

Surface Modification using Polydopamine to adhere a novel anticoagulant Antithrombin-Heparin Complex to the surface of PDMS Oxygenators used as a Lung Assist Device for Neonates

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Introduction: Respiratory insufficiency is a major cause for mortality among preterm and term infants. The current clinical solution is to provide mechanical ventilation; however, this treatment can cause long term complications such as bronchopulmonary dysplasia and is not in all cases adequate to prevent death. Our research teams have developed a promising solution, providing supplementary blood oxygenation through the umbilical vessels using a miniaturized microfluidic oxygenator (Figure 1), thus allowing the lungs to heal and develop naturally [1]. The vascular network of the microfluidic oxygenator is casted on polydimethylsiloxane (PDMS). The concept provides an application in which blood circulates, driven solely by the infants heart, via the umbilical artery, through the microfluidic oxygenator, and returned to the body through the umbilical vein.

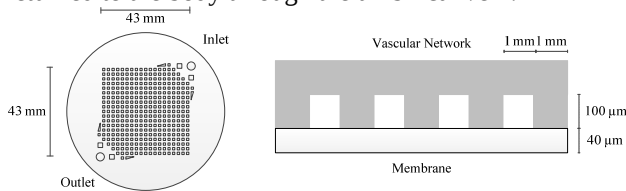


Figure 1: Schematic showing the dimensions of a single oxygenator unit.

A critical aspect of the project is the hemocompatibility of the blood contacting surfaces. Current extracorporeal membrane oxygenator devices require systemic anticoagulation with heparin; however, since preterm infants have a high risk for intraventricular hemorrhage, this approach is not feasible. The anticoagulation property must be built into the device. Our proposed approach is to coat blood contacting surfaces of the PDMS microfluidic oxygenator with a novel covalent antithrombin-heparin (ATH) complex [2] via an intermediate adhesive polydopamine (PDA) layer [3].

Objectives: (1) Quantification and Evaluation of ATH on PDMS-PDA. (2) Evaluation of the bioactivity of ATH on PDMS-PDA.

Methods: Oxygenators were incubated with a dopamine hydrochloride solution (1 mg/mL in PBS, pH 8.5), circulating for 24 hours in a closed circuit. Attachment of the ATH to the PDMS-PDA surfaces (PDMS-PDA-ATH) was carried out through incubation in ATH (0.1 mg/mL in PBS, pH 7.4) in a similar manner for 3 hours.

To determine the quantity of ATH bound to PDMS-PDA, ¹²⁵I-labeled ATH (0.1 mg/mL ATH, in PBS, pH 7.4, 5% labeled) was used for incubation. Using surfaces prepared with labeled ATH, the stability of the surface-attached ATH in blood contact was evaluated by exposure to reconstituted whole blood (erythrocyte concentrate mixed with fresh frozen plasma (FFP), hematocrit 0.5) over several days.

The anticoagulant activity of the ATH-modified oxygenators were evaluated by measuring the uptake of antithrombin (AT) from plasma. The heparin component of ATH, if active, should bind antithrombin selectively for acceleration of the inhibition of thrombin [2]. AT was radiolabeled with ¹²⁵I and added to plasma as a tracer. The oxygenators were incubated with labeled plasma for 3 hours and adsorption levels determined.

Results and Discussion:

Quantification and Evaluation of ATH on PDMS-PDA:

As shown in Table 1, 0.23 μg/cm² of ATH was bound to the PDMS-PDA oxygenator surfaces after 3 hours incubation. This level suggests that monolayers were formed. Subsequent exposure to reconstituted whole blood over a 48 hour period removed only about 35% indicating that the ATH is relatively stable on the PDMS-PDA surface.

Initial quantity bound	0.23
After 48 h blood contact	0.15

Table 1: Quantity (μg/cm²) of ATH bound to PDMS-PDA oxygenator surfaces before and after exposure to reconstituted whole blood.

Evaluation of bioactivity of ATH on PDMS-PDA:

As shown in Figure 2, the PDMS-PDA-ATH oxygenators bound significantly more AT from plasma than the precursor PDMS-PDA, thus demonstrating that the anticoagulant activity of the heparin component is conserved and the ATH remains active when attached through polydopamine.

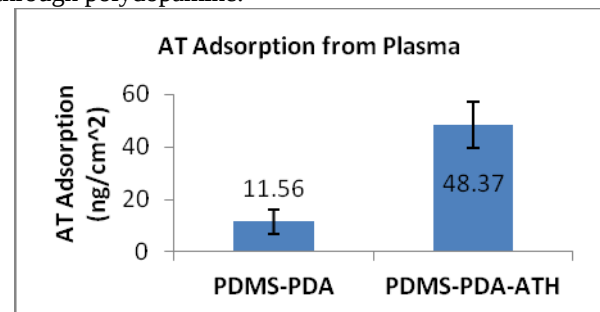


Figure 2: Comparison of bioactivity between PDMS-PDA and PDMS-PDA-ATH surfaces.

Conclusion: Polydopamine used as an adhesive agent (essentially a 'biogluue') to attach ATH to PDMS microfluidic oxygenators, provides high density, good stability in blood and anticoagulant activity from the bound ATH.

References: [1] Rochow, N., et al. Artificial Organs, 2013: 0391-3988 [2] Berry, L., Chan, A., Biomaterials Fabrication and Processing Handbook: 18, 535 [3] Lee, H., et al, Science, 2007: 318, 426