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FACTOR VIII AND CORONARY HEART DISEASE

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Key words: Factor VIII - Coronary Heart disease

In plasma, Factor VIII is bound to its carrier protein, von Willebrand Factor (vWF). Therefore, the levels of these two factors vary together. From studies in the general population, in patients with coronary heart disease and in hemophilia patients, an association between Factor VIII levels and coronary heart disease clearly emerges.

INTRODUCTION

In the last decade it has become increasingly clear that the hemostatic system plays a central role in the development of coronary heart disease. Not only has it been demonstrated that coronary thrombosis is the final and crucial event in myocardial infarction (4, 5), but also that hypercoagulability, i.e. high blood levels of clotting factors, are long term predictors of coronary heart disease. In the Nortwick Park Heart Study it was prospectively shown that the levels of clotting factor VII and fibrinogen were strongly related to the risk of the development of myocardial infarction (12). These associations have been confirmed in several other studies (2, 8, 23).

The presence of occlusing thrombi in the coronary arteries causing myocardial infarction and the predictive power of factor VII and fibronogen establish the role of coagulation in coronary heart disease. With regard to fibrinogen, it has to be noted that this protein contibutes substantially to blood viscosity. Hyperfibrinogenemia, therefore, leads to hyperviscosity as well as hypercoagulability, which may also explain the association with coronary heart disease. Further evidence for the clotting system as a major determinant of coronary heart disease is provided by the efficacy of oral anticoagulation in the prevention of recurrent myocardial infarction (20, 21).

In this paper we will consider the role of clotting factor VIII. In response to tissue damage, blood coagulation is initiated by factor VII in combination with cell surface bound tissue factor and phospholipid surfaces. In the initial phase factor X is activated and the product, factor Xa activates factor VII into factor VIIa, which has higher enzymatic potency that its precursor. Subsequently, the process follows the alternative pathway where factor IX is activated by factor VIIa and factor X is activated predominantly by factor IXa. Finally, factor Xa activates prothrombin into thrombin, the major effector enzyme of the system (Figure 1).

The three enzymes VIIa, IXa and Xa require non-enzymatic cofactors for their catalytic efficiency: tissue factor, factor VIII and factor V, respectively. A powerful positive feedback is provided by thrombin activating factor VIII to VIIIa and factor V to Va. Since hemophilia A, hereditary factor VIII deficiency, is associated with severe bleeding, we know that factor VIII is an essential component of the system.

In plasma, factor VIII is bound to its carrier protein, von Willebrand factor (vWF). The levels of these two factors covary and are related to blood group. Since von Willebrand factor may itself be a determinant of the risk of CHD, given its function in promoting platelet adhesion, this covariation poses a problem in evaluating studies on factor VIII levels and coronary heart disease.

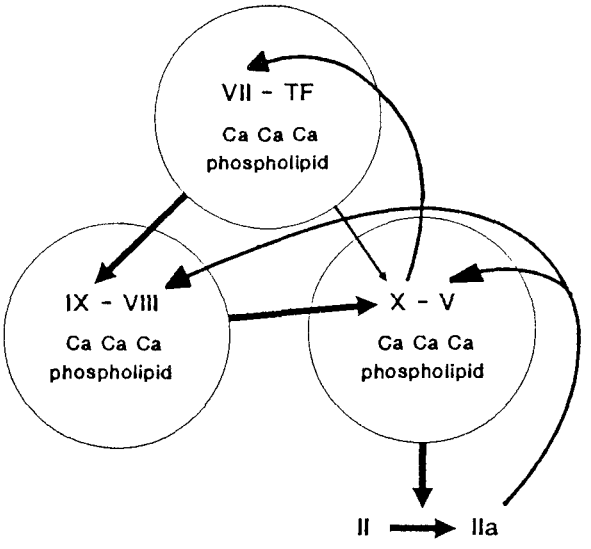

Figure 1. - The central part of the clotting system.

Blood group, factor VIII and von Willebrand factor

Since von Willebrand factor is the carrier protein of factor VIII, low levels of vWF as in von Willebrand's disease, cause a shortened half-life of factor VIII and low plasma levels of factor VIII. This forms the main cause of bleeding problems in von Willebrand's disease. In the normal population the levels of both factors also vary together, and are related to blood group. Table 1 shows this relation and covariation by the results of a study we performed on 93 healthy volunteers.

In several studies a higher risk of coronary heart disease (by about 20 percent), as well as of atherosclerosis, has been demonstrated for individuals with non-O blood groups (9, 13, 22). This is likely to be caused by the higher levels of von Willebrand factor and factor VIII in these individuals (14).

TABLE 1. - Relation between blood group, FVIII and vWf.

	Blood group	
	O (n = 40)	non-O (n = 53)
FVIII (IU / ml)	0.88	1.25
vWF (IU / ml)	0.86	1.16
Ratio FVIII / vWF	1.02	1.06

Normal mean for FVIII and vWF is 1.0 IU/ml. FVIII coagulant activity (FVIII:C) measured by a one-stage clotting assay, vWF activity as ristocetin cofactor activity (vWF:Rco) by the use of formalin fixed platelets.

In this paper we will restrict ourselves to clotting factor VIII. However, since platelet adhesion mediated by von Willebrand factor may play a role in the pathogenesis of myocardial infarction (6), this background information on the covariation of vWF and FVIII is essential in interpreting the evidence on the relation between factor VIII and coronary heart disease.

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Three types of studies can be considered. First, studies in the general population, in which baseline measurements are associated with subsequent coronary events. These are (prospective) cohort studies in initially healthy individuals. Secondly, studies in patients with coronary heart disease, in whom clotting factors are measured after the disease has manifested itself. These are studies in which the clotting factor levels of the patients are compared to those of healthy controls. Thirdly, studies in hemophilia patients, who lack factor VIII. These are 'experiments of nature', in which the frequency of coronary disease (or mortality) is compared with the general population.

Cohort studies

At present there is only one completed prospective cohort study in which factor VIII was measured, The Northwick Park Heart Study (12), whereas one study is still in progress (the PROCAM study in Germany). Table 2 shows the relative risks for myocardial infarction associated with different levels of factor VIII that were observed in the 1500 men followed in the Northwick Park Heart Study.

These results of the Northwick Park Heart Study indicate that in the one third of the population with the highest factor VIII levels, the risk of the development of coronary heart disease may be as much as 44 percent greater than in the one third of the population with the lowest factor VIII levels, although the association was not statistically significant ($p = 0.2$). Because of the covariation of factor VIII and von Willebrand factor, this association might have been brought about by a relation between vWF levels and the risk of CHD. However, when mean values at entry were compared for 15 cardiovascular deaths and 45 survivors, no differece in vWF levels was discerned (11).

TABLE 2. - Risk of coronary heart disease and factor VIII levels (Northwick Park Heart Study).

FVIII	CHD	relative risk
low	27	1.00
middle	36	1.33
high	39	1.44

The cohort was divided in thirds of the FVIII distribution. The risk of CHD to the lowest third was calculated from the paper under the assumption of equal follow-up time in all three groups.

Studies in patients with coronary heart disease

If a high plasma concentration of factor VIII increases the risk of CHD, one would expect higher levels of factor VIII in patients with coronary disease than in healthy individuals. Cucuianu and colleagues reported elevated levels of FVIII and vWF shortly after myocardial infarction (3). The observed clotting factor levels in the patients were so high (two- to fourfold increase) that the authors concluded that this was most likely brought about by the infarction, either as the result of endothelial injury or as a systemic acute phase reaction. Haines et al. studied 272 patients with myocardial infarction (7) and also observed substantially elevated factor VIII levels (approx. 1.4 IU/ml, normal value 1.0 IU/ml) in these patients. Subsequently, the patients were followed for one year. The 68 patients who died had had a mean factor VIII level of 1.65 IU/ml (at admission), whereas the 204 patients who were alive at one year had had a mean factor VIII level of 1.27 IU/ml. Von Willebrand factor levels were also higher in the patients than the population mean, and also had prognostic value in the one year follow-up. In this paper too it was discussed that the raised clotting factor levels might have resulted from the infarction, and that the extent of the elevation might be a reflection of infarction size, thus offering an alternative explanation than hypercoagulability for the prognostic value of factor VIII levels after myocardial infarction.

Studies in hemophilia patients

Hemophilia A, which accounts for 85% of all cases of hemophilia, is a deficiency of factor VIII. Factor VIII may be completely absent, as in severe hemophilia, or present to some extent, as in moderate and mild hemophilia. Von Willebrand factor and platelet function is not affected in hemophilia. Until the 1960s, before the introduction of cryoprecipitate, hemophilia could not be adequately treated, and most patients died of bleeding at a young age (17). Since clotting preparations became available, the life expectancy has increased to an almost normal life span, which makes it possible to study the occurrence of other causes of death, i.e. coronary heart disease. Table 3 lists the five most recent studies on mortality in hemopilia, comprising a total of 1214 deaths.

Among 1214 deaths in hemophilia patients, only 5.4 percent was caused by coronary heart disease. In the general population in the Netherlands, which among the industrialised countries has an intermediate incidence of CHD, 21 percent of all deaths can be attributed to coronary disease. Since the proportional mortality of CHD may have been influenced by competing causes of deaths, i.e. bleeding, and the lower mean age of hemophilia patients, we compared CHD mortality with cancer mortality, the ratio of which is fairly constant ove age. The ratio of CHD deaths to cancer deaths was 0.8, whereas in the general population of many countries CHD mortality exceeds cancer mortality (ratio CHD to cancer deaths: USA 1.5, The Netherlands 0.8).

In our study on mortality in hemophilia we followed 717 patients from 1973 to 1986, and calculated the expected number of deaths of each cause by application of the mortality rates of the general population (18). This patient-year method largely avoids the problem of competing causes, whereas age is adjusted for. The observed to expected ratio (SMR) for coronary heart disease was 0.20, i.e. CHD mortality was reduced by 80 percent.

The major drawback in these studies is that hemophilia patients suffer from a chronic disease, that affects life in many ways. One may wonder whether the factor VIII deficiency is the only difference between these patients and the general population, and whether other factors in these patients, e.g. lifestyle, might influence the incidence of CHD. To this effect, we studied the major risk factors for CHD, blood pressure, cholesterol, smoking and Quetelet index in 95 hemophilia patients, and compared their CHD risk profile based on these factors with data

TABLE 3. - Mortality in hemophilia patients.

Study	country	total	deaths in hemophilia patients CHD %	cancer %	ratio CHD/ cancer
Larsson [10]	Sweden	87	12.6	4.6	2.8
Rizza [15]	United Kingdom	89	1.1	7.9	0.1
Schiller [19]	(East-) Germany	52	1.9	1.9	1.0
Aronson [1]	USA	949	5.5	6.0	0.9
Rosendaal [18]	The Netherlands	43	2.3	34.9	0.1
Total		1214	5.4	6.9	0.8

Two studies (18, 19) also include hemophilia B patients (factor IX deficiency), who constitute about 15% of the total number of hemophilia patients.

from the general population (16). Although differences in some of the risk factors were found (higher blood pressures, lower total cholesterol), the overall age-adjusted risk profile of the hemophilia patients was approximately equal to that of the general population. This lends further support to the notion that it is indeed the low factor VIII level that protects hemophilia patients against coronary heart disease.

CONCLUSION

There can be little doubt that the hemostatic system is a major determinant of coronary heart disease. From several types of studies, in the general population, among patients with myocardial infarction and among hemophilia patients, it has become clear that clotting factor VIII plays an important role in the pathogenesis of coronary heart disease.

Myocardial infarction is the result of many years of atherosclerosis followed by arterial thrombosis. It is unresolved whether the hemostatic system plays a role in plaque formation or only in the final thrombosis after plaque rupture.

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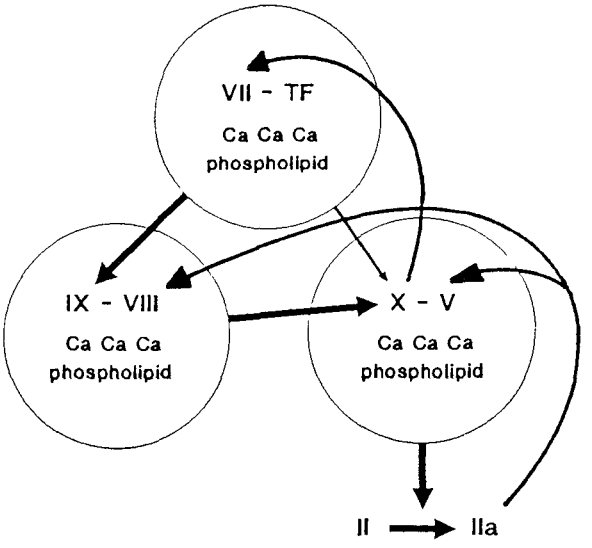

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