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Infections, inflammation and venous thrombosis; an epidemiological perspective

Tichelaar, Ynse Ieuwe Gerardus Vladimír

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Inflammation, infections and coagulation share pathways, mechanisms and markers in the blood. Evidence first came from more basic science and experimental studies and later also from clinical epidemiological studies. In **chapter 2** we provided an overview of studies on infections and inflammatory diseases that reported an absolute or relative risk of venous thrombosis by a systematic review of the literature of the last 15 years. Infections in general, and more specific human immunodeficiency virus (HIV), pneumonia and urinary tract infections appear to increase the risk of venous thrombosis about 2-fold. During more severe or acute episodes of an infectious disease, this risk might even be higher. Patients with inflammatory diseases, like inflammatory bowel disease or ANCA-associated vasculitis, were also found to be at a 2 to 4-fold increased risk of subsequent venous thrombosis. During active disease or flare-ups, the risk of venous thrombosis reached a 8-fold increase.

To determine whether self-reported, mild symptoms of inflammation or infection of common (and probably viral) origin could also be a risk factor for venous thrombosis, we performed the Beast study. In this case-control study of consecutive patients suspected of venous thrombosis, who visited the emergency department of our university medical center, we found a 2.5-fold increased risk of venous thrombosis for self-reported inflammatory or infectious symptoms, as described in **chapter 3**. Interaction with CRP was also found, and the risk of venous thrombosis was highest in patients with elevated CRP levels and a positive history of inflammatory or infectious symptoms, pointing towards an at least partial causative association for CRP with venous thrombosis (1). However, due to our study design (a case-control study with retrospectively collection of data), questions about causality could not be proven but only made likely.

In **chapter 4** we reported on 5 patients (2%) from the BEAST case-control study with an active *cytomegalovirus* infection and venous thrombosis. Because we did not find any patient with an active infection without venous thrombosis, we could not calculate a relative risk of venous thrombosis. Remarkably, all patients were female and below 37 years of age, with another known (non-genetic) risk factor and at least a mildly elevated factor VIII:C. That all these 5 subject were

women, might be explained by the fact that they are at higher risk of venous thrombosis due to oral contraception use and being in the reproductive part of their life. Also, women may be more exposed to cytomegalovirus than men, as has been observed in other population based studies (2).

Another frequently reported disease probably associated with venous thrombosis is HIV. After introduction of combined anti-retroviral therapy (cART), not only the disease but also the remedy appeared to be related with an increased risk of venous and arterial thrombosis. In **chapter 5** we performed a review of the literature to determine the risk of venous and arterial thrombosis in HIV-infected patients, as well as to determine the contribution of HIV itself and the therapy to this risk. Both HIV and cART appear to contribute to an increased procoagulant state and thus an increased risk of arterial and venous thrombosis. HIV-patients are at a 4-6 fold increased risk of venous or arterial thrombosis. Although these patients have an increased risk of venous or arterial thrombosis, this does not outweigh the benefits of anti-retroviral therapy, as shown by the remarkably increased survival of these patients during the anti-retroviral era.

Chapter 6 shows the data of a cohort of 104 patients with HIV-infection, treated at our outpatient clinic. In these patients, we determined whether active *cytomegalovirus* infection could add to the risk of venous thrombosis by disturbing the hemostasis of coagulation even more, compared to HIV-infection alone. As *cytomegalovirus* infection is more often found in patients with a more progressive stage of HIV-disease, it might be that HIV-stage alone could account for the procoagulant changes. In this cross-sectional study, active *cytomegalovirus* infection was associated with hypercoagulability independently of the stage of HIV disease. Most prominent features of this were significant higher levels of FVIII:C and fibrinogen.

In the final part of this thesis we described a number of studies on markers of inflammation or coagulation, the risk of venous thrombosis according to these markers and the influence of the acute phase reaction on the relationship between them. First, in **chapter 7**, the association between elevated glucose levels and venous thrombosis was determined, using the BEAST case-control study. Although

hyperglycemia and coagulation have been earlier described together, whether this indeed would be associated with an increased risk of venous thrombosis was only recently investigated in one epidemiological study (3). They reported a 2.2-fold increased risk of venous thrombosis in patients with hyperglycemia and in the highest quartile of the distribution of glucose levels compared to the lowest quartile, independent of manifest diabetes mellitus. However, adjustment for the acute phase reaction (which could be a confounder in the association between hyperglycemia and venous thrombosis) could not be done. The authors also asked for replication of their study. Therefore, we performed this analysis in the BEAST case-control study, showing that patients with hyperglycemia indeed had an increased risk of unprovoked first venous thrombosis, comparing the highest quartile to the lowest quartile of glucose (OR 5.2, 95%CI, 1.2-23.4). This association was at least partially influenced by the acute phase reaction, as after adjustment for CRP the odds ratio declined to 3.0 (95%CI, 0.4-22.9). Overall, hyperglycemia appears to be associated with an increased risk of venous thrombosis, also in the acute phase, but a conclusion about causality cannot be drawn due to the study design of these two studies, where blood samples were taken shortly after the event took place.

Hereditary decreased free protein S levels are associated with an increased risk of venous thrombosis, especially when these levels are very low (4, 5). In **chapter 8** we tried to replicate our previous finding (5) of the low cut-off value of <41 IU/dL for decreased free protein S levels as a risk factor for venous thrombosis, using blood that was sampled in the acute phase. If this can reliably be detected in the acute phase, i.e. when patients present at the emergency department, one could determine thrombophilic defects immediately when needed and thereby estimate the risk of recurrence of venous thrombosis without delay. We found a CRP-adjusted 1.9-fold increased risk of venous thrombosis for patients with a free protein S below 41 IU/dL in the acute setting using the BEAST case-control study. The association between free protein S and venous thrombosis was not independent of the acute phase reaction. Second, we found that total complement 4 binding protein (C4BP) levels had no influence on this association. In the acute

phase, C4BP levels increase and as C4bP binds to protein S, it is hypothesized that in this way it might be accountable for the decrease of free protein S levels in the acute phase.

Although viewed by some as an acute phase protein (6, 7), FVIII:C and the risk of (recurrent) venous thrombosis is supposed to be independent of the acute phase (8-10). However, the designs used in some studies were insufficient to determine the real relationship between the acute phase and FVIII:C. In **chapter 9** we described the follow-up of FVIII:C, CRP and fibrinogen levels in 75 patients from the BEAST case-control study. These patients were followed from baseline until end of treatment (on average 6 to 12 months later). We concluded that the acute phase reaction indeed influenced FVIII:C levels, but that most patients who had an elevated FVIII:C level at baseline, kept a persistent elevated FVIII:C level during and at the end of treatment (75%). However, the absolute value declined somewhat because of fading of the acute phase (207 to 175 IU/dL, *p* for trend 0.003). Our second observation was that those patients with a persistent elevated FVIII:C had only mild elevated CRP levels at baseline, compared to higher CRP levels in the patients with an initially elevated FVIII:C levels and a normal FVIII:C level at the end of treatment. In this way, patients with a high risk of recurrent venous thrombosis because of a persistent elevated FVIII:C might be detected as early as at the start of treatment of their first venous thrombosis.

Finally, in **chapter 10** we showed that rivaroxaban, a new oral anti factor Xa antagonist, interferes *in vitro* with the one-stage FVIII:C clotting assay. We hypothesized that this interference could be based on a new, unknown, anticoagulant or anti-inflammatory effect of rivaroxaban, mainly *in-vivo*. However, it appeared that the effect is caused by the direct blockage of newly formed factor Xa *in vitro*, i.e. while the test is being performed. Applying high dilutions could only partially diminish this effect. The chromogenic assay we used was also influenced by rivaroxaban, because factor X has to be activated during this test, which is thus also factor Xa dependent. Clinicians have to be aware that new anticoagulants, including rivaroxaban, can interfere with coagulation tests, such as the one-stage FVIII:C clotting assay.

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