

A Prospective Analysis of Creatinine Clearance During ECMO and Ultrafiltration

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Abstract

Ultrafiltration (UF) during neonatal ECMO was shown not to impair renal function in our retrospective review of 17 patients from 1986-1988. Creatinine production (UV) was assumed to be 10 mg/kg/day for creatinine clearance (CrCl) calculations. To validate this assumption and to better understand renal function during ECMO, CrCl was measured prospectively on 27 non-surgical neonates. Seven patients required hemofiltration for fluid management. Typical UF rates were 3-10 ml/kg/hour. Two patients were excluded from analysis secondary to pre-existing renal disease. Renal CrCl was defined as UV/P where U=urine creatinine (mg/dl/24h), V=urine volume (ml/24h) and P=plasma creatinine (mg/dl). In 20 control patients who did not receive UF, UV or creatinine excretion was 11.6 ± 0.4 mg/kg/24h (mean+SEM). No significant change over time was seen in mean CrCl of the control group. The UF group, however, demonstrated a steady decrease in mean CrCl. CrCl on the fourth day before the start of UF was significantly higher ($P=0.05$) than day three of UF. In conclusion: 1) the assumption of UV used in the retrospective study was supported; 2) CrCl decreases during UF; 3) the consistency of CrCl in the control population suggests no alteration in glomerular filtration during ECMO runs of 3-8 days.

Introduction

Neonatal venous arterial extracorporeal membrane oxygenation (ECMO) offers cardiopulmonary support for patients with life threatening respiratory failure (1,2,3). The most common diagnoses for its uses and overall mortalities are listed in Table 1(4). It is universally accepted that these patients both require additional blood products and have an increase in extravascular fluid during the first few days of ECMO. Most patients diurese spontaneously or with diuretics. Diuresis can be assisted by ultrafiltration (UF), a form of hemofiltration (HF). HF was reported first used during cardiopulmonary bypass to hemoconcentrate blood by Romagnoli in 1976 (5). It was proved to be safe and effective in removing extravascular lung water (6). Devices used to perform continuous HF were approved for use in the United States by the Food and Drug Administration in

1982. HF during ECMO has been reported to be a safe and effective modality for treating volume overload associated with acute renal failure (7,8). HF removes a plasma ultrafiltrate which includes water and electrolytes from the vascular space. It utilizes convective transport of fluid across hollow fiber membranes (9). Molecules with molecular weights of more than 10,000 daltons are not permeable.

Our study was designed to see if the use of continuous HF affected renal function, specifically the renal clearance of creatinine. The application of hemofiltration depends upon its indication. There are several different methods of HF.

Slow continuous ultrafiltration (SCUF) (10) is designed to prevent or treat hypervolemia that is unresponsive to diuretics. Ultrafiltration rates (UFR) are usually less than 5 ml/min and replacement fluid is not given. Continuous IV fluids and nutritional support can be maintained.

Continuous arteriovenous hemofiltration (CAVH) was conceived by Peter Kramer of Gottingen, Germany and reported in 1977 (11). CAVH is designed to treat hypervolemia and electrolyte imbalance especially in patients with acute renal failure. UFR are usually higher than in SCUF (i.e. greater than 5 ml/min.) In CAVH a replacement fluid lacking particular solutes is used to induce a dilution of those solutes in the intravascular volume. A negative balance is achieved when more ultrafiltrate is removed than volume infused.

Continuous arteriovenous hemodialysis (CAVHD) incorporates hemofiltration with hemodialysis by the addition of a dialysate around the hollow fibers of the hemofilter to promote an increased removal of toxic solutes. SCUF was the mode of HF utilized in this study, however all modalities are possible.

Patients and Methods

Twenty-seven neonates with respiratory failure, sufficient to require ECMO (Table 2), were studied in a twelve month period. Seven of these patients met our criteria for HF (Table 3). Two patients were excluded from analysis, one had polycystic kidneys and one had a pre-existing aortic thrombus above the renal arteries. Careful fluid management records were maintained. Fluid lost in con-

densation and evaporation from the membrane oxygenator were neither measured nor included in fluid balance. Furosemide was administered for diuresis (1-2mg/kg/dose) two or three times daily. Patients were cannulated for ECMO as described by Bartlett (1). Urethral catheters were placed in all patients. Urine was collected at twenty four hour intervals and urine creatinine (U) levels obtained. If patients met criteria for hemofiltration, a hemofilter (Amicon Minifilter, W.R. Grace and Co. Danvers MA.) was incorporated into the ECMO circuit (Figure 1). A venous shunt was created, pumping blood obtained pre oxygenator through the hemofilter and returning it to the venous reservoir. Ultrafiltrate was removed continuously to either induce a negative fluid balance or maintain equilibrium. This usually required UFR of 3-10 ml/kg/hr. UF was collected for the same twenty four hour interval and analyzed for creatinine concentrations. Daily serum creatinine levels were also obtained. Creatinine clearance (CrCl) was determined using the following equation (Table 4). For the retrospective study, creatinine generation (UV) was estimated to be 10mg/kg/day (12). The values of CrCl were corrected to ml/min from dl/day and adjusted to body surface area.

Results

Mean CrCl data during ultrafiltration demonstrated a decrease over time from pre-ultrafiltration (Figure 2). The fourth day before the start of UF was significantly higher than the third day during UF ($P=0.5$ Newman Keuls MRT). We found UV (creatinine excretion or generation) to be $11.6 \pm 0.4 \text{ mg/kg/24}^\circ$ (arithmetic mean $\pm$ SE) in the non UF group. In the UF group $UV = 11.4 \pm 0.6 \text{ mg/kg/24}^\circ$. Mean CrCl values for the non UF group demonstrated little change over time as represented in Figure 3. All of the patients were decannulated from ECMO and discharged home.

Discussion

ECMO did not adversely affect CrCl in the non UF population. There was little change over time suggesting that non-pulsatile pump flow for 3-8 days does not affect glomerular filtration. The decrease in CrCl needs to be evaluated clinically. UF was associated with a decrease in CrCl but the patients were in a compromised fluid state with more serious medical problems than the non UF group. They averaged longer ECMO runs, 8 days when compared to 4 days in the non UF group. It is not clear whether the decrease was due to UF, other systemic problems or both. SCUF does not remove toxic solutes present in mild uremia as effectively as CAVH, CAVHD or hemodialysis. UFR were low and often discontinued if the patients spontaneous urine output became zero. We used the ultrafiltration patients as their own control, comparing preultrafiltration values to data during UF. The clinical

significance therefore warrants further investigation with larger UF patient populations. Medical management of hypervolemia and oliguria at our institution have since improved to the extent that very few patients require HF. Creatinine generation (UV) was similar in both populations and supported work done by Al-Dahhan in neonates justifying our use of 10mg/kg/day in the retrospective study.

In conclusion ECMO runs of 3-8 days did not affect CrCl in the non UF patients, supporting adequate renal perfusion and function during partial cardiopulmonary bypass. The use of 10mg/kg/day as UV in the retrospective study was supported. CrCl did decrease during UF ($P=.05$).

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Questions and Comments

Jeff Riley, S.C.

- Q. Thank you for this data. We have been waiting for good studies on ECMO using ultrafiltration. What were the sizes of your groups?
- A. The ultrafiltration and non-ultrafiltration groups. We had 20 patients in the non-ultrafiltration group that did not actually require or receive hemofiltration. The ultrafiltration group was a much smaller group. It only represented seven patients and it's difficult to draw clinically significant data conclusions from that size patient group, but we continue to use ultrafiltration and feel that this data needs to be further analyzed.
- Q. When did you intervene with ultrafiltration? It looked like the fifth day of ECMO.
- A. It varied on patients. Generally we won't do it in the first few days because there still would be capillary leaking going on in some of these kids — third spacing, so to speak. We would generally start it on the third day if they needed it. If they met the criteria and would continue probably through the whole run of ECMO unless the urine output drastically increased and we just didn't need it anymore.
- Q. Which brings us to the conclusion that if you intervened on the first day would there have been as much capillary leak and intestinal water loss?
- A. Well, some people think that capillary leak is going to happen anyway, and if you take too much fluid off in the first few days you'll just make them intravascularly dry because all the fluid you are giving them is just leaking back out into the extravascular space.

Dick Cramer, Cleveland, Ohio

- Q. Because of the results that you have gotten, would you have any reason to project, depending on the conceptual age, starting ultrafiltration earlier on younger patients?
- A. We never actually thought about that. It's possible, but the plasma creatinine levels in a younger patient might actually be higher and generally return to normal quicker. It was not really thought of.
- Q. You would have no reason then to assume that potentially inadequate kidney development had occurred, depending on the age level, that would

have no bearing on the establishment ultrafiltration?

- A. Correct. We didn't use that as a criteria for starting it earlier than others. The group we analyzed was between 36 and 40 weeks and only recently have we begun using it on patients 34 and 36 weeks old. We haven't used it any sooner.
- Steve Thompson, Baltimore, Md.
- Q. I noticed that you chose to regulate the blood flow through the filter with a second pump and I wondered if you had any comment on the possible contribution to increased plasma hemoglobin or if you noticed any difference in that value?
 - A. Actually, there was a colleague of mine who did a study of that and he did find that there was an increase in plasma-free hemoglobin. I don't have that data but I tend to disagree with him slightly. But yes, there was another roller pump in line and that does increase hemolysis. How much of an increase is debateable. We pumped anywhere from 30 to 50 ml per minute through the hemofilter. Some people say 50 is too much. Others pump 100 ml for neonates. To get the type of volume you need, there were probably increases in hemolysis, but not drastically.
 - Q. And I have one more question. For patients who are provided ECMO support for sepsis, if the point of hemofiltration intervention was earlier to prevent further capillary leak or at what point that was intervened?
 - A. It's quite possible that in all of our septic patients, some did require exchange transfusions quite early on in the ECMO run, and that generally contributed to the fact that they became fluid positive rather quickly and they did get hemofiltration sooner but criteria used for instituting it were the same.

Table 1

ELSO January 1991

International Neonatal ECMO Registry

Primary Diagnosis:	N	%	Total
	Survival	Survival	
Meconium Aspiration	1575	93	1698
Respiratory Distress	551	84	658
Congenital Diaphragmatic			
Hernia (CDH)	478	61	784
Sepsis	433	77	566
Persistent Pulmonary			
Hypertention (PPHN)	502	88	573
Air leak syndrome	12	63	19
Other	111	83	133

Total cases reported = 4431 Total survivors = 3662 (83%)

Figure 1

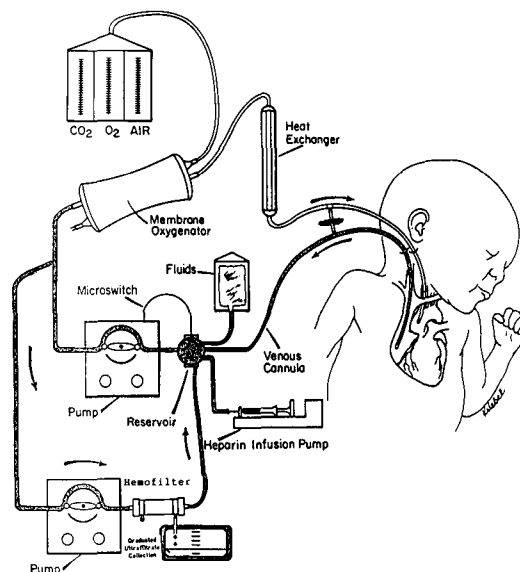


Figure 2

Table 2

Prospective Study

Primary Diagnosis

	Non UF n (%)	UF n (%)
Meconium Aspiration	10 (50)	3 (42)
PPHN	4 (20)	0 (0)
Sepsis	3 (15)	2 (29)
Respiratory Distress	3 (15)	2 (29)
Mean Conceptional Age	38±2.19 wks	38±2.3 wks
Mean Weight	3.36kg	3.50kg

(PPHN; Persistent pulmonary hypertension of the neonate)

PROSPECTIVE ULTRAFILTRATION

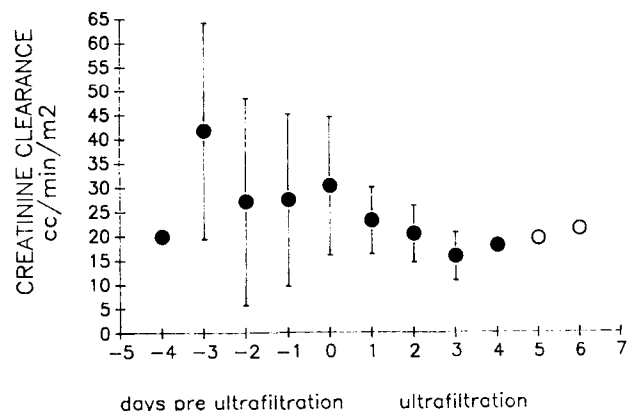


Figure 3

Table 3

Hemofiltration Criteria

During ECMO

- *Positive fluid balance
- *Urine output < 1ml/kg/hour
- *Output unresponsive to diuretic therapy

Table 4

Creatinine Clearance (CrCl)

$$CrCl = U \cdot V / P$$

U = Urine creatinine

V = Urine volume

P = Plasma creatinine

PROSPECTIVE CONTROL

