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Thrombogenicity of Heparin- and Non-Heparin-Coated Catheters: Clinical Trial

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Catheters used in clinical cerebral angiography were examined by scanning electron microscopy for buildup of thrombus. In 21 (67%) of 31 individuals studied with non-heparin-coated catheters, either cell aggregations or thrombi developed compared with seven (28%) of 25 individuals studied with heparin-coated catheters. The median size of the cell aggregations and thrombi on non-heparin- and heparin-coated catheters was significantly different ($p < 0.01$). The slopes that estimated the probable rate of thrombus formation were also significantly different ($p < 0.01$). This suggests the desirability of replacement of non-heparin-coated catheters if the angiographic procedure is extended.

The deposition of thrombi on vascular catheters has been demonstrated in laboratory animals and humans [1–3]. Platelets adhere to catheters soon after they are placed within the arteries. Later, red blood cells and white blood cells may be incorporated into the thrombi [4]. Embolization of these thrombi may result in cerebral dysfunction. This study was undertaken to determine whether thrombus formation could be reduced by the use of heparin-coated catheters.

Subjects

During a 10 month period we studied the catheters of 56 adult patients who underwent cerebral angiography. The patients were divided into two groups: (1) The control group comprised those whose identification numbers ended in an odd digit; they were examined with non-heparin-coated catheters. (2) The experimental group comprised those whose identification numbers ended in an even digit; they were studied with heparin-coated catheters.

The catheters were all tapered Hanafee catheters with an end hole inner diameter of 0.04 inch (1.02 mm). The heparin-coated catheters were all prepared by Aminkemi A B (Bromma, Sweden) according to a technique described by Lagergren and Eriksson et al. [5–7]. The technique consists of initially exposing the catheter to a cationic surfactant, then to heparin, and finally to a glutardialdehyde solution to bind the heparin to the catheter.

After the patients' groins were cleansed with Betadine and anesthetized with 5–10 ml of 1% xylocaine, the catheters were introduced into the femoral artery using the Seldinger technique. The blood that had refluxed into the catheters was then forcefully aspirated into a syringe filled with isotonic saline and heparin (5 U/ml), and a second, similarly filled syringe was reattached to the catheter and used to flush it clean. Subsequent guide wire manipulations were performed through the catheter in an attempt to place it in the appropriate cerebral vessel. Each manipulation was followed by an aspiration of blood and a flush of saline and heparin.

After the catheter had been positioned in either a carotid or vertebral artery, a heparin drip was started and continued until the appropriate diagnostic injection had been completed or the catheter had been removed. The guide wire and catheter manipulations were performed either by a neuroradiology fellow or a staff neuroradiologist. The catheter properties (heparin or nonheparin), catheter exposure time to blood (minutes), and the number of injections made through the catheters were all recorded. All test injections and

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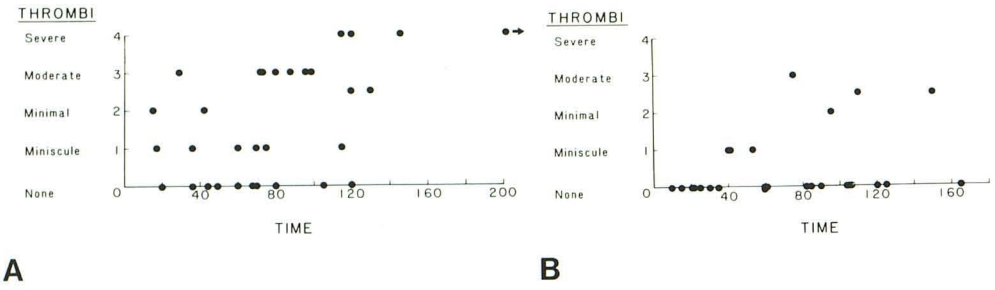


Fig. 1.—Distribution of thrombi on non-heparin- (**A**) and heparin- (**B**) coated catheters.

angiograms were performed with diatrizoate meglumine (Reno-M-60). Pull-out angiograms were also obtained on 10 heparin- and 12 non-heparin-coated catheters before they were removed. Pull-out angiograms were evaluated for possible thrombi. The continuous heparin flushes were maintained during withdrawal of the catheters to insure that clots would not form within them. Each patient's pedal pulses, groin appearance, and sensorium were checked throughout the rest of the day. A final assessment was made 24 hr after the procedure by a member of the neuroradiology staff.

As soon as the catheter was removed, the distal 1 cm of the catheter was cut off, placed in Karnovsky [8] solution, and allowed to fix for 1 week. The catheter tip was then prepared for the scanning electron microscope by splitting it in half, dehydrating it through a graded ethanol series, and, finally, by critical point-drying it with liquid carbon dioxide. The catheter was mounted to permit examination of half of the outer and half of the inner surfaces. The catheter halves were then sputter-coated with 100 Å of gold in a Polaron E5000 scanning electron microscope-coating unit. All catheters were processed in a similar manner. The catheters were examined in an AMR-900 scanning electron microscope 20 kV accelerating voltage.

The degree of cell aggregation and thrombus formation visible on the inner and outer catheter surfaces was graded as: none, no cells or thrombi present; miniscule, cells or thrombi covering less than 1% of the surface; minimal, cells or thrombi covering 1%–10% of the surface; moderate, thrombi covering 10%–50% of the surface; and severe, thrombi covering more than 50% of the surface. In addition, the scanning electron microscope was used to determine whether the catheter tips were smooth or rough.

The chi-square test was used to determine whether the difference in the number of thrombi in the moderate and severe group was statistically significant. The Mann-Whitney test (a nonparametric method for testing the equality of medians) was used to determine whether the difference in the median size of the cell aggregations and thrombi formed on heparin- and non-heparin-coated catheters was statistically significant. Only the inner surface was evaluated by these two tests because it was believed that cell aggregations and thrombi on this surface were more likely to be dislodged during angiography.

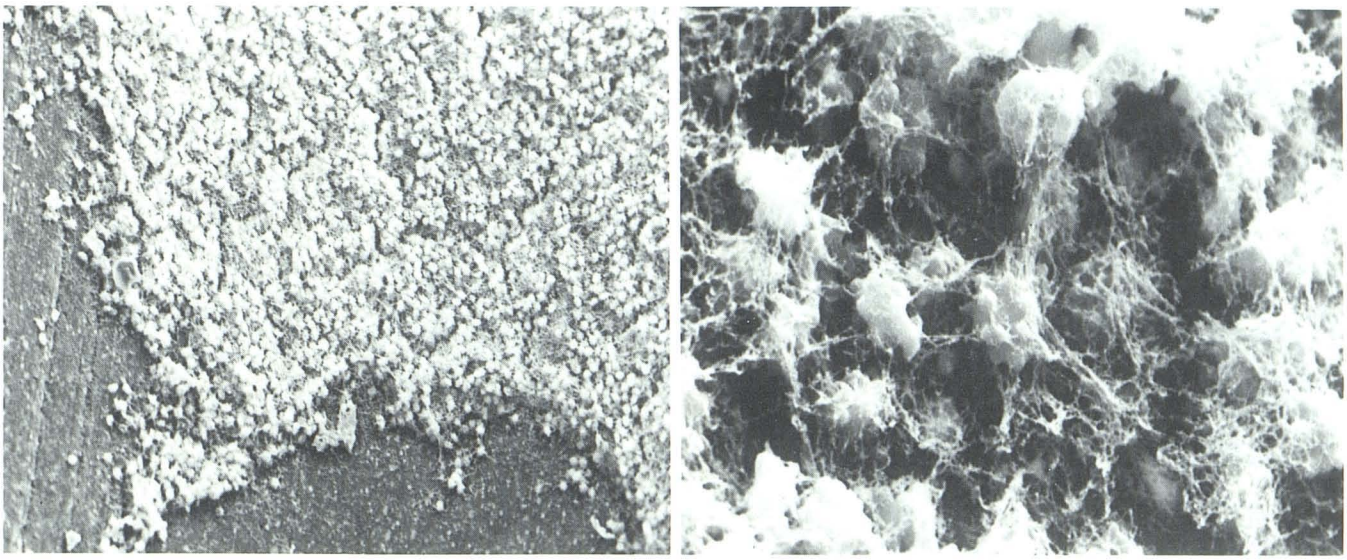
The probability that a clot would appear at any given time was calculated by fitting the following model: $p = e^{\beta_0 - \beta_1 T}$ in the control group, and $p = e^{\beta_0 - \beta_2 T}$ in the experimental group, where p = probability of clot forming; β_1 = instantaneous conditional probability that a clot will form on a non-heparin-coated catheter, provided that none has so far; β_2 = instantaneous conditional probability that a clot will form on a heparin-coated catheter, provided that none has so far; and T = time in minutes. The constant β_0 was found to be unnecessary and the estimated probabilities are: $p = e^{(-0.0160T)}$ for the nonheparin group and $p = e^{(-0.0048T)}$ for the heparinized group.

In these calculations, the distribution of the length of time without thrombi was assumed to be exponential. These probabilities were subsequently plotted against time (fig. 5). Finally, the model fit was evaluated by comparing the predicted and observed number of thrombi.

Results

Cell aggregations and thrombi were more frequently demonstrated on the inner surfaces of non-heparin-coated catheters (21 of 31) than on heparin-coated catheters (seven of 25) (fig. 1). A further breakdown showed that there were more moderate and severe grade thrombi on the inner surface of non-heparin-coated catheters (10 of 31) than on heparin-coated catheters (one of 25) ($p < 0.05$). Although the outer surfaces were not analyzed statistically, it was evident that cell aggregations and thrombi formed more frequently on the outer surfaces of non-heparin-coated catheters (15 of 31) than they did on heparin-coated catheters (five of 25). The number of cell aggregations and thrombi that formed on the outer surface was the same or less than the amount that formed on the inner surface in 49 of 56 catheters. The non-heparin-coated catheters were used for a mean time of 79 ± 45 min and the heparin-coated catheters for a mean time of 71 ± 44 min.

The non-heparin-coated catheters formed cell aggregations and thrombi that conformed to all four grades. Those that covered less than 1% of the catheter surfaces usually consisted of poorly organized clusters of cells that could not be considered to be thrombi. Sometimes these aggregations were related to catheter surface defects that had occurred either during manufacture or during guide wire manipulations. Some red blood cell aggregations appeared to have undergone echinocyte transformation. The cell aggregations that covered 1%–10% of the catheter surfaces were usually larger and better formed, and many could be considered to be thrombi. These cell aggregations were usually oval but could take a variety of forms. When thrombi became more extensive, they frequently coalesced and grew irregularly into the lumen; less frequently, they formed flat sheets (fig. 2). Sometimes these more extensive thrombi, which were always in the moderate or severe grades, had a cellular appearance; at other times, they had a more fibrinoid appearance. Sometimes the cellular thrombi were made up of echinocytes (fig. 3). The thrombi on the heparin-coated catheters did not appear markedly different from those on the non-heparin-coated catheters except for one moderate-sized thrombus (fig. 4). This thrombus differed from the



A B

Fig. 2.—Sheet of thrombus on non-heparin-coated catheter. **A**, Thrombus is juxtaposed with normal-appearing catheter surface (×170). **B**, Fibrin network has enmeshed red blood cells and platelets (×1,700).

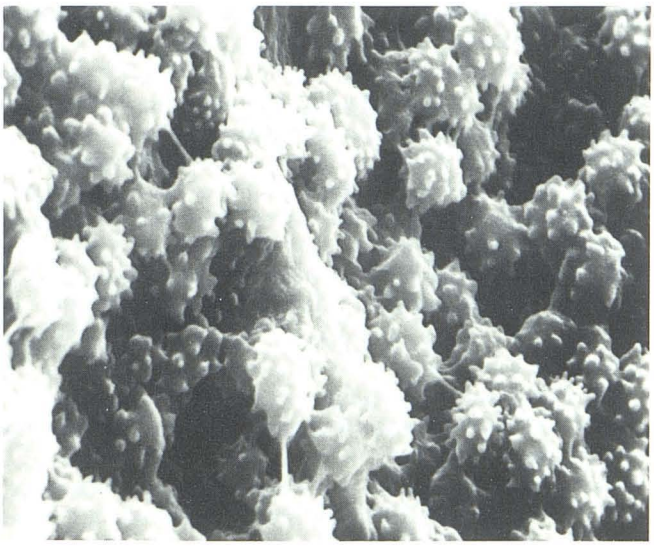


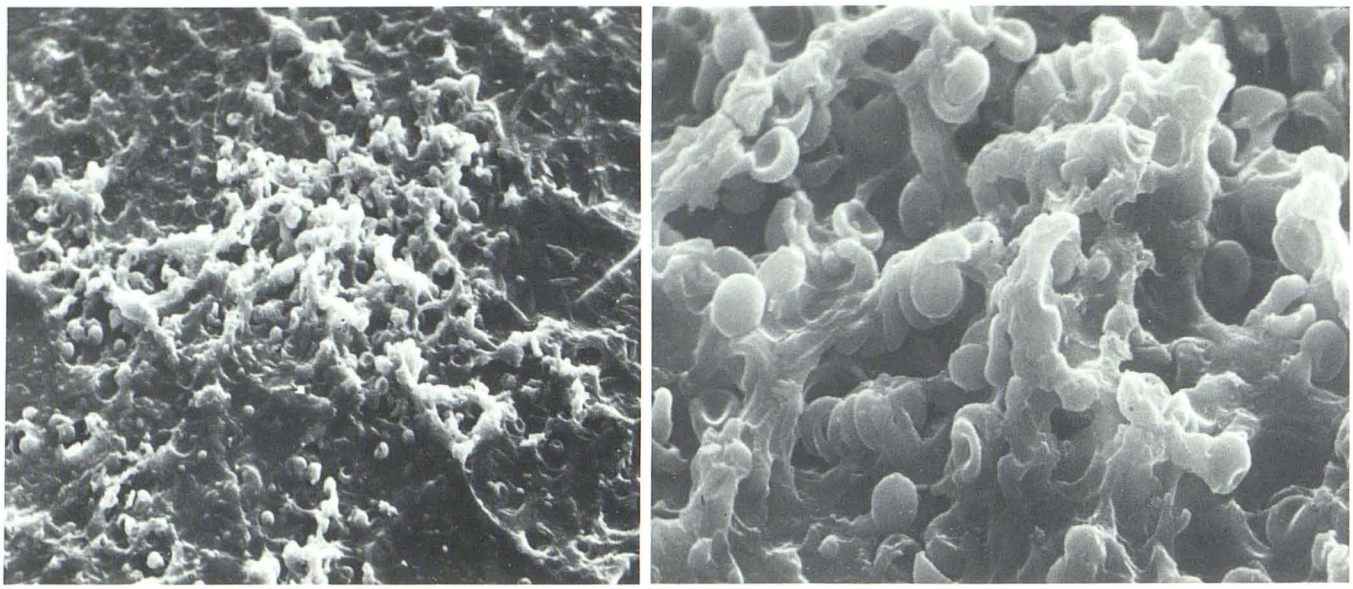
Fig. 3.—Cellular thrombus composed mainly of echinocytes in non-heparin-coated catheter (×1,700).

other moderate and severe thrombi by having small aggregations of cells that rose into the lumen of the catheter.

Cell aggregations and thrombi were not only more frequent in the nonheparinized group, but their median size was significantly larger. The Mann-Whitney test showed this difference to be significant at $p < 0.01$. In addition, the area covered by thrombi on a non-heparin-coated catheter, at any given time, was estimated to be roughly one grade higher than it would have been on a corresponding heparin-coated catheter.

The probability that cell aggregations and thrombi would appear on the inner surfaces of heparin- and non-heparin-coated catheters was plotted over 200 min from data present in figure 1 (fig. 5). The estimated slopes and, therefore, the estimated probabilities of thrombi forming, are significantly different in the heparinized and nonheparinized groups ($p < 0.01$). The standard error for the nonheparinized slope was 0.0039 and for the heparinized slope was 0.0018. At 1 hr, 25% of heparin- and 62% of non-heparin-coated catheters could be expected to have developed cell aggregations or thrombi, while at 2 hr, 44% of the former group and 85% of the latter group could be expected to have developed thrombi. The expected number of cell aggregations and thrombi at any given time correlated well with the observed number.

Although the two types of catheters showed different numbers of cell aggregations and thrombi, the two groups of patients showed no significant differences in age, gender, or admitting diagnoses. The presence of thrombi also showed no significant difference when it was correlated with the number of injections or the roughness of the catheter tip. An almost equal number of rough catheter tips was present in the heparinized and nonheparinized catheter groups. Pull-out angiograms, which were obtained in more than one-third of individuals, were normal in both groups of patients. No changes in pedal pulse or neurologic status were noted in the first 24 hr after angiography in either group. Groin hematomas appeared in four of 25 individuals studied with heparin-coated catheters as compared with two of 31 individuals studied with non-heparin-coated catheters. In three of the six individuals who developed hematomas, neither the inner nor outer surfaces of the catheters showed any cell aggregations or thrombi (two heparinized, one nonheparinized). No complications resulted from these hematomas.



A B

Fig. 4.—Moderate grade thrombus on heparin-coated catheter. Irregular small collections of cells protrude into catheter lumen. **A**, ×230. **B**, ×2,300.

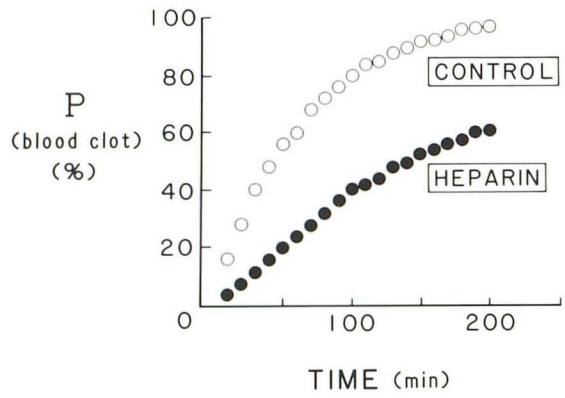


Fig. 5.—Probability that blood clot would appear on heparin- and non-heparin- (control) coated catheters.

Discussion

The potentially serious sequelae of embolization from catheters have led to several attempts to reduce thrombus formation. Some investigators have attempted to identify the thrombogenic properties of various catheters [3, 9, 10]. Others have premedicated the patients with salicylates, dextran, and heparin [9, 11–13]. The catheters have also been coated with heparin. Initially, these efforts were unsuccessful because heparin leached from the catheters when they were exposed to blood [2, 14–16]. This drawback was overcome by the development of a technique that stabilizes heparin to catheters [5, 6]. We have used these stably-bound heparin-coated catheters to determine whether their use would reduce thrombus formation as detected by a scanning electron microscope. Our results suggest that, within similar time frames, heparin-coated catheters accumulate fewer thrombi and, thus, should reduce cerebral embolic complications. However, although heparin coating reduces thrombus formation, it does not eliminate it as an earlier report suggests [17].

The importance of thrombus formation on the inner surface of catheters lies in the fact that these thrombi are likely to be dislodged during injections of contrast material and guide wire manipulations. In contrast, thrombi on the outer surfaces are less likely to be dislodged because they are only subject to the constant flow of arterial blood and its relatively small pressure variations. However, the fact that few thrombi were seen on the outer surface of both groups of catheters may be deceiving and may really indicate that thrombi had been stripped from the outer surfaces during their withdrawal.

The identification of echinocytes in many cell aggregations and thrombi may be important. It is known that normal biconcave red blood cells (discocytes) can undergo a variety of changes, one change being its transformation into spheres covered with crenations or spicules (echinocytes) [18]. The transformation of red blood cells into echinocytes may occur after several isotonic sodium chloride washes and in the presence of heparin [18, 19]. Transformation under these conditions may be significant since an analogous situation exists when normal saline and heparin is flushed through a catheter in an attempt to keep it clean and dripped through the catheter to keep it open. The echinocyte transformation may also occur when normal red blood cells come into contact with substances such as barbiturates, phenylbutazone, and salicylates and with changes in the environment itself (i.e., pH and tonicity of the medium) [20, 21]. The change in tonicity of the medium may be especially important during the injection of a con-

trast material such as Reno-M-60, since this agent has five times the milliosmole concentration of normal plasma.

An awareness that about two-thirds of nonheparin catheters can be expected to have cell aggregations or thrombi at 1 hr should encourage the cerebral angiographer to perform the procedure with a concern for time. If the arteriogram is unduly prolonged, one might consider replacing the catheter or using a heparin-coated catheter. Our suggestion, when using non-heparin-coated catheters, is that this replacement be considered at 1 hr and be mandatory by 2 hr, the cell aggregates being rather low grade at 1 hr but moderate to severe grade at 2 hr. The angiographer should also remember the interdependence of thrombus formation and technique since the rate of thrombus formation on the inner surface of the catheter is largely related to the amount of blood that is allowed to reflux into the lumen. Finally, the angiographer should remember that rough guide wire manipulations may abrade the catheter surface and make it more susceptible to thrombus formation and that repeated injections of contrast material and saline may change the very nature of the thrombus itself.

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