# Coagulation Derangements as a Tool for Toxicity Examination During Hemodialytic Treatment

Natale G. De Santo, Daniela Molino, Rosa Marotta and Domenico De Lucia
First Chair of Nephrology, and Laboratory of Hemostasis and Thrombosis/Departmment of General Pathology, Second University of Naples, Naples, Italy

**Introduction**

Bleeding is a medical problem which has always attracted physicians, scientists and philosophers. For example Plato and Aristotle reported that blood contains earth, water and air and that by cooling its fibres congeal. Hippocrates and Galen also supported this view. Malpighi in 1686 was finally ready to separate under microscope the fibres of the clot postulated by the Greek philosophers. Nearly two centuries after (1882) Bizzozero showed that platelets adherent to the cut edges of injured blood vessels might form the nidus for a thrombus.

There is no question about the primacy of Morgagni concerning uremic bleeding as it is evident in his Sermo de urina suppressione (Epistula XLI), Opera Omnia.. Venice, Typographia Remondiniana, 1764). Richard Bright in this occasion was only the second.

**Uremic bleeding**

Patients with end stage renal disease are prone to hemorrhagic complications and simultaneously they are at risk for a variety of thrombotic complications such as thrombosis of dialysis blood access, subclavian vein, coronary arteries, cerebral vessel and retinal veins, as well as priapism. Uremic bleeding depends on alterations of primary hemostasis and is related to platelet dysfunction, intermittent anticoagulation used during dialysis,as well as to anemia. However with the advent of erythropoiethin the risk of bleeding is reduced consistently, however it is still a problem for the patient eventually needing surgical procedures.

As summarized by Noris and Remuzzi (1) uremic bleeding depends on 1. abnormal platelet-vessel wall interactions ( enhanced vascular PGI2 production, altered PGI2 degradation, altered ratio of Factor VIII to von Willebrand Factor), anemia (altered platelet adesion, altered blood rheology), 3. abnormal production of Nitric Oxide and 4. platelet dysfunction (decreased platelet calcium content, reduced ADP platelet pool, reduced cAMP platelet content, reduced platelet capacity to form TxA2 in response to Platelet Activating Factor.

Hemorrhagic events which affect every organ were thoroughly described at the beginning of the last century and include purpura epistaxis, pericarditis, gastrointestinal hemorrhage, bleeding from the venipuncture site. A particular bleeding is that associated with Hematoma of Rectus Abdominis (2) which occurs at the site of anastomosis of superior and inferior epigastric arteries and is associated with severe abdominal pain of sudden or gradual onset, nausea and vomiting. A tender fixed abdominal mass was felt, while the wall was guarded or rigid. The skin over the mass was warm as well as discoloured (2).

Abnormalities of coagulation and fibrinolysis in uremia

Prothrombin Time (PT) and Activated Prothrombin Time (APTT) are normal, Fibrinogen (Fg), Factor VIII (FVIII), Plasminogen Activator Inhibitor type 1 (PAI-1) and α2antiplasmin (α2APL) are increased. Factor VII (FVII) and von Willebrand Factor (vWF) are inconstantly increased. A reduction occurs for Antithrombin III (ATIII) and tissue Plasminogen Activator (t-PA). Protein C (PC) and Protein S (PS) are inconstantly elevated.

Abnormalities of coagulation and fibrynolysis in patients with thrombosis/arteriovenous fistula dysfunction

This is an emerging serious problem (3,4) which affects the quality of life of hemodialyzed patients and increases the cost of uremia therapy. In these patients coagulation and fibrinolysis have been extensively studied. Increased Fg, Factor VII (FVII), FVIII, PAI-1, α2APL have been reported. On turn Factor XII (FXII) and vWF are inconstantly elevated. A reduction is seen for AT-III and tPA, while PC and PS are high-normal. High prevalence of anticardiolipin antibodies (ACA) and Lupus Anticoagulant (LAC) is a rule.

**Aim of the study**

The study was devised to 1. identify the marker sof thrombophilia in hemodialyzed patients, 2. to establish a role for antiphospholipid antibodies in thrombosis of the vacsular access, 3.to characterize phospholipid antibodies in hemodialysis patients, 4. to study the effects of dialysis on coagulation cascade.

**Patients and methods**

A group of 20 patients on hemodialysis with no thrombotic complications (NTC) and 20 patients on hemodialysis with thrombotic complications (TC) were studied along with 400 volunteer blood donors. Patients with LES were excluded. Also patients with nephrotic syndrome were excluded. We evaluated Fibrinogen (Fg), Facor III (FIII), Factor V (FV), Factor VII (FVII), Factor VIII (FVIII), Factor IX (FIX), Factor X (FX), AT-III, F1+2, vWF, α2APL, ACA IgG and IgM, antiProtrombin Antibodies IgG and IgM ( aPT IgG, and aPT IgM.

**Results**

*Correspondence to:* Natale G. De Santo, MD, Via Pansini 5, Pad. 17, 1st Chair of Nephrology, Second University of Naples, I-80131 Naples (Italy), Tel: +39 081 5666 6650, Fax: +39 081 5666655, e-mail: nataleg.desanto@unina2.it

FII, FV, FVII, FX, FXII were identical in all experimental groups. Statistical analysis did not disclose differences between controls, NTC and TC.
vWF was significantly increased over controls both in NTC and TC however the increase in TC was significantly greater than in NTC.
Also FVIII increased significantly in TC and NTC over control, however the increase in TC was significantly higher than in NTC.
TPA in controls was significantly higher than in TC and NTC, while studies on Plasminogen did not disclose differences between experimental groups. Fibrinogen concentration in both dialyzed groups of patients was higher than in controls, but there was no difference between TC and NTC.
PAI-1 and F1+2 in TC and NTC were significantly higher than in controls, however the increase in TC was significantly higher than in NTC. AT-III was identical in all experimental groups.
ACA-IgG and ACA IgM, in controls were significantly lower than in TC and NTC, however titres in NTC were significantly lower than in TC. AntiProthrombin antibodies in controls were lower than in TC and NTC. However the increase in TC was significantly greater than in NTC. Antiprotrombin Antibodies IgM increased significantly over controls both TC and NTC and the titres in TC were greater than in NTC.
Dialysis reduced significantlty FXII but did not affect the other factors.

**The meaning of the data**

The data collected in this paper allow to appreciate the following differences between TC and NTC groups.In TC FVII, PAI-1, F1+2, ACA-IgG, ACA-IgM and aPT-IgM are significantly increased findings in NTC as indicated in Table 1.

**The meaning of the data**

In the study we have demonstrated the presence of increased plasma levels of PAI-1, which causes hypofibrinolysis and hypercoagulability. Increased plasma levels of Factor VIII were also found, which points to a greater activation of the coagulation pathway. This allows to hypothesize that in chronic uremia hypercoagulability is caused by modifications in the coagulation pathway and in fibrinolysis (5, 6). These modifications were induced by endothelial cell activation and damage.
Endothelium is not a container where all important biochemical reactions take place. Endothelium has a primary role and an important function in haemostatic balance. In uremia the oxidative stress and inflammation damage endothelial cells, which is proved by the presence of in

**Table 1 – Differences between TC and NTC**

| TC | NTC | |
|---|---|---|
| FII | = | = |
| FV | = | = |
| FVII | = | = |
| FIX | = | = |
| FX | = | = |
| FXII | = | = |
| AT-III | = | = |
| VWF | ↑ | ↑ |
| FVIII | ↑ | ↑↑ |
| FG | ↑ | ↑ |
| TPA | ↓ | ↓ |
| PAI-1 | ↑ | ↑↑ |
| F1+2 | ↑ | ↑↑ |
| ACA-IgG | ↑ | ↑↑ |
| ACA-IgM | ↑ | ↑↑ |
| antiPT-IgG | ↑ | ↑ |
| antiPT-IgM | ↑ | ↑↑ |

= unchanged, ↑ increased over control, ↑↑ increased over NTC

creased plasma levels of PAI-1, produced for the most important part by endothelium cells. The continuous endothelial damage is expresse d by the increase of PAI-1 and Factor VIII plasma levels. These factors should be considered as direct and indirect markers of endothelium dysfunction, like others such as von Willebrand Factor and thrombomodulin. Additionally the damaged endothelium activates in excess Factor VIII. This may lead to a greater production of thrombin and fibrin deposition which is not sufficiently removed from the vasculature, because the fibrinolysis system is inhibited by the increased PAI-1. Therefore, uremic patients under hemodialytic treatment show a state of hypercoagulability when compared to healthy subjects. Patients with thrombotic complications (TC) have a greater state of blood hypercoagulability and endothelium damage compared to patients without thrombotic complications (NTC), due to important abnormalities of coagulation cascade, such as increased levels of PAI-1 and Factor VIII.

**References**

1. Noris M, Remuzzi G. Uremic Bleeding : Closing the Circle After 30 Years of Controversies. Blood 1999; 94: 2559-2574.
2. De Santo NG, Capodicasa G, Perna N, De Pascale C, Giordano C. Haematoma of Rectus Abdominis Associated with Dialaysis. Br Med J 1972; 3: 281-282
3. Vaziri ND, Gonzales EC, Wang J, Said S. Blood coagulation, fibrinlolytic and inhibitory proteins in end-stage renal disease. Effect of hemodialysis. Am J Kidney dis 1994; 23: 628-835.
4. Risk Factors for Vascular Disease and Arteriovenous Fistola Dysfunction in Hemodialysis Patients. J Am Soc Nephrol 1996; 7: 1169-1177
5. Molino D, De Santo NG, De Lucia D, Anastasio P, De Santo NG. Fibrinolysis in patients with thrombosis of arteriovenous fistulae. J Nephrol 2001; 14: 547 (abstract)