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Authors: Alejandro Cruz-Utrilla, Elena Puerto García Martín, Laura Domínguez Pérez, Anibal Ruiz Curiel, Andrés Quezada, Alejandro Durante López, Lourdes Vicent, Roberto Martín Asenjo, Williams Hinojosa, Andrea Eixerés, Laura Forcén Acebal, María Galindo, Fernando Arribas Ynsaurriaga, Pilar Escribano-Subias, Héctor Bueno

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Alejandro Cruz-Utrilla[1, 2], Elena Puerto García Martín[2, 3], Laura Domínguez Pérez[2, 3], Anibal Ruiz Curiel[2, 4], Andrés Quezada[2, 5], Alejandro Durante López[2, 3], Lourdes Vicent[2, 3], Roberto Martín Asenjo[2, 3], Williams Hinojosa[1, 2], Andrea Eixerés[2, 6], Laura Forcén Acebal[2, 7], María Galindo[2, 8], Fernando Arribas Ynsaurriaga[2, 4, 9, 10], Pilar Escribano-Subias[1, 2, 9, 10], Héctor Bueno[2, 4, 9, 10]

[1]Pulmonary Hypertension Unit, Department of Cardiology, Hospital Universitario 12 de Octubre, Madrid, Spain

[2]European Reference Network of Rare Respiratory Disease (ERN-Lung), Brussels, Belgium

[3]Intensive Cardiac Care Unit, Department of Cardiology, Hospital Universitario 12 de Octubre, Madrid, Spain

[4]Department of Cardiology, Hospital Universitario 12 de Octubre, Madrid, Spain

[5]Department of Pneumology, Hospital Universitario 12 de Octubre, Madrid, Spain

[6]Department of Cardiac Surgery, Hospital Universitario 12 de Octubre, Madrid, Spain

[7]Department of Obstetrics and Gynecology, Hospital Universitario 12 de Octubre, Madrid

[8]Department of Reumatology, Hospital Universitario 12 de Octubre, Madrid, Spain

[9]Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Instituto de Salud Carlos III (ISCIII), Madrid, Spain

[10]Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain

Correspondence to:

Pilar Escribano-Subias, MD,

Pulmonary Hypertension Unit, Department of Cardiology,

Hospital Universitario 12 de Octubre,

Avenida de Córdoba S/N. 28041, Madrid, C.Madrid, Spain,

phone: +34 629 019 500.

e-mail: pilar.escribano.subias@gmail.com

INTRODUCTION

Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are severe diseases in which pulmonary vasculopathy may cause the failure of the right ventricle and ventilatory lung function [1]. The use of pulmonary endarterectomy (PEA) or balloon pulmonary angioplasty in CTEPH [2, 3] and pulmonary vasodilators in both entities has led to an important increase in life expectancy [4]. Cardiogenic shock (CS) is a catastrophic complication in these patients, either as the initial presentation or developed after a triggering event in previously stable cases [5]. During recent years, the use of extracorporeal membrane oxygenation (ECMO) in patients with refractory CS or massive pulmonary embolism (PE) has expanded. This may be an option in critically ill patients with PAH or CTEPH. However, evidence in this setting is scarce [6]. A multidisciplinary approach to determine the specific strategy in each case is crucial [7]. We present the first results of a newly created ECMO program in CS as a bridge to therapy (BTTh) for PAH/CTEPH in our critical cardiovascular care unit (CCCU).

METHODS

Consecutive patients with PAH or CTEPH needing ECMO from January 2021 until June 2022 in the Hospital Universitario 12 de Octubre (Madrid, Spain), were included. Clinical management was decided individually upon daily consensus, including PAH and CCCU specialists, in coordination with other specialists of the multidisciplinary pulmonary

hypertension (PH) unit. This unit is one of the two Spanish reference centres for PH, with the possibility of lung transplantation and complete interventional management for PAH and CTEPH. All patients signed an informed consent before their inclusion in the Spanish Registry of Pulmonary Hypertension (REHAP).

RESULTS AND DISCUSSION

ECMO was implanted in four patients in that period as a BTTh, with a veno-arterial (VA) configuration in two cases, and veno-venous (VV) in the remaining two. Weaning of the mechanical support was possible in three patients, and hospital discharge was possible in two cases (Table 1). Only one patient is still alive after two years of follow-up:

Case 1. A 46-year-old woman with previously known PAH associated with systemic sclerosis on triple vasodilator therapy and severe immunosuppressive therapy presented a rapid respiratory deterioration, attributed to an immune-related pneumonitis. Considering the severity of respiratory insufficiency, the patient needed mechanical support with VV-ECMO. Treatment with corticosteroids caused rapid clinical amelioration, allowing ECMO weaning and patient discharge. Eleven months later, the patient died due to severe COVID-19 bilateral pneumonia.

C**ase 2.** A 32-year-old woman without known PAH, was admitted to the hospital in CS. She was found to have a 12-week pregnancy at that moment. A VA-ECMO was implanted as a bridge to pregnancy termination, which was then successfully carried out. Nevertheless, she developed severe thrombocytopenia and an alveolar hemorrhage, which caused a progressive decline in lung function, changing then the configuration of the ECMO to VAV. After initiation of immunosuppressive drugs and up-titration of pulmonary vasodilators, and a dramatic haemodynamic improvement, the patient could be weaned from ECMO. She was finally discharged on triple vasodilator therapy.

Case 3. A 56-year-old male with severe distal CTEPH presented severe bilateral interstitial oedema after the initiation of intravenous epoprostenol, which finally needed VV-ECMO implantation. Due to further hemodynamic impairment, a switch to VA-ECMO was done. After stabilization, BPA was used as a rescue therapy. Despite an initial improvement after three BPA procedures, he presented severe repetitive episodes of hemoptysis, which required tracheal intubation and mechanical ventilation. The patient died due to ventilator-associated

pneumonia after 34 days of mechanical support, being still supported by ECMO at that moment.

Case 4. A 59-year-old woman presented with CS and severe respiratory insufficiency. The initial evaluation revealed a probable subacute episode of PE on top of a previously unknown central CTEPH. Treatment with percutaneous mechanical thrombectomy was decided. During the procedure, the patient further deteriorated hemodynamically, and a VA-ECMO was emergently implanted in the cath laboratory. The patient remained stable for one week when an elective PEA was done, with excellent results. The ECMO was withdrawn two days after surgery. Thirteen days later, being clinically stable at that moment, the patient died suddenly due to a new episode of massive PE.

ECMO as a BTTh may be a useful option in critically ill patients with PAH or CTEPH. Our results are in line with those published by Rosenzweig et al [8]. In this last study, survival of 31.6% was communicated with ECMO as a bridge to recovery (BTR), and more than 75% of patients survived to ECMO decannulation. The selection of candidates for mechanical support is of critical importance [9]. Likely, the reduction of right ventricular pressure overload and the increase in systemic blood pressure are key features involved in the hemodynamic improvement after ECMO cannulation. Additionally, the reduction in the hypoxic pulmonary vasoconstrictive response, and of the right-to-left shunting might also be beneficial effects of ECMO implantation. Our experience suggests that cases with acute decompensation triggered by factors like immune disorders or pregnancy could be good candidates for ECMO as a BTTh. We present a case of VA-ECMO as a bridge to pregnancy termination, representing one of the first reports in the literature [10]. CTEPH is a more challenging scenario for ECMO support, as ventilatory impairment and coagulation disturbances are usually more advanced. Nevertheless, ECMO during the postoperative period of PEA as a BTR has usually good results [2]. The use of ECMO as a bridge to lung transplantation in Spain demonstrates good results [11]. A complementary and interesting option for end-stage patients, or those waiting for lung transplantation, could be the creation of an interatrial septostomy [12].

ECMO management in pulmonary hypertension requires specific considerations. The initial configuration should be based on the severity of hemodynamic impairment and respiratory insufficiency, trying to minimize the need for tracheal intubation and mechanical ventilation, considering the high risk of clinical deterioration during sedation if right ventricular dysfunction. In candidates for lung transplantation, tracheal intubation should also be avoided,

as this is a relative contraindication for transplantation. We opted for VA-ECMO when a more profound shock was established (SCAI index D-level in both cases) and for initial VV-ECMO when respiratory impairment was the predominant problem (SCAI index C). The dose of inotropic or vasopressor therapy was similar in both groups, with comparable vasoactive-inotropic scores. CCCU specialists should also be aware of the possibility of upper-body hypoxaemia since the perfusion of coronary arteries and the brain in VA-ECMO is frequently provided by deoxygenated blood, especially when lung gas exchange is impaired. In cases of baseline impaired lung function, or expectation of worsening after cannulation, an initial axillar configuration or switching to VAV-ECMO could provide adequate oxygenation for the upper body. After the initiation and up-titration of pulmonary vasodilators, with haemodynamic improvement, the arterial cannula can often be removed. In these cases, if respiratory amelioration continues, ECMO weaning is feasible. Thrombocytopaenia is another relevant aspect. In our series, three patients started with moderate or severe reduction of the platelet count, all of them with bleeding episodes. None of our patients had ischemic or embolic events. Therefore, our protocol considers the maintenance of high ECMO flows and low coagulation times, especially in patients at risk of bleeding events.

In conclusion, we report the initial experience of a multidisciplinary PH unit with ECMO support as a BTTh in patients with PAH or CTEPH. The positive results, with ECMO weaning possible in three out of four critically ill cases, emphasize the need to maintain a coordinated approach involving different specialists in this complex scenario.

Article information

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Table 1. PAH and CTEPH cases undergoing ECMO in the 2020–2021 period

	Case 1	Case 2	Case 3	Case 4
Previous condition				
Age, years	46	32	56	59
Sex	Female	Female	Male	Female
Weight, kg	55	95	89	85
BMI, kg/m^2	22.6	34.9	29.7	31.2
PH group	PAH associated with CTD	PAH associated with overlap mixed CTD and primary biliary cirrhosis	CTEPH	CTEPH
Time to diagnosis of PH	7 years	3 weeks	12 months	2 months
Predominant clinic on admission	Respiratory insufficiency	Cardiogenic shock	Respiratory insufficiency	Cardiogenic shock
Previous treatment	Bosentan, tadalafil and selexipag	Ursobilane, levothyroxine and omeprazole	Tadalafil and ambrisentan	Insulin, enoxaparin
HR, bpm	100	110	115	100
Situation prior ECMO cannulation				
BP, mm Hg	110/66	110/65	95/55	127/89
pH	-	7.52	7.49	7.31
Pre-ECMO lactic acid, mmol/l	1.8	1.5	0.7	10

$PaCO_2$, mm Hg	-	20	41	29
PaO_2, mm Hg)	-	108	46	68
Creatinine, mg/dl	1.21	0.55	1.36	1.99
Hemoglobin, g/dl	11	12.8	11.3	10.3
Platelet count,/cc	91000	32000	81000	161000
NT-proBNP, pg/ml	2992	4495	8295	-
Baseline oxygen saturation, %	60	98	86	91
TTE parameters				
RV diameter, mm	37	61	63	54
Diastolic EI	1.2	1.9	1.2	1.6
Estimated RVSP, mm Hg	109	117	70	86
TAPSE, mm	14	14	19	13
S', cm/s	15	8	14	8
FAC, %	27	10	20	22.5
TR, 0–4	1	4	2-3	4
RA area, cm^2	19	23	39	22
LVIV, cc/m^2	43	-	67	-
LV diameter, mm	35	27	37	41
LVEF, %	72	60	72	60
LV diastolic function, 1–4	2	2	2	2

IVC, dilated	Yes	Yes	Yes	Yes
IVC, collapse >50%	No	No	No	No
Pericardial effusion, 0–4	2-3	1	1	0
RV hemodynamics				
mPAP, mm Hg	71	70	45	52
RAP, mm Hg	6	14	19	28
RVSP, mm Hg	94	120	85	96
PCWP, mm Hg	9	14	16	—[a]
Cardiac output, l/min	4	—	2.6	—
Cardiac index, l/min/m^2	2.5	—	1.5	—
PVR (WU)	15.5	—	11	—
Associated conditions	Neumonitis of unknown origin	12-weeks pregnancy, severe thrombocytopenia, and alveolar haemorrhage	Interstitial oedema after initiation of intravenous epoprostenol	Subacute PE on a previously unknown chronic CTEPH
ECMO				
Time from ICCU admission to ECMO implantation, days	6	5	1	1
Initial configuration	VV	VA	VV	VA

Configuration change	No	VAV, and VV	VAV (peripheral and central)	No
Distal perfusion cannula during VA or VAV ECMO	No	No	Yes	Yes
Initial blood flow, lpm	3.3	3.2	3.3	3.4
Initial sweep gas flow rate (lpm) and FiO_2 ECMO (%). HFNC (lpm/FiO_2) or LFNC (lpm)	7 and 1. HFNC 40/0.9.	0.3 and 0.6. HFNC 30/100.	3 and 1. HFNC 50/40.	2 and 0.8. LFNC a 0.5.
Duration of ECMO support, days	12	21	34	13
Peak lactic acid, mmol/l, during ECMO	2.9	6.4	0.7	10
Haemoglobin, g/dl, nadir	8.9	9.3	8.7	7.8
Platelet count,/cc, nadir	34000	16000	41000	52000
Serious bleeding event	Yes	Yes	Yes	No
Requires transfusion	Yes	Yes	Yes	Yes
Membrane thrombosis	No	No	Yes	No
Cerebral, lower limb or another embolic event	No	No	No	No

Clinically significant lower limb ischemia	-	No	No	No
Peak creatinine, mg/dl, during ECMO	1.92	0.76	2.06	2.2
Requires CRRT	No	No	Yes	No
Definite infection requiring antibiotic	Yes	No	Yes	Yes
Type of infection	Pneumonia	—	Pneumonia	Urinary tract infection and bacteremia
Antibiotic without confirmed infection	—	Yes	—	—
Treatment while being on ECMO				
Pulmonary vasodilators PDE5 inhibitor Endothelin receptor antagonist Inhaled vasodilator Intravenous or subcutaneous prostacyclins	 Tadalafil — — Epoprostenol 8 ng/kg/min	 Sildenafil Macitentan — Epoprostenol 20 ng/kg/min	 Tadalafil Macitentan — Epoprostenol 8 ng/kg/min	 — — — —
Inotropic support	Dobutamine	Dobutamine	Dobutamine	Dobutamine

Vasopressors	No	Norepinephrine	Norepinephrine and vasopressin	No
Systemic vasodilator	No	No	No	Nitroprusside
Maximum ventilatory support	HFNC	HFNC	IMV (maximum PEEP of 18 cm H_2O)	LFNC
Duration of mechanical ventilation, days	—	—	—	—
Duration of HFNC, days	24	25	12	—
Tracheostomy during hospitalization	No	No	Yes	No
Additional treatments	Corticosteroids	Pregnancy termination, corticosteroids, cyclophosphamide, rituximab and immunoglobulin G	Balloon pulmonary angioplasty	Pulmonary endarterectomy
Outcome	Discharged alive	Discharged alive	Died while on ECMO	Weaned from ECMO. Death on the postoperative period of PEA
ICCU length of stay, days	25	30	32	14
Hospital length of stay, days	67	46	38	27

[a]PCWP not achieved due to PE

Abbreviations: BMI, body mass index; BP, blood pressure; CCU, coronary care unit; CTD, connective tissue disease; CRRT, continuous renal replacement therapy; CTEPH, chronic thromboembolic pulmonary hypertension; ECMO, extracorporeal membrane oxygenation; EI, eccentricity index; FAC, fractional area change of right ventricle; FiO_2, fraction of inspired oxygen; HFNC, high-flow nasal cannula; HR, heart rate; IMV, invasive mechanical ventilation; IVC, inferior vena cava; LFNC, low flow nasal cannula; LV diastolic function (1-4), 1 normal, 2 impaired relaxation, 3 pseudo-normal pattern, 4 restrictive pattern; LVEF, left ventricular ejection fraction; LVIV, left ventricular index volume; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; PaCO2, partial pressure of carbon dioxide in arterial blood; PaO2, partial pressure of oxygen in arterial blood; PCWP, pulmonary capillary wedge pressure; PDE5 inhibitor, phosphodiesterase type 5 inhibitor; PE, pulmonary embolism; PEEP, positive end-expiratory pressure; PEA, pulmonary endarterectomy; Pericardial effusion (0-4), 0 absent, 1 light, 2 moderate, 3 serious, 4 pericardial tamponade; PH, pulmonary hypertension; PVR (WU), pulmonary vascular resistance (Wood units); RA, right atrium; RAP, right atrial pressure; RV, right ventricle; RVSP, right ventricle systolic pressure; TTE, transthoracic echocardiogram parameters; TR (0–4), tricuspid regurgitation (0 absent, 1 light, 2–3 moderate, 4 serious); VA, Veno-Arterial; VAV, Veno-Arterio-Venous; VV, Veno-Venous