Vascular Bed Specific Alterations in Coagulation and Fibrinolytic Parameters in Young Women following Myocardial Infarction, Lacunar Cerebral Infarction and Deep Vein Thrombosis

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Key Words

Young women · Myocardial infarction · Lacunar cerebral infarction · Venous thrombosis · Fibrinolysis · Coagulation

Abstract

The possible existence of distinctive, vascular bed specific alterations of coagulation and fibrinolytic parameters associated with three different types of thrombosis was investigated in young women ($n = 68$, <45 years at onset of the event) following myocardial infarction (MI) ($n = 22$), lacunar cerebral infarction (LACI) ($n = 16$), idiopathic deep vein thrombosis (VT) ($n = 14$) and venous thrombosis due to oral contraceptive use ($n = 16$) in the stable period after the acute thrombotic event. Coagulation and fibrinolytic parameters, as well as classical metabolic variables, were measured and compared with 52 age-matched, healthy controls. In MI women we observed elevated tissue type plasminogen activator (t-PA) antigen levels, which correlated significantly with parameters of the plurimetabolic syndrome. In LACI women we found elevated fibrinogen, which correlated with D-dimer, systolic blood pressure, smoking, and sedimentation rate. Prolonged euglobulin clot lysis time, ele-

vated t-PA antigen, PAI-1 antigen and activity, which all correlated with parameters of the plurimetabolic syndrome, were found in women with idiopathic VT, who were also clearly obese but not in women in whom oral contraceptives were the triggering factor for VT. Our results showed not parallel, but different profiles of alterations in fibrinolytic and coagulation parameters in line with the prediction of a vascular bed specific thrombosis process.

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Introduction

It is well known that the process of thrombosis occurs more often in specific regions of the vascular tree, such as coronary arteries, brain arteries and deep veins of the legs [1]. It is widely believed that the fibrinolytic and coagulation systems contribute to the process of thrombosis in a similar way, with a different emphasis at different sites. However, despite the quantitative differences, qualitative differences might also exist. Regardless of similarities in the basic mechanisms of thrombosis, significant differences might exist between the factors involved in triggering and facilitating the process of thrombosis in different

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segments of the vascular tree. Of these factors, the imbalance between coagulation and fibrinolytic factors appears to be the important one. However, the classic risk factors of myocardial infarction, ischemic (thrombotic) stroke and deep vein thrombosis – which are stronger risk factors than coagulation/fibrinolysis imbalance – might, if pronounced, hamper the estimation of the specific roles of coagulation and fibrinolytic factors. For this reason, alterations in fibrinolytic and coagulation parameters would ideally be studied in patients without (or only slightly expressed) classical risk factors, i.e. arterial hypertension, hyperlipidemia, diabetes mellitus, smoking and male sex (for myocardial infarction, MI, and stroke), and operations, immobilization or malignancy (for deep vein thrombosis). Young women are a specific subgroup who commonly suffer thrombotic events in the absence of pronounced classical risk factors [2–5].

Thus, the aim of our study was to evaluate some important components of the fibrinolytic and coagulation systems, which could play an important role in the pathogenesis of thrombus formation and/or degradation, in young women who had developed thrombosis, despite the relatively low risk of thrombosis according to classical risk factors. Our specific aim was to compare imbalance in fibrinolytic and coagulation parameters in women with three different types of thrombosis: (1) thrombosis in coronary arteries, as occurs in MI, (2) thrombosis in small, penetrating brain arteries, as takes place in lacunar cerebral infarction (LACI) and (3) thrombosis in deep veins (VT).

Subjects and Methods

Subjects

Slovenia participated in large, epidemiological, multicenter WHO study on the associations of cardiovascular diseases with combined oral contraceptive use [6]. From this study we recruited 68 women with three different types of thrombosis but a low risk of thrombosis according to the classical risk factor profile for further evaluation of changes in fibrinolytic and/or coagulation system. The group comprised 22 women with MI, who had a risk of coronary heart disease below 10% in the next 10 years estimated by the classic risk factors, as proposed by the Second Joint Task force of European and other Societies on Coronary Prevention [7], 16 women with LACI, and 30 women with VT, who were divided into two subgroups: group VT1 – women with idiopathic VT ($n = 14$) and group VT2 – women who were taking oral contraceptives at the time of the acute event ($n = 16$).

MI was based on the WHO criteria of typical chest pain, enzyme patterns, and/or diagnostic electrocardiographic changes [8]. LACI was established according to computed tomography of the head and clinical criteria, as proposed by Bamford et al. [9]. VT was estab-

lished by clinical criteria and confirmed by venography, duplex scanning or radioisotope studies. The control group comprised 52, healthy women with a mean age of 41 years (28–49); a subgroup of 20 women with a mean age of 34 years (28–44) served as controls for women from the VT2 group; selection criteria were described in the WHO study [6]. All women gave full informed consent. The study was approved by the State Ethical Committee on human research.

Women were recruited in the study in the chronic stable phase of disease 6 months to 6 years (mean 3.5 years) after the acute thrombotic event. Clinical examination was done on the same day as blood sampling. At the time of blood sampling, 16 and 8 patients with MI and LACI, respectively, were taking aspirin; none of the VT women was taking aspirin. No patient used oral anticoagulants. At the time of blood sampling, patients did not differ from the controls in smoking habits. Neither patients nor controls were taking oral contraceptives at the time of blood sampling nor did patients and controls differ in menstrual status.

Blood Sampling

Blood samples were drawn from the antecubital vein between 7 and 9 a.m. with minimal venous stasis. Women were fasting, and rested prior to blood sampling for 20 min in a sitting position. Plasma was prepared by centrifugation at 2,000 g and 4 °C for 30 min, snap frozen in liquid nitrogen and stored at –70 °C until analyzed.

Laboratory Methods

The metabolic variables, i.e. fasting glucose, triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol, were determined by routine biochemical methods. Fibrinogen was determined by a clotting assay (Multifibren, Behring, Germany), protein C and antithrombin III by a kinetic spectrophotometric assay (Berichrom-Protein C and Berichrom Antithrombin III; Behring, Marburg/Lahn, Germany). Activated protein C resistance was determined according to Dahlback et al. [10]. Euglobulin clot lysis time was measured according to Buckell [11] and D-dimer by enzyme-linked immunosorbent assay (Tintelize®, Biopool, Sweden). Plasminogen was determined by kinetic spectrophotometry (Berichrom Plasminogen, Behring). Tissue type plasminogen activator (t-PA) and plasminogen activator-1 (PAI-1) antigens were determined by enzyme-linked immunosorbent assay (Imulyse™ tPA and Imulyse™ PAI-1, respectively, both from Biopool, Sweden). t-PA activity and PAI activity were determined by amidolytic assays (Spectrolyse®/fibrin, Biopool, Sweden).

Statistical Methods

Normally distributed continuous clinical, biochemical and haemostatic variables of patient groups and controls were compared using the t test for independent samples. Continuous variables, which were not normally distributed, were expressed as medians with ranges between the first and the third quartile, and differences between groups assessed by the Mann-Whitney U test. According to the number of cases, the χ^2 test or Fischer's exact test was used for comparison of the differences between patient groups and controls for discrete variables. Depending on the distribution, Pearson's or Spearman's correlation coefficients were calculated to test associations between different variables. Multiple linear regression analysis was performed to evaluate the independence of associations. Statistical analyses were performed by the Statistica for Windows computer program (Stat Soft, Inc., Tulsa, Okla., USA). A p value of <0.05 was taken as statistically significant.

Table 1. Anthropometric and biochemical characteristics

	Controls (n = 52)	MI group (n = 22)	LACI group (n = 16)	VT1 group (n = 14)	VT2 group (n = 16)
Age, years	41 (28–49)	42 (36–47)	42 (36–48)	39 (31–49)	33 (23–45)****
BMI, kg/m ²	26 ± 4	26 ± 5	27.2 ± 5.1	32 ± 8*	24 ± 4**
Waist/hip ratio, rel.	0.80 ± 0.06	0.80 ± 0.05	0.81 ± 0.06	0.79 ± 0.04	0.80 ± 0.10
Systolic blood pressure, mm Hg	128 ± 3	129 ± 15	130 ± 26	126 ± 22	123 ± 20
Diastolic blood pressure, mm Hg	82 ± 11	81 ± 7	82 ± 11	84 ± 13	81 ± 11
Total cholesterol, mmol/l	5.7 ± 1.4	6.5 ± 1.5*	5.6 ± 1.1	5.5 ± 0.9	5.5 ± 1.3
LDL-cholesterol, mmol/l	3.5 ± 1.1	4.3 ± 1.3**	3.5 ± 0.95	3.4 ± 0.9	3.4 ± 1.2
HDL-cholesterol, mmol/l	1.6 ± 0.4	1.3 ± 0.3**	1.6 ± 0.5	1.6 ± 0.5	1.8 ± 0.5
Triglycerides, mmol/l	1.0 (0.7–1.3)	1.6 (0.9–1.9)*	1.0 (0.8–1.2)	1.0 (0.5–1.4)	0.8 (0.6–1.0)
Blood glucose, mmol/l	5.1 ± 0.6	5.2 ± 0.7	5.5 ± 0.7*	5.1 ± 0.8	4.8 ± 0.5
Insulin level, mIE/l	11.7 ± 5.1	10.0 ± 3.3	10.9 ± 6.3	12.5 ± 3.8	8.0 ± 2.3**
Sedimentation rate, mm/h	7 (4–12)	9 (5–12)	8 (5–12)	15 (6–19)*	5 (4–12)

Values are shown as means ± SD or as medians with ranges between the first and the third quartile, with the exception of age, which is shown as means and ranges in parenthesis. * $p < 0.05$, ** $p < 0.01$, **** $p < 0.0001$ compared with controls.

Results

Clinical Characteristics

In the MI group compared with controls (all $p < 0.05$) significantly more women had arterial hypertension (41 vs. 20%), mild hyperlipidemia (41 vs. 0%) and smoked at the time of the acute event (64 vs. 36%). However, at the time of clinical examination, there were no differences in smoking status (32 vs. 36%, $p = \text{NS}$) or blood pressure, which was probably the result of antihypertensive treatment. Only small but significant differences in all lipids were observed, despite dietary and hypolipemic treatment. MI women and controls also did not differ in body mass index (BMI) or levels of glucose and insulin (table 1).

In the LACI group compared with controls there were no differences in arterial hypertension (31 vs. 20%) and or the percentage of women who smoked at the time of the acute event (44 vs. 36%, all $p = \text{NS}$). Although significantly more LACI women had mild hyperlipidemia (31 vs. 0%, $p < 0.001$) there were no differences in levels of lipids, again probably due to diet and hypolipemic treatment. LACI women and controls also did not differ in blood pressure, BMI or insulin level; blood glucose was slightly and significantly higher in LACI women (table 1).

In the VT group no significant differences were found in hypertension (7 vs. 20%), hyperlipidemia (3 vs. 0%) or the percentage of women who smoked at the time of the acute event (33 vs. 36%, all $p = \text{NS}$). Women from the

VT1 group were significantly more obese and had higher values of insulin compared with women from the VT2 group and controls; additionally, women from the VT2 group had lower insulin concentrations compared with controls (table 1). Women from the VT2 group did not have significantly different anthropometric and metabolic parameters compared with their age-matched controls (data not shown).

Coagulation and Fibrinolytic Parameters in All Patients

All patients had significantly higher fibrinogen, t-PA antigen and PAI-1 antigen levels compared with controls (table 2).

Coagulation and Fibrinolytic Parameters in the MI Group

MI women had significantly higher t-PA antigen than controls, other differences in fibrinolytic and coagulation parameters not being significant (table 2). t-PA antigen correlated significantly with PAI-1 antigen ($r = 0.62$, $p < 0.0001$) and PAI-1 activity ($r = 0.76$, $p < 0.0001$) but not with t-PA activity ($r = -0.17$, NS). t-PA antigen also correlated significantly with BMI ($r = 0.63$, $p < 0.005$), waist/hip ratio ($r = 0.68$, $p < 0.01$), triglycerides ($r = 0.59$, $p < 0.005$), blood glucose ($r = 0.71$, $p < 0.0001$) and insulin ($r = 0.53$, $p < 0.05$). Correlation with sedimentation rate almost reached statistical significance ($r = 0.38$, $p = 0.08$). In multivariate linear regression analysis only the waist/

Table 2. Coagulation and fibrinolytic parameters

	Controls (n = 52)	All patients (n = 68)	MI group (n = 22)	LACI group (n = 16)	VT1 group (n = 14)	VT2 group (n = 16)
Fibrinogen, g/l	2.3 (1.0–2.4)	2.4 (2.1–2.7)*	2.2 (2.1–2.7)	2.4 (2.4–2.7)*	2.3 (1.9–2.6)	2.3 (2.0–2.7)
Antithrombin III, rel.	1.08 ± 0.16	1.08 ± 0.16	1.04 ± 0.17	1.05 ± 0.22	1.02 ± 0.12	1.12 ± 0.19
Protein C activity, rel.	0.96 ± 0.18	0.98 ± 0.16	0.98 ± 0.19	0.94 ± 0.23	0.99 ± 0.17	0.90 ± 0.29
APCR, rel.	3.5 ± 0.6	3.5 ± 1.0	3.2 ± 0.6	3.5 ± 0.5	3.5 ± 0.6	3.2 ± 0.7
ECLT, min	340 (300–370)	332 (280–378)	345 (280–373)	320 (270–358)	378 (323–4.7)**	288 (253–340)##
D-dimer, ng/ml	59 (50–73)	61 (52–79)	65 (54–71)	57 (55–83)	74 (49–85)	55 (48–86)
Plasminogen, rel.	0.98 ± 0.16	0.99 ± 0.16	1.01 ± 0.19	0.96 ± 0.18	1.03 ± 0.15	0.97 ± 0.09
t-PA antigen, ng/ml	5.7 (4.3–8.2)	7.6 (5.3–8.9)*	7.0 (5.9–8.3)*	6.9 (5.8–8.5)	8.9 (4.9–11.1)*	5.9 (4.4–7.3)##
t-PA activity, IU/ml	0.5 (0.3–0.8)	0.6 (0.4–0.8)	0.5 (0.3–0.9)	0.5 (0.4–0.7)	0.4 (0.3–0.6)	0.7 (0.4–0.9)
PAI-1 antigen, ng/ml	9.1 (6.1–16.6)	14.9 (5.8–20.6)*	12.4 (7.5–25)	10.6 (5.9–16.4)	17.6 (7.8–25.1)*	6.0 (3.9–17.4)##
PAI activity, IU/ml	6.7 (2.8–14.3)	10.2 (2.8–15.3)	7.2 (1.8–15.6)	9.5 (5.6–15.4)	11.9 (5.4–16.2)	2.9 (0.9–14.1)#

All values are expressed as medians with ranges between the first and the third quartile or as means ± SD. APCR = Activated protein C resistance; ECLT = euglobulin clotting time; t-PA = tissue type plasminogen activator; PAI = plasminogen activator inhibitor. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ patients vs. controls, # $p < 0.05$ and ## $p < 0.005$ VT1 vs. VT2.

hip ratio ($\beta = 0.48$, $p < 0.05$) remained significantly and independently associated with t-PA antigen and explained 51% (adjusted $R^2 = 0.51$, $p < 0.005$) of t-PA antigen variability together with sedimentation rate ($\beta = 0.25$, $p = 0.1$) and glucose ($\beta = 0.28$, $p = 0.2$).

Coagulation and Fibrinolytic Parameters in the LACI Group

LACI women had slightly but significantly higher fibrinogen levels than controls (all $p < 0.05$); no other differences in coagulation and fibrinolytic parameters were significant (table 2). Fibrinogen correlated significantly with D-dimer ($r = 0.54$, $p < 0.05$) and sedimentation rate ($r = 0.57$, $p < 0.05$), whereas other correlations with coagulation, fibrinolytic and metabolic parameters were not significant (data not shown). In multivariate linear regression analysis only smoking status at the time of blood sampling ($\beta = 0.67$, $p < 0.05$) was significantly and independently associated with fibrinogen and explained 45% (adjusted $R^2 = 0.45$, $p < 0.005$) of fibrinogen variability along with D-dimer ($\beta = 0.50$, $p = 0.08$), systolic blood pressure ($\beta = 0.40$, $p = 0.1$) and sedimentation rate ($\beta = 0.29$, $p = 0.3$).

Coagulation and Fibrinolytic Parameters in the VT Group

Women from the VT1 group had significantly higher PAI-1 antigen, PAI activity and t-PA antigen, and significantly longer euglobulin clotting time (ECLT), compared with women from the VT2 group and controls (table 2). In the VT1 group PAI-1 antigen correlated significantly with

PAI-1 activity ($r = 0.59$, $p < 0.05$) and PAI-1 activity with t-PA antigen ($r = 0.61$, $p < 0.05$). t-PA antigen correlated significantly only with the waist/hip ratio ($r = 0.61$, $p < 0.05$), but the correlation with sedimentation rate almost reached significance ($r = 0.46$, $p = 0.09$). In multivariate linear regression analysis both waist/hip ratio ($\beta = 0.71$, $p < 0.005$) and sedimentation rate ($\beta = 0.51$, $p = 0.01$) remained significantly and independently associated with t-PA antigen and explained 72% (adjusted $R^2 = 0.72$, $p < 0.005$) of t-PA antigen variability together with HDL ($\beta = 0.54$, $p < 0.005$). PAI-1 antigen significantly correlated with BMI ($r = 0.59$, $p < 0.05$), waist/hip ratio ($r = 0.69$, $p < 0.01$), triglycerides ($r = 0.63$, $p < 0.05$), HDL cholesterol ($r = -0.61$, $p < 0.05$) and insulin ($r = 0.75$, $p < 0.005$). In multivariate linear regression analysis waist/hip ratio ($\beta = 0.42$, $p < 0.05$), insulin ($\beta = 0.43$, $p < 0.05$) and HDL ($\beta = -0.30$, $p = 0.05$) explained 78% (adjusted $R^2 = 0.78$, $p < 0.0005$) of PAI-1 antigen variability. Women from the VT2 group did not have significantly different coagulation and fibrinolytic parameters compared with their age-matched controls (data not shown).

Discussion

The aim of our study was to explore the potential vascular bed specific alterations of coagulation and fibrinolytic parameters in young women following MI (arterial thrombosis with ruptured plaque), LACI and VT. Young women were chosen since they commonly suffer thrombosis in the absence of pronounced classical risk factors

[2–5] that might hinder the exploration of the specific roles of coagulation and fibrinolytic parameters. We found that fibrinolysis was impaired in MI and idiopathic VT, in the context of the plurimetabolic syndrome, while in LACI patients fibrinogen was elevated.

In women with MI we found significantly increased levels of t-PA antigen, which has already been recognized as a risk factor for MI [12]. The most important parameters which independently explained almost half the t-PA antigen variability were the waist to hip ratio, an indicator of abdominal obesity and the consequent plurimetabolic syndrome, and sedimentation rate, an indicator of inflammation. It has been shown previously that the predictive capacity of t-PA antigen for MI is highly dependent on parameters of the plurimetabolic syndrome and inflammation markers [13]. Thus it seems plausible that both the plurimetabolic syndrome and inflammation might contribute to impaired fibrinolysis and thrombosis in coronary arteries in young women with MI.

Women with LACI had a slightly hypercoagulable state characterized by increased levels of fibrinogen compared with controls. Hypercoagulability due to increased fibrinogen has been found to be an independent risk factor for stroke in the young as well as in the elderly population [14–16]. It might contribute to the pathogenesis of LACI stroke through increased blood viscosity and/or increased thrombus formation at the site of local injury or stasis in small brain arteries [17]. We found that the most important parameters, which explained almost half of the fibrinogen variability were smoking, D-dimer, systolic blood pressure and sedimentation rate. All these parameters might be involved in vascular damage through a direct mechanical influence or through inflammatory processes in small brain arteries.

In women with VT we found significantly impaired fibrinolysis revealed by increased t-PA antigen, PAI-1 antigen and activity, and prolonged euglobulin clot lysis

in women with idiopathic VT but not in users of oral contraceptives. Fibrinolytic parameters significantly correlated with parameters of the plurimetabolic syndrome, and women with idiopathic VT were also clearly obese and had higher insulin levels compared with both controls and users of oral contraceptives. Accordingly, it seems that the plurimetabolic syndrome associated with impaired fibrinolysis, which is otherwise a well-known risk factor for arterial thrombosis [18, 19], is also present in young women with idiopathic VT and might increase the risk of disease. Since women with idiopathic VT had also increased sedimentation rate, which significantly correlated with t-PA antigen and explained a large proportion of its variability in multivariate analysis it seems that inflammation might also contribute to impairment of fibrinolysis in young obese women with idiopathic VT. This proposal is supported by the fact that some inflammatory cytokines could impair fibrinolytic activity through induction of PAI-1 expression in adipose tissue [19, 20].

In conclusion, we found different profiles for alterations of coagulation and fibrinolysis parameters in young women with MI, LACI and VT. Our results are in agreement with the prediction of a vascular bed specific thrombosis process. Thus, it seems straightforward to further study the vascular bed specific characteristics of the thrombosis process.

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