

Role of Coronary Risk Factors in Blood Thrombogenicity and Acute Coronary Syndromes

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Recent advances in basic science have linked some systemic risk factors to endothelial dysfunction which gives rise to atherosclerotic disease and triggers the progression of thrombotic complications. Superficial erosion of the stenotic plaque can be observed in one-third of acute coronary syndromes (ACS). In these cases the presence of classic risk factors such as diabetes mellitus, hypercholesterolemia and smoking favor a state of «vulnerable blood» or high risk. Increased thrombogenicity can exacerbate thrombus formation and is able to trigger an ACS. The vessel endothelium regulates contractile, mitogenic and thrombotic activities of the vessel wall. Risk factors impair both homeostasis and hemostasis of the vessel wall and promote inflammatory signals. Platelet and monocyte activation favors the expression of tissue factor (TF), thus triggering the coagulation cascade with thrombin generation and clot formation. Increased blood thrombogenicity linked to classic risk factors may be associated with circulating TF levels which are much higher than those observed in healthy subjects without risk factors. These observations not only emphasize the usefulness of aggressive management of risk factors but open a new avenue for future studies to devise therapeutic strategies to treat ACS by inhibiting TF expression.

Key words: *Risk factors. Tissue factor. Acute coronary syndrome.*

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INTRODUCTION

The pathogenesis of coronary disease involves two interdependent processes, atherosclerosis and thrombosis, which give rise to the term

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Papel de los factores de riesgo en la trombogenicidad sanguínea y los síndromes coronarios agudos

Recientes avances en las ciencias básicas han vinculado algunos factores de riesgo con la disfunción endotelial que inicia la enfermedad aterosclerótica y desencadena la progresión de sus complicaciones trombóticas. En una tercera parte de los síndromes coronarios agudos sólo existe una erosión de la placa. En estos casos, la presencia de algunos factores de riesgo, como la diabetes mellitus, la hipercolesterolemia y el tabaquismo, promueve un estado de «sangre vulnerable o de alto riesgo». La elevada trombogenicidad sanguínea existente bajo estas condiciones puede exacerbar la formación trombótica y es capaz de desencadenar un síndrome coronario agudo (SCA). El endotelio vascular regula la actividad contráctil, mitogénica y trombótica de la pared vascular. Los factores de riesgo alteran la homeostasis y la hemostasis de la pared vascular y promueven las señales inflamatorias. Se activan las plaquetas y los monocitos, lo que favorece la expresión del factor tisular (FT), desencadenando la cascada de coagulación con la generación de trombina y la formación del trombo vascular. La hipertrombogenicidad sanguínea vinculada a los factores de riesgo podría estar mediada por los valores elevados de FT circulante, que son muy superiores a los que presentan los sujetos sanos sin factores de riesgo. Estas observaciones enfatizan la necesidad de un manejo agresivo de los factores de riesgo y de futuros estudios dirigidos a conseguir estrategias terapéuticas que inhiban la expresión del FT.

Palabras clave: *Factores de riesgo. Factor tisular. Síndrome coronario agudo.*

«atherothrombosis.» Atherothrombosis is a chronic, dynamic process in blood vessel walls in which patients may present with acute coronary syndrome (ACS) during the inflammation and thrombotic activity phases.¹⁻³ Endothelial dysfunction and inflammation are the major facilitators of atherosclerotic disease. Multiple factors, both local (oxidative stress, shearing forces) and systemic (traditional risk factors such as diabetes mellitus

ABBREVIATIONS

ACS: acute coronary syndrome.
 ADP: adenosine diphosphate.
 aFVII: activated factor VII.
 aFX: activated factor X.
 BT: blood thrombogenicity.
 CRP: C-reactive protein.
 DM: diabetes mellitus.
 EC: endothelial cells.
 ET-1: endothelin-1.
 GF, GF2: growth factor, growth factor 2.
 GPIa, Ib, IIb/IIIa: glycoproteins Ia, Ib, IIb/IIIa.
 HBP: high blood pressure.
 HDL: high density lipoprotein.
 HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A.
 ICAM-1: intercellular adhesion molecule 1.
 IL-1, IL-6, IL-8: interleukins 1,6,8.
 LDL: low density lipoproteins.
 MCP-1: monocyte chemotactic protein.
 MPI-1: metalloproteinase I-1.
 MMP: matrix metalloproteinase.
 NF- κ B: nuclear factor kappa B.
 NO: nitric oxide.
 PA: plasminogen activator.
 PAI-1: plasminogen activator inhibitor.
 PGI₂: prostaglandin I₂.
 RNA: ribonucleic acid.
 ROS: reactive oxygen species (free radicals).
 SMC: smooth muscle cells.
 TF: tissue factor.
 TFag: tissue factor antigen.
 TFPI: tissue factor pathway inhibitor.
 TNF α : tumor necrosis factor α .
 t-PA: tissue plasminogen activator.
 TXA₂: thromboxane A₂.
 VCAM-1: vascular-cellular adhesion molecule 1.
 VEGF: vascular endothelial growth factor.
 VLDL: very low density lipoproteins.
 vWF: von Willebrand factor.

[DM], smoking, hypercholesterolemia and high blood pressure [HBP]) have been implicated in the initiation, progress and maintenance of endothelial dysfunction.⁴ These traditional risk factors have been epidemiologically linked to a high incidence of atherothrombotic complications, and recent experimental and clinical pathological studies have helped explain the underlying cellular and molecular mechanisms that relate them to the atherosclerotic process. Further, they have helped explain why their aggressive control can reduce or prevent new episodes

of ACS in patients with atherosclerosis.⁵⁻⁸

Although the last decade saw great advances in the prevention of coronary disease through the modification of its causes, in the coming years it will probably remain the most common cause of death in industrialized countries. Therefore, even though atherothrombotic disease is treatable, we must continue to emphasize prevention and the modification of its risk factors.

BLOOD THROMBOGENICITY AND ACUTE CORONARY SYNDROMES

The composition of an atherosclerotic plaque — even more so than the degree of stenosis— is the main factor that determines its vulnerability. «Vulnerable» or «high risk» atherosclerotic plaques are the most dangerous, not just because of their fragility but also because once ruptured they are the most thrombogenic. They are characterized by their thin, fibrous capsule, a large number of macrophages, and a nucleus rich in lipids with a high tissue factor (TF) content —a property conferring greater thrombogenicity^{9,10} (Figure 1). Tissue factor is probably generated, in part, by macrophages, and is



Fig. 1. A: Eroded plaque. Two mural thrombi protrude into the lumen of a coronary artery. The underlying atheroma plaque is eroded, with severe, extensive endothelial loss and marked macrophage infiltration.



Fig. 1. B: Histology of an eccentric, fatty, coronary plaque. The fatty deposit is separated from the vessel lumen (L) by the cap, formed by connective tissue and smooth muscle cells.

activated on contact with apoptotic vascular endothelial cells. Knowing the type of rupture (ulceration, fissure or erosion) an atheroma plaque has undergone is essential for determining local arterial thrombogenicity. When a plaque ruptures, TF from the lesion comes into contact with the circulating blood, resulting in the generation of thrombin via the coagulation cascade. Thrombin perpetuates the activation of this cascade and stimulates platelet aggregation which is essential to the stability of the mural thrombus. The latter, which forms over the plaque, releases growth factors and platelet vasoconstrictors that contribute to stenosis of the vessel lumen, and therefore to the appearance of ischemic events.

In one third of all ACS, particularly sudden death by infarction, there is no rupture of a lipid-rich, slightly stenotic plaque. Rather, superficial erosion of a markedly stenotic and fibrotic plaque is seen.¹¹ In such cases, thrombotic complications might depend on a systemic thrombogenic condition promoted by factors such as smoking, HBP and hypercholesterolemia.⁵ Some studies have shown a relationship to exist between glycemic control, smoking and hypercholesterolemia, and a predisposition towards the formation of clots.^{6,7} More recently, it has been reported that this hyperthrombotic state might be mediated by high levels of circulating TF—much higher than those seen in healthy subjects with no risk factors.⁸

CONTRIBUTION OF RISK FACTORS TOWARDS THROMBOSIS

Epidemiological and clinical studies show that cardiovascular risk factors such as DM, hyperlipidemia and smoking are associated with a greater number of thrombotic complications.^{12,13} Some clinical and experimental studies have shown that

these risk factors can promote a hypercoagulable state which can trigger blood thrombogenicity (BT).^{14,15} In particular it has been reported that hyperlipidemia promotes plaque rupture in patients with ACS whereas cigarette smoking favors acute thrombosis.⁵

Therefore, alongside the established concept of the «vulnerable» or «high risk» plaque, the concept of «vulnerable» or «high risk» blood can be used to refer to the prethrombotic state associated with these risk factors. These factors can initiate the atherothrombotic process, causing endothelial dysfunction and the activation of inflammation and clotting.

ROLE OF RISK FACTORS IN ENDOTHELIAL DYSFUNCTION

Endothelial dysfunction marks the beginning of atherothrombotic disease. The endothelium plays a central role in vascular homeostasis via the balanced production of vasodilatory molecules and antimotogens (nitric oxide [NO] and prostacyclin), and vasoconstrictors and mitogens (endothelin-1 [ET-1] and angiotensin II).¹⁶ The endothelium also has antithrombotic and fibrinolytic properties, activating antithrombin III, tissue factor pathway inhibitor (TFPI) and tissue plasminogen activator (t-PA), and impeding the expression of activated TF and plasminogen activator inhibitor (PAI-1). The NO released by the endothelium is a key molecule in the maintenance of homeostasis. As well as its vasoregulatory function, it reduces platelet aggregation and the adhesion of monocytes, prevents the proliferation of smooth muscle cells (SMC), and prevents the oxidation of low density lipoproteins (LDL).¹⁷ This molecule also has an anti-inflammatory effect, increasing the production of nuclear factor kappa B (NF- κ B, a transcription factor involved in the regulation of many pro-inflammatory genes that express cytokines), intercellular adhesion molecule 1 (ICAM-1), vascular-cellular adhesion molecule 1 (VCAM-1) and E-selectin, which together facilitate the activation and migration of monocytes.¹⁸ The endothelial dysfunction that occurs because of classic as well as other risk factors impedes vascular homeostasis and activates vascular wall repair mechanisms (Figure 2).

DIABETES MELLITUS: ETIOLOGIC AND PATHOGENIC MECHANISMS IN VASCULAR THROMBOSIS

Recent clinical trials such as GISSI 2 and GUSTO I^{19,20} indicate that the incidence of acute thrombotic coronary events is higher in patients with DM than in nondiabetics. The clinical course of their disease is also worse. Further, in patients with diabetes,

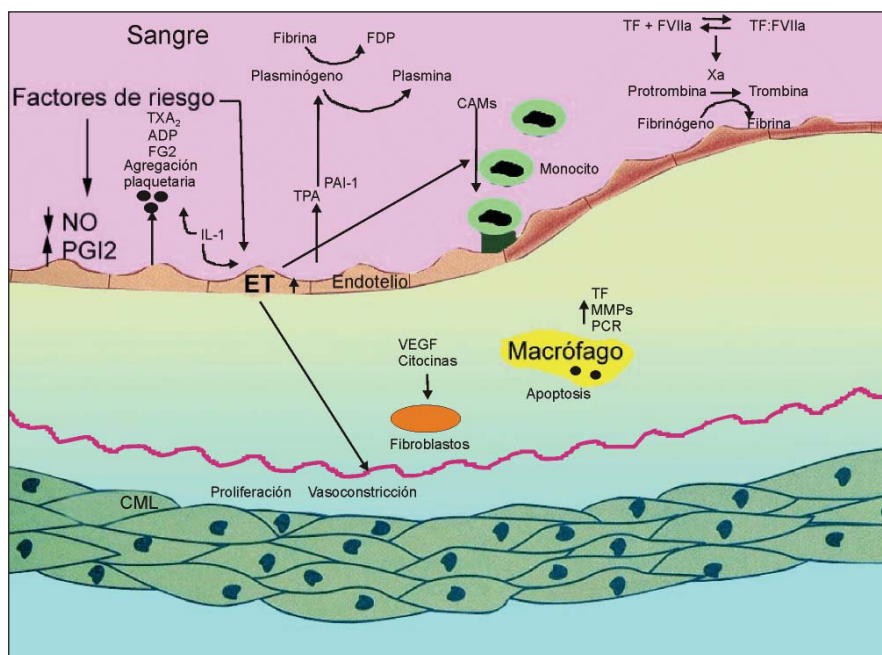


Fig. 2. Advanced endothelial dysfunction. Endothelial dysfunction causes vasoconstriction. The expression of VCAM and ICAM-1 by EC increases, which facilitates the adhesion of monocytes and platelets to the vessel wall. Inflammatory mediators cause apoptosis in the EC and SMC, and produce proteinases such as MMP-2 regulated by oxidized lipoproteins and cytokines. MMP-2 contributes to the activation of platelet aggregation, along with the granules released by the platelets themselves (TXA₂, ADP and GF₂). Apoptotic cells release activated TF which initiates the coagulation cascade. TF interacts with FVII and activates FX, which in turn activates the conversion of prothrombin into thrombin. Finally, fibrin is generated, which, along with platelet activity, creates the stability required for the formation of a mural thrombus. TF activated by the systemic risk factors contributes towards procoagulant activity in the atherosclerotic lesions, and therefore towards clot formation.

atherosclerotic lesions arising from atherectomies are characterized by their greater lipid density, higher macrophage count, and greater content of material of thrombotic origin.²¹

Several factors contribute to hypercoagulability in patients with diabetes. The oxidative stress caused by hyperglycemia leads to the glycosylation of collagen in the artery walls. This has been proposed as one of the mechanisms responsible for the accelerated progress of arteriosclerotic disease in patients with diabetes.²² Advanced glycation end products favor endothelial dysfunction, upset hemostatic and fibrinolytic mechanisms, and interfere with the TF pathway (Figure 3).

In patients with diabetes, platelets show hyper-reactivity, hyper-aggregability and increased adhesiveness in response to ADP.²³ They also interact with endothelial cells (EC) and leukocytes, producing a greater number of circulating leukocyte-platelet aggregates. The procoagulant activity patients in with diabetes has been attributed to leukocytes.²⁴ In patients with microalbuminuria, an increase in the expression of monocytes with procoagulant activity is seen.¹⁵ High levels of activated factor VII (aFVII), activated factor VIII (aFVIII), fibrinogen, PAI-1, and von Willebrand factor (vWF) are also observed, which further contribute to the increased BT associated with DM.²⁵

Advanced glycation end products induce the expression of TF in macrophages and monocytes in vitro.²⁶ Recently, it has been reported that diabetic patients have high levels of TFPI as a consequence of TF activation.²⁷ However, the relationship between

hypercoagulability and glycemic control is controversial.^{25,28} Even so, several studies have shown that adequate control can reduce the risk of thrombotic complications.^{15,17} In a recent study we reported that high BT in patients with diabetes was associated with high circulating levels of active TF. More important was the observation that effective control of glycemia is associated with reduced plasma levels of activated TF and BT. These observations stress the importance of control of blood glucose concentrations for BT, mainly through the inhibition of circulating TF.⁸

HYPERCHOLESTEROLEMIA: ETIOLOGIC AND PATHOGENIC MECHANISMS IN VASCULAR THROMBOSIS

Hypercholesterolemia has been associated with the generation of oxidized LDL and reactive oxygen species (ROS) in the vascular wall and circulating blood.²⁹ These are activators of endothelial dysfunction (particularly in stress zones) and of macrophages and monocytes in lipid-rich media.^{29,30} Endothelial cells modulate the permeability of the vascular membrane to the flow of LDL. Some risk factors such as HBP and hypercholesterolemia facilitate penetration of the intima by LDL. Through the intervention of EC, SMC and macrophages, LDLs can become oxidized LDLs —molecules of greater atherogenicity. The process of endothelial dysfunction induced by oxidized LDL begins with a reduction in NO production and an increase in the expression of adhesion molecules (VCAM-1 and ICAM-I and P-selectin), which help the monocytes adhere to the

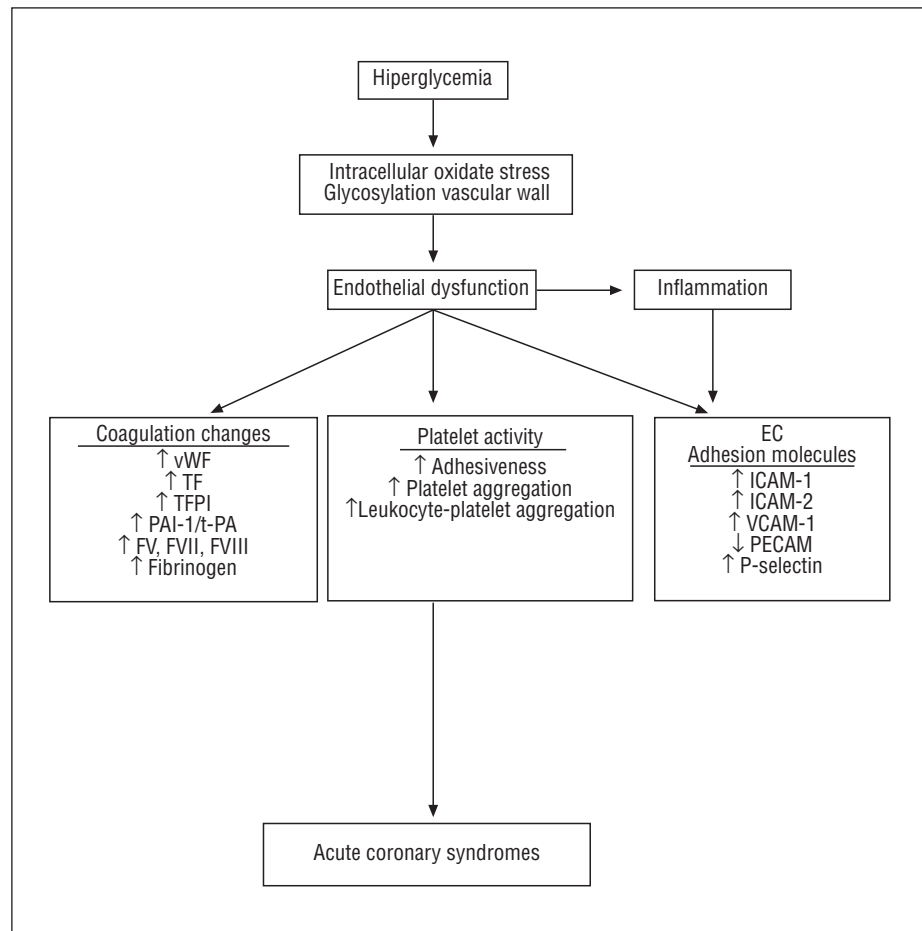


Fig. 3. Atherothrombotic mechanisms in diabetes mellitus. Rupture of the plaque. The advanced glycation end products produced by constant hyperglycemia induce endothelial dysfunction in the vessel wall. This leads to changes in the vascular hemostatic and fibrinolytic mechanisms, which in turn lead to a state of hypercoagulability which favors the appearance of acute coronary syndromes.

damaged endothelium. Circulating monocytes attracted by monocyte chemoattractant protein (MCP-1) penetrate the vessel wall, whereupon oxidized LDL facilitates their conversion into macrophages. These take up molecules of oxidized LDL and become foam cells, leading to apoptosis in the EC.³¹ Angiogenesis also contributes to the atherosclerotic process. Smooth muscle cells are activated by cytokines (TNF α , IL-1, IL-6, IL-8) and growth factor (GF), and these migrate from the medial layer to the intima of the vascular endothelium, contributing to the development of the lesion.³² In addition, lipoprotein A has a similar structure to plasminogen and can reduce the formation of plasmin, impeding thrombolysis.³³

The oxidation of LDL and the activation of ROS, EC, macrophages and monocytes can generate TF (and its corresponding mRNA).³⁴ This TF may then be released into the bloodstream as microparticles—and as such is considered to originate in the blood.³⁵ These TF microparticles can fuse together or be transported by lipoproteins (including LDL, very low density lipoprotein [VLDL] and high density lipoprotein [HDL]). Further, hyperlipidemia per se can increase the number of TF microparticles in the blood.³⁶

High levels of LDL increase the growth of clots

under certain rheological conditions. A recent study reports that patients with high LDL levels also had high levels of TF, suggesting a possible link with the predisposition towards thrombosis seen in patients with hyperlipidemia.⁸ In contrast, HDL protects against the oxidation of LDL. Experiments have shown that when HDL levels increase, the number of activated macrophages decreases, a change presumably accompanied by the stabilization of the plaque rupture. This prevents clot formation from progressing.³⁷

Several clinical studies with inhibitors of HMG-CoA reductase and statins have clearly shown them to decrease the number of cardiovascular events, and not just through a reduction in LDL levels.^{38,39} The reduction of LDL levels by statins can reduce clot growth by 20%, vasoconstriction and the size of the lipid-rich plaque core are also reduced, and the fibrinolytic profiles of patients with coronary disease are improved.^{6,40} In experiments with high doses of statins, possible pleiotropic effects have been seen, leading to a reduction in inflammatory and thrombotic potential and stabilizing the atherosclerotic plaque. In human cell cultures and in animal models, lipophilic statins (fluvastatin and simvastatin) have been shown

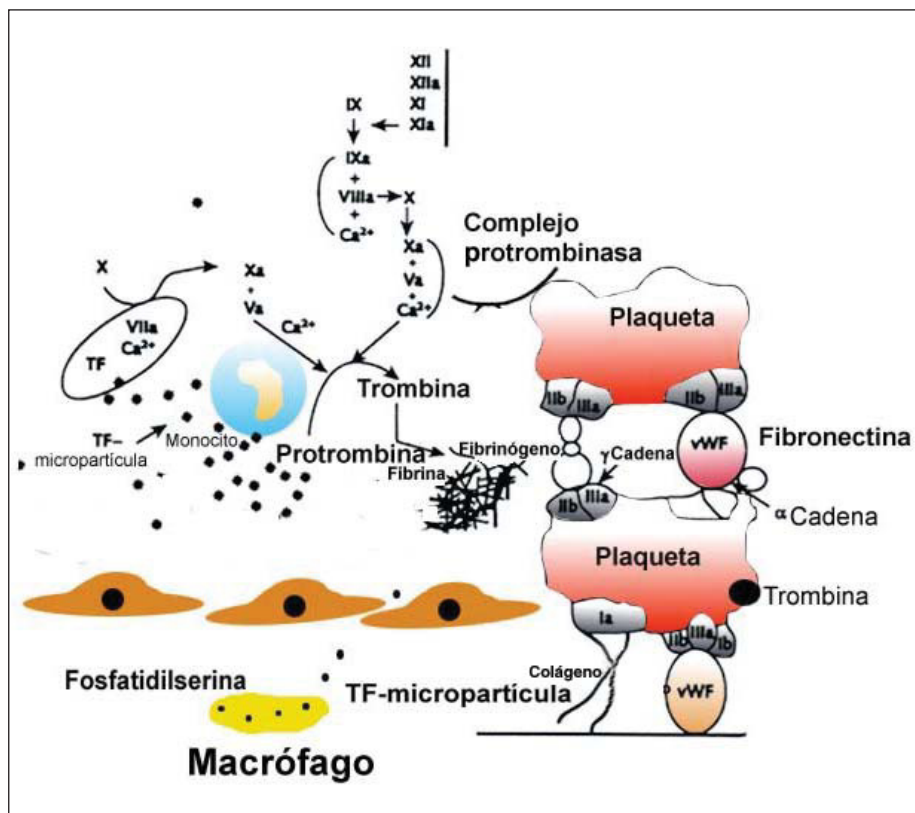


Fig. 4. Tissue factor and the activation of the coagulation cascade. The rupture of the plaque places its contents in contact with the blood, activating hemostasis and generating thrombin. The platelets bind to FvW and collagen via GPIb and GPIa receptors. Fibrinogen binds to GPIIb/GPIIIa receptors to form bridges with the platelets, facilitating platelet aggregation. TF from the atherosclerotic plaque is activated when it contacts phosphatidylserine on the surface of apoptotic cells, and forms procoagulant microparticles. Together with the particles transported by the monocytes, these activate the coagulation cascade, generating thrombin. In association with cell membranes and platelets, thrombin converts fibrinogen to fibrin, activates the platelets and factors V and VIII, and stabilizes the growth of the clot.

to prevent the expression of TF from monocytes/macrophages by inhibiting a protein involved in its biosynthesis. The number of activated macrophages is also reduced, and so therefore is the release of metalloproteinase I-1 (MPI-1).^{34,41} The levels of inflammatory markers involved in endothelial function (VCAM-1 and C reactive protein [CRP]) are also reduced.^{33,42} In addition, TF levels also decline; therefore the binding of aFVII and aFX is reduced.³⁶ These findings suggest that qualitative changes in the atherosclerotic plaques and the underlying thrombotic process are responsible for the large reduction in the number of cardiovascular events in patients taking statins.

SMOKING: ETIOLOGIC AND PATHOGENIC MECHANISMS IN VASCULAR THROMBOSIS

Smoking has been identified as a major risk factor for atherosclerotic problems.¹ The association between smoking and an increased risk of ACS and sudden death has been clearly established.^{5,43} It has been suggested that interference with the antithrombotic and fibrinolytic functions of the blood and blood vessel walls might be responsible for the majority of vascular events that occur in smokers —although the mechanisms by which smoking increases the risk of atherothrombotic problems are not entirely understood. Smoking causes the EC changes and the NO reduction

responsible for endothelial dysfunction, probably via nicotine dependence,^{44,45} which activates the central nervous system. The release of catecholamines can potentiate platelet aggregation and increase blood fibrinogen levels, activate monocytes and generate thrombin, as well as promoting LDL oxidation as a result of the ROS produced by smoking.^{46,47} The data available on the effects of smoking on thrombohemostatic and fibrinolytic factors are scarce and controversial.^{45,48,49} However, some authors have observed an association between endothelial dysfunction and the increase in procoagulant activity in smokers, which occurs basically via a reduction in the t-PA/PAI-1 ratio and in the level of TFPI.^{45,48,49} In mice exposed to cigarette smoke, the expression of TF and VCAM-1 increases, as does the number of macrophages in the atherosclerotic lesions.⁴⁹ It has also been reported that TFPI is reduced in smokers.⁵⁰ The reduction in the number ischemic episodes in smokers who quit has a striking immediate and delayed effect. Problems such as vasospasm, reduced lung capacity, and above all platelet activation, are rapidly improved if abstinence is maintained; this may explain the rapid benefits of quitting.⁵¹ A recent study showed that circulating activated TF was increased by 30% two hours after smoking. This suggests that smoking favors the rapid release of TF, and may partly explain its association with vascular thrombosis and the prompt benefits of quitting.⁸

RISK FACTORS, TISSUE FACTORS AND HYPERTHROMBOGENICITY

As mentioned, risk factors such as DM, hyperlipidemia and smoking contribute to the atherothrombotic process via a common mechanism: endothelial dysfunction. This activates interactions between leukocytes and platelets, leading to the release of TF, the production of thrombin and the formation of clots.

Tissue factor is a low-molecular-weight glycoprotein that initiates the activation of the intrinsic coagulation cascade. It is thought to be a major regulator of coagulation, hemostasis and thrombosis.^{4,52} Tissue factor forms a high affinity complex with coagulation factors VII/VIIIa. This activates factors IX and X, generating thrombin⁵³ (Figure 4). The activity of the TF:aFVII complex is regulated by the endogenous inhibitor TFPI. This molecule forms a complex with TF, aFVII and aFX which inhibits the TF involved in the coagulation cascade⁵⁴ (Figure 4).

Normally, TF is present only in the adventitia of healthy arteries, but it has been found in arteriosclerotic arteries, mainly in atherosclerotic plaques. It is abundant in the acellular lipid nucleus and in the underlying luminal region, where it is prominently expressed by macrophages derived from monocytes. The high TF content of the lipid-rich core is the main factor behind the high thrombogenicity of atherosclerotic plaques, and therefore of the clotting process common to ACS.^{9,10} Further, tissue factor antigen (Tfag) levels are higher in patients with ACS than in those with stable angina. In the plaques of patients with unstable angina, more TF is seen than in those with stable angina,⁵⁵ and this is associated with unfavorable events.⁵⁶ This suggests there is direct relationship between the presence of TF in the substrate of a complicated plaque and arterial thrombosis.

The TF content of the plaque can be reduced by the presence of TFPI, which specifically inhibits TF, leading to a significant reduction in the thrombotic capacity of lipid-rich plaques.⁵⁷ Some authors have reported that inhibition of TF expression in the intima by TFPI reduces post-angioplasty hyperplasia in a pig model, suggesting a relationship between post-angioplasty restenosis and TF expression-mediated thrombogenicity.⁵⁸

Circulating tissue factor and arterial thrombosis

The macrophage infiltrate in atherectomy specimens from patients with unstable angina correlates with the TF content,⁹ suggesting these cells may be responsible for TF production. The systemic expression of high levels of TF by circulating monocytes in patients with

ACS suggests that it contributes to the thrombogenic state. Furthermore, patients with unstable angina have high circulating levels of TF and TFPI.⁵⁹

Circulating microparticles with procoagulant activity have been identified.^{60,61} During apoptosis (mainly of macrophages in the arterial wall), an anionic phospholipid (phosphatidylserine) is displayed on the cell surface, conferring potent procoagulant activity.⁶¹ It has been suggested that these apoptotic microparticles are responsible for almost all the TF activity of the lipid-rich core. In patients with ACS, high blood levels of procoagulant microparticles have been found, whereas the levels are similar in patients with stable angina and noncoronary disease.⁶⁰ These findings suggest that the particles contribute towards the perpetuation and maintenance of the thrombotic process. In addition to their effects on the promotion and amplification of the coagulation cascade, these microparticles may be responsible for the dissemination of potential procoagulants and pro-inflammatory agents at sites remote from their origin.⁶² More recently, these microparticles have been identified as a possible cause of endothelial dysfunction in patients with myocardial infarction.⁶³

Risk factors such as smoking, hypercholesterolemia and type II diabetes might activate leukocytes and promote the circulation of procoagulant microparticles, thus contributing to the thrombotic process. In the thrombogenic conditions caused by these risk factors, high blood levels of CRP have been found,⁴¹ suggesting a possible relationship between inflammation, the systemic circulation or the vascular wall and thrombosis.

C reactive protein is a very sensitive marker of low levels of inflammation. It reflects the inflammatory component of the atherosclerotic plaque, can predict heart attacks,⁶⁴ and might activate leukocytes and coronary thrombosis. This would explain the relationship between inflammation and thrombosis in the development of complications from atherosclerotic plaque.

CONCLUSIONS

In summary, in one-third of all ACS, particularly in sudden death by infarction, there is no rupture of the atherosclerotic plaque; rather, it shows signs of superficial erosion. In these cases thrombotic complications may depend on a systemic thrombogenic state activated by systemic factors such as smoking, diabetes and hypercholesterolemia. It has recently been observed that this hyperthrombotic state might be mediated by high levels of circulating TF — much higher than those seen in healthy persons with no risk factors. These observations emphasize the need for aggressive management of the risk factors reviewed above, through changes in lifestyle and

specific therapy. The increased activity of circulating tissue factors, associated with the blood thrombogenicity caused by these factors, may form the basis for the development of strategic treatments directed towards the inhibition of tissue factors.

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