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Age-dependency of thrombin generation

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The paper “Age dependency measured by calibrated automated thrombinography (CAT)” by Haidl et al. (1) is one in a series of investigations from the Graz group that significantly contributes to the understanding of paediatric haemostasis. More or less as a by-product of these studies they now found that adults of over 35 years of age have a significantly higher thrombin generation potential (ETP) than those aged from 18 – 35. The figure in this publication suggests an apparently linear increase with age that is as high as ~30% between the ages of 20 and 50. This is an important observation because it shows that, also in a group of apparently healthy volunteers without known prothrombotic traits, the age group that is more likely to get thrombosis is also the one that generates more thrombin.

In a series of congenital conditions, such as antithrombin deficiency (2), congenital hyperprothrombinaemia (G20210A mutation) (3), and dysfunction of the protein C-system (unpublished observation), it is evident that the genetic defect primarily causes higher thrombin generation, and one concludes that higher thrombin generation leads to a higher risk of venous thrombosis. If we observe APC-resistance in the presence of the lupus anti-(-)coagulant (4) or in women using oral contraceptives (5), it is not a long shot to surmise that in these cases, as in congenital conditions, higher thrombin generation is the cause of the thrombotic tendency. Taken together, the body of circumstantial evidence for high thrombin generation potential being the cause of a prothrombotic condition becomes rather impressive. It is reinforced again by the inverse observation, i.e. the fact that all antithrombotic drugs decrease thrombin generation [see further (6)].

The observation by Haidl et al. carries the subject a step further. It has been observed that thrombin generation is rather variable in a normal population. Where the intrapersonal variation of the ETP is ~5%, the interindividual variation is >15% (7). This means that 99% of all normal individuals have a thrombin generating capacity of between 55 and 145 % of the mean. In other words: some people in the normal population generate twice as much thrombin as others. In congenital conditions such as antithrombin deficiency or the prothrombin A20210G mutation, such large variations can be attributed to one single cause. Apparently, in the normal population they can also be caused by a combination of circumstances. “Mr. Low” who, by chance, has a low normal set of procoagulant factors and a high normal set of anticoagulant factors may produce half as much thrombin when his plasma is triggered compared to “Mrs. High”, a person with high procoagulant and low anticoagulant factors. The question now is whether, as a consequence, he has a much smaller risk of developing thrombosis.

Now that automated calibrated measurement of thrombin generation allows such variations to be measured, we feel that the time is ripe for larger epidemiological studies relating the parameters of thrombin generation to thrombotic risk in those populations where no recognised risk factors can be found.

Before embarking upon such studies, epidemiologist may well ask why thrombin generation might do better than the time honoured clotting times, which have essentially failed as predictors of thrombotic disease. The answer can be given on different levels: i) Clotting times are insensitive to variations in clotting function in the region of interest, i.e. in a large area around the normal mean. If the thromboplastin time, as defined by Armand Quick, is invariably 12 seconds in the normal, this is because it does not distinguish between the clotting system of Mr. Low and Mrs. High. This again is caused by the fact that the clotting time already approaches its minimum when the concentration of prothrombin (or of any other clotting factor) exceeds the ~25% level (8). ii) At the moment that the clotting time is recorded there is only very little thrombin formed. The large majority of all prothrombin (> 98%) still has to be converted. So, not enough thrombin is formed for the protein C system to start, and the plasma antithrombins are not yet of significant influence. Contrary to the clotting time, thrombin generation is very sensitive to variations of prothrombin and antithrombins around the normal mean as well as to the activity of the APC system. iii) The conditions of a thrombin generation experiment can be obtained reproducibly at almost any concentration of tissue factor (TF). For clotting times we have essentially the choice between an unphysiologically large excess of TF, as in the thromboplastin time, or an equally unphysiological absence of TF as in the activated partial thromboplastin time (aPTT). Measuring clotting times at lower TF concentrations is possible and has been practiced in the...
last century but has never become a routine measurement, primarily because such clotting times are notoriously difficult to standardise and validate. Thrombin generation curves can be obtained reproducibly at any TF concentration, be it that in the present technique, for technical reasons, a lag time (= clotting time) of minimally 30 seconds is required, so that very high TF concentrations cannot be accommodated.

What concentration of TF must be considered “physiologically” is a question that is impossible to answer for the good reason that, in vivo, TF is not present in free solution. It is incorporated in a membrane that is very large compared to molecular dimensions, and reaction velocities are determined by physical transport rather than by chemical rate laws. The same holds true for thrombomodulin (TM). TF and TM, representing the wound or vessel wall in our experiments, are in practice simply added in concentrations that make the thrombogram behave “physiologically”; i.e. in such amounts that it becomes sensitive to low concentrations of factor VIII and IX, to the defect in factor V Leiden, to the effect of the pill etc. The crux of the matter lies in the fact that with the calibrated automated thrombography we have a method at hand that is capable of giving reproducible results under such circumstances. This, essentially, is also the underlying reason for Haidl et al. to surmise that the ETP “may become a new tool better reflecting overall haemostasis than global tests or specific factor analysis” (1).

There is one additional reason of interest in measuring the thrombin forming capacity in the 55–145% range. If, for a moment, we assume that epidemiology would show that the population with an ETP between 100 and 145% has a higher incidence of thrombosis than the 55–100% half, then the logical conclusion must be that mild anticoagulation would have a preventive effect. The literature abounds with antithrombotic drugs that do not or hardly affect the clotting time, such as low doses of low molecular weight heparin, fondoparinux, dermcan sulphate, pentosan polysulfate and others. It is more than likely that such drugs do influence the thrombin forming capacity to an efficient extent that, however, is not so large as to be measurable with a clotting time. Large scale safe thrombosis prevention might be obtained by some innocuous drug that does not diminish thrombin generation by more than 25%. Until now such effects were hard to measure. This posed problems for drug development and control. With the CAT technique this becomes readily possible.

Finally, the thrombosis mentioned above silently implied venous thrombosis. For arterial thrombosis the situation remains as yet blurred – but as in venous thrombosis a central role of thrombin in the pathogenesis cannot be denied (9, 10), and ETP-lowering therapies such as oral anticoagulation and heparin diminish the rate of re-infarction (11–13). It may be that the links between arterial thrombosis and thrombin generation become clearer when epidemiological studies include thrombin generation in platelet rich plasma. In this context it should not be overlooked that “antiplatelet” agents invariably also diminish thrombin generation in platelet rich plasma (6, 14).

References