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[Michael Eisenhut](#) *

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Hypothesis

The Causes of Hypoxia in Localized Lower Respiratory Tract Infection

Michael Eisenhut

Paediatric Department, Luton&Dunstable University Hospital, Lewsey Road, Luton, LU40DZ, United Kingdom; michael_eisenhut@yahoo.com

Abstract

Background: Localized lower respiratory tract infection including unilobar and round pneumonia can be associated with hypoxia and oxygen requirements. This is unexplained. **Hypothesis:** Spread of fluid absorption inhibiting cytokines in the alveolar spaces of the inflamed lung is cause of hypoxia in localized lower respiratory tract infection by spread of CFTR dysfunction in alveolar epithelial cells to more areas including those not infected. **Evidence supporting the hypothesis:** There is no evidence of pulmonary shunting to explain hypoxia in localized pneumonia. Systemic inflammatory response syndrome (SIRS) related generalized increase in alveolar capillary barrier or pulmonary vasoconstriction not visible on a chest x-ray cannot explain the hypoxia detected. **Testing the hypothesis:** Confirmation of the hypothesis could be achieved using pulmonary MRI or high resolution CT to confirm spread of alveolar fluid accumulation from the localized pneumonia focus as opposed to generalized SIRS related pulmonary oedema together with cytokine and chloride measurement in bronchoalveolar lavage samples from the lung segments near the affected lung segment and unaffected contralateral lung. Ventilation/perfusion scintigraphy could investigate for involvement of vasoconstriction or microemboli from intravascular coagulation. **Implications of a confirmation of the hypothesis:** Should the posed hypothesis be confirmed adjuvant strategies including small molecule CFTR activators and CFTR activating combination of beta-agonists, phosphodiesterase inhibitors and steroids could be used to treat hypoxia.

Keywords: lobar pneumonia; round pneumonia; CFTR; cystic fibrosis transmembrane conductance regulator chloride channel; interleukin-1; interleukin-8; tumor necrosis factor; transforming growth factor; pulmonary edema; vasoconstriction

Introduction

Hypoxia in Radiologically Localized Pneumonia is Unexplained

Death in lower respiratory tract infections is due to hypoxia secondary to pulmonary fluid accumulation caused by acute lung injury [1–3]. Globally the median prevalence of hypoxaemia in WHO-defined pneumonia requiring hospitalisation (severe and very severe classifications) was 13%, but prevalence varied widely. This corresponds to at least 1.5 to 2.7 million annual cases of hypoxaemic pneumonia presenting to health-care facilities. Many more people do not access health care. Hypoxemia is a recognized risk factor for death in pneumonia [2,3].

An understanding of the pathophysiology leading to hypoxia in acute lung injury (ALI) is therefore pivotal as it provides the basis for interventions to prevent and treat this condition in addition to vaccines which are not available for all bacterial and viral pathogens involved in the pathogenesis. Lobar pneumonia is limited to lung lobes because the infection and inflammation spreads from one affected alveolus to another through connective passages including pores of Kohn and canals of Lambert rather than through the larger airways. The spread is effectively contained at

the boundaries of the lobes by pleural connective tissue planes. A further key features of lobar pneumonia is that the airways contained in the affected lobes remain air filled.

Lobar pneumonia, which constitutes 29 to 47% of cases can be associated with oxygen requirements due to lower saturations than patients with lower respiratory tract infection and no lobar consolidation [4,5]. Round pneumonia has been defined as an oval or round-shaped consolidation distributed in a nonsegmental pattern and is regarded as more common in children with their less developed small connecting passages (pores of Kohn and canals of Lambert) [6]. In round pneumonia hypoxia had been documented in 4 published case reports previously (for patient characteristics see Table 1) [7–10].

Table 1. Clinical features of patients with round pneumonia and hypoxia.

Age and gender	Radiological features	Oxygen levels	Features of sepsis ¹	Reference
37 years, male	Round density in left upper lobe	PaO ₂ =51mm Hg in air, saturation 80% in 100% oxygen by face mask	Septic shock requiring Saline boluses and dopamine infusion followed by death with ARDS	[7]
46 years, male	3cm round homogeneous opacity in left lower lung field	PaO ₂ =42mmHg and O ₂ saturation 82% in air	None, pulmonary embolus ruled out by CT angiography	[8]
58 years, female	4cm round consolidation in left lower lobe	PaO ₂ 58mmHg in air	None	[9]
70 years, female	6 cm round consolidation in right upper lobe on CT	“hypoxaemic”	None	[10]

¹ Requirement of fluid bolus and/or inotrope infusion for hypotension, features of renal failure, reduced level of consciousness, features of coagulopathy or disseminated intravascular coagulation.

Hypoxia in unilobar or round pneumonia cannot be explained by a whole or part of a lung lobe being unable to participate in gas exchange: Operative removal of half of an entire lung may not cause oxygen requirements [11].

Previously Posed Hypotheses and Theories Explaining Hypoxia in Localized Lower Respiratory Tract Infection

Systemic inflammatory response in pneumonia causes pulmonary fluid accumulation in parts of the lung distant from the infected lung lobe

Almost 80% of patients with ARDS have sepsis, with 46% resulting from a direct pulmonary infection and others from extrapulmonary sources [12–14].

The fact that extrapulmonary infection can result in pulmonary fluid accumulation points to a role of proinflammatory cytokines in the peripheral blood causing increased capillary and

subsequent pulmonary alveolar epithelial permeability leading the alveolar edema. The association of systemic cytokine levels with pulmonary fluid accumulation has been demonstrated for IL-6 and IL-8 levels [15]. The progression from a localized (round) pneumonia focus through a systemic inflammatory response leading to generalized pulmonary fluid accumulation in ARDS is illustrated in the first case [7] listed in Table 1.

Intrapulmonary shunting of deoxygenated blood and hypoxia in lobar pneumonia.

Investigations into the role of intrapulmonary shunting in lower respiratory tract infection used the same pulmonary vascular investigation used in the diagnosis of pulmonary embolism: Dual energy computer tomography to check for changes in pulmonary perfusion distribution as cause for hypoxia by increased blood flow through poorly ventilated lung areas and various methods of ventilation/perfusion scanning using radioisotope labelled markers and inert gas elimination [16,17]. Other investigations employed the vaso-active gas nitric oxide to check for supportive findings. Inhaled nitric oxide given in pneumonia should vaso-dilate ventilated and therefore oxygenated areas of the lung more than fluid filled areas. In a trial of inhaled nitric oxide in 8 patients with unilateral pneumonia arterial PaO₂ improved dose dependent after NO application through the endotracheal tube in those mechanically ventilated (4 patients) [18]. This was seen as support for intrapulmonary shunting causing hypoxia.

The hypothesis that blood flow distribution changes observed in those experiments lead to hypoxia rests on the following assumptions:

a) In areas of the lung with fluid accumulation due to infection, blood flow is directed to poorly ventilated areas, leading to a mismatch in ventilation and perfusion

b) Inhaled NO improves oxygenation by acting as a selective pulmonary vasodilator, relaxing blood vessels only in the well-ventilated regions of the lung where the gas can reach. Inhaled nitric oxide hereby redirects blood flow to areas where gas exchange is efficient, thereby improving overall blood oxygenation.

Against a) is that in areas of lung inflammation blood flow is in fact diminished as evident from worsening of oxygenation in Chronic Obstructive pulmonary disease [17].

Dominant cytokines associated with worsening of outcome in pulmonary inflammation include the vasoconstriction causing cytokines TNF and IL-1 [19–21].

Detailed investigation of pulmonary perfusion in and around areas of lobar pneumonia in COVID-19 lung disease used dual energy CT and found evidence of vasoconstriction in areas on lung consolidation [22].

Against b) is that inhaled nitric oxide cannot improve oxygenation from well ventilated lungs [23].

Hypoxia in lobar pneumonia is correctable by supplementary oxygen given to the patient which is against shunting being the most important cause.

The Hypothesis

Spread of fluid absorption inhibiting cytokines in the alveolar spaces of the inflamed lung is cause of hypoxia in lower respiratory tract infection by spread of CFTR dysfunction in the alveolar epithelial cells to more areas including those not infected.

Explanation of the Hypothesis

The hypothesis implies that cytokines, which can reduce CFTR function are transported in the airway surface liquid out of the inflamed lung lobe up bronchioli and the bronchial tree where they can via diffusion reach other parts of the same lung and the contralateral lung half and there reduce CFTR function and thus increase the depth of the alveolar fluid film slightly causing an increase in the alveolar-capillary barrier leading to hypoxia.

Evidence Supporting the Hypothesis

It has previously been established that features of dysfunction of the Cystic Fibrosis Conductance Regulator chloride channel on the surface of respiratory epithelial cells correlate with pulmonary fluid accumulation in the alveolar space [24]. Cytokines including transforming growth factor-1, interleukin-1, interleukin-8 and tumor necrosis factor which reduce fluid absorption by causing a down regulation of CFTR expression on alveolar epithelial cells have been found in bronchioalveolar lavage samples of patients with acute lung injury in levels which strongly correlate with severity of hypoxia. In three of the four case reports of round pneumonia listed in Table 1 there was no evidence of a systemic inflammatory response severe enough to cause diffuse pulmonary oedema or pulmonary arterial vasospasm as explanation of the hypoxia observed.

There is evidence for rapid convectional fluid movement out of the fluid filled alveoli to the surrounding alveolar spaces [25].

Testing the Hypothesis

Confirmation of the hypothesis could be achieved using pulmonary MRI or high resolution CT to confirm spread of alveolar fluid accumulation from the localized pneumonia focus as opposed to generalized SIRS related pulmonary oedema together with cytokine and chloride measurement in bronchoalveolar lavage samples from the lung segments near the affected lung segment and unaffected contralateral lung. During bronchio-alveolar lavage gamma ray emitting radiolabelled anti-cytokine (IL-1, IL-8, TGF beta and TNF) antibodies could be instilled into the affected lung lobe and then the pattern of emitted gamma rays in sequential gamma camera recordings documented. One could also attempt to investigate the influence on CFTR dysfunction in different parts of the lung away from the inflamed lobe by selective sampling of exhaled breath condensate (EBC) from briefly bronchoscopically intubated bronchi in the affected and the contralateral radiologically unaffected side and compared to healthy control subjects. Congenital CFTR dysfunction has previously been associated with reduced chloride concentration in EBC [26].

Ventilation/perfusion scintigraphy could investigate for involvement of vasoconstriction or micro-emboli from intravascular coagulation.

Implications of a Confirmation of the Hypothesis

Should the posed hypothesis be confirmed adjuvant strategies including small molecule CFTR activators and CFTR activating combination of beta-agonists, phosphodiesterase inhibitors and steroids could be used to treat hypoxia as explained previously [24].

Conflicts of Interest: The author declares no conflict of interest.

Author Contributions: Dr. Eisenhut is the sole author of this manuscript.

References

1. Subhi, R., Adamson, M., Campbell, H., Weber, M., Smith, K., Duke, T. Hypoxaemia in Developing Countries Study Group. The prevalence of hypoxaemia among ill children in developing countries: a systematic review. *Lancet Infect Dis.* **2009**, 9(4), pp.219-227.
2. Duke, T., Frank, D., Mgone, J. Hypoxaemia in children with severe pneumonia in Papua New Guinea. *Int J TB Lung Dis* **2000**,5, pp.511–519.
3. Onyango, F.E., Steinhoff, M.C., Wafula, E.M., Wariua, S., Musia, J., Kitonyi, J. Hypoxaemia in young Kenyan children with acute lower respiratory infection. *BMJ* **1993**, 306, 612–615.
4. Mackenzie, G.A., McLellan, J., Machuka, E, et al. Aetiology of lobar pneumonia determined by multiplex molecular analyses of lung and pleural aspirate specimens in the Gambia: findings from population-based pneumonia surveillance *BMJ Open* **2022**, 12:e056706.

5. 5. Pneumonia Etiology Research for Child Health (PERCH) Study Group. Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. *Lancet* **2019**, 394(10200), pp.757-779.
6. 6. Camargo, J.J., Camargo, S.M., Machuca, T.N., Perin, F.A. Round pneumonia: a rare condition mimicking bronchogenic carcinoma. Case report and review of the literature. *Sao Paulo Med J.* **2008**, 126(4), pp.236-238.
7. 7.Soubani, A.O., Epstein, S.K. Life-threatening "round pneumonia". *Am J Emerg Med* **1996** , 14(2),pp.189-191.
8. 8. Çimen, D., Bulcun, E., Ekici, A., Güngör, Ö., Ekici, M. Case of round pneumonia: pulmonary infarct and a rare situation that is similar with the lung cancer. *Clin Respir J* **2015**, 9(4), pp.512-515.
9. 9. Durning, S.J., Sweet, J.M., Chambers, S.L. Pulmonary mass in tachypneic, febrile adult. *Chest* **2003**,124(1),pp.372-375.
10. 10. Harvey, E., Varatharaj, A. Round pneumonia. *QJM* **2014**, 107(3),239.
11. 11.Yano, T., Shoji, F., Koga, T. Is oxygen supplementation needed after standard pulmonary resection for primary lung cancer? *Ann Thorac Cardiovasc Surg* **2006** ,12(6), pp.393-396.
12. 12. Rubenfeld, G.D., Caldwell, E., Peabody, E., Weaver, J., Martin, D.P., Neff, M., Stern, E.J., Hudson, L.D. Incidence and outcomes of acute lung injury. *N Engl J Med* **2005**, 353(16), pp.1685-1693.
13. 13. Brun-Buisson, C., Minelli, C., Bertolini, G., et al. Epidemiology and outcome of acute lung injury in European intensive care units. Results from the ALIVE study. *Intensive Care Med* **2004**, 30(1), pp.51-61.
14. 14. Englert, J.A., Bobba, C., Baron, R.M. Integrating molecular pathogenesis and clinical translation in sepsis-induced acute respiratory distress syndrome. *JCI Insight* **2019**, 4(2):e124061.
15. 15. Calfee, C.S., Delucchi, K., Parsons, P.E., Thompson, B.T., Ware, L.B., Matthay, M.A.; NHLBI ARDS Network. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. *Lancet Respir Med* **2014**, 2(8), pp.611-620.
16. 16. Roca, J., Wagner, P.D. Contribution of multiple inert gas elimination technique to pulmonary medicine 1: principles and information content of the multiple inert gas elimination technique. *Thorax* **1994**, 49: pp.815-824.
17. 17. Barberà, J.A., Roger, N., Roca, J., Rovira, I., Higenbottam, T.W., Rodriguez-Roisin, R. Worsening of pulmonary gas exchange with nitric oxide inhalation in chronic obstructive pulmonary disease. *Lancet* **1996**, 347(8999), pp.436-440.
18. 18. Gómez, F.P., Amado, V.M., Roca, J., Torres, A., Nicolas, J.M., Rodriguez-Roisin, R., Barberà, J.A. Effect of nitric oxide inhalation on gas exchange in acute severe pneumonia. *Respir Physiol Neurobiol* **2013**, 187(2), pp.157-163.
19. 19. Suter, P.M., Suter, S., Girardin, E., Roux-Lombard, P., Grau, G.E., Dayer, J.M. High bronchoalveolar levels of tumor necrosis factor and its inhibitors, interleukin-1, interferon, and elastase, in patients with adult respiratory distress syndrome after trauma, shock, or sepsis. *Am Rev Respir Dis* **1992**, 145, pp.1016-1022.
20. 20. Pugin, J., Ricou, B., Steinberg, K.P., Suter, P.M., Martin, T.R. Proinflammatory activity in bronchoalveolar lavage fluids from patients with ARDS, a prominent role for interleukin-1. *Am J Respir Crit Care Med* **1996**, 153(6 Pt 1), 1850-1846.
21. 21.Vila, E., Salaices, M. Cytokines and vascular reactivity in resistance arteries. *Am J Physiol Heart Circ Physiol* **2005**, 288(3), H1016-1021.
22. 22.Lang, M., Som, A., Mendoza, D.P., Flores, E.J., Reid, N., Carey, D., Li, M.D., Witkin, A., Rodriguez-Lopez, J.M., Shepard, J.O., Little, B.P. Hypoxaemia related to COVID-19: vascular and perfusion abnormalities on dual-energy CT. *Lancet Infect Dis* **2020**, 20(12), pp.1365-1366.
23. 23.Brotto, A.R., Phillips, D.B., Meah, V.L., Ross, B.A., Fuhr, D.P., Beaudry, R.I., van Diepen, S., Stickland, M.K. Inhaled nitric oxide does not improve maximal oxygen consumption in endurance trained and untrained healthy individuals. *Eur J Appl Physiol* **2022**,122(3), pp.703-715.
24. 24. Eisenhut, M., Wallace, H. Acquired cystic fibrosis transmembrane conductance regulator dysfunction. *Pflugers Arch* **2025**, 477(11-12), pp.1309-1322.
25. 25. Wang, P.M., Ashino, Y., Ichimura, H., Bhattacharya, J. Rapid alveolar liquid removal by a novel convective mechanism. *Am J Physiol Lung Cell Mol Physiol* **2001**, 281(6), L1327-1334.

26. 26. Wheatley, C.M., Morgan, W.J., Cassuto, N.A., Foxx-Lupo, W.T., Daines, C.L., Morgan, M.A., Phan, H., Snyder, E.M. Exhaled breath condensate detects baseline reductions in chloride and increases in response to albuterol in cystic fibrosis patients. *Clin Med Insights Circ Respir Pulm Med* **2013**, 7, pp.79–90.

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