Blood Purification

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Effect of Mechanical Vibration on Kinetics of Solute Adsorption

Gonzalo Ramírez-Guerrero[a, b, c] Thiago Reis[a, d, e] Anna Lorenzin[a, f]
Matteo Marcello[a, f] Massimo de Cal[a, f] Monica Zanella[a, f] Claudio Ronco[a, f]

[a]International Renal Research Institute of Vicenza, Vicenza, Italy; [b]Nephrology and Dialysis Unit, Carlos Van Buren Hospital, Valparaíso, Chile; [c]Department of Medicine, Universidad de Valparaíso, Valparaíso, Chile; [d]Hospital Sírio-Libanês, Sao Paulo, Brazil; [e]Laboratory of Molecular Pharmacology, University of Brasília, Brasília, Brazil; [f]Department of Nephrology, Dialysis and Kidney Transplantation, San Bortolo Hospital, Vicenza, Italy

Keywords
Hemadsorption · Vibration · Blood purification · Cartridge · Solutes

Abstract
Introduction: Hemadsorption with new sorbent cartridges is an emerging extracorporeal blood purification technique. Flow distribution inside the sorbent is one of the main issues concerning the device's performance and optimal sorbent utilization. In this experiment, we aimed to investigate the efficacy of vibration during adsorption by measuring the removal of vancomycin. ***Methods:*** In this experimental study, 1,000 mL of saline with 10 g of vancomycin was circulated in a closed circuit (set flow of 250 mL/min) simulating a hemadsorption blood run using HA380 minimodule cartridge containing 75 g of wet resin. This vibration model was implemented with a damping head device installed in front of the adsorption cartridge during the experiment. The kinetics of the vancomycin were assessed by removal ratio over 120 min. ***Results:*** We found no difference between the two models. Adsorption with and without vibration did not differ significantly for partial reduction ratios, overall amount of adsorbed molecule, or adsorption kinetics. ***Conclusion:*** The current design and structure of the minimodule cartridge demonstrated no difference in small-middle solute removal. Further improvement with the addition of mechanical vibration to the device was not observed.
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Introduction

Hemadsorption (HA) with new sorbent cartridges is one of the emerging extracorporeal blood purification techniques. Enhanced cartridge design and improved biocompatibility of the sorbent material allow for safe and effective blood circulation through the sorbent bed. Flow distribution inside the sorbent cartridge is one of the main issues concerning the device's performance and optimal sorbent utilization [1, 2]. The structure and design of the sorbent cartridge is usually quite complex and its performance depends on several factors including packing density, inter-particle space and path tortuosity, length and diameter of the unit, and possible turbulence of the flow (Reynolds number). The resulting flow pattern is extremely complex and governed by physical laws such

Gonzalo Ramírez-Guerrero, Thiago Reis, and Claudio Ronco contributed equally to this work.

karger@karger.com
www.karger.com/bpu
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Correspondence to:
Claudio Ronco, cronco@goldnet.it

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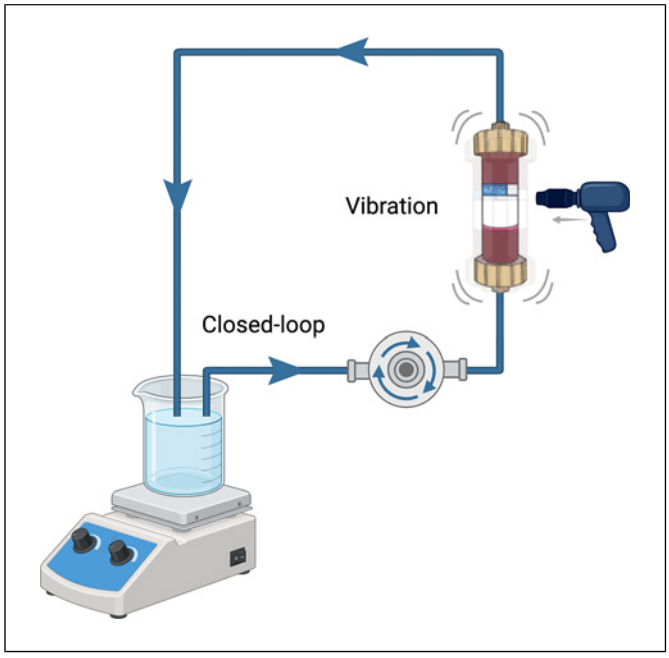

Fig. 1. In vitro experimental setup. A customized extracorporeal circuit with HA380 minimodule is applied to Galileo testing platform. The reservoir is positioned on a magnetic hotplate stirrer.

as the Darcy's law and the Carman-Kozeny equation [1, 2]. The packed beads can be approximated to a bundle of tortuous capillary tubes with some wide-diameter channels and gaps in between, where the local flow velocity is relatively low with a relative increase in blood viscosity and enhanced risk of coagulation [2]. At the same time, inhomogeneous distribution of sorbent beads inside the unit may result in the undesirable phenomenon of "channeling of the flow" that creates a preferential pathway of the fluid phase (blood) and may preclude complete utilization of the available sorbent surface [1, 2].

In modern sorbent cartridges, imaging studies have shown negligible local differences in flow velocity at various cross-sectional points of the cartridge due to optimal cartridge design and packing density [2]. Peripheral areas of the cartridge characterized by lower bead concentration tend to achieve slightly higher velocities. However, the difference with the bulk flow velocity at the central region of the unit is negligible [2].

Despite flow pattern optimization, further improvements could be theoretically achieved. For example, the application of vibration with different frequencies, amplitudes, and directions might result in beads motion-induced vortices with disruption of preferential flow pathways and channeling. In medical applications, enhanced shear stress induced by vibration can improve plasma exchange efficiency and the ultrafiltration rate in hemofiltration [2–5]. We hypothesized that the presence of these vibration vortices might enhance the contact between blood and beads, promoting a more efficient adsorption of toxins and molecules. The experiment aimed to explore this theory and make a preliminary analysis on the effects of mechanical vibration during HA.

Experimental Method

An in vitro model of HA to characterize adsorption kinetics with and without vibration of a marker solute was developed. Vancomycin was selected as a marker molecule for this study. The model involves recirculation through an adsorption cartridge a 1,000 mL thermostatic batch of saline solution (37°C) containing 10 g of vancomycin (Fig. 1). This concentration was used due to knowing the kinetics of this vancomycin concentration in a previous study by our group [6]. It was used as a marker molecule and not in a clinical dose. Adequate mixing was ensured by a magnetic hotplate stirrer. A dedicated testing platform (GALILEO) developed in our institute, equipped with flow and pressure sensors and pumps, was used to perform a closed-loop direct HA with a minimodule sorbent cartridge (25% of the regular size HA380 cartridge, Jafron, Zuhai, China) containing 75 g of wet neutro-meso/macroporous beads of styrene-divinylbenzene. Different cartridges with the same characteristics were used to perform the experiments with and without vibration. The pore size diameters of the beads are distributed in a wide range of dimensions, allowing the adsorption of solutes between 500 and 60,000 Da. Solute removal is achieved through ionic bonds, van der Waals forces, and hydrophobic bonds. The device was primed according to the instructions for use. Pump flow was set at 250 mL/min and the duration of the circulation was 120 min. The vibration model was implemented with a damping head device, with a speed setting at 1,800 percussion per minute, an amplitude of 10 mm, and a frequency of 30 Hz. The vibration device was installed in front of the adsorption cartridge, both in vertical position, targeting the middle segment of the cartridge as the contact area with the percussion head of the vibration device. The direction of flow in the cartridge minimodule was from the bottom to the top. Vancomycin was reconstituted according to the manufacturer´s recommendations and injected into the 1,000 mL saline batch prior to the experiment.

For each study point (0, 10, 30, 90, and 120 min), 3 mL of saline was drawn from the fluid batch container. Each sample was analyzed in triplicate. Vancomycin concentrations were measured using the QMS assay (Thermo Fisher Scientific, Waltham, MA, USA) using the ILab 650 platform (Instrumentation Laboratory, Werfen, Bedford, MA, USA). Removal rate equation was used to calculate the partial removal ratio (pRR) of vancomycin at each time point:

$$pRR_x\ (\%) = 100\ (C_0 - C_x) \,/\, C_0,$$

where C_0 is the concentration at baseline and C_x is the concentration at a defined time point.

Total removal ratio was calculated using the formula:

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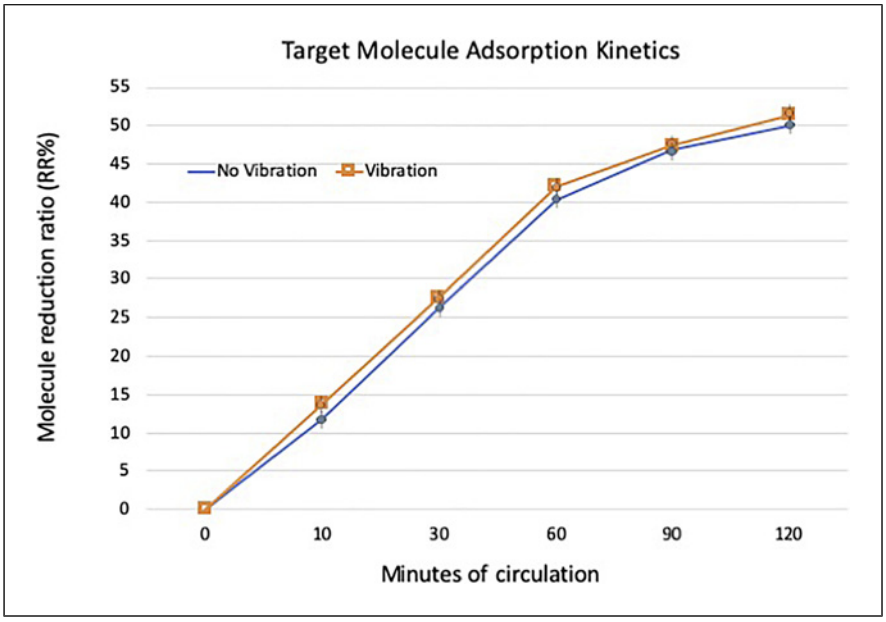

Fig. 2. Reduction ratio graph with and without vibration.

$$tRR\ (\%) = 100\ (C_0 - C_t) / C_0$$

where C_0 is the concentration at baseline and C_t is the concentration at the end of the experiment.

Two experimental models were carried out, both with 120 min of duration. The dose of vancomycin, volume of saline solution pump flow, and minimodule cartridge were the same. They only differed in the use of a vibration device. The results were compared between setups with and without vibration.

Statistical Analysis

The nonparametric Kruskal-Wallis H test was used to compare the results of each time point and different pickup points between the experiments with and without vibration. A p value <0.05 was considered for significant differences. All analyses were conducted using the SPSS 25 program.

Results

The experiments were carried out without advertising inconveniences. In vitro experiments confirm the affinity of beads material in binding vancomycin molecules. In all the adsorption simulations, the antibiotics have been adsorbed significantly.

The partial vancomycin reduction ratios (pRR) at the various time points are reported in Figure 2 for both conditions: vibration and no vibration mode. The pRR at different time points (10 min, 30 min, 60 min, 90 min, and 120 min) were vibration mode 13.8%, 27.6%, 42.1%, 47.4%, 51.4% and no vibration mode 11.7%, 26.3%, 40.3%, 46.9%, 50%, respectively.

In spite of a slight signal in favor of the vibration mode, adsorption kinetics was statistically not different between the two models (p = 0.153). The overall amount of vancomycin adsorbed at 120 min was 5.14 g with vibration and 5.01 g without vibration. In general, the two modalities did not differ significantly in terms of partial reduction ratios, overall amount of adsorbed molecule, or kinetics of adsorption (Fig. 2).

Discussion

In order to optimize the efficiency of extracorporeal therapies, some studies support the rationale for mechanical shaking of hemodialyzers to induce perturbation of flow patterns, thus enhancing mass transfer mechanisms and solute diffusion [7–9]. Furthermore, in hollow fiber hemodialyzers, mechanical vibration seems to increase solute convective transport by disrupting the protein layer at the blood-membrane interface and reducing the thickness of the secondary layer due to concentration polarization of proteins. The final effect is an enhanced diffusive and convective clearance due to increased membrane permeability and single fiber wall shear rate without significant negative effects on RBCs [7–9].

Transverse vibration induces a substantial amount of radial mixing in the fluid. It creates a swirling or spiraling motion in the fluid, represented by vorticity contours with the potential beneficial effects of increasing contact time [2, 10]. Given the observations carried out in hollow fiber

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hemodialyzers applying vibration during extracorporeal circulation, we have designed a similar model for HA with application of a transversal vibration to an adsorption cartridge. The aim of the present study was to analyze the adequacy of a sorbent cartridge design comparing in vitro the kinetics of adsorption of a target molecule in the presence or absence of mechanical vibration applied to the unit. In this case, we selected vancomycin as a marker molecule since previous experiments had been carried out to study adsorption kinetics of this molecule [6, 11]. The hypothesis was that adding mechanical vibration to the unit during a HA session of 120 min could increase both the instantaneous adsorption rate and overall adsorption of the marker molecule.

The hypothesis was not supported confirming previous findings of optimal flow distribution in the studied sorbent cartridge and the optimal packing density and unit design. The HA380 cartridge has a packing density of approximately 60%, preventing channeling of the flow and with a housing (cylinder) of 19 cm on its longitudinal axis and 6 cm in diameter. The adsorption process occurs throughout the entire cartridge due to its configuration [1, 2]. The two studied modalities did not differ significantly demonstrating that the addition of mechanical vibration is of no benefit. This study has limitations: (a) the analysis was carried out with saline and not whole blood. In case of experiments with blood, however, while potential benefits could be found due to disruption of stagnation and low-flow areas, a careful analysis of potential red cell damage should be planned. (b) The analysis was carried out on a single marker molecule and a wider spectrum of molecules should probably be evaluated. (c) The HA380 minimodule cartridge displays a randomly packed bed structure and the beads are free to move and relocate in the cylinder. (d) Finally, only one direction for the batch fluid flow and only one single vibration pattern were evaluated. Different frequencies, amplitudes, and directions of fluid flow and vibration through the sorbent should potentially be explored.

We may conclude that the current design and structure of the studied HA cartridge is adequate and flow pathway within the sorbet bed does not benefit from vibration. These results suggest that the structure and design of the cartridge during vancomycin removal is not optimized with vibration.

Statement of Ethics

An ethics statement was not required for this study type; no human or animal subjects or materials were used.

Conflict of Interest Statement

CR has received funding for lectures and been consultant or advisory board member for Asahi, Astute, B. Braun, Baxter, bioM´erieux, Bioporto, CytoSorbents, Estor, Fresenius Medical Care, General Electric (GE), Jafron, Medtronic, and Toray. TR has received funding for lectures and been consultant or advisory board member for AstraZeneca, B. Braun, Baxter, bioMérieux, Boehringer Ingelheim, Contatti Medical (CytoSorbents), Eurofarma, Fresenius Medical Care, Jafron, Lifepharma, and Nova Biomedical. None of the other authors declare any competing interests. The authors alone are responsible for the content and writing of this article.

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Author Contributions

Gonzalo Ramírez-Guerrero, Thiago Reis, Anna Lorenzin, and Claudio Ronco designed the work, Gonzalo Ramírez-Guerrero, Thiago Reis, Anna Lorenzin, Massimo de Cal, Matteo Marcello, Monica Zanella, and Claudio Ronco collected and analyzed the data, Gonzalo Ramírez-Guerrero, Thiago Reis, and Claudio Ronco drafted the work or substantively revised it, and all authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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