Abstract

Background: pulmonary edema results from the shift of excessive fluid into the alveoli space due to alteration in the balance between various Starling’s forces, and is clinically classified into cardiogenic or non-cardiogenic pulmonary edema. This study aimed to elucidate the mechanism, outcomes, and prevention of poisoning induced non-cardiogenic pulmonary edema (PINCPE).

Materials and methods: we conducted a study on etiology, epidemiology, mechanism, risk, and length of hospital stay in PINCPE. A PubMed search using terms: poisoning and non-cardiogenic pulmonary edema. From 1986 to 2017, a total of 15 articles with 16 cases (2 cases in one article) were included. Cut-off value of mean age was used for classification of subjects into younger group and older group, and length of stay (LOS) was compared between the two groups.

Results: the age range of the patients was 7 to 72 years, and the average age (mean±SD [standard deviation]) was 35.7±19.5 years. Among the reported substances in PINCPE, calcium channel blockers (CCBs) were most frequently used (n=8; 50%). In electrocardiogram (ECG), sinus tachycardia (n=8; 50%) was the most common finding. The overall rate of intubation with mechanical ventilator support was 81.3%. The mortality rate was 12.5%. Among patients with PINCPE, LOS was significantly shorter in the younger group aged <35.7 years than in the older group (5.7 vs. 8.9; p=.022).

Conclusion: CCB was the most common etiologic agent in PINCPE. Up to 81.3% of PINCPE cases required intubation with ventilator support due to respiratory failure. LOS may increase 3.2 days if the case is complicated with extra-pulmonary organ failure.

Keywords

poisoning • non-cardiogenic lung edema • prevention

Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| ABG | Arterial blood gas |
| ADHF | Acute decompensated heart failure |
| AMS | Altered mental status |
| BNP | B-type natriuretic peptide |
| CCB | Calcium channel blocker |
| CI | Confidence interval |
| CNS | Central nerve system |
| DBP | Diastolic blood pressure |
| ECG | Electrocardiogram |
| HR | Heart rate |
| ICU | Intensive care unit |
| LOS | Length of stay |
| MAP | Mean arterial pressure |
| MD | Mean difference |
| MDMA | 3,4-methylenedioxy-methamphetamine |
| MOF | Multiorgan failure |
| NT-proBNP | N-terminal proBNP |
| PEEP | Positive end expiratory pressure |
| PINCPE | Poisoning induced non-cardiogenic pulmonary edema |
| RR | Respiratory rate |
| SBP | Systolic blood pressure |

Introduction

Pulmonary edema results from a shift of excessive fluid into the alveoli space due to alteration in the balance between various Starling’s forces, and is clinically classified into cardiogenic or non-cardiogenic based on pathophysiology. In non-cardiogenic pulmonary edema, medications or
illicit drugs are the common etiological agents [1]. A study enrolling 241 patients with pulmonary complications after heroin use reported that pulmonary edema is one of the major complications in 24 patients (10%) [2]. Another retrospective study enrolling 149 patients with AMS with depressed respiratory status after heroin use reported that pulmonary edema was confirmed in 71 patients (48%) [3]. Multiple mechanisms implicated in drug-induced pulmonary edema include inhibition of prostacyclin synthesis by aspirin, and opiate-related mast cell degranulation [4]. Calcium entry blockers can cause selective systemic precapillary vasodilation with associated peripheral edema, and the lung edema may contribute to precapillary vasodilatation resulting in excess pulmonary capillary transudate [5, 6]. Pulmonary edema is a true medical emergency, and treatment varies according to the underlying pathophysiologic mechanisms. This study aimed to clarify the mechanism, outcome, and prevention in PINCPE through PubMed search of previous published cases reports.

Materials and Methods

Database search
This article was designed as a systematic review on etiology, epidemiology, mechanism, risk, and LOS in PINCPE. Since no human or animal subjects were involved in the study, ethics approval was not required. Electronic search was performed in PubMed from January, 1991 to December, 2018. To maximize sensitivity of the search strategy and identify all studies, a combination of terms was used as follows: poisoning and non-cardiogenic pulmonary edema. From 1986 to 2017, total 36 case reports were retrieved, and those were reviewed for further identification of potentially relevant studies. All identified articles were systematically assessed using inclusion and exclusion criteria as follows.

Selection criteria
In this systematic review, inclusion criteria were as follows: toxic substances, patient’s sex, age (years), comorbidity, toxidrome, blood pressure (mmHg) at the time of PINCPE, pulmonary capillary wedge pressure (mmHg), heart rate (beats per minute), electrocardiogram, echocardiogram results, with or without intubation, and length of hospital stay. All data were extracted from the text, tables, and figures of each article. Reviews and articles without detailed case report, and laboratory data were excluded. The flow diagram of the article screening process is shown in Figure 1. In the initial literature search of PubMed, 36 articles were identified, and of those, 21 articles were excluded based on the selection criteria. Finally, a total of 15 articles with 16 cases (2 cases in one article) were included.

Statistical analysis
The subjects were classified into younger group and older group using the cut-off value of mean age, and LOS was compared between the two age groups. Statistical analyses were conducted using IBM Statistical Package for the Social Sciences (SPSS) software (version 25 (International Business Machines Corp., New York, USA). Independent sample t-test was used for comparisons between the two groups. The number of patients, means, and standard deviations were pooled to calculate the effect size, MD, and 95% CI. Statistical significance was set at p-value <0.05.

Results

General data of 16 PINCPE cases enrolled are shown in Table 1. Cases in the US (25%), Turkey (18.75%), UK (12.5%), India (12.5%), Greece (12.5%), France (6.25%), Germany (6.25%), and Denmark (6.25%) were noted. The age range was from 7 to 72 years with mean ± SD (standard deviation) of 35.7±19.5 years. Male sex was predominant (n=10). Among the reported substances in PINCPE, CCBs were most common (n=8, 50%), followed in decreasing order by MDMA (n=1; 6.25%), methadone (n=1; 6.25%), methaqualone (n=1; 6.25%), organophosphate (n=1; 6.25%), sodium azide (n=1; 6.25%), salicylate acid (n=1; 6.25%), anti-snake venom serum (n=1; 6.25%), and ethylene glycol (n=1; 6.25%). The range of SBP was from 58 to 179 mmHg, with mean ± SD of 99.4±44.4 mmHg. The range of DBP was from 30 to 100 mmHg, with mean ± SD of 56.7±23.7 mmHg. In electrocardiogram (ECG), sinus tachycardia (n=8; 50%) was the most common finding, followed by sinus bradycardia and normal sinus rhythm (n=2; 12.5%). The overall rate of intubation with mechanical ventilator support was 81.3% (n=13), and the mortality rate was 12.5%. Among all cases of PINCPE, the average LOS was 7.1±3.6 days. All PINCPE cases were classified according to mean age of > or <35.7 years. Relative shorter LOS was observed in the younger group (age <35.7 years), with significance (5.7 vs. 8.9; p=0.022). The heart rate in male patients of poisoning induced non-cardiogenic pulmonary edema is significantly fast than female patients (Figure 2 and Table 2). No statistical difference in terms of SBP, DBP, HR and MAP was observed. The relationship between blood pressures and age is showed in Figure 3.

Discussion

Pulmonary edema is characterized by excessive accumulation of fluid in the extravascular compartments
in cardiogenic pulmonary edema, high pulmonary capillary pressure affects the flow of fluid; whereas, in non-cardiogenic pulmonary edema, damage and leakage of the alveolar-capillary membrane allows increased movement of water and proteins from the intravascular space to the interstitial space. The difference of mechanisms contribute to the result of interstitial protein concentration <45 % compared to the plasma value, and >60% in cases of non-cardiogenic pulmonary edema [7].

Many clinicians distinguish PINCPE from cardiogenic pulmonary edema based on clinical evaluation, plasma BNP or NT-proBNP, with or without trans-thoracic echocardiography to confirm or exclude pulmonary edema. The response to diuretics can confirm the diagnosis of cardiogenic lung edema retrospectively. In addition, the findings of a third heart sound or murmurs of valvular regurgitation, or aortic stenosis suggest suspicious cardiogenic pulmonary edema. One observational study reported that plasma BNP level <100 pg/mL was an effective diagnostic tool in ARDS with a sensitivity and specificity of 27 and 95%, respectively [8]. However, those studies have a disadvantage of non-specific findings. For example, acute heart failure could also be caused by ARDS in case of septic shock, and conversely, volume overloading without cardiogenic factors could lead to pulmonary edema. Patients with non-cardiogenic pulmonary edema require long-term ventilator support with higher fraction of inspiration oxygen by combined PEEP support, as compared to those with cardiogenic type [9]. In our study, up to 81.3% of PINCPE cases required intubation with mechanical ventilator support due to respiratory failure. In the comparison of images, chest radiograph in case of cardiogenic pulmonary edema revealed cardiomegaly with fluffy air-space opacities in both the central and peripheral lungs, patchy distribution of edema while that in non-cardiogenic pulmonary edema revealed peripheral distribution of edema and absence of cardiomegaly [10, 11]. The major causes of non-cardiogenic pulmonary edema include ARDS, high altitude, and neurogenic pulmonary edema; whereas, opioid overdose, pulmonary embolism, eclampsia, and transfusion-related acute lung injury are considered as less common causes of pulmonary edema [12]. PINCPE is a relatively rare form of ARDS; nevertheless, more than 350 drugs have capability to damage the lung parenchyma, airways, pulmonary circulation, pleura, mediastinum, lymph nodes, and neuromuscular system [13]. Hypertension is a common condition in cardiogenic and non-cardiogenic pulmonary edema and develops through various mechanistic pathways: chronic dysregulation of the autonomic nervous system in cardiogenic pulmonary edema, and massive adrenergic discharge due to direct stimulation of the central nervous system centers in PINCPE. During massive surges in the catecholamine level, the blood volume is shifted from the systemic to pulmonary circulation which causes secondary elevation of the left atrial and pulmonary capillary pressures, and consequently, systemic hypertension and pulmonary edema. Norepinephrine and epinephrine are contributing factors for release of secondary mediators (endorphins, histamine, bradykinin) that can cause brain injury and autonomic dysfunction [14].

The mechanism of PINCPE remains unclear. Thompson et al. proposed that drug overdose is a potential risk factor for PINCPE, such as opioid overdose, salicylate, and calcium channel blocker toxicity [15-19]. Moreover, the mechanism may involve interruption in the balance of prostacyclin synthesis and the cell membrane of the mast cells [4]. The change of hydrostatic forces disrupts the vascular osmotic and oncotic pressure, and compromises the epithelial integrity of the lung alveoli, which increases the interstitial flow of the lymphatic system, and pulmonary pressure. As compared to edematous fluid in pulmonary edema, pulmonary fluid in PINCPE may contain a higher amount of protein then in cardiogenic pulmonary edema [20]. In our study, CCBs causing PINCPE included amiodipine, verapamil and diltiazem, which act by blocking the flow of calcium at the level of the cell membrane in the cardiovascular system. Overdose of CCBs may increase prostacyclin synthesis in the vascular system causing precapillary vasodilation and excessive transudation in the pulmonary capillaries [6]. In cases of PINCPE, although we observed both atrioventricular block and bradycardia, ECG mainly indicated sinus tachycardia (50%). With regard to primary physiologic effects, amiodipine, a dihydropyridine type of CCB, reduces the rate of cardiac contraction and conduction by targeting the L-type channel and therefore, is useful in anti-hypertension treatment. However, overdose with dihydropyridine CCB is characterized by responsive tachycardia and strong positive inotropic effect due to drug properties of strong vascular selectivity and vasodilatory action. Verapamil and diltiazem, members of the non-dihydropyridine class of CCB act at the level of both the myocardium and vascular membrane, but target the myocardium more selectively than the dihydropyridine type CCB. Verapamil and diltiazem are highly lipophilic agents that cause precapillary peripheral vasodilatation and decrease of cardiac contractility, which results in excess transudate in the capillaries of the lungs [6].

Hengameh H. et al. reported that narcotic analgesics, such as heroin, morphine, methadone, and meperidine are the most common drugs causing PINCPE [6]. In general, fatality cases due to heroin overdose present PINCPE as the main pathologic finding. Narcotic agents may increase permeability of the pulmonary capillaries and lower the left atrial pressure, which
can cause progression to coma due to hypoxemia. However, clinicians should be aware that the patient may not present typical clinical features of sedative toxidrome [20, 21]. Cooper et al. reported that the mechanism of PINCPE due to narcotic use may be similar to that of neurogenic pulmonary edema due to high sympathetic discharge [4]. PINCPE caused by overdose of salicylate and MDMA may involve the same mechanism as that of narcotic agent of over-production of catecholamine and adverse effects in the CNS and hypothalamus. Further venous return and hypoxemia cause pulmonary capillary constriction and loss of integrity of the vascular endothelium in the pulmonary system which results in PINCPE [14, 22]. Patients with PINCPE due to MDMA use may present elevated systemic blood pressure, and bradycardia reflex due to increase in interstitial fluid and alveolar transudate with capillary damage, which lead to hypoxemia by direct action of MDMA [22].

In our study, the younger group of <35.7 years achieved shorter LOS than the older group (5.7±1.7 vs 8.9±3.2; p=0.022), which may be due to the fact that LOS was prolonged in two of three cases with severe complication after intoxication in the older age group [23, 24]; the first case experienced severe metabolic acidosis and underwent treatment by emergent hemodialysis for 15 days, and the second case progressed to MOF after ingestion of organophosphate and expired 12 days later in the ICU. With regard to prognosis, PINCPE cases showed a mortality rate of 12.5%, which is within the range of intra-hospital mortality rate of 2.1% to 21.9% in 32229 hospitalized patients with ADHF in a previous report [25].

Conclusion

CCB was the most common agent causing PINCPE. Up to 81.3% of PINCPE cases required intubation with mechanical ventilator support due to respiratory failure. Sinus tachycardia was the most common ECG finding (50%). LOS may increase 3.2 days in older group aged ≥35.7 years, if the case is complicated with extra-pulmonary organ failure.

Limitations

Our study has some limitations. First, retrospective search of PubMed database may cause bias in sampling due to under-reported cases worldwide. Second, relatively small number of cases were enrolled which may cause difficulty in the normal distribution of data. Study including large number of cases of PINCPE are required to confirm the result of the present study.

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Author contributions

Hsu C.C. Lin N.H., Yang H.W.: Data curation, writing – original draft preparation.
Su Y.J.: Conceptualization, methodology, formal analysis, writing – reviewing and editing.

Conflict of Interest Statement

None declared.

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References

1. Ware LB, Matthay MA. Clinical practice. Acute pulmonary edema. N Engl J Med. 2005;353(26):2788–96. https://doi.org/10.1056/NEJMcp052699
2. Gottlieb LS, Boylen TC. Pulmonary complications of drug abuse. West J Med. 1974;120:8–16.
3. Duberstein JL, Kaufman DM. A clinical study of an epidemic of heroin intoxication and heroin-induced pulmonary edema. Am J Med. 1971;51(6):704–14. https://doi.org/10.1016/0002-9343(71)90298-1
4. Cooper JA Jr, White DA, Matthay RA. Drug-induced pulmonary disease. Part 2: Noncytotoxic drugs. Am Rev Respir Dis. 1986;133(3):488–505.
5. Low RI, Takeda P, Mason DT, DeMaria AN. The effects of calcium channel blocking agents on cardiovascular function. Am J Cardiol. 1982;49(3):547–53. https://doi.org/10.1016/S0002-9149(82)80010-6
6. Humbert VH Jr, Munn NJ, Hawkins RF. Noncardiogenic pulmonary edema complicating massive diltiazem overdose. Chest. 1991;99:258–9. https://doi.org/10.1378/chest.99.1.258
7. Fein A, Grossman RF, Jones JG, Overland E, Pitts L, Murray JF, et al. The value of edema fluid protein measurement in patients with pulmonary edema. Am J Med. 1979;67(1):32–8. https://doi.org/10.1016/0002-9343(79)90066-4
8. Levitt JE, Vinayak AG, Gehlbach BK, Pohlman A, Van Cleve W, Hall JB, et al. Diagnostic utility of B-type natriuretic peptide in critically ill patients with pulmonary edema: a prospective cohort study. Crit Care. 2008;12(1):R3. https://doi.org/10.1186/cc6764
9. Sibbald WJ, Cunningham DR, Chinn DN. Non-cardiac or cardiac pulmonary edema? A practical approach to clinical differentiation in critically ill patients. Chest. 1983;84(4):452–61. https://doi.org/10.1378/chest.84.4.452
10. Belice T, Yuce S, Kizilkaya B, Kurt A, Cure E. Noncardiac Pulmonary Edema induced by Sitagliptin Treatment. J Family Med Prim Care. 2014;3(4):456–7. https://doi.org/10.4103/2249-4863.148149
11. Dobbe L, Rahman R, Elmassry M, Paz P, Nugent K. Cardiogenic Pulmonary Edema. Am J Med Sci. 2019;358(6):389–97. https://doi.org/10.1016/j.amjms.2019.09.011
12. Givertz MM, Colucci WS, Braunwald E. Clinical aspects of heart failure; pulmonary edema, high-output failure. Zipes DP, Libby P, Braunwald E, editors. Heart disease: a textbook of cardiovascular medicine. 7th ed. Philadelphia: Elsevier Saunders; 2004. p. 539.
13. Camus P, Bonniaud P, Fanton A, Camus C, Baudaun N, Foucher P. Drug-induced and iatrogenic infiltrative lung disease. Clin Chest Med. 2004;25(3):479–519, vi. https://doi.org/10.1016/j.ccem.2004.05.006
14. Yuklyaeva N, Chaudhry A, Gorantla R, Bischof E. Salicylate-induced pulmonary edema – a near-miss diagnosis. Am J Emerg Med. 2014;32(5):490.e5–6. https://doi.org/10.1016/j.ajem.2013.11.021
15. Thompson BT, Chambers RC, Liu KD. Acute Respiratory Distress Syndrome. N Engl J Med. 2017;377(6):562–72. https://doi.org/10.1056/NEJMr1608077
16. Clark SB, Soos MP. Noncardiogenic Pulmonary Edema. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020. [cited 2020 Oct 12]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK542230/
17. Sporer KA, Dorn E. Heroin-related noncardiogenic pulmonary edema: a case series. Chest. 2001;120(5):1628–32. https://doi.org/10.1378/chest.120.5.1628
18. Sporer KA. Acute heroin overdose. Ann Intern Med. 1999;130(7):584–90. https://doi.org/10.7326/0003-4819-130-7-199904060-00019
19. Siddiqi TA, Hill J, Huckleberry Y, Parthasarathy S. Non-cardiogenic pulmonary edema and life-threatening shock due to calcium channel blocker overdose: a case report and clinical review. Respir Care. 2014;59(2):e15–21. https://doi.org/10.4187/respcare.02244
20. Keaney NP. Respiratory disorders. Davies DM, Ferner RE, Glanville H de, editors. Textbook of Adverse Drug Reactions. 5th ed. New York: Chapman & Hall Medical; 1998. p. 202–23.
21. Kakourois NS, Kakourois SN. Clinical Assessment in Acute Heart Failure. Hellenic J Cardiol. 2015;56(4):285–301.
22. Thakkar A, Parekh K, El Hachem K, Mohanraj EM. A Case of MDMA-Associated Cerebral and Pulmonary Edema Requiring ECMO. Case Rep Crit Care. 2017;2017:6417012. https://doi.org/10.1155/2017/6417012
23. Bauer P, Weber M, Mur JM, Protois JC, Bolhaar PE, Condi A, et al. Transient non-cardiogenic pulmonary edema following massive ingestion of ethylene glycol butyl ether. Intensive Care Med. 1992;18(4):250–1. https://doi.org/10.1007/BF01709843
24. Betrosian A, Balla M, Kafri G, Kofinas G, Makri R, Kakouri A. Multiple systems organ failure from organophosphate poisoning. J Toxicol Clin Toxicol. 1995;33(3):257–60. https://doi.org/10.3109/15563659509017994
25. Fonarow GC, Adams KF Jr, Abraham WT, Yancy CW, Boscardin WJ; ADHERE Scientific Advisory Committee, Study Group, and Investigators. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. JAMA. 2005;293(5):572–80. https://doi.org/10.1001/jama.293.5.572
Figure 1. Process of case enrollment

PubMed search with 'poisoning' and 'non-cardiogenic pulmonary edema' from 1986 to 2018: 36 articles

21 articles without detailed data of toxic substances, gender, age, comorbidity, toxidrome, blood pressure (mmHg) pulmonary capillary wedge pressure (mmHg), heart rate, electrocardiogram, echocardiogram, intubation or not, and length of hospital stay.

15 articles (16 cases, one article reported two cases) met criteria of poisoning related non-cardiogenic pulmonary edema (PINCE) were enrolled into this study.
Figure 2. Relationship between length of stay and age in poisoning induced non-cardiogenic pulmonary edema

Figure 3. Fluctuations of blood pressures to age relationship in non-cardiogenic lung edema cases
# Tables

**Table 1.** General data of 16 cases of poison induced non-cardiogenic pulmonary edema enrolled in the study

| SEX (N, %)          | Male (10, 62.5%); Female (6, 37.5%) |
|---------------------|--------------------------------------|
| ELDERLY (N, %)      | (2, 12.5%)                           |
| AGE (YEARS)         | 35.7±19.5                            |
| SYSTOLIC BLOOD PRESSURE (MMHG) | 99.4±44.4                           |
| DIASTOLIC BLOOD PRESSURE (MMHG) | 56.7±23.7                           |
| HEART RATE (BEATS/MIN) | 87.9±34.4                           |
| ECG (N, %)          | Sinus tachycardia (8, 50%)           |
|                     | Sinus bradycardia (2, 12.5%)         |
|                     | Normal sinus rhythm (2, 12.5%)        |
|                     | First degree AVB (1, 6.25%)           |
|                     | Third degree AVB (1, 6.25%)           |
|                     | Not available (2, 12.5%)              |
| TOXIDROME-SUBSTANCE (N, %) | CCB (8, 50%)                     |
| SYMPATHOLYTIC       | CCB (8, 50%)                          |
| SYMPATHOMIMETIC     | MDMA (1, 6.25%)                       |
| SEDATIVE-OPIOID     | Methadone (1, 6.25%)                  |
| SEDATIVE-HYPNOTIC   | Methaqualone (1, 6.25%)               |
| CHOLINERGIC         | Organophosphate (1, 6.25%)            |
| ASPHYXIANT          | Sodium azide (1, 6.25%)               |
| MISCELLANEOUS       | Salicylate acid (1, 6.25%)            |
|                     | Anti-snake venom serum (1, 6.25%)     |
|                     | Ethylene glycol (1, 6.25%)            |
| INTUBATION WITH MV SUPPORT (N, %) | (13, 81.3%)                             |
| LOS (DAYS)          | 7.1±3.6                               |
| MORTALITY (N, %)    | (2, 12.5%)                            |

AVB = Atrioventricular block;  
ECG = Electrocardiogram;  
LOS = Length of stay;  
MV = Mechanical ventilator;  
CCB = Calcium channel blocker;  
MDMA = 3,4-methylenedioxy-methamphetamine.
Table 2. Distributions of the blood pressure, heart rate, and length of stay according to the age group.

| AGE (y) | All Mean±SD (N) | ≥35.7 Mean±SD (N) | <35.7 Mean±SD (N) | Two-tailed p-value |
|---------|-----------------|-------------------|-------------------|-------------------|
| SBP (mmHg) | 99.4±44.4 (16) | 104.9±55.1 (7) | 95.1±37.1 (9) | 0.679 |
| DBP (mmHg) | 56.7±23.7 (16) | 58.7±27.6 (7) | 55.1±21.7 (9) | 0.774 |
| MAP (mmHg) | 71.1±30 | 74.3±36.4 (7) | 68.6±26.1 (9) | 0.719 |
| HR (beats/min) | 87.9±34.4 (16) | 92.4±31.8 (7) | 84.4±37.8 (9) | 0.661 |
| LOS (days) | 7.1±3.6 (11) | 8.9±3.2 (3) | 5.7±1.7 (8) | 0.022* |

Due to small number of enrolled cases, Mann-Whitney U test was used for comparisons in mean age and gender.

SBP = Systolic blood pressure;
DBP = Diastolic blood pressure;
MAP = Mean blood pressure;
HR = Heart rate;
LOS = Length of stay.
N= available case number
*indicates reaching statistical difference.