Altered Fibrin Architecture Is Associated With Hypofibrinolysis and Premature Coronary Atherothrombosis


Objective—Hypofibrinolysis promotes atherosclerosis progression and recurrent ischemic events in premature coronary artery disease. We investigated the role of fibrin physical properties in this particular setting.

Methods and Results—Biomarkers of recurrent thrombosis and premature coronary artery disease (CAD) were measured in 33 young post–myocardial infarction patients with angiographic-proven CAD and in 33 healthy volunteers matched for age and sex. Ex vivo plasma fibrin physical properties were assessed by measuring fibrin rigidity and fibrin morphological properties using a torsion pendulum and optical confocal microscopy. The fibrinolysis rate was derived from continuous monitoring of the viscoelastic properties after addition of lytic enzymes. Young CAD patients had a significant increase in plasma concentration of fibrinogen, von Willebrand factor, plasminogen activator inhibitor type 1, and lipoprotein(a) as compared with controls ($P < 0.05$). Fibrin of young CAD patients was stiffer ($P < 0.002$), made of numerous ($P < 0.002$) and shorter fibers ($P < 0.04$), and lysed at a slower rate than that of controls ($P < 0.03$). Fibrin stiffness was an independent predictor for both premature CAD and hypofibrinolysis.

Conclusions—This first detailed study of clot properties in such a group of patients demonstrated that abnormal plasma fibrin architecture is an important feature of both premature CAD and fibrinolysis rate. The determinants of this particular phenotype warrant further investigation. (Arterioscler Thromb Vasc Biol. 2006;26:2567-2573.)

Key Words: acute coronary syndromes ■ coagulation ■ fibrinolysis ■ pathophysiology ■ fibrinogen ■ thrombophilia

The mechanical properties of clots and their major constituent fibrin are normally finely tuned to optimize bleeding control while also minimizing their effect on atherothrombosis. A decreased rate of fibrinolysis and increased thrombosis are generally associated with stiff clots, although such relationships are complex. Many factors that affect clot structure have a great impact on the mechanical properties fibrin and fibrinolysis through modifications of various steps in the fibrin polymerization process and clot stabilization.

Premature coronary artery disease (CAD) is associated with increased plasma levels of prothrombotic and proinflammatory biomarkers, including fibrinogen and plasminogen activator inhibitor (PAI) type 1, which are known to favor hypofibrinolysis and to be independent predictors of CAD. Epidemiological studies have also revealed a relationship between myocardial infarction (MI) and reduced permeability and increased stiffness of fibrin, especially in young post-MI patients. These aspects of altered fibrin clot network architecture were not found to be attributable to classic risk factors including fibrinogen concentrations or common polymorphisms. However, the relationships among premature CAD, abnormal fibrin physical properties, and hypofibrinolysis remain little explored. The lack of appropriately designed studies of the physical properties of fibrin, including simultaneous determination of viscoelastic and morphological properties of fibrin, and how they affect fibrinolysis may account for the gap in knowledge.

Our aim was to measure accurately morphological properties (fiber diameter, fiber length, and porosity) and viscoelastic properties of plasma fibrin clots (PFCs) of patients with premature CAD and healthy informed controls matched for age and sex. We hypothesized that fibrin physical properties was an independent predictor of hypofibrinolysis and of the occurrence of premature CAD in young post-MI patients. This is actually the first publication with detailed measures of
plasma fibrin physical and viscoelastic properties and fibrin assembly and lysis in such a group of patients.

Materials and Methods

Human thrombin was purchased from Enzyme Research Laboratories Inc (South Bend, Ind) and stored at 1000 IU/mL. Unconjugated colloidal gold solution for light microscopy was from British Biocell International (UK). Recombinant tissue plasminogen activator (rt-PA) was purchased from Boehringer Ingelheim (Germany).

Patients and Controls

Consecutive acute coronary syndrome patients aged <45 years recruited in the e-Pitié-Salpêtrière Registry on Ischemic coronary Syndromes were selected for the present study.10 Premature CAD was defined as a past history of acute coronary syndrome or coronary revascularization with angiographically significant CAD (at least 1 stenosis >70%). Healthy controls without known diabetes and without personal history of cardiovascular disease were recruited from a primary prevention program run at the same hospital. Controls were matched for age and sex with patients. The sample size was determined according to the hypothesis of an expected mean difference in fibrin stiffness between patients and controls of 13 kilodyne/cm² with a common SD of 18 kilodyne/cm² based on previous findings.11 To ensure the study a power of 80% with a type I error rate of 0.05, 32 subjects per group had to be included in the study. This study was promoted by the Assistance Publique-Hôpitaux de Paris and was reviewed by the Pitié-Salpêtrière University Hospital Ethics Committee. All patients gave informed consent according to the study protocol.

Blood Sampling and Data Collection

Blood sampling was performed >3 months after the last acute coronary event. After an 8-hour overnight fast, 50 mL of blood was collected in lithium heparin for lipid fraction analysis and in a 10-mL tube containing 1 mL of 0.9% citrate (pH 8.8) at room temperature for assay of fibrinogen and fibrin structure and at 4°C for assay of tissue Plasminogen Activator (tissue-type plasminogen activator [t-PA]), PAI-1, and fibrin D-dimer. Citrated samples were centrifuged at 3000 rpm for 20 minutes, and aliquots of 0.5 mL of plasma supernatant were stored at ~80°C until assay. Blood pressure was measured to the nearest 2 mm Hg and calculated as a mean of 3 consecutive readings. Hypertension was identified as an average blood pressure >140/90 mm Hg. Individuals were qualified as diabetic if on prior antidiabetic drugs or if fasting glycermia >1.26 g/L twice.

Biological Factor Measurement

Plasma fibrinogen was determined by the Clauss method. Determination of von Willebrand factor (vWF) antigen, PAI-1, and D-dimer antigen levels was performed using commercially available ELISA kits (Asserachrom, Stago, France). Ultrasensitive C-reactive protein (CRP) was also measured with commercially available ELISA kits (Dade Behring, France). A Hitachi 747 autoanalyzer was used for estimation of triglycerides and total cholesterol. High-density lipoprotein (HDL) cholesterol was measured after precipitation of low-density lipoprotein (LDL), chylomicrons, and very-low-density lipoprotein with phosphotungstic acid and magnesium chloride. LDL cholesterol was calculated by the Friedewald equation.

Preparation of Cross-Linked PFCs

PFCs were formed by adding CaCl₂ (10 mmol/L final concentration) and thrombin (0.9 IU/mL final concentration) to 0.12 mL of platelet poor plasma.12 Clotting was allowed to proceed for at least 20 minutes in a moist atmosphere at room temperature.13 PFCs were made in the same conditions for both viscoelastic and morphological analyses, which were performed in all individuals.

PFC Imaging

PFCs were made in special designed microchambers to allow fibrin labeling with 5-nm diameter colloidal gold particles (5×10⁹/mL final concentration).3 Labeled specimens were scanned with a LSM 510 interactive laser cytometer (Carl Zeiss Inc, Thornwood, NY) linked to an inverted microscope equipped with a ×63 water immersion objective set up in reflection mode. Scans were collected in a format of 512×512 pixels with 1024 gradations of intensity. Optical sections were collected at intervals of 0.5 μm in the z-axis. Optical resolution in the x-y axis was 0.2 μm and ~0.4 μm in the z-axis.

The scans were projected and combined into one image and a morphological filter was applied on each micrograph to obtain a binary mask of the fibrin fibers.12 This allowed the separation of features from the background of the confocal micrograph, so that counting and measurement could be performed. The average number of fibrin fibers per cubic area was determined on reconstructed images of intermediate magnification (48×48×48 μm³). Average fibrin fiber diameter was also measured in an average of 25 fibers per individual. Fibrin porosity was determined by measuring the fiber-free surface area using a specific morphological granulometry algorithm on larger images (73×73×73 μm³). All of these analyses were performed using the Visilog software (V5.1, Noesis, Courtaboeuf, France).

Fibrin length was measured only when a fiber segment between 2 branch points was carefully identified on 3D reconstructions of intermediate magnification images (73×73×73 μm³) obtained by using the KHEOPS software package (Noesis). The 3D reconstruction allowed branch points to be carefully distinguished from fibers crossing at different depths.13 An average of 25 fibers per individual was picked up for such measurement.

Clot Viscoelastic Properties

Viscoelastic properties of PFCs were measured using the theory of the torsion pendulum as previously described.14 Recordings of free oscillations allowed the calculation of the maximum elastic stored modulus (EM) (dynes per centimeter squared), which reflects the stiffness of the clot. All measurements were performed with the RM-2 analyzer (Hemodyne, Richmond, Va). Clotting time (CT) was defined as the time needed to reach the maximum EM.

Fibrinolysis

Fibrin assembly and fibrinolysis were assessed by continuous monitoring of the EM of PFC using the RM-2 analyzer (Hemodyne). At a final concentration of 10 nmol/L t-PA was added before clotting. The same conditions of clotting were used as above. Fibrinolysis curves were normalized with respect to the maximum value of EM and the rate of lysis (in per seconds) was determined from the slope of the latter part of the fibrinolysis curve, where the slope becomes constant (Figure 1).14 Normalization of the slope of the lysis curve to the maximum EM was performed to improve the accuracy of lysis speed measurement. Indeed, clots may display a similar slope of lysis curve, although having great differences in the clot lysis time. The accuracy of this assay has been shown to be similar to the determination of the lysis front velocity (or fiber lysis rate).12,14 Clot lysis time (CLT) was defined as the time needed for the maximum EM to decrease by 50%.

Objectives of the Study

The primary objective of the study was to examine whether fibrin physical properties, including fibrin stiffness and fibrin architecture, and hypofibrinolysis were independent correlates for premature CAD. The secondary objectives were to determine correlations among hypofibrinolysis and fibrin physical properties and inflammatory and prothrombotic biomarkers.

Statistical Analysis

Continuous variables were expressed as mean±SD. The comparability between groups was assessed using Mann–Whitney test for continuous variables and Fisher exact test for qualitative variables,
respectively. The α level was set at 0.05. Correlations between fibrin physical properties were tested by using Spearman correlation coefficients. Potential associations between fibrinolysis rate or fibrin stiffness and covariates were first tested in univariate analysis by using Spearman correlation for continuous variables and Wilcoxon rank-sum test for categorical variables. Univariate variables with a probability value of <0.05 were then included in a multivariate analysis of covariance. Relationships between premature CAD and covariates were first studied using a univariate conditional logistic regression for matched pairs data. Univariate variables with a probability value of <0.05 were then included in a forward multivariate logistic regression for matched pairs data. Analyses were performed with the SAS software package V8.2 (SAS Institute, Cary, NC).

**Results**

**Population Characteristics**

A total of 33 coronary patients and 33 controls matched for age and sex entered the study. The majority of patients were young males with a high prevalence of smoking habits and of familial history of CAD (Table 1). Other conventional risk factors for CAD were infrequent. ST-segment elevation MI was the most frequent clinical presentation of premature CAD, underlying the importance of acute coronary thrombosis. As opposed to controls, all of these patients were on long-term treatment with aspirin and statins. The majority were also on β blockers, angiotensin converting enzyme inhibitors, and thienopyridines.

Compared with controls, young patients had higher concentrations of both prothrombotic and inflammatory biomarkers (Table 2). As opposed to PAI-1, neither CRP nor D-dimers were found significantly increased in patients as compared with controls, although there was a consistent trend for a 60% increase in the plasma concentration of these biomarkers.

**Fibrin Physical Properties**

A unique opportunity of the present investigation was the possibility of measuring accurately fibrin mechanical and morphological properties using the same fully hydrated plasma fibrin gel in all individuals who entered the study. Patients with premature CAD produced stiffer plasma fibrin (Figure 1 and Table 2) with similar CT between patients and controls (249 ± 110 versus 241 ± 151 seconds; P = 0.79) (Figure 1).

Fibrin networks visualized with confocal microscopy consisted of straight, rod-like elements organized in a 3D network with compact areas alternating with looser areas of fibrin fibers (Figure 2). To provide an accurate morphological analysis, random areas were picked for analysis of fiber diameter and the number of fibers per volume area. Consistent with mechanical properties, plasma fibrin from patients was made up of shorter, thinner, and more numerous fibrin fibers as compared with clots from healthy controls, leading to a more compact architecture with smaller pores (Table 2).

Figure 2 illustrates the fibrin conformation observed with confocal microscopy in a patient and in a control with similar fibrinogen concentration. The 3D analysis allowed for the first time an accurate discrimination between branch points and fibers crossing at different depths, and therefore fiber segment lengths could be measured (Figure 3).

Although there were a great variety of fibrin conformations in patients and healthy controls, significant correlations were observed between the number of fibrin fibers per volume and

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**TABLE 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=33)</th>
<th>Patients (n=33)</th>
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</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>38.5±4.5</td>
<td>39±5.2</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>87.8</td>
<td>87.8</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>25.0±2.3</td>
<td>26.3±2.8</td>
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<tr>
<td>Known diabetes (%)</td>
<td>0</td>
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<tr>
<td>Familial CAD (%)</td>
<td>9.1</td>
<td>30.3*</td>
</tr>
<tr>
<td>Known dyslipidemia (%)</td>
<td>10.2</td>
<td>38.1*</td>
</tr>
<tr>
<td>Prior or active smoker (%)</td>
<td>24.2</td>
<td>75.8*</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>0</td>
<td>6.1</td>
</tr>
<tr>
<td>Prior ST-segment elevation MI (%)</td>
<td>0</td>
<td>51.5*</td>
</tr>
<tr>
<td>Prior coronary revascularization (%)</td>
<td>0</td>
<td>30.3*</td>
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<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.4±0.9</td>
<td>6.1±1.3*</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.4±0.5</td>
<td>1.3±0.5</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.5±0.9</td>
<td>4.1±1.2*</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.2±0.9</td>
<td>1.7±0.9*</td>
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</table>

*Indicates a significant difference (P<0.05) between patients and controls.
average fiber segment length (−0.56; P<0.0001), the number of fibrin fibers per cubic area and fibrin stiffness (0.44; P=0.0002). Plasma fibrinogen concentration demonstrated a significant relationship with the number of fibrin fibers per cubic area (0.39; P=0.001). A similar trend was observed with CRP which was found to be significantly correlated with the number of fibrin fibers per cubic area (0.27; P=0.03).

**Fibrinolysis Rate**
Continuous monitoring of plasma mechanical properties allowed real-time assessment of internal or intrinsic fibrinolysis. rt-PA concentration was chosen, so that lysis started after completion of fibrin formation including full stabilization of fibrin by activated factor XIII and lysis occurred at a very slow rate as previously described.12

**Figure 2.** Images of 2D reconstructions of optical sections of control (A and B) and patient (C and D) plasma fibrin networks obtained by scanning confocal laser microscopy at low (146×146 μm² for A and C) and intermediate (73×73 μm² for B and D) magnifications. The fibrinogen concentration was similar in this pair matched for age and sex (2.1 g/L).
Altered fibrin properties from young CAD patients led to a reduced fibrinolysis speed. Indeed, young patients displayed a longer CLT than controls (638 ± 268 versus 473 ± 260 seconds; P = 0.013). When normalized with respect to the maximum EM, fibrin from young patients was lysed at slower rate than control fibrin (Table 2).

In the whole study group, the fibrinolysis rate was correlated with fibrin stiffness (0.38; P = 0.002) and the number of fibrin fibers per volume (0.26; P = 0.04), which indicate that the stiffer the clot, the higher is the number of fibrin fibers per cubic volume and the slower is the fibrinolysis reaction. It was also negatively correlated with fiber segment length (−0.26; P = 0.0035) but not with fibrin porosity (−0.096; P = 0.44).

**Independent Correlation of Premature CAD and of Fibrinolysis Rate**

The first significant finding was that all parameters used to characterize fibrin physical properties were significantly related to premature CAD after univariate analysis, along with established risk factors including fibrinogen level, total cholesterol, LDL cholesterol, lipoprotein(a) and von Willebrand factor (vWF) (Table 3). Of interest was the finding that only fibrin stiffness was found to be an independent correlate for premature CAD after multivariate analysis, further emphasizing the critical role of fibrin physical properties in the development of premature CAD (Table 3).

Besides the PAI-1 level and premature CAD, well-known established factors of hypofibrinolysis, 3 of the major determinants of the physical properties of fibrin, including fibrin stiffness, fibrin fiber density, and fiber segment length, were related to hypofibrinolysis after univariate analysis. Of interest, fiber segment length, fibrin stiffness, PAI-1 level, and sex were independent correlates for the fibrinolysis rate after multivariate analysis. Finally, premature CAD (P = 0.02) was an independent correlate of fibrin stiffness.

**Discussion**

The present investigation has demonstrated that patients with premature CAD produce ex vivo abnormal plasma fibrin clots that are resistant to fibrinolysis. Indeed, these clots were stiffer, made up of shorter and more numerous fiber segments and took much longer to dissolve than those of a well-characterized and highly comparable group of control subjects without premature CAD. Fibrin stiffness was the only independent correlate for premature CAD, further highlighting the critical role of fibrin in the pathogenesis of atherothrombosis. Fibrin stiffness together with fiber segment length were also identified as independent correlates for hypofibrinolysis along with PAI-1, an established prothrombotic factor in premature CAD. All of these findings were obtained in patients with an effective secondary prevention treatment including statins and aspirin.

For the first time, fibrin viscoelastic properties, fibrin morphological properties, and fibrinolysis rate were simultaneously determined using fully hydrated undamaged fibrin gels made under identical conditions. Previous clinical studies have examined fibrin structure/functions in the setting of premature CAD but with incomplete and divergent findings. The lack of accuracy of gel permeation techniques and of light scattering used to characterize fibrin porosity and fibrin fiber size together with the absence of lysis studies and/or evaluation of the mechanical properties of fibrin should be acknowledged as limitations of these studies. As a consequence, none of the studies could draw definite conclusions regarding the complex relationships between premature CAD, abnormal fibrin properties, and hypofibrinolysis. For example, Greilich et al found patients with severe CAD to have more rigid clot structures and an elevated fiber mass/length ratio, but neither morphological properties of fibrin nor lysis experiments were performed. Fatah et al identified reduced permeability and reduced fiber mass/length ratio in the fibrin gels from young patients after MI. However, fibrin mechanical properties and fibrinolysis rates were not evaluated.

Our finding that fibrin stiffness is an independent correlate for premature CAD is novel and provides new insights into the pathogenesis of atherothrombosis. Scant data on how blood clot stiffness may affect the natural history of athero-
thrombosis are available. A single recent investigation has described whole blood clot strength as a novel independent predictor of ischemic events after percutaneous coronary intervention.16 Data on how elevated fibrinogen concentration may translate into a higher risk of MI 8 relies on a single investigation showing a highly significant inverse correlation between plasma fibrinogen concentration and the extent of clot deformability made of purified fibrin.17

A unique opportunity of the present investigation was the possibility of evaluating whether there was a correlation between mechanical and morphological properties of plasma fibrin. This specific issue was previously addressed using networks of purified fibrin manipulated by varying the concentrations of fibrinogen, thrombin, and calcium.1 The 3D reconstruction of optical sections of all samples has allowed an accurate determination of the fiber segment length, of the fiber density per cubic area, and the distinction between crossing fibers and fiber branching points. This was made possible because fully hydrated plasma fibrin gels without all the artifacts of specimen preservation that are common with scanning electron microscopy were used. Labeling with colloidal beads has avoided thermal degradation and photobleaching, which can occur with fluorescent samples.5 As a consequence, we were able to confirm that plasma fibrin stiffness is enhanced by increasing the number of fibrin fibers. The ability of fiber segment length to predict hypofibrinolysis further emphasizes the critical importance of measuring fibrin morphological properties together with fibrin mechanical properties, as previously reported.1,13,14,18

The significant increase in both fibrinogen and PAI-1 plasma levels among young patients as compared with controls was expected6 and may have contributed to hypofibrinolysis,19 fibrin accumulation and therefore to the occurrence of acute coronary thrombosis.2 The fact that fibrin stiffness was correlated to premature CAD and to hypofibrinolysis irrespective of the plasma concentration of these 2 biomarkers supports the hypothesis that hypofibrinolysis is mainly driven by altered fibrin properties.3,5 The fibrinolysis resistance of this so-called thrombogenic tight fibrin conformation has been primarily related to a decrease of rt-PA binding as compared with the coarse fibrin conformation made of fewer fibers that are thicker.5 Indeed, the spatial distribution of fibers is a major determinant in regulating rt-PA binding and fibrinolysis speed.5

We acknowledge several limitations of the present study. Although platelets have a critical impact on fibrin assembly, fibrin mechanical properties and fibrinolysis, properties of platelet-rich fibrin could not be routinely assessed given the

<table>
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<th>Premature CAD</th>
<th>Fibrinolysis Rate</th>
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<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate</td>
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<tr>
<td>Fiber density (n/48)</td>
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<td>0.04</td>
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<tr>
<td>Fiber length (µm)</td>
<td>0.040</td>
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<td>Fibrin porosity (µm²)</td>
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<tr>
<td>Fibrinolysis (sec⁻¹)</td>
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<tr>
<td>Premature CAD (yes/no)</td>
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<td>...</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
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<td>0.27</td>
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<tr>
<td>Elastic Modulus (kilodyne/cm²)</td>
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<td>0.003</td>
</tr>
<tr>
<td>PAI-1 (ng/mL)</td>
<td>0.150</td>
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<tr>
<td>CRP (mg/mL)</td>
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<td>Body mass index (kg/m²)</td>
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<td>HDL cholesterol (mmol/L)</td>
<td>0.600</td>
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<td>Lipoprotein(a) (g/L)</td>
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<td>D-Dimer (ng/mL)</td>
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Univariate variables with a P value of <0.05 were included in the forward multivariate logistic regression for matched pairs data.
limited timing required for such studies. The 3D analysis of plasma fibrin was a novel approach in the context of such a clinical study. This extensive investigation did not allow us to increase the number of patients and to monitor extrinsic fibrinolysis based on monitoring of the lysis front velocity after addition of fibrinolytic enzymes to a preformed clot. Instead, we have investigated intrinsic fibrinolysis by adding fibrinolytic enzymes before clot formation. The accuracy of both methods has been shown to be similar as soon as fibrinolytic concentrations were finely adjusted so that lysis started after fibrin formation and fibrin stabilization as previously described. Unfortunately, the impact of aspirin therapy on fibrin properties could not be assessed because all patients were given aspirin as secondary prevention treatment strategy. One would have expected even greater differences between fibrin properties of patients and of controls because low-dose aspirin has been shown to increase fiber diameter and fibrin permeability leading to a faster fibrinolysis rate.

In conclusion, stiff and highly compact fibrin characterizes premature CAD and the resulting hypofibrinolytic state. The determinants of this particular phenotype warrant further mechanistic investigations, including gene polymorphisms and determination of plasma concentration of fibrinogen variants but also of other variations of fibrinogen, which have been shown to alter fibrin clot properties.

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Disclosure(s)

None.

References

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