history of COPD is far from being determined.

Competing interests None.

REFERENCES

1. **Janssens W,** Lehouck A, Carremans C, et al. Vitamin D beyond bones in chronic obstructive pulmonary disease: time to act. *Am J Respir Crit Care Med* 2009;**179**:630—6.
2. **Mora JR,** Iwata M, von Andrian UH. Vitamin effects on the immune system: vitamins A and D take centre stage. *Nat Rev Immunol* 2008;**8**:685—98.
3. **Holik MF.** Vitamin D deficiency. *N Engl J Med* 2007;**357**:266—81.
4. **Waterhouse JC,** Perez TH, Albert PJ. Reversing bacteria-induced vitamin D receptor dysfunction is key to autoimmune disease. *Ann NY Acad Sci* 2009;**1173**:757—65.
5. **Norman AW,** Bouillon R, Whiting SJ, et al. 13th Workshop consensus for vitamin D nutritional guidelines. *J Steroid Biochem Mol Biol* 2007;**103**:204—5.
6. **Janssens W,** Bouillon R, Claes B, et al. Vitamin D deficiency is highly prevalent in COPD and correlates with variants in the vitamin D-binding gene. *Thorax* 2010;**65**:215—20.
7. **Black PN,** Scragg R. Relationship between serum 25-hydroxyvitamin d and pulmonary function in the third national health and nutrition examination survey. *Chest* 2005;**128**:3792—8.
8. **Camargo CA Jr,** Rifas-Shiman SL, Litonjua AA, et al. Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. *Am J Clin Nutr* 2007;**85**:788—95.
9. **Hyppönen E,** Sovio E, Wjst M, et al. Infant vitamin D supplementation and allergic conditions in adulthood: Northern Finland birth cohort 1966. *Ann NY Acad Sci* 2004;**1037**:84—95.
10. **Brehm JM,** Celedón JC, Soto-Quiros ME, et al. Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. *Am J Respir Crit Care Med* 2009;**179**:765—71.
11. **Donaldson GC,** Wilkinson TMA, Hurst JR, et al. Exacerbations and time spent outdoors in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;**171**:446—52.
12. **Schellenberg D,** Pare PD, Weir TD, et al. Vitamin D binding protein variants and the risk of COPD. *Am J Respir Crit Care Med* 1998;**157**:957—61.
13. **Lauridsen AL,** Vestergaard P, Hermann AP, et al. Plasma concentrations of 25-hydroxy-vitamin D and 1,25-dihydroxy-vitamin D are related to the phenotype of Gc (vitamin D-binding protein): a cross-sectional study on 595 early postmenopausal women. *Calcif Tissue Int* 2005;**77**:15—22.
14. **Uitterlinden AG,** Fang Y, Van Meurs JB, et al. Genetics and biology of vitamin D receptor polymorphisms. *Gene* 2004;**338**:143—56.
15. **Hopkinson NS,** Li KW, Kehoe A, et al. Vitamin D receptor genotypes influence quadriceps strength in chronic obstructive pulmonary disease. *Am J Clin Nutr* 2008;**87**:385—90.
16. **Donaldson GC,** Seemungal TAR, Bhowmik A, et al. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002;**57**:847—52.
17. **Hope-Simpson RE.** The role of season in the epidemiology of influenza. *J Hyg (Lond)* 1981;**86**:35—47.
18. **Quint JK,** Donaldson GC, Goldring JJP, et al. Serum IP-10 as a biomarker of human rhinovirus infection at exacerbation of COPD. *Chest*. Published Online First: 16 October 2009. doi:10.1378/chest.09-1541.
19. **Hewison M,** Zehnder D, Chakraverty R, et al. Vitamin D and barrier function: a novel role for extra-renal 1 alpha-hydroxylase. *Mol Cell Endocrinol* 2004;**215**:31—8.
20. **Helming L,** Böse J, Ehrchen J, et al. 1alpha,25-Dihydroxyvitamin D3 is a potent suppressor of interferon gamma-mediated macrophage activation. *Blood* 2005;**106**:4351—8.
21. **Abu-Amer Y,** Bar-Shavit Z. Impaired bone marrow-derived macrophage differentiation in vitamin D deficiency. *Cell Immunol* 1993;**151**:356—68.
22. **Cohen MS,** Mesler DE, Snipes RG, et al. 1,25-Dihydroxyvitamin D3 activates secretion of hydrogen peroxide by human monocytes. *J Immunol* 1986;**136**:1049—53.
23. **Grange JM,** Davies PD, Brown RC, et al. A study of vitamin D levels in Indonesian patients with untreated pulmonary tuberculosis. *Tubercle* 1985;**66**:187—91.
24. **Nnoaham KE,** Clarke A. Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. *Int J Epidemiol* 2008;**37**:113—19.
25. **Gibney KB,** MacGregor L, Leder K, et al. Vitamin D deficiency is associated with tuberculosis and latent tuberculosis infection in immigrants from Sub-Saharan Africa. *Clin Infect Dis* 2008;**46**:443—6.
26. **Martineau AR,** Wilkinson RJ, Wilkinson KA, et al. A single dose of vitamin D enhances immunity to mycobacteria. *Am J Respir Crit Care Med* 2007;**176**:208—13.
27. **Wejse C,** Gomes VF, Rabna P, et al. Vitamin D as supplementary treatment for tuberculosis: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2009;**179**:843—50.
28. **Roth DE,** Jones AB, Prosser C, et al. Vitamin D receptor polymorphisms and the risk of acute lower respiratory tract infection in early childhood. *J Infect Dis* 2008;**197**:676—80.
29. **Sadeghi K,** Wessner B, Laggner U, et al. Vitamin D3 down-regulates monocyte TLR expression and triggers hyporesponsiveness to pathogen associated molecular patterns. *Eur J Immunol* 2006;**36**:361—70.
30. **Bhalla AK,** Amento EP, Krane SM. Differential effects of 1,25 dihydroxyvitamin D3 on human lymphocytes and monocyte/macrophages: inhibition of interleukin 2 and augmentation of interleukin1 production. *Cell Immunol* 1986;**98**:311—22.
31. **Liu PT,** Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 2006;**311**:1770—3.

ECMO in adults for severe respiratory failure finally comes of age: just in time?

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The idea of employing cardiopulmonary bypass technology as a means of oxygenating (extracorporeal membrane oxygenation (ECMO)) or removing carbon dioxide (ECCO$_2$R) in patients with acute respiratory failure (ARF) was first assessed in randomised controlled trials in the 1970s and 1980s.[1][2] Poor rates of survival and major complications, particularly massive haemorrhage, led to most intensivists believing that ECMO was inappropriate in adults. A small number of centres worldwide—including that in Leicester, UK—continued to refine the use of ECMO in small numbers of adult patients whom it proved impossible to oxygenate by conventional means. Following the publication of their case series with improved results,[3] Peek and colleagues embarked upon a randomised controlled trial of conventional ventilation or ECMO in patients with severe ARF (CESAR), the results of which have just been reported.[4]

Patients (n=766) were screened for inclusion over a 5-year period and those with potentially reversible severe ARF (defined as a Murray score >3 or uncontrolled hypercapnia (pH <7.20); n=188) were entered in the trial. Many had multiorgan failure. The mean PaO$_2$/FIO$_2$ ratio at study entry was 10 kPa, with a positive end-expiratory pressure of 14 cm H$_2$O. Exclusion criteria included irreversible disease, the receipt of high-pressure high-inspired oxygen ventilation for >7 days and contraindications to anticoagulation. Patients were randomised to receive conventional treatment at the referring hospital or an approved tertiary centre where they received mechanical ventilation alone (which could include

oscillation, inhaled nitric oxide and prone positioning) or transfer to Leicester where, in addition, ECMO could be provided. Encouragingly, 63% of those allocated to the ECMO centre survived without severe disability at 6 months compared with 47% of those receiving conventional support. Economic analysis estimated the cost per additional quality of life year at about £20 000. The study was analysed on an intention-to-treat basis; the improved outcome occurred despite five patients dying before or during transfer and only 75% of those transferred received ECMO.

The publication of this study represents an extraordinary achievement. It was conceived and led in an atmosphere of scepticism among the critical care community, driven partly by the markedly improved outcomes for patients with acute lung injury that emerged following the development of new ventilatory techniques.[5] Furthermore, moving such critically ill patients is complex and difficult, and the fact that so few succumbed as a consequence is a testimony to the skill and dedication of the investigators.

By contrast, the study had significant limitations about which the authors are open. First, differences in non-ECMO-related therapies received by the intervention group might have explained its better outcome. Thus, patients receiving ECMO were more likely to be given corticosteroids and artificial liver support, although neither therapy alone has been shown to improve mortality in patients either with severe acute respiratory distress syndrome (ARDS)[6 7] or liver failure.[8] Second, patients moved to Leicester were more likely to receive low-volume low-pressure mechanical ventilation, a strategy that has been shown to improve outcome[5] and minimise further pulmonary injury.[9] However, whether this was because ECMO facilitated that goal by partially supporting gas exchange is not known.

What does the study mean for respiratory physicians, aside from those who also practise critical care? First and foremost it has shown that ECMO can safely bridge patients with reversible severe ARF to recovery without the complications documented previously. However, selecting the most appropriate patients to receive ECMO should involve those with the diagnostic and prognostic skills to identify the underlying pathology, the natural history of disease and the most appropriate adjunctive therapies. Second, survivors often require prolonged inpatient and outpatient care that necessitates respiratory expertise. Thus, the current study and others[10 11] demonstrate that, at 6 months, spirometric measurements are about 75% predicted while patients have ongoing pulmonary symptoms and reduced exercise capacity.

Where are the lessons for healthcare planners? The study provides powerful support for the concept that centralised care should be provided for patients with severe ARF, probably in a limited number of centres with the necessary resources and expertise including ECMO. Such centres should be able to collect and move patients on ECMO, a model adopted in Scandinavia and Germany. The perceived risk of transfer is a barrier for many referring clinicians. However, because of the limitations of the study, the precise place of ECMO in hypoxaemic adults will remain controversial, if only in terms of the threshold for its application. Thus, some patients will arrive in the receiving centre and be found not to require or be unsuitable for ECMO (20% in the current study). Establishing precise thresholds for referral is therefore likely to prove difficult.

The advent of H1N1 infection has focused attention on young critically ill patients with severe ARF. Data from Australia and Canada suggest that those who require intensive care develop severe refractory hypoxaemia for which ECMO may prove to be highly effective. Evidence is now available to suggest that building capacity to provide such support is timely.

REFERENCES

1. **Morris AH,** Wallace CJ, Menlove RL, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO_2 removal for adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1994;**149**(2 Pt 1):295—305.
2. **Zapol WM,** Snider MT, Schneider RC. Extracorporeal membrane oxygenation for acute respiratory failure. *Anesthesiology* 1977;**46**:272—85.
3. **Peek GJ,** Moore HM, Moore N, et al. Extracorporeal membrane oxygenation for adult respiratory failure. *Chest* 1997;**112**:759—64.
4. **Peek GJ,** Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional respiratory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* 2009;**374**:1351—63.
5. **The Acute Respiratory Distress Syndrome Network.** Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;**342**:1301—8.
6. **Meduri GU,** Golden E, Freire AX, et al. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. *Chest* 2007;**131**:954—63.
7. **Steinberg KP,** Hudson LD, Goodman RB, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med* 2006;**354**:1671—84.
8. **Karvellas CJ,** Gibney N, Kutsogiannis D, et al. Bench-to-bedside review: current evidence for extracorporeal albumin dialysis systems in liver failure. *Crit Care* 2007;**11**:215.
9. **Pinhu L,** Whitehead T, Evans T, et al. Ventilator-associated lung injury. *Lancet* 2003;**361**:332—40.
10. **Herridge MS,** Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003;**348**:683—93.
11. **Heyland DK,** Groll D, Caeser M. Survivors of acute respiratory distress syndrome: relationship between pulmonary dysfunction and long-term health-related quality of life. *Crit Care Med* 2005;**33**:1549—56.