Coagulation and haemodialysis access thrombosis

Johannes H. M. Smits¹, Joke van der Linden², Peter J. Blankestijn¹ and Ton J. Rabelink³

¹Department of Nephrology, University Medical Center, Utrecht, ²Department of Internal Medicine, Medisch Centrum Rijnmond-Zuid, location Clara, Rotterdam and ³Department of Internal Medicine, University Medical Center, Utrecht, The Netherlands

Introduction

An increased thrombotic tendency is an important cause of complications in chronic haemodialysis patients, leading not only to possibly fatal complications like ischaemic heart disease or stroke, but also to thrombosis of the vascular access [1]. This latter complication remains the main problem in vascular access for haemodialysis, particularly in polytetrafluoroethylene (PTFE) grafts. It accounts for considerable morbidity and mortality with an estimated annual cost of close to $1 billion in the United States. Moreover, vascular access complications mainly consisting of thrombotic events are responsible for 17–25% of all hospitalizations in dialysis patients [2–4].

In most cases thrombosis is associated with low access blood flow [5–7]. The most important reason for a decreasing access blood flow is intimal hyperplasia formation at the venous anastomosis or in the outflow tract of the graft [8–13]. However, not all decreases in access blood flow are related to intimal hyperplasia or stenosis formation. Other causes for low access flow leading to access thrombosis have been proposed (Table 1). Hypotension, hypovolaemia, or external compression may be involved in these non-stenotic thrombotic events [14]. Also, there has been a growing appreciation of the role of hypercoagulability states found in these patients.

This review will discuss coagulability abnormalities in relation to haemodialysis access thrombosis. First, an outline will be given regarding normal haemostatic and fibrinolytic responses. Subsequently, we will focus on coagulation abnormalities leading to the thrombotic tendency in chronic haemodialysis patients. Finally, preventative measures for these coagulation defects will be discussed.

Normal haemostasis and fibrinolysis

Normal haemostatic responses are initiated by damage of the vessel wall with exposure of subendothelial structures to flowing blood and results in the formation of a solid haemostatic plug. The first step of this haemostatic response involves platelet adherence to the subendothelium [15–17]. The number of platelets available for this process is determined by platelet count. It is, however, even more dependent on red blood cell-mediated transport of circulating platelets towards the vessel wall [17–19]. The adhesion of platelets to the site of injury is initially mediated by interactions between specific platelet receptors (e.g. glycoprotein Ib) and adhesive proteins in or deposited on the subendothelium (e.g. von Willebrand factor, vWF) [20–22]. The quality of the platelet adhesion depends strongly on subsequent platelet activation. Platelet activation is initiated by stimuli originating from the vessel wall but is sustained by products released from activated platelets themselves, for example thromboxane and adenosine diphosphate (ADP) [22]. Platelet activation leads to expression of additional receptors on platelet membranes which support platelet interaction with subendothelium (e.g. glycoprotein IIb/IIIa) [22–25]. Most importantly, however, these receptors mediate platelet–platelet interactions, resulting in aggregate formation.

Normal haemostasis also involves initiation of coagulation at sites of vessel wall injury that starts with activation of factor VII from flowing blood by tissue factor present in the vessel wall. The key products of the coagulation cascade are thrombin and fibrinogen. Thrombin proteolytically converts fibrinogen to insoluble fibrin, which in its turn activates factor XIII that causes cross-linking of fibrin fibres [26]. With collagen, thrombin is also a main stimulus of platelet activation and aggregation [22]. Fibrin is able to
stabilize platelet aggregates and other cellular elements in a shear stress-resistant network. Pathological thrombin formation is prevented by natural anticoagulant systems, of which antithrombin III and the vitamin K-dependent protein C systems are the most important ones. In addition to these anticoagulant systems, the fibrinolytic system generates plasmin by the action of tissue plasminogen activator on plasminogen. Plasmin dissolves the fibrin clot and thereby prevents pathological thrombus formation. Thus, normal haemostatic responses require both coagulation- and platelet-dependent processes.

In haemodialysis patients, complex coagulation abnormalities occur, ranging from bleeding to thrombosis [1,27]. On the one hand, the enhanced bleeding tendency in these patients is primarily based on functional platelet abnormalities and defective adhesion to the vessel wall [28,29]. On the other hand, a variety of coagulation abnormalities contribute to an increased thrombotic tendency.

Factors in chronic haemodialysis patients contributing to thrombotic tendency

Hypercoagulability in patients on chronic haemodialysis can be caused by a variety of factors, mainly consisting of platelet abnormalities and plasma factor abnormalities (Table 2).

Platelet abnormalities

Platelet abnormalities are common in patients on haemodialysis. Paradoxically, most studies on platelet abnormalities in haemodialysis patients have focused on adhesion defects leading to an increased bleeding tendency. So, first of all, do these platelets actually play a role in the thrombotic tendency seen in patients on haemodialysis? In other words, are there abnormal circumstances leading to an increase of thromboembolic complications in a setting of dysfunctional platelets? Indeed, there are indications that this is the case. Although platelet abnormalities exist which favour a bleeding tendency, other circumstances may actually lead to an increase in thrombotic complications. First of all, although some studies suggest a decreased membrane expression or an abnormal activation of platelet receptors (glycoprotein Ib and IIb/IIIa) [30,31], an increase in platelet receptor number may be related to frequent access obstruction [32]. Also, haemodialysis is thought to activate platelets by adherence to the extracorporeal circuit [33,34]. In addition to extracorporeal activation, high shear stress and turbulence in the vascular access may be responsible for further platelet activation [35,36]. Another condition favouring vascular access clotting is that the artificial surface of the PTFE graft, and to a lesser extent the native arteriovenous (AV) fistula, promotes the adhesion of fibrinogen [37,38]. Serum fibrinogen, which is increased in haemodialysis patients, adheres to glycoprotein IIb/IIIa on the surface of the platelet. Once attached to the surface (solid-phase fibrinogen) it can also bind to inactivated platelets, thereby activate them, and further enhance platelet deposition on the surface [37]. Indeed, Windus et al. [39] have shown that platelets are deposited along the vascular access surface. Another possible complementary explanation could be that clotting factor (contact factors like factor XII) deposition may lead to local thrombin formation, platelet activation, and enhanced platelet deposition [40].

Adherent platelets may release factors (platelet-derived growth factor (PDGF), for example) which lead to or enhance intimal hyperplasia in the vascular access and thereby reduce blood flow through the access, which allows other activated or non-activated platelets to aggregate more easily. This creates, despite a bleeding tendency, a favourable situation for thrombosis.

Plasma factor abnormalities

Uraemic subjects have higher levels of fibrinogen while at the same time thrombin formation is increased [41,42]. Song et al. [43] showed that a high plasma fibrinogen level is an independent risk factor for vascular access failure in haemodialysis patients. In addition, levels of antithrombin III may be decreased and antithrombin III activity may be reduced [44,45]. The subsequent increase of in vivo fibrinogen–fibrin transformation is reflected by increased fibrinopeptide A formation.

Erdem et al. [46] also provided evidence for a substantial contribution of the vascular access itself to the modulation of the thrombotic tendency. By taking blood samples from the vascular access and from contralateral large veins in end-stage renal disease (ESRD) patients and from peripheral veins in control subjects, they showed not only a difference in parameters of thrombotic tendency between peripheral vein samples of ESRD patients and controls, but more importantly, also between vascular access samples and peripheral vein samples in the same ESRD patient group.

Table 2. Factors contributing to an increased thrombotic tendency in patients on chronic haemodialysis

<table>
<thead>
<tr>
<th>Platelet factors</th>
<th>Plasma factor abnormalities</th>
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<tr>
<td>blood-artificial surface interaction</td>
<td>increased levels of vWF</td>
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<tr>
<td>treatment with recombinant human erythropoietin</td>
<td>hyperfibrinogenaemia</td>
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<tr>
<td>increased platelet count</td>
<td>increased thrombin formation</td>
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<td>platelet activation due to high shear stress in the vascular access</td>
<td>reduced levels of protein C anticoagulant activity</td>
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<tr>
<td>Plasma factor abnormalities</td>
<td>high levels of factor VIII procoagulant</td>
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<tr>
<td>increased levels of vWF</td>
<td>decreased levels and reduced activity of antithrombin III</td>
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<tr>
<td>hyperfibrinogenaemia</td>
<td>impaired release of plasminogen activator</td>
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<tr>
<td>increased levels of antiphospholipid antibodies</td>
<td>increased levels of homocysteine</td>
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Others have shown that antiphospholipid antibodies are predictive of vascular access thrombosis [45,47–49]. These antibodies include lupus anticoagulant (LA), anticardiolipin antibodies (ACA), and antiphosphatidyl serum antibodies. Higher titres of both ACA and LA antibodies have been demonstrated in patients with ESRD than in the general population [48,50,51]. Elevated LA antibody titres are present in up to one-third of haemodialysis patients [48]. Elevated ACA antibody titres have been found in 0–29% of them [48,52,53], with a greater prevalence in patients with AV grafts (22%) than with native AV fistulae (6%) [47]. However, the association between elevated ACA antibody titres and increased access thrombosis is not fully established yet. While several studies found no association [48,52,54], Prakash et al. [47] demonstrated in a retrospective study a 3.7 times increased risk of recurrent thrombosis in patients with PTFE grafts having elevated ACA antibody titres. The latter finding was recently confirmed in a prospective study: the survival time of PTFE grafts in patients with elevated titres was significantly shorter than in patients with normal titres. Interestingly, this difference was not found in patients with native AV fistula [53].

Hyperhomocysteinaemia is an independent risk factor for recurrent and early-onset venous thrombosis in patients with normal renal function [55–57]. Fasting homocysteine levels have been shown to be elevated in patients with ESRD [58] and may contribute to atherosclerosis and subsequent cardiovascular events in haemodialysis patients [59,60]. The underlying mechanism by which hyperhomocysteinaemia provokes thrombosis is uncertain. It may involve a change in factor V and protein C complex activity as well as effects on platelet function [56,61,62].

Studies on the association of homocysteine and access thrombosis are limited and the results are controversial. In a retrospective study by Manns et al. [52] no association between homocysteine level and access thrombosis was found. Two recent prospective studies showed conflicting results. Shemin et al. [63] demonstrated a 4% increase in the risk of access thrombosis with each 1 µmol/l increase of plasma homocysteine concentration for both AV fistulae and grafts. Similarly, Ducloux et al. [64] suggested that hyperhomocysteinaemia is a risk factor for vascular access thrombosis. However, such an association could not be demonstrated in a population of 96 patients with only native AV fistulae. The patients with the lowest levels even appeared to have an increased mortality risk [65]. These conflicting differences in outcome may be related to the type of fistula, the length of follow-up, and to other variables. Obviously, long-term prospective studies with serial, instead of occasional, determinations of plasma homocysteine are needed to solve this issue.

Therapeutic considerations

Antiplatelet therapy

The usefulness of antiplatelet therapy for the maintenance of internal haemodialysis access devices was reviewed by the Antiplatelet Trialists’ Collaboration Group [66]. Outcomes of nine placebo-controlled, randomized trials showed an occlusion rate of 17% in the antiplatelet groups vs 39% in the control groups. Antiplatelet regimens consisted of ticlopidine (five studies), aspirin (two studies), and sulphinpyrazone (two studies). Unfortunately, most of the evaluated studies were conducted in the late 1970s and the beginning of the 1980s. At that time some of the achievements in modern dialysis were not yet available, and dialysis populations differed from those of today. Moreover, these studies had only a short follow-up (mean 2 months). Finally, the analysis report was difficult to interpret in terms of excess bleeding due to antiplatelet therapy.

Only one randomized, placebo-controlled clinical trial comparing access thrombosis frequency in patients treated with antiplatelet therapy (dipyridamole 75 mg orally three times a day, or aspirin 325 mg orally daily) was conducted in the last decade. Surprisingly, dipyridamole alone, which is considered as a relatively weak platelet inhibitor, had the best outcome, while patients on aspirin had the highest frequency of thrombosis, even higher than with placebo or the combination of dipyridamole and aspirin [67]. The results of this study became more understandable after the authors conducted a series of in vitro experiments using vascular smooth-muscle cells [68,69]. They could show that aspirin potentiated PDGF-induced vascular smooth-muscle cell proliferation by shunting arachidonic acid from cyclo-oxygenase into lipoxygenase pathways. On the other hand, dipyridamole profoundly inhibited PDGF- and bFGF-induced vascular smooth-muscle cell proliferation. This suggests that the observed direct effect of aspirin and dipyridamole on vascular smooth-muscle cell proliferation (rather than the antiplatelet effect) is a better explanation for the reported clinical efficiency of dipyridamole. Gastrointestinal bleeding occurred in 16% of the treated patients vs 8% in the placebo group. Unfortunately, no anatomical or functional data (e.g. vascular access flow) was collected in the randomized trial [67]. This could have provided further in vivo evidence for the experimental in vitro data.

Finally, Windus et al. [70] showed that aspirin and ticlopidine both reduced dialysis-associated platelet deposition in PTFE grafts, although they did not completely prevent it.

Oral anticoagulation

Current opinion on the use of systemic anticoagulant therapy to improve access patency is primarily based on personal belief, rather than on evidence. Not surprisingly, the reason is that systematic data on this subject are very limited. Interestingly, despite the lack of consensus, nephrologists do not refrain from prescribing anticoagulants. As a consequence numerous different anticoagulant strategies exist from centre to centre as to patient selection, dosing scheme, and treatment duration.
In 1967, the effect of coumadin in reducing the clotting frequency of AV Scribner shunts was first reported in three dialysis patients [71]. A few years later coumadin was shown to prolong cannula shunt life in non-uraemic sheep [72]. However, in several recent studies aimed at evaluating risk factors for vascular access dysfunction, anticoagulants were either not used in the study population or their use was not mentioned. Nevertheless, the use of anticoagulants was advocated based on the hypercoagulable state often found in the dialysis patients under study [48,73]. In a recent Japanese study of 83 dialysis patients with AV fistula dysfunction, no association was found with prior anticoagulant use or prothrombin time [74]. However, the criteria mentioned for fistula dysfunction were vague and the distribution of various access types (AV fistula or PTFE) in this population was not mentioned. Dialysis patients with a history of early vascular access graft loss or frequent thrombosis showed a twofold prolongation of access survival time and less frequent clotting after initiation of coumadin [53,75]. However, these results were based on small numbers and obtained with patients being their own controls. Bleeding complications seen in these studies occurred in patients with high international normalized ratio (INR) levels. Also, LeSar et al. [45] showed in a subgroup of dialysis patients with frequent PTFE graft thrombosis and a hypercoagulable state (i.e. prevalence of antiphospholipid antibodies, anti-thrombin III and protein C system abnormalities), that oral anticoagulant therapy effectively decreased thrombosis frequency, particularly with INR values maintained at 2.7–3.0. However, the incidence of significant bleeding complications in this subset of patients was 10% per year. By administering coumadin, Valeri et al. [53] increased the survival of access grafts in 16 patients with elevated ACA antibody titres and frequent access thrombosis. However, the absolute duration of graft survival in the treated group was not impressive (48 ± 12 days in the untreated group vs 103 ± 26 days in the coumadin-treated patients with target INR values of 2.0–3.0). Two patients suffered major bleeding complications, although both had an overshoot of target INR (> 8).

Conclusion

Despite the bleeding tendency of chronic haemodialysis patients, vascular access thrombosis is a frequent complication. Hypercoagulability is one of the causes contributing to the high frequency of access thrombosis. The hypercoagulable state can be explained by platelet and coagulation factor abnormalities. Unfortunately, few randomized placebo-controlled trials have been conducted using antiplatelet or oral anticoagulation therapy. Therefore, no evidence-based consensus has been established regarding pharmacological prevention of access thrombosis. It still needs to be determined whether the potential benefits of anticoagulation and antiplatelet therapy outweigh the risk of adverse events.

In the meantime it seems reasonable to give some form of anticoagulant therapy based on pathophysiologic considerations and the high incidence of thrombotic complications. Our group recently demonstrated that graft flow measurements could effectively predict thrombotic vascular access events [76]. Risk tables that take into account such parameters as well as plasma markers of hypercoagulability may help to develop rationally designed trials and guidelines.

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