Partial liquid ventilation for preventing death and morbidity in adults with acute lung injury and acute respiratory distress syndrome (Review)

Davies MW, Fraser JF

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ABSTRACT

Background
Acute lung injury (ALI), and acute respiratory distress syndrome (ARDS), are syndromes of severe respiratory failure. Adults with ALI or ARDS have high mortality and significant morbidity. Partial liquid ventilation (PLV) may be better (i.e., cause less lung damage) for these patients than other forms of respiratory support. Uncontrolled studies in adults have shown improvement in gas exchange and lung compliance with partial liquid ventilation.

Objectives
To assess whether partial liquid ventilation reduces morbidity and mortality in adults with ALI or ARDS.

Search strategy
We searched The Cochrane Central Register of Controlled Trials (CENTRAL), The Cochrane Library Issue 2, 2004; MEDLINE (1966 to May 2004); and CINAHL (1982 to May 2004); intensive care journals and conference proceedings; reference lists and unpublished literature.

Selection criteria
Randomized controlled trials which compared partial liquid ventilation with other forms of ventilation, in adults (16 years old or greater) with ALI or ARDS, reporting one or more of the following: mortality; duration of mechanical ventilation, respiratory support, oxygen therapy, stay in the intensive care unit, or stay in hospital; infection; long term cognitive impairment or health related quality of life; long term lung function; or cost.

Data collection and analysis
Two reviewers independently evaluated the quality of the relevant studies and extracted the data from the included studies.

Main results
Problems with the inadequacy of the primary report of the one included study do not allow us to report any quantitative results for patients with ALI or ARDS. The only outcome we considered to be of clinical significance and reported for all enrolled patients (i.e., patients with ALI and ARDS and less severe respiratory insufficiency) was 28 day mortality. There was no statistically significant difference between groups for this outcome with a relative risk for 28 day mortality in the PLV group of 1.15 (95% confidence intervals of 0.64 to 2.10).

Authors' conclusions
There is no evidence from randomized controlled trials to support or refute the use of partial liquid ventilation in adults with ALI or ARDS; adequately powered, high quality randomized controlled trials are still needed to assess its efficacy. Clinically relevant outcome measures should be assessed (especially mortality at discharge and later, duration of respiratory support and hospital stay, and long term cognitive and quality of life outcomes) and the studies should be published in full.
BACKGROUND

Acute lung injury (ALI), and the more severe subset acute respiratory distress syndrome (ARDS), are syndromes of severe respiratory failure characterized by acute onset, severe hypoxaemia and bilateral chest infiltrates on chest x-ray (CXR), without evidence of left heart failure. ARDS was first described by Ashbaugh in 1967 (Ashbaugh 1967). The causes of ALI or ARDS are many and they may result from primary lung disease (pneumonia, aspiration or inhalation injury, lung trauma, fat emboli, near-drowning) or extra-pulmonary causes (septicaemia, trauma and shock, cardiopulmonary bypass, drug overdose, acute pancreatitis, transfusion) (Ware 2000).

ALI or ARDS results in mismatch between ventilation and perfusion (V/Q mismatch), with well ventilated but poorly perfused areas in the lung and well perfused but poorly ventilated areas, leading to severe hypoxaemia. They are also characterized by severe heterogeneous atelectasis (differing degrees of collapse throughout the lung) and decreased lung compliance (decreased ease with which the lung expands). Hence, patients with ALI or ARDS universally require respiratory support and the mainstay of treatment is endotracheal intubation and mechanical ventilation (Tobin 2001). The syndromes are also characterized by a prominent pulmonary and systemic inflammatory response. There is loss of integrity of the alveolar-capillary barrier in the lung with increased inflammatory cell and oxygen free radical mediated injury and increased pulmonary and systemic pro-inflammatory cytokines (Ware 2000).

Mechanical ventilation for ALI or ARDS may cause physical damage to the lungs, with the use of high pressures (barotrauma) and large tidal volumes (volutrauma), causing ventilator-induced lung injury (VILI) and its secondary inflammatory effects. Decreasing baro- and volu-trauma may lower mortality and morbidity (Tobin 2001; van der Werf 2001).

Generally accepted mortality figures for ALI or ARDS have ranged from 40 to 60% (Ware 2000); although recent studies have shown decreasing mortality (Abel 1998; Milberg 1995). Mortality in this condition is often due to the primary disease process, especially sepsis, or the associated multi-organ dysfunction rather than respiratory failure per se (Monchi 1998; Ware 2000; Zilberberg 1998) and therefore may not be amenable to alterations in ventilatory techniques. However more recent studies show a lower mortality with ‘protective’ ventilatory strategies and, or, an ‘open-lung’ approach (i.e., maximising lung recruitment and functional residual capacity) in adults with ARDS, suggesting that VILI does have a role in increasing mortality; and that decreasing baro- and volu-trauma may lead to improved survival (Abel 1998; Amato 1998; ARDS Network 2000; Baudouin 2001; Tobin 2001, van der Werf 2001). A recent Cochrane review (Petrucci 2004) concluded that mechanical ventilation with lower tidal volumes in adults with ALI or ARDS reduced mortality. Mortality and other outcomes have been shown to vary by the age of the patient, the initial severity of the ALI or ARDS or patients condition (e.g. by APACHE score) and by the underlying cause of the ALI or ARDS (Monchi 1998; Suntharalingam 2001; Ware 2000).

There is also substantial short and long term morbidity associated with these syndromes. Short term morbidity leads to prolonged ventilator dependence and prolonged stay in intensive care units (ICU) and hospital. Long term morbidity includes decreased lung function, decreased health related quality of life, cognitive impairments, and high rates of disability and un-employment (Rothenhausler 2001; Schelling 2000).

The mainstay of treatment of ALI and ARDS is mechanical ventilation. Many forms of additional therapies have been considered and some of these subjected to randomized controlled trials. Adjuncts to mechanical ventilation have included: extracorporeal life support (ECLS), inhaled nitric oxide, endogenous surfactant, prone positioning, high frequency ventilation and a variety of pharmaceutical therapies (anti-inflammatory medication, antioxidants, anticytokine agents, prostaglandins) (Conner 2000). The ventilatory techniques that seem to improve outcomes in ALI or ARDS are the ‘lung-protective’ strategies that aim to decrease VILI (Brower 2000; van der Werf 2001).

Partial liquid ventilation (PLV) has been proposed as a less injurious form of respiratory support for patients with severe respiratory failure, ALI and ARDS. In 1991 Fuhrman et al (Fuhrman 1991) introduced the technique of using functional residual ca-
Partial liquid ventilation for preventing death and morbidity in adults with acute lung injury and acute respiratory distress syndrome (Review)

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Partial liquid ventilation (PLV) and liquid ventilation (LV) are a range of techniques that use perfluorocarbon liquids (PFC) to improve oxygenation and reduce pulmonary shunting in patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). The technique involves partial filling of the lungs with PFC, which has a high oxygen-carrying capacity and low surface tension, allowing it to mimic alveolar capillary lining fluid and improve gas exchange.

**Objective**

The primary objective was to assess whether partial liquid ventilation reduces morbidity and mortality in adults with ALI or ARDS. Sub-group analyses were planned to determine whether the results differ by:

- **Population:**
  - age
  - severity of: a) overall illness (e.g. APACHE or SAPS score), or b) of ALI or ARDS
  - aetiology of ALI or ARDS (e.g. septicaemia, pneumonia, trauma, burns, etc)

Mortality and other outcomes have been shown to vary by the age of the patient, the initial severity of the ALI or ARDS or patients condition (e.g. by APACHE score) and by the underlying cause of the ALI or ARDS (Monchi 1998; Suntharalingam 2001; Ware 2000).

**Intervention:**

- initial amount or dose of PFC
- whether continuous PLV or intermittent doses of PFC
- type of PFC (e.g. perfluorbron, Rimar, etc)

The correct dose of PFC to use when initiating PLV is unknown. Variations in the technique of PLV may also include giving an initial dose of PFC with or without further top-up doses to maintain partial filling of the lungs. Various types of PFC with different physical and chemical properties may be used. (Davies 1999).

The use of co-interventions in addition to PLV:

- use of inhaled nitric oxide
- use of surfactant
- use of prone position
- high frequency ventilation

Whilst the mainstay of treatment of ALI or ARDS is mechanical ventilation, additional therapies have been considered and some of these subjected to randomized controlled trials. Adjuncts to mechanical ventilation have included: inhaled nitric oxide, endogenous surfactant, prone positioning, and high frequency ventilation (Conner 2000); all can be used in conjunction with PLV.

**Criteria for Considering Studies for This Review**

**Types of studies**

Randomized controlled trials (RCTs) of adequate quality - at least two of the following criteria (each rated as either adequate, unclear or inadequate) must be rated as adequate for the study to be included in the review:

1. allocation concealment (blinding of randomization)
2. blinding of intervention
3. completeness of follow up and
4. blinding of outcome measurement.

Cross-over studies will be excluded.

**Types of participants**

Adults, (aged 16 years old or greater), with ALI or ARDS from any cause who are intubated and are being supported by a mechanical ventilator.

**Definition of ALI** (Bernard 1994):

1. acute onset respiratory failure
2. bilateral opacities on CXR consistent with pulmonary oedema
3. pulmonary artery wedge pressure <18mmHg or no clinical evidence of raised left atrial pressure
4. \(\text{PaO}_2/\text{FiO}_2\) ratio \(\leq 300\text{mmHg}\).

Definition of ARDS (Bernard 1994):
1. acute onset respiratory failure;
2. bilateral opacities on CXR consistent with pulmonary oedema;
3. pulmonary artery wedge pressure <18mmHg or no clinical evidence of raised left atrial pressure;
4. \(\text{PaO}_2/\text{FiO}_2\) ratio \(\leq 200\text{mmHg}\).

Types of intervention
Partial liquid ventilation compared with other forms of ventilatory management without the use of perfluorocarbon liquids or vapour.

Types of outcome measures
One or more of the following outcomes must be reported:

Primary:
- Mortality (28 day, at discharge from ICU, at discharge from hospital, and at 1, 2, and 5 years).

Secondary:
- duration of mechanical ventilation;
- duration of respiratory support;
- duration of oxygen therapy;
- duration of stay in the ICU;
- duration of stay in hospital;
- infection (sepsicaemia, pneumonia);
- long term cognitive impairment;
- long term health related quality of life;
- long term lung function;
- Cost.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Anaesthesia Group methods used in reviews.

We searched The Cochrane Central Register of Controlled Trials (CENTRAL), The Cochrane Library, Issue 2, 2004; MEDLINE (1966 to May 2004); and CINAHL (1982 to May 2004).

RCTs of PLV in ALI or ARDS were identified from MEDLINE using the MeSH heading 'RESPIRATORY DISTRESS SYNDROME, ADULT' or the textwords 'ARDS', 'ALI' or 'acute lung injury' and the MeSH heading 'FLUOROCARBONS' or the textword 'partial liquid ventilation'.

The MEDLINE search will be found in the 'Additional tables (Table 01).'

Other databases, including CINAHL and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched using a similar strategy. Bibliographies of published trials and conference proceedings were also reviewed.

No language restrictions were applied.

We also attempted to identify unpublished trials by contacting experts in the field of PLV research.

METHODS OF THE REVIEW

The standard methods of the Cochrane Collaboration and its Anaesthesia Review Group were used. The two reviewers worked independently to search for and assess trials for inclusion and methodological quality. Differences were resolved by discussion and consensus of the reviewers.

Studies were assessed using the following key criteria:
1. allocation concealment (blinding of randomization);
2. blinding of intervention;
3. completeness of follow up, and;
4. blinding of outcome measurement.

Each were rated as either adequate, unclear or inadequate. At least two criteria must have been rated as adequate for the study to be included in the review.

Data were extracted independently by the reviewers. Differences were resolved by discussion and consensus of the reviewers. Investigators were contacted for additional information or data where appropriate.

It was planned that if sufficient studies had been identified and included in this review we would perform a sensitivity analysis based on the methodological quality of the studies.

For individual trials, where possible, mean differences (and 95% confidence intervals) were to be reported for continuous variables such as duration of oxygen therapy. For categorical outcomes such as mortality, the relative risk and risk difference (and 95% confidence intervals) were to be reported.

For the meta-analysis, where possible, weighted mean differences (and 95% confidence intervals) were to be reported for continuous variables, and the relative risk and risk difference (and 95% confidence intervals) were to be reported for categorical outcomes. A random effects model was to be used.

DESCRIPTION OF STUDIES

195 titles and abstracts were found using this search strategy. Of these 195 papers, ten were reviewed in full. Three reports of studies (Alliance 2002; Hirschl 2002; Schuster 2001) were identified as potentially meeting the inclusion criteria for this review.
The most recent study has not been published and the preliminary results have only been announced in a press release from Alliance Pharmaceutical Corporation: a “phase 2-3 clinical study that evaluated the use of Partial Liquid Ventilation™ (PLV) with LiquiVent® for adult patients with Acute Respiratory Distress Syndrome (ARDS) being supported by a mechanical ventilator” (Alliance 2002). The study investigators mentioned in the press release have been contacted but no further information about the trial or data from it have been made available. The press release noted that: "Efficacy data from the study revealed that PLV with LiquiVent did not meet either the primary study endpoint for improvement in "ventilator free days" or the secondary endpoint of improvement in 28-day mortality”.

Schuster et al (Schuster 2001) reported on a post hoc analysis of 16 patients from another trial (as yet, not published) examining the radiographic appearances during treatment with PLV with either high or low dose PFC. The study design was randomized (to high or low volume PFC; randomization method is not stated). The primary end point was the CXR homogeneity of PFC filling over a 48 hour period and secondary end points included oxygenation as a function of CXR appearance. Oxygenation was reported as better at 24 hours (p<0.05) with homogenous filling. It is unclear from the report (and no further information is available after contacting the study investigators) if there were other patients in the larger study (i.e., were there other patients in the study that received either low or high dose PFC and, if there were, were these 16 the only patients reported because they were the only ones who had the appropriate x-rays?). It is therefore unknown how many patients were randomized to either treatment group.

Therefore, only one study was identified and found eligible for inclusion in this review (Hirschl 2002) (see Table: 'Characteristics of Included Studies'). This was a prospective multi-centre randomized controlled trial done in 18 centres between July 1995 and August 1996. Each study centre enrolled an average of only five patients into the study (90 patients in 18 centres, only four sites enrolled more than five patients and those four sites overall enrolled 52 of the 90 patients); many of these centres would only have enrolled one or two patients into the study and many would have only treated one patient with PLV. This may have led to wide variation in the application of PLV, the success of which may well be determined in part by how the PLV is applied. Initially patients who developed ALI or ARDS (who met the criteria of ARDS for less than 24 hours prior) were randomized to receive PLV or conventional ventilation for a maximum of five days. Patients with multiple organ failure were excluded. The entry criteria changed a number of times during the study: in particular after the enrolment of 45 subjects the entry criteria were changed such that patients with respiratory failure that was less severe than ALI or ARDS were enrolled. The initial primary outcome was oxygenation, but this was changed during the study to the number of ventilator free days. Secondary outcomes included 28 day mortality, PaO₂/FiO₂ ratio and A-a gradient. It is not clear why more clinically important outcomes (see ‘Criteria for considering studies for this review: Types of outcome measures’ above) were not reported. A large number of post hoc analyses were reported. It is unknown whether the analysis is based on an intention to treat. We have contacted the first author of this study and the company that sponsored it and no further information or data are forthcoming from either source.

**METHODOLOGICAL QUALITY**

In Hirschl et al’s study (Hirschl 2002):
1. treatment allocation was randomized (exact method not stated);
2. group allocation was concealed - “a central office at Alliance Pharmaceutical was contacted for group assignment...”;
3. treatment was not blinded;
4. follow-up was assumed to be complete for the unambiguous outcome of 28 day mortality;
5. whether the published outcomes were assessed by blinded evaluators is unknown (blinding of the assessment of death is not applicable).

**RESULTS**

Problems with the inadequacy of the primary report of the one included study (Hirschl 2002) do not allow us to report any quantitative results. This is because some of the patients enrolled in the trial did not have ALI or ARDS and the exact numbers of patients that met the criteria for ALI or ARDS are not stated nor are the exact numbers given for each outcome for these subgroups of patients. This trial also reports a large number of post hoc analyses that have not been considered in this review: they should be interpreted with great caution (see notes in ‘Characteristics of included studies’).

The only outcome, that we considered to be of clinical significance, reported for all enrolled patients (i.e., patients with ALI and ARDS and less severe respiratory insufficiency) was 28 day mortality. Although not reported we assumed 100% follow-up for analysis of this short-term outcome. There was no statistically significant difference between groups for this outcome with a relative risk for 28 day mortality in the PLV group of 1.15 (95% confidence intervals of 0.64 to 2.10). None of the following outcomes were reported: mortality at any time after day 28, duration of mechanical ventilation, duration of respiratory support, duration of oxygen therapy, duration of stay in the intensive care unit, duration of stay in hospital, infection, long term cognitive impairment, long term health related quality of life, long term lung function, cost.
**DISCUSSION**

While it has been suggested that PLV is a promising alternative mode of mechanical ventilation for adults with ALI or ARDS, there are no data from adequately powered RCTs available to determine whether PLV is effective or not in decreasing morbidity or mortality. The wide confidence intervals for 28 day mortality seen in the study by Hirschl et al (Hirschl 2002) mean that a clinically significant difference in either direction cannot be excluded.

It is unfortunate that the only RCT investigating PLV in adults with ALI or ARDS reported so far (Hirschl 2002) has little data on clinically relevant outcomes (especially, mortality at discharge and later; duration of respiratory support and hospital stay; and long term outcomes). It is also unfortunate that the study entry criteria were changed to allow patients with less severe respiratory insufficiency to be enrolled in the study without reporting the exact numbers of patients that met the original study entry criteria (i.e., ALI or ARDS). The limited information available on completeness of follow-up or blinding of outcome assessment also makes it difficult to make a complete assessment of study quality. No further information is forthcoming from the study investigators or the company that sponsored the trial.

It is also unfortunate that the latest RCT (Alliance 2002) has not been published and that no data are forthcoming from the study investigators or the company that sponsored the trial.

The under-reporting of RCTs due to publication bias has been well described (Dickersin 1987; Dickersin 1990; Dickersin 1993). In a systematic review of pharmaceutical industry sponsorship and research outcome Lexchin et al (Lexchin 2003) found that research funded by drug companies was less likely to be published. Some consider the selection of reports for publication on the basis of “positive results”, or the failure of investigators to publish results with sufficient detail to allow judgments to be made about their validity as scientific misconduct (Chalmers 1990). It is unknown whether any of these factors are operating here.

**AUTHORS’ CONCLUSIONS**

**Implications for practice**

There is no evidence from RCTs to support or refute the use of PLV in adults with ALI or ARDS.

**Implications for research**

If adults with ALI or ARDS are to be treated with PLV then adequately powered, high quality RCTs are still needed to assess its efficacy. Clinically relevant outcome measures should be assessed (especially, mortality at discharge and later; duration of respiratory support and hospital stay; and long term cognitive and quality of life outcomes) and the studies should be published in full.

**POTENTIAL CONFLICT OF INTEREST**

None known

**ACKNOWLEDGEMENTS**

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- Royal Children’s Hospital, Brisbane AUSTRALIA
- Royal Children’s Hospital Foundation, Royal Children's Hospital, Brisbane, Queensland AUSTRALIA
- Dept of Intensive Care Medicine, The Prince Charles Hospital, Brisbane AUSTRALIA
References to studies included in this review

Hirschl 2002 *(published data only)*


References to studies excluded from this review

Hirschl 2001


Schuster 2004


Additional references

Abel 1998


Amato 1998


ARDS Network 2000


ASHBAUGH 1967


Baudouin 2001


Bernard 1994


Brower 2000


Chalmers 1990


Conner 2000


Davies 1999


Davies 2004


Dickersin 1987

Dickersin 1990

Dickersin 1993
Dickersin K, Min YI. NIH clinical trials and publication bias. Online Journal of Current Clinical Trials 1993; Doc No 50.

Fuhrman 1991

Lexchin 2003

Milberg 1995

Monchi 1998

Petrucci 2004

Rothenhausler 2001

Schelling 2000

Suntharalingam 2001

Tobin 2001

van der Werf 2001

Ware 2000

Wiedemann 2000

Zilberberg 1998

* Indicates the major publication for the study

TABLES

Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Hirschl 2002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Prospective, multi-centre, randomized controlled trial.</td>
</tr>
<tr>
<td></td>
<td>Done between July 1995 and August 1996.</td>
</tr>
<tr>
<td>Participants</td>
<td>Ninety patients with ALI/ARDS.</td>
</tr>
<tr>
<td></td>
<td>Entry criteria:</td>
</tr>
<tr>
<td></td>
<td>bilateral infiltrates on CXR for &lt;=5 days,</td>
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Characteristics of included studies (Continued)

ventilated for $\leq 5$ days,
$\text{FiO}_2 = 0.5$,
$\text{PaO}_2/\text{FiO}_2$ ratio $> 60$ and $< 300$,
aged 15 - 75 years.

The first 45 patients were stratified according to Murray lung Injury score - $\leq 2.5$ or $> 2.5$. They had their $\text{PaO}_2/\text{FiO}_2$ ratios determined at an $\text{FiO}_2$ of 1.

The second 45 patients also had to have an APACHE 2 score of $< 30$. They had their $\text{PaO}_2/\text{FiO}_2$ ratios determined at an $\text{FiO}_2$ of $\geq 0.5$.

Exclusion criteria:
1. On ventilator support for diagnosed ALI/ARDS or with $\text{FiO}_2 > 0.4$ for more than 24 h.
2. On ventilator support for reasons other than diagnosed ALI/ARDS for more than 3 d in the previous 21 d.
3. Tidal volume $< 4$ ml/kg.
4. Neuromuscular respiratory failure or cardiac disease ($\text{Ppc, we} > 18$ mmHg or clinical signs of left atrial hypertension) causing the compromise in gas exchange.
5. Lung parenchymal or airway surgery within 30 d of screening.
6. Status asthmaticus or severe asthma currently under treatment with acute doses of systemic corticosteroids, or severe chronic obstructive pulmonary disease requiring chronic oxygen therapy.
7. Systolic blood pressure $< 90$ mmHg, which cannot be adequately maintained with intravenous fluids and high-dose pressors.
8. Intubation primarily for chronic interstitial lung disease (e.g., sarcoidosis, idiopathic pulmonary fibrosis).
9. Any active leak from the lung into the pleural space.
10. Seizures refractory to anticonvulsant therapy.
11. High risk of mortality within 3 mo of screening for reasons other than ALI or ARDS or associated complications (e.g., terminal cancer with a high short-term risk of mortality).
12. Hypersensitivity to perfluorocarbons.
13. Pregnant females.
15. Significant renal dysfunction defined by (1) serum creatinine greater than $3.0$ mg/dl or (2) an increase in serum creatinine of $0.8$ mg/dl in 24 h.
16. Significant hepatic dysfunction defined by serum total bilirubin greater than $2.0$ mg/dl and albumin less than $2.5$ g/dl; or a prothrombin time $3$ s greater than control or $> 1.5$ times the upper limit of normal and an activated partial thromboplastin time $> 1.5$ times the upper limit of normal.
17. Significant haematologic dysfunction defined by platelet count $< 75,000$ mm$^3$; a total white blood cell count $< 1,000$ ul; or evidence of disseminated intravascular coagulation.
18. In patients 46-90, high risk of mortality as defined by an APACHE II score $\geq 30$.

Interventions
Randomized to receive: partial liquid ventilation (PLV), or conventional ventilation (CMV) for a maximum of four days for the first 45 patients and a maximum of five days for subsequent patients. Groups were allocated at a PLV to CMV ratio of 2:1.

Outcomes
The initial primary outcome was oxygenation, but this was changed during the study to mean no. of ventilator free days to day 28. Secondary outcomes included 28 day mortality, $\text{PaO}_2/\text{FiO}_2$ ratio, $\text{A-a}$ gradient, and lung mechanics.

The study showed that there was no difference in:
1. No. of ventilator free days ($p = 0.85$),
2. Mortality at day 28 ($p = 0.63$),
3. Any pulmonary related parameters.

Ventilator free days to day 28 is defined as “On Day 28, each survivor received 1 point for every day following discontinuation of mechanical ventilation, including the day of extubation, if the patient remained...
Characteristics of included studies (Continued)

successfully weaned for the remainder of the day. Patients who died during the first 28 days of the study received a VFD score of zero. Patients who were reintubated had days counted toward a VFD only if they remained off the ventilator for the remainder of the 28-day period. For instance, if a patient was extubated for two days and then reintubated for the remainder of the 28 days, the VFD was zero. Only those days for which the patient was extubated and remained extubated for the remainder of the 28-day experimental period counted toward VFD.”

The following outcomes which we considered clinically relevant were not reported:
Mortality (at discharge from ICU, at discharge from hospital, and at 1, 2, and 5 years)
Duration of mechanical ventilation
Duration of respiratory support
Duration of oxygen therapy
Duration of stay in the intensive care unit
Duration of stay in hospital
Infection (septicaemia, pneumonia)
Long term cognitive impairment
Long term health related quality of life
Long term lung function
Cost

Notes
A large number of post hoc analyses are also reported.
Post hoc analyses showed a more rapid discontinuation of ventilation in the PLV arm (p = 0.045) though patients who were randomized to PLV had a longer length of CMV prior to randomization (p = 0.12). Thus, a beta error may be present, as the lag time involved may explain the difference in rapidity of discontinuation. There was also a trend towards increase in VFD in those patients under 55 (p = 0.06).

18 centres were involved, though only 4 centres enrolled more than 5 patients of the total 90 patients.

It is not clear whether the data are analysed by ‘intention-to-treat.’

There are a number of concerns with this study: the large number of changes in admission criteria; the change in primary end points; the duration of the study period; the exclusion criteria, excluding patients with multiple organ failure seems to limit generalizability as most patients die with ARDS rather than because of it.

Allocation concealment A

A-a - alveolar-arterial,
ALI - acute lung injury,
APACHE - acute physiology and chronic health evaluation system,
ARDS - acute respiratory distress syndrome,
CMV - conventional mechanical ventilation
CXR - chest x-ray,
d - days
FiO2 - fraction of inspired oxygen
h - hours
ICU - intensive care unit
mo - months
PaO2 - arterial oxygen tension,
PFC - perfluorocarbon liquid,
PLV - partial liquid ventilation,
Ppc,we - pulmonary capillary wedge pressure
s - seconds,
VFD - ventilator free days.
Characteristics of included studies (Continued)

Characteristics of excluded studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Randomization</th>
<th>Control group</th>
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<tr>
<td>Hirschl 1995</td>
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<tr>
<td>Reickert 2001</td>
<td>Not randomized</td>
<td>No control group</td>
<td></td>
</tr>
<tr>
<td>Schuster 2001</td>
<td>This RCT involved the post hoc analysis of 16 patients from another trial (as yet, not published). It is unclear from the paper (and there was no further information available after contacting the study investigators) if there were other patients in the larger study. That is, were there other patients in the study that received either 10 or 20 ml/kg of perflubron but these 16 were the only ones reported because they were the only ones who had the appropriate x-rays?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RCT - randomized controlled trial

ADDITIONAL TABLES

Table 01. MEDLINE search

PLV search

1 exp RESPIRATORY DISTRESS SYNDROME, ADULT/
2 ALL.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
3 ARDS.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
4 acute lung injury.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
5 exp FLUOROCARBONS/
6 partial liquid ventilation.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
7 (1 or 2 or 3 or 4) and (5 or 6)

ANALYSES

Comparison 01. Partial liquid ventilation (PLV) versus conventional mechanical ventilation (CMV)

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 28 day mortality</td>
<td></td>
<td></td>
<td>Relative Risk (Random) 95% CI</td>
<td>Subtotals only</td>
</tr>
</tbody>
</table>

INDEX TERMS

Medical Subject Headings (MeSH)

Adult; Liquid Ventilation [*methods]; Morbidity; Randomized Controlled Trials; Respiratory Distress Syndrome, Adult [mortality; *therapy]
**COVER SHEET**

**Title**  
Partial liquid ventilation for preventing death and morbidity in adults with acute lung injury and acute respiratory distress syndrome

**Authors**  
Davies MW, Fraser JF

**Contribution of author(s)**  
MWD - conceived the question, wrote the protocol, searched for studies, assessed all potential studies for inclusion, extracted data, analysed the results and wrote the review.  
JFF - co-wrote protocol, searched for studies, assessed all potential studies for inclusion, extracted data, analysed the results and co-wrote the review.

**Issue protocol first published**  
2002/3

**Review first published**  
2004/4

**Date of most recent amendment**  
26 April 2005

**Date of most recent SUBSTANTIVE amendment**  
25 August 2004

**What's New**  
Information not supplied by author

**Date new studies sought but none found**  
Information not supplied by author

**Date new studies found but not yet included/excluded**  
Information not supplied by author

**Date new studies found and included/excluded**  
Information not supplied by author

**Date authors' conclusions section amended**  
Information not supplied by author

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### Analysis 01.01. Comparison 01 Partial liquid ventilation (PLV) versus conventional mechanical ventilation (CMV), Outcome 01 28 day mortality

Review: Partial liquid ventilation for preventing death and morbidity in adults with acute lung injury and acute respiratory distress syndrome

Comparison: 01 Partial liquid ventilation (PLV) versus conventional mechanical ventilation (CMV)

Outcome: 01 28 day mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>PLV n/N</th>
<th>CMV n/N</th>
<th>Relative Risk (Random)</th>
<th>Weight (%)</th>
<th>Relative Risk (Random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirsch 2002</td>
<td>27/65</td>
<td>9/25</td>
<td>1.15 [ 0.64, 2.10 ]</td>
<td>100.0</td>
<td>1.15 [ 0.64, 2.10 ]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>65</td>
<td>25</td>
<td>1.15 [ 0.64, 2.10 ]</td>
<td>100.0</td>
<td>1.15 [ 0.64, 2.10 ]</td>
</tr>
</tbody>
</table>

Total events: 27 (PLV), 9 (CMV)

Test for heterogeneity: not applicable

Test for overall effect z=0.47  p=0.6

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