

VV ECMO in ARDS: Is it v. v. good?

Nepean WTET summary 21/4/20

Rationale and Background

- ARDS clinically manifests as marked hypoxia and usually impaired lung compliance (subject of debate as to whether compliance should have been included in the Berlin definition)
- Severe hypoxic respiratory failure in ARDS can usually be managed using ventilatory (e.g. increasing mean airway pressure, recruitment maneuvers) and non-ventilatory (e.g. prone ventilation) strategies alone, allowing time for the underlying driver to be treated / resolve
- When severe hypoxaemia (and/or respiratory acidosis from hypoventilation and impaired gas exchange) threatens organ function and this cannot be managed within the safe limits of 'lung protective ventilation' (LPV) and standard adjunctive therapies, consideration regarding the trade-off between tolerating hypoxaemia/hypercapnoea versus risking further lung injury (ventilator induced lung injury -VILI) to achieve adequate O₂ delivery to organs would otherwise need to be made
- Venovenous extracorporeal membrane oxygenation (VV ECMO) allows gas exchange (oxygenation and CO₂ clearance) to varying degrees (up to >100% of native healthy lung function) to be taken outside of the body and therefore allowing the lungs to maximally 'rest' and not be subjected to the high amounts of 'stress' and 'strain' (main determinants of VILI). The ventilator is then set to very low minute ventilation to minimise lung work and maximise recovery potential (usually PCV 20/10 rate 10, purely to prevent alveolar collapse)
- Furthermore, the passage of well oxygenated, adequately de-carbonated, non-acidic blood into the pulmonary circulation via VV ECMO may reduce RV afterload which can be beneficial for myocardial function (ARDS increases RV afterload, as do many of our rescue strategies for management of severe hypoxia too)

Advantages and Disadvantages of VV ECMO

- Advantages
 - Able to minimise lung work and allow optimal lung recovery conditions
 - Reduce RV afterload, improve pulmonary hypertension and thereby improve RV/LV function
 - Can tightly titrate O₂ administration and CO₂ clearance to desired parameters
 - Once established does not necessarily require deep sedation/paralysis and associated complications (vasopressors, critical illness weakness)
 - Temperature control benefits of extracorporeal circuit for patients in hypermetabolic states
 - *(Potentially reverse diffusion -INTO alveoli- may assist in recruitment of collapsed alveoli shunting)*
- Disadvantages
 - Requires specialist center (+/- transfer) and services, trained staff
 - Expensive (equipment, staff training, adjunctive tests)
 - Invasive procedure, potential for vascular injury
 - Flows dependent on intravascular volume (trade off with 'dry' strategy) and venous return
 - Requires systemic anticoagulation and potential associated complications (bleeding, thromboses)
 - Increased volume of distribution – drug (antibiotic) dosing difficult without drug monitoring

Evidence

- Small, non-randomised studies (retrospective and prospective) seemed to suggest benefit of ECMO
- CESAR: Lancet 2009: UK (MC RCT)
 - Glenfield (Leicester) ECMO center with referral units (68 enrolled into study) → 2001-2006; n=180 randomised 1:1 consideration of ECMO vs conventional management in severe respiratory failure. Conventional group managed in tertiary ICU, ECMO arm at Glenfield
 - Included: 18-65y/o severe (potentially reversible) resp failure & Murray score ≥ 3 , OR uncompensated hypercapnoea with pH < 7.2 despite optimum conventional treatment
 - Excluded: P_{peak}(!) > 30 / high FiO₂ > 0.8 for > 7d, or intracranial haemorrhage / other contraindication for anticoagulation
 - Death or severe disability at 6m significantly higher in conventional arm (53% vs 37%) compared to ECMO arm → 'positive study' for ECMO

- Comments:
 - Only 75% in ecmo arm received ecmo (16/90 improved without ecmo, at Glenfield)
 - No protocol for conventional arm due to failure to agree/participate by referring sites
 - Arguably this study concludes that outcomes of severe respiratory failure are better if managed in an ecmo center (irrespective of whether you received ecmo or not)
- H1N1: not randomised, but shown to be effective and beneficial → question therefore remained
- EOLIA: NEJM 2018: French (MC RCT)
 - AECC definition ARDS ventilated <7d and despite optimisation of ventilation and use of usual adjunctive therapies (iNO, recruitment, prone, oscillation) had either; P/F <50 for >3h, P/F <80 for >6h, or pH<7.25 with PaCO₂>60 for >6h. Randomised to VV ecmo vs lung protective ventilation (NMBA and early proning strongly encouraged; but recruitment maneuvers, inspired nitric/prostacyclin as other adjuncts at clinician discretion). If SaO₂ <80% for >6h despite these can be considered for crossover to ecmo -if deemed appropriate by treating clinician)
 - 64 centers, n=249 (of target 331; stopped early for futility)
 - 60d mortality: 35% in ecmo group versus 46% control group = not statistically significant (according to usual, arbitrarily decided p values of <0.05)
 - Comments:
 - Underpowered: stopped early; power calculation based on 60% mortality with 20% ARR (NB mortality estimate too high based on previous studies etc)
 - High cross-over: 28% of control group crossed over into ecmo group; not ethical to do 'ecmo' vs 'non-ecmo' → perhaps therefore 'treatment failure' outcome (which includes cross-over and death and was significant) is more important than 'mortality'?
 - If you assume those who had 'rescue ecmo' in conventional arm would have all died, ecmo arm would have been very significant (in fact even if 33% of cross over group didn't receive ecmo but still survived –very unlikely– this would still have been statistically significant)
 - Other secondary outcomes show ecmo is safe (e.g. less stroke, all organ failures etc)
 - 57% of patients who received 'rescue ecmo' died (versus 35% in ecmo group) showing a very late strategy is probably not beneficial (increased organ failures)
- Post hoc Bayesian analysis of EOLIA: JAMA 2019
 - Bayesian analysis estimates the probability of the hypothesis, using the data (rather than estimating the probability of the data, given the hypothesis = frequentist approach). Arguably a more logical way to interpret clinical trials, as like in real life it uses previous/known information (priors) to help answer the question 'how likely is ecmo to be beneficial in patients with very severe ARDS?' and quantifies that based on skeptical versus enthusiastic interpretation of already available information
 - Suggests ecmo beneficial in very severe ARDS (even if skeptical attitude to previous studies)

Summary (my practice)

- Ecmo is not a therapy to treat ARDS, rather a supportive strategy to minimise further lung injury and maximise possible lung recovery where safe ventilation strategies and conventional therapies with a good evidence base (e.g. proning) cannot achieve adequate systemic oxygenation and safe levels of CO₂ clearance
- For those patients who cannot achieve adequate gas exchange by conventional means, ecmo is a safe therapy best utilised early, before other organ failures develop as a consequence
- I therefore consider referral to an ecmo center early in patients who are likely to benefit (i.e. single or two organ failures) failing conventional strategies and with no contraindications (e.g. to anticoagulation). Where I am uncertain of benefit discussions with ecmo specialists are still important for shared decision making
- My local ecmo referral center uses criteria similar to inclusion criteria for Eolia. However whilst refractory hypoxaemia is the main indication, the degree of hypercapnoea a patient can safely tolerate is individual and in practice the hypercapnoeic inclusion parameters are far more open to individualised patient assessment

Murray score

	0	1	2	3	4
P/F ratio (kPa)	≥40	30-39.9	23.3 – 29.9	13.3 – 23.2	<13.3
PEEP (cmH ₂ O)	≤5	6-8	9-11	11-14	≥15
Compliance (ml/cmH ₂ O)	≥80	60-79	40-59	20-39	≤19
CXR quadrants infiltrated	0	1	2	3	4