

Cardiac related pleural effusions: a narrative review

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Background and Objective: Pleural effusions (PEs) are commonly seen in various pathologies and have a significant impact on patient health and quality of life. Unlike for malignant PEs, non-malignant PEs (NMPEs) do not have well-established guidelines. Much of the evidence base in this field is from a handful of randomised controlled trials (RCTs) and the majority are from retrospective cohort analyses and cases series. Cardiac related PEs fall within the entity of NMPEs and the aim of this narrative review is to gather the existing evidence in the field of congestive heart failure (CHF), pericarditis and post-cardiac injury syndrome (PCIS). This narrative review investigates the pathophysiology, diagnostic criteria and treatment options for the various cause of cardiac related PEs.

Methods: This narrative review is based on a comprehensive literature search analysing RCTs, prospective and retrospective cohort analyses and published case series.

Key Content and Findings: CHF related PEs have a substantial mortality rate and carry a worse prognosis if the PEs are bilateral and transudative in nature. Light's criteria have often shown to misclassify transudative effusions in CHF (pseudo-exudates) and hence measuring serum-pleural albumin gradient is an invaluable tool to accurately identify transudates. Elevated serum and pleural N-terminal pro-B type natriuretic peptide (NT-proBNP) has shown increasing evidence of correctly identifying PEs secondary to CHF. However, they should be considered with the pre-test probability of CHF. Therapeutic thoracentesis and indwelling pleural catheter (IPC) placement may be necessary if medical management has failed. PEs can also occur secondary to pericarditis and are often small, bilateral and exudative. PCIS also results in PEs and are commonly seen in post-coronary artery bypass graft (CABG) surgery. Both entities need management of the underlying cause first, but in cases where PEs are refractory, individualised pleural interventions may be necessary.

Conclusions: This comprehensive narrative review provides valuable insights into the aetiology, diagnosis and management of PEs secondary to CHF, pericarditis and PCIS. The aim is to enhance the clinicians' knowledge of this complex and controversial topic to improve patient care of cardiac-related PEs. Ongoing trials in this field will be able to provide valuable insights.

Keywords: Non-malignant pleural effusions (NMPEs); cardiac related pleural effusions; congestive heart failure (CHF); indwelling pleural catheter (IPC); pericarditis

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Introduction

Pleural effusions (PEs) are commonly seen in various pathologies and develop in approximately 1.5 million people each year in the United States (US). An estimated 1.1–1.3 million of these are due to non-malignant PEs (NMPEs) (1). In the UK, there are approximately 200,000–250,000 cases of new PEs each year (2). Although 70–80% of all PEs are NMPEs, their management has been largely derived from the techniques established and validated in malignant PEs (MPEs) (1). NMPEs are caused by either systemic factors such as renal, hepatic or cardiac failure or by local disease processes such as inflammatory pleuritis, infection, pulmonary embolism or thoracic surgery. PEs secondary to congestive heart failure (CHF) represent the leading cause amongst all NMPEs with an estimated annual incidence in the US of 500,000 (1,3).

Guidelines have been produced by the British Thoracic Society and American Thoracic Society for malignant PEs, but there are no equivalent guidelines that exist for NMPEs (4,5). The development of cardiac related PEs can cause dyspnoea and poor quality of life and it is important that healthcare professionals manage such patients efficiently with the current evidence base that is present in this field.

There are numerous causes for cardiac related PEs with the vast majority attributed to CHF. The other main causes are PEs related to pericarditis and post-cardiac injury syndrome (PCIS). In recent years, there has been a noteworthy accumulation of case series, retrospective and prospective studies and a few randomised controlled trials (RCTs) in the field of NMPEs. The objective of this

narrative review was to extract the pertinent evidence base to enhance the readers' understanding of this subject area and thereby allow them to incorporate this into their daily clinical practice. We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1731/rc).

Methods

An in-depth literature search was performed in Ovid MEDLINE database and the full search strategy can be seen below (*Table 1*).

Discussion

Cardiac related PEs and mortality

MPEs are known to be associated with a high mortality but there is increasing evidence that patients with NMPEs also carry a high mortality rate especially when the PEs are related to CHF (6). A prospective analysis carried out in a single English institute of 356 NMPEs showed that CHF had the highest mortality out of all other causes of NMPEs with a 6-month and 1 year mortality of 40% and 50% respectively (7). This study also showed that if the PEs were bilateral [hazard ratio (HR), 3.55; 95% confidence interval (CI): 2.22–5.68, P<0.001] and transudative (HR, 2.78; 95% CI: 1.81–4.28, P<0.001), they carried a significantly worse prognosis than being unilateral and exudative with a 1-year mortality of 57% and 43%, respectively. These findings were also echoed

Table 1 Search strategy and study selection

Items	Specification
Date of search	10 th September 2023
Databases and other sources searched	Ovid MEDLINE
Search terms used	Pleural effusion, heart failure, coronary artery bypass, post-CABG syndrome, cardiac surgery, thoracic surgery, pericarditis, Dressler syndrome, thoracentesis, pleural aspiration, pleural tap, indwelling pleural catheter, IPC
Timeframe	2000–2023
Inclusion and exclusion criteria	All available studies (case series, prospective/retrospective cohort studies, randomised control trials, review articles, systematic reviews and meta-analyses) were included. Language limited to studies only published in English
Selection process	Two authors (T.W., A.Y.) independently reviewed and selected studies and review articles. Where consensus was not met, third author (R.P.) was involved

CABG, coronary artery bypass graft; IPC, indwelling pleural catheter.

by another prospective analysis performed in the US (8). CHF related PEs are classified as a "benign" process, but given the significant mortality risk and poor prognosis, we are of the opinion that this label is a misnomer.

CHF and PEs

The formation of a PE in the context of CHF follows Starling's principles. Elevation of left ventricular end-diastolic pressure and left atrial pressure causes the hydrostatic pressure in the interstitial capillaries to increase. This results in an increase in the volume of interstitial fluid in the lung which then moves across the visceral pleura into the pleural space (9). The production of fluid overrides the reabsorption capacity of the pleural lymphatics which results in the formation of unilateral or bilateral PEs (10). Although PEs are commonly seen in left sided heart failure, they occur in right heart failure as well. These PEs are generally small in size and approximately 13% of patients with familial or idiopathic pulmonary arterial hypertension have PEs secondary to right sided heart failure (11).

CHF related PEs can be seen in 87% of patients who have decompensated CHF undergoing diuresis (3). In patients who have uncomplicated CHF, bilateral PEs occur in 73% of cases (12). Patients who have CHF, complain of breathlessness and in most occasions this is multifactorial. Patients can have various other comorbidities such as respiratory ailments which can contribute to this. It is important to understand that the presence of PEs in CHF may not necessarily make the patient breathless and the size of the PE(s) may not necessarily correlate with the degree of breathlessness. The sensation of breathlessness in the presence of PEs could arise from both a combination of reduction in tidal volume due to the mass effect of fluid in the chest cavity and also due to limitation in normal diaphragmatic movement (13).

CHF should be suspected if there is clinical evidence of jugular venous distension, orthopnoea, third heart sound and peripheral oedema. Radiologically, chest radiographs and computed tomography (CT) scans typically show evidence of cardiomegaly, interstitial oedema, left atrial enlargement and bilateral PEs. CHF related PEs can be unilateral and they are often more common on the right side (27%) and the exact pathophysiology of this phenomenon is unclear (14). More than 80% of CHF related PEs are small in size occupying less than one-third of the hemithorax and rarely (2%) occupy more than two-thirds of the hemithorax (15,16). In certain situations, pleural fluid may collect

between interlobular fissures which can mimic a mass. This collection of fluid resolves with diuretic therapy, a phenomenon that is referred to as a "vanishing tumour" (17).

Breathlessness in CHF is not always due to the presence of PEs and in most cases, the underlying cause of CHF can make the patients breathless. Treatment of CHF itself is important and the exact treatment options depend on the underlying cause. However, if PEs secondary to CHF are deemed to be causing breathlessness, it is imperative to optimise with one or more diuretics/other cardiac medication prior to invasive pleural procedures.

In a prospective study of 60 patients with CHF related PEs, 89% of patients who underwent diuretic treatment, no longer had PEs after 2 weeks of follow up (3). Failure to achieve a significant resolution of PEs despite optimum medical therapy is not uncommon. Moreover, patients also develop electrolyte imbalances, renal impairment and low blood pressure due to increased doses of diuretics. Approximately, 10% of patients with CHF related PEs do not respond to medical management (3). In such situations where PEs are refractory to medical management, patients usually need invasive therapeutic interventions such as thoracocentesis or placement of an indwelling pleural catheter (IPC). The evidence for management of PEs with thoracentesis vs. IPCs will be discussed in detail later in this review.

Pleural fluid analysis in CHF related PEs: are they all transudates?

A diagnostic aspiration is not always necessary especially when clinical features are typical of CHF. However, a diagnostic aspiration should be considered if the PEs are unilateral, lack of other radiological features of CHF such as cardiomegaly, PEs are greatly unequal in size (one side bigger than the other) or lack of adequate response to diuretics (18). Furthermore, it is imperative to note that PEs in the context of CHF may not solely be due to the underlying cause (CHF). They could also result from other conditions such as pneumonia (parapneumonic effusions), empyema or pulmonary embolisms. Clinicians should be vigilant for other symptoms and signs such as fever, pleuritic chest pain and raised inflammatory markers in blood analysis (17).

Recently, there has been a discussion in published literature regarding the incidence of transudative malignant effusions. The exact incidence of this is unclear; however, Ferreiro *et al.* suggest that the existing literature shows

Table 2 Studies investigating serum-pleural albumin gradient

Study	Sample size	Sensitivity, %	Specificity, %
Roth et al. [1990] (29)	59	95	100
Gonlugur et al. [2005] (30)	381	69.4	92.4
Romero-Candeira et al. [2002] (21)	249	88	86
Sangsayunh et al. [2012] (31)	86	90.1	33.3
Bielsa et al. [2012] (24)	364	95	N/A
Burgees et al. [1995] (32)	293	87	92
Sandeesha et al. [2020] (33)	66	93.2	N/A

the incidence of transudative malignant effusions to be between 1–17.4% (19). It is always important to review the patients' history, clinical examination findings and existing radiology when interpreting pleural fluid results and as a routine all patients should have a cytological analysis of their pleural fluid performed. It is also imperative to note that malignancy and CHF can co-exist and if the overall clinical picture suggests that there might be a possibility of malignancy, further investigations such as pleural biopsy or medical thoracoscopy may need to be considered.

Analysis of pleural fluid further reinforces a diagnosis of CHF if Light's criteria for a transudate are met. CHF causes more than 75% of all transudative effusions (20). Light's criteria are consistently more reliable in ascertaining the final diagnosis of a cardiac transudate, as the clinical judgement of the physician without thoracentesis has a sensitivity of less than 60% (21). In two studies that each had 64 and 75 transudative effusions, clinical judgement without thoracentesis misidentified 28 of 64 (44%) and 36 of 75 (48%) transudates, respectively (21,22). Application of Light's criteria improved the misclassification rate to 25% and 36%, respectively (21,22).

Whilst Light's criteria remain the gold standard for discriminating exudates from transudates, the main associated limitation is incorrect identification of transudative effusions. Cardiac PEs can be classified as transudative effusions as per Light's criteria in 72% of cases (23). The remainder of effusions are commonly labelled as exudative according to Light's criteria, however, due to the nature of their pathogenesis and relatively low protein and lactate dehydrogenase (LDH) values, these could be described as mislabelled (24). Mislabelled transudative effusions barely meet exudative criteria and is usually seen when the patients undergo diuretic treatment prior to thoracentesis or if the pleural fluid red blood cell count is greater than

10,000×10⁶/L (17). Diuretic therapy has the potential of converting an initially labelled transudative effusion to an exudate (25). Among patients undergoing diuresis, pleural fluid protein, LDH and the respective fluid/serum ratios get progressively concentrated thus giving a falsely positive exudate (pseudoexudate) (26). Romero-Candeira *et al.* performed thoracentesis at 48-hour intervals in patients undergoing diuresis and found that the pleural fluid protein increased by 43% and pleural fluid LDH increased by 67% which resulted in an increase in pseudo-exudates (26). The mechanism driving this change is thought to be due to losing water from the pleural fluid (27) and the thoracic lymphatics remove larger protein molecules at a slower rate, thus increasing the relative concentration of the pleural fluid protein (25).

Approximately, 80% of PEs can be reclassified as "true transudates" by comparing the pleural fluid protein and albumin levels with respective values in serum and calculating serum-pleural protein gradient and serum-pleural albumin gradient (28). If the serum-pleural fluid protein gradient >3.1 grams per decilitre (g/dL) or serum-pleural fluid albumin gradient >1.2 g/dL is met, such effusions could be classified as transudates (28). *Table 2* has listed below the studies investigating the serum-pleural albumin gradient.

In patients who undergo diuresis, serum-pleural albumin gradient has a higher diagnostic accuracy of correctly identifying transudates than Light's criteria (21). Bielsa *et al.* [2012] showed that the serum-pleural albumin gradient has a higher diagnostic accuracy than the serum-pleural protein gradient (24). Out of 857 transudates, Light's criteria misclassified 29% of all transudates due to CHF and using the serum-pleural albumin gradient >1.2 g/dL, 80.5% of these misclassified effusions were correctly identified as transudates. Using a serum-pleural protein gradient

Table 3 Studies evaluating pleural fluid NT-proBNP

Study	Sample size	Pleural fluid NT-proBNP cut off level (pg/mL)	Sensitivity, %	Specificity, %
Porcel et al. [2004] (40)	117	>1,500	91	93
Kolditz et al. [2006] (41)	101	>4,000	92	91
Porcel et al. [2007] (42)	93	≥1,500	92	87
Liao et al. [2008] (43)	40	>2,220	100	96.7
Han et al. [2008] (44)	240	>1,714	99	99
Seyhan [2009] (45)	115	≥1,092	92	95
Long et al. [2010] (46)	80	≥2,000	80	73
Valdés et al. [2011] (47)	398	>894	85.1	79.9
Cincin et al. [2013] (48)	66	>2,300	70.8	97.6

NT-proBNP, N-terminal pro-B type natriuretic peptide.

>3.1 g/dL, only 62% of these misclassified samples were identified as transudates. Using both serum-pleural albumin and protein gradients, the authors managed to yield a sensitivity of 100% in CHF related PEs.

Role of natriuretic peptides in CHF related PEs

Natriuretic peptides are an array of hormones secreted by the cardiac muscle in response to myocyte stress and/ or increased tension (34). In clinical practice, serum brain natriuretic peptide (BNP) and N-terminal pro-B type natriuretic peptide (NT-proBNP) are widely used for diagnosis, exclusion, management and prognostication of CHF. A BNP <35 picograms per millilitre (pg/mL) and/or an NT-proBNP <125 pg/mL make a CHF diagnosis less likely (35). As the serum BNP or NT-proBNP levels rise, the likelihood of CHF increases and they are particularly beneficial and accurate to exclude CHF when the values are low [negative likelihood ratio (NLR) =0.18] (36).

A considerable number of studies have evaluated the effectiveness of measuring pleural fluid BNP and NT-proBNP. As a pleural fluid biomarker, NT-proBNP is more accurate than BNP for identifying CHF related PEs (37). A meta-analysis comprising ten studies (total of 1,120 patients) found that the average pleural fluid NT-proBNP level in CHF related PEs was 6,140 pg/mL with a sensitivity and specificity of 94% (95% CI: 90–97%) and 94% (95% CI: 89–97%), respectively. The positive likelihood ratio (PLR) was 15.2 (95% CI: 8.1–28.7) and NLR was 0.06 (95% CI: 0.03–0.11). The area under the curve (AUC) was 0.98 (95% CI: 0.96–0.99) (38).

A more recent meta-analysis comprising 12 studies (total of 1,654 patients with PEs), showed that pleural fluid NT-proBNP (threshold of \geq 1,500 pg/mL) had a sensitivity of 94% (95% CI: 90–96%) and a specificity of 91% (95% CI: 86–95%). The PLR was 10.9 (95% CI: 6.4–18.6), NLR was 0.07 (95% CI: 0.04–0.12) and AUC was 0.96 (95% CI: 0.94–0.98) in CHF related PEs (39).

Similar to using serum to pleural fluid albumin and protein gradients to identify misclassified transudates/pseudo-exudates by Light's criteria, pleural fluid NT-proBNP could be used to correctly identify these pseudo-exudates if the pre-test probability is equivocal (38).

Furthermore, it is also evident from these metaanalyses that the correlation between serum and pleural fluid levels of NT-proBNP is high and therefore, invasive pleural procedures such as thoracentesis could be avoided in patients with a clinical probability of CHF without any co-existing suspicious cause of PEs. Whilst it is difficult to be accurate regarding the exact threshold for pleural fluid NT-proBNP, a threshold of approximately ≥1,500 pg/mL provides a good diagnostic accuracy (38). *Table 3* shows various studies evaluating pleural fluid NT-proBNP levels.

The use of NT-proBNP in the management of CHF related PEs can be applied in several clinical scenarios. Firstly, if the pre-test probability of CHF is high (alternative diagnoses are less likely), an elevated serum NT-proBNP level can avoid invasive pleural procedures such as thoracentesis. Secondly, if the pre-test probability of CHF is low and alternative diagnoses cannot be excluded, a diagnostic thoracentesis should be performed. If the pleural fluid NT-proBNP level is high, CHF related PE becomes

Table 4 Studies evaluating use of IPCs in CHF related pleural effusions

Study	Sample size	Primary outcome	Patients achieving pleurodesis (%)	Time to pleurodesis (days)	Complications
Borgeson et al. [2009] (54)	22	Rate of pleurodesis	41	109 (median)	Infection, catheter occlusion
Srour et al. [2013] (55)	43	Improvement in breathlessness	29	66 (median)	Nil
Freeman et al. [2014] (56)	40	Palliation of effusion	35	150 (mean)	Nil
Majid <i>et al.</i> [2016] Group 1 [†] (57)	15	Improvement in breathlessness and pleurodesis	80	11 (median)	Cellulitis
Majid <i>et al.</i> [2016] Group 2 [‡] (57)	28	Improvement in breathlessness and pleurodesis	25	66 (median)	Empyema (2/28), cellulitis
Frost et al. [2020] (58)	30	Symptom control	24	NR	Cellulitis, IPC malfunction
Walker et al. [2022] (59)	21	Mean daily dyspnoea score over 12 weeks from randomisation	Disease specific data not recorded	Disease specific data not recorded	Cellulitis, empyema

[†], medical thoracoscopy, talc pleurodesis and IPC placement; [‡], IPC placement only. IPCs, indwelling pleural catheters; CHF, congestive heart failure; NR, not recorded.

the likely diagnosis.

The recently published British Thoracic Society guideline for pleural disease has advocated the use of serum and pleural fluid NT-proBNP for investigation of a unilateral PE in the context of CHF. However, this approach needs caution as there could be multiple coexisting conditions contributing to PEs (4). Current evidence base reinforces the idea that an elevated pleural fluid NT-proBNP level adds weight to a suspected diagnosis of CHF related PEs or triggers the consideration of the clinician to consider CHF when the diagnosis is unknown.

Management of CHF related PEs

The initial approach to manage CHF related PEs involve in optimising the overall control of heart failure with one or more diuretics or other heart failure medication. If PEs do not resolve with heart failure medication, periodic drainage of the pleural space can be achieved through therapeutic aspirations which leads to an immediate, long-standing (weeks to months) improvement in most patients with CHF (49).

In CHF, therapeutic aspirations may be required repeatedly as PEs are often recurrent. It is not unreasonable to consider the insertion of an IPC in these cases. IPCs were initially approved for use by the Food and Drug Administration (FDA) federal agency in 1997 and this was mainly investigated as a treatment option in the

context of MPE (50). IPCs have been shown to improve breathlessness, reduce hospitalisation and the number of invasive pleural interventions (mainly therapeutic thoracentesis) when compared to talc pleurodesis in the context of MPE (51). However, over the last decade, IPCs have been gaining popularity in the management of recurrent NMPEs, including in CHF related PEs. In 2017, IPCs were approved for use by the FDA for the management of refractory NMPEs despite the lack of data from RCT (52).

Herlihy et al. reported the use of IPCs in CHF related PEs for the first time in 2009 (53). In this case series, five patients had recurrent PEs despite optimal medical therapy and had undergone at least two therapeutic pleural aspirations within a fortnight. All study participants experienced an improvement in breathlessness and New York Heart Association (NYHA) classification from class IV to class II following placement of an IPC. However, the complication rate was high. One patient developed a loculated effusion and two patients developed empyema (one died from septic shock 15 months post-IPC insertion). The IPC drainages in this study have been mostly done by patients themselves which arguably increases the risk of infection. The authors concluded that IPCs were effective in CHF related PEs but advised caution with long-term use.

Subsequently, there have been other studies assessing the efficacy, safety and frequency of pleurodesis with IPCs in CHF related PEs. These are listed in *Table 4*.

Currently, there is only one published randomised controlled trial (REDUCE) by Walker et al. (59) evaluating the role of repeated therapeutic pleural aspirations versus IPC in NMPEs including CHF related PEs. The REDUCE trial recruited 68 patients of which 46 had CHF related PEs. Twenty-five patients were randomised to therapeutic pleural aspiration arm and 21 to the IPC arm. The primary outcome was the mean daily dyspnoea score over 12 weeks from randomisation. There was no statistically significant difference in breathlessness between the two arms demonstrating that IPCs were not superior to repeated therapeutic aspirations in the context of CHF related PEs. This is despite large differences in the volumes of fluid drained between the two groups. On average, the IPC arm drained at least 6 times more fluid than the therapeutic aspirations arm. The mean breathlessness score in the IPC arm was 40.7±27.5 and in therapeutic aspirations arm this was 48.5±24.6 (P=0.62). The study was under-powered and may have been unable to detect small differences in breathlessness scores between the two groups. Overall, there were more adverse events in the IPC arm and 59% (n=39) had at least one adverse event compared to 37% (n=24) of patients in the therapeutic aspirations arm. Commonly seen adverse event with IPCs were cellulitis and pleural space infection.

A systematic review and meta-analysis by Patil et al. [2017] analysing the efficacy and safety of IPC use in NMPEs demonstrated that IPCs are an effective and viable option in the management of CHF related PEs (60). Thirteen studies (mostly case series and retrospective cohort studies) were included in this meta-analysis. Of the total of 325 patients, 49% (n=162) had CHF related PEs. The sub-group analysis showed that spontaneous pleurodesis was achieved in 42.1% [95% CI: 20.1–64.1%, I^2 =88.4%, Q=51.8 (P<0.001)] in CHF related PEs. The meta-analysis also reported that overall, patients who had an IPC had a reduction in hospital stay (including readmission rates) when compared with patients who did not have an IPC (mean of 4 days less in the IPC group). One of the major complications in the IPC group was empyema with 9 reported cases. These were all treated medically with intravenous antibiotics and none required surgical intervention. Three patients required IPC removal and one patient died due to severe sepsis. Post-IPC placement and drainage, none of the studies reported any electrolyte imbalances. The studies in this meta-analysis were non-randomised trials with low quality of evidencethis is currently the best available data related to this topic.

Managing CHF related PEs can be challenging.

Therapeutic thoracentesis of pleural fluid is a viable option in these patients however, this approach requires multiple hospital visits. An additional challenge for repeat procedures is withholding anti-coagulations or antiplatelets. IPCs seem to be a feasible therapeutic option in these patients but this should be carefully assessed by the clinician once medical management has been fully exhausted. The treating clinician must consider patient preference and circumstances in selecting the most appropriate intervention strategy. IPC is an optimal solution to avoid repeated hospital admissions, in those who do not tolerate repeated thoracenteses and where repeated interruption of anticoagulant therapy is undesirable.

PEs in pericarditis

Pericarditis, inflammation of the pericardium can be due to multiple causes such as viral/bacterial infections, diffuse carcinomatosis, tuberculosis and autoimmune pathologies. In Western countries, around 55% of cases are idiopathic in nature (61,62). PEs can occur with pericarditis (63). Due to the anatomical boundaries of the pleural and pericardial surfaces, PEs are thought to develop due to contiguous inflammation in the context of acute pericarditis (64,65). Much of the evidence on this topic is from case series that have been derived from databases and/or patient registries.

Lazaros et al. [2019] analysed a cohort of 177 patients with a first episode of acute pericarditis who had been hospitalised. These patients were prospectively followed up over a median follow-up period of 12 months (range, 1-18 months) (66). A total of 94 cases (53.1%) had evidence of a PE(s) of which 53.2% were bilateral, 28.7% were left sided and 18.1% were right-sided. The presence of a PE was strongly associated with the C-reactive protein (CRP) levels at admission (rho=0.328, P<0.001). Furthermore, they found that female sex [odds ratio (OR) =2.46, 95% CI: 1.03-5.83], age (per 1-year increment OR = 1.030, 95% CI: 1.005-1.056) and size of pericardial effusion (per 1 cm increment, OR =1.899, 95% CI: 1.228-2.935) were independent predictors for PEs in the context of pericarditis. Bilateral PEs increased the risk of occurrence of cardiac tamponade (OR =7.52, 95% CI: 2.16-26.21). PEs were not associated with new onset atrial fibrillation or recurrence of pericarditis in long-term follow-up. Authors of this study did not analyse the pleural fluid which is in contrast to other cases series that have been published.

Similarly, Porcel et al. [2014] analysed 3,077 consecutive patients who underwent diagnostic thoracentesis and

reported that 4% were due to pericardial disease and were mostly bilateral (64). The same author group carried out an evaluation of 82 patients with acute idiopathic pericarditis and bilateral PEs were present in 41% of cases and left sided PE was present in 55% of cases. 90% occupied less than a third of the hemithorax. 99% of these effusions were exudative as per Light's criteria and in three quarters of cases, the effusions were lymphocytic in nature.

More recently, Ahmed *et al.* [2022] analysed a cohort of 60 patients with pericarditis and 24 (39%) had presence of PEs on simultaneous imaging (63). Twenty PEs were bilateral and four PEs were left sided. Pleural fluid analysis was performed in ten cases. In these patients, the mean pH was 7.46 (7.33–7.60), mean LDH level was 210 U/L (74–393 U/L), mean protein level was 36.1 g/L (19–56 g/L), mean glucose level was 5.8 mmol/L (4.8–6.8 mmol/L) and cytology was negative for any form of malignancy. Six patients had large volume therapeutic aspirations to aid breathlessness while an IPC was inserted in three cases due to refractory PEs. Two patients underwent auto-pleurodesis and one patient with an IPC developed an empyema and required intrapleural fibrinolytics and removal of the IPC.

Typically, patients are treated for their underlying cause (pericarditis) with a combination of ibuprofen, colchicine and steroids for a few weeks (e.g., up to 3 weeks) and the PEs resolve gradually (63). Based on the current evidence, it is noted that PEs in the context of pericarditis are usually small, bilateral and exudative in nature. This should be noted when investigating such patients with invasive pleural interventions being reserved for those patients where adequate response to treatment is not achieved, PEs that are refractory despite treatment or history/examination reveals any red flags that are concerning for other causes.

PEs in PCIS

PCIS refers to an autoimmune mediated group of conditions which causes inflammation of the pericardium, epicardium and to a certain extent the myocardium (67). This can be diagnosed in the presence of fever and signs of pericardial and/or pleural inflammation typically days to weeks after myocardial injury secondary to acute myocardial infarction (Dressler's syndrome), valvular cardiac surgery, coronary artery bypass grafting (CABG) or pacemaker implantation. Patients can have electrocardiogram (ECG) changes such as widespread ST segment elevation and PR depression in multiple leads along with a pleural friction rub which aids diagnosis (67).

PEs after CABG surgery are not uncommon and can be seen in 10% of patients in the month following surgery (68). They are typically small and can be bilateral. Vargas et al. demonstrated that most PEs (57%) were bilateral at 7 days post-CABG surgery and 67% were left sided at 30 days post-surgery (69). It has been noted that the prevalence of PEs are generally higher when patients have received an internal mammary artery graft (69,70). The exact pathogenesis of post-CABG surgery PEs is not clearly understood; however, it is thought that the early small, leftsided effusions are probably related to the trauma of the surgical procedure which results in inflammation (68,69). Transforming growth factor-beta (TGF-beta) and vascular endothelial growth factor (VEGF) have been found to be raised in pleural fluid pre-operatively which are thought to increase the permeability of the pleural surface which results in PEs (71). Interleukin-6 (IL-6) has been also found to be raised in pleural fluid post-operatively which suggests that CABG surgery may result in an inflammatory state (72).

PEs occupying more than 25% of the hemithorax can occur early (within the first 30 days post-surgery) or late. The early PEs are usually haemorrhagic, exudative and eosinophilic in nature along with a high LDH level. The mean pleural fluid LDH level has been reported to be 3 times the upper limit of normal of serum LDH level. In contrast, late PEs are non-haemorrhagic and are lymphocyte predominant with a low LDH level (73). The observation that late PEs are lymphocytic in nature suggests an inflammatory-mediated process (73).

In most cases where the PE is small, pleural intervention is not necessary as spontaneous resolution is common. However, if patients are symptomatic with dyspnoea, a therapeutic pleural aspiration should normally suffice. On the rare occasion, when an effusion is recurrent, further thoracentesis or an intercostal drainage could be performed.

Lee *et al.* [2001] describes cases of patients with recurrent symptomatic PEs despite multiple thoracocentesis attempts who underwent further surgery in the form of thoracoscopic decortication to remove the fibrous tissue coating of the visceral pleura. This allows the lung to re-expand and prevents further accumulation of pleural fluid. However, it is not absolutely clear if decortication of the visceral pleura or mechanical/chemical pleurodesis at the time of thoracoscopy was responsible for resolution of the PEs (74).

A recent large scale retrospective analysis by Welch *et al.* [2023] explored the possible association of post-CABG PEs and prior asbestos exposure in the period of 30 days to 1 year following CABG surgery (75). The authors found

that with asbestos exposure, there was a modest increase in the odds of developing a PE post-CABG surgery. The odds of diagnosis of a PE or requirement of a pleural procedure (thoracentesis or chest drain insertion) had an adjusted OR of 1.35 (95% CI: 1.03–1.76, P=0.04). The risk association was doubled in patients who had radiological evidence of asbestos exposure (pleural plaques or asbestosis) [OR of 2.16 (95% CI: 1.38–3.37, P=0.002) requiring a pleural procedure for post-CABG PE]. The authors concluded that this observation could be due to possible priming of the pleura with asbestos exposure which results in a greater propensity of developing a PE after the physiological insult of CABG surgery.

Looking into the future: ongoing clinical trials

A search carried out in the International Standard Randomised Controlled Trial (ISRCT) registry revealed that, at the time of writing this narrative review, there is an ongoing randomised feasibility study (REDUCE 2, ISRCTN10499680) studying the effect of IPC insertion in CHF related PEs with aggressive drainage and talc pleurodesis vs. repeated therapeutic thoracentesis on an as required basis. Study participants will be randomised on a 1:1 basis and will be followed up over a 12-week period. As per the study protocol, in periodic visits, patients will have monitoring of the pleural fluid drainage via IPC (if applicable), clinical assessments, chest radiograph and thoracic ultrasound assessment along with the evaluation of the degree of breathlessness using validated scoring systems.

A search carried out in the US clinical trials registry has shown that there is an ongoing RCT in Denmark (TAP-IT study, ClinicalTrials.gov ID: NCT05017753) whereby patients with CHF related PEs will be randomised to have standard medical therapy only *vs* medical therapy treatment along with therapeutic thoracentesis. The trial group has hypothesised that in those patients who will have thoracentesis, will have a greater number of days alive outside of hospital during the follow up period of 90 days.

Another ongoing prospective case-control study from Hong Kong is studying the discriminative properties of pleural fluid NT-proBNP levels in CHF related PEs (ClinicalTrials.gov ID: NCT05797649). The trial group has hypothesised that the diagnostic performance of pleural fluid NT-proBNP is better than using the Light's criteria and/or the serum-pleural fluid protein and albumin gradients in CHF related PEs.

The TREAT-CHF trial (ClinicalTrials.gov ID:

NCT03696524) which was a RCT assessing to manage CHF related PEs either with IPC and standard medical management vs standard medical management alone has been withdrawn due to lack of enrolment of study participants.

Conclusions

Over the last 10–15 years, there has been a slow but growing body of evidence in the diagnosis and treatment of cardiac related PEs. Much of this has been from relatively small prospective studies, case series and a handful of RCTs. With an aging population with increasing cardiovascular morbidity, this area of pleural medicine will require good quality, large, multi-centre prospective and/or RCTs to draw more concrete conclusions. At present, we are able to draw the following conclusions:

- (I) Cardiac PEs are the most common entity within NMPEs for which there are no specific management guidelines at present.
- (II) Cardiac PEs are mostly due to CHF but can be seen in pericarditis and PCIS. CHF related PEs carry a high mortality risk.
- (III) The commonest symptom with CHF related PEs is dyspnoea and the degree of dyspnoea does not correlate with the size of the PE(s).
- (IV) First line treatment of CHF related PEs is optimum diuresis before attempting any invasive pleural procedures.
- (V) A diagnostic pleural aspiration of PEs in the context of CHF should be considered if the PE is unilateral, bilateral without cardiomegaly or if there is lack of response to diuresis.
- (VI) Whilst Light's criteria remain the gold standard tool to identify exudates/transudates, patients who undergo diuretic treatment can have pseudo-exudates. In such cases, serum-pleural protein gradient of >3.1 g/dL or serum-pleural fluid albumin gradient >1.2 g/dL can be used to classify such effusions as transudative.
- (VII) Pleural fluid NT-proBNP can be used to correctly identify CHF related PEs. This parameter should not be used in isolation and needs to be considered with the pre-test probability of CHF. Pleural fluid NT-proBNP threshold of ≥1,500 pg/mL provides a good diagnostic accuracy.
- (VIII) With respect to IPCs in CHF related PEs and a recent randomised trial (REDUCE) has shown

that there is no difference in breathlessness between repeated thoracentesis or having an IPC. We propose that these decisions need to be patient-centred and the pros and cons of each intervention should be discussed with patients and their families. IPCs can be used as a palliative therapy when all other treatment avenues have been exhausted or where repeated thoracocentesis and/or interruption of anticoagulation is undesirable.

- (IX) PEs in pericarditis are often bilateral and small. Treatment of underlying disease process (pericarditis) normally resolves the PEs. However, in cases where PEs make patients dyspnoeic, therapeutic thoracentesis may be necessary.
- (X) PEs are not uncommon in PCIS and post CABG surgery remains the commonest cause. Early PEs post CABG surgery are haemorrhagic, exudative, eosinophilic and have a high LDH level. Late PEs are lymphocytic in nature with a low LDH level. Invasive pleural procedures may be necessary in symptomatic patients and/or the PEs are recurrent.

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