Acquired hypercoagulable state in renal transplant recipients

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Summary
Stable renal transplant recipients manifest a chronic hypercoagulable state with an increased risk of thromboembolic complications, which appears to be multifactorial. While this group of patients could present the known risk factors for thromboembolism in the general population (e.g., diabetes, cancer, pregnancy), they may also suffer from other situations which are mostly related to transplantation and are consequently specific to them. Here, we review briefly the clinical aspects and controversies of the most important of these factors including immunosuppressive agents, antiphospholipid antibodies, hyperhomocysteinemia, pre-transplant dialysis modality, and post-transplant erythrocytosis. In addition, other more recent topics including hypercysteinemia, recurrent proteinuria, and acute CMV infection are discussed.

Keywords
Renal transplantation, thromboembolism, hypercoagulability, thrombosis

Introduction
Stable renal transplant recipients (RTRs) manifest a chronic hypercoagulable state contributing to an increased incidence of thromboembolic (TE) complications. The prothrombotic changes in these patients are present without any additional disease complications, suggesting that renal transplantation (Tx) per se is associated with a state of hypercoagulability (1). This situation appears to persist throughout life, but the risk is found to be at its greatest in the first 6 months (2, 3).

Early series of pulmonary embolism (PE) in RTRs reported an incidence of 2-14% with a mortality rate of 13.4% (4). More recently, in 1983, the European Dialysis and Transplant Association reported that 4.4% of all deaths in RTRs were secondary to PE (5). In a retrospective study on 480 RTRs over a 10-year period, 8.3% of the patients experienced a venous TE event (2). In this cohort, the incidence of deep venous thrombosis (DVT) and PE was highest within the first 4 months, and PE was found to be the fourth leading cause of death during the study period.

Once the surgical aspect of renal transplantation is considered, the timing of TE events in RTRs shows a different pattern compared to other surgical patients. Humar et al reported a fair number of DVT episodes in the third to fifth months post-transplant (3). They also found that DVT formation was 2.5 times more likely on the side of the allograft in the first month, while its overall incidence was similar on either side over the period of the study. These observations suggest that although TE events occurring very early after transplantation may, in part, be related to local surgical factors, those presenting later are to be explained by a number of medical factors causing a hypercoagulable state.

Although a great number of papers have been published on coagulopathy in patients with renal diseases, our knowledge regarding coagulation/fibrinolysis state in RTRs remains limited. Moreover, the number of questions and controversies on the subject seems even to be increasing as new publications appear. Therefore, there are no clear world-wide recommendations, based on the results of large clinical trials, concerning the management of RTRs at higher risk for TE complications.
The increased risk of TE events in RTRs appears to be multifactorial. While these patients can present the known risk factors for TE complications in the general population (e.g., diabetes, cancer, pregnancy, inherited thrombophilia), they may suffer from other situations which are specific to them. Here we discuss some of the most important of these factors.

Bleeding tendency may be found in some of RTRs presenting a certain level of renal dysfunction. It is not, however, mainly due to renal Tx, but to renal insufficiency-related coagulation/fibrinolysis disorders. This pathologic situation has thus not been discussed in this paper. Also, surgical aspects of TE events in RTRs are beyond the scope of this article.

**Immunosuppressive agents**

**Calcineurin inhibitors**

A major drawback of Cyclosporine (CsA) therapy in RTRs has traditionally been considered the increased risk of TE complications associated with this drug (6). Several studies have addressed the possible role of CsA in the development of TE events in RTRs. However, the current data (biological and clinical) on the subject remain contradictory and conflicting.

Undoubtedly, CsA has multiple in vitro procoagulant effects, including activation of monocytes to express tissue factor (7), increased platelet aggregation (8), endothelial dysfunction and activation of intrinsic coagulation pathway (9), impaired fibrinolysis (10), and impaired activation of protein C (11). In addition, it causes increased level of thromboxane (12), and reduces the production of prostacyclin by endothelial cells (13). CsA has been shown to increase interleukin-6 gene expression and IL-6 production in monocytes (14). IL-6 is the principal cytokine that mediates the acute phase response and induces coordinate transcription of the three fibrinogen genes (15). Malyszko et al observed significantly elevated levels of von Willebrand Factor (vWF) in CsA-treated patients, which could reflect vascular endothelial injury and platelet hyperactivity (16).

In contrast to the findings of Malyszko, Huser et al showed that the median antigenic and functional levels of plasma vWF and factor VIII in RTRs were already elevated before Tx, and that comparable levels could be observed four months after Tx in CsA-treated recipients (17). They concluded that marked elevation of vWF and factor VIII associated with TE complications in RTRs, could not be attributable to CsA. Also, in another study, CsA-treated RTRs showed higher concentrations of antithrombin III, compared to those treated by Aza and normal subjects. The CsA group however showed increased concentrations of protein C, factor VIIIC, and fibrinogen in this study (6).

This controversy in biological data is also found in the results of the clinical trials. The impaired fibrinolytic activity in RTRs has been reported to improve significantly once CsA is replaced by Azathioprine (Aza) (18). In a study by Vanrenteghem et al, TE events were significantly more frequent in 90 RTRs treated with CsA and low-dose steroids, compared to the same number of recipients who received anti-lymphocyte globulin, Aza, and high-dose steroids (6). In this retrospective study, 17 TE events (including 10 PE) occurred in the first group, while only 1 patient in the second group presented an episode of superficial thrombophlebitis. Interestingly, in a prospective study, Brunkwall et al did not find any increased frequency of DVT in RTRs who received CsA and low-dose steroids compared to those who had received Aza and high-dose steroids (19). Also, in a prospective randomised study on 224 RTRs by Gruber et al, CsA did not appear to be a risk factor for TE diseases (20). They even suggested that CsA may lower the incidence of post-Tx TE events in diabetic RTRs.

Indeed, the largest retrospective (21) or prospective (22) clinical trials have failed to support a significant difference in TE events, at least at allograft vascular level, between CsA-treated and non-CsA-treated recipients. Since no study presented a control for the possibility of thrombophilia, variability in these reports, however, may well reflect confounding by inherited hypercoagulability (23). In addition, most of the trials have included patients treated with two or more immunosuppressive agents, which make it difficult to establish a true causal effect. Thus, while long-term CsA-treated RTRs manifest features of a hypercoagulable state in vitro (1), a causal in vivo relationship remains yet to be proven in clinical practice.

Compared to CsA, the role of Tacrolimus, a newer calcineurin inhibitor, in the development of TE events has not yet been largely explored. The primary animal studies found that it has an inhibitory effect on platelet-rich thrombosis (24). This effect was supported by in vitro studies in human, which showed antithrombotic effects of Tacrolimus by inhibition of platelet activity and coagulation (25). In a study by Freudenberger et al, blood thrombogenicity was evaluated in 17 cardiac transplant patients (7 patients with Tacrolimus and 10 receiving CsA) by using an ex vivo perfusion chamber that mimics the cylindrical shape of the vessels (26). They found that treatment with Tacrolimus was associated with a statistically significant reduction in platelet thrombus formation compared to CsA-treated patients. However, the results of this study should be considered cautiously, because of small number of patients. In a study by Pirsch et al, the efficacy and safety of Tacrolimus and CsA were compared in 412 RTRs (205 and 207 patients in each group respectively) (27). DVT was reported more frequently in Tacrolimus group compared to the CsA group (11 patients vs. 1 patient, p = 0.003). The authors claimed that all of these patients had factors known to be associated with a predisposition to DVT, and that 5 of the 11 RTRs were reported by a single study center.

**Corticosteroids**

The thrombotic effects of glucocorticoids have been described in the literature (28). These substances may enhance the
endothelial synthesis of vWF (29) and impair the fibrinolytic capacity by both suppressing tissue plasminogen activator (t-PA) production, and increasing plasminogen activator inhibitor type 1 (PAI-1) synthesis (30). In RTRs, long-term steroid treatment is found to create a hypercoagulable and hypofibrinolytic state similar to patients with Cushing’s disease (31) leading to thrombotic complications.

Patrassi et al evaluated the fibrinolytic potential in 19 corticosteroid-treated RTRs by means of a venous occlusion (VO) test, and then compared the results with those of patients with Cushing’s disease as well as normal subjects (32). They found that a VO test shows similar patterns of impairment in fibrinolytic potential (significant pathological increase in PAI-1 activity and concentration) in both RTRs and Cushing group. The authors suggested that fibrinolytic imbalance and elevated risk of thromboembolism in RTRs could mainly be attributed to long-term steroid treatment. To confirm this hypothesis, the same authors showed in a more recent study that the decreased fibrinolytic capacity in RTRs would significantly be improved, even though not normalized, after steroid withdrawal, arguing for a causal effect (33). Also, Sartori et al performed a fibrinolytic evaluation, 1 and 6 months after Tx in 27 RTRs who had received randomly either peri-operative or long-term steroids in addition to other immunosuppressive agents (34). Impaired fibrinolytic activity was observed in all patients 1 month after Tx, but persisted at 6 months only in RTRs with long-term treatment. They concluded that avoiding long-term steroid therapy is associated with a better fibrinolytic capacity.

**OKT3**

Muromonab-CD3 (OKT3) is an IgG2a murine monoclonal antibody that targets the \( \psi \) chain of CD3-T cell receptor complex (35). It has been used in the prophylaxis and treatment of acute allograft rejection (35), but with the advent of more potent anti-rejection agents that present less adverse effects, its use has largely been reduced. Treatment with OKT3 results in the activation of complement and release of cytokines which activate coagulation by several mechanisms (36). Lozano et al found that RTRs receiving OKT3 as prophylaxis of acute allograft rejection, manifested a statistically significant increase in the procoagulant activity of platelets after the second administration (37). In clinical practice, Abramowicz reported an increased incidence of irreversible intragraft thrombosis in RTRs receiving high doses of OKT3 (38). In their series, among 93 RTRs who received prophylactic OKT3 (10 mg/day) for two weeks, 9 patients presented with thrombotic events. Also, in another study they found that high-dose corticosteroids (30 mg/kg of methylprednisolone) administered before the first dose of OKT3, increased its procoagulant activity (39). They then studied the effects of methylprednisolone on the procoagulant activity induced by OKT3 on peripheral mononuclear cells *in vitro*, which confirmed the presence of this synergistic effect already found *in vivo*.

Shankar et al also reported a case of renal transplant artery thrombosis occurring some hours after the first administration of OKT3 (40). OKT3 was, however, preceded by administration of high-dose corticosteroids and the patient was on a CsA-based immunosuppression protocol.

**Sirolimus**

It has been shown that Sirolimus, a new macrolid immunosuppressive agent, is an *in vitro* potent enhancer of platelet aggregation and secretion at concentrations, which may occur at peak plasma levels (41). These effects are exerted directly, and do not require the presence of additional plasma factors.

In April 2002, the United States Food and Drug Administration issued a warning of an increased incidence of hepatic artery thrombosis among liver transplant recipients treated with Sirolimus in combination with either CsA or Tacrolimus. A recent international trial was halted because of a greater incidence of hepatic artery thrombosis in patients administered Sirolimus with Tacrolimus (42). After careful review, the study was continued, although no new patients are being enrolled. Dunkelberg et al have recently studied the role of Sirolimus in the development of hepatic artery complications in 170 adult liver transplant recipients (43). They failed to show any greater incidence of hepatic artery thrombosis in Sirolimus-treated patients compared to historic controls.

The role of Sirolimus in the development of TE events has not yet been extensively explored in RTRs. MacDonald et al compared renal vein and artery thrombosis in RTRs who received Sirolimus, 2 mg/d, 5 mg/d, or placebo in addition to CsA and corticosteroids (44). There was no greater incidence of renal artery or vein thrombosis in Sirolimus-treated RTRs. Langer et al have also recently studied the risk of TE events among RTRs treated with Sirolimus (45). In this retrospective study, they compared two groups of patients: the first group had a regimen consisting of CsA and steroids, with or without Aza, while the second group received CsA, Sirolimus, and a short course of steroids. The overall incidence of TE events was not statistically different in the two groups (5.1 vs. 5.6 percent). They concluded then that the addition of Sirolimus to a CsA-steroid regimen does not increase the incidence of TE events in RTRs. However, in this study the target average concentrations of CsA were significantly lower in the Sirolimus group, which might have interfered with the final conclusion. In the absence of a prospective randomised trial, this study should only be considered a preliminary report that needs to be confirmed.

**Mycophenolate Mofetil**

The true relationship between Mycophenolate Mofetil (MMF) and TE events has not yet been established. Studies have shown that MMF is capable of decreasing the *in vitro* aggregation of
platelets in normal subjects (46) as well as uremic patients and RTRs (47). However, the MMF monograph reports the incidence of thrombosis (without any other precision), as an adverse effect in RTRs, as 3 to <10 percent. In fact, this complication seems to be local and related to the intravenous administration of MMF, which is reported to cause phlebitis and thrombosis in 4% of RTRs, and thus not to a general hypercoagulable state. Nevertheless, Cherney et al recently reported a patient treated with MMF that manifested recurrent DVTs (48). In this RTR, MMF was administered on two separate occasions, several months apart, in the fourth year post-Tx. The patient developed a DVT soon after receiving the MMF on both occasions. Subsequent hematologic investigations revealed that the patient was heterozygous for factor V Leiden. The authors hypothesized that MMF might alter the non-Leiden factor V so that the patient effectively becomes homozygous. The recurrence of DVT in the same anatomic location (left femoropopliteal vein), while the patient was anticoagulated, seems, however, to argue also for a possible local predisposing factor. Further investigations are needed to confirm this hypothesized causal relationship.

**Antiphospholipid antibodies**

Antiphospholipid antibodies (APAs) are a heterogeneous group of immunoglobulins acting against negatively charged phospholipids, protein-phospholipid complexes, or plasma proteins (49). APAs include antcardiolipin antibodies (ACAs), lupus anticoagulant (LAC), and false positive serologic test for syphilis. While these antibodies manifest an anticoagulant activity in vitro, they are most often associated with both venous and arterial thrombosis in vivo (23) and even bilateral renal artery thrombosis has been reported in patients with APAs (50).

The precise mechanisms by which ACAs act are not well known. Abnormal platelet aggregation, decreased endothelial cell prostacyclin production, inhibition of protein C, and decreased fibrinolysis have been proposed (51-54). Our team has previously reported that the prevalence of APAs in RTRs is as high as 28.1% (55). In this study on 178 RTRs, the lupus patients were excluded. We found that the incidence of post-Tx vascular thrombosis (both arterial and venous) was significantly higher in APA-positive patients compared to APA-negative RTRs (26% and 8.5% respectively). Most of the APAs were acquired before transplantation, and both pre- and post-Tx APAs were associated with an increased risk of vascular thrombosis in the post-Tx period. Of note, APA-positive RTRs had a longer hemodialysis duration. More than half of patients with pre-Tx APAs lose their antibodies after Tx (55).

TE events could be very severe and renal transplant outcome may then be negatively affected in APA-positive RTRs. In our study, one patient presented allograft venous thrombosis resulting in graft loss (56). In two other reports, the outcome of three APA-positive RTRs has been described: they developed renal artery thrombosis necessitating transplant nephrectomy (57, 58). Two of these patients were re-transplanted, one with concomitant anticoagulation therapy, but both had with the same outcome: they developed thrombosis in their transplant kidneys. Also, Wagenknecht et al compared the presence of APAs in RTRs with functioning or non-functioning grafts (59). They found that significantly higher levels of APAs were present in RTRs, whose transplant failed to function compared to recipients with functioning grafts. In a recently published paper by our team, it was shown that only persistence of pre-Tx APAs in the post-Tx period is associated with an excess risk of vascular events. Thus, prophylactic measures are probably not indicated in RTRs with APAs during the early post-Tx period, whereas this treatment should highly be considered if APAs persist over months post-Tx (55).

**Homocysteine – Cysteine**

Homocysteine (Hcy) is a sulfur-containing amino-acid derived from dietary methionine metabolism. There is increasing evidence that Hcy may affect the coagulation system as well as the resistance of endothelium to thrombosis, and that it may interfere with vasodilator and antithrombotic functions of nitric oxide (60).

Hyperhomocysteinemia has been shown to be associated with both arterial (61) (in a linear relationship) and venous (62) (in a threshold effect) thrombotic risk in the general population. The mechanism(s) by which Hcy contributes to vascular disease is uncertain, but endothelial toxicity along with pro-coagulant effects are proposed (1). Increased thromboxane-mediated platelet aggregation, inhibition of cell surface thrombomodulin expression and protein C activation, enhancement of lipoprotein(a)-fibrin binding, and activation of factors V, X, and XII have also been described as potential mechanisms of Hcy-induced thrombosis (63).

Stable RTRs have an excess prevalence of hyperhomocysteinemia (64). In a study previously published by our team, hyperhomocysteinemia was found in as high as 70% of 207 stable RTRs, with a mean total serum level of 21.1 μmol/l (65). We have also reported that the main determinant of serum Hcy concentration in RTRs is the level of renal function (66).

Alternatively, some authors have suggested that immunosuppressive drugs such as CsA may modify Hcy metabolism (67, 68). Others have not confirmed this finding (66, 69). We demonstrated that hyperhomocysteinemia is an independent risk factor for TE events in RTRs, but it remains unclear whether the risk of thrombosis is independently increased, or is limited to those with co-inherited thrombophilic states (65, 70, 71). In another study, we showed that, contrary to dialysis patients, effective treatment of hyper-homocysteinemia in RTRs can be achieved with the administration of folic acid at pharmacological doses (72). We propose that RTRs with high serum levels of Hcy receive this treatment in order to decrease their TE events.
Cysteine is also a sulfur-containing amino-acid with great structural similarity to Hcy. Preliminary data available in the literature found that high levels of cysteine in the general population is a risk factor for deep venous thrombosis, independently of high Hcy levels (73). Its role in post-Tx thromboembolism, however, has not been extensively discussed. In a study by Marcucci et al on 70 RTRs, serum level of cysteine, homocysteine, and PAI-1 was significantly higher in this population compared to the control group of normal subjects (74). In this study, high cysteine levels were detected in about one third of RTRs. After two months of vitamin supplementation, serum Hcy and PAI-1 levels decreased significantly whereas cysteine levels showed a small reduction which was not statistically significant. It seems likely that hypercysteinemia found in RTRs could contribute to an elevated risk of vascular thrombosis similar to the general population.

Original nephropathy

It is plausible to consider that the original nephropathy, which has led to end-stage renal disease, if associated with a high risk of thromboembolism, could contribute to similar risk once the patient is transplanted. Lupus nephropathy may be an example of these systemic diseases. APAs have been reported to be present in 30-44% of patients with systemic lupus erythematosus (SLE) (75). In these patients, thrombotic complications play an important role in early graft loss, specially when APAs are present (75). The impact of APAs in a large group of 96 lupus RTRs over a follow-up period of 5 years has been evaluated by Stone et al (76). Twenty five (29.4%) patients presented APAs. Ten of these patients (10.4%) either died of APA syndrome or had an APA-associated clinical event within 3 months of Tx (DVT or PE in 6 patients, and renal artery or vein thrombosis in 4).

There are some reports emphasizing the thrombogenic role of APAs in lupus patients, who undergo renal Tx. Radhakrishnan et al reported 4 thrombotic events in 5 lupus RTRs who were APA-positive compared to none in 5 APA-negative lupus recipients (77). Of note, the risk of thromboembolism remains high and the thrombotic event may even occur in the late post-Tx period. Karassa et al reported a case of late transplant arterial thrombosis in an APA-positive lupus RTR that occurred two years after intervention (78).

In the absence of a controlled prospective trial, the proposition of Thervet et al seems reasonable that lupus patients with APAs and a history of recurrent thrombosis who undergo renal Tx, should be treated with effective anticoagulation both during and after Tx (75).

Fabry’s disease is another example that has been reported to be responsible for a pattern of thrombotic events including DVT, retinal vein thrombosis and ischemic stroke in non-transplanted patients (79). In transplant recipients with Fabry’s disease, case reports of renal allograft or other solid organ transplant loss due to graft thrombosis are plentiful (80, 81). Friedman et al demonstrated for the first time the coexistence of resistance to protein C activation (APCR) in 3 of 5 RTRs with Fabry’s disease (79). Pending further analysis, they suggested screening transplant candidates with Fabry’s disease for APCR, and anticoagulating those RTRs who present with this coexistence.

Nephrotic syndrome is known to carry an increased risk of TE complications by a number of mechanisms. Elevated levels of coagulation factors (fibrinogen, factors V, VIII, and XIII) (82), decreased level of some anticoagulant proteins (antithrombin III and protein S) (83), thrombocytosis (82), platelet hypercoagulability (84), and hypofibrinolysis (85) are among the main mechanisms contributing to hypercoagulability in these patients. Increased urinary protein excretion in RTRs may occur in different circumstances. A number of these patients may experience chronic allograft nephropathy with subsequent progressively increasing proteinuria, sometimes in the nephrotic range. Although there is no study specifically assessing the risk of TE complications in this subgroup compared to other RTRs or the general population, there is no reason that we should consider their TE risk different from non-transplant proteinuric patients. Also, some RTRs experience the recurrence of the original nephropathy in their allograft contributing to similar risk of TE complications. Biesenbach et al studied the course and outcome of recurrent glomerulonephritis in 15 RTRs with 20 kidney transplants (86). They found that the recurrence of GN (mainly focal segmental glomerulosclerosis) increased the risk of TE events once severe proteinuria (> 2 g/24-hour urine) developed. High serum fibrinogen and low AT-III levels were found in these patients. The authors proposed that all RTRs in whom recurrent GN is diagnosed, should be given anticoagulation therapy after the occurrence of severe proteinuria.

Pre-transplant dialysis modality

Hypercoagulability state has been reported to occur in patients with continuous ambulatory peritoneal dialysis (PD) by a mechanism resembling that of the nephrotic syndrome due to transperitoneal protein loss (87). Kobayashi et al have found that PD patients have significantly higher levels of blood coagulation factors (e.g. factors VII, IX, X, anti-thrombin III, and fibrinogen) compared to a matched control group of healthy individuals (88). They then suggested that PD patients present a state of hypercoagulability and secondary hyperfibrinolysis. Once these patients are transplanted, it is then plausible to suppose that they manifest clinical thromboembolic patterns in the early post-transplant period, which are different from those who had been on hemodialysis (HD) before transplantation.

There are reports, which support this hypothesis showing that patients with PD, once transplanted, are more likely to present allograft thrombosis compared to patients treated with HD.
In a study by Snyder et al, PD was clearly associated with a higher risk for graft failure in the early post-Tx period (91). Graft thrombosis was also significantly more frequent in PD patients compared to those with HD and, in a small subset of patients with available data, was the most common cause of early graft failure. They then suggested that graft thrombosis might contribute to the higher rate of early graft failure found in patients with pre-Tx PD. In this study, the long-term transplant outcome was similar in the two groups, and it seems likely that allograft thrombosis represents only a transient short-term accentuation of hypercoagulability in RTRs with pre-Tx PD compared to those with HD.

Post-transplant erythrocytosis

Erythrocytosis or polycythaemia is defined as a hematocrit >52% in men and >49% in women. Its incidence in RTRs has been reported to vary between 8 and 22 percent (92, 93). Long duration of dialysis, acquired cystic disease, polycystic kidney disease, graft artery stenosis, graft hydrenephrosis, diabetes, smoking, and hypertension may contribute to the development of post-Tx erythrocytosis (94). Wickre et al studied a series of 53 RTRs with post-Tx erythrocytosis, and compared them to a matched control group of 49 RTRs over a follow-up period of 3.5 years. Eleven TE events occurred in 10 of the 53 erythrocytosis patients, but none of the controls (95). In another study on 31 RTRs with post-Tx erythrocytosis, Hestin et al found that the incidence of TE complications was as high as 22% (96).

It is thus reasonable to consider the post-Tx erythrocytosis a risk factor for post-Tx TE events among RTRs. In the European guidelines for post-Tx Erythrocytosis, it is assumed that in RTRs, as in polycythaemia vera, the higher the hematocrit, the higher is the risk of life-threatening complications (97). Angiotensin-converting enzyme inhibitors or angiotensin-II receptor antagonists may be used to reduce the hematocrit in RTRs (98, 99). Theophylline has also been proposed to be effective (100). Repeated phlebotomies is used in patients who do not respond to drug treatment.

Acute CMV infection

Our team has recently proposed that acute cytomegalovirus (CMV) infection might also contribute to TE events in RTRs (Kazory et al, Transplantation 2003, in press). The virus has a particular tropism for endothelial cells and its effects on vascular biology have been reported in different circumstances. CMV can be found in venous or arterial walls, which present a site of latency for it (101). Several reports have addressed the mechanisms of CMV-associated endothelial cell (EC) injury by cellular immunity (101, 102). They have suggested increased EC procoagulant activity by CMV, increased EC-leukocyte adhesion molecules on CMV-infected ECs, increased neutrophil and mononuclear cell adherence to CMV-infected ECs, and increased alloantigen expression on CMV-infected ECs. Toyoda et al have shown that humoral immune activation and CMV-induced anti-EC antibodies also play a role in CMV-induced EC injuries (103). Active CMV infection is thus capable of modifying the endothelial phenotype from anticoagulant into procoagulant by many mechanisms.

Clinical observations have confirmed the accuracy of these biological arguments. In a prospective study, Neumann et al found that previous CMV infection increased the risk of coronary artery thrombotic events after stent placement (104). In a recent literature review, Abgueguen found 11 reported cases of venous thrombosis associated with acute CMV infection in immunocompetent patients (105). This association has not been extensively discussed in RTRs. In 1996, Muldoon et al reported the first case of CMV gastrointestinal vasculitis in a RTR with involvement of large veins resulting in ischemic colitis (106). In our center we observed that 7 of 13 RTRs (53.8%) who presented with a TE event (DVT or PE) had a simultaneous acute CMV infection. All of the patients were non-hospitalized ambulatory RTRs, who had no special predisposing risk factors for thrombosis compared to other transplant recipients. In fact, six of these patients had never presented a TE event before the episode of CMV infection. Then we suggested that acute CMV infection could be considered a predisposing factor for development of post-Tx TE events in RTRs. Considering the small number of patients in our observation, it should be considered a preliminary report which needs to be confirmed.

Conclusion

The hypercoagulable state in RTRs is a multifactorial pathologic situation with risk factors which are in part specific to this population. Renal transplantation per se is a major surgical intervention, which could certainly predispose kidney recipients to TE complications in immediate and early postoperative period. For example, surgical trauma while making venous or arterial anastomosis may play an important role in regional blood flow disturbances contributing to an increased risk of TE event. However, the risk of thromboembolism remains high beyond this period because of a number of immunologic and metabolic factors among which the immunosuppressive agents seem to play a major role. Transplant physicians then ought to search for these risk factors both in pre- and post-Tx period in order to detect high-risk patients and apply the suitable prophylactic measures.
References


8. Laung WE. Glucocorticoids inhibit plasminogen activator plasminogen activator (8436): 999-1002.


23. Langer RM, Kahana BD. Sirolimus does not increase the risk for postoperative thrombo-
89. Van Der Vliet JA, Barendregt WB, Hoitsma AJ et al. Increased incidence of renal allo-graft thrombosis after continuous ambulatory