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Extracorporeal Membrane Oxygenation: A Case for Salvage Treatment in Influenza Induced Acute Respiratory Distress Syndrome Complicated by Heart Failure

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Abstract

The influenza virus accounts for thousands of hospitalizations and deaths annually. Advanced cases can be complicated by acute respiratory distress syndrome and even heart failure. After exhausting traditional ventilatory strategies, salvage techniques such as Extracorporeal Membrane Oxygenation (ECMO) have been successfully employed. At the University of Louisville and Kentucky One Jewish Hospital, we have developed ECMO protocols in the Cardiovascular Intensive Care Unit in an effort to salvage patients with advanced ARDS resulting from influenza. Herein, we review the literature and describe a case of a 36 year-old female who presented with influenza and required emergency initiation of ECMO. The case highlights the ECMO protocol and demonstrates a successful salvage strategy in a critically ill patient with heart failure from advanced influenza infection.

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Introduction

The outbreak of H1N1 influenza A (swine flu) reached pandemic status in April 2009 with estimates of up to 89,000,000 cases, leading to up to 403,000 hospitalizations in the United States alone [1]. Globally, this resulted in over 200,000 respiratory deaths and an additional 83,300 H1N1 associated cardiovascular deaths between April 2009 and April 2010 [1,2]. Viral infection lead to life threatening respiratory illness, often affecting pregnant women, obese patients and patients with multiple comorbidities [3-6]. Notably, Dawood and colleagues estimate 80% of deaths were in people younger than 65 years old, differing from typical seasonal influenza in which the majority of deaths occur in the older population [2]. In 2010, the World Health Organization declared the pandemic had ended but many lessions regarding patient management had been learned. Influenza, commonly referred to as "the flu", has multiple common strains resulting in viral illness accounting for 9.7 per 100,000 inpatient hospitalizations annually [1]. Influenza is often thought of as a rather benign and self-limiting viral illness. In addition to potentially progressing to Acute Respiratory Distress Syndrome (ARDS) and severe Acute Lung Injury (ALI), Influenza is also implicated in the development of acute myocardial dysfunction [6]. Myocarditis is a rare complication of infection with influenza. Although the pathogenesis of this process is not delineated, it is thought viral myocardial involvement leads to production of pro-inflammatory cytokines resulting in endothelial cell dysfunction [7]. Cellular dysfunction initiates a low-flow state leading to hypoxia-induced right heart failure and ensuing biventricular heart failure. Cardiogenic shock results in multi-system organ failure and death in up to 30% of patients who progress to fulminant cardiac failure [8]. Veno-Venous Extracorporeal Membrane Oxygenation (V-V ECMO) has emerged as a technique for management of ARDS [9,10]; and Veno-Arterial ECMO (V-A ECMO) has proven an effective treatment for combined respiratory and cardiac failure resulting from influenza A [11]. This case report describes the use of V-A ECMO transitioned to V-V ECMO for treatment of ARDS and transient heart failure in an adult woman with influenza infection.

Case Presentation

A 36 year-old female presented to an outside hospital with complaints of shortness of breath. She rapidly developed respiratory insufficiency requiring intubation and was transferred to the intensive care unit for further treatment where she was diagnosed with influenza A. Over the ensuing 48 hr the

Table 1: Hemodynamic and Respiratory Parameters. Parameters are given in percent and range. Abbreviations; MAP, mean arterial pressure; ECMO, extracorporeal membrane oxygenation; FIO2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; PaO2/FiO2, ratio of partial pressure of arterial oxygen and fraction of inspired oxygen; PC, pressure controlled ventilation; VC, volume controlled ventilation; PS, pressure support ventilation; V-A ECMO, veno-arterial extracorporeal membrane oxygenation; V-V ECMO, veno-venous extracorporeal membrane oxygenation.

	Pre-ECMO	ECMO Day 1: V-A ECMO Cannulation	ECMO Day 1	ECMO Day 3	ECMO Day 4: Conversion to V-V ECMO	ECMO Day 5	ECMO Day 7: Inhaled Epoprostenol Initiated	ECMO Day 8	ECMO Day 10	ECMO Day 11: ECMO Explantation	Day 1 Post ECMO Explantation	Day 2 Post ECMO Explantation: Inhaled Epoprostenol discontinued	Day 3 Post ECMO Explantation	Day 3 Post ECMO Explantation: Extubation
Hemodynamic Parameters														
Heart Rate	80		53-71	81-105		97-119		105-121	93-115		84-119		78-113	
MAP (mmHg)	73		52-89	61-83		62-90		70-82	72-93		67-91		65-86	
Norepinephrine (µg/kg/min)	1.0		0.02-0.05	0.01-0.02		0-0.05		0.01-0.04	0		0		0	
ECMO Parameters														
Flow (L/min)	X		3.4-4	3.5-3.7		3.6-3.8		4-4.3	4-4.4		X		X	
Sweep (L/min)			2-3	2.5-3		3.5-5		6	6					
ECMO FIO2			100%	100%		100%		100%	80-100%					
Cannulation			V-A	V-A		V-V		V-V	V-V					
Pulmonary Parameters														
Ventilator Modality	PC		PC/VC	VC		VC		VC	VC		VC		VC/PS	
Highest Ventilator FIO2	100%		100%	70%		60%		60%	40%		40%		40%	
Highest PEEP (cmH2O)	20		20	18		16		16	15		12.5		6	
Highest PIP (cmH2O)	42		39	39		44		40	39		32		17	
Tidal Volume (mL)	-		450	500		300		300	300		400		450	
Respiratory Rate / minute	38		14-18	20-22		10-25		17-25	12-25		15-26		16-35	
Pulmonary Compliance (mL/cmH2O)	-		24	24		11		13	13		21		41	
PaO2 / FIO2 (mmHg)	54		162	137		108		178	265		235		210	
Radial Artery Blood Gas														
pH	7.36		7.565	7.514		7.367		7.397	7.478		7.383		7.46	
pCO2 (mmHg)	51		28.3	31.4		47.2		41.3	35.7		49.7		41.7	
pO2 (mmHg)	54		162	96		64.6		107	106		94		83.9	
FIO2	100%		100%	70%		60%		60%	40%		40%		40%	

patient's clinical picture worsened. The outside hospital pulmonology and critical care teams exhausted traditional ventilatory strategies and employed prone positioning in an effort to overcome severe hypoxia. Due to hypotension, she was started on Levophed and an echocardiogram confirmed right heart failure. A consult was called for emergency salvage ECMO. A team from Kentucky One Jewish Hospital received emergency privileges and placed percutaneous arterial and venous cannulas and initiated V-A ECMO. The patient was stabilized and transferred to Kentucky One Jewish Hospital Cardiovascular Intensive Care Unit (CVICU) for further treatment. Upon arrival to the CVICU the patient was paralyzed, a low volume ventilatory strategy was initiated, and cardiovascular support with Levophed was continued. The patient's hospital course is summarized in Table 1 and 2. In summary, with the implementation of full support with V-A ECMO, her oxygenation was optimized as her heart failure resolved. After 72 hr of V-A ECMO the patient was hemodynamically stable and transitioned to V-V ECMO to support her ongoing respiratory failure. Inhaled epoprostenol was added on ECMO day 7 and she abruptly responded. She was subsequently decannulated on ECMO day 11 and extubated three days later. Her total length of stay was 20 days including 18 days in the ICU/CVICU. She was recently seen, nearly a year after the hospitalization, and is in good health and doing well.

Discussion

The mortality rate for ARDS remains high at 30% to 40% [12]. ARDS patients are initially supported with mechanical ventilation using a lung-protective ventilation strategy of low tidal volume (4 mL/kg to 6 mL/kg) and plateau pressures less than 30 cm of water [13]. When traditional therapies fail, alternative and salvage techniques have emerged to mitigate the high mortality rate. Veno-venous ECMO has developed as an adjunct to mechanical ventilation in the treatment of refractory hypoxia [12]. Two cannulae are inserted into central veins, and blood is withdrawn from one cannula and passed through an oxygenator. The oxygenated blood is warmed and then returned to the patient via the second cannula. ECMO allows oxygen delivery to end-organs when *in vivo* gas exchange is insufficient. This in turn permits lung-protective ventilation, allowing pulmonary recovery [12]. Transient development of myocarditis or cardiomyopathy related to influenza infection can occur, although the incidence is not well known [14]. Patients may complain of pleuritic chest pain and shortness of breath in addition to typical influenza symptoms, alternatively patients may be asymptomatic [15]. Although non-specific, patients with influenza-related cardiac involvement may have ECG changes, depressed function on echocardiography, or elevated cardiac markers such as troponin I and CK-MB [16]. In a retrospective study from Brown et al. [17] reviewing patients admitted to the ICU with H1N1, right ventricular impairment was present in 23% and left ventricular impairment in 17%. Martin et al. [18] retrospectively reported a 5% rate of left ventricular dysfunction in patients admitted to a single-center for influenza A. Historically,

Table 2: Management, Fluid Balance, and Laboratory Values. X indicates parameter was given. Abbreviations; midaz, midazolam; DEX, dexmedetomidine.

	Pre-ECMO	ECMO Day 1: V-A ECMO Cannulation	ECMO Day 1	ECMO Day 3	ECMO Day 4: Conversion to V-V ECMO	ECMO Day 5	ECMO Day 7: Inhaled Epoprostenol Initiated	ECMO Day 8	ECMO Day 10	ECMO Day 11: ECMO Explantation	Day 1 Post ECMO Explantation	Day 2 Post ECMO Explantation: Inhaled Epoprostenol Discontinued	Day 3 Post ECMO Explantation	Day 3 Post ECMO Explantation: Extubation
Inhaled Epoprostenol Use								X	X		X			
Chemical Paralysis	X		X	X		X								
Sedation	propofol fentanyl DEX		midaz fentanyl	midaz fentanyl		midaz fentanyl		fentanyl	fentanyl		DEX		DEX	
Cumulative Fluid Balance (mL)	+824		+55	+3231		+162		+1527	-73		-820		-3290	
Laboratory Values														
WBC Count (1000/mL)	2.8		3.9-4.4	5.5-5.8		5.2-7.1		8.2-9.1	9.5-11.2		11.4-12.1		9.6	
Lowest Hemoglobin (g/dL)	14.4		10.7	9		7.7		8.1	7.5		8		7.6	
Lowest Platelet Count (1000/mL)	134		109	65		56		57	58		104		288	
Highest AST (U/L)	115		281	212		136		48	45		42		30	
Highest ALT (U/L)	24		39	42		58		26	23		28		22	
Highest bilirubin (mg/dL)	-		0.8	0.8		1.3		0.8	0.6		1.1		0.7	

heart failure and cardiogenic shock treatment has been limited to supportive care, resulting in mortality rates from 20% to 100% of patients who develop fulminant heart failure [7]. Recently, data has emerged regarding the use of V-A ECMO as therapy for severe heart dysfunction associated with influenza A [6]. Bonacchi et al. [19] describe a case of successful rescue of a patient from an atypical presentation of respiratory and cardiac associated complications from H1N1. Antonitsis et al. [11] report two patients undergoing treatment for H1N1-induced myocarditis with veno-arterial ECMO with 1 of 2 patients surviving. Despite isolated cases of successful treatment, the use of ECMO is still considered a salvage technique; further demonstrated by a retrospective case series from Stohr et al. [20] of 9 patients undergoing V-A ECMO for ARDS with all causes mortality of 75%. In the largest prospective study examining ECMO outcomes, Peek et al. [21] demonstrate a survival benefit for the use of ECMO in ARDS. As part of this multi-institutional study, 90 patients were assigned to receive ECMO treatment and 90 patients were assigned conventional treatment. Sixty-eight patients assigned to the ECMO arm were actually treated with ECMO at a specialized center. Although this study was limited by a non-standardization of conventional treatment and low enrollment, this study demonstrates the benefit to early consideration for ECMO and early transfer to a tertiary care center that regularly performs ECMO. It has been our practice to initiate lung-protective ventilation strategies as a first line treatment with a low threshold for instituting V-V ECMO. This strategy not only preserves end-organ oxygenation, but also potentially prevents right heart failure. In situations such as the case described, all conventional strategies had failed and the patient progressed to cardiogenic shock by the time ECMO was considered. Early recognition of a deteriorating clinical picture and immediate escalation to V-V ECMO has proven a more effective strategy. The use of lung-protective ventilation strategies has largely been implicated in the reduction in mortality of patients with ARDS; however, improvements in ECMO technology have led to increased usage and likely improved mortality [22,23]. Veno-venous ECMO has primarily been used for treatment of conventional ventilation-refractory ARDS, but use of V-A ECMO is increasing in support of the now well-recognized cardiac dysfunction associated with influenza [18-20,22]. Overall, despite limited evidence, V-A ECMO holds promise for treatment of multi-organ dysfunction resulting from influenza. Further research must be done to clearly delineate the role of both V-V ECMO and V-A ECMO. Despite this uncertainty, it does appear that early transfer to a specialized ECMO center and early consideration of ECMO positively influences patient outcomes [24,25]. It is imperative to identify patients early in the hospital course who are at high risk of development of respiratory and cardiac failure and transfer these patients to an ECMO capable center. Our case report demonstrates the feasibility of the successful use of V-A ECMO for influenza-associated respiratory and cardiac failure.

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