Dusart Syndrome: A New Concept of the Relationship Between Fibrin Clot Architecture and Fibrin Clot Degradability: Hypofibrinolysis Related to an Abnormal Clot Structure

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Fibrinogen Dusart is a congenital dysfibrinogenemia (A-α 554 Arginine → Cysteine) associated with severe thrombotic disorder, high incidence of thrombosis, and abnormal fibrin polymerization. This thrombotic disorder was attributed to an abnormal clot thrombolysis with reduced plasminogen binding to fibrin and defective plasminogen activation by tissue plasminogen activator. The purpose of this work was to assess whether clot architecture could be involved in the thromboresistance of the fibrin Dusart and the high incidence of embolism. An important change in Dusart fibrin clot structure was identified with dramatic decrease of gel porosity (Ks), fiber diameters (d), and fiber mass-length ratios (μ) derived from permeation analysis. In addition, rigidity of the Dusart clot was found to be greatly increased compared with normal fibrin.

HYPOFIBRINOLYSIS is the most common finding in patients with thrombotic tendency. This may be related either to an increased baseline of plasminogen activator inhibitor (PAI) or to a deficient release of tissue-type plasminogen activator (t-PA). Such situations are well illustrated by venous stasis or other stimuli.

In 1983, a new cause of hypofibrinolysis was described in studies of a dysfibrinogenemia associated with a severe thrombotic disorder. Abnormal fibrin polymerization consisting of defective lateral aggregation was thought to be the cause. Furthermore, plasminogen binding to the abnormal clot was lower than in normal control clots. Therefore, it was argued that the severe thrombotic disease observed in the patient, which led to the death of his two brothers, could be related to the abnormal polymerization that decreased the availability of the plasminogen at the fibrin surface. This state was called the Dusart syndrome from the name of the family in whom the anomaly was discovered. However, it was not clear whether this anomaly was due to an abnormal plasminogen binding site or to a decrease in accessibility of binding sites in the abnormal clot structure. Indeed, the fibrin network of Dusart clots consisted of thin fibrin fibers resulting from a defective lateral aggregation of the protofibrils. The more recent discovery that a mutation in the A-α chain, where the arginine 554 was replaced by a cysteine, causes the dysfibrinogenemia emphasizes the importance of the C terminal portion of the molecule in lateral aggregation of the protofibrils. Defective thrombolysis related to abnormal clot structure is also found in patients suffering from thrombotic disorder without any detectable qualitative anomaly of fibrinogen, because a recent clinical study showed that about 10% of patients presenting deep vein thrombosis (DVT) had impaired fibrinolysis. This was suggested by a slight elevation of the plasma D-dimer levels as a function of the thrombus size, although plasma levels of t-PA and PAI were not different from patients having an efficient thrombolysis in vivo with high plasma D-dimer levels. This group of patients with poor lysis did not improve under heparin or thrombolytic therapy.

The present study investigates the relationship between abnormal clot architecture and defective thrombolysis in fibrinogen Dusart. Evidence is reported that the mutation A-α 554 Arginine → Cysteine dramatically alters the clot structure and function, diminishing plasminogen availability to the fibrin network and causing severely defective thrombolysis. Furthermore, dextran reverses the clot resistance to thrombolysis by restoring a normal clot architecture. Because such compounds are available in clinical practice, this suggests the usefulness of modifying clot architecture to improve thrombolysis.

**MATERIALS AND METHODS**

**Materials**

Blood samples from normal individuals and the patient were collected in trisodium citrate (1 vol of 0.13 mol/L citrate for 9 vol of blood), and plasma was prepared by centrifugation (2,500g for 20 minutes). Platelet-poor plasma was obtained by recentrifugation of the plasma at 10,000g for 20 minutes and stored at −80°C. Thrombin was purchased from Roche Laboratory (Basel, Switzerland). rt-PA was from Boehringer (Ingelheim, Germany). Glu-plasminogen was from Kabi Vitrum (Mölndal, Sweden). Aprotinin was from Bayer (Wuppertal, Germany). Dextran 40,000 molecular weight...
(MW) was from Assistance Publique (Paris, France). Bovine serum albumin (BSA) was from Sigma (St Louis, MO).

Methods

All experiments were performed using plasma fibrin clots with or without dextran 40,000 MW at various concentrations. Dextran was added to plasma before clotting. The functional plasma fibrinogen concentration was determined according to Claus.\(^6\)

Viscoelastic Properties of the Clot

Viscoelastic properties of the clot were studied using permeation analysis of the fibrin gel and the compaction technique.

Permeation. Plasma samples were recalcified with 0.5 mol/L CaCl\(_2\) to a final concentration of 25 mmol/L. Then thrombin was added to a final concentration of 1.25 IU/mL and 1 mL of the mixture was used to fill preetched plastic tubes in which one end was sealed with parafilm. The tubes were placed in a moist-atmosphere chamber for 4 hours so that gelation could occur. Permeation was performed as previously described by Okada and Blomback.\(^7\) Tubes were placed in a holder and connected to a reservoir containing deaerated buffer (phosphate buffer pH 7.4) and bovine serum albumin (BSA) at a concentration of 1 mg/mL. Permeation was performed at different pressure heads above the gel; pressure was calculated from the distance between the buffer level in the reservoir and the tip of the gel. A coloring agent (BPP) was added at the perfusing liquid as a probe for detecting leaks that could occur between gel and tube and also inside the gel. The presence of an uniformly progressing colored front was taken as evidence that the gel was devoid of leaks. Flow measurements were performed at different hydrostatic pressures by determining the volume eluted from the gel after indicated time. For each experiment, at least three replicate measurements were made at four different hydrostatic pressures. The flow rates (in milliliters per hour) plotted against the pressure (dynes per square centimeter) fit a straight line.

Compaction. The clot rigidity was assessed by measuring compaction as previously described by Dhall and Nair.\(^8\) Plasma fibrin gels were formed as mentioned above in 1.5 mL Eppendorff centrifuge tubes (Hamburg, Germany) which were presprayed with mineral oil to render the surface nonadherent. After gelation occurs, the tubes were centrifuged at 8,000 g for 45 seconds in an Eppendorff centrifuge. The volume of fluid expelled from the network by the initial volume of the clot and was called the compaction coefficient.

Measurements of the Fibrin Network’s Physical Constants

These were made as described by Blomback and Okada\(^9\) and Blomback et al.\(^10\) Because it has been shown that the flow of liquid through the gel is viscous, Poiseuille’s law applies, and the permeability coefficient or Darcy constant provides information on the surface of the gel allowing flow through the network. The Darcy constant \((K_s)\) as shown previously by Signer and Egli,\(^11\) assuming that fibers are rod-like elements. For this calculation, one must know the fractional volume of the hydrated fibers in the gel. First, the fractional volume of the dehydrated fiber was derived from the fibrinogen concentration in plasma and the density of the fibrinogen (0.74 mL/g).\(^12\) Fibrinogen concentrations in control and dysfibrinogemic plasma were 2.92 and 3.80 mg/mL, respectively. Then, because fibrin fibers in a gel are hydrated, and according to Blomback et al.,\(^13\) a correction was made assuming a hydration of the fibers of 6 g of water per gram of protein. A reference \(K_s\) (\(K_s^0\)) calculated for networks containing fibers of 0.01-cm diameter was obtained from Signer and Egli tabulations using the logarithmic function \(K_s^0 = 0.2266 \times 10^{-9}\), in this equation, \(x\) represents the fractional volume of the hydrated fibers in the gel calculated above. Fiber diameters \((d)\) of the plasma fibrin network were then deduced from the Signer and Egli equation:\(^11\)

\[
d^2 \cdot K_s^0 = (d')^2 \cdot K_s^0
\]

where \(d\) and \(d'\) are fibers diameter (in centimeters) of the plasma fibrin and the reference networks \((d' = 0.01\ cm)\), respectively, and \(K_s\) and \(K_s^0\) are Darcy constants (in square centimeters) of plasma fibrin and reference networks, respectively. \(X\) is the fractional volume of the hydrated fibers of the fibrin network.

The mass-length ratios \((\mu)\) of the fibers were derived from the fiber diameter \((d)\) according to Carr et al.\(^4\)

\[
\mu = \pi \cdot d^2 \cdot c \cdot X / 4 \cdot \gamma
\]

where \(\mu\) is the fiber mass-length ratio in dalton/centimeter (using the Avogadro number \(6.023 \times 10^{23}\)), \(c\) the fiber diameter in centimeters, \(\gamma\) the fibrinogen concentration in milligrams per milliliters, and \(X\) the fractional volume of the hydrated fibers (derived from the fibrinogen concentration, the fibrinogen density, and the hydration factor: 6 g H\(_2\)O per gram of protein).

Clot Lysis

Clot lysis was evaluated by the generation of fibrin degradation product (D-dimer) as the clot was degraded by fibrinolytic enzymes in two different systems described below. The D-dimer assay was performed by enzyme-linked immunosorbant assay (ELISA), using Asserachrom D-dimer from Diagnostica Stago (Athis-Merciers, France).

In the suspended clot system, standard clots were obtained after clotting 500 \(\mu\)L of citrated blood containing various amount of dextran by thrombin (1.25 IU/mL final concentration) in the presence of CaCl\(_2\) (25 mmol/L final concentration). After 4 hours of incubation at room temperature, the clots were washed thoroughly 3 times with a large volume of 0.15 mol/L NaCl. Clots were then suspended in 2 mL of phosphate-buffered saline (PBS) buffer containing BSA at 1 mg/mL and rt-PA at a final concentration of 100 ng/mL. Aliquots of 100 \(\mu\)L were removed after various incubation times with gentle rocking, and plasmin generation was inhibited by addition of aprotinin at 10,000 IU/mL. After centrifugation of the aliquots (1,000 g for 3 minutes), D-dimer concentrations were determined by ELISA. In addition, the time for complete lysis was measured.

In the perfused clot system, the procedure used was that described for permeation studies except for the fact that clots were perfused with PBS + 1 mg/mL albumin containing rt-PA at a concentration of 500 ng/mL. Thrombolysis was expressed as the amount of D-dimers in the liquid eluted from the clot in a certain time and the time required to break the gel. Both systems were used simultaneously because they represented
Plasma were recalcified (CaCl₂, 25 mmol/L) and clotted with thrombin at 1.25 IU/mL at 24°C. Darcy constant (Kₛ), fiber diameter (d), and fiber mass-length ratio (μ) were determined from permeation analysis. For each plasma sample, at least 4 gels were made and tested during each experiment. Average values of 4 experiments were taken. Standard deviations for the same replicates did not exceed 12.5%. Differences between control and Dusan were statistically significant as determined by student’s t-test.

These impaired mechanical properties of the Dusart fibrin clot were corrected in a dose-dependent manner by adding dextran to plasma before coagulation. At a final dextran concentration of 30 mg/mL, Dusart clot permeability recovered to almost the same value as the normal control clot that was prepared without dextran (Table 2). This dose-dependent effect of dextran on viscoelastic properties of the fibrin gel was also observed in normal plasma but with much less intensity than with Dusart plasma (Table 2). For example, 30 mg/mL dextran increases the Darcy constant of the Dusart clot 126 times but only increases 2.6 times for a normal clot. In the same manner, 30 mg/mL dextran increases the compaction coefficient 7.5 times for Dusart clot but only increases 2 times for a normal clot.

Effect of Dextran on the Degradability of Dusart Fibrin

The time required for complete clot degradation in the system using suspended clots was 3 times longer for Dusart than for the control clot, 72 ± 24 hours (Fig 2). Addition of dextran either to normal or to Dusart plasma before clotting significantly shortened the clot lysis time (8 ± 24 hours and 8 ± 72 hours, respectively; Fig 2). At a final concentration of 30 mg/mL, the clot lysis time of Dusart was the same as that of the control without dextran. This improvement of clot degradation induced by dextran was also evidenced by
evaluation of D-dimer concentrations (Fig 3). Because the tight network configuration observed in the Dusart gel was responsible for its defective permeability, we have evaluated the effect of dextran on clot degradation using the perfused clot system to determine whether this effect was due to the modified clot structure. Measurements of clot lysis were begun after 1 clot volume of buffer containing rt-PA was infused into each clot. The degradability of both normal and Dusart clots formed in presence of dextran was greatly improved compared with clots formed without dextran. The effect of dextran addition was much more pronounced with Dusart clots and appeared to be greater than that obtained in the suspended clot system (Fig 4). This suggests that the improvement of Dusart clot degradability could be related to the dextran-induced clot-structure modifications leading to a great enhancement of the surface for flow available for the fibrinolytic enzymes.

Ultrastructure Study

As can be seen in Fig 5A and B, Dusart clot ultrastructure as observed by electron microscopy freeze-etched specimens appeared to be dramatically different from the normal clot. In the conditions of these experiments, images of Dusart specimens (Fig 5A) indicated that clots were made up of a network of very thin, highly branched, and numerous fibers displaying very small, interstitial pores. On the contrary, normal clots (Fig 5B) are made up of a network of thicker, less numerous, and less branched fibers displaying large interstitial pores. In addition, the fibers of Dusart specimens are more homogeneous than normal ones, which usually display a bimodal distribution of fiber diameters as described by Shah et al.17 The thick fibers form the major network, and the thin ones form the minor network located in the interstitial spaces between the thick fibers. Consistent with the earlier results,17 as shown by measurements of micrographs (data not shown), thick fibers range in size from 2 to 6 times the thickness of the thin fibers and represent the main part of total fibrin (90%). Such a range of fiber size can be observed in Fig 5A. This bimodal distribution has completely disappeared in the fibrin Dusart, composed only of thin, short fiber strands (Fig 5B).

### Table 2. Effect of Dextran 40 at Different Concentrations on Ks, Mass-Length Ratio, and Average Diameter of Fibrin Fibers as Determined by Permeability Analysis of Normal and Pathologic Fibrin Gels

<table>
<thead>
<tr>
<th></th>
<th>No Dextran</th>
<th>Dextran (10 mg/mL)</th>
<th>Dextran (20 mg/mL)</th>
<th>Dextran (30 mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ks (10^6 cm²)</td>
<td>Control 2.81</td>
<td>DuSart 0.016</td>
<td>Control 4.11</td>
<td>DuSart 0.067</td>
</tr>
<tr>
<td>d (µm)</td>
<td>Control 0.194</td>
<td>DuSart 0.018</td>
<td>Control 0.235</td>
<td>DuSart 0.114</td>
</tr>
<tr>
<td>µ (10⁻¹² dalton/cm)</td>
<td>Control 35.6</td>
<td>DuSart 0.301</td>
<td>Control 52.2</td>
<td>DuSart 12.3</td>
</tr>
<tr>
<td></td>
<td>Control 68.4</td>
<td>DuSart 22.7</td>
<td>Control 93.2</td>
<td>DuSart 37.1</td>
</tr>
</tbody>
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Plasmas were recalcified with CaCl₂ 25 mmol/L and clotted with thrombin at 1.25 IU/mL at 24°C. Darcy constant (Ks), fiber diameter (d), and fibrin mass-length ratio were determined from permeation analysis of fibrin gels. For each plasma sample, 4 gels were made and tested during each experiment. Average values were taken. Standard deviations for the replicates did not exceed 12.5%.
Addition of dextran at a final concentration of 30 mg/mL before coagulation switches the tight network configuration of the fibrin Dusart to a coarse configuration usually seen in normal plasmas. As shown in Fig 6, fibrin fibers were fewer but thicker and less branched than those usually observed in Dusart fibrin, leading to an increase of the size of the interstitial spaces. Moreover, the bimodal distribution of the fiber diameters was restored with both thin and thick fibers. This complete correction of the Dusart clot ultrastructure is in good agreement with the results concerning the viscoelastic properties of the fibrin. Addition of dextran to control plasma before coagulation modify slightly the fibrin network configuration compared with the great difference observed with the fibrin Dusart. The main feature was the presence of larger interstitial pores, although the fiber diameter did not differ significantly (data not shown).

DISCUSSION

The severe and recurrent thrombotic disease observed in the Dusart family was initially attributed to a defective thrombolytic mechanism, possibly associated with an abnormal plasminogen binding to fibrin. The lower affinity between plasminogen and fibrinogen may be explained either by structural perturbations of latent sites exposed during fibrin polymerization and required for plasminogen activation by t-PA or by a diminished expression of these sites in the fibrin network because of the abnormal polymerization. This work reports that the anomaly of polymerization related to an abnormal lateral aggregation of the protofibrils led to an important modification of the fibrin clot architecture. Indeed, viscoelastic and ultrastructure studies show that fibrin Dusart is abnormal, consisting of an extremely rigid and tight fibrin gel structure. Dusart fibrin networks display a high density of very thin and short fibers that are highly branched, forming a very homogeneous structure with small interstitial pores, without the bimodal distribution of the fiber diameters usually observed in normal fibrin (Fig 5B). Thick fibers that range in size from around 2 to 6 times the thickness of thin fibers and represent the main part of the fibrin content of a clot are not present in the Dusart clot. This tight configuration may explain the modification of the rheological properties of the clot as reported by the permeation analysis (Table 1). The dramatic decrease of the fibrin gel permeability is evidenced by the evaluation of the Darcy constant, ie, the surface of the fibrin network available to flow, which is 175-fold lower than that of the control. Fiber diameters and fiber mass-length ratios derived from permeation analysis are in good agreement with those obtained from the ultrastructure study, confirming the abnormal tightness of the clot architecture. The abnormal clot rigidity assessed by the dramatic decrease of the clot compaction coefficient may be explained by the high level of interconnection between fibers or branching points, which has been shown to be crucial for three-dimensional network stabilization. Such a drastic modification in fibrin clot architecture seems to have clinical implications, because it renders the clot more susceptible to disruption by mechanical forces found naturally in the circulatory system. Thus, we assume that the high incidence of pulmonary embolism observed in this family is probably the end result of fragmentation of the brittle clots that easily break under the circulatory stress.

Our results show that the abnormal clot architecture observed in fibrin Dusart is responsible for the resistance to thrombolysis. First, the refractive thrombolytic is much more evident in the system using the perfused clot, where all the clot surface is available for fibrinolytic enzymes, than in the system using the suspended clots, where clot lysis only occurs at its external area. This suggests the importance of the clot surface available for thrombolysis to occur. Decreasing the surface area for flow in the abnormal clot architecture renders the clot less susceptible to lysis. Secondly, addition of dextran to the plasma before coagulation at a final concentration of 30 mg/mL simultaneously corrects the viscoelastic parameters and the susceptibility to fibrinolytic enzyme of Dusart fibrin. This effect is dose-dependent both in normal and Dusart plasma but much more intensely in the former.

Dextran has previously been shown to modify fibrin polymerization in vitro, producing thicker fibers. As suggested by Carr and Gabriel, it may be incorporated into fibers, but it remains unclear whether it binds to fibrinogen. Dextran exerts its effect by removing water from the reacting molecules; fibrinogen and thrombin are excluded from the water phase, leaving less space for the reaction to occur, and consequently, a coarse network structure is formed. Dextran is also active in vivo, and its effect on clot rheology may explain its better efficiency in the reduction of the incidence of pulmonary embolism in comparison with heparin therapy in patients undergoing surgery. By providing more collapsible and coarser fibrin gels that give way...
Fig 5. Electron micrograph of fibrin gel networks from normal and dysfibrinogenemic plasmas prepared by the freeze-etching technique. Normal (A) and dysfibrinogenemic (B) plasmas were recalcified (CaCl₂ 25 mmol/L) and clotted with thrombin at 1.25 IU/mL (final concentration) at room temperature. Fibrinogen concentration were 3.80 and 2.92 mg/mL for (A) and (B), respectively. Note the homogeneous structure of Dusart fibrin (B) composed of very thin (+) and highly branched fibers (tight configuration) without thick fibers (D) and large pores as usually seen in normal fibrin (A). Original magnification × 43,000; bar, 0.3 μm; →, minor network; ⤋, major network.

easily to the flow and coalesce with the vessel under circulatory stress, the addition of dextran avoids fragmentated clots in the vasculature.

Recently, the structural defect of fibrinogen Dusart inferred from DNA analysis has been shown to be a single base substitution in the A-α gene, where arginine 554 is replaced by a cysteine. Furthermore, as a consequence, a substantial amount of albumin was found to be linked to the fibrinogen by disulfide bounds. Our results support the fact that the COOH-terminal part of the A α-chain (α-C domain) is involved in fibrin assembly and affects the final clot architecture. The exact role of this part of the fibrinogen molecule remains unclear, although there is strong evidence that it is important for fibrin polymerization and for the branching process. Recent results reported by Veklich et al25 show that the α-C domain consists of a globular structure connected to the distal end of the molecule and usually associated to the central domain in fibrinogen but not in fibrin. After fibrinopeptide removal, α-C domains are released from the central domain allowing intermolecular associations. Cierniewski and Budzynski26 have shown that monoclonal antibodies directed against α-C domains strongly inhibit fibrin polymerization; these studies reinforce the role of α-C domains in polymerization.26 How-
ever, polymerization and branching occur with fibrinogen molecules lacking their α-C domains, fragment X, showing that they are not indispensable. In the case of fibrinogen Dusart, because the mutation is located in a hydrophilic sequence, accessible in the normal native molecule and possibly involved in binding sites for lateral aggregation of the protofibrils, we hypothesize that the mutation disrupts the interaction between the α-C domains and the rest of the molecule and that albumin, covalently linked to the fibrinogen, may play an important role in this defect. Recent results reported by Siebenlist et al. support this hypothesis. They show that most of the albumin bound to the abnormal fibrinogen (α-C region) is released after the removal of the α-C domains by plasmin degradation of fibrinogen Dusart. Moreover, this plasmin-degraded abnormal fibrinogen (I-9D), when treated with thrombin, recovered both normal polymerization rate and fibrin ultrastructure relative to normal I-9D fibrinogen. We assume that the direct consequence of this mutation might be a conformational change of the α-C domains leading to a less flexible fibrinogen molecule and a decrease of intermolecular interactions via α-C domains. An intrinsic twist of the fibrinogen molecule required for its flexibility is essential for normal fiber growth as reported by Weisel et al. Because fibers are made of twisted protofibrils, the degree to which a protofibril can be stretched limits the radius of a fiber. Hence, tight and extremely rigid fibrin gel network could arise from rigid fibrinogen molecule (lower intrinsic twist) giving rise to thin and rigid fibers. Because dextran binds water and, therefore, ions, we assume that it could restore normal interaction between α-C domains and the rest of the molecule (and, thus, a normal molecular flexibility) by an ionic strengthening effect. The mechanism of the defective plasminogen binding remains unclear, but perhaps one can expect a role of the α-C domains in plasminogen binding to fibrin.

This abnormal fibrinogen may represent an interesting tool for better understanding the functional role of the α-C domains in fibrin assembly and for better understanding the relation that could exist between fiber thickness, the branching process, and twisting of the fibers, because other mutations involving the α-C domains are also associated with an impaired polymerization. These studies may allow us to relate clinical symptoms to the molecular defect. This work describes the importance of the fibrin clot architecture in the propensity of the blood clot to be degraded by plasmin and to be protected from breaking up in the blood vessels under circulatory stress. Because the final clot structure can be modified by the kinetics of blood coagulation (which also depend on local fibrinogen and thrombin concentration) and by other factors such as plasma proteins and other macromolecules, it may be possible that abnormal clot architecture could arise even in the absence of dysfibrinogenemia, explaining the high percentage of hypofibrinolysis related to abnormal clot structure.

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