussed by RHDCU's medical staff in 1990 and that allowed to recognize the kind of edema and to choose a proper treatment, in terms of both medical and ventilatory therapy.

Clinical Case

A 31-year-old female, coming from another Hospital, where she had been admitted for drug intoxication (benzodiazepines) that she had taken to commit suicide (Lorazepam 1 mg >20 tablets; Trihexyphenidyl Hydrochloride 2 mg >15 tablets); Bromperidol tablets (unspecified number), and treated with Flumazenil 1 mg/10 mL

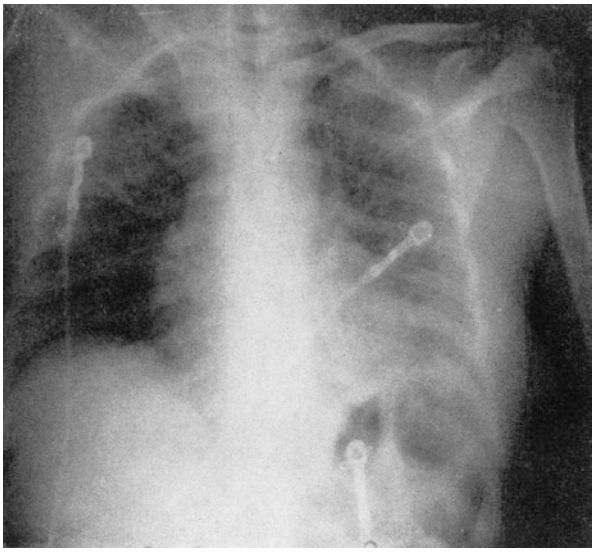

Fig. 33.1 CRX at hospital admittance

IV, diuretics, and fluid therapy (crystalloid), was admitted to the emergency department (ED) of our Hospital. ***At admittance*** she was afebrile and tachypneic—respiratory rate (RR) equal to 30 breaths/min—showing dyspnoea, light deterioration of mental status: Glasgow Coma score (GCs: 13). She was mydriatic with pupil poorly reacting to light and accommodation; moreover, auscultation of the lungs highlighted decreased breath sounds at the right base and diffuse crackling rales. No lower extremity edema. The electrocardiogram showed sinus rhythm rate 100 beats/min. Blood pressure was 130/90. A chest radiograph (CXR) revealed "*widespread ground-glass thickening of the lung parenchyma with relative sparing of the lower right half. The pleural sinuses appear free. The mediastinal image is morphologically normal with moderate widening of the vascular pedicle. CRX compatible with ARDS in early stage*" (Fig. 33.1). The arterial blood gas (ABG) showed hypoxemia (PaO_2: 59.2 mmHg; Standard PaO_2: 42 mmHg) at inspiratory oxygen fraction (FiO_2): 21%, (PaO_2/FiO_2 or P/F = 280 mmHg), hypocapnia with (acute) respiratory alkalosis ($PaCO_2$: 29.6 mmHg; pH: 7.50; HCO_3^-: 23.3 mmol/L).[1] Oxygen arterial saturation (SaO_2): 92.8%, with alveolar-arterial oxygen gradient (DA-aO_2): 54 mmHg (expected DA-aO_2 for age: 11.8 mmHg).[2] Electrolytes: hyponatraemia (Na^+: 129 mmol/L) with plasmatic hyposmolality (Osm: 255 mOsm/kg) (n.v. = 285–305 mOsm/kg), hypokalaemia (K^+: 3.1 mmol/L), Cl^-: 98 mmol/L. Other values: Urea: 90 mg/dL, Glicemia: 83 mg/dL, Red Blood Cells (RBC): 3,940,000/mm^3; White Blood Cells (WBC): 11,600/mm^3; Hb: 12.9 g%, Ht: 37%. Acute

[1] When pt was in spontaneous breathing (SB) all the ABG samples were measured in the air room (FiO_2: 21%) for at least 15 min after discontinuation of O_2T. PaO_2 Standard: $1.66 \times PaCO_2 + PaO_2 - 66.4 = 41.93$ mmHg (rounded up: 42 mmHg).

[2] Da-$aO_2 = PAO_2 - PaO_2$; $PAO_2 = (PB - PH_2O) \times FiO_2 - (1.25 \times PaCO_2)$.

Table 33.1 ABG values in spontaneous breathing (SB) on admission, 2° and 3° day (h 8 am); from the third day onwards in CPAP treatment at variable FiO_2 values (see text)

	In spontaneous breathing (SB) FiO_2: 21% [a](Standard PaO_2)			3° day MV (CPAP: PEEP 5, FiO_2: 30%)					4° day S.B. FiO_2: 35%
	Hospital admission no. 1	E.D. 24 h no. 2	RHDCU 48 h h 8 am	h 10 am 1 h	h 3 pm 5 h	h 5 pm 7 h	h 8 pm 10 h	h 10 pm 12 h	h 10 am
pH	7.50	7.42	7.28	7.33	7.41	7.43	7.42	7.40	7.38
PaO_2 (mmHg)	59.2 (42)[a]	46.7	30.4	49.2	51.8	57.5	85.7	95.6	82
$PaCO_2$ (mmHg)	29.6	36.6	56.4	50.6	48.3	43.3	41.1	47.5	46
SaO_2 (%)	92.8	83.4	55.1	72.7	84.7	90.6	96.5	97.3	88
P/F (mmHg)	282 (200)[a]	222	145	164	173	192	286	319	234
RR (breathing/ min)	30		9						
HR (beats/ min)	100		130						
GCs	13	12	11	12			15		
DA-aO_2 (11.8 mmHg)	54	57.55	49	101.5	102.1	102.3	76.8	58.9	108.2
Na^+ (mmol/L)	129	122	125						
K^+ (mmol/L)	3.1		2.9						
Cl^- (mmol/L)	98		101						
HCO_3^- (mmol/L)	23.3		22.9						
Hb (g/L)	12.9								
Osm (mOSm/ kg)	255	244	251						
APACHE II (score)	10		19						
SAPS 2 (score)	14		27						
HACOR (score, v.n ≤5)				5					

Physiology And Chronic Health Evaluation (APACHE) II score: 10 [2] (Table 33.1). The trans-cutaneous pulse oximetry saturation (SpO_2) on 100% oxygen delivered for 20 min by a non-rebreather mask was equal to 96% (Rossier test). Therapy was started with loop diuretics and fluid infusions. ***Twenty-four hours after***, the drowsiness worsened (GCs: 12); at chest, radiograph showed a dense right lower lobe consolidation. The lung examination showed inspiratory crackles, rhonchi and silence in lower (base) of the right lung. Worsening in ABG values (P/F = 222 mmHg), hyponatraemia (Na^+: 122 mmol/L) with plasmatic hyposmolality (244 mOsm/kg) and negative water balance (urine output: 1 L within the last 24 h), both furosemide

(Lasix®) 40 mg × 4/24 h, Albumine (Behring®) 200 g/L (20% 50 mL) and saline 0.9% NaCl (≈308 mOsm/L) in I.V. slow infusion were administered; the latter in order to counterbalance the hypotensive effect of diuretics. Aerosolized Ambroxol fl (Mucosolvan®) was added to antibiotics, corticosteroids, digoxin already on line. Oxygen therapy (O_2T) via Ventimask, with FiO_2 equal to 28% was set up. ***Forty-eight hours after admittance***, further worsening in neural status (GCs: 11), hemodynamics (HR: 130 b/min; PA: 90/60), increasing in WBC: 16,000/mm^3, and ABG values occurred: PaO_2: 30.4 mmHg, $PaCO_2$: 56.4 mmHg pH: 7.27 (FiO_2: 21%) (P/F = 145 mmHg) (APACHE II score: 19). CXR showed "*widespread lung parenchyma consolidation with confluent patches morphology and moderate asymmetric volumetric reduction of both lungs. Widened vascular peduncle. Pleural sinuses free from effusion. The finding is compatible with diagnosis of ARDS in the acute phase*" (Fig. 33.2).

It was necessary to start mechanical ventilation (MV) by NIV in RHDCU. NIV was performed by Bird 8.400 ST® (Bird Products Palm Springs, CA, USA) via face mask (Respironics® Murrysville, PA, USA) in continuous positive air pressure (CPAP) mode (ventilator) with positive end-expiratory pressure (PEEP) equal to 5 cmH_2O and an FiO_2 (30%) able to obtain a SaO_2 >90% and to reduce RR <25/m. In this kind of ventilator (in CPAP mode) neither backup respiratory rate, nor controlled air-leaks system was present (Table 33.1). During NIV, on-line measurements recorded included heart rate (HR) and SpO_2 (with a finger probe). At 10 h pm, after ABG measurement, the patient was disconnected and treated with a FiO_2 equal to 35%. In the following days a reduction in FiO_2 value was gradually done, thanks to an improvement in neural status and in chest infiltration (Fig. 33.4). Four days after, O_2T was definitively suspended, and patient was discharged and entrusted to a psychiatric institution.

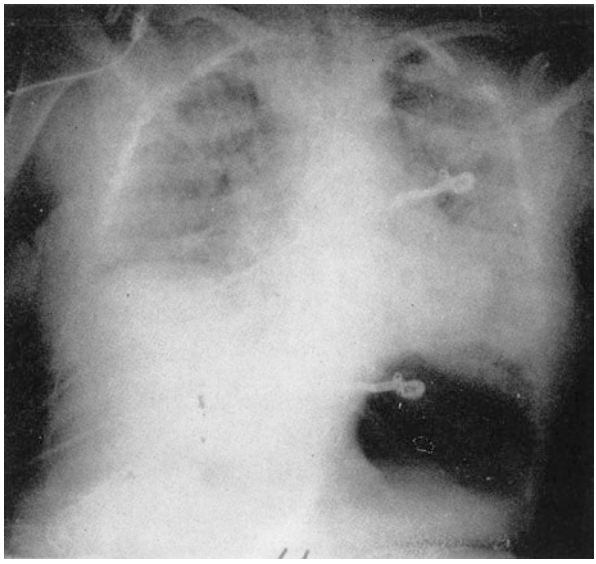

Fig. 33.2 CRX at RHDCU admittance

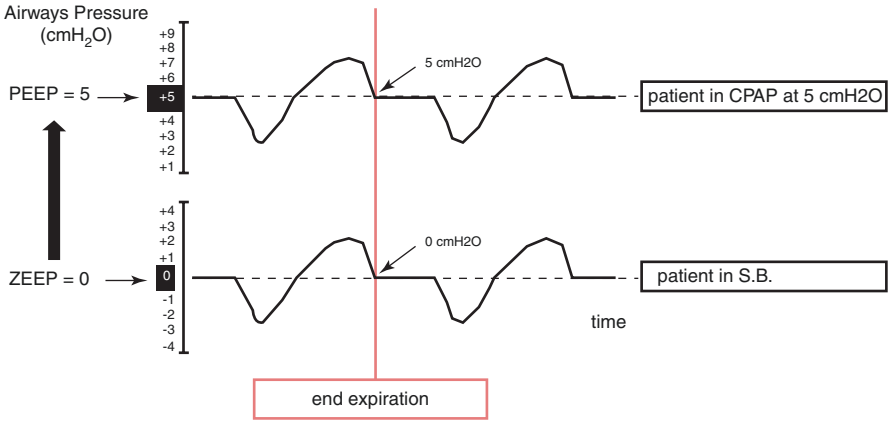

Fig. 33.3 Airways pressure (cmH_2O) and waveform in spontaneous breathing (S.B.) without PEEP (ZEEP) and in CPAP with PEEP at 5 cmH_2O. (From: Ventrella F. (2015) [46]; Courtesy of the author)

33.2 Discussion

33.2.1 Formation and Resolution of Edema

Acute pulmonary edema (APE) is caused by an excess of fluid in the lungs due to an elevated vascular pressure or to a more permeable membrane that is not matched by an adequate lymph clearance rate. It can be defined as the abnormal increase in the amount of extra-vascular lung water (EVLW). In an un-anesthetized sheep, Erdman et al. (1975) showed that EVLW content, measured post-mortem, does not change significantly until microvascular hydrostatic pressure is more than doubled, indicating a large safety factor that normally protects the lungs against fluid accumulation [3]. Nevertheless if the trans-capillary protein osmotic pressure decreases, along with lymphatic removal incapacity, pulmonary edema can develop at a lower than usual level of net filtration pressure [3]. Lung lymphatics remove edema fluid in either hydrostatic or increased permeability lung edema, but they cannot entirely compensate for an increase in intrans-vascular fluid flux or an impaired alveolar fluid clearance (AFC) [4]. The mechanism for the resolution of alveolar edema is provided by the active ion transport across the alveolar epithelium that creates an osmotic gradient that drives AFC [5]. Both type I and type II alveolar cells are involved in transepithelial ion transport. The primary driving force for alveolar fluid clearance is the active transport of sodium from the alveolar space to the interstitium by alveolar epithelial type II cells. The transport of sodium ions is the most important driver for the generation of the osmotic gradient [6]. The system of active ion-driven alveolar fluid reabsorption is the primary mechanism that removes alveolar edema fluid under both physiologic and pathological conditions, such as hypoxia [7]. If pulmonary hydrostatic pressures are elevated, the rate of AFC is also reduced.

'In vivo' studies conducted on animals, showed that net AFC was reduced under clinically relevant pathologic conditions [7]. Alveolar fluid clearance driven by active epithelial Na^+ and secondary Cl^- ions absorption counteracts edema formation in the intact lung. In left heart disease, lung edema was previously attributed to passive fluid filtration across an intact alveolo-capillary barrier. Conversely, it has been demonstrated that a major part of cardiogenic edema results from an active epithelial secretion of Cl^- and secondary fluid flux into the alveolar space [8]. As the inhibition of (Na^+)–(K^+)–(Cl^-)-cotransporters blocks alveolar fluid secretion, it has been identified as a unique therapeutic target in cardiogenic lung edema. "*This evolving concept may not be uniquely restricted to cardiogenic pulmonary edema, but it could also apply to other forms of hydrostatic lung edema*" [8].

33.2.2 Detection Methods

Criteria generally used to define hydrostatic pulmonary edema include central venous pressure (CVP) $\geq$14 mmHg, pulmonary arterial wedge pressure (PAWP) $\geq$18 mmHg, or a cardiac ejection fraction $\leq$45% by echocardiogram, radionuclide, or contrast ventriculography, and/or positive physical findings, including a third heart sound and jugular venous distension [9].

33.2.2.1 Radiological Aspects

Patients with pulmonary edema are likely to present many upholding causes (cardiogenic as opposed to non-cardiogenic). Different hemodynamic conditions and changes of the extravascular protein osmotic forces may be the main factors underlying the radiographic patterns in the various types of pulmonary edema. Conventional chest radiograph aspects can help orienting the diagnosis: as opposed to chronic cardiac failure, where the distribution of flow is usually "inverted" (base-to-apex redistribution), in overload edema, the distribution of pulmonary blood flow and pulmonary regional edema is "balanced" (homogeneous), along the horizontal axis (central), with increased pulmonary blood volume; heart size and vascular pedicle width (VPW) are enlarged;[3] lung volume is normal or increased; not commune are septal lines and air bronchogram, while peribronchial cuffs and pleural effusions are very commune findings [10].

[3] The vascular pedicle width (VPW) is the mediastinal silhouette of the great vessels. It is the distance between parallel lines drawn from the point at which the superior vena cava intersects the right main bronchus and a line drawn at the takeoff of the left subclavian artery from the aorta. It can provide a clue in the assessment of patients' intravascular volume status. Its value varies depending on the position; at the supine position the VPW can increase up to nearly 20%, compared to the upright position. Thus when the patient is supine, the "normal" VPW spans between 58 and 62 mm. A VPW value of 72 or higher is likely due to volume overload [10, 11].

As to the case in point, in the absence of echocardiogram, CVP, PAWP, or brain natriuretic peptide and troponin-T values, the only chest radiograph—using portable, supine CXR—did not offer an accurate evaluation for distinguishing causes of pulmonary edema.

There are explanations for the limited diagnostic accuracy of the chest radiograph.

Edema may not be visible until the amount of lung water increases by 30% [11]. Moreover, VPW, which could provide a clue in assessing patients' intravascular volume status, varies depending on the position; the supine position, as in our case, can increase the VPW by nearly 20% compared to the upright position [11].

Recognizing and differentiating acute hydrostatic pulmonary edema from acute respiratory distress syndrome (ARDS) is always a tricky task in the early stages. This is due to the fact that ARDS pts are not necessarily always affected by edema, as it happens, for instance, when low hydrostatic pressures in the lungs, or other factors in the Starling equation, alleviate the increased trans-vascular transport of fluid. Conversely, over-hydration by aggressive fluid therapy can affect the lungs, thus resulting in pulmonary edema but without increased permeability. This is the reason why over-hydration is hard to recognize at the bedside and hence to differentiate from ARDS. A case in point, which mirrors our present one, is that of pts infused with crystalloid fluids, in that over-hydration is likely to lower plasma colloid osmotic pressure. As a consequence of this—and even in the absence of increased permeability—we witness a lowering of the threshold value of hydrostatic pressure (i.e. pulmonary capillary wedge pressure) above which interstitial edema and thus the alveolar flooding develop [12]. Therefore, the distinction of hydrostatic from permeability pulmonary edema is difficult, especially when using portable, supine CXRs; nevertheless "*in supine, mechanically ventilated patients, measurements of high-resolution computed tomography and VPW correlate with pulmonary artery occlusion pressure*" [13]. Although the absence of clinical signs of congestive heart failure along with the hemodynamically stable situation could suggest to rule out an acute cardiogenic pulmonary edema, it is well known that APE caused by excessive infusions of blood, blood products and fluids is included among the cardiogenic types of edema, because the overload edema too, is caused by increased hydrostatic pressure [14]. As a result, the diagnosis of hydrostatic pulmonary edema usually relies on clinical information and response to treatment: if oxygenation and radiograph finding improve rapidly with diuresis, this favours hydrostatic edema [14]. As to the case in point, despite diuretic therapy, neither oxygenation nor radiograph improved in the first 24 h after admission. Quite the contrary, the clinical and functional status worsened considerably, in accordance with a CXR finding, also compatible with diagnosis of ARDS in the acute phase.

33.2.2.2 Acid Base Findings

Extravasation of fluid into the alveoli prevents oxygen from being absorbed into the bloodstream and neutralizes surfactant' s lubricating properties. The lungs become less compliant and the effort of breathing increases, causing dyspnea and CO_2

retention. The hypoxemia that occurs in alveolar flooding is more severe than in interstitial pulmonary edema—which causes ventilation-perfusion (Va/Q) mismatch—and is caused by right-to-left shunting of blood [14].

In our case, as opposed to radiological aspects of ARDS, neither aetiology (fluid overload) nor P/F value at admittance and in the first 24 h induced to a diagnosis of a (even mild) ARDS [15].

Chest radiogram, hyponatraemia with plasmatic hyposmolality and the presence of negative water balance, oriented towards over-hydration acute pulmonary edema; the history established that in 48 h before admission the patient was really resuscitated with an unspecified number of liters of crystalloid (Saline and Normosol M), the last one at hyperosmotic set up (Osm: 390 mOsm/L) that can cause interstitial fluid withdrawn into the bloodstream. Moreover, loop diuretics (and thiazides) were previously administered, which could be the cause of the electrolyte imbalance (hypokalaemia, hyponatraemia and hypochloraemic alkalosis) [16]. An "inappropriate" anti-diuretic hormone (ADH) syndrome (hyponatremia with hypervolemia) is described in situations in which ADH secretion may be increased as postoperative ADH release due to barbiturates or transient "idiopathic" hyponatremia (secondary to diuretics, especially thiazides) [16]. Furthermore it cannot be ruled out that the drowsiness was also caused by over-hydration of the central nervous system, that may occur in the presence of concentrations of plasma sodium equal to or below 120 mEq/L [16]. Hypocapnia (with respiratory alkalosis) is generally caused by hypoxemia; as to the case in point, fluid overload could be a contributing factor in leading to hypocapnia, via juxta-capillary receptors (J-receptors, or pulmonary C-fiber receptors) that are involved in events which cause a decrease in oxygenation, responding by an increase in respiration [17]. Hypocapnia in APE is often associated with the rise in serum lactate produced by a marked reduction of splanchnic and muscle blood flow associated with a high degree of hypoxemia [18, 19]. This compensatory hyperventilation is relatively slow and is not complete for 12–24 h [20]. In our case acute respiratory alkalosis ($PaCO_2$: 29.6 mmHg, pH: 7.50) at admission was not associated to metabolic acidosis[4] [21]. In the absence of serum lactate measure and despite anion gap (AG) value was normal (10.7 mEq/L; nv: 8–12 mEq/L) at admission, we cannot rule out the presence of hyperlactatemia in the continuation of the ED stay, since the AG may result from an insensitive screen for elevated lactate in critically ill patients[5] [22]. Moreover it has long been recognized that the infusion of large volumes of "normal" (0.9% NaCl) saline can cause acidosis [23]. This has been traditionally explained as a "dilutional' 'acidosis in which the serum bicarbonate is diluted by the fluid, resulting in lower serum bicarbonate and a metabolic acidosis. However, the Stuart approach offers an alternative

[4] This is a primary disorder: in (acute) respiratory alkalosis, the decrease in expected HCO_3^- is equal to 2 mmol/L for a decrease in $PaCO_2$ equal to 10 mmHg; thus for a decrease in $PaCO_2$ equal to [40 – 29.6] = 10.4 mmHg, the expected HCO_3^- is ≈23; OR (it is easier): for a decrease in $PaCO_2$ equal to 1 mmHg, the pH increase is equal to 0.01 U: thus, for a decrease in $PaCO_2$ equal to ≈10 (40 – 29.6) mmHg, the increase in pH is 0.1: that is 7.50, as in our case.

[5] Anion Gap (AG) = $[(Na^+ + K^+) - (Cl^- + HCO_3^-)] = [(129 + 3.1) - (98 + 23.3)] = 10.8$ mEq/L.

explanation [24]. Saline causes metabolic acidosis not by 'diluting' HCO_3^- but rather by its Cl^-content. The reason why this occurs with saline administration is that, although saline contains equal amounts of both Na^+ and Cl^-, plasma does not. When large amounts of salt are added, the Cl^- concentration increases much more than the sodium concentration [25]. Since normal saline has a strong ion difference (SID) of 0, its administration would tend to lower the serum SID resulting in a metabolic acidosis[6] [26]. A shift of free water from the intracellular volume to the extracellular volume in order to reach an osmolar equilibrium will result in additional dilution of the extracellular, and therefore an additional acidifying effect [27, 28]. That is why, in our case, neither hyponatraemia nor hyposmolarity were corrected with saline infusion; actually a marked mixed respiratory and metabolic acidosis on 48 h after hospital admission was highlighted (Table 33.1).[7]

33.2.3 Ventilatory Therapy

The appearance of respiratory acidosis could be ascribed to hypoventilation as a sign of pump failure, either owing to an increased load of the respiratory system, or strictly related to decreased compliance due to interstitial/alveolar flooding [29]. CPAP—also known as spontaneous PEEP—is a mode of ventilation in which the patient is in spontaneous breathing (SB) and is exposed to a continuous pressure from the ventilator (equal to 5 cmH_2O as in this case). This is the pressure in force at the end of expiration, that is named positive end-expiratory pressure (PEEP). The patient creates a negative pressure in inspiration and a positive pressure in expiration, thereby the circuit pressure varies throughout the cycle; but at the end of the expiration the pressure will return to the set PEEP value (5 cmH_2O) (Fig. 33.3). Thus, in preventing alveolar collapse at end-expiration and reducing intrapulmonary shunting of blood, CPAP redistributes excess lung water to sites where it interferes less with gas exchange, hence improving oxygenation (arterial PO_2 and lung compliance) [30]. According to Demling et al. (1975), PEEP cannot decrease EVLW, but increases the difference between pulmonary microvascular pressure and plasma colloid osmotic pressure (net intravascular filtration pressure), therefore impairing the venous return. In patients with volume overload, decreasing venous return will directly decrease the amount of pulmonary edema being generated, by decreasing right cardiac output [31].

It is noteworthy, in this regard, that the hypoxemia occurring in alveolar flooding is caused by right to-left shunting of blood that is reduced by PEEP (through a reduction in cardiac output) [32].

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[6] The difference between the sum of all strong cations [Na^+, K^+, Ca^{2+}, Mg^{2+}] and all strong anions (mainly Cl^-, Lactate and Albumine) is known as the strong ion difference (SID).

[7] This corresponds to a mixed disorder. In fact the expected HCO_3^- in acute respiratory acidosis: $[(PCO_2 - 40)/10] + 24$ should be 25.64 mmol/L instead of 22.9 mmol/L (actual value); thus there is an associated metabolic acidosis.

On the contrary, in interstitial pulmonary edema (as in ARDS), the hypoxemia is due to Va/Q mismatch—by the presence of shunt or units of very low Va/Q ratio; in these pts a fall of the cardiac output caused by PEEP leads to a decrease in the perfusion of unventilated lung and an increase in the ventilation of unperfused alveoli [32].

Moreover, when used in combination with furosemide, given intravenously, PEEP improves lung fluid resorption by increasing the plasma colloid osmotic pressure, as shown in experimental hydrostatic pulmonary edema [33].

"*In patients with hydrostatic pulmonary edema, mechanical ventilation could have either beneficial or detrimental effects on alveolar fluid clearance. Beneficial effects of positive pressure ventilation that might indirectly increase alveolar fluid clearance include decreased preload and afterload and decreased myocardial oxygen consumption due to decreased work of breathing. These factors could reduce the formation of pulmonary edema and thus promote net alveolar fluid clearance*" [34].

However, it is well established in medical literature that mechanical ventilation at high tidal volumes can promote lung injury [35]. Furthermore, high levels of PEEP may raise CVP, inhibiting lung lymphatic drainage from the interstitium and thereby limiting alveolar fluid clearance [34].

As we pointed out earlier, CPAP can reduce inspiratory work of breathing both by decreasing pulmonary resistance, related to an increase in functional residual capacity, and by increasing lung volume to a more favourable position on the pressure-volume curve [36]. Reducing the work from respiratory muscles also reduces the generation of CO_2 and lactate from these muscles, helping improve acidosis. At the same time, the decreased return may improve over-distension in the left ventricle, placing it at a more advantageous point in the Frank-Starling curve and possibly improving cardiac output [37]. Furthermore, inspiratory muscle unloaded reduce intrathoracic and left ventricular transmural pressures (and afterload), as seen in patients with congestive heart failure, thereby improving oxygenation [37]. Although CPAP decreases ventilation/min and respiratory rate, $PaCO_2$ value generally does not increase, thanks to the decrease in dead space ventilation [36]. As reported in Aliberti et al. (2010), in case of a mixed acidosis (as in ours), pH increased very fast during the first hours of CPAP treatment, possibly owing to beneficial effects on the heart and hemodynamics, as well as to tissue perfusion [29]. However, in our case, the slower decrease in $PaCO_2$ levels related to the lung decreased compliance ("stiff lung") forced to apply a low PEEP value (5 cmH_2O), given the risk of barotrauma. A light increase in $PaCO_2$ value at the 12th hour of CPAP can be explained by the fact that, unlike pressure support ventilation (PSV), CPAP does not provide inspiratory assistance to the rest of the muscles of respiration [38]. It is now established that the rise in intrathoracic pressure and not the modality of ventilation (CPAP vs PSV) seems to be important in acute cardiogenic pulmonary edema patients [39, 40].

33.2.4 Outcome

Thanks to medical therapy, the increasing in urine output dramatically reduced edema in few hours (Fig. 33.4) and CPAP reduced $PaCO_2$ within 7 h (Table 33.1).

A "post hoc" analysis according to the "risk scale score" named HACOR, at 1 h of NIV, on a value obtained by analysing five variables—i.e. heart rate (H), acidosis (pH), consciousness (GCs), oxygenation (P/F), and respiratory rate (R)—showed a low (5) prediction (NIV) failure [41].

33.3 Limits of the Present Contribution

A faster and more accurate diagnosis would have been certainly made, were hemodynamic factors (including pulmonary arterial wedge pressure and left ventricular ejection fraction) routinely measured, along with monitoring EVLW by single transpulmonary thermal dilution. Likewise, the availability of main electrolytes (Na^+, K^+, Cl^-, $Latt^-$) and serum osmolarity, together with ABG values in the same blood sample, would have allowed a more rapid assessment of the acid-base status. Most notably, a quasi-continuous monitoring of urinary pH and principal urinary electrolytes available by the applications of the K.IN.G® urinary analyzer would have helped "*to disentangle the great mosaic concerning acid-base chemistry*" [42]. It is also important to highlight that, hemodynamic factors being routinely monitored, some therapeutic errors, i.e. the administration of diuretics and of other infusion drugs, such as NaCl 9% saline (instead of an early conservative fluid

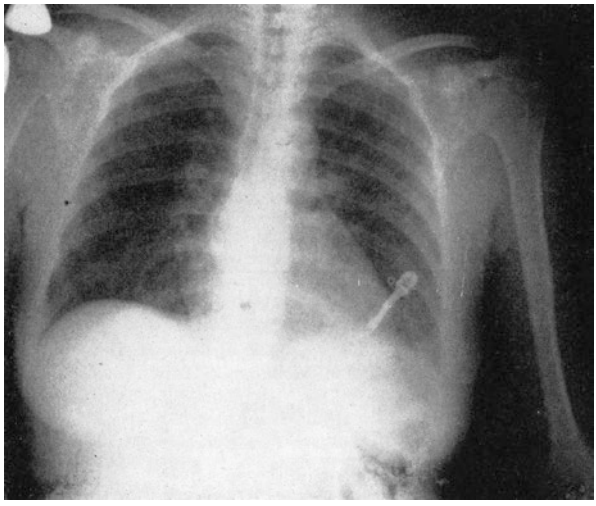

Fig. 33.4 CRX at RHDCU discharge

management strategy) which caused overload and the onset of "iatrogenic" metabolic acidosis, could have been successfully avoided. The availability of NIV-ventilators which can provide air-leaks compensation could have proved equally useful. Despite there are no significant differences in clinical outcomes when comparing CPAP vs BiPAP, would a Bi-level mode have been applied at the first occurrence of hypercapnia, the overall time of mechanical ventilation could have been perhaps reduced.

33.4 Conclusions

It has been shown that central active substances may cause pulmonary edema by increased permeability of the alveolar-capillary membrane [43–45].

The evolution of the chest radiographic findings in the present case are compatible with an initial acute increase of vascular permeability due to the intoxication. The increase in density in the peripheral regions of the lung is an indication of alveolar involvement. There are no findings compatible with an interstitial phase preceding the alveolar flooding as it happens in conditions of severe cardiogenic pulmonary edema. According to this interpretation, despite the presence of alveolar edema, there are no findings of septal lines, peribronchovascular cuffing, perihylar haze and pleural effusion that usually are hallmarks of cardiogenic pulmonary edema. From the pathophysiologic point of view this type of edema occurring after drug overdose can be considered as a normal pressure injury edema that could be reversible after the cessation of the pharmacologic injury [10]. The evolution of this case is conditioned by the presence of over-hydration with marked enlargement of the vascular pedicle and further involvement of the central regions of the lungs. Over-hydration could cause an increased hydrostatic pressure within the pulmonary capillaries favoring further development of edema. The quite rapid resolution of the radiographic findings could be related on the one hand to the removal of the toxic condition with consequent reduction of the injury component of pulmonary edema and on the other hand to the effect of CPAP facilitating the re-absorption of edema of hydrostatic origin. In summary, the radiographic aspect of this case can be speculatively defined as toxic injury edema (ARDS) with superimposed over-hydration hydrostatic edema [10].

Despite an occurrence of mild hypercapnia in the continuation of the treatment, CPAP appeared to be an effective treatment. Furthermore, the existence of a metabolic acidosis associated to the acute respiratory acidosis, also due to the high degree of hypoxemia, can affect its outcome. Careful interpretation of AB status is recommended.

Key Teaching Points

- In patients with acute pulmonary edema an initial acute increase of vascular permeability due to drug intoxication can lead to radiological finding of ARDS.
- The superimposed over-hydration can lead to hydrostatic pulmonary edema.
- The diagnosis of hydrostatic pulmonary edema usually relies on clinical information and a rapid improvement of oxygenation and of the radiograph findings after increased diuresis.
- In patients with hydrostatic pulmonary edema CPAP can reduce edema owing to beneficial effects on the heart and hemodynamics as well as on work of breathing and tissue perfusion which lead to a reduction in acidosis.
- High tidal volume ventilation and high levels of PEEP must be avoid to prevent the consequent lung injury and reduction of alveolar fluid clearance.
- Similarly, since inducing metabolic acidosis both I.V. rapidly infused saline (NaCl 0.9%) and loop diuretics (thiazides) must be avoided, or they should be administered very carefully.

Questions and Answers

1. During continuous positive airway pressure (CPAP) ventilation:

   (a) The pressure is delivered by the ventilator in the expiratory phase only and represents the positive end-expiratory pressure (PEEP)
   (b) The airways pressure has no different value both in inspiration and in expiration
   (c) The pressure delivered by the ventilator is the airways pressure at the end of expiration
   (d) None of them above

   Answer: (c) The pressure delivered by the ventilator is the airways pressure at the end of expiration

2. In Acute Hydrostatic Pulmonary Edema the occurrence of a Respiratory Alkalosis is due to:

   (a) Fluid overload involved in leading to hypocapnia
   (b) The rise in serum lactate produced by a marked reduction of splachnic and muscle blood flow, caused by hypoxemia
   (c) Can be managed with a conservative fluid strategy and oxygen therapy
   (d) All of them above

   Answer: (d) All of them above

3. In Acute Hydrostatic Pulmonary Edema the occurrence of a metabolic acidosis is due to:

   (a) Administration of diuretics (especially thiazides)
   (b) Infusion of a large volumes of fluids (NaCl 9% saline)
   (c) High degree of hypoxemia
   (d) All of them above

   Answer: (d) All of them above

4. In Acute Hydrostatic Pulmonary Edema the occurrence of a hyponatremia:

   (a) Can be transient or "idiopathic" (secondary to diuretics, especially thiazides)
   (b) Is described in situations where ADH secretion may be increased (as a post-operative ADH release due to barbiturates)
   (c) When equal to or below 120 mEq/L causes drowsiness owing to overhydration of the central nervous system
   (d) All of them above

   Answer: (d) All of them above

5. In Acute Hydrostatic Pulmonary Edema beneficial effects of CPAP that might indirectly increase alveolar fluid clearance are:
   (a) Decreased preload and afterload
   (b) Decreased work of breathing
   (c) Decreased myocardial oxygen consumption
   (d) All of them above

   Answer: (d) All of them above

Acknowledgments My gratitude goes to Andrea Rossi (MD, PhD) and Thomas Langer (MD, PhD), for their precious advice and suggestions, and to Fabrizio Bigotti (PhD), for revising the final draft of this paper. I would like also to thank Giuseppe Brunetti, MD, Mario Carlo Buscajoni, MD, Paola Marazzi (MD) and Maurizio Morandi (MD) who assisted me in the patients' treatment. Finally, I wish to dedicate this paper to Vittorio Emanuele Antonini, Claudio Balderi, and Roberto Sabato, whose memory shall for ever live with me.

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