Coagulation Changes in Elective Surgery and Trauma

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Although antithrombin-3 (AT-3), a naturally-occurring inhibitor of thrombin, has been associated with a variety of thrombotic disorders, it has not been studied in surgery and trauma. Three groups of patients were studied: Group I (20 patients) who underwent elective surgery; Group II (ten patients) who sustained moderate trauma; Group III (ten patients) who sustained severe trauma. Hypercoagulability panels were run preoperatively, intraoperatively, and postoperatively. Nine units of banked blood were also tested. The coagulation pattern changed during the stress, becoming hypercoagulable in proportion to the stress endured by the patient. In the severe trauma group, AT-3 fell significantly ($p \leq 0.002$) in all patients, indicating extreme hypercoagulability. Three of these patients sustained thrombosis and loss of the involved extremity. The banked blood was found to be hypercoagulable. It appears that patients who sustain severe trauma, have multiple transfusions, and major operative procedures are at increased risk of developing postoperative thrombotic complications, including loss of limb.

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IN RECENT YEARS, it has become apparent that the rapid and complex sequence of events resulting in a stable clot is balanced by a vanguard of circulating antagonists which are extremely efficient in limiting and localizing coagulation. In effect, they are responsible for maintaining the fluidity of the blood.

The presence of a naturally-occurring inhibitor of thrombin was first observed by Schmidt in 1892. This progressive inactivation of thrombin was ascribed to an "antithrombin." Virchow, another early investigator of coagulation, drew attention to the triad of stasis, intimal injury, and hypercoagulability (Fig. 1). His observations are as pertinent today as in 1846. If any two components of the triangle are present, clotting ensues. Although stasis and intimal damage have been studied in the past, an understanding of the so-called hypercoagulable state has been incomplete. More and more evidence points to the existence of a delicate balance between stimuli that activate coagulation and protective mechanisms that counteract their effect—the antithrombins.[1,2] Certainly, abnormalities in either system are potentially devastating.

Since the time of Schmidt and Virchow, six different antithrombin activities in blood have been described (Table 1). Of these, antithrombin-3 (AT-3), with its active alpha-2 globulin portion, appears to be, clinically, the most important naturally-occurring plasma inhibitor of thrombin.[3,4]

Low levels of AT-3 have been implicated in a variety of thrombotic disorders, including those associated with contraceptive agents,[5,6] mesenteric venous thrombosis,[7,8] postoperative myocardial infarction,[9,10] and venous thromboembolism.[9,11,12]

Although no AT-3 studies have been done with regard to trauma, the possibility of a hypercoagulable state secondary to the stress of an operative procedure has been investigated. The results, however, are conflicting, with some investigators reporting a fall in AT-3,[12–14] others finding no significant change,[15,16] and still others reporting a somewhat divided picture.[17] Closer scrutiny reveals that these studies may have been limited by excessive variables, long intervals between blood sampling, and the absence of intraoperative measurements.

The present study was designed to assess the existence of any change in coagulation during operative stress or trauma (or both), with particular reference to hypercoagulability.

Materials and Methods

Three groups of patients were studied prospectively. Group I consisted of 20 patients, and ranged in age from 3–50 years (mean: 19.7). These patients were selected at random. They underwent routine, elective orthopedic extremity procedures for which no blood

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transfusions were administered. Group I patients were receiving no medications, and had no personal or familial history of medical illness. Blood samples were obtained from a high-flow vessel (femoral vein) by plastic syringe, placed in liquid sodium citrated tubes, and separated, quick-frozen, and stored within minutes of venipuncture. All samples were drawn by one individual before, during (two hours into the procedure), and 24 hours after operation. The following tests were performed: antithrombin-3 activity assay, antithrombin-3 quantification by radial immunodiffusion, available plasminogen, thrombin clotting time, prothrombin time, partial thromboplastin time, and activated partial thromboplastin time.

Group II consisted of ten patients who had sustained moderately-severe isolated hand trauma, consisting of replantation or revascularization of one or more digits. The patients ranged in age from 14–56 years (mean: 28.3). No patient required blood tranfusion. These patients were healthy, except for this traumatic episode. The same tests and sampling patterns as for Group I patients were observed.

Group III consisted of ten patients who had sustained isolated, severe, upper (eight patients) or lower (two patients) extremity trauma, which required replantation or revascularization of a severed arm or leg. The patients ranged in age from 20–59 years (mean: 32.5).

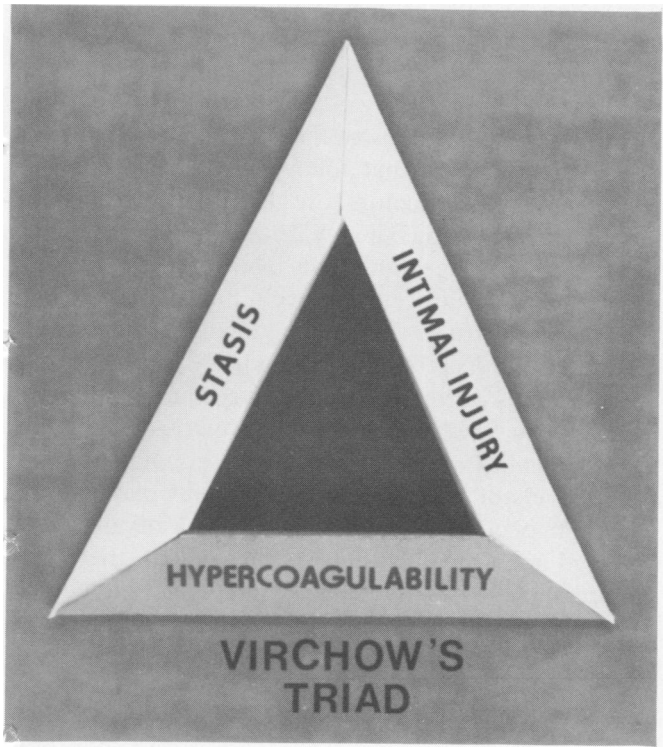

FIG. 1. Virchow's triad (1846). If any two components are present, clotting ensues.

TABLE 1. *Classes of Antithrombins*

Antithrombin	Activity
I	Refers to adsorption of thrombin to fibrin, thus removing its activity
II	Cofactor of heparin; possibly part of AT-3 molecule
III	Irreversibly binds thrombin and possibly other factors
IV	Active during clotting (existence questionable)
V	Present in certain disease states (weak)
VI	Refers to activity of fibrin degradation products

These patients all received four or more blood transfusions. In three patients, AT-3 was sampled from both the patient and from the transfused blood. Samples were not drawn before operation in certain instances, due to emergent priorities or because they had received blood en route, thereby nullifying their own control value.

Intraoperative and postoperative determinations were normalized in standard fashion with respect to the preoperative value, so that any change could be seen as a percentage of deviation from the patient's own normal pattern. Means, standard deviations, and probability values were computed in standard fashion.

In addition, nine units of banked whole blood and packed cells were assayed for AT-3 by the same methods. The mean age of the blood was 13.6 days.

Results

In Group I, AT-3, available plasminogen, and PTT levels fell in 16 of 20 patients, with thrombin clotting time falling in ten of the 20 patients (Fig. 2). PT remained normal in 18 patients and fell in two. All values were reverting toward normal at 24 hours. Postoperative convalescence was uneventful in all 20 patients.

In Group II, AT-3 fell in six of ten patients and remained in the normal range in four patients (Fig. 3); available plasminogen was depressed in seven patients. The PT remained unchanged and the PTT, APTT and thrombin clotting times were elevated as a result of the administration of heparin during the vascular repair procedure. One patient in this group sustained a thrombosis and lost the replanted part.

In Group III AT-3 levels fell to less than 80% of normal in all patients, with five decreasing to the 60% range (Fig. 4). Four of these latter patients exhibited clinical evidence of thrombosis within hours of the operation, although initially there was no evidence of compromise. Three of these patients lost the involved extremity. Available plasminogen levels and thrombin

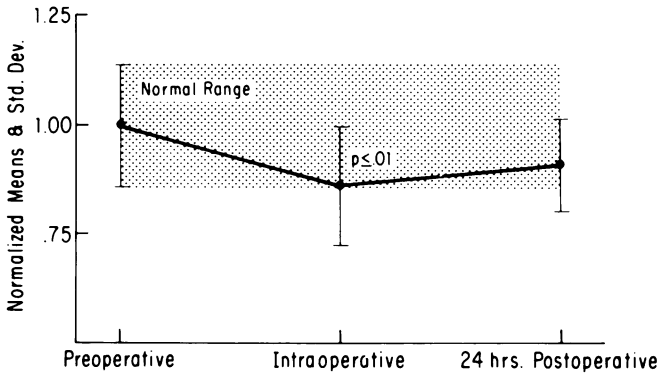

FIG. 2. The fall in AT-3 depicted here indicates that there is a trend toward accelerated clotting during elective surgery.

clotting times were extremely low (25–40% of normal), an indication of consumption of fibrinogen.

AT-3 levels were below normal range in six of nine units of banked blood (mean: 76% of normal); three units of blood were within the normal limits. In the three patients sampled simultaneously, AT-3 levels were low in both the patient and in the blood they received. One of these patients lost an extremity due to postoperative thrombosis. No correlation was noted between the age of the blood and the levels of AT-3.

Discussion

The precipitous fall in AT-3 after severe trauma noted in this study brings up several points of great interest clinically. First, it may explain why some severely-injured patients are beset with repeated thrombosis. These patients (Group III) are at the limit of their reserves, having sustained loss of blood, depletion of coagulation factors, massive fluid and blood replacement and a major vascular repair. They are primed for intravascular coagulation and have, in essence, fulfilled all three components of Virchow's

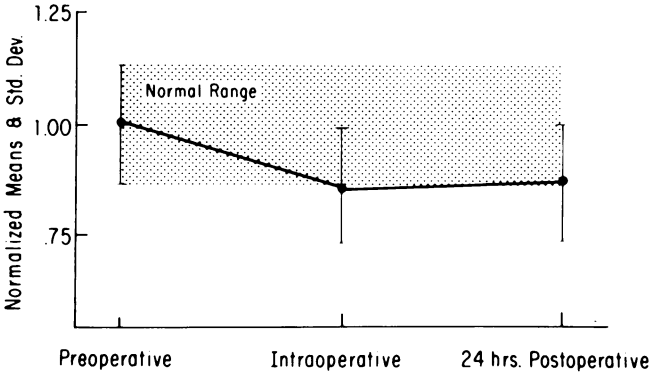

FIG. 3. The depletion of AT-3 in response to moderate trauma and surgery, although not significant, reflects a trend toward accelerated thrombosis. The low level of AT-3 is still present at 24 hours after operation.

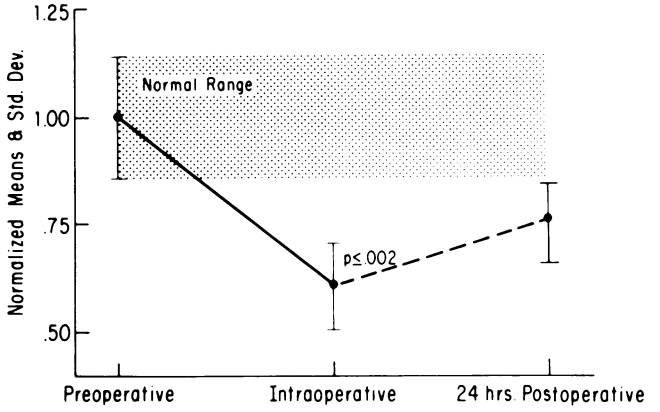

FIG. 4. AT-3 levels are significantly depressed in the patients with severe trauma. In addition, these patients exhibited a high incidence of complications. Three in this group lost the involved extremity secondary to thrombosis. The dotted line indicates a slower return to normal, although only measured in three individuals at 24 hours after operation. All patients in this group received four or more units of banked blood.

triad (Fig. 1). It is not surprising, therefore, that AT-3 levels are also depleted. In this setting, loss of limb is a very real possibility—as demonstrated by three of our patients.

Second, it appears that multiple blood transfusions (four or more) may compound the risk of thrombosis. In three of our patients AT-3 levels were extremely low in both the banked blood and simultaneously in the recipients of that blood. One of these individuals was noted to have a thrombosis postoperatively and ultimately lost the involved arm. The patients, of course, urgently required replacement of red cell mass. To what degree thrombosis was augmented by the banked blood is not known. However, it is of interest because of the complication that followed. Although certain labile coagulation factors are known to lose their activity during storage, it may be that inhibitors of clotting are also changed and that, overall, the latter may be of greater clinical importance.

Third, a spectrum is evident—ranging from the mild, controlled trauma of elective surgery in which no complications occur, to the massive injury and major operation, in which postoperative thrombosis is a grave risk. Within this range, there are corresponding changes in the levels of AT-3. It appears that, as massive coagulation occurs, clotting factors are activated and depleted rapidly. This activation exceeds the local requirements—a phenomenon which is not altogether unexpected, since the clotting enzymes are normally present in great excess.[4] As a result, the circulating antithrombins combine with the activated coagulants in order to neutralize their effect. In turn, these inhibitors are also depleted. A critical level is reached when the

antithrombins cannot keep up with the activated coagulants. At this point, uncontrollable thrombosis becomes a possibility. That the level of tolerance is different in each individual is demonstrated by the fact that six of the severe trauma patients exhibited extremely low levels of AT-3 and yet recovered without complication. It is also of interest to note the similarities between the results of Group III and those in disseminated intravascular coagulation (DIC). It is known that shock can lead to DIC and that AT-3 levels are significantly decreased in this syndrome.[18] Also, available plasminogen levels and thrombin clotting times were extremely low, reflecting continuing fibrinogen depletion. Therefore it is possible that these patients were in a very early stage of DIC.

Finally, it should be mentioned that these changes in coagulation can occur rapidly, especially in severe trauma. Three of these latter patients exhibited a sharp decline in AT-3 over a period of only two hours. During that time, they had received multiple transfusions.

Although the treatment of hypercoagulability is not established, it is known that low-dose heparin therapy can abolish decreases in AT-3 in certain patients who undergo elective surgery.[12] In the acute situation, consideration should be given to replenishment of coagulation factors and AT-3. Fresh frozen plasma can be very useful in this regard.

References

1. Tullis JL. Clot. Springfield, Charles C Thomas. 1976.
2. Lane J, Biggs R. The natural inhibitors of coagulation: antithrombin III, heparin co-factor, and antifactor Xa. *In* Poller, L (ed) Recent Advances in Blood Coagulation. London, Churchill-Livingstone. 1977.
3. Biggs R, Denson K. Natural and pathological inhibitors of blood coagulation. *In* Human Blood Coagulation, Haemostasis, and Thrombosis. London: Blackwell, 1976.
4. Hirsh J. Hypercoagulability. Semin Hematol 1977; 14(4):409.
5. Poltera A. The pathology of intercranial venous thrombosis in oral contraception. J Pathol 1972; 106:209.
6. VonKaulla E, VonKaulla A. Oral contraceptives and low antithrombin III activity. Lancet 1970; 1:36.
7. Gruenberg J, Smallridge RC, Rosenberg RD. Inherited antithrombin III deficiency causing mesenteric venous infarction. Ann Surg 1975; 181:791.
8. Collins GJ, Zuck TF, Zajtchuk R, Heymann RL. Hypercoagulability in mesenteric venous occlusion. Am J Surg 1976; 132:390.
9. VonKaulla E, VonKaulla KN. Antithrombin III and Diseases. Am J Clin Pathol 1967; 48(1):69.
10. Collins GJ, Heymann RL, Zajtchuk R. Hypercoagulability in patients with peripheral vascular disease. Am J Surg 1975; 130:2.
11. Fagerhol MK, Abildgaard U, Bergsjo P, Jacobsen JH. Oral contraceptives and low antithrombin-III concentration. Lancet 1970; 1:1175.
12. Sagar S, Stamatakis JD, Thomas DP, Kakkar VV. Oral contraceptives, antithrombin-III activity, and postoperative deep-vein thrombosis. Lancet 1976; 1:509.
13. Stathakis N, Papayannis AG, Gardikas CD. Postoperative antithrombin-III concentration. Lancet 1973; 1:430.
14. Collins GJ, Barber JA, Zajtchuk R, et al. The effects of operative stress on the coagulation profile. Am J Surg 1977; 133:612.
15. Hedner U, Nilsson IM. Antithrombin III in a clinical material. Thromb Res 1973; 3:631.
16. Donati MB, Vandenberghe K, Molla A, et al. Postoperative antithrombin III. Lancet 1973; 1:726.
17. Korvald E, Abildgaard U, Fagerhol MK. Major operations, hemostatic parameters and venous thrombosis. Thromb Res 1974; 4:147.
18. Bick RL, Bick MD, Fekete LF. Antithrombin III patterns in disseminated intravascular coagulation. Am J Clin Pathol 1980; 73(4):577.