Research Article

Blood Purification

Blood Purif
DOI: 10.1159/000499076

Received: February 22, 2019
Accepted: February 22, 2019
Published online: April 30, 2019

Fluid Dynamics Analysis by CT Imaging Technique of New Sorbent Cartridges for Extracorporeal Therapies

Anna Lorenzin[a, b] Mauro Neri[a, b] Massimo de Cal[a, b] Giordano Pajarin[c] Giuseppe Mansi Montenegro[c] Sergio Savastano[c] Alberta Alghisi[d] Claudio Ronco[a, b, e]

[a]International Renal Research Institute of Vicenza, Vicenza, Italy; [b]Department of Nephrology, Dialysis and Transplantation, St. Bortolo Hospital, Vicenza, Italy; [c]Department of Radiology, St. Bortolo Hospital, Vicenza, Italy; [d]Department of Transfusion Medicine, St. Bortolo Hospital, Vicenza, Italy; [e]Department of Medicine, University of Padua, Padua, Italy

Keywords
Renal replacement therapy · Flow distribution · Adsorption · Blood purification · Haemoperfusion

Abstract
Background: Recent innovations in biomaterials technology have led to the development of innovative sorbents adopted as adsorbing devices in the field of extracorporeal blood purification therapies. As removal mechanism, adsorption allows to remove specific molecules, selectively binding them to sorbent materials. In addition to the material properties, a quintessential aspect influencing device properties is blood flow distribution within the sorbent particles. ***Objectives:*** In order to adequately characterize the potential adsorbing properties for an effective blood purification therapy, an in vitro study assessing the fluid dynamics inside 3 new cartridges, HA130, HA230 and HA330 (Jafron, Zhuhai City, China) was conducted through CT imaging technique. ***Methods:*** The cartridges were placed in vertical position in the CT gantry. Dye solution was circulated through the cartridges at 250 mL/min, longitudinal sections, 0.5 cm thick, were recorded for 60 s. Furthermore, an in vitro test was conducted to build pressure drop profiles. Blood was circulated at a different flow rate, 100–400 mL/min, step 50 mL/min. Pre and post cartridges pressures were acquired and pressure drop calculated. ***Results:*** Sequential images demonstrated an excellent distribution of the flow inside the cartridges. Average flow velocity was 0.37 cm/s for the 3 cartridges. HA130 had a homogeneous flow profile along the entire length of the device; HA230 and HA330 showed minimal differences between central and peripheral regions. Pressure drop profiles resulted linear, increasing proportionally with blood flow rate and packing density. ***Conclusions:*** We may conclude that the structural and functional design of the studied cartridges is adequate for haemoperfusion with no channelling phenomena. This ensures maximum and optimal utilization of the sorbent contained in the devices.

KARGER

E-Mail karger@karger.com
www.karger.com/bpu

Anna Lorenzin, Eng
Department of Nephrology, Dialysis and Transplantation
St. Bortolo Hospital
Viale Ferdinando Rodolfi, 37, IT–36100 Vicenza (Italy)
E-Mail lorenzin.anna@gmail.com

Introduction

To date, extracorporeal blood purification therapies are adopted not only for kidney support but also for other dysfunctioning organs, such as liver, lungs, septic blood, embracing a wide range of applications [1, 2]. These therapies reflect the need to remove specific toxins and solutes that are produced and accumulate in blood as a consequence of impairment. Such molecules can differ in several features as dimension, shape, hydrophilicity, electrical charges and protein binding [3]. Conventional treatments achieve blood purification relying on dialysis membranes: the main mechanisms by which solutes are removed are diffusion and convection. Diffusion maximizes the clearance of smaller molecules leveraging a concentration gradient while convection, driven by pressure gradient, is applied for middle/large molecules removal. While removal of small molecules (0–500 Da) is maximized by diffusive mechanism, a technological compromise has to be achieved in terms of membrane permeability and pore size distribution, in order to guarantee, at the same time, a satisfactory convective removal of larger solutes and a low albumin loss, keeping it at the minimum.

The rise of the new concept of precision medicine resulted in the demand of having an increasingly more specific and personalized therapy [4]. In this contest, the innovation in biomaterials technology led to the development of new sorbents whose purifying mechanism is adsorption [5, 6]. Adsorption allows removing specific molecules, binding them to the sorbents materials, selectively.

In the past, this removal mechanism was applied to treat intoxication; more recently, it has been extended to the management of uremic symptoms in chronic dialysis patients, management of sepsis and inflammatory states, in haemoperfusion configuration or combined with renal replacement therapies. Adsorption implies the direct contact of blood or plasma with sorbent material; hence, it is quintessential to ensure biocompatibility of the device and to avoid side effects such as thrombocytopenia, leucopenia and clotting.

Thanks to improvements in technology, nowadays there are several cartridge specimens available in the market [5, 7]. They differ in terms of chemical (material, layers structure), physical (surface roughness) and geometric (surface area to volume ratio, size distribution) characteristics, consequently affecting the performances. An ideal sorbent device should be designed in order to guarantee favourable kinetics and transport properties for rapid sorption of target solutes, chemical and thermal stability and mechanical strength to prevent crushing and wear, as well as high resistance to fouling, to maintain long adsorbing efficiency.

In addition to the material properties, another aspect to be reckoned with is the accuracy of the sorbent design and the flow distribution within the sorbent particles. In order to adequately exploit the adsorbing characteristics of sorbent in all its extent and to perform an effective blood purification therapy, it is important to ensure that blood flow is equally distributed within the packed sorbent particles. Inlet port has to determine minimal blood stagnation and should be designed in a way to guarantee homogeneous distribution and no dead space or irregularities. Channelling phenomenon should also be considered, since it may affect the quantity of solute adsorbed and consequently, the saturation of the sorbent; local blood flow discontinuation can lead to higher risk of clotting in the region in which velocity is lower than expected. Sorbent material in the housing must guarantee an easy blood filling and not induce high resistance to blood flow.

Since these phenomena can dramatically affect the efficiency of the overall extracorporeal treatment, a preliminary fluid dynamics/haemodynamics analysis should be adequately conducted to deeply characterize the adsorbing device. The evaluation of average and local velocity, velocity gradient, variations between central and peripheral regions, shear rate, pressure drop would provide an insight into the accuracy of the delivered therapy with such devices.

In literature, some attempts were done to estimate these characteristics for dialysis filters with semipermeable membranes, but no studies have been conducted for adsorbing devices except for one [8, 9]. In order to not disrupt fluid dynamics, blood flow distribution was assessed indirectly, taking advantage of the CT imaging technique [10, 11].

One of the new adsorbing materials specifically designed for blood purification is the resin of HA cartridges from Jafron [12]: these devices contain neutro-macroporus adsorbing beads and differ in size and clinical indications. A recent study published by our group has demonstrated their biocompatibility in terms of cytotoxicity [13].

The purpose of the present study was to assess fluid dynamics inside these cartridges through the CT imaging technique.

Methods

The study was performed on HA130, HA230 and HA330 cartridges (Jafron, Zhuhai City, China).

Table 1. Technical specifications of HA cartridges

	Styrene divinylbenzene copolymer		
	HA130	HA230	HA330
Beads material			
Resin loading capacity, mL	130	230	330
Priming volume, mL	110	145	170
Packing density	0.54	0.61	0.66

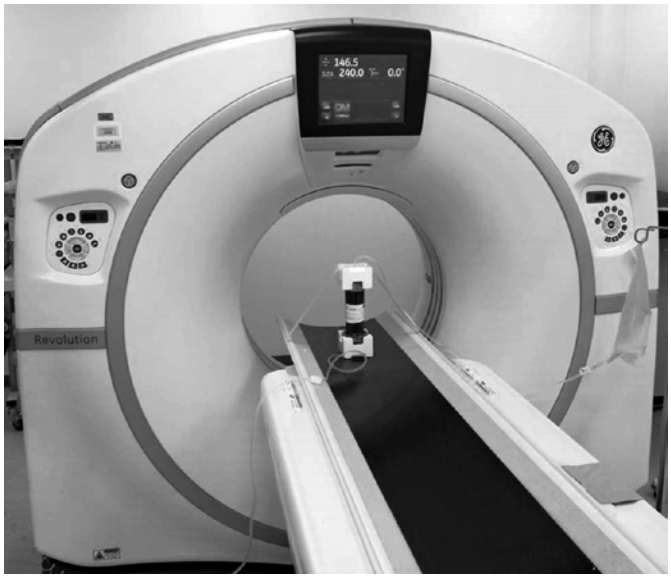


Fig. 1. Experimental set-up for CT imaging acquisition. The cartridge was held in vertical position by a support and placed in the middle of the gantry. Flow is direct from the bottom to the top.

All the cartridges contain neutron-macroporous resin adsorbing beads made of styrene-divinylbenzene copolymer but differ in geometrical characteristics (Table 1), such as cartridge dimension and pore size, according to their clinical indication. They have the ability to remove by adsorption endogenous and exogenous materials, for instance, protein bound and middle uremic toxins, hydrophobic exogenous substances, cytokines, complements, free haemoglobin and residual drugs.

HA130 is indicated for chronic patients, has a pore size distribution from 500 Da to 40 kDa with a main removed molecular range of 5–30 kDa. HA230 is applied for intoxication, its pore size distribution ranges between 200 Da and 10 kDa and has a removal molecular range of 0.5–10 kDa. HA330 is for acute inflammatory conditions, has a pore distribution from 500 Da to 10 kDa and removes molecules in the range of 10–60 kDa.

Blood flow distribution in the 3 cartridges was analyzed using a TC imaging technique.

Inlet and outlet lines were connected to the cartridges ports and then primed with saline solution. Sequential imaging was obtained with a last generation helical CT scanner (Revolution EVO 3.6, GE Medical System, Milwaukee, WI, USA), in radiology unit. The cartridge was held in a vertical position by a support inside the gantry and a longitudinal section of the device was planned (Fig. 1). A 5 mm thick longitudinal layer was analyzed with a specific software featuring 1 scan/s.

Two hundred millilitre of solution made of contrast medium (Visipaque 270 mg/mL, GE Healthcare, Milano, Italy) and saline solution, dilution 1:5, were prepared. A dedicated syringe pump (Medrad Stellant CT Injection System, Bayer HealthCare, Whippany, NJ, USA) was adopted to achieve the solution flow of 250 mL/min. The imaging scan started at the same time of the dye injection and lasted 60 s to guarantee the total filling of the cartridges. The imaging analysis was completed by the graphic reconstruction of the dye distribution pattern inside the cartridges. The central slice was selected and then analyzed over the duration of acquisition. CT images were allowed to assess the homogeneity of the dye distribution and its progression profile inside the cartridges. The density profile was generated by the dye distribution. The regional velocity was calculated as ratio of the distance between 2 different ROIs over the time required to reach the same relative increase in density.

A second in vitro experiment was performed in order to better haemodynamically characterize the cartridges. In particular, pressure drop profiles at different blood flows were built for each cartridge. The test was carried out with a dedicated testing platform for extracorporeal therapy (GALILEO) equipped with pumps and sensors. A customized circuit was assembled, composed of an inlet line with a pump segment and an outlet line, connected to inlet and outlet ports of the cartridge respectively. The connections to pressure sensors were placed close to inlet and outlet ports (Fig. 2). Five hundred millilitre of blood obtained from human healthy donors (Hct = 37%) maintained at 37 °C was circulated. A peristaltic pump was set to get a blood flow rate ranging from 100 to 400 mL/min, step of 50 mL/min. Pre and post cartridges pressures were recorded for each set blood flow rate and pressure drops were calculated accordingly.

Results

Figure 3 shows the dye entering the 3 cartridges, from the bottom to the top and then progressing through their length. The 3 images on the left refer to HA130, to HA230 in the centre and to HA330 on the right. The change in colour corresponds to the dye progression inside the devices. Dye flow rate was set at 250 mL/min for all the experiments, the complete filling of the cartridges was reached after 27s, 38s and 51s for HA130, HA230 and HA330 respectively (Fig. 4). Small black spots at inlet and outlet ports represent air bubbles inside cartridges.

The average calculated flow velocity was 0.37 cm/s for all the 3 cartridges; however, in the proximal part, the fluid progression was lower than that in the distal one (Fig. 5).

In Figure 3, dye distribution patterns are shown. The inlet port led to an irregular flow profile in the very prox-

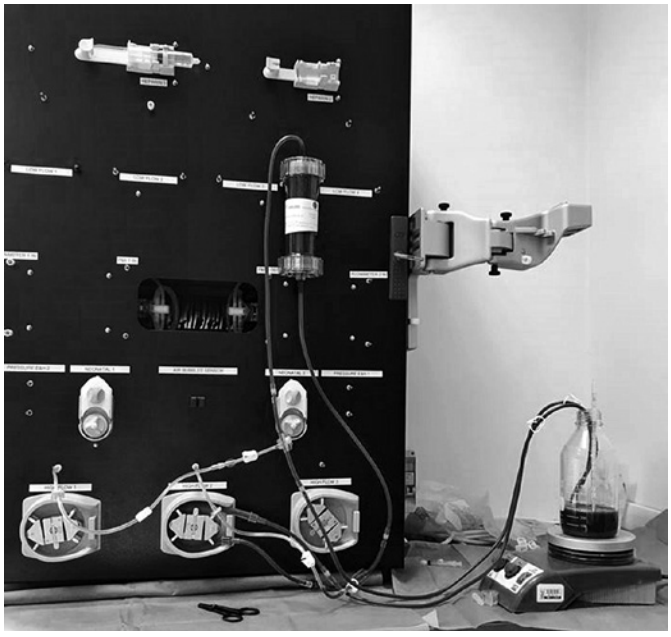


Fig. 2. Experimental set-up of the dedicated testing platform, GALILEO machine, used to acquire pressure pre and post cartridges at different blood flow rates.

imal part (images at the bottom) for all the devices; however, the progression along the longitudinal direction is different among them. HA130 had a homogenous progression profile along all the length of the device. HA230 and HA330 showed different behaviour, radially, from centre to edge (Fig. 5): higher velocity profiles were observed in the central region and in peripheral regions of the cartridges, while in the middle regions velocity was lower (Table 2). In particular, for HA230, velocity varied from 0.36 cm/s in the centre to 0.35 cm/s in the middle region and 0.43 cm/s in the periphery; for HA330 0.37, 0.35, and 0.40 cm/s respectively (Table 2).

In Figure 6, pressure drop profiles of the cartridges are reported. The trend of the pressure drops are linear, they increase increasing blood flow. At lower blood flow rates (100, 150 mL/min) the 3 cartridges had approximately similar behaviour. From 200 to 400 mL/min, the different size of the considered devices influenced the resistance to blood flow: although trends are still linear, the bigger the cartridge, the higher the pressure drop; for 50 mL/min of blood flow increasing step, the increase in pressure drop resulted, on average, 5 mm Hg, 8 mm Hg, 13 mm Hg for HA130, HA230 and HA330 respectively. The maximum pressure drops, reached at 400 mL/min, were 61 mm Hg for HA130, 80 mm Hg for HA230 and 104 mm Hg for HA330.

Discussion/Conclusion

Recently, the development in technology has favoured the launch of new sorbent cartridges and their wider applications. These devices can be applied both alone (haemoperfusion) and in combination with other purification techniques and are capable of removing specific target molecules, binding them selectively.

To deliver an effective adsorbing therapy, the applied cartridge should have a reliable sorbent material, an appropriate design and homogeneous blood flow distribution.

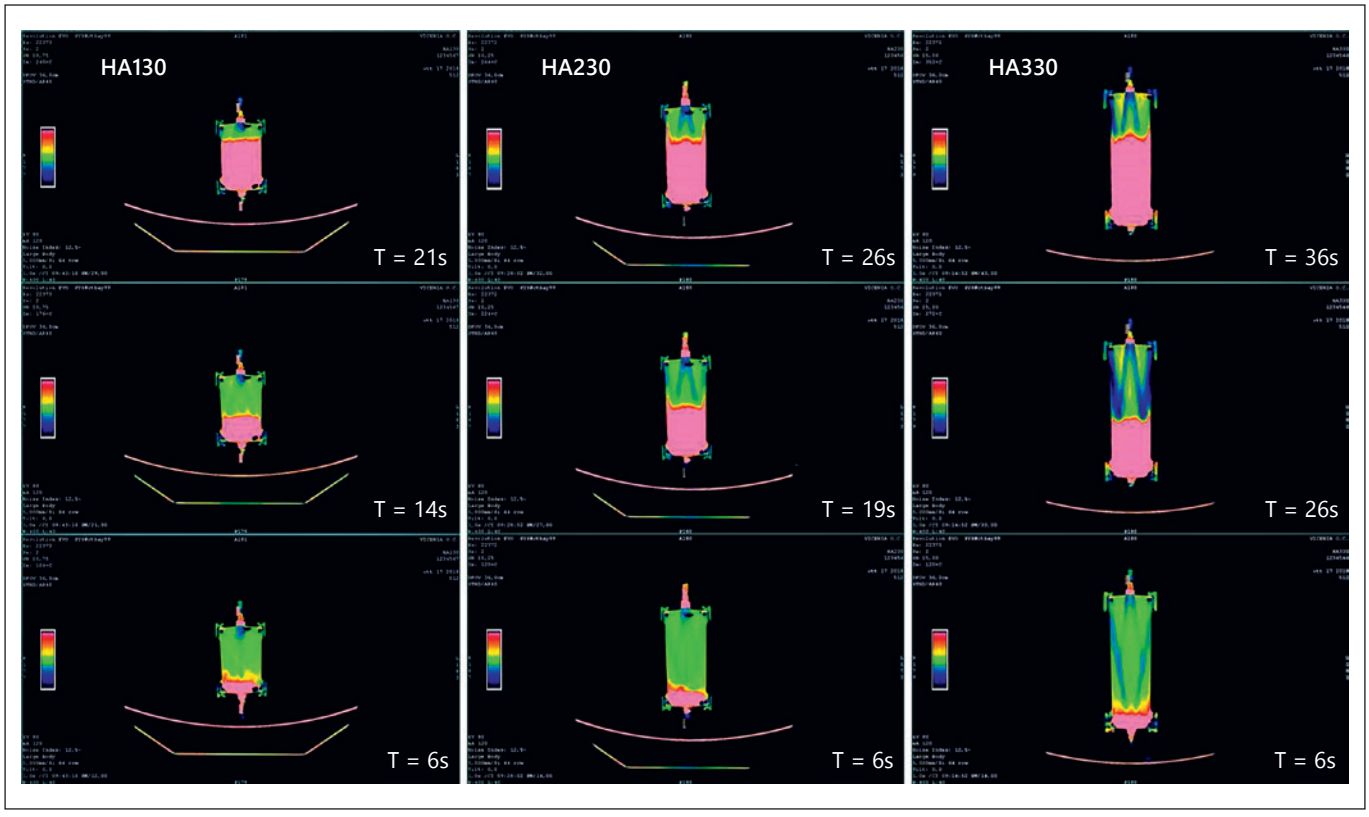
The new line of cartridges, HA relies its adsorbing capacity on neutron-macroporous beads made of styrene-divinylbenzene. A previous study carried out by our research group has demonstrated the biocompatibility, in terms of cytotoxicity, of the housing and the beads material [13]. HA cartridges are among the widely studied and used in China: several trials have been conducted and confirmed their reliability in clinical application [14–16], as reported in a recent review [12].

The present study aimed at fluid dynamic characterizes HA cartridges. A homogeneous flow distribution inside the device is one of the key points to maximize adsorbing capacity. Dead space, channelling phenomena or irregularities can lead to a suboptimal quantity of adsorbed solutes, a higher risk of clotting and lack of saturation.

Darcy's law is the fundamental principle that describes the flow through packed beads and states that flow velocity is proportional to the pressure gradient and inversely proportional to the distance between the extremities considered and to beads packing density [8]. Consequently, for a specific set blood flow rate, 2 aspects have to be taken into account: length and packing density. Packing density is the ratio between the volume occupied by the beads and the total volume of the housing. As demonstrated by our in vitro experiment, pressure gradient and resistance to blood flow of the 3 cartridges increase proportionally with their packing density and length.

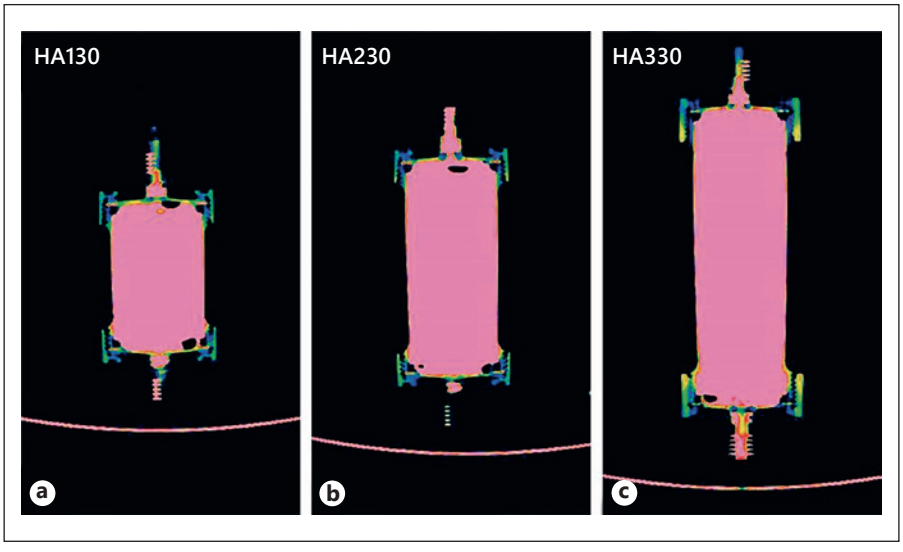
In order to adequately characterize the potential adsorbing characteristics for an effective blood purification therapy, we performed an in vitro study to assess the flow dynamics inside the 3 HA cartridges through CT imaging technique. In general, homogenous flow profiles in all the tested cartridges can be observed, demonstrating an almost full utilization of adsorbing bed. However, some aspects need to be pointed out and discussed.

First, even though the priming procedure was accurately performed, the case design did not allow a complete



Color version available online

Fig. 3. Flow distribution in the 3 cartridges – HA130, HA230, HA330. From the bottom to the top, the frames show the dye progression inside the devices.



Color version available online

Fig. 4. a–c Images of the 3 cartridges completely filled. Black spots in the extremities of the cartridges represent air bubbles inside the cartridges.

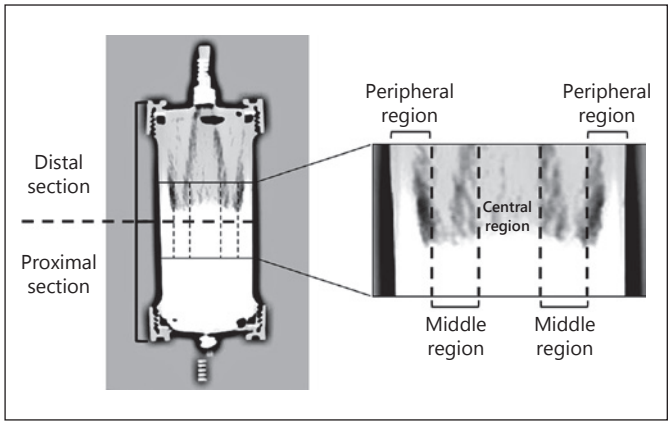


Fig. 5. Representative frame of progression profile in the distal section of cartridge HA230. Higher velocity profiles are observed in central and peripheral regions of the cartridge, while in the middle regions velocity is lower.

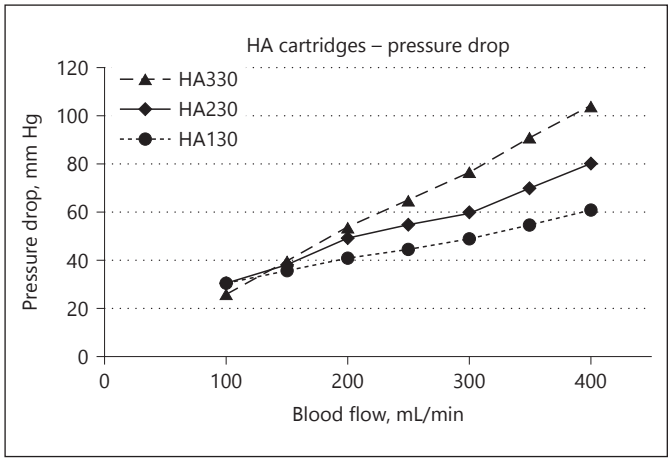


Fig. 6. Pressure drop of the 3 cartridges at different blood flow rates.

Table 2. Filling time, average and local velocities of the 3 cartridges

	HA130	HA230	HA330
Filling time, s	27	38	51
Average velocity, cm/s	0.37	0.37	0.37
Proximal velocity, cm/s	0.30	0.34	0.35
Distal velocity, cm/s	0.49	0.41	0.40
Central velocity, cm/s	0.37	0.36	0.37
Midsection velocity, cm/s	0.37	0.35	0.35
Peripheral velocity, cm/s	0.38	0.43	0.40

air elimination, probably due to the grids placed at inlet and outlet port to retain the beads inside the cartridge. This phenomenon is more evident in HA130 and HA230 (Fig. 4a b). A not good air removal during priming procedure may affect the efficiency of the therapy, as well as increase the risk of clotting inside the device. Second, although the average velocity is equal in all the 3 cartridges, different beads density gradients along the longitudinal direction of devices determined local velocity variations: in the proximal part, the fluid progression was lower than that in the distal one (Table 2), especially in HA130.

Third, HA230 and HA330 showed different local velocities, from centre to edge. In this condition, fluid dynamics can be characterized as follows: for these 2 cartridges, the central region has a higher perfusion pressure, which developed higher velocity; beads motion induced vortices in the middle regions and, consequently, lower velocity; the periphery was not affected by vortices and a lower beads concentration led to reaching the highest velocities. These vortices, although determining a small inhomogeneity in the velocity profile, may enhance the contact time between blood and beads, promoting the adsorption of toxins and molecules.

Extracorporeal devices for haemoperfusion have been rarely studied from the hydrodynamic and hydraulic points of view. In this study, a complete analysis is provided, thereby enabling us to conclude that utilization of the sorbent contained in the different cartridges is optimized. The study is corroborated by the absence of flow-through conditions for several hours after the beginning of the treatment. This is a proof of adequate structural design but also of optimized packaging of the sorbent. The low resistance and the plug flow condition in most of the experiments permit to confirm that utilization as a stand-alone as well as an additional device in series with a dialyzer is possible without problems in extracorporeal circuits. The high priming volume of the larger cartridge may represent a limitation in small size patients and may require a careful priming procedure with a pre-filled circuit.

Ethics Statement

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

References

1 Husain-Syed F, Ricci Z, Brodie D, Vincent JL, Ranieri VM, Slutsky AS, et al. Extracorporeal organ support (ECOS) in critical illness and acute kidney injury: from native to artificial organ crosstalk. Intensive Care Med. 2018 Sep;44(9):1447–59.

2 Ricci Z, Romagnoli S, Ronco C, La Manna G. From continuous renal replacement therapies to multiple organ support therapy. Contrib Nephrol. 2018;194:155–69.

3 Clark WR, Gao D, Neri M, Ronco C. Solute transport in hemodialysis: advances and limitations of current membrane technology. Contrib Nephrol. 2017;191:84–99.

4 Cerdá J, Villa G, Neri M, Ronco C. Technology in medicine: moving towards precision management of acute kidney injury. Contrib Nephrol. 2018;193:89–99.

5 Clark WR, Gao D, Lorenzin A, Ronco C. Membranes and Sorbents. Contrib Nephrol. 2018;194:70–9.

6 Clark WR, Ferrari F, La Manna G, Ronco C. Extracorporeal sorbent technologies: basic concepts and clinical application. Contrib Nephrol. 2017;190:43–57.

7 Ankawi G, Neri M, Zhang J, Breglia A, Ricci Z, Ronco C. Extracorporeal techniques for the treatment of critically ill patients with sepsis beyond conventional blood purification therapy: the promises and the pitfalls. Crit Care. 2018 Oct;22(1):262.

8 Ronco C, Ghezzi PM, Morris A, Rosales L, Wang E, Zhu F, et al. Blood flow distribution in sorbent beds: analysis of a new sorbent device for hemoperfusion. Int J Artif Organs. 2000 Feb;23(2):125–30.

9 Polaschegg HD, Ronco C, Soli M. Characterization of flow-dynamic pattern in a new sorbent cartridge for combined hemoperfusion-hemodialysis. Contrib Nephrol. 2001;133:154–65.

10 Ronco C, Ghezzi PM, Metry G, Spittle M, Brendolan A, Rodighiero M, et al. Effects of hematocrit and blood flow distribution on solute clearance in hollow-fiber hemodialyzers. Nephron. 2001 Nov;89(3):243–50.

11 Kim JC, Kim JH, Sung J, Kim HC, Kang E, Lee SH, et al. Effects of arterial port design on blood flow distribution in hemodialyzers. Blood Purif. 2009;28(3):260–7.

12 Ankawi G, Fan W, Pomarè Montin D, Lorenzin A, Neri M, Caprara C, et al. A new series of sorbent devices for multiple clinical purposes: current evidence and future directions. Blood Purif. 2019;47:94–100 .

13 Pomarè Montin D, Ankawi G, Lorenzin A, Neri M, Caprara C, Ronco C. Biocompatibility and cytotoxic evaluation of new sorbent cartridges for blood hemoperfusion. Blood Purif. 2018;46(3):187–95.

14 Li WH, Yin YM, Chen H, Wang XD, Yun H, Li H, et al. Curative effect of neutral macroporous resin hemoperfusion on treating hemodialysis patients with refractory uremic pruritus. Medicine 2017;96:e6160.

15 Dong H, Weng YB, Zhen GS, Li FJ, Jin AC, Liu J. Clinical emergency treatment of 68 critical patients with severe organophosphorus poisoning and prognosis analysis after rescue. Medicine (Baltimore). 2017 Jun;96(25):e7237.

16 Huang Z, Wang SR, Su W, Liu JY. Removal of humoral mediators and the effect on the survival of septic patients by hemoperfusion with neutral microporous resin column. Ther Apher Dial. 2010 Dec;14(6):596–602.