Letter to the Editor

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Extracorporeal Hemoperfusion as a Potential Therapeutic Option for Critical Accumulation of Rivaroxaban

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Because of its efficacy, ease of dosing, and safety, the direct oral anticoagulant rivaroxaban is increasingly applied in a number of indications, for example, prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation [1] and treatment of deep vein thrombosis and pulmonary embolism [2]. Median therapeutic peak plasma concentrations range from 46 to 270 μg/L, depending on the respective indication [3]. However, there are concerns regarding the accumulation of the drug in patients with impaired renal clearance or in case of overdosing, potentially leading to an increased risk of bleeding [4]. With its high degree of protein binding of 92–95% [3], rivaroxaban is regarded as non-dialyzable, as also suggested by results from a clinical study conducted by Dias et al. [5]. Since protein binding is regarded as not a limiting factor in hemoperfusion [6], the removal of rivaroxaban, as for example by commonly available coated charcoal cartridges, has been deemed possible, but experimental evidence is still lacking [7]. While Andexanet alfa may offer a promising approach to reverse the FXa inhibitor-mediated anticoagulation of rivaroxaban, it has not yet been approved [8]. In case of rivaroxaban-related major bleeding events or emergency interventions with a high bleeding risk, therefore, a fast and effective countermeasure is urgently needed.

Here, we present experimental work to remove rivaroxaban from the blood by means of hemoperfusion using an approved adsorption device (CytoSorb®; CytoSorbents Europe, Germany). Currently, CytoSorb is used mainly in patients with severe infections and sepsis (cytokine storm). We applied a model device containing 60 mL of the adsorbent polyvinylpyrrolidone-coated polystyrene-divinylbenzene copolymer in an in vitro recirculation system to remove high plasma concentrations of rivaroxaban (571 ± 20 μg/L) from citrate-anticoagulated human whole blood (1,000 mL, flow rate 40 mL/min) during 120 min of hemoperfusion (Fig. 1a). Molecules are captured on the internal pore surface of polystyrene-divinylbenzene by nonspecific hydrophobic interactions, whereby solutes with molecular weights equal to and larger than that of albumin, particularly clotting factors, are excluded from adsorption by adjustment of the pore size distribution [9].

Blood pH was monitored during the experiments using an ABL90 FLEX blood gas analyzer (Radiometer, Denmark) and adjusted to a range from 7.35 to 7.45 by administration of Tris buffer. Warming of the blood to 37 °C was conducted with an infrared blood warmer (Fluido; The Surgical Company, Germany). Rivaroxaban concentrations were determined photometrically using a chromogenic anti-factor Xa activity assay (BIOPHEN Heparin LRT; HYPHEN BioMed, France) and calibrators with rivaroxaban concentrations of 0, 276, and 497 ng/mL. Analyses were performed by the central laboratory of the University Medicine Rostock.

Within 1 hour of recirculation, 91.6% of the rivaroxaban was removed from the blood, resulting in a plasma concentration of 47.6 μg/L (Fig. 1b). The same recirculation system without a CytoSorb column showed only minor depletion and loss over a test period of 5 h. The final value is above the threshold of 30 μg/L for which direct oral anticoagulant antidote

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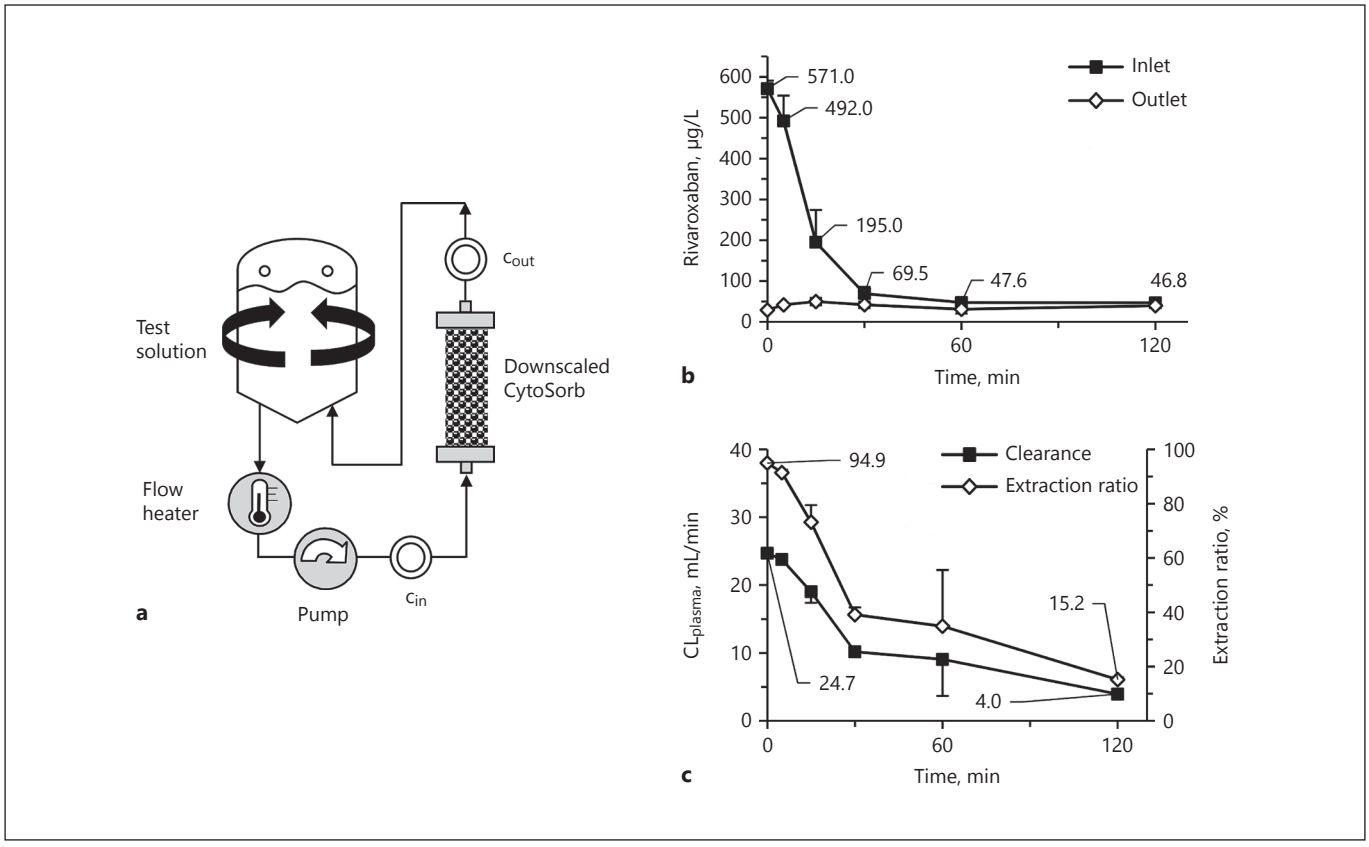

Fig. 1. a Schematic representation of the in vitro recirculation model. **b** Inlet/outlet rivaroxaban plasma concentrations, (**c**) extraction ratios $R_e = (c_{in} - c_{out})/c_{in}$ and plasma clearances $CL = Q_B \times (1 - Hct) \times R_e$ [7] during 120 min blood recirculation through the miniaturized CytoSorb columns (mean ± SD, $n = 2$). CL values were calculated considering the mean hematocrit calculated from the values measured at the start and the end of each experiment (0.349 ± 0.018, $n = 4$).

administration in patients requiring emergency interventions is recommended [8]. After 120 min of hemoperfusion, the CytoSorb was saturated as indicated by only minor changes in outlet concentration and the decreased plasma clearance and extraction ratio (Fig. 1c). Therefore, the application of a second CytoSorb after 60 min could be beneficial for a faster removal of such high accumulated plasma concentrations as applied in the present study. For normal therapeutic concentrations below 300 µg/L, however, we expect the rivaroxaban plasma concentration to be reduced below the critical threshold with a single adsorber in 30–60 min.

Considering the low volume of distribution of the drug and the terminal half-life of 0.62 L/kg and 5–13 h [3], respectively, the present results suggest that CytoSorb hemadsorption columns may offer a suitable means to rapidly reverse the anticoagulant effect of rivaroxaban in vivo. Additional testing is required to verify these findings in in vivo studies.

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Disclosure Statement

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