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Synergistic effect of hydrophobic and anionic surface groups triggers blood coagulation in vitro

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Abstract Biomaterial induced coagulation encompasses plasmatic and cellular processes. The functional loss of biomedical devices possibly resulting from these thrombotic reactions motivates the need for a better understanding of processes occurring at blood–biomaterial interfaces. Well defined model surfaces providing specific chemical–physical properties (self assembled monolayers (SAMs)) displaying hydrophobic or/and acidic terminal groups were used to uncover initial mechanisms of biomaterial induced coagulation. We investigated the influence of electrical charge and wettability on platelet- and contact activation, the two main actors of blood coagulation, which are often considered as separate mechanisms in biomaterials research. Our results show a dependence of contact activation on acidic surface groups and a correlation of platelet adhesion to surface hydrophobicity. Clot formation resulting from the interplay of blood platelets and contact activation was only found on surfaces combining both acidic and hydrophobic surface groups but not on monolayers displaying extreme hydrophobic/acidic properties.

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1 Introduction

Despite the immense number of materials used in medicine as blood contacting devices, only few fundamental mechanisms of blood material interactions are elucidated by now. Biomedical devices that implement blood contacting materials include catheters, blood vessel grafts, vascular stents, various extracorporeal tubings, hemodialysis and oxygenator membranes among others. Resulting responses at blood biomaterial interfaces might induce blood coagulation leading to the impaired function of the device and additionally cause severe host reactions like embolism or infarction. Hemocompatibility tests used to study biomaterial induced coagulation are mainly based on analytical methods focusing either on cellular or plasmatic events but disregarding the complex interplay of blood components. As known, physicochemical properties of biomaterials determine the fate of blood components like proteins, enzymes and cells and are relevant for biological responses. The adsorption of plasma proteins is the first step of a complex biochemical cascade when blood interacts with foreign surfaces. Protein adsorption has been found to correlate to surface wettability: elevated protein adsorption to hydrophobic surfaces results from preferential hydrophobic interactions at the expense of less favourable protein–water interactions [1]. Besides the amount of adsorbed proteins the specific properties of individual proteins as well as their conformation influence subsequent cellular responses and thus the materials biocompatibility. The adhesion of blood platelets to biomaterial associated fibrinogen and to other proteins with cell-adhesive capacity is mainly mediated via receptors like GPIIb/IIIa that only become exposed after an adhesion related change of conformation [2].

The contribution of platelets to coagulation processes encompasses the release of mediators (platelet factor

4 (PF4), adenosine diphosphate (ADP), platelet derived growth factor (PDGF), von Willebrand factor (vWF), fibrinogen and coagulation factors) as well as the translocation of negatively-charged phospholipids to the platelet surface mediated by cellular flippases. These phospholipids provide a catalytic surface with the charge deriving from phosphatidylserine and phosphatidylethanolamine for the tenase as well as the prothrombinase complex of the plasmatic coagulation cascade.

Additionally to the above mentioned cellular reactions, material induced thrombotic responses further depend on humoral events. The intrinsic pathway of the coagulation cascade can be described as a cascade of zymogen activation processes starting with the adsorption of FXII to surfaces and finally leading to the activation of the key enzyme thrombin. According to the leading concept, thrombin formation on biomaterials is initiated through an auto-activation process of the clotting factor FXII to FXIIa on negatively charged surfaces [3]. These processes lead to the formation of a fibrin network allowing vessel wall repair in natural environment but leading to a functional impairment of medical devices if formed on material surfaces. To address these problems biomaterial induced initiation of coagulation processes were studied using self assembled monlayers as model surfaces. Due to their unique structural integrity combined with the unparalleled uniform surface chemistry they are especially successful in mimicking biosurfaces. Moreover, the ease of control over surface chemistry, polarity and charge enables the evaluation of the influence of specific surface-property on biological reactions. Previous studies using SAM surface chemistry reported on plasma protein adsorption [4–7] as well as cell–surface interactions (leukocyte [8, 9], platelet adhesion [10, 11]). By choosing a very hydrophobic (100% $–CH_3$) and an acidic, negatively charged surface (100% –COOH) we investigated the pro-coagulant effect of extreme material properties compared to a binary surface that displays both characteristics, differing thus from the extremes (83% –COOH).

2 Materials and methods

2.1 Sample preparation and surface characterisation using physico-chemical methods

Self assembled monolayers (SAMs) of mercaptoundecanoic-acid and undecanethiol, as well as binary mixtures of these were prepared as described previously [12]. Briefly, 11-mercaptoundecanoic-acid ($HS–(CH_2)_{10}–COOH$) and undecanethiol ($HS–(CH_2)_{10}–CH_3$) were obtained from Sigma-Aldrich (Deisenhofen, Germany) and used as received. Single component SAMs named 0% COOH (100% $C_{10}–CH_3$) and 100% COOH (100% $C_{10}–COOH$), as well as a binary layer with a $C_{10}–COOH/C_{10}–CH_3$-ratio of 83/17 (83% COOH) were prepared. SAMs with a $C_{10}–COOH/C_{10}–CH_3$-ratio of 50/50 (50% COOH) were also tested, but results were more prominent on 83% COOH so data related to the latter surface is presented here. Surface analysis by advancing water contact angle, infrared reflection adsorption spectroscopy spectra (IRRAS FTIR) and by X-ray-photoelectron spectroscopy (XPS) was performed for all SAMs. Characterization details are published elsewhere [12].

2.2 Quartz crystal microbalance (QCM) measurement of fibrinogen adsorption

Protein adsorption to a SAM modified crystal (QSX301) was performed using the QCM-D model 300 (Q sense) at constant 37°C under non-flow conditions. Quartz crystals with a natural frequency of 5 MHz were precleaned with a mixture of hydrogen peroxide, ammonium hydroxide and water (1/1/5) at 70°C for 10 min before SAM formation. The crystal was stabilized in HEPES buffer (0.02 M HEPES, 0.15 M NaCl, 1 mM CaCl2, pH 7.4) to achieve a stable baseline and was subsequently incubated with a fibrinogen solution (human fibrinogen (fraction 1) Sigma-Aldrich, Deisenhofen, Germany) of 1 mg/ml in HEPES for 20 min followed by three rinsing steps. Frequency and dissipation shifts induced by adsorbed proteins were monitored in real time at 15, 25 and 35 MHz. Data acquisition of frequency and dissipation changes utilized the QSOFT software, raw data were further analyzed by the QTOOLS software. Layer thickness of adsorbed protein was calculated by Sauerbrey equation assuming a protein density of 1,000 kg/cm^3 as proposed by Rodahl et al. [13].

2.3 Surface characterisation following blood plasma or whole blood incubation

Blood was obtained from healthy donors who did not take medication during the previous 10 days. Either whole blood or platelet rich plasma (PRP) was used for the experiments detailed in Sects. 2.3 and 2.4. This study was approved by the Ethics Committee of the Dresden University Hospital, Dresden, Germany. Informed consent was obtained from the donors prior to blood donation.

2.3.1 Contact activation (FXIIa and kallikrein) in plasma

FXIIa and kallikrein activity was assayed after incubation of the samples (2 cm^2) for 1 min with 300 µl of citrated plasma using a chromogenic substrate (S 2302™; Chromogenix, Lexington, MA). For more details see [12].

2.3.2 Adhesion of platelets to SAM surfaces

The detection of platelet adhesion on surfaces based on the lactate dehydrogenase (LDH) method [14]. Briefly 300 µl PRP was incubated (45 min, 37°C) on surfaces (2 cm^2). The adherent platelets were washed with PBS and subsequently lysed with 100 µl Triton-X (1%). The LDH activity in the lysate was determined photometrically [15] and is proportional to the number of platelets. Standards were obtained from lysates of defined numbers of platelets.

2.4 In vitro blood incubation

Whole blood incubation was performed as described previously [16]. Shortly: fresh, heparinized (1.7 IU/ml, Sigma-Aldrich, Deisenhofen, Germany) whole human blood was incubated in customized incubation chambers under non-flowing conditions. 6.3 cm^2 sample surface were incubated with 1.95 ml blood for 2 h at 37°C excluding air contact. Results were obtained in two separate experiments with a triplicate set of samples. For knockout and mimicking studies whole blood was pre-incubated with either corn trypsin inhibitor (CTI, 160 µg/ml blood; CellSystems Biotechnologie Vertrieb GmbH, St. Katharinen, Germany) or phospholipids (PL, 100 µl/ml blood; Technothrombin TGA reagent RA, Technoclone GmbH, Austria, Vienna) just before surface incubation.

2.4.1 Blood and plasma analysis

Commercial enzyme-linked immunosorbent assays (ELISAs) were used to characterize blood reactions including coagulation activation (thrombin-antithrombin-complex (TAT), Enzygnost TAT micro, Dade Behring, Marburg, Germany) and platelet activation (platelet factor 4 (PF4), Haemochrom, South Bend, Il). Blood samples taken before or after incubation were mixed with specific stabilizers (TAT and PF4: CTAD (Citrat, Theophyllin, Adenosin, Dipyridamol; Becton–Dickinson, San Jose, CA) for each assay. Plasma was frozen and stored at −70°C until analysis.

2.4.2 Sample surface analysis

After blood incubation, sample surfaces were prepared either for fluorescence or electron microscopy. Fluorescence microscopy was used to determine the number of adherent leukocytes and thrombocytes. Supplementary to the DAPI-staining of cell nuclei described previously [17], blood platelets were stained with FITC-conjugated anti-CD41a (Becton–Dickinson) overnight at 4°C. Surfaces were analysed on a fluorescent microscope (Leica, DMIRE2). Sample preparation for SEM analysis has been described elsewhere [10].

3 Statistics

Statistical evaluation was performed by one-way ANOVA and a subsequent pair-wise multiple comparison procedure according to Tukey Test. Results were regarded as significantly different if $P \leq 0.05$.

4 Results

4.1 Protein adsorption

The adsorption of fibrinogen after surface incubation with fibrinogen solution was determined by QCM analysis of the adsorbed protein layer thickness (Fig. 1). Fibrinogen adsorption after surface incubation with single protein solution was significantly higher on 100% $–CH_3$ (13 nm ± 0.7) than on 100% –COOH (10.9 nm ± 1.3) ($P < 0.5$).

Platelet adhesion evaluated by measuring the level of platelet derived lactate dehydrogenase after surface incubation with PRP correlated well to surface hydrophobicity, following thus the same trend as fibrinogen adsorption. The most hydrophobic surface (100% $–CH_3$) showed a significantly higher coverage (8.4×10^5 platelets/cm^2) than all other tested surfaces ($P < 0.5$), whereas the cell surface density dropped with increasing COOH ratios and on 100% –COOH no platelets adhered (0 platelets/cm^2; value below detection limit) (Fig. 2).

The activation of the *contact system* in plasma correlated with the amount of negatively charged surface groups as postulated by others [3, 18]. FXII activation was significantly elevated on 100% –COOH and 83% –COOH (0.0058 OD/min and 0.0081 OD/min, respectively) compared to 100% $–CH_3$ (0.0014 OD/min (Fig. 3). Additionally to the above

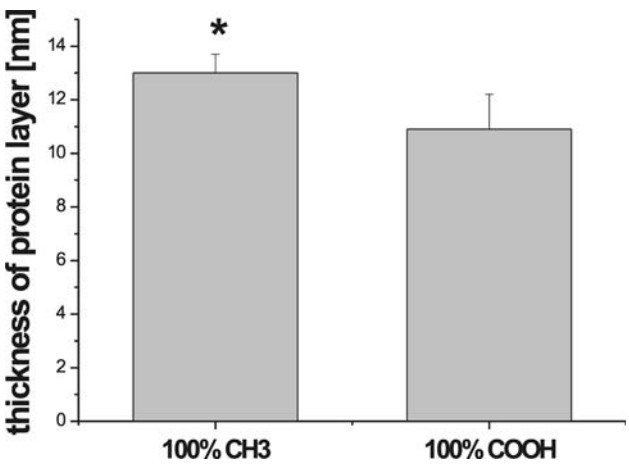


Fig. 1 Protein adsorption of human Fibrinogen (HFG) to SAMs detected by QCM measurement, * 100% $–CH_3$ is significantly different from 100% −COOH; ($P < 0.05$)

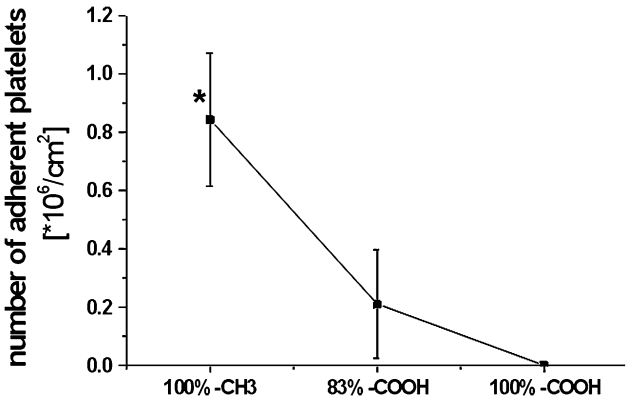


Fig. 2 Adherent platelets on SAM surfaces after incubation with platelet rich plasma (PRP), * 100% −CH3 is significantly different from 100% –COOH; ($P < 0.05$)

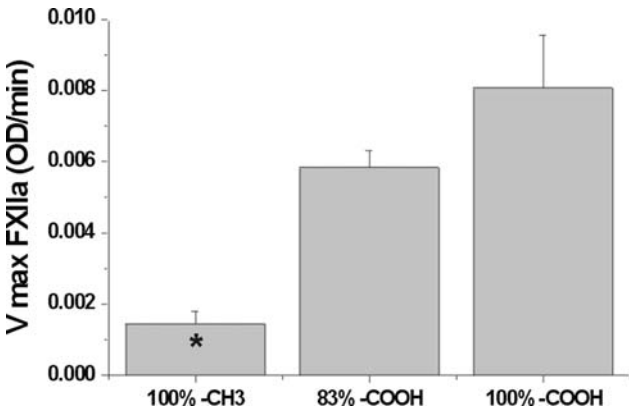


Fig. 3 Contact activation determined photometrically by measuring the conversion of a chromogenic substrate by FXIIa after incubation of surfaces with plasma; * 100% –COOH and 83% –COOH are significantly different from 100% $–CH_3$; ($P < 0.05$)

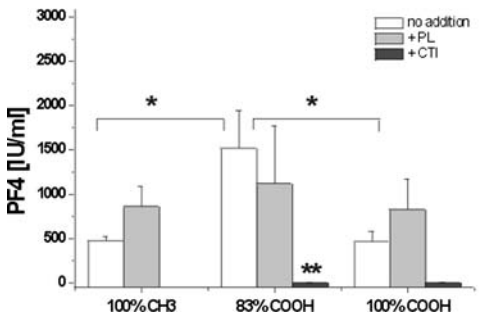
mentioned experiments that detected soluble FXIIa in plasma we measured FXIIa adsorbed to the SAM surfaces. Here we found the same tendency of contact activation (data not shown).

4.2 Blood clotting

Significantly elevated levels of coagulation activation (TAT) in whole blood were neither found on the surface with the highest contact activation (100% –COOH; TAT: 827 μg/l) nor on the SAMs showing maximum platelet adhesion (100% $–CH_3$; TAT: 608 μg/l) but on 83% –COOH (TAT: 1,400 μg/l) (Fig. 4). PF4 formation peaked on 83% –COOH as well (1,516 IU/ml vs. levels below 480 IU/ml on 100% $–CH_3$ and 100% –COOH). Microscopic analysis of SAM surfaces after the whole blood incubation assay are presented in Fig. 5. Fluorescence microscopy allowed the identification of cells adhering to the surfaces as platelets (FITC conjugated anti-CD41a; green fluorescence) and leukocytes (DAPI-staining of leukocyte DNA; blue fluorescence). Surface analysis uncovered clot formation on 83% –COOH, whereas almost no platelets and only small amounts of leukocytes adhered to 100% –COOH. The hydrophobic 100% $–CH_3$ was confluently covered by platelets showing minor leukocyte adhesion.

4.3 Mimicking and knockout studies

Additional experiments using FXII inhibitor (CTI) and phospholipids (PL) were assessed to specifically inhibit contact activation or to mimic the activated platelet membrane (Fig. 4). CTI addition significantly lowered the formation of thrombin (TAT) on 83% –COOH to levels below the negative control being 100% $–CH_3$ (TAT on 83% –COOH: 213 μg/l with CTI addition versus 1,400 μg/l without CTI). Additionally, preincubation of blood with CTI on binary 83% –COOH surfaces significantly reduced PF4 formation (0.2 IU/ml with CTI addition versus 1,516 IU/ml). This data was confirmed by microscopic analysis which showed an absence of clotting on 83% –COOH (Fig. 5). On the other hand the addition of phospholipids to whole blood before surface incubation induced



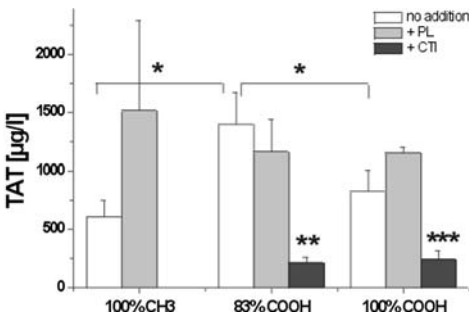


Fig. 4 PF4 and TAT levels after whole blood incubation of SAMs; normal: without any additives, +PL/+CTI: addition of phospholipids/corn trypsin inhibitor to whole blood just before whole blood incubation assay; * 83% –COOH is significantly different from 100% $–CH_3$ and 100% –COOH in the case of whole blood incubation without additives, ** 83% –COOH is significantly different from 83% –COOH pre-incubated with CTI, *** 100% –COOH is significantly different from 100% –COOH pre-incubated with PL; ($P < 0.05$) for all statistics

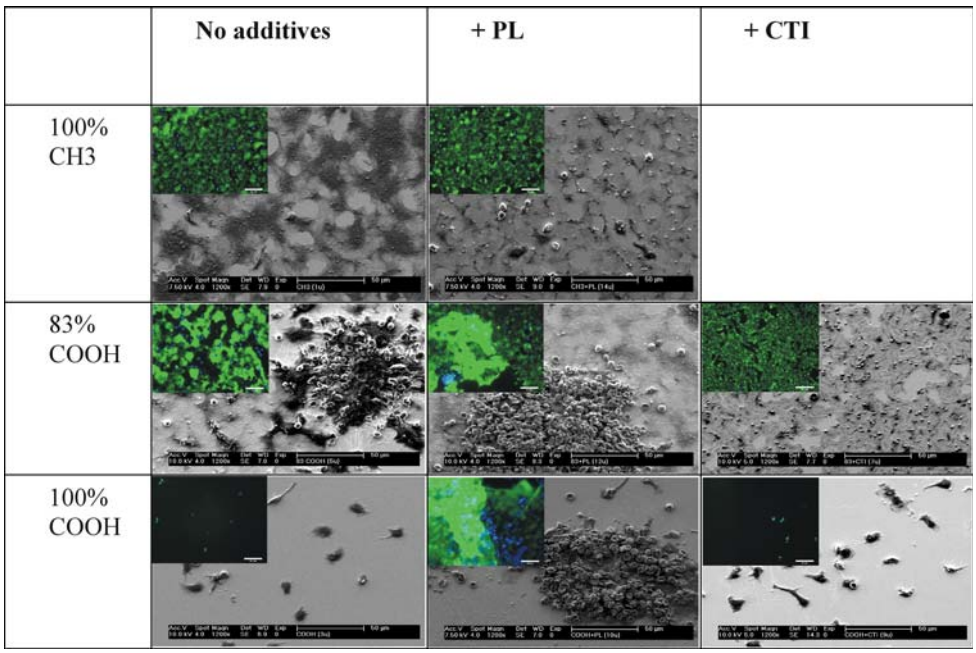


Fig. 5 SEM and fluorescence microscopy of SAM surfaces after whole blood incubation. Fluorescence microscopy: Staining of platelets with FITC-anti CD 41a und DAPI staining of leukocyte nuclei

significantly elevated thrombin formation even on 100% –COOH (TAT: 1,152 µg/l vs. 827 µg/l in additive free whole blood) as well as higher PF4 levels (PF4: 829 IU/ml vs. 467 IU/ml, respectively). Clotting of cells was further found on 100% –COOH after phospholipid addition.

Summing up the addition of CTI to whole blood just before surface incubation showed similar cell adhesion patterns as seen for 100% $–CH_3$ incubated with pure whole blood. Contrarily, addition of phospholipids to 100% –COOH restores the picture of additive-free whole blood on 83% –COOH.

5 Discussion

Initial processes of blood coagulation on a hydrophilic, negatively charged surface (100% –COOH), on a hydrophobic surface (100% $–CH_3$) and on a surface combining these two properties (83% –COOH) were investigated. The experimental focus was set on protein adsorption, cell adhesion, contact activation and blood clotting.

5.1 Protein adsorption and platelet adhesion

A strong fibrinogen adsorption to hydrophobic 100% $–CH_3$ demonstrated here has been described also by other authors [4, 19, 20] and is regarded as an elicitor for the high platelet adhesion on that surface after incubation with PRP. These results confirm previously described findings for methyl-terminated SAMs after plasma pre-adsorption [12]. In contrast, the acidic surface was mainly free of blood platelets possibly resulting from electrostatic repellence [21–23]. However, the relevance of electrostatic interaction under physiological conditions is questionable as Coloumb forces are limited under high ionic strength. The role of competitive protein adsorption known as the Vroman effect [24] seems to be more plausible.

5.2 Contact activation

FXII activation in plasma determined by activity assays was found to correlate to the amount of negatively charged surface groups as reported previously [3, 18, 25]. It was proposed that the negative charge density influences FXII conformational changes upon surface adsorption leading to a switch of function [26]. Initiation of the intrinsic pathway of coagulation is mediated by auto-activation of the clotting factor FXII to FXIIa upon surface adsorption to negatively charged (polyanionic) surfaces due to an anion-binding exosite [18, 27]. There is a strong relevance of this reaction for biomaterials although the responsible surface characteristics are still not clear in detail. Negative surfaces favour the process, however protein displacement of competing proteins might be responsible, instead of electrostatic interaction with FXIIa [28, 29]. The actual relevance of FXII activation clinically has been strongly questioned yet a strong significance for thrombus stability has been shown [30]. It is generally considered, that coagulation on foreign surfaces is initiated by that pathway, however, also here details are not fully understood and questions arise after work with purified molecules [31].

5.3 Blood clotting

The strongest formation of the coagulation factor thrombin and of cellular coagulation mediators (PF4) did not correlate either with the surface showing maximum contact activation (100% –COOH) nor with the one with highest platelet adhesion (100% $–CH_3$) but is considerably increased on binary 83% –COOH, where both acidic and anionic surface groups are present. Sample surface analysis confirmed coagulation induction on the latter surface showing the formation of a blood clot. This was surprising as surfaces with exclusively hydrophobic or acidic groups showed low coagulation potential regarding hemostatic plasmatic and cellular parameters. The presence of both acidic and hydrophobic groups shows a completely different picture than the pure monolayers (100% COOH, 100% $–CH_3$), where only either contact activation or cell adhesion occurs. Consequently the resulting combination of cellular and plasmatic events that are induced on the binary 83% –COOH seem to be indispensable for a strong coagulation reaction. To uncover the causal relationship for this we conducted additional experiments using an inhibitor for FXII as well as an imitator of activated platelet membranes. Coagulation on 83% –COOH was knocked down by the addition of FXII inhibitor CTI confirming contact activation as the essential trigger for clotting in that case. The essential role of platelets for coagulation on the other hand was shown by induction of clot formation on 100% –COOH following phospholipid addition to whole blood before surface incubation. The activated platelet membrane can thus be speculated as a dominant procoagulant mechanism if an initial activation of coagulation is found. We state that initial processes of coagulation on foreign materials require an interplay of plasmatic reactions on the one hand—leading to the formation of thrombin above a certain level that can be quickly inhibited by feed back mechanisms—as well as the presence and activation of blood platelets on the other hand—providing a platform for thrombin formation. Although surface properties leading to the maximal activation of the one pathway completely suppresses the other reaction, there is an over additive effect on coagulation for surfaces with intermediate properties.

6 Conclusion

Platelet adhesion and contact activation are induced by characteristic patterns of physicochemical surface properties on artificial materials. Both activation processes need to be combined to cause a substantial thrombus formation. This was shown through special experiments where coagulation was knocked down by specific FXIIa inhibition, whereas PL addition was able to substitute platelet derived procoagulant activities on surfaces without platelet activation. Materials with optimal surface properties regarding hemocompatibility possibly inhibit coagulation in whole blood (100% –COOH or 100% $–CH_3$ in our case). Minor concessions to the surface properties due to practical reasons, however, can induce inverse (procoagulant) effects that were lacking on the surfaces displaying extreme properties (as seen for 83% –COOH). Our findings emphasize the necessity to study biomaterial induced coagulation on each particular surface in the complex system of whole blood instead of analysis and optimization of only one hemostasis related parameter. The work thus provides important insight for the rational design of blood compatible surfaces and for adequate test systems.

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