GUEST EDITORIAL

# Establishing a diagnosis of pleural effusion due to heart failure

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Heart failure (HF) is one of the leading causes of pleural effusion, along with cancer, pneumonia and tuberculosis.[1] Despite being the most common hospital admission diagnosis in patients aged ≥65 years, some studies have reported a relatively low incidence of pleural effusions secondary to HF.[2] One reason for this is that the studies surveyed selected populations that did not include many patients with pleural effusions of this origin (e.g. only patients from respiratory medicine departments or those who underwent thoracentesis). Distinguishing patients with HF-associated pleural effusion from among those with other potential causes allows for the early implementation of appropriate therapy and avoids unnecessary exploration.

The diagnosis of HF may be challenging. Individual symptoms, such as fatigue, dyspnoea on exertion or ortophnea, and clinical signs, including tachypnea, tachycardia, peripheral oedema, hepatomegaly, pulmonary rales or cardiac murmur, have either low sensitivity or specificity for diagnosis. In addition, older patients with HF often present with non-specific symptoms such as insomnia, nocturia, irritability and anorexia that are misdiagnosed as age-related changes or ascribed to age-prevalent comorbidities. The most accurate clinical examination data to support a diagnosis of HF are a previous history of HF [likelihood ratio (LR) 5.8] and the presence of a third heart sound (LR 11), abdominojugular reflux (LR 6.4) and jugular venous distension (LR 5.1).[3] Of note, the overall clinical impression that the patient is suffering from HF is also valuable (LR 4.4).[3]

More than 80% of patients with decompensated HF have pleural effusions demonstrated by computed tomography, ultrasonography or autopsy,[4] although a much smaller proportion of these effusions are visible on routine chest radiographs (as low as 25% in a series of 447 patients with HF).[5] Chest radiological findings arguing for HF are, in descending order of positive LRs, pulmonary venous congestion (LR 12), interstitial oedema (LR 12), alveolar oedema (LR 6), cardiomegaly (LR 3.3) and pleural effusion (LR 3.2).[3,5] However, clinicians should not rule out HF in patients with no radiographic signs of congestion (interstitial oedema, pulmonary venous congestion) because this actually occurs in about one out of every five patients with acute decompensated HF.[6,7] The presence of cardiomegaly is particularly compelling because only a relatively small proportion (20%) of patients with HF lack this characteristic.[6] Radiographically, HF-associated effusions are usually bilateral (70%), but they may be unilateral right (20%) or left sided (10%). More than 80% of cardiac effusions are of a small size, occupying ≤1/3 of the hemithorax.[8] Occasionally, fluid may collect within the interlobular fissures, simulating a mass that disappears with diuretic therapy (vanishing tumour). A bilateral effusion without cardiomegaly should raise the suspicion of malignancy.

The examination of pleural fluid greatly reinforces the diagnosis of HF if Light's criteria for a transudate are met. The reason is that HF causes more than 75% of transudates.[9] However, in the typical clinical scenario (i.e. classical manifestations of HF and bilateral pleural effusions with cardiomegaly), thoracentesis is superfluous. A pleural tap becomes necessary when effusions are unilateral, not associated with cardiomegaly, greatly disparate in size or fail to respond to diuresis, or when the patient has pleuritic pain or fever that suggests an additional process such as pneumonia, pulmonary embolism or post-cardiac surgery.[10]

Clinical judgment by the physician blinded of the thoracentesis results is associated with less than 60% sensitivity for a final diagnosis of cardiac transudate, whereas Light's criteria are significantly superior to this end.[11] Light's criteria, which are based on simultaneous measurements of serum and pleural fluid protein and LDH, remain the gold standard for




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discriminating exudates from transudates.[10] In a single-centre study of 1490 patients with pleural effusion, Light's criteria correctly classified 97.5% of exudates and 80% of transudates.[9] Mislabelled transudates, which barely meet the exudative criteria, are particularly likely if a patient has been receiving diuretics before the thoracentesis or if the pleural fluid red blood cell count is greater than $10\,000 \times 10^6$/L. In the case of patients with HF undergoing diuresis, one study demonstrated that pleural fluid constituents (protein, LDH and their fluid/serum ratios) became progressively more concentrated over time, thus giving rise to false positive exudates.[12] On the other hand, a recent investigation showed that the specificity of Light's criteria for identifying exudates dropped from 81% in patients with pleural erythrocyte counts $\leq 10\,000 \times 10^6$/L to 61% in those with higher red blood cell counts.[13] Bloody fluid was found in 15% of the cardiac effusions. The misclassification of the bloody effusions as exudates was due to a change in the pleural fluid LDH values and/or the pleural fluid to serum LDH ratios.[13] If the clinical picture is consistent with HF but the pleural fluid meets exudative criteria, examination of the serum to pleural fluid protein or albumin gradients is recommended. If these gradients are greater than 3.1 g/dL and 2.1 g/dL, respectively, one can assume that the fluid is most likely a real transudate.[10]

In recent years, circulating levels of natriuretic peptides have proven to be a useful adjunctive tool in the diagnosis of HF. Both B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are secreted almost exclusively from the ventricles in response to pressure and volume overload. Patients with a serum BNP level <100 pg/mL or NT-proBNP <400 pg/mL are unlikely to have HF, whereas those with respective concentrations of >400 pg/mL and >2000 pg/mL are likely to have HF.[14] Overall, as BNP or NT-proBNP levels increase, the likelihood of HF increases. Natriuretic peptide levels are particularly powerful for ruling out HF when their values are low (LR negative = 0.18),[15] and these tests could therefore reduce the demand for echocardiography and the referrals of patients to cardiologists. In addition to their role in diagnosing HF, evidence exists to support the use of natriuretic peptides for staging, making hospitalization/discharge decisions, and identifying patients at risk for clinical events.[14]

The use of natriuretic peptide assays may help to differentiate between effusions caused by HF and those attributable to other causes.[16] The sum of six studies that measured pleural fluid NT-proBNP in a total of 228 patients with HF-associated effusions and 383 non-cardiac effusions shows that this biomarker has about 95% sensitivity and specificity and a mean area under the receiver operating characteristic curve (AUC) of 0.97 for discriminating between groups.[17–22] In addition, approximately 90% of cardiac effusions mislabelled as exudates by Light's criteria can be correctly classified by pleural NT-proBNP, a percentage that is superior to that obtained by examining the gradient between the serum and pleural fluid protein levels.[20,22] Two studies have demonstrated a comparable diagnostic utility at the same cut-off values for serum and pleural NT-proBNP.[19,20] Therefore, serum rather than pleural NT-proBNP measurement may be preferable, provided thoracentesis is not being planned. The optimal threshold value for natriuretic peptides to diagnose or exclude HF in patients with pleural effusion is unclear. In our experience, serum or pleural fluid NT-proBNP levels >1500 pg/mL are highly accurate in confirming the presence of cardiac effusions.[17,20] Although the operating characteristics of pleural fluid BNP levels are good enough at a cut-off point of 115 pg/mL, this test is less powerful than pleural NT-proBNP for decisively pointing to HF.[23] Finally, a pilot observational study examined plasma BNP concentrations in 34 patients who had HF-associated effusion and 26 patients with non-cardiac effusions.[24] When a cut-off level of 520 pg/mL was used, the sensitivity was 97% and the specificity was 89% for the diagnosis of HF.[24]

In conclusion, these results, taken together, support the use of NT-proBNP in clinical practice as a biomarker of HF, measured in either serum or pleural fluid. This test may prove particularly helpful for diagnosing cardiac pleural effusion in patients whose pleural fluid appears exudative.

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