Pediatr Nephrol (2003) 18:29–32
DOI 10.1007/s00467-002-0991-2

ORIGINAL ARTICLE

**Marta Rupérez · César Sánchez · Cristina García
Elena García · Jesús López-Herce
Francisco J. Del Cañizo · Dolores Vigil**

Continuous venovenous renal replacement therapy using a pulsatile blood pump

Received: 22 April 2002 / Revised: 5 July 2002 / Accepted: 7 August 2002 / Published online: 26 November 2002

Abstract The objective of this study was to evaluate the efficacy of a pulsatile pump for continuous renal replacement therapy in a pediatric-size animal model. A vacuum-driven, tubular, blood-pumping device was used in 13 pigs weighing 10.4±1.5 kg, connected to a neonatal hemofiltration circuit with an FH22 filter and a flow sensor. Three different flow rates [30 ml/min (8 cases), 15 ml/min (3 cases), and 5 ml/min (2 cases] were used over 2-h periods. Aspiration pressure, frequency of pulsation, blood flow rate, ultrafiltrate volume, pre- and post-filter pressures, heart rate, arterial blood pressure, temperature, pH, sodium, potassium, chloride, urea, creatinine, glucose, and hematocrit were measured at 30-min intervals. The mean ultrafiltrate flow was 0.54±0.33 ml/kg per min. The aspiration pressure and pulsation frequency needed to maintain blood flow remained stable throughout the experiment. There were no complications secondary to the use of this technique and no significant changes in heart rate, blood pressure, or analytical determinations. In conclusion, in this animal model, the pulsatile pump has been shown to be an effective method for continuous venovenous renal replacement therapy.

Keywords Continuous venovenous renal replacement therapy · Hemofiltration · Pumps · Acute renal failure

M. Rupérez · C. Sánchez · C. García · E. García
J. López-Herce (✉)
Pediatric Intensive Care Unit,
Hospital General Universitario Gregorio Marañón, Madrid, Spain
e-mail: pielvi@eresmas.net
Tel.: +34-91-5866708, Fax: +34-91-5868018

F.J. Del Cañizo
Department of Experimental Medicine,
Hospital General Universitario Gregorio Marañón, Madrid, Spain

D. Vigil
Preventive Medicine Service,
Hospital General Universitario Gregorio Marañón, Madrid, Spain

J. López-Herce
Sección de Cuidados Intensivos Pediátricos,
Hospital General Universitario Gregorio Marañón,
Dr Castelo 49, 28009 Madrid, Spain

Introduction

Acute renal failure and hypervolemia are frequent, important problems in critically ill children [1]; 2%–10% of patients admitted to pediatric or neonatal intensive care units present acute renal failure [1]. A significant proportion of these children needs renal replacement therapy. Continuous arteriovenous and venovenous hemofiltration and hemodiafiltration are the most frequently used techniques in critically ill patients [2]. Studies in adults and children have found venovenous methods to be more effective than arteriovenous techniques [3, 4].

In recent years, a number of renal replacement systems with roller pumps have been adapted to the pediatric setting, and their utility and efficacy have been demonstrated in studies both in animals [5, 6] and in children [4, 7, 8, 9]. However, these systems are not often used in critically ill neonates and children [4, 7, 8, 9, 10]. To date, pulsatile pumps have not been used for continuous renal replacement therapy. The aim of the present study was to analyze the efficacy of a new, pulsatile tubular pump for continuous venovenous renal replacement therapy in an animal model.

Materials and methods

A prospective, experimental study in a pediatric animal model was carried out between June 2000 and February 2001. The study was approved by the Institutional Review Board for the Care of Animal Subjects, and the care and handling of the animals were in strict accordance with the guidelines for ethical animal research.

The study was carried out on 14 Maryland miniature pigs, isogenic for three loci on the major histocompatibility complex, weighing 8–12 kg (mean 10.4±1.5 kg). The animals were anesthetized with ketamine 15 mg/kg and atropine 0.02 mg/kg, and after endotracheal intubation, were connected to a ventilator (Boyle Modular BOC) in volume-control mode. Anesthesia was maintained with 2% halothane, fentanyl, and pancuronium bromide. The external jugular and femoral veins were exposed via cutdown and cannulated with 18-gauges catheter, 5.1 cm in length. A femoral artery cannula (20-gauge) was inserted for blood pressure monitoring and blood gas determinations and analyses.

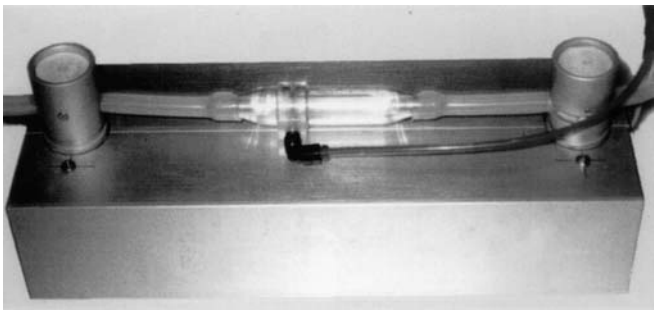

Fig. 1 Vacuum-driven, pulsatile, tubular blood pump

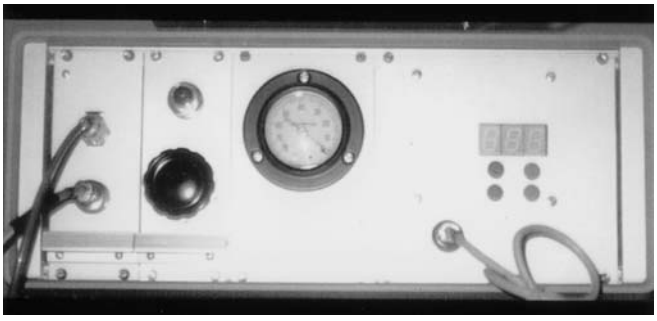

Fig. 2 Aspiration and frequency control system

A vacuum-driven, tubular, blood-pumping device, designed and patented by Madrid Community (Spain), was used [11]. The pump is a tubular device with a rigid external chamber and a flexible internal membrane that inflates and deflates due to the vacuum produced by a continuous aspiration system, simulating ventricular systole and diastole. The pulsatility of the system depends on mechanical valves that are situated at the inlet and outlet of the pump, and the flow obtained is similar to arterial flow (Figs. 1 and 2). The pump was connected to a conventional neonatal hemofiltration circuit (Gambro) with an FH22 filter (Gambro), membrane area 0.2 m^2. Three-way taps with Luer-lock connections were included in the circuit to measure pressures and for heparin infusion and post-filter fluid replacement. A flow sensor (Transonic HT 109, Transonic System) to measure blood flow was included in the circuit proximal to the pump. The prime volume of the circuit was 35 ml; prime volume of FH22 filter was 13 ml (total prime volume was 48 ml). The plan of the circuit and pump is shown in Fig. 3. The circuit and filter were purged with 2 l of normal saline containing 5,000 IU/l heparin. Venovenous hemofiltration was used in 12 animals and venovenous hemodiafiltration in 1. Replacement fluid (Ringer's lactate solution) was delivered into the post-filter limb at an initial rate of 300 ml/h, and the rate was adjusted according to the ultrafiltrate flow. Ringer's lactate solution was also used for the dialysis fluid, being passed countercurrent through the filtrate compartment at 100 ml/h. The animals were anticoagulated with an i.v. bolus of 100 IU/kg heparin followed by a continuous infusion of 30 IU/kg per hour, which was adjusted to achieve an activated coagulation time (ACT) of 150–175 s. The blood flow was maintained stable during the 2 h of the experiment by changing the aspiration pressure and/or frequency of the pump pulsations.

Prior to and on starting filtration, and each 30 min thereafter, the following measurements were taken: aspiration pressure, pulsation frequency, blood flow, pre- and post-filter pressures, heart rate, blood pressure, temperature, and ultrafiltrate flow. Each hour, blood gases and the ACT were measured and blood and ultrafiltrate fluid were taken for hematocrit, total proteins, urea, creatinine, sodium, potassium, chloride, total and ionic calcium and phosphate.

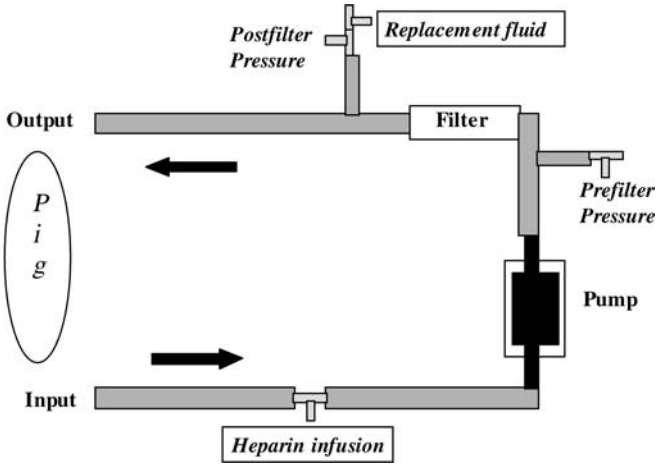

Fig. 3 Continuous venovenous renal replacement therapy circuit with the pump and filter

Statistical tests

Analysis of variance (ANOVA) for repeated measures was used to compare the values prior to starting therapy, and at 1 h and 2 h. Values of $P<0.05$ were considered significant. All values are expressed as mean±SD.

Results

One animal died due to cardiac arrest during vascular cannulation before starting renal replacement therapy; 13 animals completed the programmed 2 h of the experiment, suffering no complications secondary to the technique.

Eight experiments were carried out with a blood flow of 30 ml/min, 3 with 15 ml/min, and 2 with 5 ml/min. An aspiration pressure of 3–35 mmHg and a frequency of pulsation of 30–60/min were needed to maintain the blood flow. The aspiration pressure and the frequency of pulsation remained stable throughout the experiment (initial pressure×frequency/blood flow 45±25 and final 50.1±17.6).

Mean ultrafiltrate flow was 318±173.7 ml/h (0.54±0.33 ml/kg per min) and mean fluid replacement 268.4±102 ml/h (0.44±0.22 ml/kg per min). Ultrafiltrate flow was higher in the 1st hour (352.4±187 ml) than in the 2nd (288±166 ml) (P=0.01). Ultrafiltrate flow was 1.6 ml/kg per min when a blood flow of 30 ml/min was used, 0.3 ml/kg per min with a blood flow of 15 ml/min, and 0.1±0.01 ml/kg per min with a blood flow of 5 ml/min. The ratio between ultrafiltrate flow and blood flow (ultrafiltrate fraction of the blood flow) was 0.22 when a blood flow of 30 ml/min was used, 0.24 with a blood flow of 15 ml/min, and 0.32 with a blood flow of 5 ml/min. All the experiments were terminated on a planned basis after 2 h, with the filters working correctly.

Cross-filter pressure drop and pre- and post-filter pressures increased slightly over the course of the experiment. Cross-filter pressure drop increased from 16.9±14.1 mmHg at the beginning of the experiment to

Table 1 Evolution of analytical determinations

	Initial		1 h		2 h	
	Mean	SD	Mean	SD	Mean	SD
Arterial pH	7.38	0.12	7.39	0.09	7.38	0.09
Bicarbonate (mmol/l)	23.3	2.14	22.50	2.69	22.63	2.017
Sodium (mmol/l)	141.8	1.48	141.5	3.68	139	4.07
Potassium (mmol/l)	3.21	0.58	3.23	0.37	3.56	0.55
Chloride (mmol/l)	113	4.99	114.2	5.12	112.1	6.34
Ionic calcium (mmol/l)	1.28	0.07	1.34	0.10	1.36	0.09
Total calcium (mg/dl)	8.85	0.89	9.16	0.61	9.65	0.50
Phosphorus (mg/dl)	6.57	1.15	6.41	0.94	6.72	1.12
Hematocrit (%)	22.1	4.89	27	6.32	27	6.79
Total proteins (mg/dl)	4.56	0.47	4.89	0.65	5.25	0.88
Urea (mg/dl)	24.4	6.89	23.7	7.95	24.7	8.78
Creatinine (mg/dl)	0.54	0.09	0.54	0.08	0.53	0.07

Table 2 Ultrafiltration coefficients (sieving coefficients)

	1 h	2 h
Urea	1.02	1.01
Creatinine	0.79	0.79
Sodium	0.98	1
Potassium	0.91	0.90
Chloride	1.04	1
Calcium	0.75	0.72
Phosphate	1.08	1.06

Ultrafiltration coefficient: ultrafiltrate concentration/blood concentration

33.2±42.5 mmHg at 2 h without significant differences. The heparin infusion was maintained at 6–45 IU/kg per hour, achieving an ACT of 154–400 s. The technique was well tolerated by all animals, with no significant alterations in heart rate and mean blood pressure. Rectal temperature diminished from 34.9°C to 34.1°C ($P<0.002$). There were no significant changes in the arterial pH, bicarbonate, sodium, potassium, chloride, urea, creatinine, and phosphate over the course of the experiment. Hematocrit increased from an initial value of 22.1% to 27% at 2 h ($P=0.03$), total proteins from 4.5 g/l to 5.2 g/l ($P=0.04$), total calcium from 8.8 to 9.6 mg/dl ($P=0.005$), and ionic calcium from 1.28 to 1.36 mmol/l ($P<0.001$) (Table 1). Table 2 shows the ultrafiltration coefficients of several electrolytes.

Discussion

Roller pumps are the most frequently used pumps for continuous venovenous renal replacement therapy. These pumps have shown their utility and efficacy in adults and older children. However, many of these pumps cannot be used in neonates or infants due to the high prime volume of the system, and the fact that they do not function at low blood flow rates. Other pumps need special circuits or rollers for neonates and children. Only a small number of pumps have the appropriate characteristics for use in neonates and infants, and for these reasons the clinical experience in children is not extensive [2, 4, 7, 8, 9, 10]. Some authors have shown that conventional volumetric i.v. infusion pumps can be used for continuous venovenous renal replacement therapy [12, 13].

In an experimental hemodialysis model, Rungle et al. [14] found that pulsatile flow increased ultrafiltration volume and solute clearance in comparison with conventional pumps. However, pulsatile pumps have not yet been used for continuous venovenous renal replacement therapy in humans. Our group has designed a new, easy-to-handle, vacuum-driven, tubular, blood pumping device that can be used with a wide range of blood flows [11].

The present study demonstrates that this pump can be used for continuous venovenous renal replacement therapy in an animal model using pigs weighing less than 15 kg. The pump runs well with low blood flow rates (5–30 ml/min, 0.5–3 ml/kg per min). These flow rates are lower than those generally used in children, where the normal range is 3–10 ml/kg per min. The low resistance of our circuit is due in part to the relative low blood flow rates. Despite this, we obtained a high ultrafiltrate flow, 320 ml/h (14–49 ml/kg per hour). The ultrafiltrate fraction was similar with the three different blood flow rates used. The ratio of pressure×frequency/blood flow was no different between the three flow rates used and showed no significant changes over the course of the experiment. This finding demonstrates that pump functioning was similar with the three blood flow rates and did not change over time; there were no problems with venous access, no partial thrombosis, or saturation of the filter membrane. This may be an important finding for the future clinical application of the technique, as, after the connection and initial stabilization of the system, important modifications of the aspiration pressure or frequency of pulsation will probably not be necessary, except when a change in blood flow rate is desired. Although it is easy to increase blood flow rate with this pump, increasing the frequency of pulsations and/or aspiration pressure, we did not analyze pump function at high blood flow rates. Our objective was to evaluate whether this pump could be used at the low blood flow rates used in neonates and infants.

No significant alterations in urea and creatinine concentrations were observed over the course of the experiment, as the pigs were not in renal failure and had normal urea and creatinine levels before the start of the experiment. Furthermore, the continuous venovenous renal

replacement technique was maintained for only 2 h. The blood concentrations of the other electrolytes analyzed remained normal throughout the experiment. The increases in hematocrit and total protein levels were probably due to the moderate negative fluid balance obtained during the experiment, with an ultrafiltrate volume 10 ml/kg higher than fluid replacement volume.

The technique was well tolerated by all animals, with no hemodynamic repercussions. There were no significant changes in heart rate or blood pressure either at the time of connection of the system, as the prime volume is low, or during the 2 h of filtration, despite the 10 ml/kg negative fluid balance obtained. This represents a significant advantage for the possible clinical application of this technique in neonates, infants, and children with severe hemodynamic disturbances, in whom connection to an extracorporeal renal replacement therapy circuit with a large prime volume can produce marked hypotension.

During the course of the experiment a slight increase was observed in the cross-filter pressure drop (pre-filter pressure minus post-filter pressure), with no significant differences between the three different blood flow rates used. This is probably due to coagulation of some of the fibers of the filter, despite having maintained adequate levels of anticoagulation. This progressive increase in the cross-filter pressure drop is a common finding in continuous renal replacement techniques. Although in our study the increase in the cross-filter pressure drop was very small by the end of the experiment, the short duration of each experiment does not allow us to establish whether the pulsatile pump may have an influence on the life-span of the filter. Studies are necessary that analyze these parameters and evaluate whether the efficacy of the pump is maintained over time, and with a single- or double-lumen catheter.

We conclude that in this animal model, the pulsatile tubular pump is an effective and safe technique for continuous venovenous renal replacement therapy over a range of blood flow rates. The possible advantages of this pump over conventional continuous venovenous renal replacement roller pumps are the low cost, its ease of handling, the wide range of blood flow rates at which it can function, and the low prime volume. These allow its use in infants and neonates, and even in premature babies. Further studies are necessary with pulsatile and roller pumps to compare the efficacy of ultrafiltration and solute clearance, the efficacy over 24–48 h, the life-span of filter, hemodynamic repercussions, hemolysis, risks, and costs with each type of pump.

Before the clinical application of this pulsatile pump, an air bubble trap system will have to be added to the circuit, an air detector in the venous line, pressure and flow alarms, and an automatic clamping system triggered by the alarms. After our study we made several modifications to the circuit, shorting the lines, and adding an air-bubble trap, air detector, and pressure alarms. The priming volume of this new circuit is 25 ml. When blood flow resistance appears, caused by kinking of the tubing or partial coagulation of the venous access, circuit, or filter, the response of the pulsatile pump is very different from that of roller pumps. In this situation, roller pumps automatically increase the pressure, within certain limits, to maintain the same blood flow. However, the pulsatile pump does not autoregulate the pressure and, when resistance develops in the circuit, the blood flow decreases [11]. For this reason, it is important to use very sensitive flow sensor systems and alarms to allow the physician to modify the pressure and/or frequency of pulsation according to the changes in blood flow.

Acknowledgements This work was supported by a FIS grant no. 00/0013–06 to Mercedes Adrados Plaza and Angélica Biurrun González of the Experimental Medicine Department for their help in the experiments.

References

1. Stapleton FB, Jones DP, Green RS (1987) Acute renal failure in neonates: incidence, etiology and outcome. Pediatr Nephrol 1:314–320
2. Zobel G, Ring E, Rödl S (1996) Continuous renal replacement therapy in critically ill pediatric patients. Am J Kidney Dis 28 [Suppl 3]:S28–34
3. Bellomo R, Parkin G, Boyce N (1993) Acute renal failure in the critically ill: management by continuous venovenous hemodiafiltration. J Crit Care 8:140–144
4. García Sánchez E, Moreno de Guerra Girón M, López-Herce Cid J, Antona García MS, Díaz Franco A. Garrido Cantarero G (2000) Eficacia de las técnicas de depuración extrarrenal continua arteriovenosa y venovenosa en el niño críticamente enfermo. Rev Esp Pediatr 56:466–472
5. Werner HA, Herbertson MJ, Sear MD (1994) Functional characteristics of pediatric veno-venous hemofiltration. Crit Care Med 22:320–325
6. Jouvet P, Colomer S, Jugle M, Meftali Y, Vassault A, Man NJ (1998) Continuous venovenous hemodialysis in a neonate model: a two-pump system. Crit Care Med 26:115–119
7. Bunchman TE, Maxvold MD, Kershaw DB, Sedman AB, Custer SR (1995) Continuous venovenous hemodiafiltration in infants and children. Am J Kidney Dis 25:17–21
8. Klee KM, Fouser L, Greenleaf K, Watkins SL (1996) Continuous venovenous diahemofiltration with and without dialysis in pediatric patients. ANNA J 23:35–39
9. López-Herce J, Carrillo A, Panadero E, Sánchez C, Moral R, Bustinza A (1998) Técnicas de depuración extrarrenal continua venovenosa en neonatos y niños críticamente enfermos. An Esp Pediatr 49:39–45
10. Smoyer WE, McAdams C, Kaplan BS, Sherbotic JR (1995) Determinants of survival in pediatrics continuous hemofiltration. J Am Soc Nephrol 6:1401–1409
11. Del Cañizo JF, Antoranz JC, Duarte J, Desco MM, García-Barreno P (1996) Tubular vacuum-powered blood pumping device with active valves. Artif Organs 20:789–793
12. Ellis EN, Pearson D, Belsha C, Berry PL (1997) Use of pump-assisted hemofiltration in children with acute renal failure. Pediatr Nephrol 11:196–200
13. Sánchez C, López-Herce J, García E, Moreno de Guerra M, Moral R, Carrillo A (2001) Continuous venovenous renal replacement therapy using a conventional infusion pump. ASAIO J 47:321–324
14. Rungle TM, Briceno JC, Sheller ME (1993) Hemodyalisis: evidence of enhanced molecular clearance and ultrafiltration volume by using pulsatile flow. Int J Artif Organs 16:645–652