Outcome of patients with infective endocarditis who were treated with extracorporeal membrane oxygenation and continuous renal replacement therapy

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Abstract

Infective endocarditis is a potentially life threatening condition. It is associated with high mortality and morbidity resulting mostly due to cardiorespiratory failure. Extracorporeal membrane oxygenation is a modality of treatment used to support hypoxic respiratory failure especially in patients who are already on mechanical ventilation. Continuous renal replacement therapy is added mainly for maintaining fluid and electrolyte balance. Here we report a case series of patients diagnosed with infective endocarditis who were treated with combined extracorporeal membrane oxygenation and continuous renal replacement therapy. Three patients in the age group 20-60 years were admitted with clinical features suggestive of infective endocarditis. During the course of hospital stay they developed cardiorespiratory failure requiring mechanical ventilation and extracorporeal membrane oxygenation support for refractory hypoxia. It was complicated by heart failure, renal failure and fluid overload which required initiation of continuous renal replacement therapy. All the three patients succumbed in spite of the aggressive treatment. In addition to the role played by each complication, delayed start of continuous renal replacement therapy might have also contributed to the high mortality. Early initiation of continuous renal replacement therapy for management of fluid overload needs to be considered in the management of these critically ill patients.

Introduction

Infective endocarditis is a potentially life-threatening condition associated with high morbidity and mortality.[1] Infective endocarditis patients can develop multifactorial cardiorespiratory failure and extracorporeal membrane oxygenation (ECMO) is used to improve gas exchange in patients with refractory hypoxia resistant to conventional mechanical ventilator support. Continuous renal replacement therapy (CRRT) is sometimes added to ECMO therapy mainly for correction of fluid and electrolyte imbalance in the setting of acute kidney injury. Although the survival of patients of ECMO has been improving over the years, addition of CRRT portends a worse prognosis.[2] The mortality of patients needing combined ECMO and CRRT was found to be around 83% as per the data from a single center retrospective study.[3] Whether the severity of underlying illness or the late initiation of CRRT is responsible for this high morality is still debated. Here we discuss the clinical course and outcome of 3 patients with infective endocarditis who were treated with combined ECMO and CRRT.

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Key words: acute renal failure, fluid overload, continuous renal replacement therapy, extracorporeal membrane oxygenation, infective endocarditis.

Conflicts of interest: the authors declare no potential conflicts of interest.

Rceived for publication: 7 June 2014.
Revision received: 21 September 2014.
Accepted for publication: 30 September 2014.

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Licensee PAGEPress, Italy
Clinics and Practice 2014; 4:670
doi:10.4081/cp.2014.670

Case Reports

Case #1

A 24-year old Caucasian male presented with history of respiratory distress and fever of 1-week duration. Past medical history was significant for history of intravenous drug abuse. Physical examination was remarkable for temperature of 38.8°C, heart rate of 120/min, blood pressure of 85 mmHg systolic, jugular venous distension and bilateral crackles as well as end expiratory wheezes on auscultation of chest. Blood culture showed growth of methicillin sensitive coagulase positive *Staphylococcus aureus* for which treatment with intravenous nafcillin sodium (1 gram every four hours) was started. Chest radiography showed bilateral pulmonary edema and pleural effusion. Trans-esophageal echocardiogram (TEE) showed a 2.1 cm vegetation on the tricuspid valve, ejection fraction of 30-39% and right ventricular pressure of 50 mmHg. He was placed on mechanical ventilation and subsequently on veno-arterial ECMO (day 3 of hospital admission) for refractory hypoxia. ECMO in our institution is performed using a centrifugal pump (Centrimag, Levitronix LLC, Waltham, MA, USA) and Quadrox oxygenator. The method of bypass, *viz*, veno-venous or veno-arterial was at the discretion of an intensive care physician trained in ECMO. He also received parenteral fluids throughout this period in the form of vasopressors, inotropes, blood products transfusion (5 units of packed red blood cells, 3 units of fresh frozen plasma) and medications to maintain sedation. Although intravenous diuretic (dose ranged 40-200 mg/day intravenous) was tried initially there was only marginal response. He subsequently became oligo-anuric and CRRT was started at that point for fluid overload and electrolyte imbalance. Hemodynamic status continued to deteriorate which resulted in escalation of inotropic and vasopressor requirement. In view of high surgical risk and refractory shock, it was decided not to proceed with any aggressive treatment including surgery. He eventually died. Pertinent laboratory tests and clinical features at admission and at the time of initiation of CRRT are represented in Tables 1 and 2.

Case #2

A 52-year old Caucasian female presented with history of fever and myalgia of 3 days duration. Past medical history was significant for aortic stenosis for which mechanical prosthetic aortic valve was placed. Physical examination was remarkable only for fever of 38°C. Pertinent laboratory tests and clinical characteristics at admission represented in Table 1. Blood culture showed growth of methicillin resistant coagulase positive *S. aureus* for which treatment with intravenous vancomycin (dose adjusted based on renal function and with use of CRRT to achieve trough of 15-20 µg/mL) was started. Chest radiography was normal. TEE showed 0.8 cm vegetation on the aortic valve complicated by abscess, ejection fraction (EF) of 55-60% and right ventricular pressure of 30 mmHg. She underwent aortic valve replacement. Post operatively she developed biventricular failure and required placement of biventricular assist device. She also had disseminated intravascular coagulation and hypotension which required massive amounts of blood product transfusion (12 units of packed red blood cells, 8 units of fresh frozen plasma) along with vasopressors and

inotropes. Repeat chest radiogram showed bilateral pulmonary edema and pleural effusion. Veno-arterial ECMO (VA ECMO) was initiated (day 8 of hospital admission) for refractory hypoxia on mechanical ventilation along with CRRT to manage the fluid overload. In view of poor prognosis and requirement for multiple pressors to maintain hemodynamic instability it was decided not to pursue any further aggressive management. She subsequently died. Pertinent laboratory tests and clinical features at admission and at time of initiation of CRRT are represented in Tables 1 and 2.

Case #3

A 36-year old African American female presented with history of fever and altered mental status of 4 days duration. Her past medical history was significant for Graves disease, use of intrauterine device for contraception and bronchial asthma. Physical examination was remarkable for heart rate of 110/min, blood pressure of 70 mmHg systolic, diastolic murmur at aortic area on precordial examination and bilateral crackles at lung bases. Pertinent laboratory tests and baseline creatinine represented in Table 1. Blood culture showed growth of *Lactobacillus acidophilus* for which treatment with intravenous penicillin (12 million units continuous 24 h infusion) and gentamicin (dose adjusted for renal function) were started. Chest radiography showed bilateral pulmonary edema. A TEE showed vegetation involving non-coronary cusp of aortic valve, EF>60%, moderate aortic regurgitation and pulmonary arterial pressure of 55 mmHg. He required mechanical ventilation and subsequent placement on VA ECMO (day 2 of hospital admission) because of refractory hypoxia. Vasopressors and inotropes were initiated for hemodynamic instability in addition to, blood products transfusion (2 units of packed red blood cells) and intravenous medications to maintain sedation. Although there was some response to diuretics (intravenous furosemide 20-120 mg daily) initially, urine output eventually dropped while on diuretics and CRRT was started mainly with the intention of maintaining fluid balance. In view of high surgical risk and refractory shock it was decided not to proceed with any aggressive treatment including surgery. She eventually died. Pertinent laboratory tests and clinical features at admission and at time of initiation of CRRT are represented in Tables 1 and 2.

Discussion

This case series represents the outcome of 3 patients with infective endocarditis complicated by heart failure, acute kidney injury, fluid overload, lactic acidosis (in 2 patients) and refractory shock requiring multiple pressors. The mortality was 100% in this case series. Although mortality in case 1 could be attributed to high simplified acute physiology score II score at admission, that is not the case in other two patients. Hence it is important to discuss the contribution of each complication to the mortality and measures to improve survival in these patients. In this context it is also important to note that the CRRT was initiated either along with ECMO or 1-2 days after initiation of ECMO in all the three patients.

Causes of heart failure and cardiogenic shock in patients with infective endocarditis include valvular dysfunction from destruction of valve or rupture of papillary muscle as well as chordae, myocardial dysfunction from ischemia due to embolism or occlusion from vegetation of coronary arteries, myocarditis, heart block and ventricular psuedoaneurysm.[1,4] Development of heart failure and cardiogenic shock are independent predictors of mortality.[1] ECMO is an effective means of providing cardio-respiratory support for these patients. The potential benefits of ECMO are mainly related to improving perfusion and oxygenation.[2,5] Early provision of ECMO support may prevent the myocardial damage that can be caused by inotropic agents or hypoxia and promote hasty recovery of myocardial function.[5,6] This has been shown to have survival benefit in these patients.[6] But the use of ECMO by itself can precipitate cardiac dysfunction. Mechanisms responsible for heart failure due to ECMO include retrograde non-pulsatile blood flow especially in the background of underlying left ventricular dysfunction, elevation in left ventricular after load, coronary hypoxia due to higher oxyhemoglobin saturation in the lower extremities compared to upper extremities especially with use of femoral arterial line in a veno-arterial ECMO system and myocardial stunning.[5,7,8]

Causes of renal failure, another major association of infective endocarditis and contributor to mortality include post infectious glomerulonephritis, membranoproliferative glomerulonephritis (GN), crescentic GN, acute interstitial nephritis, renal infarction, cortical necrosis, immunoglobulin A nephropathy (post infectious), vasculitic glomerulonephritis and acute tubular injury due to ischemia.[9] They can also develop renal failure post cardiac surgery due to decompensated heart failure, post-operative hypotension, septicemia, use of vasoactive medications, acute tubular injury, use of

Table 1. Clinical characteristics at the time of admission.

Characteristics	Case #1	Case #2	Case #3
Age (years)	24	52	36
Weight (kg)	115	88	86
Temperature (°C)	38.8	38	37
Heart rate	120	88	110
Systolic blood pressure (mmHg)	85	120	70
MAP (mmHg)	55	85	48
PO_2 (mmHg)	46	-	65
PCO_2 (mmHg)	32	-	32
Lactate (mmol/L)	5	-	1.3
WBC (10^9/L)	16.1	18	13.6
Platelets (10^9/L)	112	164	144
Albumin (g/L)	23	40	35
BUN (mmol/L)	22.84	7.49	15.70
Creatinine (µmol/L)	185.64	79.56	97.24
Bilirubin (µmol/L)	39.33	13.68	6.84
pH	7.44	-	7.43
GCS	13	15	15
Urine output (cc/kg/h)	0.8	0.9	1.16-1.74
Sodium (mmol/L)	139	140	137
Potassium (mmol/L)	5.3	4.1	3.8
Bicarbonate (mmol/L)	18	23	22
Hematocrit	31	41	38
Ionized calcium (mmol/L)	1.01	1.15	1.1
SAPS II score	32	13	17

MAP, mean arterial pressure; PO_2, partial pressure of oxygen; PCO_2, partial pressure of carbondioxide; WBC, white cell count; BUN, blood urea nitrogen; GCS, Glasgow coma scale; SAPS, simplified acute physiology score.

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nephrotoxic agents and pigment induced nephropathy due to hemolysis (prosthetic heart valves and devices). ECMO initiation by itself can lead to acute kidney injury; the mechanisms include ischemia/reperfusion injury from rapid hemodynamic fluctuation in renal blood flow secondary to adjustments in vasopressors/inotropes, pigment nephropathy due to hemoglobinuria resulting from hemolysis secondary to exposure of blood to artificial surfaces, non-pulsatile retrograde renal perfusion, activation of complement system and accumulation and cytokines.[4,7] Development of acute kidney injury (AKI) in critically ill and post cardiac surgery patients is associated with high mortality.[10]

Many critically ill patients receive massive amounts of fluids for resuscitation especially in the background of heart failure and acute kidney injury leading to fluid overload and pulmonary edema. Fluid overload is independently associated with worse tissue oxygenation, longer length of Intensive Care Unit (ICU) stay, mechanical ventilation and mortality in critically ill patients receiving continuous renal replacement therapy.[11,12] The same holds true for patients who are on ECMO as well.[12,13] Excessive fluid resuscitation has been found to be associated with prolonged ECMO duration, mechanical ventilation, longer length of stay in the ICU and mortality in patients treated supported with ECMO.[13] In unstable patients with multiple organ failure and fluid overload, even though ECMO alone can improve hemodynamic stability by increasing cardiac output via an ECMO pump (in venoarterial ECMO) and improved myocardial oxygenation, presence of fluid overload can nullify these advantages. Hence maintenance of fluid balance is very essential in treatment of critically ill patients even if they are supported with ECMO and CRRT which might also explain the cause of high mortality in our patients.

There is no established consensus for the optimal timing of initiation of CRRT in critically ill patients including those on ECMO support. Efforts to keep a negative fluid balance may not be effective once patients become fluid overloaded and hemodynamically unstable requiring multiple vasopressors. This was true in all the three cases where inspite of initiating CRRT patients maintained a positive fluid balance throughout. Hence early initiation of CRRT before the onset of fluid overload should be key

Table 2. Clinical characteristics at the time of initiation of continuous renal replacement therapy.

Characteristics	Case #1	Case #2	Case #3
Weight (kg)	125	122	101
Temperature (°C)	35.5	36.6	37.2
Heart rate	112	103	96
Systolic blood pressure (mmHg)	90	95	84
MAP (mmHg)	65	90	58
PO_2 (mmHg)	90	80	110
PCO_2 (mmHg)	30	34	44
Lactate (mmol/L)	14.2	13.5	1
WBC (10^9/L)	24.3	10.9	19.5
Platelets (10^9/L)	57	141	147
Albumin (g/dL)	1.2	3.4	1.4
BUN (mmol/L)	47.83	1.21	2.1
Creatinine (µmol/L)	300.56	150.28	123.76
Bilirubin (µmol/L)	68.4	18.81	10.26
pH	7.19	7.21	7.42
GCS	13	15	15
Urine output (cc/kg/h)	0.04-0.08	0.16-0.24	0.04-0.09
Sodium (mmol/L)	134	145	135
Potassium (mmol/L)	5.7	5	4.5
Bicarbonate (mmol/L)	13	14	29
Hematocrit	27	33	35
Ionized calcium (mmol/L)	0.99	0.98	1.04
SAPS II score	62	47	34
Fluid balance (in mL)*	20,000	25,000	12,000
Fluid balance (in mL)°	24,000	22,500	11,000
Days on ECMO before CRRT	1	0	2
Indication for initiation of CRRT	Fluid overload/acidosis/hyperkalemia	Fluid overload/acidosis	Fluid overload
Modality of CRRT	CVVHDF	CVVHDF	CVVH
No of pressors and inotropes at initiation of CRRT	4 (norepinephrine 30 mcg/min, vasopressin 0.06 units/min, phenylephrine 150 mcg/min, dopamine 10 mcg/kg/min)	3 (dopamine 10 mcg/kg/min, norepinephrine 30 mcg/min, epinephrine 15 mcg/min)	2 (dopamine 10 mcg/kg/min, (dopamine 10 mcg/kg/min, norepinephrine 12 mcg/min)

MAP, mean arterial pressure; PO_2, partial pressure of oxygen; PCO_2, partial pressure of carbondioxide; WBC, white cell count; BUN, blood urea nitrogen; GCS, Glasgow coma scale; SAPS, simplified acute physiology score; ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; CVVHDF, continuous veno-venous hemodiafiltration; CVVH, continuous veno-venous hemofiltration.
*Fluid balance is defined as difference between the total fluid input and total fluid output (since admission to hospital) at time of initiation of CRRT; °fluid balance at the time of termination of CRRT.

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to improve outcomes of these patients.[13,14] Improvement in fluid overload or improving fluid balance has been found to be associated with improved lung function, faster recovery of left ventricular function, better diastolic compliance, better contractility and less myocardial edema and time to weaning off ECMO and ventilator support.[12-14] It is also been shown that odds ratio for death was higher when CRRT was started later and longer it was performed.[13,14] In addition to above mentioned advantages, initiation of RRT also allows for the administration of adequate nutrition, medications, and blood products, while avoiding further fluid accumulation.[7] At the same time it can correct azotemia as well as acid-base, electrolyte imbalance and decrease levels of inflammatory cytokines and systemic inflammatory response syndrome induced by ECMO.[13,14] The latter might be beneficial in terms of decreasing ECMO induced renal injury.

Patients with cardiac failure, acute kidney injury and fluid overload requiring cardiac surgery may benefit from receiving CRRT intraoperatively or very early in the postoperative period. In liver transplant surgery, intraoperative use of CRRT maintained suitable electrolyte and acid-base balance.[15,16] Its beneficial effects included significant reduction of lactic acidosis intraoperatively, prevention of major fluid shifts, maintenance of cardiovascular and metabolic stability and promoted effective recovery of kidney function during the postoperative period.[15] Although there is a biological rationale for the use of intraoperative CRRT for patients with concomitant preoperative AKI, there is a paucity of available data, which are generally restricted to a few case reports or small series.

High lactate at the time of initiation of ECMO was another feature observed in 2 of the patients. Higher arterial lactate values are a surrogate marker of tissue hypoperfusion. High lactate also predicts postoperative mortality after cardiac surgery.[17] Adding ECMO itself might result in normalization of lactic acidosis especially with correction of hypoxia.[18] Observational studies using CRRT with bicarbonate-based solutions showed efficient management of severe lactic acidosis avoiding fluid overload and hypocalcemia in hemodynamically unstable patients.[19] Hence combined ECMO with CRRT might result in rapid reversal of the metabolic sequelae of lactic acidosis. Now whether this will convert in terms of better outcome is not known. But at the same time, early support before lactate levels become precarious, could improve outcomes in these patients.

Conclusions

In conclusion we are trying to highlight the potential role of fluid overload in determining morbidity as well as mortality and impact of early initiation of CRRT in improving the outcomes of critically ill patients in the context of infective endocarditis complicated by heart failure, and acute kidney injury. Through the complications by itself might be playing a major role in determining the mortality in these patients, the role of fluid overload should not be dismissed completely. With CRRT being an effective treatment to handle the fluid overload, initiation of CRRT early in advance even before fluid overload manifests might have a positive impact on the survival of these patients. Randomized controlled studies comparing early vs. late initiation of CRRT before and after the occurrence of fluid overload in patients on ECMO would be needed to further address this issue.

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