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Unproven and Expensive before Proven and Cheap – Extracorporeal Membrane Oxygenation vs. Prone Position in ARDS

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ABSTRACT We identified 810 reports that described ECMO in ARDS, and 61 fulfilled our inclusion criteria (Figure). 61 reports were included, and the authors of 26 (43%) responded to email requests for confirmation (or clarification). Based on the aggregate (published and emailed) information, 9 papers were excluded because key data were unclear; unambiguous data were available relating to 17 papers. These 17 papers represented 672 patients with ARDS who were cannulated with VV-ECMO; of these patients, 208 (31%) received a trial of prone positioning before ECMO, and 464 (69%) did not. The proportion of studies that clearly identified whether prone positioning was used prior to ECMO was similar before (30% of 20 papers) and after (34% of 32 papers) the publication in 2013 of a key RCT reporting a survival benefit associated with prone positioning (P>0.05) (3). However, the proportion of all VV-ECMO patients in whom prone positioning was used before ECMO was lower in the more recent studies (84/452, 19%) vs. those published before 2013 (124/220, 56%; P<0.05).

These data suggest a systematic bias in the literature reporting outcomes after ECMO. The vast majority of reported patients who receive ECMO did not first receive therapy that (in contrast to ECMO), is simple, cheap and of proven benefit; therefore, inferences about the efficacy of ECMO in ARDS are of limited use.

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INTRODUCTION Mortality for adults with ARDS is substantial and has changed little (40%) in the last 2 decades (1). Current management is focused on treating any underlying cause, supporting gas exchange, and minimizing ventilator-associated lung injury; there is no cure for ARDS *per se*. Prone positioning, as opposed to the usual supine position, was first proposed 40 years ago (2); and accumulating evidence suggests a substantial survival benefit of prone positioning in severe ARDS (3-7). The maneuver is simple, and although may have complications, including tube dislodgement or obstruction, pressure ulceration (3) or cardiac arrest (4), it requires no additional equipment, has no associated incremental cost, and it reduces mortality in severe disease.

Extracorporeal membrane oxygenation (ECMO) has been a rescue therapy for intractable hypoxemia in severe ARDS (also since the 1970s), and improvements in design and management have mirrored its increased utilization. ECMO entails high economic cost and resource utilization, may necessitate transport of critically ill patients to a specialized center (8), and is associated with potentially life-threatening complications (9); however, while the subject of many publications, ECMO *per se* has not been shown to improve outcome in ARDS. Thus, in severe ARDS, ECMO contrasts almost perfectly with prone positioning in terms of cost, complexity and risk of complications (all far greater with ECMO), as well as proof of benefit (strong for prone position, not for ECMO).

Because both ECMO and prone positioning are considered in patients who are severely hypoxemic due to severe ARDS, we wondered how physicians would ordinarily choose between two such alternatives. While it is often possible to track use of ECMO using procedure and billing codes, such data are not readily available for prone positioning. We therefore examined published reports of the use of ECMO in patients with ARDS, assuming that any patient who was placed on ECMO should first

have had a trial of prone positioning.

METHODS A PubMed database search was conducted using the following search MeSH terms: "Extracorporeal Membrane Oxygenation [MeSH] AND Respiratory Distress Syndrome, Adult [MeSH]", and restricted to articles written in English and published between January 1995 and March 2017. Each article was reviewed by two investigators (XL, BPK) in order to identify original reports of adults with ARDS treated with veno-venous ECMO (VV-ECMO). VV-ECMO was specified to ensure that respiratory (not cardiac) support was being offered. Disagreements were resolved by consensus. The following information was sought from the papers: number of patients with ARDS treated with VV-ECMO; and, patients with ARDS treated with VV-ECMO who were given a trial of prone positioning before ECMO. We sent a standardized email to corresponding authors of all included studies to request (or confirm) the information, asking: (a) how many patients with ARDS were cannulated for VV-ECMO; and, (b) how many of these patients were first given a trial of prone positioning. The Chi-square test was used to compare proportions. The definition of "Clear" was a clear statement describing the number of patients with confirmed ARDS who were cannulated for veno-venous ECMO; and, of these, the number who were first given a trial of prone positioning ("unclear" indicated that one -or both- of these numbers were not clearly described).

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RESULTS We identified 810 reports that described ECMO in ARDS, and 61 fulfilled our inclusion criteria (Figure). 749 reports were excluded from further consideration (*full details available from authors*).

61 reports were included (Supplement), and the authors of 26 (43%) responded to email requests for confirmation (or clarification). Following review of the manuscripts and all responses to email requests, 9 papers were excluded because key data were unclear. Thus, clear data were available relating to 17 papers representing 672 patients with ARDS who were cannulated with VV-ECMO; of these patients, 208 (31%) received a trial of prone positioning before ECMO, and 464 (69%) did not.

The proportion of studies that clearly identified whether prone positioning was used prior to ECMO was similar before (31% of 16 papers) and after (34% of 32 papers) the publication in 2013 of a key RCT reporting a survival benefit associated with prone positioning ($P>0.05$); 4 papers published in 2013, one of which presented clear information, were excluded from this analysis to avoid confusion about month of publication (4). However, the proportion of all VV-ECMO patients in whom prone positioning was used before ECMO was lower in the more recent studies (84/452, 19%) *vs.* those published before 2013 (116/210, 55%; $P<0.05$).

COMMENT These data indicate a systematic bias in the literature reporting outcomes after ECMO, and suggest a systematic bias in daily practice. The vast majority of reported patients who receive ECMO did not first receive therapy that (in contrast to ECMO), is simple, cheap and of proven benefit; therefore, inferences about the efficacy of ECMO in severe ARDS are of limited use.

We are unable to say why prone positioning was used so infrequently in these reports prior to initiation of ECMO, given that it has been shown to increase survival (4, 6, 7). While, Peek *et al* demonstrated a survival benefit associated with transfer to a specialist ECMO centre (10), there are no randomized controlled trials reporting a survival benefit from ECMO in ARDS. We do know that prone positioning is used infrequently; in fact, outside the context of ECMO, only 16% of patients who die after ARDS will have a trial of prone positioning (1). It is possible that the reasons for lack of use are the same, for example a lack of familiarity, inadequate training, concern about complications, or lack of belief in its impact. Nonetheless, the ability to manage prone positioning should easily exceed the ability to cannulate for -and manage- ECMO. It is also possible that clinicians assume that a more complicated treatment is superior. Alternatively, economics may be a factor; while there is extensive variability -and recent declines- in fees and charges associated with ECMO, recently published rates suggest that a busy ECMO program could profit institutions by millions of dollars per year (11). In contrast, prone position is not reimbursed as an additional procedure.

Second, we do not know why most studies were unclear in stating whether patients treated with ECMO were first given a trial of prone positioning. The prone position is not subtle, and most reports provide substantial details about other aspects of patient care (such as blood gas, respiratory mechanics, and use of vasopressors, nitric oxide and adjunctive ventilation). It is possible (though

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speculative) that because prone positioning was seldom used –and 'should' have been used more frequently– it was considered preferable to omit the data. However, peer reviewers could have raised this issue, and journal editors could have insisted on its inclusion.

The main limitation to the current data is that the sample may be biased because naturally only a small fraction of patients who undergo ECMO cannulation are reported in the scientific literature; indeed, of those reported, we can only be certain of the data in 21% of patients. However, we doubt that a greater use of prone positioning is clustered in unclear reports or among non-reported patients.

There are two major implications of the current data. *First*, patients may be exposed –perhaps routinely, in some systems– to a treatment that is complex, high-risk and expensive, and that has no proof of benefit, in preference to a treatment that is simple, low-risk and inexpensive, and for which there is substantial evidence of benefit. This imbalance might not optimally serve individual patients, payors, clinicians-in-training, or health systems. *Second*, clinical trials on the impact of ECMO for ARDS should either incorporate a test of prone positioning as an entry criterion for all patients, or include a direct comparison to prone positioning; if not, positive trials might be reported because simpler therapy was omitted, and this could potentially result in abandonment of a simple and effective therapy.

In summary, use of a therapy should be guided by weighing its potential benefit, as well as the risks and cost; the current data raise the concern that in the case of ECMO *vs*. prone positioning for patients with ARDS, this balance is not currently achieved.

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Figure: Flowchart illustrating the selection of manuscripts and the final results. ***Abbreviations***: ARDS Acute Respiratory Distress Syndrome; VV-ECMO Veno-Venous Extracorporeal Membrane Oxygenation;

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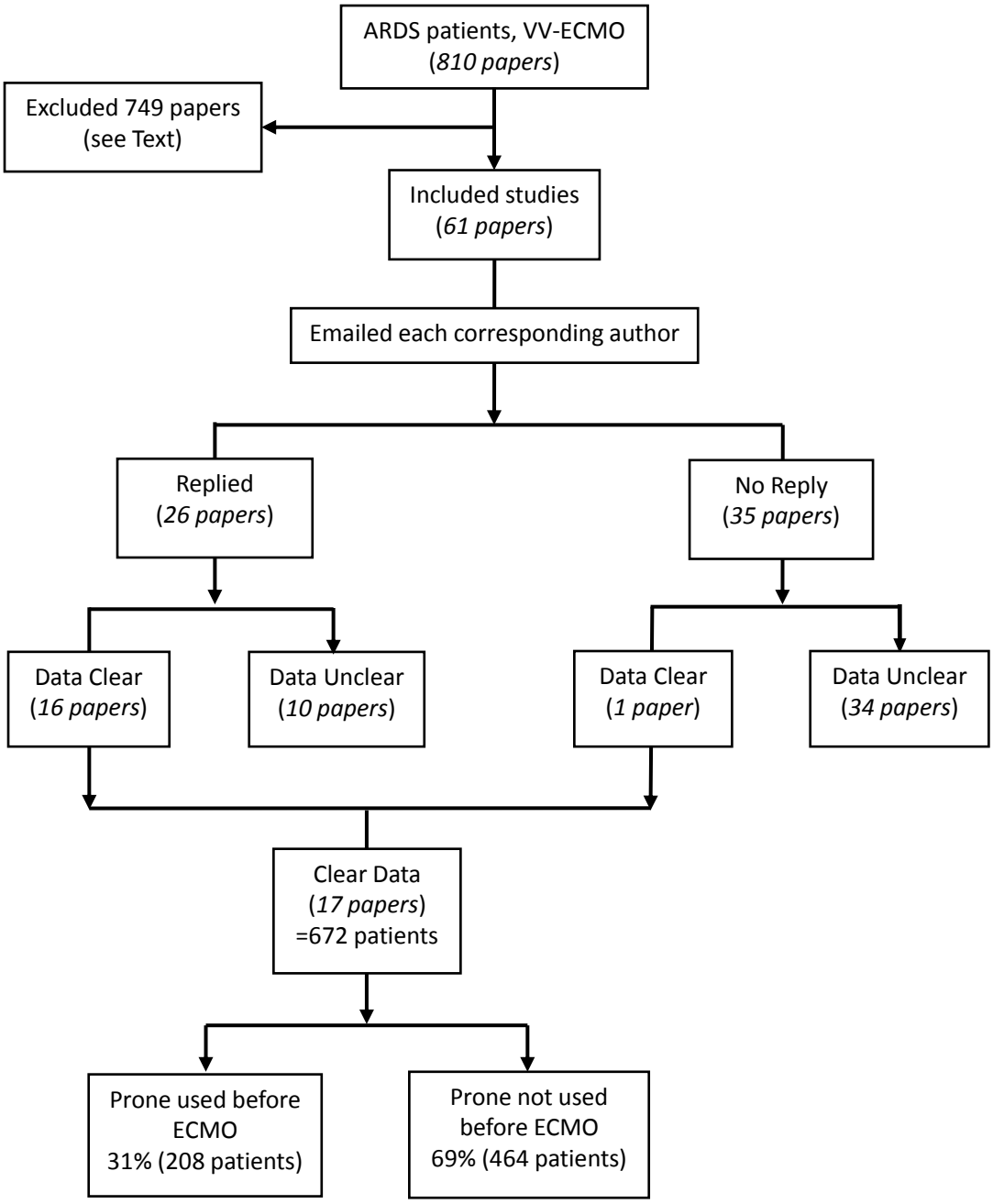

NAME	YEAR	JOURNAL	VOLUME	PAGE	DATA CLEAR
Kolla S et al	1997	Ann Surg	226(4)	544-64	Y
Lewandowski K et al	1997	Intensive Care Med	23(8)	819-35	N
Mols G et al	2000	Am J Surg	180(2)	144-54	N
Beiderlinden M et al	2006	Intensive Care Med	32(10)	1627-31	N
Hermans G et al	2007	Thorac Cardiovasc Surg	55(4)	223-8	N
Rega FR et al	2007	Artif Organs	31(5)	384-9	N
Lehle K et al	2008	ASAIO J	54(6)	612-7	N
Davies A et al	2009	JAMA	302(17)	1888-95	Y
Lindén VB et al	2009	Acta Anaesthesiol Scand	53(4)	489-95	N
Müller T et al	2009	Crit Care	13(6)	R205	N
Bonacchi M et al	2011	J Thorac Cardiovasc Surg	142(5)	1197-204	Y
Forrest P et al	2011	Intensive Care Med	37(5)	824-30	Y
Guinot PG et al	2011	Crit Care	15(5)	R216	Y
Isgrò S et al	2011	Int J Artif Organs	34(11)	1052-60	N
Javidfar J et al	2011	ASAIO J	57(5)	421-5	N
Noah MA et al	2011	JAMA	306(15)	1659-68	N
Stöhr F et al	2011	Interact Cardiovasc Thorac Surg	12(5)	676-80	N
Dirkmann D et al	2012	Eur J Anaesthesiol	29(12)	602-4	N
Haneya A et al	2012	Perfusion	27(2)	150-5	N
Hodgson CL et al	2012	Crit Care	16(5)	R202	N
Lazoura O et al	2012	J Crit Care	27(6)	602-8	N
Chimot L et al	2013	ASAIO J	59(2)	157-61	N
Pappalardo F et al	2013	Intensive Care Med	39(2)	275-81	N
Pham T et al	2013	Am J Respir Crit Care Med	187(3)	276-85	N
Schmidt M et al	2013	Intensive Care Med	39(10)	1704-13	N
Schmidt M et al	2013	Intensive Care Med	39(5)	838-46	Y
Bryner B et al	2014	Perfusion	29(1)	39-43	N
Enger T et al	2014	Crit Care	18(2)	R67	N
Hsiao CC et al	2014	Ann Thorac Surg	97(6)	1939-44	N
Kredel M et al	2014	ASAIO J	60(6)	694-700	N
Kutleša M et al	2014	Int J Artif Organs	37(10)	748-52	N
Lubnow M et al	2014	PLoS One	9(12)	e112316	N
Lubnow M et al	2014	J Crit Care	29(3)	473.e1-5	N
Robak O et al	2014	Int J Artif Organs	37(11)	839-46	N
Roch A et al	2014	Intensive Care Med	40(1)	74-83	Y
Roncon-Albuquerque R Jr et al	2014	Intensive Care Med	40(6)	910-1	Y
Töpfer L et al	2014	J Crit Care	29(3)	340-6	N
Wohlfarth P et al	2014	Crit Care	18(1)	R20	N
Wu MY et al	2014	Scand J Trauma Resusc Emerg Med	22	56	Y
Agerstrand CL et al	2015	Ann Thorac Surg	99(2)	590-5	Y
Chiu LC et al	2015	Ann Thorac Surg	99(1)	243-50	Y
Gothner M et al	2015	Scand J Trauma Resusc Emerg Med	23	30	N
Haneya A et al	2015	Crit Care Med	43(9)	1898-906	N
Klinzing S et al	2015	Crit Care	19	142	Y
Kon ZN et al	2015	Ann Thorac Surg	100(5)	1855-60	N
Kon ZN et al	2015	Ann Thorac Surg	100(6)	2059-63	N
Michaels AJ et al	2015	ASAIO J	61(3)	345-9	N
Reis Miranda D et al	2015	Am J Respir Crit Care Med	191(3)	346-8	Y
Tsai HC et al	2015	Ann Thorac Surg	100(2)	458-64	N
Voelker MT et al	2015	Artif Organs	39(4)	374-8	N
Bohman JK et al	2016	Heart Lung	45(3)	227-31	N
Huang L et al	2016	Chin Med J (Engl)	129(14)	1688-95	N
Lazzeri C et al	2016	Acta Anaesthesiol Scand	60(4)	485-91	Y
Lee S et al	2016	J Korean Med Sci	31(6)	932-8	Y
Liu X et al	2016	PLoS One	11(6)	e0158061	N
Malfertheiner MV et al	2016	Crit Care Med	44(4)	747-54	N
Nigoghossian CD et al	2016	Pharmacotherapy	36(6)	607-16	Y
Crotti S et al	2017	Anesthesiology	126(4)	678-687	N
Gutsche JT et al	2017	Anesth Analg	124(3)	846-848	N
Huang L et al	2017	Med Sci Monit	23	741-750	N
Lazzeri C et al	2017	J Artif Organs	20(1)	50-56	Y