CASE REPORT

Re-expansion pulmonary oedema: a novel emergency therapeutic option

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Accepted 15 April 2016

SUMMARY

Re-expansion pulmonary oedema (REPO) is a rare complication of pleural fluid thoracocentesis and has been associated with a high mortality rate. There is limited evidence to inform on its most effective management. We present two cases of large volume thoracocentesis resulting in acute respiratory decompensation that was treated by reintroducing the drained pleural fluid back into the pleural cavity. We also present a review of the literature specifically assessing the reported incidence rate of REPO after pleural fluid drainage. In both of our cases, symptoms and signs of respiratory instability were promptly reversed on reintroduction of the drained pleural fluid into the patient's pleural space—a therapy we have termed 'rapid pleural space re-expansion'. This was not associated with any short-term adverse outcomes. The occurrence of REPO is a rare event with most cohort studies reporting an incidence of between 0% and 1%.

BACKGROUND

Re-expansion pulmonary oedema (REPO) is a rare complication of thoracocentesis and has been associated with a high mortality rate.^{1 2} Rapid recognition and treatment of the condition is therefore essential. However, there is scant evidence to guide management of this potentially fatal complication.³ We present two cases of large volume thoracocentesis resulting in acute respiratory decompensation, which occurred on the same acute medical unit, and on the same day. In both cases, symptoms and signs of respiratory instability were promptly reversed on reintroduction of the drained pleural fluid into the patient's pleural space.

CASE PRESENTATION

Case 1

A 68-year-old woman, with a background of metastatic breast cancer, type-2 diabetes mellitus and hypercholesterolaemia, presented with a 1-week history of dyspnoea, palpitations and presyncope when mobilising. She also reported of a dry cough and had recently finished a course of palliative capecitabine chemotherapy. She lived with her family and was largely independent. She was a non-smoker.

A chest X-ray demonstrated a large left-sided pleural effusion (figure 1A). A left-sided 12G intercostal pleural drain was inserted and 1000 mL of serous pleural fluid drained into an underwater sealed drain primed with 200 mL of sterile water. Over 15 min, the patient became increasingly distressed with coughing fits—at this point the drain

was clamped. The drainage rate was slowed, but after the drainage of an additional 300 mL, she became acutely dyspnoeic and her oxygen saturations fell to 92% (on 5 L of oxygen via simple facemask). An urgent repeat chest X-ray revealed ipsilateral pulmonary oedema (figure 1B). Advice was sought from a respiratory consultant (author EK) who advised elevation of the chest drain bottle to allow reintroduction of the drained pleural fluid back into the pleural space. Therefore, 300 mL of pleural fluid was allowed to drain back into the left pleural space; this resulted in immediate resolution of the patient's symptoms and improvement in her oxygen saturations. She was monitored on an acute medical unit with continuous oximetry and daily blood tests for the next 48 h. The remaining pleural effusion was gradually drained—200 mL at a time—checking for symptoms of cough and dyspnoea each time.

Case 2

A 72-year-old woman with a background of ovarian cancer was referred to the general medical take with a 1.5-week history of gradually increasing dyspnoea. She also reported of a worsening non-productive cough over several months. Her exercise tolerance had reduced from 200 yards in the week prior to admission, to being short of breath at rest. She lived alone, was fully independent and was a non-smoker. She took no regular medications.

A chest X-ray revealed a large right-sided pleural effusion (figure 2A). A 12G intercostal pleural drain was inserted and 500 mL of serous pleural fluid was allowed to freely drain. This was followed by another 500 mL shortly after. Within minutes of the second drainage, the patient became acutely dyspnoeic and sweaty, and started coughing. Her oxygen saturation level dropped to 86%. As described previously, the chest drain bottle was immediately elevated above the level of the chest to allow reintroduction of the drained pleural fluid back into the pleural space. After 700–800 mL of fluid had been reintroduced, 2–3 min later, the patient's dyspnoea and coughing subsided, and the oximetry readings climbed to within the normal range.

A repeat chest X-ray showed a slightly smaller pleural effusion but minimal radiological evidence of ipsilateral pulmonary oedema (figure 2B). Subsequent pleural fluid drainage was limited to 200 mL at a time, under strict supervision, which resulted in successful, asymptomatic drainage to dryness. A subsequent CT of the chest showed the percutaneous drain, a moderate right-sided pleural effusion and thickening of the right oblique fissure.

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To cite: Sunderland N, Maweni R, Akunuri S, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-215076

Figure 1 Plain chest radiographs - case 1.

DISCUSSION

Literature review

To address the question of whether this technique has been described before, and to assess the incidence of this ‘rare’ complication of REPO (given two potential cases on the same day), a comprehensive literature review was conducted using the Ovid SP interface. We searched MEDLINE and EMBASE from inception up to 27 October 2015, using the following search strategy:

[(lung OR pulmonary) AND (oedema OR edema) AND (re-expansion OR reexpansion)]

Titles and abstracts were manually searched for relevant material. Duplicate, irrelevant and non-English citations were excluded. Citations for which the original manuscript was not available for examination were also excluded.

The remaining citations were coded according to publication type (case report, cohort study, RCT, etc). The primary aetiological issue was also documented (eg, pleural effusion drainage, pneumothorax drainage, etc).

Publications dealing with REPO following pleural effusion drainage were taken for in-depth analysis. Cohort studies were analysed for a documented incidence rate of REPO and case reports were analysed for patient symptoms during development of REPO, investigations performed and management delivered (table 1).

Results

Eight-hundred and two citations were found, using our database search strategy—the results are summarised in figure 3.

Of these, 265 were duplicates, 82 did not address re-expansion pulmonary oedema (irrelevant), 78 were non-English language and 48 publications were unavailable for

analysis. This left 329 citations that were appropriate for further analysis.

One hundred and ninety publications were case reports of REPO. By far the most reported aetiology was REPO following drainage of a pneumothorax (46%, n=88). The second most common aetiology was ‘other’, a heterogeneous mix of pathologies that largely comprised cases of REPO following removal of large thoracic or abdominal tumours, single lung ventilation during surgery and repairs of diaphragmatic herniation (36%, n=68). REPO following pleural effusion drainage was the third most common aetiology reported in the case report literature (14%, n=26).

A summary of the analysis of the case reports is presented in table 1. In patients who developed REPO following pleural effusion drainage, the most commonly reported signs and symptoms were: respiratory distress (72%), desaturation (72%) and cough (24%). Chest X-rays (CXRs) were reportedly used in 84% of cases and a CT of the chest was used in 28% of cases. Supplemental oxygen (48%) and invasive ventilation (40%) were the most commonly used treatments. Recovery and discharge of the patient were described in 58% of case reports. In 10 of the 24 case reports that mentioned patient outcome, the patient in question died.

Fifty-six publications were cohort studies of at least five patients: 26 looked at patients undergoing pleural effusion drainage, 18 looked at patients undergoing pneumothorax drainage, seven at drainage in mixed cohorts and 5 looked at other issues such as postcardiothoracic surgery. The reported incidence of REPO following pleural effusion drainage varies by several-fold—the incidences are graphed against cohort size in figure 4. The largest cohort looked at 9320 pleural fluid drainages and reported 10 cases of REPO.² The smallest cohort, of

Figure 2 Plain chest radiographs - case 2.

Table 1 Summary of case report details

	Value	Number of cases/available data*
Demographics		
Age±SD	49±20	26
Male %	59%	16/26
Aetiology		
Cancer	48%	11/23
Parapneumonic/infectious	17%	4/23
Liver cirrhosis associated	17%	4/23
Other	17%	4/23
Laterality		
Right	54%	14/26
Left	39%	10/26
Bilateral	8%	2/26
Fluid drained		
Millilitres±SD	2301±1341	26
Investigations		
CXR	84%	21/25
CT of the chest	28%	7/25
Bronchoscopy	12%	3/25
Echocardiogram	4%	1/25
Symptoms and signs		
Dyspnoea/respiratory distress/tachypnoea	72%	18/25
Desaturation	72%	18/25
Cough	24%	6/25
Sputum	20%	5/25
Hypotension	20%	5/25
Tachycardia	12%	3/25
Chest pain	4%	1/25
Asymptomatic	4%	1/25
Treatment		
Oxygen	48%	12/25
Intubation and ventilation	40%	10/25
Diuretic	28%	7/25
Non-invasive ventilation	16%	4/25
Inotropes	16%	4/25
Intravenous albumin solution	12%	3/25
Resuscitation	8%	2/25
Steroid	4%	1/25
Drain negative suction	4%	1/25
Intravenous protease inhibitor	4%	1/25
Lateral decubitus position	4%	1/25
Antibiotics	4%	1/25
No treatment given	4%	1/25
Outcome		
Death	42%	10/24

*Not all case reports documented aetiology/signs and symptoms/investigations/treatment/outcome.
CXR, chest X-ray.

only five pleural fluid drainages, reported that all five developed radiological evident REPO.⁴

Discussion

REPO, first described over 150 years ago,⁵ is a rare but potentially life-threatening complication of thoracocentesis, with a reported mortality as high as 20%.¹ Since being described as a complication of draining pleural fluid it has also been described after rapid lung expansion after thoracic/abdominal tumour

removal,⁶ and with drainage of pneumothoraces⁷—indeed these make up the largest single aetiological cause in the case report literature (46%).

Given the common conception that REPO is a rare occurrence, two cases in quick succession on our acute medical unit led us to investigate the reported incidence in the literature. Here we show that reported incidence of REPO postpleural fluid drainage ranges from 0% to 100%, however, the majority of the reported incidences sit between 0% and 1% (figure 4). The several-fold variations in reported rates are highly likely to be due to large differences in cohort population size, as well as varying clinical presentations, unfamiliarity with the diagnosis and difficulty differentiating it from concurrent lung pathologies (eg, underlying patchy consolidation).

The largest study to date reports on 9320 pleural fluid drainages of which 10 (0.01%) developed REPO. In this cohort, data were collected on patients going through the pleural service at a large tertiary referral centre, all drainages were performed or supervised by a single experienced clinician and pleural effusions were drained via manual hand pumping with the aim of draining to dryness where possible.² REPO was diagnosed if there was acute respiratory decompensation (increased work of breathing or oxygen needs) AND unilateral pulmonary oedema on chest X-ray within 24 h of the procedure, OR isolated unilateral pulmonary oedema with lack of another more likely diagnosis. Routine follow-up CXR were not performed. Seven hundred and ninety-nine (8.7%) patients had >1.5 L of fluid drained and the volume of fluid drained was significantly associated with the risk of developing REPO.

The second highest reported incidence of 3.13% came from a heterogeneous study of 32 pleural procedures including diagnostic aspirations and drain insertions, carried out by doctors or a trained nurse practitioner—a single case of REPO was described. The limited number and heterogeneous nature of the procedures makes this value unreliable.

One report of the drainage of five large pleural effusions documents a 100% rate of ‘focal’ REPO in the underlying atelectatic lung, however, that study used –20 cm H₂O suction drainage on four of the five patients and a radiological diagnosis of REPO.⁴ The study’s data should therefore be analysed separately from the majority of the other cohorts as it differs significantly in several important aspects, making it incomparable.

The mortality associated with REPO is often quoted as up to 20%. This value comes from a cohort of 53 cases of REPO following pneumothorax drainage,¹ therefore it is possible that this may not be generalisable to patients undergoing pleural fluid drainage. Unfortunately, the cohorts analysed here did not routinely report mortality. The largest study—of 9320 pleural fluid drainages—of which there were 10 cases of REPO, however, reported no deaths from REPO.² Of our analysed REPO case reports, 42% reported death of the patient—this figure seems high and it is probably unrepresentative of the actual REPO-associated mortality, as the case report literature will be strongly affected by publication bias.⁸

Re-expansion pulmonary oedema should be suspected after an acute deterioration in respiratory function, usually within 1 h of intercostal drainage—the most commonly documented symptoms in the case report literature are: dyspnoea, respiratory distress or tachypnoea (72%), desaturation (72%) and cough (24%). Chest X-ray changes normally show unilateral pulmonary oedema, although bilateral and contralateral pulmonary oedema patterns have been described.^{9 10}

The most reported management strategies in the case report literature were: supplemental oxygen (48%), intubation and

Figure 3 Citation work flow for paper analysis. REPO, Re-expansion pulmonary oedema.

ventilation (40%), and diuretic therapy (28%). It is hard to believe that the use of supplemental oxygen is so low given the proportion of patients reported as demonstrating desaturation in oxygen levels—it is more likely that this simple initial treatment is under-reported in the literature. The high percentage of patients requiring intubation and ventilation gives an idea of the severity of these patients' illness, and to some extent explains the high mortality rate in the case report literature. The British Thoracic Society (BTS) Guidelines 2010 recommend close monitoring and oxygen therapy in the first instance, and acknowledge that continuous positive airway pressure (CPAP) has been used successfully in a number of cases.³ Little evidence exists for diuretics or steroids in the treatment of REPO.

The pathophysiological mechanisms underlying re-expansion pulmonary oedema are poorly understood, however, it is thought that rapid alterations in pleural pressures, decreased surfactant production and accumulation of inflammatory cytokines or free-radical production may underlie the phenomenon.^{11 12} The BTS Guidelines 2010 recognise that pleural manometry is not in routine clinical practice in the UK and reiterates the commonly quoted pleural pressure cut-off value of -20 cm H₂O for termination of thoracocentesis.³ This cut-off value is solely based on animal models using a pneumothorax model,^{13 14} and there remains a small amount of strong human data to support it.

Very low pleural pressures are thought to occur when pleural fluid drainage continues in the presence of a lung that cannot fully expand (entrapped lung) and the resulting increase in transpulmonary pressures may lead to development of chest

pain, pneumothorax ex vacuo, or REPO.¹⁵ The 'entrapped lung' initially displays normal pleural elastance but then, as more fluid is removed, the elastance increases sharply creating very negative pleural pressures; causes of lung entrapment include active pleural inflammation and malignancy, indeed up to 32% of malignant effusions may fit the description of an entrapped lung.^{16 17} We did not use manometry in these two cases. Given that in case 2 thickening of the right oblique fissure was seen on CT, we cannot rule out that this may have contributed to entrapped lung physiology and possibly an increased risk of REPO. Although CT images were not available for the patient described in case 1, postdrainage CXRs showed evidence of neither pleural thickening nor trapped lung.

Despite the lack of strong human data, the fact that a pleural pressure cut-off of -20 cm H₂O has successfully been used in a cohort of 169 patients undergoing thoracocentesis, some of whom had as much as 6 L of pleural fluid removed without development of REPO, may be taken as evidence to support its use.¹² However, attempts to demonstrate a correlation between pleural pressures or pleural elastance, and the development of REPO in a cohort of 185 patients have failed—the caveat to this being that, in the study, there was only a single case of clinical REPO.¹⁸ There are mixed reports as to the efficacy of using manometry to predict clinical endpoints—Pannu *et al*¹⁹ reported that manometry had no significant impact on symptoms (chest discomfort or dyspnoea) during thoracocentesis, whereas, more recently, Galal *et al*²⁰ reported significantly lower pleural closing pressures and higher elastance in patients who became symptomatic during thoracocentesis.

The volume of fluid that can be safely drained is not clear, with some studies reporting drainage of up to 6500 mL without complication,¹⁸ while others suggest smaller volumes.² However, given the uncertainty surrounding defining a 'safe volume' and the potentially high mortality rate,¹ the BTS Guidelines 2010 recommend that drainage be stopped when 1500 mL has been withdrawn, or if the patient develops symptoms of cough or chest discomfort³—of note, both of our patients had less than 1500 mL of pleural fluid drained quickly and freely, and subsequently developed symptoms of re-expansion pulmonary oedema.

In summary, the use of a drainage cut-off of <1.5 L and a manometry pressure cut-off of <-20 cm H₂O appears safe, but perhaps overly so, with the existence of reports of successful high-volume drainage and of lack of correlation between pleural pressures and development of REPO. One must, however,

Figure 5 Process of rapid pleural space re-expansion to relieve symptoms of REPO. REPO, Re-expansion pulmonary oedema.

appreciate that the apparent rarity of REPO episodes makes the analysis of contributory factors difficult, and that senior assessment on a case-by-case basis is currently required to guide further fluid removal until better data are available.

Rapid pleural space re-expansion

In both cases of REPO presented here, we describe successful use of ‘rapid pleural space re-expansion’, using the patient’s own pleural fluid to re-compress the lung (figure 5). To the best of our knowledge, this is the first documentation of this approach used to avert respiratory decompensation and development of REPO after pleural fluid drainage. We hypothesise that reintroducing pleural fluid into the pleural space resolves ventilation-perfusion (V-Q) mismatch, therefore restoring normal oxygenation. This is not the first time this logic has been applied in an attempt to prevent REPO. Nonaka *et al*²¹ have described a case of pneumothorax in which drainage was associated with the development of clinical features of REPO. They describe successful reversal of their patient’s symptoms with opening of the chest drain to the atmosphere, thereby allowing re-collapse of the affected lung—they too propose that this solves a rapidly progressing V-Q mismatch.

In our first case, symptoms persisted for approximately 1.5 h, in which time an interval CXR was performed, which revealed true re-expansion pulmonary oedema, only then was ‘rapid pleural space re-expansion’ used. In our second case, ‘rapid pleural space re-expansion’ was used within minutes of respiratory compromise, consequently an interval CXR could not be obtained. A relatively clear follow-up chest X-ray in the second case may suggest that a potentially severe episode of re-expansion pulmonary oedema was averted. In both cases, pleural space re-expansion resulted in rapid resolution of symptoms and respiratory parameters.

Safety concerns

Both patients were closely monitored in an acute medical unit for at least 48 h after drain insertion. No temperature spikes were recorded and daily blood tests confirmed stable inflammatory markers. Serum electrolytes were also stable throughout their admissions. On the basis of our experience with only two cases, we cannot currently recommend the routine use of pleural space re-expansion as a treatment for REPO. We would,

however, welcome analysis of this technique in a controlled clinical trial setting. Circumstances in which we would advise against its use is when there is suspicion of empyema or when the drained pleural fluid has been out of the pleural cavity for a significant period of time. In both of our cases, the effusions were comprised of a clear watery yellow fluid, and the time between drainage and reintroduction of fluid into the pleural space was less than 2 h. It is also important to note that the water used to prime the water-lock drainage bottle was sterile.

Conclusion

REPO is a rare but potentially life-threatening complication of intercostal drainage. Possible risk factors for developing re-expansion pulmonary oedema include large volume pleural fluid thoracocentesis and the chronicity of the pleural effusion. Guidelines recommend that no more than 1500 mL be drained at a time—the evidence for this is weak but it is considered safe practice. In susceptible patients in whom REPO does occur, the treatment is largely supportive. We report two cases in which rapid pleural space re-expansion resulted in immediate resolution of symptoms and signs of respiratory decompensation, with no associated safety concerns. We would like to see further study into the factors affecting the development of REPO and into its treatment. Although we cannot advocate routine use of rapid pleural space re-expansion due to the scarcity of evidence, we would welcome colleagues’ opinions on this technique and assessment in a controlled clinical trial environment.

Learning points

- ▶ The incidence of re-expansion pulmonary oedema after pleural fluid drainage is between 0% and 1%.
- ▶ Re-expansion pulmonary oedema can present with rapid respiratory decompensation.
- ▶ In the acute setting, allowing the drained pleural fluid to flow back into the pleural cavity appears to be a safe way of reversing the signs and symptoms of respiratory decompensation associated with re-expansion pulmonary oedema, however, more research is needed before its routine use can be recommended.

Contributors NS and RM wrote and prepared the article. SA and EK edited and supervised the project.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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