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Short Communication

Population pharmacokinetics and dose simulation of vancomycin in critically ill patients during high-volume haemofiltration

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ABSTRACT

This study aimed to describe the population pharmacokinetics of vancomycin in critically ill patients with refractory septic shock undergoing continuous venovenous high-volume haemofiltration (HVHF) and to define appropriate dosing for these patients. This was a prospective pharmacokinetic study in the ICU of a university hospital. Eight blood samples were taken over one vancomycin dosing interval. Samples were analysed by a validated liquid chromatography–tandem mass spectrometry assay. Non-linear mixed-effects modelling was used to describe the population pharmacokinetics. Dosing simulations were used to define therapeutic vancomycin doses for different HVHF settings. Nine patients were included (five male). The mean weight and SOFA score were 70 kg and 11, respectively. Mean HVHF settings were: blood flow rate, 240 mL/min; and haemofiltration exchange rate, 100 mL/kg/h. A linear two-compartment model with zero-order input adequately described the data. Mean parameter estimates were: clearance, 2.9 L/h; volume of distribution of central compartment (V_1), 11.8 L; volume of distribution of peripheral compartment (V_2), 18.0 L; and intercompartmental clearance, 9.3 L/h. HVHF intensity was strongly associated with vancomycin clearance ($P < 0.05$) and was a covariate in the final model. Simulations indicate that after a loading dose, vancomycin doses required for different HVHF intensities would be 750 mg every 12 h (q12 h) for 69 mL/kg/h, 1000 mg q12 h for 100 mL/kg/h and 1500 mg q12 h for 123 mL/kg/h. Continuous infusion would also be a valuable administration strategy. In conclusion, variable and much higher than standard vancomycin doses are required to achieve therapeutic concentrations during different HVHF settings.

1. Introduction

Continuous venovenous haemofiltration with high-volume exchange is used in intensive care units (ICUs) as part of the management of patients with refractory septic shock and/or acute kidney injury [1]. This form of renal replacement therapy (RRT) is commonly termed high-volume haemofiltration (HVHF) and employs haemofiltration rates that may exceed 100 mL/kg/h. Because HVHF removes pro-inflammatory mediators that are associated with haemodynamic compromise, it can be prescribed as either pulse 6-h treatments [2], as a continuous treatment for ≥12 h or as RRT to improve haemodynamics and other physiological conditions in critically ill patients with progressive refractory hypotension and lactic acidosis [3].

The amount of solute removed during HVHF is still uncertain. For antibiotics, effective dosing is a significant challenge because robust dosing recommendations in this context are scarce. A HVHF study of a hydrophilic antibiotic suggests that a higher dose is required in the presence of HVHF because of dramatically increased drug clearance [4].

Vancomycin is a widely used antibiotic in critically ill patients with sepsis. It is still the first-line treatment for meticillin-resistant *Staphylococcus aureus* (MRSA) infections in many countries. Previous studies of vancomycin pharmacokinetics during RRT have shown different vancomycin clearances [5,6], resulting in variable achievement of target plasma concentrations [7,8]. Dosing recommendations have been proposed for haemofiltration rates <45 mL/kg/h but not for higher substitution volumes. Therefore, if

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standard vancomycin doses are used during HVHF, subtherapeutic concentrations are highly likely to result.

To date, we are unaware of any studies investigating the effect of HVHF of ca. 100 mL/kg/h on vancomycin pharmacokinetics in critically ill septic patients and are not aware of any dosing guidelines in this scenario.

The aim of this study was to describe the population pharmacokinetics of vancomycin in patients undergoing HVHF for septic shock treatment and to propose appropriate doses for achievement of target concentrations.

2. Materials and methods

This was an observational prospective pharmacokinetic study performed in the ICU of Universidad Católica Clinical Hospital (Santiago, Chile). The institutional review board approved the study, and written informed consent was obtained from the legally authorised representative of each patient.

Eligible patients aged ≥18 years with sepsis or severe septic shock requiring HVHF who were prescribed vancomycin were recruited over a 1-year period (June 2011 to June 2012).

2.1. High-volume haemofiltration settings

HVHF was performed in pre-dilution mode (Diapact™ CRRT machine; B. Braun, Melsungen, Germany) with a polysulfone haemofilter (1.5 m^2 or 2 m^2 surface area membrane) (Diacap® Acute; B. Braun). The substitution flow rate was targeted at ca. 100 mL/kg/h and the blood flow rate (Q_b) at ca. 250 mL/min. A neutral fluid balance was prescribed and the need for anticoagulation was assessed in individual patients.

2.2. Blood sampling

Vancomycin (Hospira Inc., Lake Forest, IL) dosing was 1 g daily by central venous catheter infusion in every patient. Each dose was reconstituted and diluted in 100 mL of normal saline solution and was given with a standard 1-h infusion time.

Blood samples were obtained from the pre-filter port on the HVHF machine at 0, 0.5, 1, 2, 4, 6, 9 and 12 h relative to the commencement of the 1-h vancomycin infusion.

2.3. Vancomycin assay

A validated liquid chromatography–tandem mass spectrometry (Acquity™ UPLC System; Waters Corp., Milford, MA) assay was used for the determination of vancomycin plasma concentrations. A BEH C18 column was employed for chromatographic separation in isocratic run. For detection, the transition mass/charge was 725.2 → 144.0 in positive mode. Linearity was achieved between 0.63 mg/L to 80.00 mg/L (R^2 = 0.999). Intraday and interday imprecision were also <5% for all the levels evaluated. The limit of detection and limit of quantification were 0.22 mg/L and 0.63 mg/L, respectively.

2.4. Population pharmacokinetic analysis

Vancomycin concentration–time data were analysed using nonlinear mixed-effects modelling (NONMEM™ 7.2; Globomax LLC, Hanover, MD). One- and two-compartment models were initially evaluated. Between-subject variability (BSV) for all parameters was evaluated using an exponential variability model. For the residual unexplained variability (RUV), additive, exponential and combined random-error models were tested.

A decrease of at least 3.84 points of the objective function value was required to demonstrate a statistically significant improvement for a more complex model ($P < 0.05$, χ^2 distribution). Visual inspection of diagnostic scatter plots was used to evaluate goodness of fit. Serum creatinine concentration, Acute Physiology and Chronic Health Evaluation (APACHE) II score and Sequential Organ Failure Assessment (SOFA) score on the day of enrolment, HVHF intensity, sex, filter surface area, body weight, body mass index (BMI), Q_b and patient age were evaluated as possible covariates for inclusion in the final model. The appropriateness of the model was confirmed based on graphical and statistical criteria. A non-parametric bootstrap (n = 1000) was used to confirm the robustness of the parameters of the final covariate model.

2.5. Other pharmacokinetic calculations and statistical methods

The area under the concentration–time curve from 0 to 12 h (AUC_{0-12}) was calculated using the trapezoidal rule. The maximum (C_{max}) and minimum (C_{min}) concentrations for the dosing period were the observed values.

Descriptive statistics were applied and the results are presented as the mean ± standard deviation (S.D.). Microsoft Excel 2010 (Microsoft Corp., Redmond, WA) and GraphPad Prism v.5.03 for Windows (GraphPad Software, San Diego, CA) were used to process data and to generate figures and tables.

2.6. Pharmacokinetic simulations

The final covariate model from the population pharmacokinetic analysis was used to simulate vancomycin dosing based on a 70-kg patient (mean body weight of the recruited patients). Various simulations of loading doses, maintenance doses and continuous infusions were simulated according to the possible posology of vancomycin. The effects of different rates of HVHF were evaluated using 69, 100 and 123 mL/kg/h (minimum, mean and maximum HVHF intensities observed in this study). The target trough concentrations of the loading dose and intermittent infusions were defined as 15–20 mg/L [9] and for continuous infusion was 20–30 mg/L [10]. The duration of infusion for loading and maintenance doses was evaluated to describe a non-toxic C_{max}. An adequate dose for each HVHF rate was described according to the above criteria.

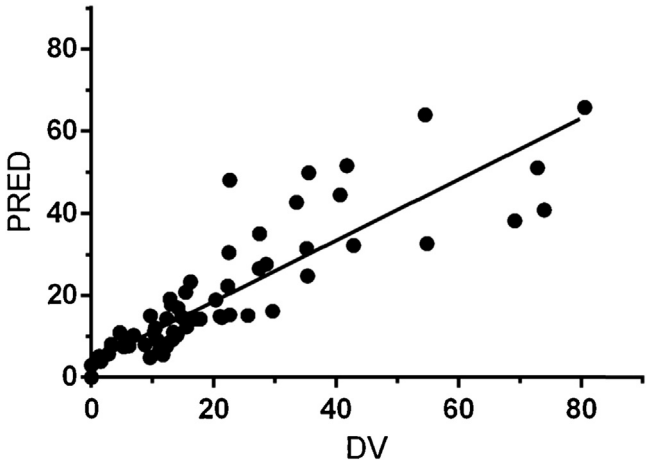

Fig. 1. Goodness-of-fit plot. Correlation between observed and predicted plasma concentrations of vancomycin by the final covariate model. R^2 = 0.80. DV, dependent variable [vancomycin plasma concentrations (mg/L) of the patients studied]; PRED, population-predicted concentrations [vancomycin plasma concentrations (mg/L) obtained from the final covariate model].

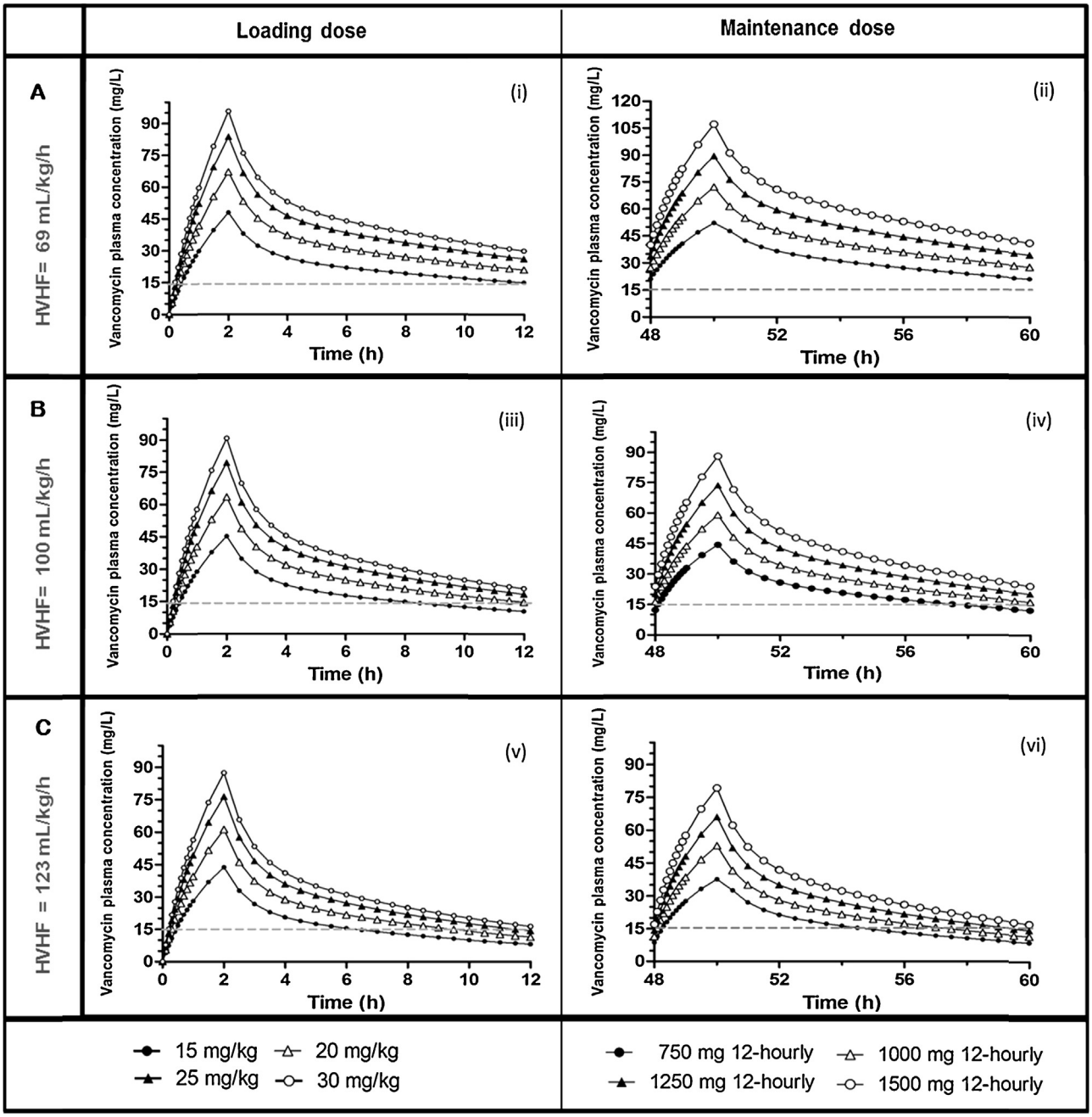

Fig. 2. Simulation of vancomycin plasma concentrations depending on high-volume haemofiltration (HVHF) rates using different loading and maintenance doses. (A) (i) Loading dose of 20 mg/kg selected and (ii) a maintenance dose of 750 mg every 12 h (q12 h) for HVHF = 69 mL/kg/h. (B) (iii) Loading dose of 25 mg/kg selected and (iv) a maintenance dose of 1000 mg q12 h for HVHF = 100 mL/kg/h. (C) (v) Loading dose of 30 mg/kg selected and (vi) a maintenance dose of 1500 mg q12 h for HVHF = 123 mL/kg/h. - - -, target trough vancomycin plasma concentration of 15 mg/L.

3. Results

3.1. Clinical and demographic characteristics and high-volume haemofiltration prescription

As HVHF is not a frequently used rescue treatment in the ICU, only nine severe septic shock patients were included (five male). The mean ± S.D. age was 57 ± 14 years, weight 70 ± 18 kg and BMI 27 ± 9 kg/m^2, respectively. The mean ± S.D. APACHE II and SOFA scores were 31 ± 7 and 11 ± 4, respectively. Six patients were anuric and three were oliguric before HVHF. The vancomycin prescription was 1000 mg intravenous daily as a 1-h infusion in all patients. The HVHF settings were a mean Q_b of 240 ± 20 mL/min and a haemofiltration dose of 100 ± 18 mL/kg/h (range 69–123 mL/kg/h).

3.2. Vancomycin pharmacokinetics

The mean vancomycin plasma C_{max} was 72.7 ± 53.9 mg/L and C_{min} was 12.2 ± 10.6 mg/L. The $AUC_{0–12}$ was 319 ± 251 mg h/L. After 12 h of HVHF, only two patients had a vancomycin C_{min} > 20 mg/L. In all other patients the vancomycin C_{min} was <11 mg/L.

The 68 vancomycin plasma samples were best described as a two-compartment linear model with zero-order input. An additive

and exponential model was used to describe RUV variability error. BSV was supported on all parameters.

Of all the covariates studied, only HVHF intensity was identified as a statistically significant covariate associated with vancomycin clearance ($P < 0.05$) as follows:

$$\text{TVCL} = \frac{\theta_1}{100}$$

where TVCL is the typical value of clearance and θ_1 is the HVHF rate.

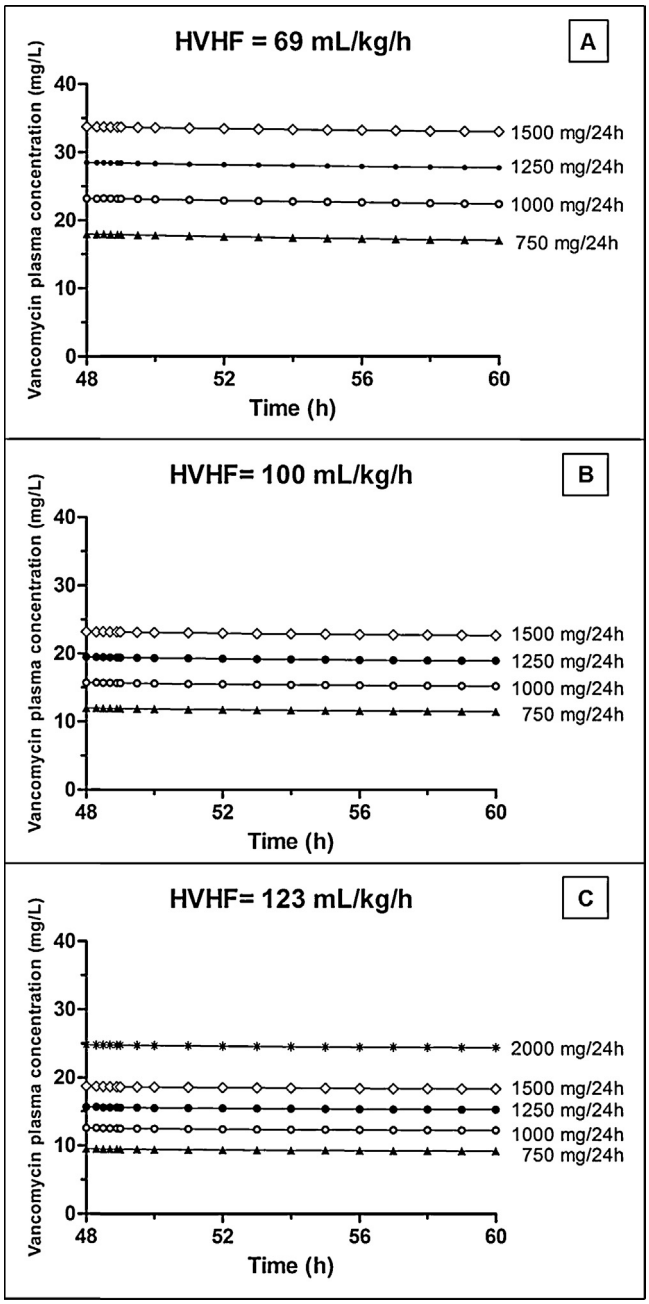

Fig. 3. Simulation of vancomycin plasma concentration for continuous infusion. Doses to achieve optimal range: 20–30 mg/L [10]. (A) Continuous infusion of 1000–1250 mg of vancomycin over 24 h during HVHF = 69 mL/kg/h after a loading dose of 20 mg/kg. (B) Continuous infusion of 1500 mg of vancomycin over 24 h during HVHF = 100 mL/kg/h after a loading dose of 25 mg/kg. (C) Continuous infusion of 2000 mg of vancomycin over 24 h during HVHF = 123 mL/kg/h after a loading dose of 30 mg/kg. HVHF, high-volume haemofiltration.

The goodness-of-fit plots showed that the final covariate pharmacokinetic model adequately described the observed vancomycin concentrations. Acceptable correlations of both the population ($R^2 = 0.80$) and individual ($R^2 = 0.98$) predicted vancomycin concentration versus the observed vancomycin concentration were obtained (Fig. 1).

The parameter estimates from this model matched the bootstrap results sufficiently: mean population clearance (CL) = 2.7 L/h (bootstrap mean 2.9 ± 0.5); volume of distribution of the central compartment (V_1) = 11.9 L (bootstrap mean 11.8 ± 1.4); volume of distribution of the peripheral compartment (V_2) = 17.3 L (bootstrap mean 18.0 ± 3.1); and intercompartmental clearance (Q) = 4.9 L/h (bootstrap mean 9.3 ± 5.3).

3.3. Dosing simulations

As HVHF intensity was the main covariate in the model, the simulations of vancomycin doses were performed using three different haemofiltration rates. These were the minimum, mean and maximum HVHF intensities used in our patients. The simulated profiles are shown in Fig. 2. The appropriate loading dose to achieve the target concentrations for each HVHF rate was first defined. Then, this loading dose was used to evaluate the appropriate maintenance dose.

The appropriate loading doses for 69, 100 and 123 mL/kg/h HVHF rates were 20, 25 and 30 mg/kg vancomycin, respectively.

Intermittent infusion frequencies were simulated at every 8, 12 and 24 h, with 12 h being shown to be the most convenient interval to achieve target concentrations. Moreover, an infusion duration for loading and maintenance doses of 2 h was shown to be adequate to avoid possible toxic C_{max}.

The maintenance doses for 69, 100 and 123 mL/kg/h were 750, 1000 and 1500 mg every 12 h, respectively.

Continuous infusion during 24 h was also simulated in combination with the selected loading dose. In Fig. 3, the simulated vancomycin plasma concentration versus time and the adequate dose for each HVHF rate are shown. The suggested doses for 69, 100 and 123 mL/kg/h were 1000, 1500 and 2000 mg over 24 h to achieve a vancomycin plasma concentration of 20–30 mg/L.

4. Discussion

This study shows the inadequate vancomycin plasma concentrations achieved after a standard dose during HVHF rates close to 100 mL/kg/h. Even with much lower HVHF rates (ca. 56 mL/kg/h [8]), concentrations were insufficient.

This pharmacokinetic analysis showed a mean vancomycin clearance surprisingly similar to previous studies (<45 mL/kg/h) [7,11,12] despite the higher ultrafiltration rate. This observation might be explained by the residual renal function of the patients included in the other studies that contribute to the total vancomycin clearance. Total drug clearance is the sum of the renal and extracorporeal clearance values. Thus, in anuric or oliguric patients such as in the current study, a higher HVHF rate would compensate for a lack of renal function.

For that reason, the intensity of the HVHF dose was the only covariate that could be included in the final pharmacokinetic model. This effect has also been demonstrated in other studies, although these had far lower haemofiltration intensities [12,13].

These results show that a standard vancomycin dose of 1000 mg/day should not be applied to all patients during HVHF. To avoid subtherapeutic vancomycin concentrations, a loading dose of ≥20 mg/kg is required. The maintenance dose should also consider the HVHF rate. A recent review suggests a slightly lower loading dose of 15–20 mg/kg followed by 10–15 mg/kg every 24 h for

a haemofiltration rate of 25 mL/kg/h in patients with acute kidney injury [14]. Our dosing simulations at higher HVHF rates (ca. 100 mL/kg/h) suggest that the maintenance doses should be higher and every 12 h. Continuous infusion may also be considered a useful alternative for vancomycin administration to maintain stable vancomycin concentrations [10,15].

This observational study has the limitation of a small sample size owing to a low number of eligible patients. Nevertheless, it is important to obtain data to guide empirical dosing during RRT in critically ill patients with refractory septic shock, particularly given that therapeutic drug monitoring (TDM) is not always available (vancomycin TDM is not available at the hospital where the study was undertaken). Given that a delay in achievement of therapeutic concentrations is likely to be associated with suboptimal outcomes, these data and dosing recommendations may improve the efficiency of dosing during HVHF.

In conclusion, vancomycin clearance during HVHF depends mainly on haemofiltration rate. Higher than standard doses of vancomycin are required to achieve therapeutic concentrations. A higher loading dose of vancomycin of ≥20 mg/kg given over 2 h followed by an intermittent 12-hourly or continuous infusion dose is recommended to provide target vancomycin concentrations in these patients. Further validation of these simulations could be helpful to develop more information during HVHF treatment.

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Competing interests: None declared.

Ethical approval: The study protocol was approved by the Institutional Ethics Committee of the Universidad Católica Clinical Hospital (Santiago, Chile) [project no. 10-176]. Written informed consent was obtained from the legally authorised representative of each patient.

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