Platelet and Fibrin Modification by Radiographic Contrast Media

Don A. Gabriel, Marsha R. Jones, Neil S. Reece, Emily Boothroyd, and Thomas Bashore

The effect of the radiographic contrast agents, iopamidol and diatrizoate, on fibrin assembly and structure as well as platelet surface charge was studied. Increasing the iopamidol concentration from 0 to 4.5 mM prolongs the fibrin gelation time from 20 to 105 seconds (an anticoagulant effect) and reduces the fibrin fiber mass/length ratio from $3.2 \times 10^{12}$ to $0.5 \times 10^{12}$ Da/cm (i.e., produces very thin fibrin fibers). Ultraviolet difference spectroscopy of fibrinogen showed both a 15-nm shift in the ultraviolet difference maximum for iopamidol (suggesting binding) and a perturbation of the aromatic amino acid side chain region for fibrinogen (suggesting a conformational change in fibrinogen) as the concentration of iopamidol was increased from 0 to 9 mg/ml. Binding of iopamidol to fibrinogen was also shown by affinity chromatography using a Sepharose-fibrinogen column. Electrophoretic quasi elastic light scattering was used to show platelet interaction with iopamidol as reflected in a reduction in the platelet electrophoretic mobility from 2.0 to 0.5 ($\mu$m-cm)/(V-sec) as the concentration of iopamidol was increased from 0 to 4.5 mM. In addition, the ionic radiopaque contrast agent, Renografin, was also studied and found to inhibit fibrin monomer assembly. Although iopamidol is not shown to be thrombogenic, iopamidol does appear to reduce platelet surface charge, bind fibrinogen, and modify fibrin clot structure. (Circulation Research 1991;68:881–887)

It is reported that nonionic agents appear to have less anticoagulant activity than ionic agents and, thus, permit expression of the inherent thrombogenic risks related to the invasive nature of the catheterization technique.1 Thrombus formation during the catheterization procedure has occasionally been observed with the use of nonionic radiopaque contrast media.2 On rare occasions, a thrombus has been observed to propagate at the catheter tip and then embolize to the coronary artery, requiring lytic therapy for resolution. Patients with thrombotic diseases who require diagnostic evaluation with radiopaque contrast media are often a subset of the population at highest risk for thrombotic complications. Therefore, nonionic contrast agents may exert a pathological influence through effects on fibrin assembly and platelet function. Grollman et al2 reported thromboembolic complications presumed to be related to the nonionic contrast media in three patients undergoing coronary artery catheterization despite heparinization. Of approximately 10,000 patients in whom nonionic contrast has been used during cardiac catheterization at Duke University Medical Center, 12 cases of unexplained coronary thrombosis or adherent clots at the catheter tip have been reported. Thus, although the incidence of clinical thrombosis is low, the effects may be devastating. These unexplained thromboembolic complications prompted an investigation of the influence of nonionic contrast media on fibrin assembly and structure and on fibrinolysis and platelet function. We sought to investigate the in vitro effects of a nonionic radiographic contrast agent, iopamidol, on platelet surface charge and fibrin assembly in an effort to further elucidate the potential thrombogenicity of these nonionic contrast agents. A comparison between iopamidol and an ionic radiopaque agent, Renografin, is shown.

Materials and Methods

Fibrinogen Preparation

Buffered human fibrinogen (Kabi, Stockholm) was purchased as a lyophilized powder and dissolved in water. After equilibration with the appropriate buffer, the fibrinogen was further purified over lysine Sepharose and gelatin Sepharose (BioRad, Richmond, Calif.) columns to remove plasmin(ogen) and...
fibronectin, then dialyzed against 0.3 M NaCl, aliquoted, and frozen at –70°C. Clottable fibrinogen was greater than 95%. Reduced sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) of fibrinogen gave the typical triple band pattern without other detectable contaminating proteins. Fibrinogen concentration was measured spectrophotometrically at 280 nm using an extinction coefficient of 1.6 mg/(cm·ml).

Iopamidol (Isovue 370, E.R. Squibb & Sons, Inc., Princeton, N.J.), with $M_t$ of 777, was obtained as a 0.972 M solution buffered with 8.26 mM Tris and 1.3 mM EDTA, pH 7.1. Dilutions of iopamidol were maintained in buffers calculated to be identical to those used for actual injection in the catheterization procedure. Renografin (816 mM meglumine diatrizoate plus 157 mM sodium diatrizoate) was a gift of Squibb. Sodium diatrizoate, with $M_t$ of 636, and meglumine, with $M_t$ of 195, were purchased from Sigma Chemical Co., St. Louis.

**Turbitdity**

Fibrin gels for turbidity measurements were formed directly in 1-cm polystyrene cuvettes by mixing purified fibrinogen solutions (1 g/l) with buffered solutions of $\alpha$-thrombin (Sigma and Dr. Frank Church, University of North Carolina, Chapel Hill). The final thrombin concentration was 1 NIH unit/ml. Gels were formed at 0.05 M Tris, pH 7.4, and 5 mM CaCl$_2$, and the ionic strength was adjusted to 0.15 with NaCl. In these experiments, ionic strength and variation in polymerization buffers were carefully controlled so that the effect of iopamidol could be isolated and studied.

Turbidity measurements were made at 37°C with a spectrophotometer (model 118C, Cary, Palo Alto, Calif.) as previously described.$^3$ Refractive index measurements were made in a temperature-controlled Abbe-3L refractometer (Bausch & Lomb, Rochester, N.Y.), and refractive index increments were made in a differential refractometer (Brice-Phoenix, Newton, Pa.) equipped with a HeNe laser as the light source.

**Ultraviolet Difference Spectroscopy and Derivative Spectroscopy**

Measurements were made on a ratio recording dual beam Cary 118C spectrophotometer equipped with temperature-controlled cell holders. Identical samples from the same stock solution were introduced into matched tandem cuvettes (Precision Cells, Hicksville, N.Y.) and placed in temperature-regulated cell holders. Identical concentrations of the contrast and fibrinogen were used in both the reference and sample tandem cells. The front compartment of the reference tandem cell contained buffer and iopamidol, and the back compartment contained buffer and fibrinogen. The front compartment of the sample tandem cell contained only buffer, and the back compartment contained buffer, iopamidol, and fibrinogen. Thus, difference spectra could be obtained between the two samples, which were identical in sample concentration but different in sample composition.$^4$ Scans were obtained from 260 to 300 nm. Conformational changes induced in fibrinogen by iopamidol were reflected by alteration in the absorption spectra of fibrinogen and seen in the difference spectra. The concentration of iopamidol was varied so that the binding characteristics of the iopamidol to fibrinogen could be determined. First-derivative spectra from 260 to 300 nm were obtained for reference aromatic amino acids as well as for fibrinogen and iopamidol. Changes observed in fibrinogen caused by iopamidol could then be compared with derivative spectra for tryptophan, tyrosine, and phenylalanine.$^5$

**Platelet Preparation**

Human platelets were drawn fresh daily from normal donors into standard adenosine-citrate-dextrose (ACD) anticoagulant, 7 ml/50 ml whole blood. Platelets were isolated as platelet-rich plasma by differential centrifugation at 50g for 20 minutes at 25°C. The platelets were then pelleted at 450g for 15 minutes and resuspended in citrate buffered saline (13 mM sodium citrate, pH 7.4, and 0.15 M NaCl). Platelets were washed twice with citrate buffered saline and used within 1–3 hours. Platelets for light scattering experiments were suspended in buffer containing the desired molarity of NaCl (5–150 mM), 2 mM HEPES buffer, pH 7.4, and enough sucrose to maintain isomolar conditions of 280 siemens.$^6$

**Electrophoretic Quasi Elastic Light Scattering**

Electrophoretic light scattering measurements were made on a quasi elastic light scattering spectrometer (DELSA, Coulter Corp., Hialeah, Fla.) mounted on a Newport vibration isolation table (Fountain Valley, Calif.). Measurements were made at four different scattering angles simultaneously. The electrophoretic effect was obtained by superimposing a uniform electric field (usually 150–500 V/cm) across the sample. The field was pulsed, and the polarity of the field was alternated so that Joule heating and mass accumulation were avoided. The measured signal is scattered light from platelets moving in an electric field. At a fixed observation angle, the scattered light is observed as an oscillating intensity described in the heterodyne experiment as a second-order field autocorrelation function$^6,7$:

$$G^{(2)}_{\text{Lheter}}(\tau) = I^2_L + 2I_L <I_x \cos(K \cdot n_x \tau) e^{-D \kappa^2}$$

where $I_L$ is the intensity of the reference beam (local oscillator); $I_x$ is the intensity of the scattered light; $K$ is the scattering vector defined by $K=(4\pi n/\lambda)\sin(\theta_z/2)$, where $\theta_z$ is the scattering angle, $n$ is the refractive index, and $\lambda$ is the wavelength of light; $v_x$ is the velocity of the scattering particle; and D is the diffusion coefficient. The important quantity in this experiment is $K \cdot n_x$, which is the Doppler shift of the signal resulting from the particle motion. The Fourier transform of the measured autocorrelation function gives the power spectrum from which the particle electrophoretic mobilities are calculated.$^6,7$ Data
validation requires that identical mobilities be obtained at all scattering angles. Sample temperature, ionic strength, pH, osmolarity, and conductivity were carefully controlled. Joule heating was minimized by regulation of the pulse frequency and the pulse duration of the superimposed electric field. Thermal lensing was avoided by regulation of the laser power incident on the sample. Electroosmosis was minimized by coating the scattering cell first with (γ-glycidoxypropyl)trimethoxysilane (Dow Corning) followed by methylcellulose. Lack of electroosmosis was proven by demonstration of flat electrophoretic mobility profiles across the scattering cell. Conductivities were measured using a conductance–resistance meter (YSI model 34, Yellow Springs Instrument Co., Yellow Springs, Ohio) in addition to the built-in conductance function of the eletrophoretic light scattering spectrometer.

Fibrinogen Affinity Column Preparation

The affinity columns were prepared using a modification of the method outline by Coller.9 Affi-Gel 15 (BioRad) was stirred and centrifuged at 10,000g for 2 minutes to remove the isopropanol. The supernatant was removed, and the beads were suspended in 0.01 M sodium acetate, pH 6.0 (1.2 ml buffer for 1 ml beads). This procedure was repeated three times to ensure complete removal of the contaminating alcohol. The beads were then dried and resuspended in a 2 mg/ml fibrinogen solution in 0.03 M sodium citrate, pH 7.5 (1.5 ml solution/1 ml gel). This mixture was allowed to rock for 4 hours at 4°C. The gel was then dialyzed for 24 hours against 0.03 M sodium citrate, pH 7.5, to remove any reaction byproducts. The fibrinogen coupled with an efficiency of 80–87%. The fibrinogen-conjugated beads were then washed extensively with 0.15 M NaCl, 0.01 M Tris, and 0.05% sodium azide, pH 7.4, until the supernatant fibrinogen concentration approached 0 mg/ml. The beads were next washed with a solution of 3% SDS, 8 M urea, and 20 mM NaH2PO4 at 37°C for 1 hour to remove adsorbed protein. The solution was then reconstituted with 0.1 M NaCl, 0.05 M Tris, and 5 mM CaCl2, pH 7.4. A control column without fibrinogen conjugated to the support matrix was prepared to rule out nonspecific binding of iopamidol to the column matrix.

Results

Electrophoretic Light Scattering Studies

The effect of iopamidol on platelet surface charge was evaluated by electrophoretic quasi elastic light scattering. Typical electrophoretic quasi elastic light scattering spectra are shown in Figure 1. The important measured experimental platelet property is the magnitude of the shift in the platelet electrophoretic mobility that results from changes in the platelet surface resulting either from the activation process or from interaction with other solution molecules (e.g., by ligand binding). In run A of Figure 1, freshly prepared platelets in the absence of iopamidol are shown to have an electrophoretic mobility of −1.97 (μm-cm)/(V-sec). As ligands are bound to the platelet, its surface potential is altered and is reflected by a different electrophoretic mobility. Run B of Figure 1 shows a change in the platelet mobility from −1.97 to −0.65 (μm-cm)/(V-sec) when 250 mM iopamidol is present. Therefore, the presence of iopamidol changes the platelet mobility and, hence, its surface properties.

Experiments at 25°C to determine the platelet electrophoretic mobility as a function of increasing iopamidol are shown in Figure 2. The ionic strength and conductivity at each different iopamidol concentration were rigidly maintained constant throughout all iopamidol experiments so that platelet mobilities at different iopamidol concentrations could be compared. At concentrations of iopamidol less than 100 mM, the mobility of the platelets increases from −2.0 to −2.3 (μm-cm)/(V-sec). Above 100 mM the mobility rapidly decreases to −0.5 (μm-cm)/(V-sec) at 600 mM iopamidol, reflecting a reduction in the platelet surface charge. Typical concentrations of contrast media obtained in vivo during cardiac catheterization based on 20 patients include the following: left
coronary artery immediately after injection, 100–450 mM; left ventricle as soon after left ventricle injection as possible, 50 mM; and femoral vein after procedure, less than 50 mM (authors’ unpublished observations). High concentrations of iopamidol reduced the platelet surface charge to near that of platelets activated with ADP. When platelets were activated with 1 μM ADP, the electrophoretic mobility decreased to a minimum, and no further modification of the surface potential could be observed by iopamidol. The decreased mobility at least in part reflects a decreased surface charge. In vivo, a decrease in the platelet surface charge would promote platelet–platelet interaction and decrease the work required for the platelet to approach the negatively charged endothelial cell surface.

**Fibrin Studies**

Figure 3 shows the effect of iopamidol on fibrin assembly kinetics. Buffered fibrinogen solutions containing 1 g/l human fibrinogen, 5 mM CaCl₂, and 0.05 M Tris, pH 7.4, were prepared as a function of increasing iopamidol concentrations. The ionic strength was maintained constant at 0.15 by the addition of NaCl. All measurements were made at 37°C. Fibrinogen was added at time 0 to the buffered human α-thrombin–iopamidol solution (final thrombin concentration was 1 NIH unit/ml), and the turbidity was followed as a function of time. The first appearance of the gel is indicated as an increase in turbidity. Figure 3 shows two important effects of iopamidol on fibrin assembly. As the concentration of iopamidol is increased from 0 to 4.5 mM, the turbidity decreases from 0.288 to 0.063 o.d. units and indicates that the fibrin fibers become thinner (or, alternatively, the mass density of the fibers is decreased) as the iopamidol concentration is increased. Because the effect of iopamidol on fibrin assembly was great, clinical concentrations of iopamidol were diluted from 972 mM to the range of 1–10 mM, so that measurements could be made. A second feature seen in Figure 3 is an anticoagulant effect, shown as an increase in the gelation time (the first appearance of an increase in turbidity) from 20 to 105 seconds as the concentration of iopamidol is increased from 0 to 4.5 mM.

The dramatic effects of iopamidol, a nonionic radiopaque agent, were compared with those of an ionic contrast agent, Renografin. Renografin is a mixture of diatrizoate (a cationic molecule) and meglumine (a positively charged paramagnetic molecule). The effects of Renografin on the fibrin fiber mass/length ratio are more dramatic than those of iopamidol since a lower concentration of dye is required to decrease the mass/length ratio of the fibrin fibers than for iopamidol (open triangles in Figure 4).

**Figure 2.** Graph showing the effect of increasing amounts of iopamidol on platelet mobility (open circles) as a plot of platelet mobility versus iopamidol concentration. Platelets were suspended in 5 mM NaCl, 2 mM HEPES, pH 7.4, and 0.28 M sucrose; the concentration of iopamidol varied as indicated. Similar experiments for 1 μM ADP–activated platelets are shown as filled circles. ADP-activated platelets have a much lower mobility and, thus, surface charge than resting platelets. Iopamidol does not appear to influence platelet surface potential on ADP-activated platelets.

**Figure 3.** Graph of fibrin assembly kinetics shown as turbidity versus increasing iopamidol concentration at 37°C. Initial fibrinogen is 1 g/l in 5 mM CaCl₂, 0.05 M Tris, pH 7.4, and a variable concentration of iopamidol (0 mM [○], 0.39 mM [●], 0.64 mM [△], 1.03 mM [▲], 1.29 mM [□], 3.22 mM [▲], and 4.5 mM [▽]) with enough NaCl to maintain the ionic strength at 0.15. Thrombin, final concentration of 1 NIH unit/ml, is added at time 0. Lower turbidity indicates thinner fibrin fibers.

**Figure 4.** Graph showing mass/length ratios as a function of increasing contrast agent: Renografin and megluminediatrizoate (●), diatrizoate alone (○), and iopamidol (△). Iopamidol has less effect on the mass/length ratio at contrast media concentrations less than 2 mM, but at higher concentrations of dye, the effects are similar.
However, at in vivo dye concentrations typical for cardiac catheterization, both contrast agents will have a similar effect on fibrin structure. The mass/length ratio is seen to decrease from \(3.0 \times 10^{12}\) to \(0.28 \times 10^{12}\) Da/cm as the percent dilution of neat Renografin is increased. Studies using either Renografin or meglumine diatrizoate are identical, as evidenced by the flat line. As the iopamidol concentration is increased, absorption differences appear in the aromatic side chain region. Tandem cells were used in a double beam ultraviolet spectrophotometer.\(^5\)

![Graph](http://circres.ahajournals.org/)

**Figure 5.** First derivative spectra for the aromatic amino acid region of fibrinogen as a function of increasing iopamidol concentration. Four different spectra are shown at four different iopamidol concentrations. In the absence of iopamidol, fibrinogen in both the reference and sample chambers is identical, as evidenced by the flat line. As the iopamidol concentration is increased, absorption differences appear in the aromatic side chain region. Tandem cells were used in a double beam ultraviolet spectrophotometer.\(^5\)

![Graph](http://circres.ahajournals.org/)

**Figure 6.** Graphs showing binding of iopamidol to a fibrogen affinity column. Fibrinogen affinity chromatography was performed on either fibrinogen-Sepharose or Affi-Gel 15 fibrinogen, which had been washed with 3% sodium dodecyl sulfate and 6 M urea and equilibrated with 0.1 M NaCl, 0.05 M Tris, and 5 mM CaCl\(_2\), pH 7.4. Iopamidol (10 mg) was loaded onto the column. Unbound iopamidol was washed through with the elution buffer. In the left panel, the control column (\(\triangle\)) of Sepharose alone shows that iopamidol is not bound to the column matrix. Iopamidol bound to the fibrinogen-Sepharose is not eluted with either a pH gradient (\(\bullet\)) or a NaCl gradient (\(\bigcirc\)). However, in the right panel, the bound iopamidol is eluted with 3% sodium dodecyl sulfate and 6 M urea.
iopamidol when the fibrinogen-Sepharose gel was scanned. Iopamidol was eluted only when 3% SDS, 6 M urea, and 0.02 M NaH$_2$PO$_4$ was used as the eluting buffer (Figure 6, right panel). After elution with 3% SDS and 6 M urea, no iopamidol was detected on the affinity column. Iopamidol was not bound to the Sepharose or Affi-Gel 15 matrix, since no binding was noted when iopamidol was exposed to Sepharose alone (Figure 6, left panel). Reversible binding of iopamidol to fibrin was not shown, which prevented further thermodynamic analysis of ligand binding.

**Discussion**

The unusual occurrence of clot formation and subsequent embolization to the coronary arteries during cardiac catheterization suggests interaction between the coagulation system and contrast media.$^9$ Since the composition of the thrombus is most likely fibrin and platelets, our study examined the effect of in vitro iopamidol and diatrizoate on fibrin assembly and platelets.

**Fibrin Studies**

Clinically relevant structural features of fibrin include fibrin fiber diameter and density, fibrin gel pore size, and fibrin mechanical rigidity. These material properties of fibrin are important for normal physiological function and are influenced by affector assembly kinetics.$^{10,11}$ Fibrin structure can be greatly modified by microenvironmental effects such as small shifts in pH and ionic strength or the presence of nonnongelling molecules.$^{12-16}$ Disturbance of the assembly kinetics governing these conditions by changes in rate of fibrin monomer production from fibrinogen, by interaction of nonnongelling molecules with fibrin monomers, or by changes in viscosity and, hence, the diffusion coefficient of the forming protofibrils results in modification of the final fibrin structure. In addition to the slower rate of clot formation and different mechanical rigidity, the altered fibrin structure may also influence fibrin dissolution. Two specific material properties may be of great importance to fibrinolytic kinetics, namely, the fiber size$^{17}$ and the gel pore size. The fiber size provides surface for binding of nongel molecules such as Factor XIIIa, tissue plasminogen activator, plasmin(ogen), and fibrinolytic inhibitors (e.g., α₂-antiplasmin).

We show in this study that the ionic contrast agent, diatrizoate (a component of Renografin), and the nonionic contrast agent, iopamidol (the major constituent of Isovue 370), alter fibrin assembly.$^{18}$ Prolonged thrombin clotting times for the nonionic contrast agents are recognized but are less dramatic compared with the ionic contrast media, suggesting a mild anticoagulant effect.$^{18}$ Kinetic data presented here show a marked fibrin polymerization delay induced by increasing amounts of iopamidol (Figure 3). The effect of iopamidol on fibrin structure was so great that the iopamidol concentration used in the turbidity experiments was diluted from 972 mM, the usual concentration of iopamidol for cardiac catheterization, to 4.5 mM. As shown in this study, both iopamidol and diatrizoate modify fibrin structure by producing extremely thin fibrin fibers. Thin fibers modified by iopamidol or diatrizoate may result by modification of the lateral binding site on the fibrin protofibril so that protofibril–protofibril interaction is decreased and, thus, protofibril assembly time is extended, resulting in abnormally long protofibrils. The extended assembly time is reflected in a prolonged thrombin clotting time. Although high ionic strength will also reduce the fibrin mass/length ratio, the effect observed by diatrizoate cannot be explained by its contribution to the solution ionic strength. In dilute solutions, ionic contrast media show more effect on fibrin modification than do the nonionic agents, since lower concentrations of the ionic agents are required to modify fibrin. The ultraviolet difference spectra show that iopamidol binds to fibrinogen and that the binding is associated with a conformational change in fibrinogen as indicated by perturbation of the aromatic side chain portion of the difference spectra. The chemical nature of the iopamidol-fibrinogen interaction was further studied by fibrinogen affinity chromatography. Once iopamidol was bound to the fibrinogen-Sepharose column, iopamidol was removed by 3% SDS, 6 M urea, and 20 mM phosphate buffer, pH 7.4. No binding of iopamidol to Sepharose alone was noted. Temperature did not influence the iopamidol binding to fibrinogen. We offer compelling evidence that alteration of fibrinogen by the interaction with contrast media underlies the basis for fibrin modification by the contrast agents.

The internal structure of the fibrin gels has been previously studied by holographic relaxation spectroscopy, which can monitor the diffusion of small nongel molecules within fibrin gels$^{19}$ and has indicated that fibrin remains very porous even in the presence of iopamidol (data not shown). The volume fraction of fibrin in the clot is very low, typically less than 10%. The combination of the findings of thin fibers and an open gel suggests that iopamidol-modified fibrin fibers may be very dense. A previous study$^{17}$ suggests that thin fibrin fibers are more resistant to fibrinolysis by plasmin. Thus, the formation of clots with thin fibers may resist intrinsic fibrinolytic mechanisms. Thin fibrin fibers produced by the effect of the contrast media are more resistant to fibrinolysis based on experiments including the following: light scattering methods, reduced SDS-PAGE gels to follow the rate of fibrinolysis, and an enzyme-linked immunosorbent assay to assess plasmin binding to fibrin (authors' unpublished observations). Although iopamidol retards fibrin formation, if enough thrombin is present to clot fibrinogen at the catheter tip, the iopamidol-modified clot is more difficult to lyse because of the thinner fibrin fibers.

**Platelet Studies**

The platelet surface charge may be reduced by the undiluted contrast media at the catheter tip. Less inhibition of platelet aggregation has been reported for the nonionic contrast media, but no data on
Summary

Contrast media have multiple effects on the coagulation system. The platelet surface charge is reduced so that less coulombic repulsion between platelets is present, but no consistent spontaneous platelet aggregation was observed in these studies. Fibrin is modified with the production of very thin fibrin fibers. We emphasize that there is an anticoagulant effect of iopamidol as evidenced by the prolonged fibrin gelation time and that iopamidol itself is not sufficient to initiate fibrin assembly. However, if the generation of small amounts of thrombin during the catheterization procedure occurs, it could be sufficient to further stimulate platelets and to initiate abnormal fibrin structure. It is likely that a complex combination of events must occur before clinically relevant clot formation is observed. Clearly, better understanding of the coagulation effects of contrast agents in general and nonionic agents in particular is warranted as these agents become more widespread in their usage. Understanding the sequence of events that lead to thrombus formation should allow strategies to be developed for the prevention of thrombosis.

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