Thrombogenicity of Angiographic Catheters

GEORGE D. WILNER, WILLIAM J. CASARELLA, ROBERT BAIER, AND CECILIA M. FENOGLIO

SUMMARY A radioimmunoassay for measurement of canine fibrinopeptide A, which provides a quantitative index of thrombin action on fibrinogen, has been applied to measurements of the thrombogenicity of five angiographic catheters commercially available and presently in clinical use. Examples of thin-walled polyethylene, wired polyethylene, Teflon, polyurethane, and woven Dacron catheters were characterized in terms of chemical composition, surface physiochemical properties, and their procoagulant activities assessed in vivo in an experimental system that closely simulated their actual clinical use. The catheters could be divided into three groups based on the fibrinopeptide A levels generated during a 30-minute test period as well as on the surface deposition of fibrin and platelets, as judged by scanning electron microscopy. Group I (thin-walled polyethylene) showed no increase in fibrinopeptide A levels over control and no fibrin deposition, but moderate platelet deposition. Group II (wired polyethylene and Teflon) showed moderate increases in fibrinopeptide A levels, with moderate fibrin and platelet deposition. Group III catheters (polyurethane and woven Dacron) showed marked fibrinopeptide A production and extensive fibrin deposition that contained variable numbers of platelet aggregates. We conclude that fibrinopeptide A levels correlate well with surface fibrin deposition and therefore are useful to assess the degree to which different catheters stimulate fibrin production. It may be that the procoagulant effects of these catheters are mediated through the textural and physicochemical properties of the surfaces of these devices, which are in contact with blood.

THE frequency of thromboembolic complications reported in association with angiographic procedures ranges from 0.3% to 14%. It is likely that the frequency of these complications is critically dependent on the nature of the studies performed and the care used in patient selection, as well as the experience and skills of the angiographic team. However, it has been demonstrated that thrombus forms on catheter surfaces during most angiographic procedures, and the clot-promoting properties of the catheters and guidewires used also may significantly influence the rate of thrombotic complications.

The procoagulant properties of angiographic catheters have been studied by a variety of techniques, including gravimetric analysis of clot formed on the catheter surface, and accumulation of radiolabeled red blood cells (RBCs), platelets, or fibrinogen following exposure of catheters to blood. Scanning electron microscopy (SEM) also has been used both to evaluate clot formation and to correlate surface textural properties of catheters with their thrombogenicity.

Recently, radioimmunoassay measurements of fibrinopeptide A (FPA) levels in the blood have been proposed by Nossel and co-workers and others as a quantitative and specific index of thrombin action in vivo. Wilner and Birkin have synthesized canine fibrinopeptide A (cFPA) and developed a radioimmunoassay specific for the peptide. Fibrinopeptide A represents a unique product of thrombin proteolysis whose release defines fibrin monomer formation and coincides with the rate of fibrin polymerization. The clearance of FPA from blood occurs rapidly ($t_{1/2} = 3$ minutes), and elevated levels of FPA therefore reflect recent thrombin action and active fibrin formation. In a recent study, cFPA measurements were used to assess the clot-promoting activity of angiographic guidewires in an in vivo canine model system. This paper represents an extension of these studies to the evaluation of angiographic catheters.

Methods

Adult mongrel dogs of either sex weighing 12–25 kg (average, 19 kg) were used. Healthy dogs with no signs of skin trauma were selected. They were anesthetized with a single intravenous injection of pentobarbital sodium (10 mg/kg). Twenty minutes later, a 5-ml sample of peripheral venous blood was obtained and collected into tubes containing heparin and Trasylol, as previously described.

After preparation of the skin area, the femoral artery was punctured with an 18-gauge disposable needle and the test catheter inserted a distance of 20 cm into the artery over a 0.038-inch Teflon-coated spring guide, using standard percutaneous technique. A 5-ml sample of blood was withdrawn immediately from the catheter into a heparinized syringe and collected in the same manner as the peripheral vein sample. A constant pump-controlled infusion of isotonic saline at the rate of 1 ml/min was begun through the catheter. Immedi-
**Table 1**  
**Surface Chemical and Procoagulant Properties of Angiographic Catheters**

<table>
<thead>
<tr>
<th>Group</th>
<th>Catheter</th>
<th>Surface properties</th>
<th>Critical surface tension (dynes/cm)</th>
<th>Inorganic fillers</th>
<th>Mean cFPA levels (pmol/ml)</th>
<th>Fibrin deposition</th>
<th>Platelet deposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Thin-walled polyethylene</td>
<td>Intact long chain fatty acid layer</td>
<td>25</td>
<td>Cadmium sulfide and silica compounds</td>
<td>1.0 (±0.2)</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>II</td>
<td>Teflon</td>
<td>Teflon, filler</td>
<td>20</td>
<td>Carbon, sulfates, silica, and calcium carbonate</td>
<td>16.4 (±5.8)</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>wired polyethylene</td>
<td>Patchy long chain fatty acid layers, fillers</td>
<td>Variable*</td>
<td>Titanium sulfide, silica and steel wire</td>
<td>14.6 (±4.9)</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>III</td>
<td>Polyurethane</td>
<td>Polyurethane</td>
<td>33</td>
<td>Bismuth and silicon compounds</td>
<td>37.2 (±10.4)</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Woven Dacron</td>
<td>Polyethylene terephthalate</td>
<td>42</td>
<td>Titanium dioxide</td>
<td>84.8 (±24)</td>
<td>+++</td>
<td>+</td>
</tr>
</tbody>
</table>

Catheters are categorized according to the mean cFPA levels generated over the 30-minute test period following insertion. Number of complete experiments performed for each group is indicated. Surface properties determined by internal reflectance infrared spectroscopy; critical surface tension determined by pre-implant contact measurements; inorganic fillers determined by energy-dispersive x-ray analysis; fibrin and platelet deposition estimated from scanning electron micrographs. Control level of cFPA in absence of catheter is 1.8 pmol/ml ± 0.3 SEM. Values in parentheses indicate ± SEM.

* Heterogeneous patches varying from 24 to 39 dynes/cm.

Results

Based on the mean cFPA levels measured in blood samples drawn back through the implanted catheters during the 30-minute test period, it was possible to place these catheters arbitrarily into three groups, depending on whether low, intermediate, or high cFPA levels resulted from catheter insertion (Table 1, Figs. 1-3).

Five different types of catheters were selected for study. All catheters were approximately 7F in outer diameter and had either a 0.038- or 0.032-inch end hole and multiple side holes. Seven examples of each thin-walled polyethylene ("PERT," Cook, Inc.), Teflon ("Hilal," Cook, Inc.), wired polyethylene ("TORCON," Cook, Inc.), polyurethane ("DUCOR," Cordis Corp.), and woven Dacron ("Sones," United States Catheter Co.) were chosen for study.

Examples of each type of catheter also were studied by SEM in the pre-implant state and following their removal after 30 minutes in the circulation. The catheters were processed for SEM as previously described. Fixed, critical-point dried transverse and longitudinal sections of catheters were coated with gold-palladium and examined in a JELCO 7A SEM at an accelerating voltage of 25 kV. Internal reflection infrared spectroscopy, energy-dispersive x-ray analysis, and critical surface tension measurements were performed as described by Baier and his co-workers.

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SEM studies of the pre-implant group I catheter lumen showed a smooth surface containing irregular electron-light areas of unknown composition (Fig. 4A). The post-implant group I catheter lumen showed isolated aggregates of platelets and WBCs. No fibrin strands were visible (Table 1, Fig. 4B). SEM studies of the pre-implant group II catheters showed that the surfaces of both catheters consisted of small ridges containing irregular electron-light
areas of unknown composition (Fig. 4C). Post-implantation, the wired polyethylene catheter lumen showed dense aggregation of platelets, WBCs, and RBCs trapped in thick fibrin strands and mats (Fig. 4D). The lumen of the Teflon catheter showed occasional fibrin strands among which crenated RBCs were imbedded. In contrast to the wired polyethylene catheter, aggregates of platelets and WBCs could not be identified (Table 1). Like group II catheters, the surfaces of the pre-implant group III catheters also appeared to be irregular. The woven Dacron catheter showed a basket-weave pattern of cords with each cord consisting of 12 individual fibers. The surface of the polyurethane catheter showed numerous protrusions and grooves, some of which appeared electron-light (Fig. 4E).

Post-implantation, the lumina of both catheters contained well-developed fibrin mats with variable numbers of trapped platelet aggregates, RBCs, and occasional WBCs (Table 1, Fig. 4F).

Analyses of the catheters by means of energy-dispersive x-ray techniques and infrared spectroscopy showed that, in addition to the putative base...
polymeric material, all catheters tested contained variable amounts of inorganic fillers (Table 1). These fillers were present at the surfaces of both group II catheters (Table 1) and, presumably, could contact blood. Somewhat surprising was the finding that the surface of the group I catheter was coated with an intact layer of long chain fatty acid molecules. This aliphatic layer, rather than base polymer, would therefore be in contact with blood (Table 1). Incomplete focal patches of similar aliphatic fatty acid coating were also found on the wired polyethylene catheter (Table 1).

To further relate the surface properties of these catheters with their observed procoagulant effects, estimates of the surface free energy of pre-implant catheters were obtained by means of contact angle measurements. It was found that the critical surface tensions for each of these groups of catheters were different, with the group I catheter having critical surface tensions near 25 dynes/cm (Table 1). The other catheter classes had critical surface tensions significantly below and above this value (Table 1).

Discussion

The model system employed in these studies very closely simulates the actual clinical application of these devices and provides a dynamic index of their procoagulant activities within a time span comparable to that during which these catheters would actually be used. As shown by the SEM data, the cFPA measurements appear to correlate best with fibrin formation and seem to provide little information with regard to the contribution of platelets to the thrombotic process. It is important to note that the catheters studied were unused devices selected randomly from our regular clinical supplies and are therefore representative of the catheters in use at this and other medical centers.

A critical question raised by these studies concerns the mechanisms by which catheters exert their procoagulant effects. Bourassa and co-workers examined polyurethane and polyethylene angiographic catheters by SEM and found a correlation between adherent platelet-fibrin thrombi and catheter surface texture. While our findings in regard to surface texture are consistent with the observations of these workers, the contribution of surface roughness to catheter procoagulant effects is unclear. One cannot be certain from purely morphological studies whether smooth catheters lack procoagulant activity or more readily shed clots as they are forming. In the present study, the group I catheter showed low cFPA generation as well as reduced intraluminal clot accumulation, suggesting that the latter was not due simply to accelerated shedding of forming clot.

Determinants of catheter thrombogenicity likely are related to the physiochemical properties of the catheter surface present at the blood interface. Our finding that inorganic fillers, including silicates, were present at the blood interface of the group II catheters suggests that these catheters are capable of initiating blood clotting directly by activating factor XII.

The interaction with and adsorption of other clotting factors to various catheter surfaces also may affect the hemostatic compatibility of these devices. Based on surface chemical and biological analysis of a variety of synthetic materials, Baier and associates have hypothesized that surfaces with critical surface tensions that are within the range of 20–30 dynes/cm are likely to exhibit the least interactions with the biological milieu, including the least thrombus formation. Our findings show that, of all the catheters tested, only the group I catheter fell near the center of this hypothetical "biocompatible zone." Although the precise mechanism by which the surface free energy of these devices influences clot formation is now known, one possibility is direct activation of clotting zymogens due to severe conformational alterations associated with the adsorption of these proteins to the high and very low energy catheter surfaces, and the lesser modifications of proteins adsorbed to materials exhibiting the mid-range of critical surface tensions.

Alternatively, activated clotting factors generated by introduction of these devices may differentially adsorb to the catheter surfaces, producing clots localized to the catheter, which may either obstruct its lumen or cause emboli.

The origin of the fatty acid layer coating the group I catheter is not certain, but may be a result of the soaps used as extrusion aids in the manufacturing process. Recognizing that aqueous suspensions of sodium stearate and palmitate are procoagulant due to activation of factor XII, the features of the bound fatty acid coating on the group I catheter deserve special mention.

The substratum-bound configuration exposes only closely packed methyl end groups of the fatty chains to the aqueous phase, contrasted with the preferential exposure of fatty acids' polar end groups when present as micelles in suspension or as adsorbed to aliphatic boundary structures. Contact angle measurements clearly differentiate the polar and methyl terminal ends from one another, and from the hydrocarbon chain structure which separates them. Polar groups available at a surface cause low contact angles to be formed with all wetting liquids (therefore, giving high critical surface tensions); hydrocarbon chains give intermediate values of contact angle and critical surface tension (usually in the low 30's dynes/cm), whereas the -CH₃ end groups exhibit high contact angles (and low critical surface tensions). Only by going to nonbiological materials of the fluorocarbon type (e.g., Teflon) can even higher contact angles (and very low critical surface tensions) be obtained.

Contact angle data similar to those characterizing the group I catheter were obtained when thrombo-resistant heart valve cages which had been polished...
with tallow-based formulations were tested, and when filler-free silicone (polydimethylsiloxane) and polyalkylsulfone coatings—both exhibiting good blood compatibility—were studied. Critical surface tensions between 20 and 30 dynes/cm are found for all these materials, despite their considerable differences in backbone structure, because predominantly methyl-terminated side chains are exposed to the environment in each case. The probable extrusion aid used in making the group I catheter was a commercial mixture of starches and palmitates. The specific heavy metal salts of the fatty acids used and the particular mix of chain lengths are not controlling factors in the surface properties displayed by the residual coatings, given proper binding and orientation as described above.

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References


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