Editorial II

Haemodilution enhances coagulation

The effect of haemodilution on enhancing coagulation is well described. In this issue, Ng, Lam and Chan have avoided all the confounding variables of the stress response induced by surgery, and have identified enhanced coagulation to be a result of the haemodilution itself. This was achieved by comparing the onset of coagulation in two groups undergoing anaesthesia: one group received fluid after starting anaesthesia; the other, acting as the control group, received no intravenous fluid after starting anaesthesia. The two groups were compared, using Thrombelastograph® and routine tests, before commencing any surgical stimulus. In doing so, the enhancement of clot formation after haemodilution has been reconfirmed.

In analysing the effect of enhanced coagulation occurring with haemodilution, the entire clotting cascade has been explored in order to define exactly at which point, and through which mechanism, this occurs. There may well be many factors that have an impact on the fine balance of coagulation enhancement and inhibition. A lowering of haematocrit has been described as decreasing coagulation, on the basis of decreased blood viscosity leading to a faster arterial blood flow, but these authors did not comment on the microvascular circulation. On the other hand, the enhancement of clot formation, both in vitro and in vivo, following haemodilution with 0.9% saline and other crystalloid solutions, has been addressed by several authors. Furthermore, coagulation following haemodilution is not mediated via platelet–endothelial interaction, as it still persists after platelet function has been removed through the administration of aspirin.

The effect is significant because it casts doubt on previous studies on coagulation effects caused by various colloids while using Thrombelastograph and routine tests, before commencing any surgical stimulus. In doing so, the enhancement of clot formation after haemodilution has been reconfirmed.

The enhancement of coagulation following crystalloid haemodilution was first described in the 1950s by Monkhouse and Tocantins. In 1975, Vinnazzer and colleagues found a postoperative hypercoagulable state in the control (saline) group, and an insignificant change in the test (hydroxyethyl starch) group of their investigation. However, it is difficult to determine if the enhanced coagulation was the result of the saline therapy, or surgery; similarly, the apparently normal coagulation profile in the starch group could be interpreted either as a negligible effect of the starch on coagulation, or as an impairment of surgery-induced enhanced coagulation. In another study, Popov-Cenic and colleagues referred to the effect of surgery on enhancing coagulation and the modification thereof by hydroxyethyl starch, but did not attribute the enhancement as being the result of haemodilution with crystalloid. The effect has been demonstrated in vivo in normal volunteers, in whom rapid administration of crystalloid resulted in the onset of enhanced coagulation, with the effect being absent in the colloid (hydroxyethyl starch) group. Janvrin, in 1980, not only described the enhancement of coagulation, but also demonstrated an increased risk of deep vein thrombosis in a group of patients receiving perioperative intravenous fluid, compared with a control group receiving no intravenous infusion.

When a blood vessel is damaged, it is essential that the final products of the haemostatic system are restricted to the site of damage. At the same time, an adequate flow needs to be maintained through the vascular system in order to have sufficient organ perfusion. The entire clotting process, from its initiation through to fibrin production, must therefore be spatially restricted in the vasculature to prevent an unrestricted coagulopathy. Coagulation is an intricate system, with multiple interactions between factors, including the coagulation and fibrinolytic proteins, platelets, activators and inhibitors. The extrinsic and intrinsic pathways do not function independently, but rather sequentially. Initial thrombin production via the faster extrinsic pathway is amplified by the slower intrinsic pathway. This occurs through both the direct activation of factor IX by factor VIIa/tissue factor complex, and via the positive thrombin feedback into the intrinsic pathway. Thus, haemostasis involves a highly complex interaction between clot formation and clot lysis to avoid uncontrolled action in either direction. This is accomplished by numerous positive and negative inhibiting and activating feedback mechanisms.

It must be emphasized that thrombin generation is the central biochemical reaction in both normal haemostasis and thrombosis. The production of thrombin is self-reinforcing because of its feedback activation of numerous coagulation proteins (factors V, VIII, XI and VII) that contribute to thrombin production. Positive feedback in coagulation plays a major role in the architecture of the system. While thrombin is also involved in other pathways such as platelet aggregation and in the stimulation of the fibrinolytic pathway, its positive feedback into the intrinsic pathway is the most important factor. The cause for the
enhanced coagulation occurring after haemodilution may well be attributed to a decrease in the concentration of the coagulation inhibitors, lowering the threshold for positive feedback to occur into the coagulation pathway. Nossel and co-workers have demonstrated that activated fibrinopeptides are continuously being formed in plasma, and concluded that, in vivo, normal plasma contains background levels of activated thrombin.20 21 On the other hand, Jesty and colleagues found that inhibition of the positive-feedback loop, through the effect of anticoagulants, plays a role in modulating the exponential enhancement of the coagulation cascades.22 This in turn confers threshold properties on the system: if the level of activated thrombin is below the threshold, no response occurs, whereas if the level rises above the threshold, the response should be, or near, maximum. As a result, once the thrombin level has overcome the anticoagulant-induced threshold, there is an exponential increase of further thrombin formation, thus ensuring that a clot is formed. The ability of the entire system to cope with background non-zero levels of activated clotting enzymes, without generating a response, implies that the balance of intravascular coagulation is protected against sub-threshold stimuli. The second-order kinetics of the action of anti-thrombin III (AT III) mean that the rates of inhibition of its target enzymes are a function of its concentration.22–24 Clinical evidence has shown that a decrease in concentration of AT III, to below 70% of normal is linked to an increased risk of thrombosis, particularly venous thrombosis. Since at this level there is still a massive excess of AT III relative to activated thrombin, partial inhibitor deficiency is likely to be a kinetic rather than a capacity defect. The role of inhibitors (AT III, proteins C and S, and tissue factor inhibitor inter alia) is therefore important in control and cessation of this cascade, thereby preventing dissemination of intravascular thrombosis. Moreover, the actual quantity or level of an individual factor does not necessarily reflect its functional status. It is interesting to note that in their findings, Ng and colleagues1 describe a dilution-related percentage decrease in all the measured factors. This included AT III and fibrin, which showed a trend towards a greater decrease from time zero than did haemoglobin. However, the thrombin–anti-thrombin (TAT) levels remained at a predilutional value in the dilution group, even showing an increase at 30 min. This occurred in spite of the haemodilution, while in the control group a decrease in TAT values occurred after initiation of anaesthesia. One may speculate that this represents an increase in the generation of activated thrombin following haemodilution, which was deactivated by the AT III, thus increasing the level of TAT. Because the activated thrombin makes up a minute fraction of the total prothrombin and anti-thrombin concentrations, and there is a one-to-one enzyme-to-inhibitor reaction of thrombin with AT III,25 even a doubling of the activated-thrombin levels will not necessarily result in a significant decrease in the absolute level of AT III.

Conversely, when partially maintaining the coagulation threshold after dilution has occurred by keeping the concentration of AT III within the normal range in the diluent, the effect of enhanced coagulability resulting from dilution can be attenuated but not completely inhibited.17 Since AT III is only one of several positive-feedback inhibitors acting on the coagulation cascade24 (accounting for only 40–50% of the effect), it is possible that one could produce greater attenuation of the dilution-enhanced coagulation by keeping the levels of the other naturally occurring inhibitors of coagulation constant.

Does this have a clinical effect? Given the findings of an enhancement of coagulation following haemodilution, one can speculate that when an individual has a significant loss of blood, with rapid restoration of circulating blood volume from the interstitium, the onset of coagulation may be enhanced. It is interesting to observe that there may have been a survival benefit for the evolution of such a mechanism – when internal haemodilution occurs after blood loss, enhanced coagulability may prevent further haemorrhage in the wild state. However, a point may be reached where bleeding occurs as the clotting factors are used up through enhanced clot formation at a capillary level. This in turn leads to a marked increase in bleeding, as an imbalance between procoagulant factor activation and anticoagulants, or enhanced fibrinolysis, occurs – the syndrome of disseminated intravascular coagulopathy (DIC). In the natural state, this may well result in the death of the individual. Indeed, decreased plasma concentration of AT III may be indicative of the role of DIC in the pathogenesis of multiple organ dysfunction syndrome,20 its baseline value correlating with mortality, and its plasma concentration being decreased in DIC, particularly in sepsis and shock.

This poses the question of whether any individual at risk of DIC could be prevented from sparking off their original enhancement of coagulation, before the entire chain reaction of DIC is started, and whether this may be achieved by preventing too rapid a fluid replacement, thereby preventing rapid dilution. In a less overwhelming reaction, the formation of deep vein thromboses and pulmonary emboli could be prevented by decreasing or avoiding haemodilution.16

In a recent study (unpublished observation) examining the effect of blood loss and autodilution, it appeared that a slow autodilution of blood to replace a 10% loss does not show the imbalance between anticoagulants and spontaneously activated coagulants that occurs after a rapid large-volume (20–30%) haemodilution. It is of interest to note that a 10% loss of blood volume in a healthy person is easily compensated for by the sympathetic response, through an increase in blood-vessel tone. This maintains end-organ perfusion and results in a slow re-expansion of blood volume, as is evidenced by the fact that donation of a unit of blood, which makes up 10% of circulating blood volume, does not impair the donor’s normal daily function, nor render them hypercoagulable.
How does one put all of this together? Suffice it to say that Ng and colleagues1 have again demonstrated the effect of enhanced coagulation following haemodilution. Their work is done in a controlled in vivo setting, which confirms the findings without the effect of any confounding variables. While it is still difficult to prove a clinical difference in outcome between diluted and undiluted groups, these findings, when seen in the context of previous work, suggest that for minor surgery in healthy individuals, intravascular fluid infusions should be avoided, or, if rapid infusion is necessary, a low-molecular-weight starch should be considered.4 Patients will compensate for their blood loss without haemodilution, and so will not be exposed to the potential risk of enhanced coagulation associated with rapid haemodilution. As Janvrin16 indicated, perioperative administration of intravenous fluid is potentially harmful, and is not necessarily needed. In practical terms, having venous access does not imply the need to have an infusion running.

T. G. Ruttmann
Department of Anaesthesia
University of Cape Town Medical School
Observatory, Cape 7925
South Africa

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