

Accelerated Venovenous Hemofiltration: Early Technical and Clinical Experience

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Background: Renal replacement therapies other than intermittent hemodialysis are often required in hemodynamically unstable patients. Continuous renal replacement therapies use a slow blood flow rate, necessitating anticoagulation and prolonged treatment times that may create difficulties with staffing and limit patient diagnostic and therapeutic procedures. We developed an alternative strategy based on a higher blood flow rate that allows increased rates of hemofiltration, no anticoagulation, and a shorter ("accelerated") treatment period. We report our technical and clinical experience with accelerated venovenous hemofiltration (AVVH).

Study Design: Case series.

Setting & Participants: Hemodynamically unstable patients requiring renal replacement therapy in the medical or surgical intensive care unit of an academic medical center.

Outcomes & Measurements: Achieved dose, blood flow rate, mean arterial pressure, serum chemistry test results, patient weight, filter clotting, and patient survival.

Results: 100 patients received 457 AVVH treatments (average, 4.1 treatments/patient during 5.6 days). Mean Acute Physiology, Age, and Chronic Health Evaluation II score was 24 ± 7.1 . Treatment consisted of 36 L of predilution hemofiltration during 9 hours. Mean blood flow was 362 mL/min, and net fluid removal was 2.5 L/treatment. Anticoagulation was not used and filter clotting was seen in only 3.3% of treatments. 86% of patients received the prescribed dose. Pre- and post-AVVH chemistry test results showed a significant decrease in blood urea nitrogen (from 69.6 ± 24.8 to 50.7 ± 22.0 mg/dL) and serum creatinine levels (from 4.3 ± 2.0 to 2.9 ± 1.3 mg/dL). Weight was decreased significantly (from 98.8 ± 26.4 to 93.4 ± 23.1 kg). Pre- and post-AVVH mean arterial pressure comparison showed an increase from 72.8 ± 13.6 to 74.4 ± 15.2 mm Hg. Patient survival rate was 53%.

Limitations: Retrospective analysis, absence of a comparison group.

Conclusion: AVVH is an alternate renal replacement therapy for patients in the intensive care unit and appears to provide adequate volume and solute control without the need for anticoagulation. The shorter treatment period offers flexibility for staffing and other patient diagnostic and therapeutic procedures.

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INDEX WORDS: Continuous renal replacement therapy; hemodialysis; acute kidney injury.

After the introduction of continuous arteriovenous hemofiltration in 1977 by Kramer et al,¹ a family of continuous venovenous renal replacement therapies (RRTs) using convective-based hemofiltration or diffusive-based hemodialysis (HD) or a combination of both, hemodiafiltration, emerged to provide RRT for critically ill patients with renal failure. Despite the lack of convincing evidence for an added survival ben-

efit with these continuous RRTs (CRRTs) over conventional intermittent HD (IHD),²⁻⁴ they offer greater hemodynamic and metabolic stability⁵ and are used routinely for unstable patients in the intensive care setting. Although it generally is accepted that CRRTs are better tolerated because of slower blood flow rates (≤ 150 mL/min) and prolonged treatment times of up to 24 hours per day, these modalities require continuous anticoagulation, burden the nursing staff, and limit patient availability for diagnostic and therapeutic procedures.

Slow low-efficiency daily dialysis (SLEDD) has emerged as a conceptual and technical hybrid of CRRT and IHD⁶ and has the advantage of shorter daily treatment times. However, SLEDD still requires a standard HD machine (often requiring constant HD personnel monitoring), water treatment, and, in most cases, anticoagulation. In addition, clearance is predominantly diffusive,

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providing lower middle-molecular clearances than seen with hemofiltration.

To circumvent the aforementioned practical difficulties associated with CRRT and SLEDD, we developed an alternative hemofiltration strategy based on higher extracorporeal blood flow rates now available with newer CRRT machines. Using an increased blood flow rate (350 to 400 mL/min), higher hourly hemofiltration rates became feasible, which allowed a truncated (“accelerated”) treatment period. With the shortened treatment time and higher blood flow rate, in addition to the administration of replacement fluid in the “predilution” mode, we predicted that anticoagulation would not be necessary. We believed a treatment modality that was convective based and had a shortened time frame with decreased nursing requirements that also did not require water treatment or anticoagulation would be attractive to many institutions. We entitled this hybrid therapy accelerated venovenous hemofiltration (AVVH). We report our technical and clinical experience with AVVH as an alternative to the traditional models of CRRT or SLEDD in hemodynamically unstable patients in need of RRT in the intensive care setting.

METHODS

Data were collected retrospectively from a review of electronic and paper medical records for 100 consecutive hemodynamically unstable patients with either acute kidney injury (AKI) from all causes ($n = 89$) or end-stage renal disease (ESRD; $n = 11$) who received AVVH (total of 457 treatments) in the medical or surgical intensive care units (ICUs) at Rush University Medical Center, Chicago, IL, from December 2004 to April 2006. Investigational review board approval was obtained, and informed consent was not deemed necessary given the retrospective nature of the study. The decision for AVVH was at the discretion of the attending nephrologist and was based on hemodynamic instability or need for large volume ultrafiltration. Conventional HD and AVVH were the only forms of acute RRT available at the institution. AVVH treatments were performed during the day. The decision to perform AVVH on a daily or as-needed basis was at the discretion of the attending nephrologist (initiation of AVVH did not mandate daily AVVH).

Patient data were collected and included such demographic characteristics as age, sex, and weight. For patients with AKI, the cause was considered surgical if the diagnosis of postoperative acute tubular necrosis was established by the consulting nephrology team. Sepsis, septic shock, or systemic inflammatory response syndrome were all considered as one entity and determined to be present if they had *International Classification of Diseases, Ninth Revision* cod-

ing for septic shock. Oliguria was defined as urine output of less than 400 mL/d. Illness severity on ICU admission was determined by means of the Acute Physiology, Age, and Chronic Health Evaluation (APACHE II) score. Patients who had an established diagnosis of cirrhosis from any cause, were immediately post-liver transplantation, or had liver function test results more than twice their baseline were considered to have liver dysfunction.

Outcomes included mortality, renal recovery, and dialysis dependency at the time of discharge. Renal recovery was defined as a patient no longer requiring RRT. Serum chemistry test results were obtained from the morning (before initiation) of the first AVVH treatment and the morning after the last AVVH treatment. If AVVH treatments were interrupted by 1 or more conventional HD treatments, serum chemistry tests were collected to reflect each period of uninterrupted AVVH for calculations of solute and volume control. Weights before the first AVVH treatment and the morning after the last AVVH treatment were collected for assessment of volume control. Mean arterial pressure (MAP) before the initiation of every treatment and immediately after the completion of that treatment was collected and compared for assessment of hemodynamic tolerability.

Treatment data included delivered ultrafiltration volumes, blood flow rates, filter clotting, and reasons for early termination of the treatment, such as hemodynamic instability, access malfunction, and the need for diagnostic or therapeutic procedures. Early termination was defined as any reason the full prescribed dose was not delivered. Filter clotting was not a cause for early termination of treatments because the therapy was restarted after the cartridge was changed and treatment time was extended to deliver the prescribed dose.

Technical Description

AVVH treatments were performed only in the intensive care setting using the NxStage System One machine (NxStage Medical Inc, Lawrence, MA). It uses a single-use drop-in cartridge with preattached filter (1.5 m² polyethersulfone, gamma sterilized) and blood tubing. Ultrafiltration is measured volumetrically and disposed directly into a sink or wall drain without the need for hourly dumping. Continuous data (eg, blood flow, hemofiltration rates, and net ultrafiltration) are visualized on a screen and stored in a built-in computer. Replacement fluid was prepared by an outsourced fluid compounding company (PharMedium, Lake Forest, IL) in 4-L bags and was lactate based (297 mg/dL [33 mmol/L]). The other constituents were sodium, 140 mEq/L (mmol/L); potassium, 2.0 mEq/L (mmol/L); calcium, 3.0 mEq/L (1.5 mmol/L); magnesium, 1.0 mEq/L (mmol/L); and dextrose, 100 mg/dL. All patients were prescribed 36 L of hemofiltration during 9 hours with a hemofiltration rate and thus replacement fluid rate of 4.0 L/h. The cartridge tubing has 9 spikes for replacement fluid bags and therefore all replacement fluid bags were attached at the beginning of the AVVH therapy. Replacement fluid was administered in the predilution mode. No anticoagulation was used. Only double-lumen dialysis catheters were used, and blood flow rate was set at 400 mL/min as angioaccess permitted. Treatments were initiated and terminated by a dialysis staff member and monitored by a critical care nurse. A dedicated dialysis staff member was available within the institution at

Table 1. Patient Characteristics

Demographics	
Age (y)	58.0 ± 14.7
Body weight (kg)	86.6 ± 29.2
Sex (%)	
Men	51
Women	49
Patients with ESRD (%)	11
Patients with AKI (%)	89
Medical	63
Surgical	37
Clinical characteristics	
Presence of sepsis (%)	78
Presence of oliguria (%)	85
Use of vasopressors (%)	79
Liver dysfunction (%)	68
APACHE II score	24 ± 7.1

Note: n = 100. Values expressed as mean ± SD or percent.

Abbreviations: ESRD, end-stage renal disease; AKI, acute kidney injury; APACHE, Acute Physiology, Age, and Chronic Health Evaluation.

all times during the treatments for troubleshooting. The intensive care nursing staff received in-service training to handle simple alarms. One-on-one nursing requirements were patient and not AVVH therapy dependent. Statistical comparisons of pretreatment and posttreatment values were made by using paired *t*-tests with GraphPad InStat version 3.05 for Windows 95 (GraphPad Software, San Diego, CA).

RESULTS

Patient characteristics are listed in Table 1. Of 100 patients included in the study, 89 had AKI and 11 had a diagnosis of ESRD and were on long-term HD therapy before their ICU admission. About two thirds of patients with AKI had medical causes, and the remaining one third had AKI secondary to postoperative acute tubular necrosis. Mean APACHE II score was 24 ± 7.1. A high percentage of patients (78%) had sepsis. A total of 13 patients crossed over to IHD therapy (had enough hemodynamic stability to receive HD, but became unstable, requiring AVVH again). Two patients who crossed over had ESRD and 11 had AKI. Solute and volume control data were collected for periods of uninterrupted AAVH treatment.

Treatment Outcomes

A total of 457 AVVH treatments were performed. Average hospital stay was 36.5 ± 27.8 days, with average ICU stay of 27.5 ± 23.4 days. Patients received an average of 4.1 treatments

during 5.6 days (AVVH was not always a daily therapy) with mean net fluid removal of 2.5 L/treatment (Table 2). Blood flow averaged 362 mL/min (range, 200 to 410 mL/min). Filter clotting was rare (occurring in 3.3% of treatments), and the majority of patients received the prescribed 36-L clearance (85.6%).

Solute and Volume Control

Chemistry values before the initiation of AVVH (pretreatment) and the morning after the last AVVH treatment (posttreatment) are listed in Table 3. Serum bicarbonate levels remained stable at the end of the treatment period despite the use of lactate-based replacement fluid and a high prevalence (68%) of liver dysfunction. There were significant decreases in blood urea nitrogen, serum creatinine, and phosphate levels during the course of the AVVH treatments, and mean patient weight decreased by more than 5 kg. Serum albumin levels remained stable. MAP increased to 74.4 ± 13.6 mm Hg after the completion of treatment compared with pretreatment MAP of 72.8 ± 13.6 mm Hg (*P* = 0.02) despite high blood flow rates and shortened treatment time.

Patient Outcomes

The overall observed patient hospital mortality rate was 47%, with a predicted mortality rate based on APACHE II scores of 50%. Of the

Table 2. AVVH Treatment Characteristics

Time on AVVH (d)	5.6 ± 5.8
No. of treatments	4.1 ± 3.6
Range	1-18
Net fluid removal (mL/treatment)	2,497 ± 1,909
Range	0-9,000
Blood flow rate (mL/min)	362.0 ± 42.7
Range	200-410
Filter clotting (%)	3.3
Treatments receiving prescribed dose (%)	85.6
Reasons for early treatment termination (%)	
Access malfunction	29.4
Need for diagnostic or therapeutic procedure	37.3
Patient instability	33.3

Note: Values expressed as mean ± SD or percent unless noted otherwise. Patients, n = 100; treatments, n = 457.

Abbreviation: AVVH, accelerated venovenous hemofiltration.

Table 3. Clinical and Laboratory Data Pre- and Post-AVVH

	Pretreatment*	Posttreatment†	P
Sodium (mEq/L)	138.6 ± 5.1	136.4 ± 3.9	<0.001
Potassium (mEq/L)	4.3 ± 0.7	3.9 ± 0.6	<0.001
Bicarbonate (mEq/L)	22.1 ± 4.8	22.7 ± 3.9	0.1
Calcium (mg/dL)	8.0 ± 1.1	8.1 ± 0.9	0.3
Phosphate (mg/dL)	5.5 ± 2.2	4.3 ± 1.6	<0.001
Albumin (g/dL)	2.3 ± 0.6	2.3 ± 0.6	0.5
Urea nitrogen (mg/dL)	69.6 ± 24.8	50.7 ± 22.0	<0.001
Creatinine (mg/dL)	4.3 ± 2.0	2.9 ± 1.3	<0.001
Weight (kg)	98.8 ± 26.4	93.4 ± 23.1	<0.001
MAP (mm Hg)‡	72.8 ± 13.6	74.4 ± 15.2	0.02

Note: Values expressed as mean ± SD. To convert calcium in mg/dL to mmol/L, multiply by 0.2495; phosphate in mg/dL to mmol/L, multiply by 0.3229; albumin in g/dL to g/L, multiply by 10; urea nitrogen in mg/dL to mmol/L, multiply by 0.357; creatinine in mg/dL to μ mol/L, multiply by 88.4. Sodium, potassium, and bicarbonate levels expressed in mEq/L and mmol/L are equivalent.

Abbreviations: MAP, mean arterial pressure; AVVH, accelerated venovenous hemofiltration.

*Obtained the morning before the first AVVH treatment.

†Obtained the morning after the last AVVH treatment.

‡Pretreatment MAP obtained before the initiation of each AVVH treatment, and posttreatment MAP obtained immediately after the completion or termination of the treatment.

survivors (53 patients), 21 (39.6%) had recovery from their AKI and no longer required any form of RRT. The remaining 32 patients (60.4%) were stable from a hemodynamic stand-point and were switched to conventional HD therapy. Seven patients in the latter group had an admission diagnosis of ESRD and were on HD therapy before admission. In analysis of data including only patients with AKI, 24% recovered renal function and 28% were dialysis dependent at the time of the study, with a 48% mortality rate in this group.

DISCUSSION

Optimal RRT in critically ill ICU patients has long been a topic of investigation. Although an obvious survival advantage of CRRT over IHD has not been proven in any clinical trial,²⁻⁴ it is widely accepted that CRRT has a better cardiovascular tolerability profile in hemodynamically unstable patients.⁷

Continuous Renal Replacement Therapies are not without disadvantages. In addition to higher cost,⁸ CRRT is labor intensive, requires anticoagulation, and creates difficulties with patient mobilization. We felt that although a 3- to 4-hour IHD treatment may not be well tolerated, it may not be necessary to extend treatment time to 24 hours to show improved tolerability. To achieve this goal, we increased ordered blood flow rates

to 400 mL/min, which allowed higher hemofiltration rates and provided therapy that delivered our clearance and ultrafiltration goals in a shorter time than would have been required using conventional CRRT.

Clotting of the extracorporeal circuit is the most common technical problem during CRRT. In addition to patient blood loss and the need for filter and tubing replacement, clotting reduces the delivery of prescribed dose. In early reports of SLEDD as an alternative to CRRT in the ICU, Kumar et al⁹ reported use of heparin in 68% of treatments. Filter clotting was significant (17%) with the use of heparin and even more significant (27%) in heparin-free treatments. Marshall et al⁶ reported similarly high incidences of filter clotting (20% to 30%) in their report of SLEDD regardless of the use of heparin. One of the major advantages of AVVH is the lack of anticoagulation. Predilution mode for replacement fluid administration was used because it significantly attenuates the procoagulant effect of hemoconcentration seen as a result of blood plasma ultrafiltration when hemofiltration is done in the postdilution mode. This, in addition to the higher blood flow rates and perhaps shorter treatment times, allowed us to avoid anticoagulation. This strategy was successful because filter clotting was observed in only 15 of the total 457 treatments (3.3%). Avoidance of anticoagulation in criti-

cally ill often postsurgical patients offers an immense advantage. This lack of anticoagulation also simplifies the treatment because there are one (heparin) to two (citrate and calcium) less infusions and no need to follow partial thromboplastin times (heparin protocols) or calcium and bicarbonate levels (citrate protocols). We would expect this to translate into cost savings and possibly decreased risk of bleeding.

The level of technical complexity and nursing time requirements are substantially reduced when comparing AVVH with traditional CRRT. All replacement fluid bags were spiked and hung simultaneously at the beginning of the treatment. This eliminates the need for frequent bag changes. The direct-to-drain effluent disposal with automatic computer data entry eliminates the need for hourly volume measurement and written data recording, which are both laborious and time consuming. In addition, the shorter treatment time delivers the prescribed dose during the day and reduces the burden of monitoring the treatment at night.

When replacement fluid is administered post-dilution, clearance is equal to the hemofiltration rate. When replacement fluid is administered predilution, actual clearance is less than the hemofiltration rate because some of the hemofiltrate is replacement fluid.^{10,11} The degree of this effect depends on the replacement fluid rate: replacement fluid rate (equal to hemofiltration rate) relative to blood flow rate. This is easy to calculate using the following equation: $(Q_B / [Q_B + Q_{HF}]) \times 100$, where Q_B is blood flow rate in milliliters per minute and Q_{HF} is hemofiltration rate in milliliters per minute.¹² Thus, at a blood flow rate of 400 mL/min and hemofiltration rate of 4 L/h (66.6 mL/min), the treatment delivers a clearance rate that is 86% of the hemofiltration rate.¹³ This relationship stresses the importance of using a high blood flow rate in AVVH. For example, if a hemofiltration rate of 4 L/h (with predilution fluid administration) was achieved with a blood flow rate of only 200 mL/min, effective clearance decreases to 75% of the hemofiltration rate.

The issue of dosing remains an important consideration. Regardless of the mode of clearance (diffusive versus convective), higher doses were shown to improve survival in patients with AKI. Using the diffusive modality of HD, Schiffl

et al¹⁴ showed the superiority of daily HD over IHD, with improvement in survival from 54% to 78%. Ronco et al¹⁵ showed that patients who received convective hemofiltration doses of 55.7 L/24 h or higher had significantly improved survival compared with those who received 30.9 L/24 h (57% versus 41%, respectively). More recently, Saudan et al¹⁶ showed that increasing clearance (diffusively) by the addition of dialysate (continuous venovenous hemodiafiltration) to the purely convective therapy of CVVH improved 28-day survival rates from 39% to 59%. Thus, there is more evidence that dose influences survival than does treatment modality. However, actual delivery of prescribed doses during the 24-hour period of CRRT is challenging. In a retrospective study of 115 ICU patients treated with CRRT, patients received only 68% (16.5 mL/kg/h) of the 24.5-mL/kg/h dose that was prescribed.¹⁷ This decrease in delivered dose was attributed to interruptions in therapy and clotting of the system. In our experience, 86% of patients completed their treatments; thus, the shorter treatment time and low filter clotting (3.3%) afforded by AVVH allowed for improved delivery of the prescribed dose.

There currently are two large multicenter randomized controlled trials in the United States (the Acute Renal Failure Trial Network [ATN] study)¹⁸ and Australia (the Randomized Evaluation of Normal versus Augmented Level of RRT [RENAL] Study),¹⁹ which are further investigating the impact of dosing in critically ill patients. Results of these trials could impact our prescriptions toward higher delivered doses. If we increase our hemofiltration rate to 5 L/h for 12 hours, our prescribed treatment increases from 36 to 60 L. Our delivered clearance decreases from 86% to 83% of the prescribed dose because the higher hemofiltration rate (and thus higher replacement fluid rate) will have a greater effect on predilution clearance because blood flow rate cannot be concomitantly increased. However, 83% of 60 L (approximately 50 L) is much greater than 86% of 36 L (31 L). We therefore believe that our model offers adequate flexibility to increase the delivered dose if the aforementioned Acute Renal Failure Trial Network and RENAL trials indicate that we are delivering inadequate clearance doses.

Table 4. Survival Rates in Recent Trials of Continuous RRT

Reference	No. of Patients	RRT Modality	APACHE II	Survival (%)
Ronco et al, ¹⁵ 2000	146	CVVH (low dose)	22	41
	139	CVVH (medium dose)	24	57
	140	CVVH (high dose)	22	58
Kumar et al, ⁹ 2000	25	SLEDD	20.1	16
	17	CVVH	17.7	35
Mehta et al, ³ 2001	84	CVVHDF	25.5	40.5
Venkataraman et al, ¹⁷ 2002	115	CVVH/HDF	Not reported	33.6
Augustine et al, ² 2004	80	CVVHD	*	32.5
Marshall et al, ⁶ 2004	24	SLEDD	25.9	54.2
Saudan et al, ¹⁶ 2006	89	CVVH	26	39
	91	CVVHDF	24	59
Present study	100	AVVH	24	53

Abbreviations: RRT, renal replacement therapy; APACHE, Acute Physiology, Age, and Chronic Health Evaluation; CVVH, continuous venovenous hemofiltration; SLEDD, slow low-efficiency daily dialysis; CVVHDF, continuous venovenous hemodiafiltration; CVVHD, continuous venovenous hemodialysis; AVVH, accelerated venovenous hemofiltration.

*Cleveland Clinic scores used.

With considerations of survival in mind, how do our data compare with reports using other forms of CRRT and SLEDD? Have we traded outcome for simplicity? Our survival rate was 53%, similar to that predicted based on APACHE II scores (50%). More importantly, the observed survival is in the range of other reports of various RRTs in ICU patients with similar APACHE II scores (Table 4).

Because the optimal dose of RRT has not been established in the setting of AKI, solute and volume control are often considered surrogate markers of safety and efficiency in the evaluation of a new therapy.²⁰ Accelerated venovenous hemofiltration provides a significant decrease in blood urea nitrogen and serum creatinine levels during the course of the treatment (Table 3). Serum potassium and phosphate levels were both corrected toward the median of the reference range. Use of lactate-buffered replacement solution has been associated with transient hyperlactatemia in patients with septic shock, although this does not produce clinically significant acidosis.²¹ In our experience, serum bicarbonate levels were unchanged despite administration of 132 mmol/h of lactate in a population of patients with a high prevalence of liver dysfunction and sepsis in which the ability to handle an exogenous lactate load would be impaired. In patients with lactic acidosis before starting AVVH, a bicarbonate drip may be necessary because metabolic acidosis may be worsened by the convective loss of bicarbonate in the setting of an

inability to convert lactate-based replacement fluid to bicarbonate.

The major attractive feature of CRRT and SLEDD is slower blood flow that is better tailored to the hemodynamic needs of critically ill patients. This tolerability is believed to be a function of slower volume removal and less dramatic electrolyte and solute shifts in the prolonged treatments. In our experience, despite higher blood flow rates of up to 400 mL/min and shortened treatment times, patients tolerated the procedure well, and only 22 of the total 456 treatments had to be terminated because of patient instability. MAP after termination of AVVH was higher than MAP before the start of therapy.

Our experience should be interpreted within the context of study limitations. These include limitations inherent to any retrospective study. In addition, because AVVH was the only therapeutic option in patients with hemodynamic instability and there is lack of a control group, survival comparisons with other forms of RRT are limited to reported data from other studies.

In conclusion, AVVH appears to be a viable alternative to traditional CRRT and SLEDD. The short duration of treatment, easy handling of the effluent, minimal monitoring for the staff, and adequate volume and solute control make this an efficient protocol. Our experience suggests that patients tolerate AVVH from a hemodynamic standpoint. The low incidence of filter clotting and lack of anticoagulation not only provide

better delivery of the prescribed dose (86%) and less frequent interruptions in treatment, but may also reduce the risk of bleeding from systemic anticoagulation in the ICU setting. The shorter treatment period offers flexibility for staffing and other patient diagnostic and therapeutic procedures.

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