



Spontaneous Pneumothorax after Physical Exertion on Adolescents with Vaping History in Diponegoro National Hospital, Semarang: A Case Report



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Keywords:

Electronic Cigarette
Exercise
Pneumothorax
Toxicology
Vaping

ABSTRACT

Background: Vaping is a popular and widely used alternative for tobacco-smoking. Despite the popularity, there are limited studies and regulations regarding its side effects. Several studies have shown that there has been an increase in the prevalence of vaping-associated spontaneous pneumothorax (VASP) cases. Pneumothorax is a condition characterized by air accumulation in the pleural cavity, which can progress to an emergency case. However, the condition is rarely associated with physical exercise.

Case Presentation: A total of 2 spontaneous pneumothorax cases were found in Diponegoro National Hospital that presented with chest pain and cough post-exercise in vaping adolescents. The diagnosis was established based on medical history, physical examination, and chest X-ray. Both patients were then treated with water-sealed drainage (WSD) and intensive care.

Conclusion: Pneumothorax is an important diagnosis to consider in patients with vaping history, resulting in long stay and high-cost hospitalization. Adolescents with VASP must receive special attention by conducting electronic cigarette studies and regulations in Indonesia.

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Article history:

Received 20-11-2025
Accepted 22-12-2025
Available online 23-12-2025

DIMJ, 2025, 6(2), 12-18 DOI: <https://doi.org/10.14710/dimj.v6i1.30130>

1. Introduction

Pneumothorax is the accumulation of air in the pleural cavity that can progress to an emergency case. The air accumulation increases the intrapleural cavity pressure, causing the lung to collapse and forcing the major blood vessels to flow backwards, a condition known as tension pneumothorax.^{1,2} The clinical symptoms of this condition include cough, breathlessness, chest pain, and a fast respiratory rate that can happen immediately.³ Several studies have shown that the incidence of pneumothorax without trauma is known as spontaneous pneumothorax (SPT).⁴ For people with good tolerance, spontaneous pneumothorax can occur with minimal symptoms.² The disease is usually found in 20-30-year-old adolescents with a recurrence rate of 25-50%.²

According to previous studies, vaping is the consumption of aerosol from the heating of substances produced by an electronic cigarette (e-cigarette).^{5,6} An e-cigarette is an electronic device that evaporates electronic liquid (e-liquid), which is inhaled through the mouthpiece.⁷ The common substances used in this device include nicotine, cannabinoids, synthetic flavours, and additives.⁶ Initially, e-cigarette was made for tobacco alternatives and were promoted to be a safer choice.^{8,9} However, the compounds used vary, and the lack of standardisation makes it difficult to conduct further studies.⁸

In recent years, there has been an increase in the number of dual users, a term used to describe tobacco and e-cigarette users. This phenomenon causes the main purpose of e-cigarettes to stray from the original intent.¹⁰ An Indonesian study showed an increase in e-cigarette use among the majority of adolescents from the age of 17-24 and a tenfold increase within 1 decade.^{11,12} Several people believe e-cigarettes are safer and a remedy for tobacco smokers, but there is little evidence of their safety and long-term effects.^{8,10}

Several e-cigarette-associated pneumothorax cases, vaping, and its products have recently been widely reported and labelled as vaping-associated spontaneous pneumothorax (VASP) that can progress into a serious illness, or death.^{13,14} Spontaneous pneumothorax post-exercise is a rare condition, but was once found in an athlete.¹⁵ Based on results, this is the first study that reports spontaneous pneumothorax associated with vaping and exercise in Indonesia.

2. Case Presentation

Case 1

Patient A was 22 years old male, a collage student lives in Semarang. He was admitted to the emergency room (ER) with shortness of breath that worsened 3 hours after waking up. This individual also felt chest pain with a puncturing sensation that spread to the right back after a weight-lifting

session 3 days ago. The symptoms were not affected by position and activity, and a dry cough was also experienced for 3 days without medication. The patient stated that the weight-lifting sessions had been for the last week. Fever, allergy, and cold sweat were denied. Furthermore, there was no history of lung infection for the last 2 years, as well as trauma or injury in the chest region for the past month.

The patient was weighing 55 kg, and 170 cm tall, with a normal Body Mass Index (BMI). No history of chronic disease or congenital disabilities was observed. However, the patient had been an active smoker for the last 8 years, with a smoking frequency of 1 pack of cigarettes a day. The patient started using a vape from the past 6 months ago, consisting of 3 pieces of 60 ml bottles with 6 mg nicotine in a mod vape every month. There was also a history of the use of a pod vape with a bottle of 30 ml, consisting of 13 to 15 mg of nicotine per month.

In the initial evaluation, the patient was fully conscious, respiratory rate of 30 times per minute, and a room air saturation of 94%. Blood pressure, pulse, and temperature were all within normal ranges. Thorax physical examination did not show any scar, but there was an asymmetrical chest movement with the right hemithorax slower than the left. Tactile fremitus was decreasing in the right hemithorax, hypersonorous percussion in the right hemithorax, and a decreased vesicular sound of the right hemithorax.

Chest X-ray showed a collapsing full hemithorax, a full avascular lucency in the right hemithorax, and a pleural visceral line, showing a right tension pneumothorax and full collapse of the right lung (see Fig.1a). Initial therapy consisted of nasal canule oxygenation at 3 liters per minute (LPM). Saturation increased to 99% subsequently. The patient got a WSD and chest tube insertion. After WSD, thoracic movement remained asymmetrical, but vesicular sound was heard on both hemithorax. Undulation and bubble air were observed on WSD.

Post-WSD chest X-ray showed a decreasing right pneumothorax with an inflated right lung (see Fig.1b). Subsequently, the patient obtained intravenous infusion Ringer's Lactate (RL) 20 drops per minute, ketorolac injection 30 mg/8 hours intravenous (IV), omeprazole injection 40 mg/12 hours IV. A high-protein diet was also administered during hospitalization.

The third-day evaluation reported that the patient felt short of breath and looked in pain. Chest X-ray evaluation showed a minimal increase in pneumothorax of the right lung compared to previous ones (see Fig. 1c and d). The patient then got referred to a higher-grade hospital for further treatment of chest tube reinsertion with negative WSD and physiotherapy during a 10-day hospitalization. A non-contrast multislice computed tomography (MSCT) examination was performed at the referral hospital. Consolidation with air bronchograms was found in segments 6, 9, and 10 of the right lung, suggesting

pulmonary contusion or pneumonia. Subcutaneous emphysema was found in the right hemithorax. The total duration of hospitalization was 13 days until the outpatient.

Case 2

Patient B was 21 years old male. He also a collage student lives in semarang. Patient B came to the ER with symptoms of chest pain and a dry cough for the last day. Chest pain was affected by cough, and felt shortness of breath. The patient admitted to choking after smoking and taking a vape longer than before. The symptoms were not affected by position and weather. Fever, chronic disease, allergy, and congenital disabilities were denied. The patient has been having routine jogging sessions for the last week. The patient weighth was 58 kg and height was 170 cm tall. This individual admitted to smoking 1 to 2 packs of filter cigarettes per day for the last 8 years. Approximately 2 bottles of 60 ml liquor with a pod vape were also consumed over the past two years. A day before hospitalization, the patient mentioned trying the mod vape after a 1 km run, then coughing.

The initial physical exam showed that the patient was fully conscious, had a fast respiratory rate of 30 times per minute, free air saturation of 89%, blood pressure of 145/75 mmHg, and pulse of 82 times per minute. Physical examination showed intercostal retraction, decreasing right tactile fremitus, hypersonorous percussion on the right hemithorax, and decreasing vesicular sound on the right hemithorax.

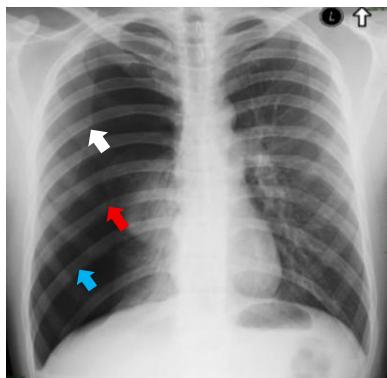
Chest X-ray interpretation showed right pneumothorax with a collapsing superior lobe of the right lung (see Fig.2a).

Initial therapy of 3 LPM oxygenation was performed, and saturation was increased to 97%. Subsequently, the patient got a 32 FR chest tube insertion with negative pressure WSD (thopaz +). Undulation and air bubbles were observed after it.

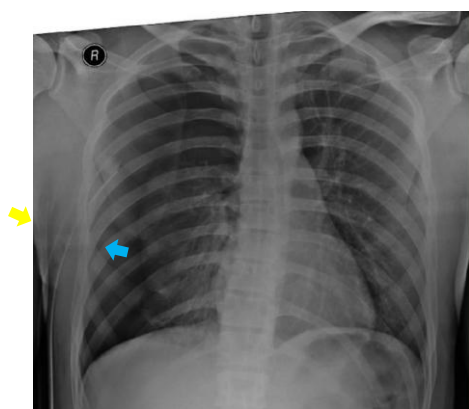
Post-treatment chest X-ray showed a decrease in right pneumothorax and right lung pneumonia (see Fig.2b). The patient was hospitalized and got IV infusion RL 20 drops per minute, ketorolac injection 30 mg/8 hours IV, ambroxol 30 mg/8 hours per oral (PO) nebulizer: salbutamol bisolvon /6 hours, and WSD monitoring.

The fourth day evaluation showed an addition to symptoms of fever and shortness of breath. In physical examination, subcutaneous emphysema on the right and left regions of the neck was found minimally. Rhonchi sound was found on the right lung. On the fifth day of in situ chest tube insertion, WSD Topaz was functioning, fluid production was 0 ml/24 hours, and air leak was 60-70 ml/minute. On the sixth day, an air leak of 500 to 600 ml/minute, a decrease in shortness of breath, and no subcutaneous emphysema were found. Meanwhile, on day 8, chest X-ray of Anteroposterior (AP) and lateral position showed better condition, despite not fully recovered. The

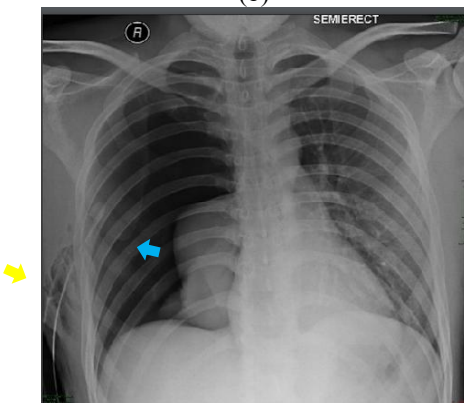
patient got treatment of ambroxol 30 mg/8 hours, cefixime 200 mg/12 hours, mefenamic acid 500mg/8 hours, omeprazole 20 mg/12 hours, Pulmicort nebulization, ventolin, and bisolvon 1 respule/8 hours. The condition was getting better on the ninth day, and the chest tube was removed.



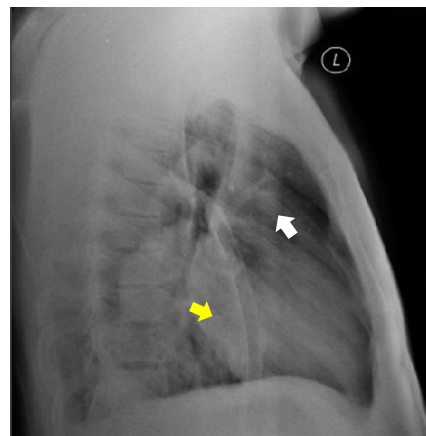
(a)



(b)

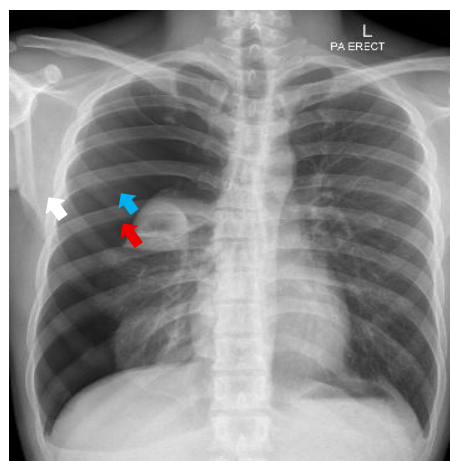


(c)

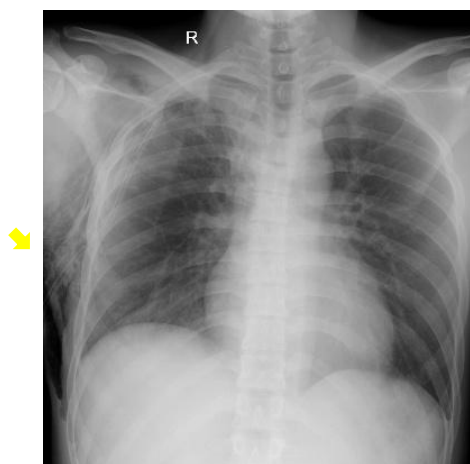


(d)

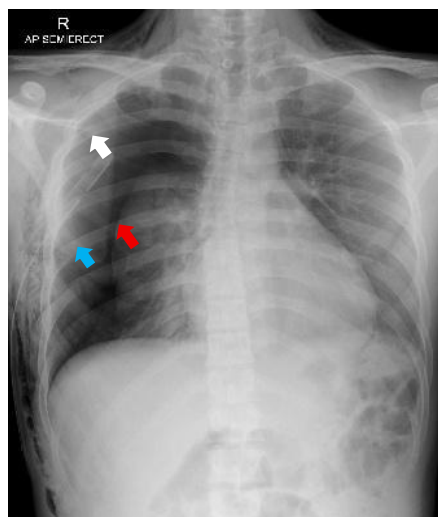
Figure 1. Chest X-Ray on Patient A: (a) Chest X-ray in posteroanterior (PA) position in the emergency room. (b) Chest X-Ray in the anteroposterior (AP) position, one hour after water-sealed drainage (WSD) treatment. (c) Chest X-ray in anteroposterior (AP) position showing a worsening condition of pneumothorax. (d) The lateral position on the third day shows a minimal air increase in the right pneumothorax. The avascular lucency region of pneumothorax (white arrow), the pleural visceral line (blue arrow) and the collapsed right lung (red arrow) are shown. Yellow arrow shows the WSD tube.



(a)



(b)



(c)



(d)

Figure 2. Chest X-Ray on Patient B: (a) Chest X-ray of patient B in posteroanterior (PA) position in the ER showed the avascular lucency of right pneumothorax (white arrow) with collapsing superior lobe of the right lung (red arrow). The pleural visceral line was also visible (blue arrow). (b) Chest X-ray in anteroposterior (AP) position, 1 hour after water-sealed drainage (WSD) treatment (yellow arrow). (c) Chest X-ray in anteroposterior (AP) position and (d) lateral position on the eighth day of hospitalization, the lateral shifting of the pleural visceral line (blue arrow) shows a decrease of right pneumothorax (white arrow) and an inflated right lung (red arrow).

Table 1. Patient Characteristic

Characteristic	Patient A	Patient B
Ethnic	Javanese	Javanese
Domicile	Semarang city	Semarang city
Occupation	Collage student	Collage student
Age	22 years old	21 years old
Sex	Male	Male
Exercise	Weight lifting	Jogging
E-cigarettes type	Mod & pod vape	Mod & pod vape
E-cigarettes frequency	- Mod vape 180 ml liquid nicotine 6mg/month - Pod vape 30ml nicotine 15mg/month	- Pod vape 120ml liquid nicotine 6mg /month - New mod vape
E-cigarettes duration	6 month	2 years
Smoking duration	8 years	8 years
Pneumothorax case	Right	Right
Length of stay	13 days	9 days

Table 2. Patient Laboratory Result

Haematology	Patient A	Patient B	Normal Value
Hemoglobin	15,5	15,6	13,2-17,3 gr/dL
Leukocyte	8.9	10,9	3.8-10.6 10 ³ μ L
Thrombocyte	285	327	150-440 10 ³ μ L
Hematocrit	42,9	44,7	39-49 %
Erythrocyte	5.1	4,9	10 ⁶ μ L
MCV	84,1	90,9	fL
MCH	30,4	31,7	Pg
MCHC	36,1	34,9	g/dL
RDW-CV	11.7	12,8	11.5-14.5 %

3. Discussion

Pneumothorax in both cases was classified as non-traumatic, directing the diagnosis to spontaneous pneumothorax. Primary spontaneous pneumothorax was diagnosed in patients with no history of lung disease, while secondary spontaneous pneumothorax was the opposite.¹⁶ Based on the observation from both cases, without any significant history of disease, lung tuberculosis (TBC) examination was not performed due to the patient's clinical characteristics and lack of sputum. Detailed pathological abnormalities in the lungs could be seen with MSCT. Patient A was suspected of contusio pulmonum or pneumonia. Unfortunately, MSCT was not performed on the second patient due to limited insurance coverage.

In 2019, an outbreak of Lipoid pneumonia was reported because of vaping, where the suspicion was led to deposits of aerosol oil from e-cigarettes that initiated local inflammation in the distal respiratory tract and alveoli. This theory was supported by the result of neutrophil, lymphocyte, and vacuole-laden macrophage on staining of the patient's bronchoalveolar lavage sample. Lipoid pneumonia in vaping was usually found without symptoms, which caused a delay in diagnosis.¹⁷

Both patients reported using 2 similar vape devices, a pod system vape and a mod vape. Mod vape referred to a bulky and complex vaping device with customizable components, a large battery capacity, and adjustable wattage. Pod system vape was generally the opposite of mod vape with simpler, smaller, cheaper, and pen-like design. Pod liquids exhibited a higher nicotine concentration and nicotine salt content than mod liquids. Despite the differences between pod and mod vapes, a 2022 study of pod and mod vape smoker groups proved that both groups were similar in urinary cotinine levels, resulting in similar nicotine amounts. This phenomenon was likely due to the user's behavior of compensation, where pod vape users inhaled a lesser amount than mod vape users.¹⁸

Pneumothorax pathophysiology was known to be multifactorial. Spontaneous pneumothorax occurred in people without underlying disease, and it was usually found in tall smoking males, as in both cases. Pathogenesis was unknown, but bulla rupture or subpleural bleb was suspected to occur from distal respiratory tract inflammation, abnormal connective tissue, low BMI, anatomical abnormality in bronchial bifurcation, and an increase in negative intrapleural pressure.¹⁶

Toxic substances such as Diacetyl, 2,3-Pentanedione, and Acetoin were found in flavoured e-cigarettes that were also known to be related to chronic respiratory diseases.¹⁹ E-cigarettes also altered the genetic expression of the respiratory immune system by increasing Matrix Metalloproteinase-9 (MMP-9) and causing inflammation.¹⁶ Nicotine in e-cigarettes was found to be a factor in inflammation and epithelial tissue damage.²⁰ Another suspected toxic substance was vitamin E-acetate, which was used as a liquid solvent. Vitamin E-acetate was a chemical substance in the form of oil that could be deposited long enough in the lungs and was associated with lipoid pneumonia and popcorn lung.²¹ This toxin caused inflammation, damage, and thinning of alveoli, which led to blebs.¹⁶

Large lung bullae were reported in vaping patients, suggesting a possible causal role for pneumothorax pathogenesis.²² A case of pneumomediastinum was reported in a marijuana vape user, caused by forced expiration, or what was called the Valsalva maneuver.²³ Vaping caused an increase in negative intra-thoracic pressure, increasing inspiration with high resistance, like the Muller maneuver.

Both of the maneuvers caused barotrauma and could result in pneumothorax.²⁴

Pneumothorax treatment was decided based on the air volume in the pleural cavity. The air volume that exceeded 3 cm from the apex and 2 cm from the hilum was categorized as high volume.⁶ In both cases, chest X-ray results showed a high volume of air in pneumothorax, resulting in emergency chest tube insertion even though it was not classified as tension pneumothorax.

Some cases were found in athletes.¹⁵ Pneumothorax cases were previously found to be associated with sport-related trauma.²⁵ In the first case report, pneumothorax onset was suspected to start after a weight-lifting session. Another similar case was reported on a weightlifter with identical symptoms of chest pain initially and no respiratory problems, where it was risky to be misdiagnosed as post-exercise muscle spasm.²⁶ On the second patient, pneumothorax was suspected to have occurred after the running session. This was similar to a reported case of a running athlete.^{27,28} Valsalva maneuver involves taking a deep breath, holding it, bracing the core, and forcing expiration against a closed glottis that could increase intrathoracic and intra-abdominal pressure. During training, the Valsalva maneuver was unavoidable as the body lifted a weight more than approximately 80% of maximal voluntary contraction.^{29,30} The increase of intrathoracic pressure could induce barotrauma as the mechanism for pneumothorax.³¹

4. Conclusion

In conclusion, pneumothorax is an important diagnosis to consider in vaping patients with cough and sudden-onset chest pain or breathlessness, specifically in adolescents with a sports or exercise history. Minimal symptoms in adolescents can lead to misdiagnosis on initial examination. As a result, an appropriate physical exam and chest X-ray are needed as initial evaluations. Further studies in toxicology, e-cigarette, vaping, and their association with pneumothorax cases in society are required. We recommend MSCT examination in further studies to rule out other pathological conditions. E-cigarette distribution, currently a non-regulated commodity, must be a focus. Education on e-cigarette dangers has to be widely broadcast to raise public awareness.

Ethical Approval

We have obtained patient's approval to publish clinical data and radiological images anonymously and maintain the confidentiality safeguards with written consent.

Conflicts of Interest

The authors declare no conflict of interest.

Funding

No specific funding was provided for this article.

Author Contributions

For study articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used as follows: “conceptualization, QNQ, MW and LA; data collecting, QNQ, HAB; writing—original draft preparation, QNQ, MW, HAB; writing—review and editing, QNQ and MW; supervision, H and LA.

References

1. Imran JB, Eastman AL. Pneumothorax. *JAMA*. 2017 Sep 12;318(10):974. Available from: <https://doi.org/10.1001/jama.2017.10476>
2. McKnight CL, Burns B. Pneumothorax. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2023. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK441885/>
3. Iqbal B, Hallifax R, Rahman NM. Pneumothorax: an update on clinical spectrum, diagnosis and management. *Clin Med (Northfield Il)*. 2025;25(3):100327. Available from: <https://www.sciencedirect.com/science/article/pii/S1470211825000454>
4. Sayar A, et al. Size of pneumothorax can be a new indication for surgical treatment in primary spontaneous pneumothorax: a prospective study. *Ann Thorac Cardiovasc Surg*. 2014;20(3):192–7.
5. Marques P, Piqueras L, Sanz MJ. An updated overview of e-cigarette impact on human health. *Respir Res*. 2021;22(1):1–14. Available from: <https://doi.org/10.1186/s12931-021-01737-5>
6. Gotts JE, Jordt S-E, McConnell R, Tarran R. What are the respiratory effects of e-cigarettes? *BMJ*. 2019 Sep;366:l5275.
7. Bertholon JF, Becquemin MH, Annesi-Maesano I, Dautzenberg B. Electronic cigarettes: a short review. *Respiration*. 2013;86(5):433–8.
8. Hiemstra PS, Bals R. Basic science of electronic cigarettes: assessment in cell culture and in vivo models. *Respir Res*. 2016;17(1):127. Available from: <https://doi.org/10.1186/s12931-016-0447-z>
9. Jones RD, Asare M, Lanning B. A retrospective cross-sectional study on the prevalence of e-cigarette use among college students. *J Community Health*. 2021 Feb;46(1):195–202.
10. Syawqie A, et al. The characteristics of electronic cigarette users in Indonesia: a cross-sectional study. *Open Dent J*. 2025;19(1):1–16.
11. Masan GE, Raksanagara AS, Rinawam FR. Knowledge, attitude, and behavior in e-cigar users community in Indonesia. *Althea Med J*. 2023;10(3):167-74.
12. World Health Organization. Global adult tobacco survey: comparison fact sheet Indonesia 2011 & 2021. *Glob Adult Tob Surv*. 2021:1-2. Available from: <https://cdn.who.int/media/docs/default-source/ncds/ncd-surveillance/data-reporting/indonesia/indonesia-national-2021----2011-comparison-factsheet.pdf>
13. Kligerman S, et al. Radiologic, pathologic, clinical, and physiologic findings of electronic cigarette or vaping product use-associated lung injury (EVALI): evolving knowledge and remaining questions. *Radiology*. 2020 Mar;294(3):491-505.
14. Layden JE, et al. Pulmonary illness related to e-cigarette use in Illinois and Wisconsin - final report. *N Engl J Med*. 2020 Mar;382(10):903-16.
15. Aghajanzadeh M, et al. Evaluation of the relationship between primary spontaneous pneumothorax and exercise and return to previous activities in patients referring to hospitals of Rasht during 2015-2017. *Ethiop J Health Sci*. 2021 May;31(3):619-24.
16. Noppen M. Spontaneous pneumothorax: epidemiology, pathophysiology and cause. *Eur Respir Rev*. 2010;19(117):217-9. Available from: <https://publications.ersnet.org/content/errev/19/117/217.abstract>
17. Davidson K, et al. Outbreak of electronic-cigarette-associated acute lipoid pneumonia - North Carolina. *MMWR Morb Mortal Wkly Rep*. 2019;68:784-6.
18. Felicione NJ, et al. Comparing POD and MOD ENDS users' product characteristics, use behaviors, and nicotine exposure. *Nicotine Tob Res*. 2023 Feb;25(3):498-504. Available from: <https://doi.org/10.1093/ntr/ntac211>
19. Allen JG, et al. Flavoring chemicals in e-cigarettes: diacetyl, 2,3-pentanedione, and acetoin in a sample of 51 products, including fruit-, candy-, and cocktail-flavored e-cigarettes. *Environ Health Perspect*. 2016 Jun;124(6):733-9. Available from: <https://doi.org/10.1289/ehp.1510185>
20. Bonilla A, et al. Recurrent spontaneous pneumothoraces and vaping in an 18-year-old man: a case report and review of the literature. *J Med Case Rep*. 2019 Sep;13(1):283.
21. Boudi FB, Patel S, Boudi A, Chan C. Vitamin E acetate as a plausible cause of acute vaping-related illness. *Cureus*. 2019;11(12):e6350. Available from: <http://dx.doi.org/10.7759/cureus.6350>
22. Johnson MK, Smith RP, Morrison D, Laszlo G, White RJ. Large lung bullae in marijuana smokers. *Thorax*. 2000;55(4):340-2. Available from: <https://thorax.bmj.com/content/55/4/340>

23. Miller WE, Spiekerman RE, Hepper NG. Pneumomediastinum resulting from performing Valsalva maneuvers during marijuana smoking. *Chest*. 1972 Aug;62(2):233-4. Available from: <https://doi.org/10.1378/chest.62.2.233>
24. Hazouard E, Koninck J-C, Attucci S, Fauchier-Rolland F, Brunereau L, Diot P. Pneumothorax and pneumomediastinum caused by repeated Müller's maneuvers: complications of marijuana smoking. *Ann Emerg Med*. 2001 Dec;38(6):694-7. Available from: <https://doi.org/10.1067/mem.2001.118016>
25. Partridge RA, Coley A, Bowie R, Woolard RH. Sports-related pneumothorax. *Ann Emerg Med*. 1997;30(4):539-41. Available from: <https://www.sciencedirect.com/science/article/pii/S0196064497700180>
26. Michael J, Caswell S. Pneumothorax in a recreational athlete. *Int J Athl Ther Train*. 2013;18(6):27-31.
27. Townes DA. Spontaneous pneumomediastinum in a marathon runner. *Br J Sports Med*. 2006 Oct;40(10):878-9.
28. Pfeiffer RP, Young TR. Case report: spontaneous pneumothorax in a jogger. *Phys Sportsmed*. 1980;8(12):65-7. Available from: <https://doi.org/10.1080/00913847.1980.11948667>
29. Hackett DA, Chow C-M. The Valsalva maneuver: its effect on intra-abdominal pressure and safety issues during resistance exercise. *J Strength Cond Res*. 2013 Aug;27(8):2338-45.
30. Karkos, P, et al. Application of the Valsalva maneuver in medicine and sport. *Quality in Sport*. 2024;20:53363. Available from: <https://doi.org/10.12775/QS.2024.20.53363>
31. Weerawardane TDS, Bürgisser N, Berner A, Coen M. Valsalva Manoeuvre-Induced Pneumothorax and Pneumomediastinum in a Covid-19 Patient with ARDS: An Unusual Mechanism for this Complication. *Eur J Case Rep Intern Med*. 2024 Feb 28;11(3):004217. Available from: https://doi.org/10.12890/2024_004217