Increased blood volume following resolution of acute cardiogenic pulmonary oedema: a retrospective analysis

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Accurate diagnosis and appropriate management of acute cardiogenic pulmonary oedema (APO) has important short-term and long-term consequences.[1] APO typically presents with acute onset dyspnoea, tachypnoea, arterial hypoxia and severe respiratory failure.[2] It can occur as flash pulmonary oedema precipitated by myocardial ischaemia, acute dysfunction of the mitral or aortic valves or hypertension, or as an exacerbation of chronic heart failure (CHF).

Several studies have examined the natural history of APO. The pathophysiology involves a sudden increase in pulmonary microvascular pressure that leads to fluid accumulation in the interstitial and alveolar spaces, resulting in hypoxia, abnormal respiratory mechanics and an increase in the work of breathing.[3] Accumulation of hypo-oncotic fluid in the interstitium[4] may lead to contraction of the circulating volume.[5,6] We aimed to confirm these findings, and determine whether resolution of APO leads to this fluid being reabsorbed into the systemic vasculature, re-expanding the circulating volume.

Previous studies did not use control groups to exclude non-specific effects. To address this concern, we used patients with chronic obstructive pulmonary disease (COPD) exacerbation as controls, as these patients have similar presentation but considerably different pathophysiology to APO. Haematocrit changes were used to estimate the intravascular volume alterations among patients with APO before and after treatment, and these changes were compared with data from patients with an acute exacerbation of COPD.

Abbreviations

APO	Acute cardiogenic pulmonary oedema
CHF	Chronic heart failure
COPD	Chronic obstructive pulmonary disease
APACHE	Acute Physiology, Age and Chronic Health Evaluation
Hb	Haemoglobin
Hct	Haematocrit
BV	Blood volume
PV	Plasma volume
CV	Cell volume
Pmv	Pulmonary microvascular pressure
LAP	Left atrial pressure
mPAP	Mean pulmonary arterial pressure

ABSTRACT

Background: Acute cardiogenic pulmonary oedema (APO) occurs due to an increase in pulmonary microvascular pressure and massive transvascular fluid filtration into the lungs, causing respiratory insufficiency.

Objective: To determine whether fluid sequestration in the lungs effectively leads to contraction of the circulating blood volume, leading to relative hypovolaemia, and whether resolution of APO and fluid shift to the vascular compartment restores the circulating volume.

Methods: A retrospective analysis was conducted in the intensive care unit of a university teaching hospital, April – September 2007. It comprised a cohort of APO patients and a control group of patients with acute exacerbation of chronic obstructive pulmonary disease (COPD) with similar demographics. Patient demographics, haematocrit, haemoglobin levels, total protein and albumin levels, and arterial blood gas were analysed at presentation and after clinical resolution or at 24 hours. Fluid balance charts were reviewed. Blood, plasma and cell volume changes were calculated using haemoglobin levels and haematocrit.

Results: 52 patients (27 with APO; 25 with COPD) were included. Median haematocrit decreased significantly and the calculated blood and plasma volumes showed statistically significant increases after treatment in the APO group when compared with the COPD group ($P < 0.001$). Fluid intake and output were well balanced in both groups.

Conclusions: Patients with APO are hypovolaemic at the onset relative to their state after treatment. With treatment and resolution of APO, hypovolaemia is corrected and circulating volume is restored.

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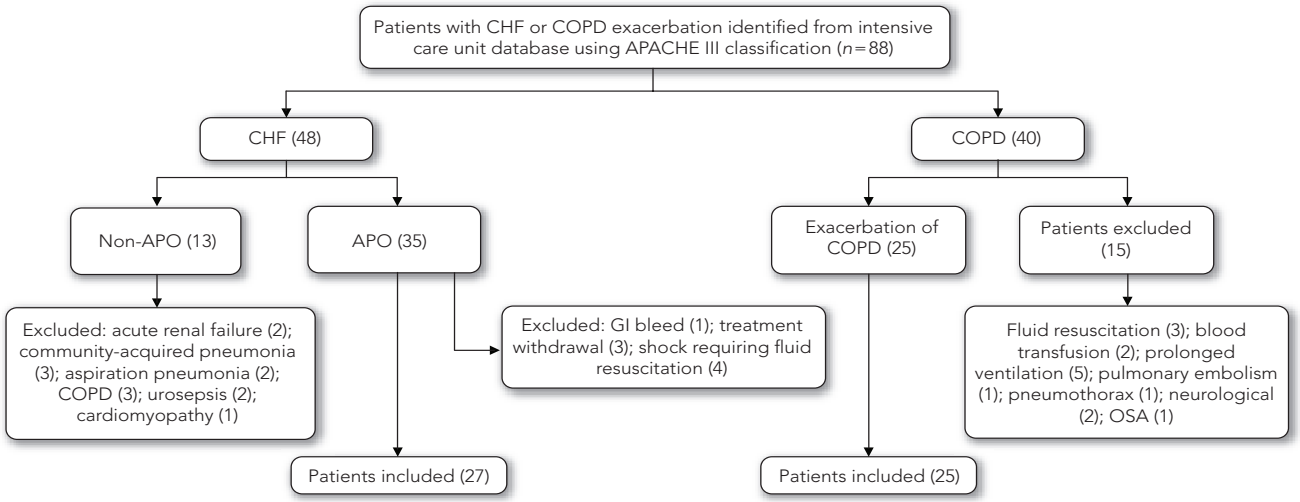
Methods

Design

This retrospective study was conducted in the intensive care unit of a tertiary university teaching hospital. The study was approved by the Flinders Clinical Human Research Ethics Committee in conjunction with the Flinders Audit Committee. No intervention was carried out during the study. Patient anonymity was maintained during data collection

Figure 1. Inclusion and exclusion of patients with APO and exacerbation of COPD



CHF = chronic heart failure. COPD = chronic obstructive pulmonary disease. APACHE = Acute Physiology, Age and Chronic Health Evaluation. APO = acute cardiogenic pulmonary oedema. GI = gastrointestinal. OSA = obstructive sleep apnoea.

and analysis. Informed written consent from patients was therefore not required. The ICU admission database with Acute Physiology, Age and Chronic Health Evaluation (APACHE) III classifications was used to identify patients presenting with either CHF or an acute exacerbation of COPD admitted between April and September 2007. All patient records coded as CHF were reviewed to identify a subgroup of patients with APO. Records of patients admitted with COPD exacerbation during the same period were also reviewed.

Patient selection and exclusion criteria

APO was diagnosed based on the defined criteria of presentation with acute onset respiratory distress, orthopnoea, tachycardia, tachypnoea, elevated jugular venous pressure, a third heart sound, and bilateral basal pulmonary crackles in the absence of fever,[7] and was occasionally associated with expectoration of frank frothy oedema fluid. Radiological features were reviewed and included perihilar haze and Kerley B lines, or the redistribution of the pulmonary blood flow towards the upper lobes. Patients were excluded from the APO group if they had a history of chronic respiratory diseases, concurrent infection, inflammatory conditions, and clinical signs of shock or bleeding requiring fluid resuscitation and/or blood transfusion. Patients with CHF admitted to the ICU who did not have a presentation consistent with APO or who had other system involvements, such as acute or chronic renal failure, aspiration pneumonia or urosepsis, were also excluded.

Treatment for APO comprised ventilatory support, usually with mask continuous positive airway pressure, with high Fio_2, and intravenous glyceryl trinitrate. Morphine and frusemide were administered to most patients in the emergency department.[8] Patients underwent endotracheal intubation if deemed necessary.

Patients were diagnosed as having an acute exacerbation of COPD if they presented with respiratory distress, marked increase in dyspnoea, worsening hypercapnia and/or worsening hypoxaemia with bilateral widespread wheezing or poor air entry on auscultation, in the context of known COPD.[9] Management of these patients' COPD included inhaled bronchodilators, β-adrenergic agonists, anticholinergic agents and systemic corticosteroids. Antibiotics were prescribed pending culture results. Ventilator support was provided with either non-invasive or invasive ventilation.[10] Patients were excluded from the COPD group if there was clinical evidence of shock and/or bleeding requiring fluid resuscitation or blood transfusion, or if they required prolonged ventilatory support (> 72 hours).

Data collection

Patient demographics such as age, sex, medical comorbidities and clinical findings were recorded. The laboratory data included haemoglobin and haematocrit values, and serum total protein, albumin and sodium levels. Arterial blood gas measurements and serum lactate levels were also recorded.

The laboratory data were collected in two sets. The first set of values was recorded at presentation to ICU for both groups. The second set of values for the APO group was

collected at the time of clinical resolution of APO or, at the latest, 24 hours after presentation.

The assessment of clinical resolution was performed by the treating clinician. We reviewed this assessment with a careful scrutiny during the study. The second set of values for COPD patients were recorded 24 hours later. Fluid intake and output was noted during the study period and fluid balance calculated.

Calculation of blood, plasma and cell volume changes with treatment

The percentage changes in blood volume (BV), plasma volume (PV) and red cell volume (CV) were calculated using haemoglobin (Hb) and haematocrit (Hct) before (B) and after (A) treatment using the formulae suggested by Dill and Costill:[11]

$BV_A = BV_B\ (Hb_B/Hb_A)$

$CV_A = BV_A\ (Hct_A)$

$PV_A = BV_A - CV_A$

% change in $BV = 100 \times (BV_A - BV_B)/BV_B$

% change in $CV = 100 \times (CV_A - CV_B)/CV_B$

% change in $PV = 100 \times (PV_A - PV_B)/PV_B$

Statistical analysis

Statistical analysis was performed using SPSS, version 15.0 (SPSS Inc, Chicago, Ill, USA). Results are expressed as median and interquartile range (IQR) as the data were not normally distributed (Kolmogorov–Smirnov test). The Mann–Whitney U test and Fisher exact test were used to compare data from the APO and COPD groups. $P < 0.05$ was considered statistically significant.

Table 1. Baseline patient characteristics of APO and COPD groups*

	APO ($n = 27$)	COPD ($n = 25$)	*P*
Age, years	82 (77–86)	74 (56–78)	0.05
Men/women	9/18	9/16	1.00
Heart rate, beats/min	111 (68–154)	112 (68–146)	0.67
Respiratory rate, breaths/min	34 (24–44)	34 (26–46)	0.89
Mean arterial pressure, mmHg	90.3 (54.6–160.0)	96.0 (72.0–128.0)	0.13
pH	7.3 (6.9–7.5)	7.3 (7.1–7.5)	0.56
$PaCO_2$, mmHg	48 (26–123)	74 (36–113)	< 0.001
PaO_2–FiO_2 ratio	248 (71–476)	177 (103–454)	0.03
SpO_2, %	98 (73–100)	94 (55–100)	0.03

APO = acute cardiogenic pulmonary oedema. COPD = chronic obstructive pulmonary disease. * All values are expressed as median (interquartile range) unless otherwise stated.

Table 2. Pre- and post-treatment changes in haemoglobin levels, haematocrit, blood volume, plasma volume and red cell volume in APO and COPD groups

	APO ($n = 27$) median (IQR)	COPD ($n = 25$) median (IQR)	*P*
Hb_B, g/L	117 (113–129)	123 (113–136)	0.46
Hb_A, g/L	103 (91–110)	116 (108–124)	< 0.001
Hct_B	0.35 (0.33–0.39)	0.37 (0.35–0.40)	0.16
Hct_A	0.30 (0.27–0.33)	0.35 (0.33–0.38)	< 0.001
Blood volume change, %	16.7% (11.4%–23.0%)	5.3% (0–10%)	< 0.001
Plasma volume change, %	24.2% (16.3%–39.9%)	10.4 % (1.2%– 15.8%)	< 0.001
Cell volume change, %	– 0.3% (– 3.0% to – 0.9%)	0.0 (– 1.3% to 1.5%)	0.23

APO = acute cardiogenic pulmonary oedema. COPD = chronic obstructive pulmonary disease. IQR = interquartile range. Hb = haemoglobin. B= before treatment. A = after treatment. Hct = haematocrit.

Results

A total of 88 medical records were examined. Of these, 36 were excluded, leaving 52 patients in the study — 27 in the APO group and 25 in the COPD group (Figure 1).

Demographics

Sex distribution was similar in the two groups. Patients in the APO group were significantly older than those in the COPD group (median, 82 [IQR, 77–86] years v median, 74 [IQR, 56–78] years, $P < 0.05$).

Patient characteristics

Baseline patient characteristics were mostly similar. Some differences were evident due to differences in disease pathophysiology. Patients in the COPD group were more hypercapnic (Table 1). A relatively low Pao_2–Fio_2 ratio was evident in the COPD group, possibly attributable to the higher $PaCo_2$ and the use of low Fio_2 accepting lower Spo_2.

Baseline heart rate, respiratory rate and mean arterial pressure were similar in both groups (Table 1).

Haemoglobin and haematocrit

The pretreatment haemoglobin (Hb_B) levels and haematocrit (Hct_B) in the APO group were similar to those of the COPD group (Table 2). After treatment and resolution of APO, the haemoglobin levels (Hb_A) and the haematocrit (Hct_A) dropped significantly compared with the COPD group ($P < 0.001$).

Cell volumes, total proteins, albumin

No difference was noted in the cell volumes in both groups. The serum protein and albumin levels reduced significantly in the APO group after treatment, but similar changes were seen in COPD patients as well and, on comparison, no statistical difference was evident in the two groups.

Blood and plasma volumes

Calculated blood and plasma volumes increased significantly from the baseline in the APO group after treatment. As outlined in Table 2, the blood volume and plasma volume increased by 17% and 24%, respectively, in the APO group after treatment. A change of this magnitude was not evident in the COPD group.

Serum lactate and sodium levels were similar in the two groups before and after treatment. Fluid balance was constant in both groups. These results are summarised in Table 3.

Table 3. Total protein, albumin, sodium and lactate changes and fluid balance

	APO ($n = 27$), median (IQR)	COPD ($n = 25$) median (IQR)	*P*
Total protein B, g/L	73 (69–76)	70 (65–75)	0.12
Total protein A, g/L	65 (60–70)	65 (62–68)	0.90
Albumin B, g/L	35 (31–38)	32 (31–34)	0.06
Albumin A, g/L	30 (26–34)	30 (27–32)	0.83
Sodium B, mmol/L	140 (136–142)	140 (134–143)	0.81
Sodium A, mmol/L	140 (138–143)	141 (136–143)	0.81
Lactate B, mmol/L	1.90 (1.40–2.80)	1.5 (1.05–2.05)	0.10
Lactate A, mmol/L	0.9 (0.70–1.20)	0.8 (0.70–1.27)	0.96
Fluid input, mL	1148 (850–1543)	1290 (1124–2002)	0.19
Fluid output, mL	1375 (1000–1670)	1275 (1000–1630)	0.81

APO = acute cardiogenic pulmonary oedema. COPD = chronic obstructive pulmonary disease. B = before treatment. A = after treatment. IQR = interquartile range.

Discussion

This study evaluated the blood and plasma volume changes in APO after treatment using the method described by Dill and Costill.[11] As this method assumes a constant in red cell mass, we excluded patients with known blood loss.

The baseline haemoglobin levels and haematocrit were similar in the APO and COPD groups. It is possible that haemoconcentration in the APO group and secondary polycythaemia in the COPD group contributed to this finding.[12] After treatment, significant falls in the haemoglobin levels and haematocrit were noted in the APO group but not in the COPD group.

The estimated blood and plasma volume increased by 17% and 24% in the APO group compared with 5% and 10%, respectively, in the COPD group. Fluid balance was similar in the two groups, and the intravascular fluid changes were not attributable to exogenous fluid supplementation. We postulate that the increase in the circulating fluid volume was responsible for the changes in the haemoglobin levels and haematocrit.

Serum protein and albumin reduced significantly in the APO group after treatment. Recent publications have found similar results among patients with APO due to specific causes.[13,14] The estimated volume changes were believed to be responsible for these findings.[13,14] In our study, similar changes were also found in the control group. A clear explanation for these results cannot be provided on the basis of currently available evidence, but it is possible that such changes in plasma proteins may occur as a part of acute phase response in COPD exacerbation.

Supportive evidence to the theory of initial contraction of the circulating fluid volume in APO followed by re-expansion after treatment is provided by previous studies. In an animal study, Vreim and colleagues found that during APO, transudation of relatively protein-poor fluid into the interstitial and alveolar spaces in the lungs leads to contraction of the circulating plasma volume.[15] Similar results have been reported by Figueras and Weil.[6] Further support is lent by Henning and Weil, who found that plasma volume increased 4–12 hours after the initiation of treatment in APO, and during this time, the haemoglobin levels and colloid osmotic pressure progressively decreased.[16]

Schuster and coworkers investigated changes in blood volume following injection of a single dose of frusemide in 21 patients with APO and found that frusemide induced diuresis but did not deplete intravascular volume. On the contrary, the patients who responded to the treatment showed a concurrent 30% increase in plasma volume.[17]

However, all these studies are observational studies without control groups. The use of controls in the current study mitigates potential non-specific changes in fluid volume that may be seen in acute respiratory failure.

A case series suggested that patients with APO who present with cardiogenic shock and hypotension and are unresponsive to conventional therapy may benefit from volume expansion.[18]

The mechanism by which intravascular change occurs can be explained by our current understanding of the pathophysiology of APO.[19] Acute cardiogenic pulmonary oedema arises from an increase in pulmonary microvascular pressure which can be estimated from the Garr equation,

$Pmv = LAP + 0.4\ (mPAP - LAP)$

where Pmv is pulmonary microvascular pressure, LAP is left atrial pressure, and mPAP is mean pulmonary arterial pressure.[20]

An acute increase in hydrostatic pressure in pulmonary capillaries is usually due to elevated LAP caused by increased left ventricular end-diastolic pressure. This leads to a massive increase in transvascular fluid shift into the interstitium and alveolar spaces of the lungs. The accumulation of hypo-oncotic fluid in these spaces overwhelms the homeostatic control of lung water, resulting in APO. A fall in the interstitial pressure associated with a fall in mean intrapleural pressure among patients with increased work of breathing may also increase the microvascular fluid flux for any given Pmv.

The subsequent fluid sequestration in the lungs causes a state of relative hypovolaemia. This is reflected by the haemoconcentration at the onset of APO which resolves as Pmv falls.

Our study had limitations. Although the data were meticulously collected and scrutinised, there are the inherent limitations of a retrospective study. Further, the estimates of changes in plasma volume use an indirect measure. However, the data are consistent with directly measured changes in plasma volume,[5,6] and the use of patients with an acute exacerbation of COPD as a comparator group adds to the literature.

Conclusion

Patients with APO at presentation appear to be in a state of haemoconcentration due to fluid sequestered in the interstitial and alveolar spaces of the lungs. Reabsorption of this fluid after treatment and resolution of APO manifests as an increase in the blood volume and plasma volume associated with significant decline in haematocrit. This finding suggests that the haemoglobin levels and haematocrit can be a useful bedside tool to assess the course of patients with APO admitted to ICU, and is a reminder of important pathophysiological changes in APO that may influence management of individual patients.

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