Thrombus Formation at the Surface of Guide-Wire Models: Effects of Heparin-releasing or Heparin-exposing Surface Coatings

Yvette B.J. Aldenhoff, PhD, Johannes H.L. Hanssen, Menno L.W. Knetsch, PhD, and Leo H. Koole, PhD

PURPOSE: This study was conducted to investigate whether thrombus formation at the surface of guide wires occurs, and—if so—whether this can be suppressed or prevented through incorporation of heparin in the surface coating.

MATERIALS AND METHODS: Five guide wire models were examined; three had a polymeric hydrophilic surface coating (90/10 guide wire), which was either heparin-free, impregnated with sodium-heparin (Na-hep), or impregnated with benzalkonium heparin (BAK-hep). The other two guide wires had a coating of polytetrafluoroethylene (PTFE), either without heparin, or impregnated with BAK-hep. Release of heparin, exposure of heparin at the surface of the guide wires, thrombogenicity (under static and flow conditions) and their propensity to attract blood platelets were investigated.

RESULTS: The guide wire 90/10 Na-hep releases approximately 150–200 mU active heparin per cm coil within the first few minutes after incubation in buffer. The PTFE BAK-hep shows a relatively slow release of 60–70 mU active heparin per cm coil. The 90/10 BAK-hep showed no released heparin but the most exposed heparin. In a static experiment with human full blood excessive thrombus formation occurred at the heparin-free models, whereas the others remained essentially clean. In a thrombin-generation assay under flow the authors observed strong retardation of thrombin formation in the case of the 90/10 Na-hep guide wire.

CONCLUSIONS: The static and dynamic in vitro assays, taken together, show that the 90/10 Na-hep provides a coating with an extremely low level of surface thrombogenicity. Use of a guide wire with a hydrophilic distal coating that releases and exposes sodium heparin may contribute to the safety of diagnostic and therapeutic interventional procedures.

J Vasc Interv Radiol 2007; 18:419–425

Abbreviations: BAK-hep = benzalkonium heparin, BMA = *n*-butyl-methacrylate, Na-hep = sodium-heparin, NVP = *N*-vinyl-pyrrolidinone, PBS = phosphate-buffered saline, PRP = platelet-rich plasma, PTFE = poly(tetrafluoroethylene), TGT = thrombin generation time.

GUIDE wires play a predominant role in most diagnostic and therapeutic interventional procedures. The tip of the guide wire is forwarded into the target lesion at the start of the procedure. Especially if the lesion is a stenosis, it is important that formation of thrombotic emboli through contact activation is avoided. This is commonly achieved through the use of a surface coating of either poly(tetrafluoroethylene) (PTFE), which is smooth but actually thrombogenic, or an adherent hydrophobic biomaterial. In any case, the foreign surface of the guide wire is a trigger to coagulation; the patient receives systematically anticoagulant drugs to counterbalance this.

In this study, we focus on thrombus formation on guide wire surfaces. We became interested in this subject because of two arguments. (*a*) The guide wire is a relatively large foreign surface that will trigger contact activation in situ, usually just upstream of the target lesion (1–5). If guide wire–induced thrombosis produces thromboembolic particles, then these may occlude a stenosis downstream and thus cause acute complications. (*b*) Contact activation of indwelling devices is normally suppressed or prevented through systemic administration of heparin and/or an antiplatelet agent. This must always be balanced against a risk for complications due to bleeding. We hypothesized that incorporation of heparin in the guide wire coating provides a more efficient protection strategy (6–9).

Here, we report an in vitro study with five different guide wire models.

From the Centre for Biomaterials Research, Faculty of Medicine, University of Maastricht, Universiteitssingel 50, 6229 ER Maastricht, The Netherlands (Y.B.J.A., M.L.W.K., L.H.K.); Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands (M.L.W.K., L.H.K.); and MCTec BV, Venlo, The Netherlands (J.H.L.H.). Received June 27, 2006; final revision received November 20, 2006; accepted December 21, 2006. **Address correspondence to** Y.B.J.A.; E-mail: y.aldenhoff@bioch.unimaas.nl

None of the authors have identified a conflict of interest.

DOI: 10.1016/j.jvir.2006.12.733

Two have a PTFE coating, which is a common feature of commercial guide wires; one of the PTFE coatings is loaded with heparin. The other three models have a hydrophilic coating that releases heparin and/or exposes heparin from/at the surface. Thrombus formation was studied in vitro, both statically and under flow conditions. This study was undertaken to evaluate whether guide wire models with a heparin-containing coating can indeed be effective in preventing thrombus formation at their surface upon incubation in whole human blood.

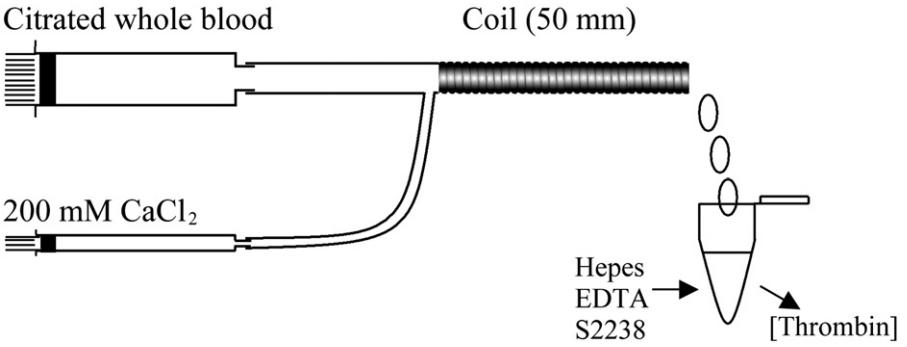

Figure 1. Schematic drawing of the apparatus used in the thrombin generation assay.

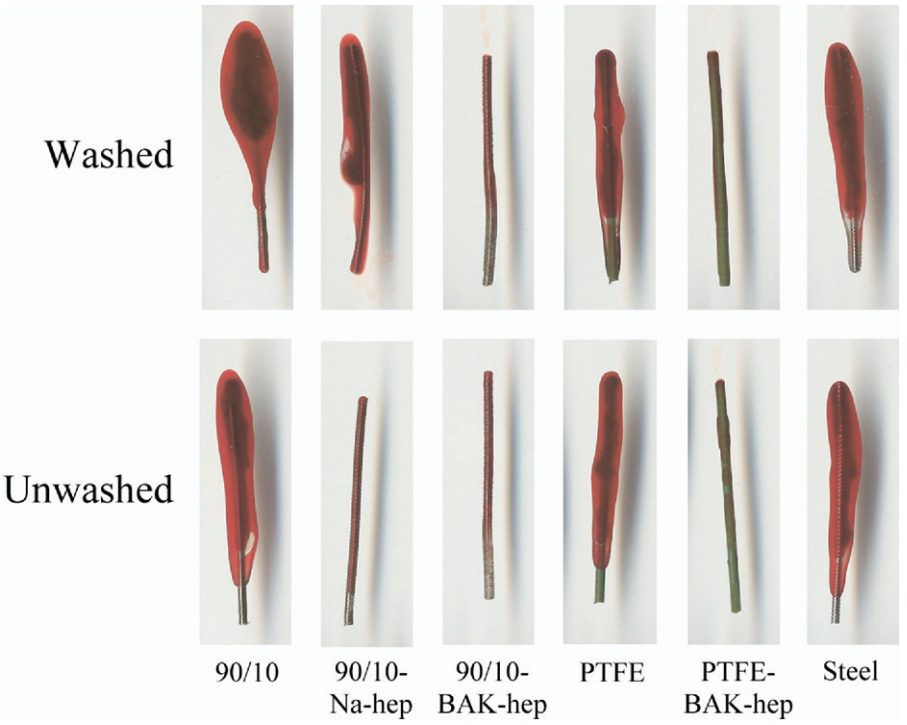

Figure 2. Guide wire models after incubation with human full blood for 1 h. Adherent thrombi are clearly seen, especially for the models that are devoid of heparin.

MATERIALS AND METHODS

Materials

Five coiled guide wire models that were identical except for their surface coating were included. Three had a polymeric hydrophilic surface coating, which was either heparin-free, impregnated with sodium-heparin (Na-hep), or impregnated with benzalkonium heparin (BAK-hep). The other two guide wires had a coating of PTFE, either without heparin or impregnated with BAK-hep. Uncoated coils (exposing a surface of stainless steel) were obtained from MCTec BV (Venlo, The Netherlands) and used as controls.

The hydrophilic coating was prepared from *N*-vinyl-pyrrolidinone (NVP), *n*-butyl-methacrylate (BMA), and 2,2′-azobis(2-methylpropionitrile) on a 100-g scale, as described previously (7–9); the NVP:BMA ratio was 90:10. The PTFE coatings were applied from aqueous dispersions of PTFE. All coatings were applied to a thin stainless steel wire with a perfectly circular cross-section and a diameter of 80 μm. The coating is an extrusion-like procedure in which the copolymer (plus heparin) is deposited on the wire's surface in a quick, concentric, highly accurate and reproducible manner. The lengths of the wires were at least 500 m for each coating. Parts of each wire were coiled around a mandril core with a diameter of 690 μm.

Direct Contact with Whole Blood

Pieces of each coil (length, 2.5 cm) were incubated in a 1-mL Eppendorf vial with 600 μL whole blood (not citrated) for 1 hour at room temperature. The coils were removed carefully, and digital pictures were taken.

Released Heparin

Coils with a heparin-containing coating were first cut with a pair of pincers to a length of 10 cm. The coils were cut into 10 smaller parts, which were immersed in phosphate-buffered saline (PBS; 10 mL, pH 7.4) at 37°C. Aliquots of 400 μL were withdrawn at regular time points, and these were analyzed for their heparin content using a standard protocol. The heparin-specific chromogenic substrate Msc-Val-Arg-pNA·HCl was used (10).

Immobilized Heparin

A slightly modified version of the method of Smith et al was used to determine heparin molecules that remain exposed at the surface of each coil after extensive washing (11). The principle is that toluidine blue forms a complex with heparin under acidic conditions. The complex dissociates in a basic medium, and the dye concentration can be measured through ultraviolet spectroscopy.