Pancreatology 19 (2019) 519–523

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Pulmonary dysfunction due to combination of extra-pulmonary causes and alveolar damage is present from first the day of hospital admission in the early phase of acute pancreatitis

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ARTICLE INFO

Article history:
Received 27 November 2018
Received in revised form
17 April 2019
Accepted 21 April 2019
Available online 23 April 2019

Keywords:
Respiratory dysfunction
Gas exchange
Diffusion capacity
Atelectasis
Pleural effusion
Pancreatitis

ABSTRACT

Background: Only few studies have attempted to evaluate the pulmonary function in the early phase of acute pancreatitis (AP), although pulmonary dysfunction is the most frequent complication in the early phase of AP. We aimed to evaluate the changes in pulmonary function tests during the early phase of AP.
Methods: Prospective cohort study including 44 patients (52% men; median age 54 years) admitted with first attack of AP and 22 healthy controls. Patients underwent assessments on day 1, 2, 3, 6, and 10 as well as one month after discharge. Pulmonary function tests included the % predicted: forced expiratory volume during the first second (FEV1), forced vital capacity (FVC), total lung capacity (TLC), diffusion lung capacity (DLCO) and the ratio between DLCO and alveolar volume (DLCO/VA).
Results: In total, 9% developed severe acute pancreatitis, 7% died, and 14% required treatment at the intensive or semi-intensive care unit. From admission, patients had impaired FEV1, FVC, DLCO, and TLC compared with controls ($p < 0.0001$ in all analyses). Patients with CRP >150 mg/L had significantly lower lung function tests. One month after discharge, lung function tests improved but patients had lower FEV1 ($p = 0.014$), FVC ($p = 0.022$), TLC ($p = 0.020$), and DLCO ($p < 0.001$) compared with controls.
Conclusion: This study found that patients with AP had evidence of pulmonary impairment from the first day after hospital admission. The impairment lasted several weeks after hospital discharge.

Introduction

Acute pancreatitis (AP) is an acute inflammatory process of the pancreas with variable involvement of local tissue and remote organs. The annual incidence is approximately 13–45 cases per 100.000 inhabitants [1,2]. Approximately 20% of the patients will develop severe AP, characterized by organ failure that may lead to death [3].

During the early phase, which lasts about one to two weeks, about two thirds of the patients with severe AP develop respiratory complications [4]. The severity ranges from mild hypoxia to acute respiratory distress syndrome (ARDS). The pathophysiological mechanisms are complex. Activated pancreatic enzymes are important mediators of severe pancreatic inflammation and systemic toxicity including activation of the complement system, over activation of the leucocyte system, and the involvement of the inflammatory mediators, which in turn lead to pulmonary endothelial and epithelial barrier dysfunction [5]. Several studies have evaluated pulmonary complications based on arterial blood gasses, chest X-rays and computerized tomography (CT) scans [6,7]. These methods will capture the clinical pulmonary complications, but not the pulmonary function and potential damage over the alveolar-capillary membrane. Only few studies have attempted to evaluate the pulmonary function in the early phase of AP and with conflicting results [8,9]. In the present prospective observational study, we serially evaluated the pulmonary function and gas exchange of patients admitted with their first attack of AP.

Methods

We consecutively included patients with their first attack of AP

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https://doi.org/10.1016/j.pan.2019.04.009
1424-3903/

regardless of aetiology or disease severity admitted to our department in the period February 2016 to June 2017. The study was approved by the Danish National Committee on Health Research Ethics (H-15007459). Informed consent was obtained from all patients and controls. Our inclusion criteria were first attack of AP based on revised Atlanta criteria [3]. Severe AP was defined as persistent organ failure lasting more than 48 h.

We collected baseline information including age, aetiology, comorbidities, previous lung disease, American Society of Anaesthesiologists (ASA) score, Charlson Co-morbidity Index (CCI) [10], body mass index (BMI), current and previous smoking status, interval between onset of abdominal pain and admission to the hospital.

On days 1, 3, 6, and 10 as well as one month after discharge, we evaluated patients clinically and measured plasma values of c-reactive protein CRP, white blood count (WBC), amylase and albumin, evaluated Cumulated Ambulation Score (CAS), hand-grip strength (HGS) test, and performed chest x-rays. Lung function was assessed by NDD EasyOne Pro (version 3.19), ndd Medizintechnik AG, Zürich, Switzerland. Lung assessment included % predicted forced expiratory volume during the first second (FEV1), forced vital capacity (FVC), total lung capacity (TLC) and diffusion lung capacity (DLCO). We included 22 matched healthy controls (median age 54 (IQR 38 to 61) years and 42% men) with no previous medical history. None used medication. None of the controls had asthma or chronic pulmonary disease.

Chest X-rays were reviewed by radiologists and presence of atelectasis, pleural infusion and pneumonia was registered. In addition, we registered need for oxygen supply, continuous airway pressure (CPAP), pleuroscentesis, mechanical ventilation, bronchodilators and steroids.

Statistics

We used STATA version 15 for Windows (STATA Corp, Texas, USA) for the statistical analyses. Patient characteristics were summarized using medians with interquartile range (IQR) or proportions. Groups were compared using Mann-Whitney *U* test or Chi-Square.

Results

We included 44 patients (Table 1). Included patients had AP due to gallstones (66%), alcohol (20%) or other causes (14%). Thirty-two percent had an ASA score of 3 and 73% were admitted within 24 h of the onset of symptoms. Thirteen patients (30%) were smokers at the time of enrollment. All patients had elevated plasma levels of CRP, White Blood Cell count and amylase as well as low albumin at admission. Patients had a lower median HGS compared with controls (50.5 (IQR 34.5 to 81) vs. 75.25 (IQR 63.67 to 100.1); $p = 0.0010$).

All participants received the best standard of care including intravenous and/or oral fluid resuscitation (three to 4 L/24 h) and pain management including paracetamol and morphine. Adequate pain control was ensured before lung function tests.

Thirty-four percent required oxygen therapy and continuous airway pressure. None required mechanical ventilation or pleural drainage. In total, 30% developed pleural effusion, 23% developed atelectasis, and 23% developed pneumonia treated with antibiotics. In total, 41% had a CRP >150 mg/L, 9% developed severe AP, and 14% required treatment at the intensive or semi-intensive care unit. The median number of days in hospital was 6 (IQR 5–12.5). Three patients (7%) died during admission, of whom none received mechanical ventilation. Two of the patients had severe comorbidities and were not candidates for treatment in intensive care unit. The last patient was diagnosed with Burkitt's lymphoma and was transferred to department of oncology where he deceased one month after the onset of AP.

All participants were assessed at baseline, but only 16 were assessed one month after hospital discharge as a large proportion chose to drop out.

From admission, patients had impaired FEV1, FVC, DLCO, and TLC compared with controls ($p < 0.0001$ in all analyses, Fig. 1). The DLCO/VA was similar in the two groups, but lower in smokers compared to non-smokers ($p = 0.038$). We found no difference between smokers and non-smokers in FEV1 ($p = 0.53$), FVC ($p = 0.88$), DLCO ($p = 0.24$), or TLC ($p = 0.79$). There was no difference between patients with severe vs. mild AP regarding FEV1 ($p = 0.79$), FVC ($p = 0.73$), DLCO ($p = 0.74$), TLC ($p = 0.21$), or DLCO/VA ($p = 0.14$), possibly reflecting the small number of participants with severe acute pancreatitis (Table 3). Patients with CRP> 150 mg/L had impaired lung function tests compared with patients without severe inflammation: FEV1 ($p < 0.001$), FVC ($p < 0.001$), DLCO ($p < 0.001$), TLC ($p < 0.001$), but not DLCO/VA ($p = 0.80$).

The FEV1, FVC, DLCO, and TLC remained impaired from day two to ten whereas the DLCO/VA remained stable (Table 2). On month after discharge, lung function tests improved but patients had lower FEV1 ($p = 0.014$), FVC ($p = 0.022$), TLC ($p = 0.020$), and DLCO ($p < 0.001$) compared with controls (Fig. 2). The DLCO/VA remained similar in the two groups.

Table 1
Baseline characteristics of 44 patients with acute pancreatitis.

Characteristics	Proportion or median (IQR)
Men	48%
Age	53 (38–62)
Body Mass Index (BMI)	26 (23–31.5) kg/m2
Aetiology: Gallstone/alcohol/other causes	66%/20%/14%
Charlson Comorbidity Index 0 to 1/2 to 5 points	76%/24%
American Society of Anaesthesiologists (ASA) score 1/2/3	32%/43%/25%
<24 h from onset of symptoms to admission	73%
Haemoglobin	9.3 (8.3–9.8) mmol/L
C-reactive protein	12.5 (3.5–41) mg/L
Amylase	866 (354–1500) U/L
Alanine aminotransferase	233.5 (50–471) U/L
Alkaline phosphatase	125.5 (86.5–174) U/L
Bilirubin	20 (12–45) μmol/L
INR	1.05 (1–1.1)
Albumin	37 (34.5–39.5) g/L
Creatinine	75 (60–96) μmol/L
Blood glucose	6.7 (6–9.1) mmol/L

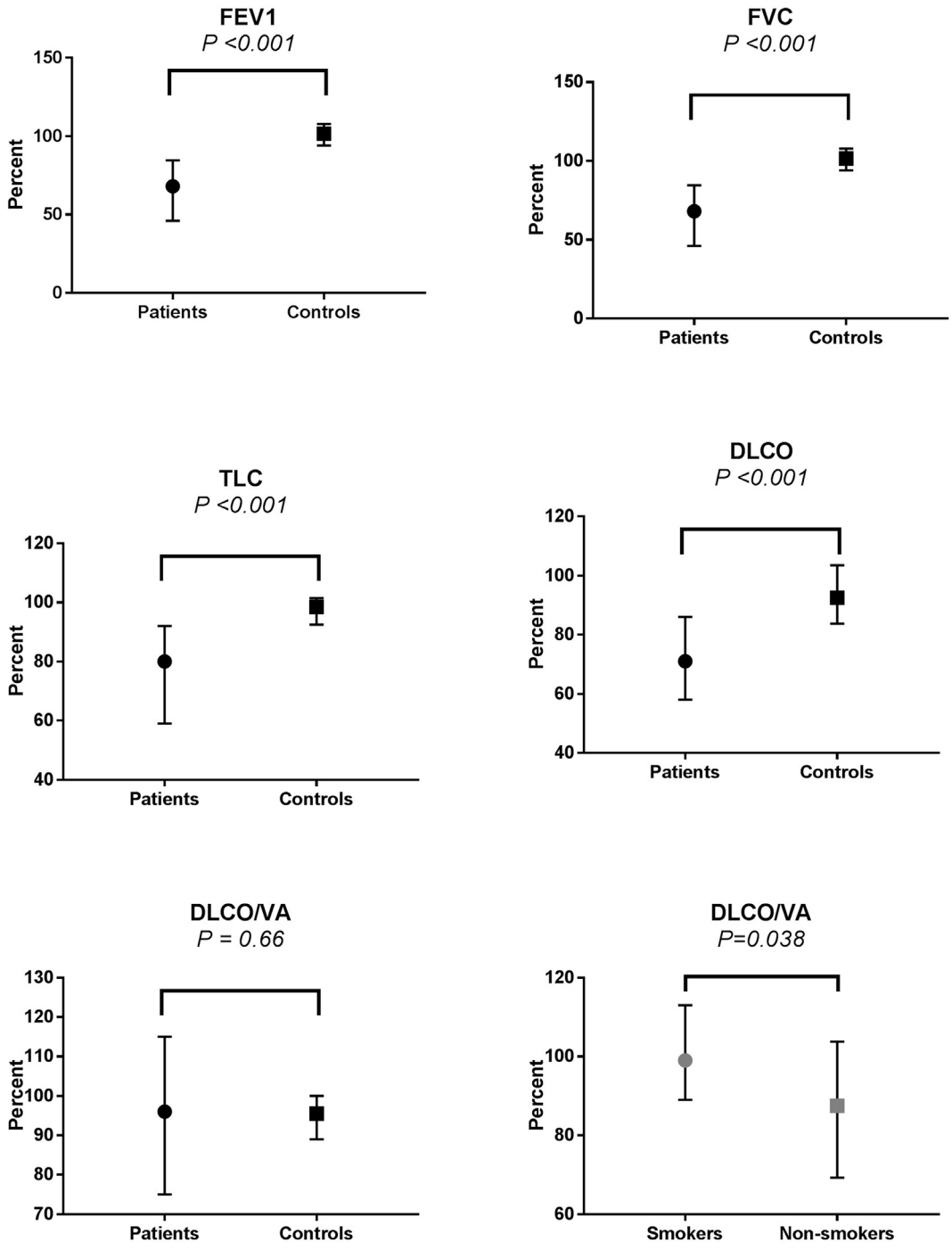

Fig. 1. Lung function tests (% predicted) in 44 patients with acute pancreatitis on the day of admission. Panel 1–5 shows patients compared with 22 healthy controls. Panel six shows the DLCO/VA in patients who are smokers compared with non-smokers. The figure shows medians with interquartile range.

Table 2
Lung function tests (% predicted) in patients with acute pancreatitis from day two to ten. The table shows medians with interquartile range.

Test	Day 2 (n = 38)	Day 3 (n = 26)	Day 6 (n = 18)	Day 10 (n = 9)
FEV1	67.5 (41.5–87)	62 (42–77)	57.5 (44–69)	61 (51–72)
TLC	78.5 (62.5–90.5)	71.5 (55–91)	67.5 (60–91)	67 (65–79)
FVC	70 (45.5–89.5)	64 (42–81)	61 (48–86)	60 (57–82)
DLCO	66.5 (51–91.5)	60 (51–77)	60.5 (52–81)	55 (48–56)
DLCO/VA	105 (81–115.5)	90 (77–119)	91 (76–109)	74 (70–85)

Table 3
Table 2. Lung function tests (% predicted) in patients with mild or severe acute pancreatitis (AP) at admission. The table shows medians with interquartile range. None of the comparisons were statistically significant.

Test	Severe AP (n = 4)	Mild AP (n = 40)
FEV1	68 (46–82)	101.5 (97–108)
TLC	80 (59–89)	97.5 (92–101)
FVC	75 (47.5–89)	101.5 (97–108)
DLCO	71 (58–86)	92 (83–103)
DLCO/VA	102 (78–115)	93.5 (88–100)

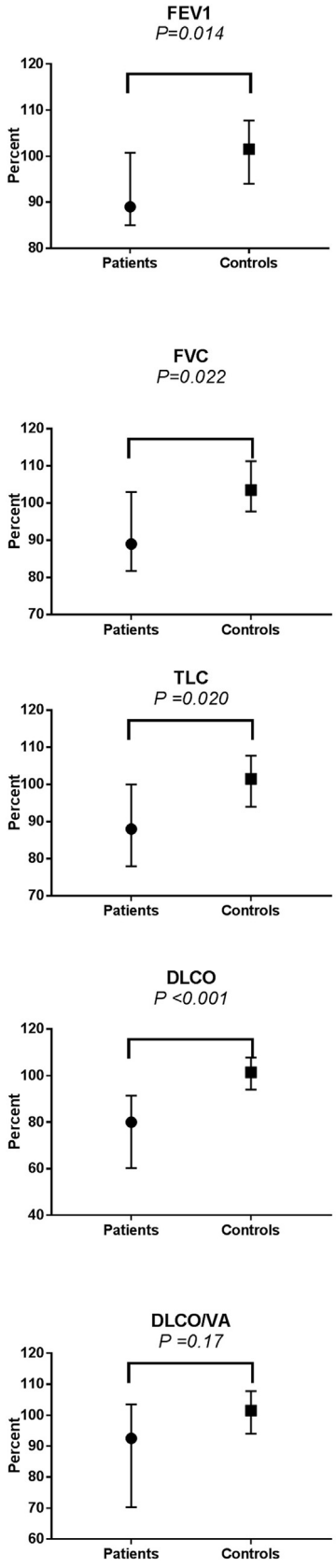

Fig. 2. Lung function tests (% predicted) in 16 patients admitted with AP, one month after hospital discharge. Patients are compared with 22 healthy controls. The figure shows medians with interquartile range.

Discussion

This paper describes a prospective cohort study including 44 patients admitted with AP characterized with clinical, laboratory, imaging and functional tests of pulmonary complications and function. All participants received the best standard of care and adequate pain management was ensured before the assessment of lung function. Serial measurements showed that patients had significantly impaired lung function tests during the first ten day. The FEV1, FVC, TLC, and DLCO were significantly reduced from admission, which is noteworthy as most patients were admitted within 24 h after the onset of symptoms. The lung function tests were significantly lower compared with healthy controls and although improvements were identified after hospital discharge, the two groups remained significantly different. Several patients were discharged after five to six days in hospital and only 36% agreed to the outpatient assessment one month after hospital discharge. Accordingly, more weight can be put on the baseline assessments than the assessments made after day five or the outpatient follow up.

More than third of the patients developed one or more pulmonary complications, pleural effusion being the most frequent. In agreement with our findings, a recent retrospective study found that 22% of patients with AP develop pleural effusion, atelectasis or pneumonia within the first two weeks of admission [6]. Three other studies found a similar risk of pulmonary complications in AP. In one study, including 539 patients with their first episode of AP and a chest radiograph performed within 24 h of admission, 14% had pleural effusions and 6% had pulmonary densifications defined as homogeneous areas of density enhancement [11]. The second study included 140 patients with AP and chest radiograph performed on admission, and found that 26% had pulmonary infiltrates defined as streaking, patching, partially confluencing inhomogeneous changes of the lung [12]. The third study included 166 patients with their first episode of AP, who all had chest radiograph performed on admission [7]. In total, 29% developed respiratory complications defined as pleural effusion, pulmonary consolidations, atelectasis or adult respiratory distress syndrome.

We found a high risk of respiratory complications. The DLCO remained low in the out-patient setting, 30 days after the discharge suggesting involvement of alveolar-capillary dysfunction. On the other hand, the DLCO/VA ratio remained stable throughout the evaluation period, thus questioning whether lung diffusion is an intrinsic alveolar dysfunction or there is a substantial mechanical suppression from atelectasis or pleural effusion. None of our patients required therapeutic pleural drainage or mechanical ventilation, but one third of the patients received CPAP. We cannot exclude the possibility that some of the included patients had impaired lung function before developing AP. Our tests showed that patients who were smokers had a lower DLCO/VA compared with non-smokers. Unfortunately, none of the included patients underwent lung function tests before inclusion. It is likely that the effect of AP will vary in different subgroups and that the detrimental effect will be worse in e.g. patients with chronic obstructive lung disease or asthma. On the other hand, the fact that lung function tests improved after hospital discharge suggests that AP had a detrimental effect on pulmonary function.

One study evaluated pulmonary function and diffusion capacity in 22 patients with mild AP and with no clinical and radiographic signs of pulmonary involvement [9]. Measurements were performed between second and fourth days of admission. There was a marked reduction in vital capacity and FEV1. DLCO was reduced to 77% of predicted, but the DLCO/VA ratio was not measured. Control studies performed after one week only in four patients with hypoxemia showed that lung vital capacity and FEV1 had returned to

normal values, and diffusion capacity was clearly increased. Our findings however suggest that diffusion capacity is suppressed beyond the early phase of AP, and in spite of normalization of other functional parameters.

A number of different pathophysiological mechanisms have been proposed involved in AP associated lung injury. The activation of neutrophils plays a key role in local tissue injury and distant organ failure. The process is mediated by release of cytotoxic molecules such as neutrophil elastase. Neutrophil elastase, free radicals, and other proteolytic enzymes destroy elastin, collagen, fibrin and proteoglycans in the extracellular matrix, which contribute to tissue damage and organ failure [6,7]. Increased neutrophil elastase activity and neutrophil activation correlate with the severity of AP and with the risk of respiratory failure [8]. These findings suggest that neutrophil elastase activity may mediate pathological outcomes including organ damage. The specific effects of pancreatic enzymes like proteases, elastase and phospholipase A2 are also associated with AP-associated lung injury. The enhanced neutrophil chemotactic activity has been coupled to elevated plasma levels of IL-8 in the lungs, which is characteristic for ARDS [9]. Local effects of IL-8 have also been evaluated, e.g. the concentration of IL-8 in broncho-alveolar lavage in patients with ARDS has been shown to correlate with mortality [10]. IL-18 levels are elevated in patients with pancreatic necrosis, and respiratory, renal and cardiovascular failure associated with severe AP [11]. In a prospective study of 75 patients with their first attack of AP, levels of both IL-6, IL-8, IL-18 and TNF-α were independent predictors of respiratory failure [13].

Interestingly, we found no differences in pulmonary function between mild and severe AP. However, we found significant differences between patients with and without CRP >150 mg/l. CRP response can be driven by cytokines, TNF-α and other mediators that also can be directly involved in the lung injury, an association that would be of interest to explore in future.

Present study has several limitations. We undertook lung function tests after ensuring that the included patients were optimized based on the best clinical standards including CPAP, but of course compliance could have been an issue in some of the patients. One important limitation of the present study is the fact that the number of participants did not allow for multivariable assessments. We found no clear differences between patient groups including comparisons between patients with or without lung complications for important clinical variables. In addition, all patients received the best standard of care adjusted based on patient needs. We therefore cannot exclude the possibility that some interventions have a beneficial effect on the risk of pulmonary complications and a positive effect on lung function tests. For example, continuous airway pressure is likely to have a beneficial effect on certain groups. Additional evidence is needed to evaluate if this potential benefit translates to clinical practice. Unfortunately, the number of participants who received this intervention was too small to make a fair assessment of this question. In addition, confounding by indication is likely to occur and may influence the results. Prospective randomised trials are needed to evaluate the benefit of interventions aiming at reducing the risk of pulmonary complications.

In conclusion, our results suggest that pulmonary impairment is common in the early phase of AP and may last for several weeks after hospital discharge.

Conflicts of interest

None.

Funding

None.

Acknowledgments

None.

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