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Original research

Development of a clot-adhesive coating to improve the performance of thrombectomy devices

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ABSTRACT

Background The first-pass complete recanalization by mechanical thrombectomy (MT) for the treatment of stroke remains limited due to the poor integration of the clot within current devices. Aspiration can help retrieval of the main clot but fails to prevent secondary embolism in the distal arterial territory. The dense meshes of extracellular DNA, recently described in stroke-related clots, might serve as an anchoring platform for MT devices. We aimed to evaluate the potential of a DNA-reacting surface to aid the retention of both the main clot and small fragments within the thrombectomy device to improve the potential of MT procedures.

Methods Device-suitable alloy samples were coated with 15 different compounds and put in contact with extracellular DNA or with human peripheral whole blood, to compare their binding to DNA versus blood elements in vitro. Clinical-grade MT devices were coated with two selected compounds and evaluated in functional bench tests to study clot retrieval efficacy and quantify distal emboli using an M1 occlusion model.

Results Binding properties of samples coated with all compounds were increased for DNA (≈ 3 -fold) and decreased (≈ 5 -fold) for blood elements, as compared with the bare alloy samples in vitro. Functional testing showed that surface modification with DNA-binding compounds improved clot retrieval and significantly reduced distal emboli during experimental MT of large vessel occlusion in a three-dimensional model.

Conclusion Our results suggest that clot retrieval devices coated with DNA-binding compounds can considerably improve the outcome of the MT procedures in stroke patients.

INTRODUCTION

Despite several effective preventive strategies, stroke remains a leading cause of permanent disability.¹ In the settings of acute intracranial large vessel occlusions, the current generation of mechanical thrombectomy (MT) devices has been associated with a significant clinical benefit.^{2–3} However, MT procedures carry the risk of iatrogenic clot fragmentation and embolism of the distal vascular bed, defined as secondary embolism (SE), or even emboli to a new territory

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ New mechanical thrombectomy devices are being improved continuously by design elements to increase the mechanical interaction with clot. However, there is little research to study chemical surface modifications specifically targeting the structure or composition of the clot.

WHAT THIS STUDY ADDS

⇒ The design of a chemical surface modification of the device opens the way for a specific targeting tool to increase the interaction with the clot on a molecular level.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This new surface modification, which can be applied to all commercially available mechanical thrombectomy devices, leads to binding of neutrophil extracellular traps and a decrease in distal embolization.

(ENT). Such SE or ENT may unfavorably influence clinical outcome.⁴ Various strategies have been employed to reduce SE rates, including the design refinement of MT devices and the study of their effectiveness to interact with the clot.^{5–7} The latter would be favored by devices able to selectively adhere to clot-enriched components but not to flowing blood elements. In this setting, recent studies have extensively described the presence of neutrophil extracellular traps (NETs), dense meshes of extracellular DNA, consistently found around and inside the retrieved clots.^{8,9} We therefore hypothesized that engrafting of DNA-binding compound on the surface of MT device struts might improve their ability to adhere to clots and retain released clot fragments, through the binding of the associated DNA meshes. In the present study, we have screened the potential of 15 known DNA-binding compounds in terms of specific capture of extracellular DNA versus non-specific stickiness to blood components when immobilized on device-suitable alloy discs in vitro. Then, the performances of clinical-grade, surface-modified, stent retrievers in a simulated



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in vitro middle cerebral artery (MCA) occlusion model were evaluated.¹⁰

MATERIAL AND METHODS

All procedures described below are demonstrated in a diagram that can be found in the supplementary materials (online supplemental information S1).

Material

Nitinol (NiTi) flat discs (4.8 mm diameter, 0.25 mm thick) were laser cut and mirror polished by a controlled industrial workshop (Vuichard Michel SAS, Dingy-en-Vuache, France) from a flat NiTi ribbon (5 mm diameter, 0.25 mm thick, Goodfellow Cambridge Ltd, Huntingdon, UK) and were used for the in vitro experiments. For the bench test evaluation, Solitaire devices (6 mm × 20 mm × 180 cm, Medtronic Neurovascular, Irvine, CA) were used.

Surface modification of NiTi material

All NiTi materials were ultrasound cleaned in successive acid, alcohol, and water baths before the functionalization process comprising three successive dip-coating steps, as described in the patent application WO2021EP64257. Briefly, the discs were first immersed in an alkaline solution of dopamine (Alfa Aesar, A11136) for 20±2 hours under stirring, to obtain a thin polydopamine (PDA) film.¹¹ Deionized water washes and ultrasound sonication was applied to withdraw PDA aggregates before immersion in the second bath, aimed at grafting an amine functionalized-cyclooctyne derivative anchor (DBCO-Sulfo-PEG(4)-NH₂, IRIS biotech GMH) on the free catechol group from the PDA film. After extensive washing with deionized water, the final step led to the immobilization of an azide derivative of each compound of interest, through a bio-orthogonal alkyne-azide copper-free click-chemistry reaction.¹² Uniform coating of the medical grade MT devices, Solitaire devices, was achieved using an automatic dip-coater (ND-DC, Nadetech, Navarra, Spain). Once coated, the medical devices were soaked in absolute ethanol for 1 min, left to dry and resheathed before the experiments.

Surface modification characterization

Surface modification of the flat samples was characterized by X-ray photoelectron spectroscopy (XPS), atomic force microscopy (AFM), and ζ-potential measurement, as detailed in the online supplemental material.

Evaluation of the binding to extracellular chromatin versus circulating blood platelets

Chromatin and platelet binding evaluation were studied as described in the patent application WO2021EP64257¹³ and detailed in the online supplemental material. Briefly, the amount of captured extracellular DNA or blood platelets was quantified by computer-assisted analysis of fluorescence microscopy images. The ability of coated surfaces to bind extracellular DNA was evaluated by applying the active surface of the experimental discs stained with the cell impermeant nuclear dye Sytox Green (S7020, Invitrogen, France) on a 3 min contact with human neutrophils stimulated with nigericin (which triggers the formation of NETs).¹⁴

Immersion in fresh whole peripheral human blood for 10 min, followed by an incubation with DAPI (4',6-diamidino-2-phenylindole) and fluorescent antibodies

directed against glycophorin and CD61, allowed quantification of adhering blood leukocytes, erythrocytes, and platelets.

Functional bench assay: MCA occlusion model

These experiments were performed by an experienced interventional neuroradiologist (VA) and aimed to evaluate the effect of surface-modified Solitaire devices compared with unmodified bare metal stents (BMS) in terms of clot retrieval and SE decrease. The model reproduces the conditions of an MCA occlusion.^{10 15} The clot used in these experiments was prepared using thrombin-induced clotting of bovine blood, and experimental clots were incubated at 37°C for 48 hours before use. The latter steps favored the formation of extracellular traps within the experimental clots.

Before initiating thrombectomy, complete vessel occlusion with a modified Thrombolysis In Cerebral Infarction (mTICI) score of 0 was confirmed by angiography and MCA flow measurements. Each Solitaire was deployed at the occlusion site and remained in place for 3 min before retrieval. Clot fragments generated during MT were collected into two collection reservoirs (one for SE to the MCA distribution and the other for ENT to the anterior cerebral artery distribution). The entire procedure is detailed in online supplemental material.

Surface-modified Solitaire devices included stents coated with MBF (mustard benzo[b]furan, a DNA mustard derivative) and Pipe-2. BMS and PDA-coated devices were used as controls.

Ten experiments were carried out for each group (BMS, PDA, MBF and Pipe-2). The maximum number of passes (thrombectomy attempts) was limited to three. All stents were randomized, numbering them from 1 to 40. Briefly, an AXS Catalyst 5F (Stryker, MI) aspiration catheter connected to a Penumbra aspiration pump (Alameda, CA) was used as an adjunctive thrombo-aspiration procedure in all experiments. The aspiration catheter was advanced over the microcatheter with the stent retriever deployed. Aspiration was initiated with the catheter positioned at the proximal end of the deployed stent and the catheter advanced until flow through the tubing ceased. During the thrombectomy, the aspiration catheter, microcatheter and stent retriever were locked as a system and withdrawn together.

RESULTS

Surface modification characterization

Surface modification characterization of uncoated and functionalized NiTi disc: PDA, PDA-DBCO (dibenzocyclooctyne) and PDA-DBCO-ligand were achieved using XPS to evaluate the chemical organization, and AFM to evaluate the microscopic modification. XPS analyses are reported in table 1. BMS samples had the expected peaks of Ti, Ni, O and C (data not shown). The surface chemistry of coated samples was instead completely

Table 1 Surface organic composition of modified device-suitable alloys detected by XPS (mean±SD)

	PDA	PDA+DBCO	PDA+DBCO+ligand
C	72.3±0.3	70.0±0.7	71.0±0.4
O	20.9±0.3	22.6±0.6	20.5±0.4
N	6.9±0.2	7.3±0.6	8.3±0.8
S	NA	NA	0.3±0.1
O/C	0.29	0.32	0.29
N/C	0.10	0.10	0.12

C, Carbon; DBCO, dibenzocyclooctyne; N, Nitrogen; NA, not applicable; O, Oxygen; PDA, polydopamine; S, Sulfur; XPS, X-ray photoelectron spectroscopy.

organic, showing strong C, O, and N peaks. As expected, the deposited PDA coating was laterally homogeneous and vertically thicker than XPS sampling depth, about 8 nm, in agreement with published data.^{16,17} Its elemental percent was in accordance with published data,¹⁶ the same way the N/C ratio of 0.10 was also in agreement with the expected value. Coupling of DBCO yielded a slight increase of the O/C ratio reflecting the chemistry of the DBCO spacer arm, which contains polyethylene glycol (PEG)—CH₂CH₂O—repeating units. After ligand coupling, further slight modification of surface stoichiometry was observed and coherent with the immobilization of a new chemical and indicated successful coupling of the ligand.

Non-contact AFM analyses are reported in online supplemental information S3. Uncoated NiTi discs showed the presence of a flat surface with a slight difference in the morphology through AFM analysis. PDA coupling led to a classic spot morphology on the surface,^{17,18} which was uniformly distributed. Scanning electron microscopy images confirmed the presence of spherical particles on the PDA surface (data not shown). Adding DBCO followed by the final addition of the ligand did not modify the morphology of the surface. The measurement in three random regions of interest of final surface profile (online supplemental information S4) demonstrated a symmetrical profile of the surface modification with respect to the mean line.

The contact between a solid surface and a water-based medium leads to the development of a surface charge (ζ -potential) at the interface. This charge is one of the surface characteristics which could affect the interaction between the material and the biological environment. In particular ζ -potential was measured as a function of pH, in the 4.5–8.5 range, in 1 mM potassium chloride solution (online supplemental information S5). In the case of bare NiTi, the pH scan is typical of a very weak acid-base interfacial activity and it is driven by pH dependent adsorption of ions. Addition of PDA shows a negative surface which is due to the presence of more phenolic groups exposed on the surface than amine. The presence of DBCO does not change the surface charge significantly; however, the presence of ligand makes the surface potential higher in value and much more negative, which may be due to the exposition of the carboxylic group which makes the surface of the material more acidic.

Evaluation of the chromatin and blood elements binding

As the main goal is to target chromatin mesh composing acute ischemic stroke thrombi, we focused on the coating of the discs with well-known chromatin interacting compounds already used in clinical routine for various applications. The binding property to chromatin and stickiness to blood platelets of 15 DNA interacting agents was studied, considering their toxicity, scalability and manufacturing cost (online supplemental information S6). Pipe-2 (piperazine derivative) and MBF-coated samples showed the most interesting results with regard to both platelet

and chromatin binding compared with bare NiTi discs. The binding data are summarized in table 2. PDA-coated discs were also evaluated to assess the binding properties of the polymer film alone. All fully coated discs demonstrated increased binding to chromatin and a low platelet adhesion compared with the bare discs (ratio 0.27), with the ratio ranging from 0.67 to 6.62. The best results were obtained for the MBF compound with a nearly threefold increase in chromatin binding affinity and almost a fivefold decrease in platelet adhesion as compared with the bare discs. Pipe-2 also showed interesting results with a good affinity for chromatin compared with platelet (ratio of 2.27). On the other hand, PDA coating demonstrated similar specificity for chromatin and platelet binding as compared with bare metal discs. Leukocytes and erythrocytes were virtually absent from all samples.

First pass recanalization and mTICI score

All devices achieved complete recanalization (mTICI 3) after a maximum of three passes (figure 1). BMS and the MBF coated device showed higher rates of first-pass recanalization with mTICI 3 in 100% of cases, compared with PDA (seven out of 10 experiments, 70%) and Pipe-2 (nine out of 10 experiments, 90%) coated devices (not significant). Higher numbers of passes were required to achieve complete recanalization in the PDA group compared with the other devices, but no significant differences among devices were seen. The clot detachment from the device is plotted in figure 1 and shows an important clot detachment in the BMS group (70% of case) compared with the MBF, PDA and Pipe-2 groups in which clot detached in 20%, 20% and 10% of cases, respectively (representative examples in online supplemental information S7).

Secondary embolism

SE rates were increased in the BMS group for each macro- and microemboli, as well as overall total count of distal emboli (table 3). The total count of macroemboli, characterized as large clot fragments >1000 μ m, was higher for the BMS (29 macroemboli) as compared with the coated devices in which 19, eight, and 18 macroemboli were recorded in the PDA, MBF, and Pipe-2 groups, respectively. The mean number of macroemboli per experiment is illustrated in figure 1. A statistically significant difference was found for the MBF group compared with BMS ($P=0.0211$).

The total count of microemboli, characterized as clot fragments ranging from 200 μ m to 1000 μ m, was similar in the BMS and PDA groups with 26 and 30 microemboli recorded, respectively. MBF and Pipe-2 groups showed a decrease in microemboli count compared with BMS and PDA (11 and seven microemboli, respectively). There were no statistically significant differences in the number of macroemboli observed in either coated group compared with BMS (figure 1). Finally, the overall count of distal emboli (including micro- and macroemboli) was higher in the BMS (55 distal emboli) and PDA coated devices (49 distal emboli) compared with MBF (19 distal emboli) and Pipe-2 (25 distal emboli) coated devices (figure 1). A statistically significant difference was found for the MBF and Pipe-2 coated devices group compared with BMS ($P=0.0418$ and 0.0416 , respectively).

DISCUSSION

Despite the tremendous advances in the design of new MT devices in the past decades,^{19,20} the MT procedure may still be optimized. In spite of radiological success in about 80% of the interventions, a completely positive clinical outcome is realized

Table 2 Binding properties of chromatin and platelets (mean \pm SEM)

Ligand	Chromatin binding (% of max)	Platelet binding (% of max)	Chromatin/platelet binding ratio
Bare metal	29.69 \pm 8.63	90.71 \pm 1.54	0.27
PDA	24.57 \pm 8.50	36.32 \pm 5.45	0.67
MBF	66.07 \pm 13.21	9.98 \pm 3.37	6.62
Pipe-2	44.23 \pm 10.64	19.45 \pm 3.90	2.27
MBF, mustard benzo[b]furan, a DNA mustard derivative; PDA, polydopamine; Pipe-2, piperazine derivative.			

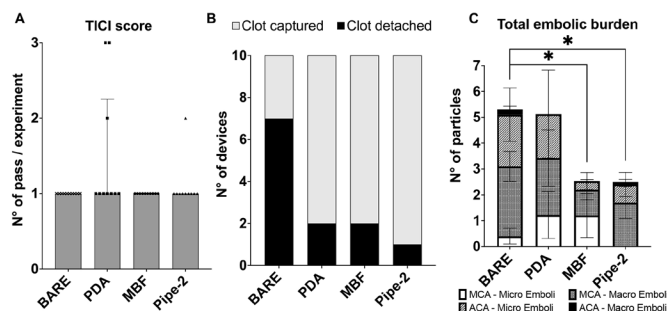


Figure 1 Number of passes to achieve mTICI score of 3 (A), clot capture versus detachment (B), and total embolic burden (number of particles released during the procedure, average±SD), according to the tested group (C). n=10/group, *P<0.05. BARE, bare metal stent; ACA: anterior cerebral artery; MBF, mustard benzo[b]furan, a DNA mustard derivative; MCA, middle cerebral artery; mTICI, modified Thrombolysis In Cerebral Infarction; PDA, polydopamine; Pipe-2, piperazine derivative.

in only half of the procedures.²¹ In addition, Wong *et al* documented the issue of SE or ENT which occurs in about 40% of cases.⁴ Lastly, Luraghi *et al* described the clot rolling phenomenon during MT that resulted in the detachment of the thrombi from the device during the procedure.²² A recent translational study suggests that thrombectomy outcome would be significantly improved by strategies aimed at increasing the incorporation of the embolus within the device and at minimizing the release of SE or ENT.²³ The quest for a surface modification able to selectively adhere the device to the clot structure, and not the components of the flowing blood, led us to exploit the extracellular chromatin material (only present in blood in very small quantities) that accumulates within and around occlusive thrombi,²⁴ likely due to the local hemodynamic stress consistently found in the clot retrieved from stroke patients.⁹

Here, we report that the immobilization of DNA-binding compounds, through a scalable surface modification process applicable to any commercially available thrombectomy device, can effectively improve the adherence of the occlusive clot to the thrombectomy device, while decreasing the release of secondary emboli in a three-dimensional phantom bench model of acute cerebral artery occlusion.¹⁰

Several compounds are known to interact with DNA, yet our in vitro data indicate that some of them were weaker binders of extracellular chromatin, likely according to the compound nature. The selection of the candidate for our purposes was guided by the best adhesiveness shown within the relatively short contact time (3 min), and this criterion was meant to match the time allowed between the stent deployment and its retrieval during MT procedures in clinical practice. Among all the tested compounds, MBF, Pipe-2 and Pipe-4 showed in vitro the highest capture affinity to DNA.

Table 3 Total count of distal emboli released during the whole study (n=10) according to the tested group

	BMS	PDA	MBF	Pipe-2
Overall macroemboli	29	19	8	18
Overall microemboli	26	30	11	7
Overall distal emboli	55	49	19	25
BMS, bare metal stent; MBF, mustard benzo[b]furan, a DNA mustard derivative; PDA, polydopamine; Pipe-2, piperazine derivative.				

Functional tests in the bench model of cerebral artery phantom occlusion effectively showed a superiority of the modified devices in terms of clot incorporation. Indeed, the main clot readily detached from the BMS in seven out of the 10 independent experiments, whereas this occurred in a minority of the experiments performed with the coated devices (2/10, 2/10 and 1/10 with PDA, Pipe-2 and MBF devices, respectively). This observation is consistent with the study by Luraghi *et al* describing the clot rolling phenomenon during the MT when using an in vitro model and a variety of commercial BMS devices.²² Interestingly, most of the tested compounds also showed a reduced (at least a twofold decrease) binding to blood platelets as compared with the control BMS. This finding further demonstrates that the clot-capture property conferred by our surface modification is specific and supports a safer use of the modified device through the arterial bed (reduced risk of platelet aggregation onto the stent retriever). In this perspective, the mere coating with PDA, which we used as an intermediate functionalization layer, could have been proposed as a candidate for its well-known adhesive property.^{25–27} Our data, however, clearly show that this ‘sticky’ property does not bring a specific binding towards DNA as compared with blood platelets; the number of total distal emboli per experiment in the PDA group was similar to the BMS, and significantly reduced with the MBF and Pipe-2 surface modifications. This observation confirms and validates the concept that a specific binding to a component enriched in the clot, and absent in the flowing blood, can significantly improve the global performance of the thrombectomy devices.

Our study has limitations. First, this is an in vitro study and further testing is required to characterize the vascular reaction to these coating concepts in vivo. We chose to use co-aspiration during our stent retriever thrombectomy as this is the clinical routine in many practices,^{28–31} which may have reduced the amount of distal emboli; however, we believe that since the technique was standardized across all experimental groups the relative differences remain valid. To maintain scientific rigor and reduce variability of technique, a single operator was used and therefore additional validation with multiple operators to ensure generalizability of the data will be performed. Although NETs are consistently present in clots that cause stroke,⁹ the spatial distribution may vary and may not always come into contact with the low porosity stent retriever construct. Finally, as with all medical devices, standard particulate testing to ensure coating integrity has not yet been performed and will be required before clinical translation.

CONCLUSION

Our work has led to the design of a surface modification procedure scalable and applicable to all commercially available MT devices. This work validates the hypothesis that a surface-modified MT device can be an interesting alternative to bare MT devices, as this modification improves the capture of the main clot to decrease the risk of distal embolization.

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