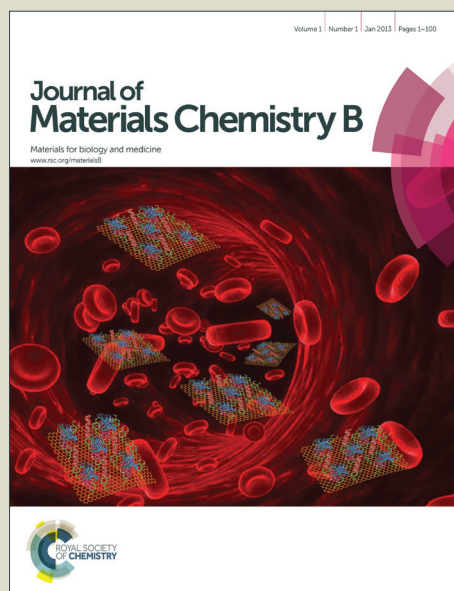


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ARTICLE

Surface modification of poly(dimethylsiloxane) with a covalent antithrombin-heparin complex for the prevention of thrombosis: use of polydopamine as bonding agent[†]

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A modified poly(dimethyl siloxane) (PDMS) material is under development for use in an extracorporeal microfluidic blood oxygenator designed as an artificial placenta to treat newborn infants suffering from severe respiratory insufficiency. To prevent thrombosis triggered by blood-material contact, an antithrombin-heparin (ATH) covalent complex was coated on PDMS surface using polydopamine (PDA) as a "bioglue". Experiments using radiolabelled ATH showed that the ATH coating on PDA-modified PDMS remained substantially intact after incubation in plasma, 2% SDS solution, or whole blood over a three day period. The anticoagulant activity of the ATH-modified surfaces was also demonstrated: in contact with plasma the ATH-coated PDMS was shown to bind antithrombin (AT) selectively from plasma and to inhibit clotting factor Xa. It is concluded that modification of PDMS with polydopamine and ATH shows promise as a means of improving the blood compatibility of PDMS and hence of the oxygenator device.

1. Introduction

Term and preterm infants may suffer from severe respiratory insufficiency due to various lung pathologies, requiring intense mechanical ventilation with its severe adverse effects [1]. Currently in our lab, a microfluidics-based membrane oxygenator is being developed as a lung assist device for such infants. The device is an extracorporeal membrane oxygenator that is perfused through the umbilical vessels by the infant's own heart and will provide supplementary respiratory support [2][3][4]. The oxygenator is fabricated with polydimethylsiloxane (PDMS) membranes which provide high gas permeability [5]. Oxygen transfer occurs across a thin, porous membrane as blood flows through a network of microchannels which provides a high surface-to-volume ratio to maximize gas transfer.

As blood from the neonate travels through the oxygenator and flows across the PDMS surfaces for gas exchange, blood-surface contact may initiate coagulation and thrombosis. Such thrombotic complications are life-threatening and the

formation of blood clots within the oxygenator may gradually reduce blood flow in the microchannels, thereby compromising gas transfer and eventually leading to device failure. Thrombotic complications are problematic generally in blood-contacting medical devices [6]. Systemic anticoagulants may be administered to prevent thrombosis in adults and older children, but in the case of neonates this practice may increase cerebral hemorrhagic risks such as germinal matrix hemorrhage [1].

The ultimate objective of this work is to improve the blood compatibility of our microfluidic oxygenator by coating the blood-contacting PDMS surfaces with an antithrombin-heparin (ATH) covalent complex, developed in our laboratory as an improved form of heparin [7,8]. Heparin itself has been studied extensively as a surface modifier for blood contacting materials as reviewed by Liu et al [6]. Indeed a number of heparinized materials have been developed commercially and are in clinical use, perhaps most notably the CBAS surface of Carmeda AB® developed from early work of Larm et al [9] in which heparin was bound covalently to the substrate via the chain ends. Compared to unmodified heparin, the complex of antithrombin and heparin (ATH) used in the present work has been shown to have higher activity, a longer half life in the circulation and to be able to inhibit clot-bound thrombin [7,8]. Ideally the ATH surface coating would reduce the formation of thrombus sufficiently that systemic anticoagulation would not be necessary, or could be used at a lower dosage to reduce the associated risk of hemorrhage.

A number of techniques for immobilizing ATH onto various materials have been developed previously [10-15]. These procedures are relatively complex, involving multiple steps that include chemical reactions and solvent treatments. For example ATH was bound covalently to polyurethane via a polyethylene oxide (PEO) linker [14] in a multistep process involving treatment with a

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diisocyanate, disuccinimidyl carbonate and several solvents. Similarly ATH was chemically attached to PDMS [15] also requiring exposure to chemical reagents and solvents. The geometry of the blood flow pathway (network) in our oxygenator is complex and it is therefore important to ensure that all of the blood contacting surface is coated. The network developed for our oxygenator consists of a grid of interconnected rectangular micro channels of channel cross section 1.0 x 0.1 mm as shown in Fig. 1. The gas transfer PDMS membrane (40 μm thickness) is pressure bonded to the main body of the grid; the surfaces to be bonded are pre-activated in an oxygen plasma. Flushing the grid with harsh solvents and chemicals, as required in the previous procedures for application of ATH, tends to cause separation of the PDMS membrane from the grid body. Moreover these procedures are complex and time-consuming. Modification of the coating process is therefore required. In the work reported here we have developed a simple coating method using polydopamine as a “bioglue” to bond ATH to PDMS. The PDMS is in the form of flat film and this may be seen as a simple test “device” used as a preliminary to the oxygenator itself.

A considerable body of recent work has shown that dopamine is easily bonded to polymers, ceramics and metals by simple coating methods [16,17]. Under slightly basic conditions the dopamine undergoes oxidative polymerization, resulting in a layer of polydopamine (PDA). In turn the PDA acts as a “bioglue” for the attachment of biomolecules containing thiol or amino groups [16,18]. Therefore it is expected that ATH can be attached to polydopamine by reaction with the ϵ -amino groups of lysine residues in the antithrombin moiety of the complex.

2. Materials and Methods

2.1 Materials

Sylgard® silicone elastomer kit used to prepare the PDMS film was purchased from Dow Corning (Midland, MI). Dopamine hydrochloride was purchased from Sigma Aldrich (Oakville, ON). ATH was prepared by incubating AT and heparin at 40°C for 14 days, followed by purification with (i) butyl-agarose to remove unreacted heparin, and with (ii) DEAE Sepharose to remove unreacted AT as described previously [7,8]. Na^{125}I was obtained from the McMaster Nuclear Reactor (Hamilton, ON). Iodogen iodination reagent was from Pierce Biotechnology (Rockford, IL). Stachrom® Heparin kit used to perform factor Xa inhibition assays was from Diagnostica Stago (Asnières sur Seine, France); this includes AT, factor Xa and chromogenic substrate CBS 31.39 used in the factor Xa assay. Heparin (sodium salt) from porcine intestinal mucosa was purchased from Sigma Aldrich (Oakville, ON). Human antithrombin was from Affinity Biologicals Inc. (Ancaster, ON). Platelet poor acid

citrate dextrose (ACD) pooled plasma was prepared from whole blood collected from multiple healthy donors, and was aliquoted and stored at -70°C. Human, outdated erythrocyte concentrate was from Transfusion Medicine, Hamilton Health Sciences (Hamilton, ON) and was combined with human plasma just before use; this fluid is referred to hereinafter as “blood”.

2.2 Surface preparation

PDMS films were prepared using the Sylgard® silicone elastomer kit by mixing the elastomer base with the curing reagent in a 10:1 ratio. The mixture was poured into a Petri dish, degassed for 30 min, and cured at room temperature for 2 days. The resulting film, of thickness about 0.5 mm, was cut into 6 mm diameter discs. PDMS discs were incubated in a 1 mg/mL dopamine solution in PBS (pH 8.5) at room temperature overnight. The discs were rinsed three times (5 min each time) in PBS (pH 7.4) to remove residual dopamine, and then incubated in a 0.1 mg/mL ATH solution for 3 h at room temperature [13]. Advancing water contact angles were determined by drop shape analysis (Krüss Drop Shape Analyzer - DSA100, KRÜSS, Hamburg, Germany).

2.3 Experiments with radiolabelled proteins

AT and ATH were radiolabelled with Na^{125}I using the Iodogen method [19]. 100 μg of protein and 5 μL of Na^{125}I were added to a vial coated with 10 μg of Iodogen iodination reagent and reacted for 15 min. The reaction mixture was transferred to a Slide-A-Lyzer® cassette and dialyzed overnight with three changes of PBS to remove unbound radioisotope. The free iodide content of the labelled AT and ATH preparations was less than 4%.

2.3.1 ATH uptake from buffer and subsequent loss in contact with plasma, SDS, and blood. To determine the quantity of ATH taken up on PDMS and PDMS-PDA, discs were incubated in 0.1 mg/mL solutions of ATH in PBS (10% radiolabelled, 90% unlabelled) for 2 h at room temperature and then rinsed three times (5 min each) with PBS to remove residual ATH. The quantity of ATH adsorbed was calculated from the radioactivity of the surfaces measured using a gamma counter.

To investigate the desorption of ATH under different conditions, surfaces were incubated either (i) in plasma overnight followed by 2% SDS for 2 h at room temperature, or (ii) in blood for 3 days at room temperature, with the blood being replaced every 24 h. After each incubation step, the surfaces were rinsed briefly with PBS before measuring surface radioactivity.

2.3.2 Antithrombin (AT) adsorption from plasma. Radiolabelled AT was added to the plasma at a concentration corresponding to 10% of the normal endogenous level. Surfaces were incubated in the plasma for 3 h, at room temperature, rinsed three times in PBS (5 min each time), and the radioactivity measured. From previous experience of protein adsorption kinetics we believe that 3 h is sufficient to reach the maximum possible quantity adsorbed under given conditions.

2.4 Anti-factor Xa assay

The anti-factor Xa activity associated with surfaces was used as a measure of the potential anticoagulant activity of the ATH surfaces. This assay was carried out using a 96-well micro-titre plate format at 37°C [20]. Each well contained one disc and 0.14 mL of AT

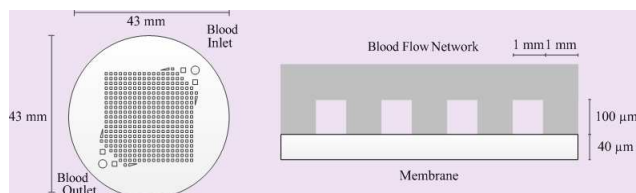


Fig. 1: Schematic of oxygenator unit.

solution (1 mg/mL). The discs were incubated in the AT solution for 10 min allowing the immobilized ATH to bind AT through the pentasaccharide sequence of the heparin moiety, forming an ATH-AT complex on the surface in which the AT is highly active for factor Xa inhibition; an excess of factor Xa solution (70 μ L, 3.5 mg/mL) was then added and incubation continued for a further 5 min to allow inhibition of factor Xa by ATH as a measure of the active heparin present. Aliquots of the solution (60 μ L) were transferred to adjacent wells containing 60 μ L of the factor Xa chromogenic substrate CBS 31.39. Absorbance of the solutions was measured at 405 nm to provide a measure of residual factor Xa which represents factor Xa that was not inactivated by ATH [21]. Using solutions of standard heparin of known concentration, a standard curve was constructed. Using the standard curve, the anti-factor Xa activity of the surfaces in terms of mass density of active heparin (ng/cm²) was estimated.

3. Results and Discussion

3.1 Contact angles

PDA surface modification of the PDMS was investigated using two dopamine concentrations and two incubation times. Water contact angle data are shown in Fig. 2. The angles for the polydopamine surfaces decreased with increasing incubation time and dopamine concentration. The angles for the ATH surfaces were less dependent on these variables and showed only slight differences from those for the corresponding PDA surfaces. Except for the surface prepared by incubating in 1 mg/mL dopamine for 3 h, the angles were in the range of 55 to 65° suggesting surfaces in the intermediate hydrophilicity/hydrophobicity category. Contact angles for polydopamine surfaces reported by others were in the range of 50 to 70° depending on the substrate [22,23]. Angles on ATH-modified polyurethane were similar to those for the ATH surfaces in Fig. 2 [24].

3.2 ATH uptake and desorption into plasma and SDS

To evaluate the effectiveness of polydopamine as an adhesive for bonding ATH to PDMS, unmodified PDMS and PDMS-PDA surfaces were compared for both ATH uptake and stability of ATH on the surface in contact with plasma and SDS. The surfaces were first incubated in labelled ATH solution and uptake was measured. As seen in Fig. 3, uptake on PDMS-PDA (0.25 μ g/cm²) was significantly

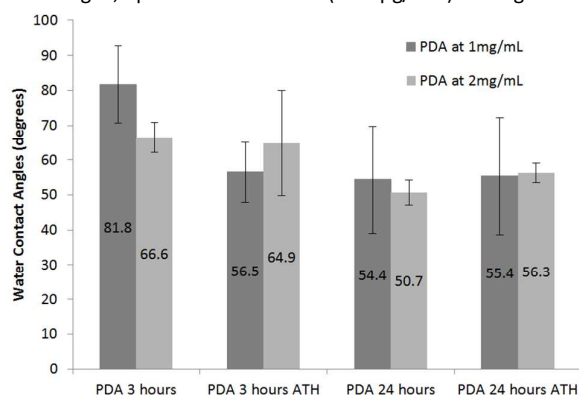


Fig. 2. Water contact angles (mean $\pm$ SD, n=4).

higher than on unmodified PDMS (0.17 μ g/cm²), showing that the PDA layer has a higher affinity than the unmodified PDMA for ATH. Indeed it seems likely that uptake on the PDA surface is in the vicinity of a monolayer given the expected dimensions of the ATH complex [12]. It should be noted that on previously developed ATH surfaces the density of ATH was similar to or less than on the PDMS-PDA surface. Thus on a polyurethane-PEO surface a density of 0.14 μ g/cm² was obtained [14] and on PDMS-PEO the density was 0.2 μ g/cm² [15].

Following ATH uptake, the surfaces were incubated in plasma and then in 2% SDS. Depending on the strength of the ATH-surface "bond", loss of ATH is expected due, respectively, to (i) desorption and exchange with proteins in plasma and (ii) displacement by SDS, a powerful protein eluent. As shown in Fig. 3, loss of ATH was greater on PDMS than on PDMS-PDA. On unmodified PDMS, 59% of the initially adsorbed ATH remained after plasma incubation, and only 6% after SDS treatment. On PDMS-PDA, 76% and 59% of the initially adsorbed ATH remained after plasma and SDS treatment, respectively. Thus, surface modification of PDMS with polydopamine clearly improved the stability of the ATH coating.

3.3 ATH desorption into blood

Since the oxygenator is required to provide respiratory support to preterm infants for several days, the ATH coating on the blood-contacting surfaces must remain stable on this time scale. To investigate this aspect, loss of ATH from coatings in contact with blood was measured at intervals over a 72 h period. As seen in Fig. 4, initial ATH uptake on the unmodified and polydopamine-modified surfaces was 0.17 μ g/cm² and 0.24 μ g/cm², respectively, similar to that seen in Fig. 3. Loss of ATH in contact with blood subsequently occurred mainly in the first 24 h. On unmodified PDMS, only 0.05 μ g/cm² of ATH, i.e. about 33%, remained after 24 h. Desorption continued slowly over the subsequent 48 h, and only 26% remained after 72 h incubation. The ATH coating on the polydopamine-modified surface was much more stable, with 0.18 μ g/cm², i.e. 75% of the initial load, remaining after 24 h, and 0.17 μ g/cm², i.e. 71% of the initial load, remaining after 72 h. Overall, the data in Fig. 4 show the effectiveness of polydopamine as a "bioglu" to modify the surface of PDMS, to increase the amount of initial ATH uptake and to improve the stability of the ATH coating in contact with blood.

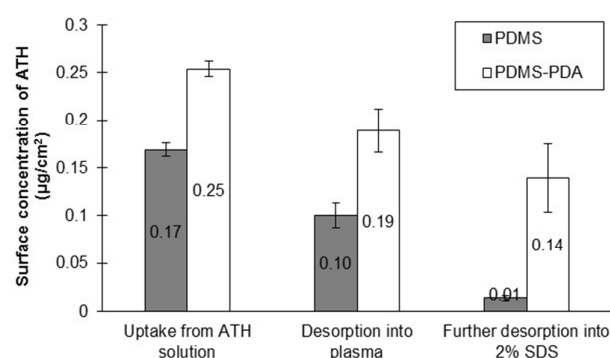


Fig. 3. Uptake of ATH from solution on unmodified and polydopamine-modified PDMS surfaces; desorption into plasma; desorption after further incubation in 2% SDS. Data are mean $\pm$ SD (n=6).

3.4 AT adsorption from plasma to ATH-coated PDMS

It is essential to show that ATH coated on PDMS via polydopamine remains bioactive or, more specifically, that it has anticoagulant activity and can inhibit activated coagulation factors such as thrombin and factor Xa. Heparin (and ATH via its heparin moiety) inhibits thrombin and factor Xa by binding and activating endogenous AT in plasma such that it accelerates inhibition of the clotting factors by a factor of about 1000 [25]. Therefore AT adsorption to the ATH surface is an essential preliminary step in the inhibition of thrombin and factor Xa, and can be used as an indirect measure of its anticoagulant activity [26].

To measure adsorption, AT was radiolabelled and added to plasma as a tracer, surfaces were incubated in the labelled plasma and surface radioactivity was measured. On unmodified PDMS, AT adsorption after 3 h was 4.0 ng/cm² (Fig. 5). This low value is not unexpected since the concentration of AT in plasma is relatively low at about 120 ng/mL [27] and represents a small fraction of the total protein (about 0.2%). On a “nonspecific” surface such as PDMS, AT will be in competition for surface sites with all the other proteins in the plasma. AT adsorption on PDMS-PDA was about 3.9 ng/cm², i.e. not significantly different from that on PDMS. Although polydopamine has generally high affinity for proteins, polydopamine modification of PDMS did not significantly increase AT adsorption from plasma. This is again likely because plasma has a high concentration of proteins of many different types which compete effectively when the surface is “nonspecific”. However,

when PDMS was modified with polydopamine and subsequently coated with ATH, AT adsorption was significantly higher at about 19.9 ng/cm², demonstrating the ability of the heparin component of the ATH to bind AT from plasma selectively and specifically, and suggesting that its anticoagulant activity is retained in the coating.

3.5 Anti-factor Xa assay

Anti-factor Xa activity was measured to investigate the anticoagulant activity of the modified surfaces directly (as opposed to indirectly using AT binding as just described). The chromogenic anti-factor Xa assay is commonly used to measure the activity of anticoagulants, including unfractionated heparin (UFH) and low molecular weight heparins (LMWH) [12,13]. Since ATH has been shown to inhibit factor Xa through its heparin moiety, this assay can be used to determine the anti-factor Xa activity of ATH in terms of quantity of active heparin [26]. The assay was designed originally for the analysis of anticoagulants in blood and plasma, i.e. in the fluid phase. We have adapted it for evaluation of anticoagulants immobilized on solid surfaces [13,20] as described above.

In these experiments, two surfaces were compared: PDMS-PDA-ATH and PDMS-PDA. The PDMS-PDA control showed anti-factor Xa activity of 0.52 ng/cm² (Table 1).

Table 1. Anti-factor Xa activity of PDMS-PDA and PDMS-PDA-ATH surfaces. Data are mean $\pm$ SD, n=8.

	Anti-factor Xa activity (mass of active heparin, ng)	Anti-factor Xa activity (surface density of active heparin, ng/cm ²)
PDMS-PDA	0.29 $\pm$ 0.05	0.52 $\pm$ 0.10
PDMS-PDA-ATH	1.20 $\pm$ 0.25	2.13 $\pm$ 0.44

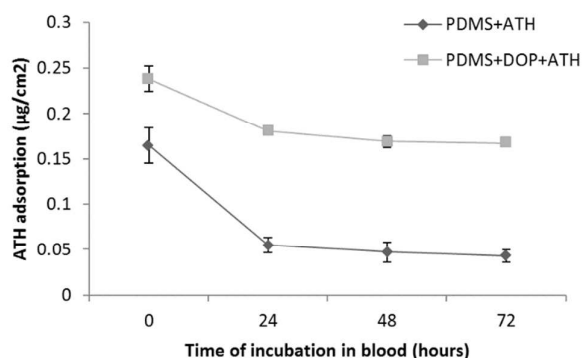


Fig. 4. Loss of ATH from unmodified and polydopamine-modified PDMS surfaces over 3 days of incubation in blood. Data are mean $\pm$ SD (n=6).

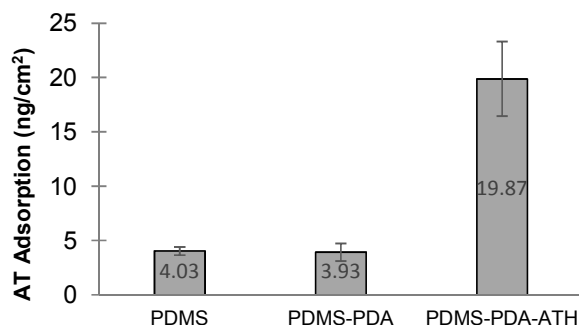


Fig. 5. AT adsorption from plasma to unmodified PDMS, polydopamine-modified PDMS, and polydopamine-modified PDMS coated with ATH. Adsorption time, 3 h. Data are mean $\pm$ SD (n=6).

Since there is no heparin on PDMS-PDA, this surface does not have the ability to bind anti-thrombin specifically and inhibit factor Xa. The apparent anti-factor Xa activity of this surface presumably reflects nonspecific adsorption and removal of factor Xa from the assay solution. It has been shown that PDA surface layers are strongly protein adsorbing so that non-specific adsorption is expected [28]. The anti-factor Xa activity associated with the PDMS-PDA-ATH surface was found to be equivalent to 2.13 ng heparin/cm², i.e. a factor of four greater than that of the precursor PDMS-PDA. This result shows that the immobilized ATH has the ability to inactivate factor Xa in the contacting fluid well beyond that of the corresponding surface without ATH, suggesting that the activity on this surface as measured by this assay is due mainly to the specific inhibition of factor Xa by the heparin moiety of the ATH.

Conclusions

An antithrombin-heparin complex was attached to PDMS using polydopamine as a “bio-glue”. In comparison to unmodified PDMS, PDMS-PDA showed greater ATH uptake and a more stable ATH coating. The PDMS-PDA-ATH surface showed selective adsorption of AT from plasma and inhibition of factor Xa in a contacting solution. PDMS-PDA-ATH was thus shown to be a stable surface with anticoagulant properties. Surface modification with PDA-ATH may therefore be seen as having potential for passivating the PDMS

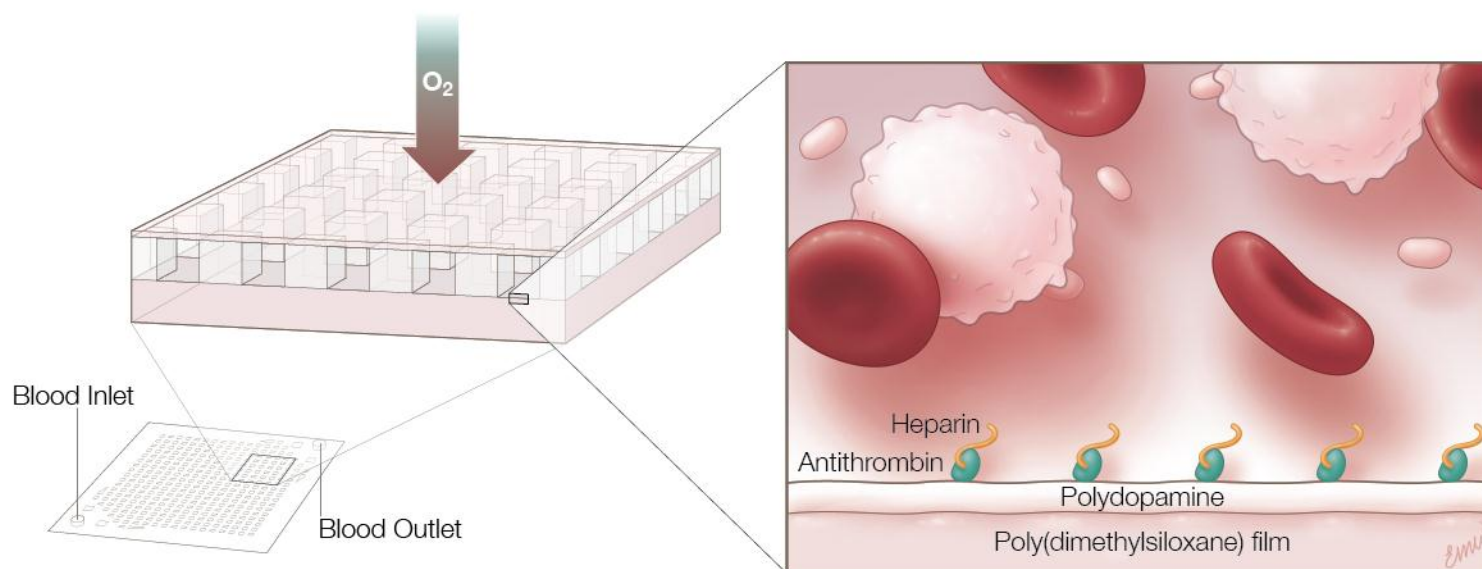
surfaces of blood contacting devices such as microfluidic membrane oxygenators.

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Poly(dimethylsiloxane) surface for blood oxygenator modified with anticoagulant antithrombin-heparin complex via polydopamine bonding.