Title: Quality of life and lung function in survivors of ECMO for acute respiratory distress syndrome

Supplemental Digital Content

Authors:

Giacomo Grasselli, Vittorio Scaravilli, Daniela Tubiolo, Riccarda Russo, Francesco Crimella, Francesca Bichi, Letizia Corinna Morlacchi, Eleonora Scotti, Lorenzo Patrini, Luciano Gattinoni, Antonio Pesenti, Davide Chiumello

Additional methods

General management of ARDS ECMO patients at Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico

The General ICU of Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico (Milano, Italy) is a 12 beds medical-surgical unit highly specialized in the treatment of acute respiratory failure with more than 30 years of experience in ECMO support and a case volume of roughly 20-30 ECMO cases per year. Our institution is part of the Italian ECMO network (see Patroniti et al., The Italian ECMO network experience during the 2009 influenza A(H1N1) pandemic: preparation for severe respiratory emergency outbreaks, Intensive Care Med, 2011, 37:1447-1457) a national network of 15 selected ICUs established in 2009 to cope with the 2009-2010 H1N1 pandemic.

Overall, patients are referred for early centralization with one of the following: 1) HbO_2 < 85%; 2) Oxygenation Index (OI, FiO_2 x mean airway pressure x 100/PaO_2) > 25; 3) PaO_2/FiO_2 < 100 mmHg with PEEP > 10 cmH_2O; 4) Hypercapnia and respiratory acidosis with pH < 7.25. The Italian ECMOnet criteria for institution of ECMO support are the following: 1) OI > 30; 2) PaO_2/FiO_2 < 70 mmHg with PEEP > 15 cmH_2O (in patients admitted to an ECMO center) or PaO_2/FiO_2 < 100 mmHg with PEEP > 10 cmH_2O (in patients still to be transferred); 3) pH < 7.25 for at least 2 hours. In general, ECMO support is started after failure of rescue therapies such as pulmonary recruitment maneuvers, inhaled nitric oxide and prone positioning. At our institution, absolute contraindication to ECMO are: 1) non-reversible cause of respiratory failure; 2) intracranial bleeding or major contraindication to anticoagulation; 3) active malignancy; 4) previous severe disability. Age and comorbidities do not constitute absolute contraindications to ECMO. A relative contraindication to ECMO is use of invasive mechanical ventilation for > 7 days prior to ECMO consideration.

Standard of care for ECMO patients at General ICU of Ospedale Maggiore Policlinico includes: orotracheal intubation and eventual late tracheostomy; nasotracheal feeding tube; urinary indwelling catheter; arterial, central venous and pulmonary artery catheterization. Notably, patients are always managed by peripheral percutaneous cannulation (when possible performed under direct fluoroscopic control) and connected to circuits featuring heparin-coated tubing, centrifugal pump, and polymethylpentene hollow fiber membrane oxygenators. Spring wire-reinforced cannulas for both drainage (21–23 Fr, HLS cannulae; MAQUET Cardiopulmonary AG) and reinfusion (21 Fr, Bio-Medicus Venous cannulae, Medtronic Inc.) are used. QUADROX PLS Oxygenator and ROTAFLOW Centrifugal Pump or HLS Set Advanced 5.0—Cardiohelp system (MAQUET Cardiopulmonary AG, Hirrlingen, Germany) are used. All circuit components, including oxygenators, centrifugal pumps and tubings, are BIOLINE coated. All procedures (cannulation, ECMO connection, circuit change) are performed with full antiseptic protocols and. Veno-venous femoro-femoral cannulation is the preferred approach. Prior to circuit connection, a IV bolus of unfractionated heparin (50-70 unit/kg) is administered. Anticoagulation is then maintained by means of continuous heparin infusion (starting at 18 UI/Kg/h) adjusted during the first 12 h to reach a target-activated clotting time (ACT, Hemocron Jr. ® Signature+) between 180 and 210 s. Subsequently, heparin infusion is titrated to a target activated partial thromboplastin time (aPTT) ratio value of 1.5–2.

Quantitative CT scan analysis

CT scan was performed from lung apices to bases, at full inspiration and a reconstruction gap of 5 mm was used. Each image was segmented by BF (with the supervision of SV), processed with a dedicated software (Maluna 3.15, Gottingen, Germany) and quantitative analysis performed as previously described (see Rouby JJ et al., Acute respiratory distress syndrome: lessons from computed tomography of

the whole lung. Crit Care Med 2003 Apr;31(4 Suppl):S285-95). Briefly, lung boundaries were drawn automatically on each image; total lung volume, total lung tissue mass and frequency distribution of lung CT numbers expressed in Hounsfield units (HUs) were computed and four different lung compartments were quantified: hyper- inflated tissue (-1000 to -900 HU), normally aerated tissue (-900 to -501 HU), poorly aerated tissue (-500 to -100 HU) and non-aerated tissue (-100 to +200 HU).

Additional results

e-Table 1. Patients' characteristics at ICU discharge, hospital discharge and 1 year follow-up.

			ECMO	Non-ECMO	Overall	p
ICU discharge	**Blood gas analysis**	pH	7.46 (7.44 -7.48)	7.46 (7.43 - 7.49)	7.46 (7.43 - 7.49)	0.844
		PaO_2 (mmHg)	88 (73 - 104)	80 (69 - 95)	83 (70 - 100)	0.264
		$PaCO_2$ (mmHg)	38 (32 - 46)	35 (33 - 42)	36 (32 - 42)	0.435
	PaO_2/FiO_2 (mmHg)		289 (228 - 383)	322 (278 - 386)	307 (236 - 385)	0.478
	FiO_2		0.30 (0.21 - 0.40)	0.21 (0.21 - 0.35)	0.29 (0.21 - 0.39)	0.188
	Need for oxygen support		9 (26%)	3 (6%)	12 (14%)	**0.023**

Data are presented as absolute frequency (% of the included patients) or as median and interquartile range. ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

e-figure 1. Representative CT scans
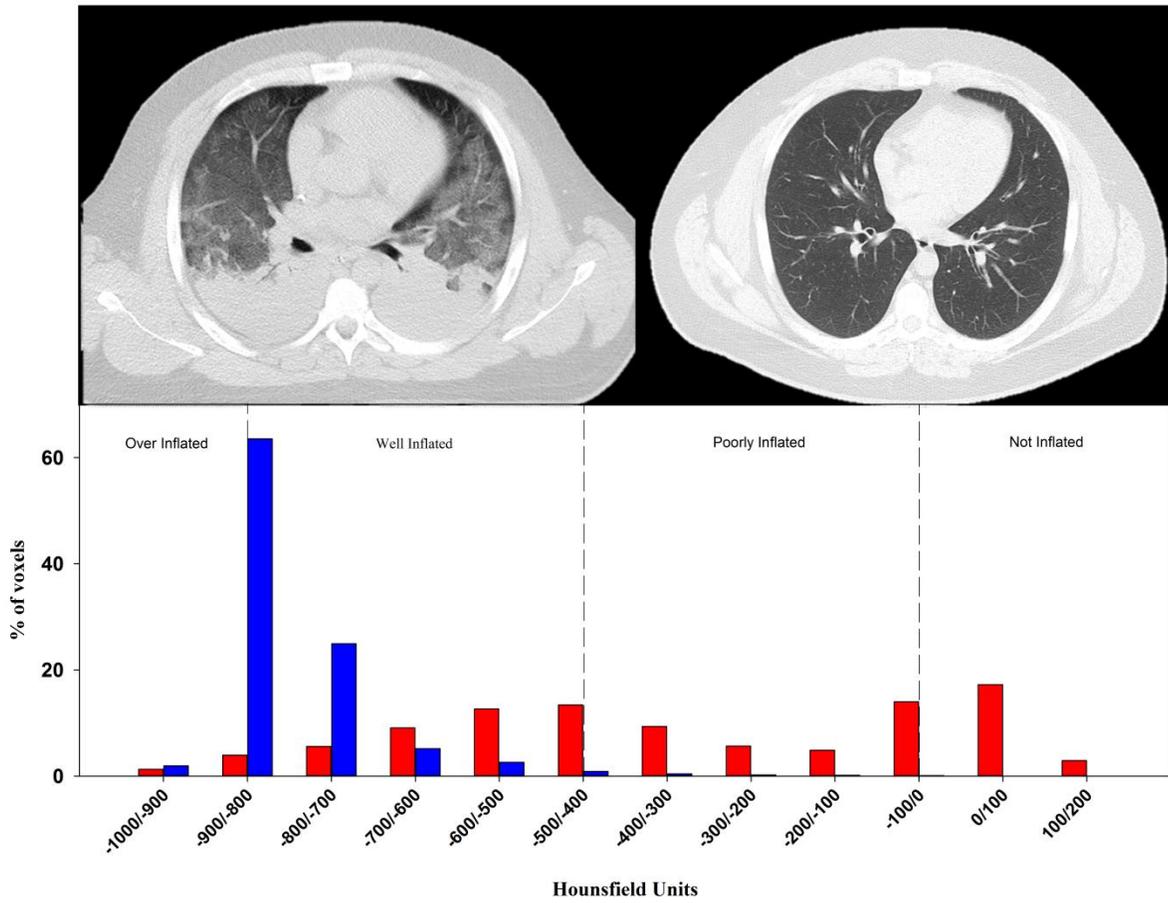
Upper frame: CT scan analysis of a patient at admission (upper left frame) and at 1-year follow up (upper right frame). In the lower frame, frequency distribution of CT numbers (Hounsfield Units) of the same patient at ICU admission (red columns) and at 1-year follow up (blue columns).

e-Table 2. Risk factors associated to death

		Alive	Dead	p	Odd Ratio
Year	**2013**	20 (40%)	13 (43%)	0.177	---
	2014	11 (22%)	11 (37%)		---
	2015	19 (38%)	6 (20%)		---
Gender (male)		32 (64%)	21 (70%)	0.581	1.312 (0.503 - 3.570)
Age (years)		50 (40 - 59)	62 (51 - 72)	**0.001**	**1.050 (1.017 - 1.090)**
Weight at admission (Kg)		73.3 (64 - 80)	70 (55 - 74)	**0.048**	**0.960 (0.920 - 0.999)**
Transferred from peripheral hospital		30 (60%)	14 (47%)	0.247	1.714 (0.689 - 4.327)
Transferred on ECMO support*		14 (28%)	6 (20%)	0.616	0.686 (0.154 - 3.062)
Infection at admission		38 (86%)	22 (85%)	0.840	0.868 (0.223 - 3.709)
H1N1 positive		9 (23%)	2 (10%)	0.177	2.850 (0.646 - 20.033)
Immunocompromise		8 (16%)	13 (43%)	**0.008**	**4.015 (1.438 - 11.866)**
ECMO		22 (44%)	11 (37%)	0.518	0.737 (0.285 - 1.851)
Tracheostomy		31 (62%)	12 (40%)	0.055	0.409 (0.158 - 1.021)
Prone position		29 (58%)	11 (37%)	0.063	0.419 (0.161 - 1.049)
RRT		15 (30%)	17 (57%)	**0.018**	**3.051 (1.204 - 8.000)**
PaO$_2$ (mmHg) <100 at admission		25 (50%)	20 (67%)	0.143	2.000 (0.793 - 5.262)
SAPS II		37 (29 - 47)	50 (42 - 56)	**0.001**	**1.065 (1.027 - 1.111)**
SOFA score		7 (5 - 11)	10 (7 - 14)	**0.001**	**1.202 (1.070 - 1.371)**
Blood gas analysis at admission	pH	7.34 (7.26 - 7.40)	7.31 (7.23 - 7.38)	0.269	0.066 (0.001 - 8.142)
	PaCO$_2$ (mmHg)	43 (36 - 60)	44 (38 - 53)	0.787	0.995 (0.962 - 1.028)
	PaO$_2$ (mmHg)	74 (61 - 92)	74 (58 - 87)	0.508	0.994 (0.978 - 1.001)
Compliance (mL/cmH$_2$O)		29 (22 - 37)	27 (22 - 34)	0.716	0.990 (0.942 - 1.040)
Driving Force (cmH$_2$O)		15 (11 - 18)	14 (11 - 18)	0.788	0.986 (0.912 - 1.127)
PEEP (cmH$_2$O)		12 (10 - 15)	12 (10 - 15)	0.688	1.022 (0.915 - 1.146)
Intrapulmonary shunt (%)		34 (25 - 43)	34 (24 - 47)	0.635	1.007 (0.976 - 1.040)
Mean arterial pulmonary pressure (mmHg)		31 (28 - 38)	35 (28 - 40)	0.677	1.018 (0.933 - 1.108)

ICU length of stay (days)	19 (9 - 32.25)	14 (5 - 27)	0.140	0.978 (1.007 - 1.022)
Hospital length of stay (days)	32 (14 - 52)	23 (11 - 38)	0.734	0.979 (0.956 - 1.001)
Duration of ECMO* (days)	9 (6 - 13)	8 (3 - 11)	0.680	0.959 (0.846 - 1.043)
IMV (days)	18 (5 - 28)	11 (4 - 27)	0.333	0.986 (0.955 - 1.014)
IMV prior to ECMO support* (days)	1 (0 - 2)	1 (0 - 4)	0.147	1.230 (0.930 - 1.762)

Data are presented as absolute frequency (% of the included patients) or as median and interquartile range. Odds Ratio of continuous variables are odds ratio per unit increase in variable. ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; RRT, renal replacement therapy, SAPS II, simplified acute physiology score; SOFA, sequential organ-failure assessment; PEEP, positive end expiratory pressure; ICU, intensive care unit; IMV, invasive mechanical ventilation. *) variables depicted only for ECMO patients. [a]) multivariate logistic analysis. Statistically significant result are highlighted in bold.

e-Table 3. Clinical outcomes and use of adjunctive therapy of survivors undergoing 1-year follow-up.

	ECMO (n=18)	Non-ECMO (n = 19)	Overall (n = 37)	p
Length of ICU stay (days)	29 (16 - 36)	13 (5 - 29)	19 (10 - 32)	**0.025**
Length of Hospital stay (days)	33 (19 - 52)	35 (13 - 51)	33 (15 - 51)	0.779
Duration of ECMO (days)	10 (6 -13)	---	---	---
IMV prior to ECMO (days)	1 (0 - 2)	---	---	---
IMV (days)	22 (11 - 34)	8 (2 - 29)	19 (5 - 29)	**0.094**
Tracheostomy	12 (66%)	9 (47%)	21 (56%)	0.192
Prone Position	14 (77%)	9 (47%)	23 (62%)	**0.041**
RRT	5 (28%)	6 (32%)	11 (29%)	1.000

Data are presented as absolute frequency (% of the included patients) or as median and interquartile range.

ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IMV, invasive mechanical ventilation;

RRT, renal replacement therapy. Statistically significant results are highlighted in bold.