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High hematocrit as a risk factor for venous thrombosis. Cause or innocent bystander?

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In the lay press it is frequently stated that long haul air travel causes venous thrombosis through dehydration in the airplane, leading to hyperviscosity of the blood, which in its turn favors thrombosis. The common advice that is given to prevent thrombosis after air travel is, therefore, 'to drink ample amounts of fluids' (http://www.britishairways.com/travel/healthmedcond/public/en_gb#DVT). This concept of thick, slowly flowing blood is apparently intuitively appealing as a cause of thrombosis. It would also fit the classical triad of Virchow, who postulated that thrombosis is due to the occurrence of stasis, to disturbances of the composition

of the blood, or to lesions of the vessel wall.[1] High viscosity could be considered to be both a disturbance of the composition of the blood and a cause of stasis. Nevertheless, viscous blood, evidenced by high hematocrit values, has been poorly studied as a risk factor for venous thrombosis in the general population. The study by Braekkan and colleagues in this issue of the Journal is, therefore, a welcome contribution to the scientific literature.[2] Their results from the Tromsø study (a large health survey in Tromsø, Norway) show a hazard ratio of 1.25 per 5% rise in hematocrit.[2] In a category-based analysis, a hematocrit in the upper 20th percentile was found to be associated with a 1.5-fold increased risk of venous thrombosis. However, the important question that is not answered by this study is whether the relation is causal, or whether it can be explained by the presence of other diseases that cause both a high hematocrit and venous thrombosis.

Venous thrombosis, as the name implies, is caused by intravascular coagulation in veins, leading to often large thrombi and venous obstruction. Thrombi can detach from the primary site and travel to the lungs, resulting in pulmonary embolism. About 10% of pulmonary emboli are immediately fatal, and an additional 5% cause death later in time, despite diagnosis and treatment. At least 10% of patients with symptomatic venous thrombosis develop a severe post-thrombotic syndrome within 5 years.[3] The annual incidence of venous thrombosis is about 2 cases per 1000 individuals[4,5] and has a steep age dependence.[6] Two-thirds of the cases of venous thrombosis are deep vein thromboses of the leg and one-third consists of pulmonary embolism with or without symptomatic deep vein thrombosis.[7,8]

Venous thrombosis has multiple causes associated with both genetic and environmental risk factors. The most common genetic risk factors for venous thrombosis are the factor V Leiden mutation[9] and the prothrombin G20210A mutation,[10] both present in several percent of the Caucasian population. Well-known environmental risk factors are age, oral contraceptive use, pregnancy, recent surgery, major trauma, immobilization and malignant diseases.[11]

Hematocrit, expressed as % (proportion of red blood cells of the total blood volume), can be calculated from the red blood cell concentration and the mean corpuscular volume. Increased hematocrit levels are caused either by an increase in the number of red blood cells (erythrocytosis) or by dehydration. Erythrocytosis can be caused by diseases affecting the bone marrow (primary erythrocytosis, such as polycythemia vera) or by diseases or an environment affecting oxygen saturation (secondary erythrocytosis). In the latter situation, the bone marrow produces more red blood cells to counterbalance the decrease in oxygen saturation. In healthy subjects, hypobaric hypoxia present at high altitude leads to an increased hematocrit. In subjects living in these conditions, the bone marrow compensates for the decrease in oxygen saturation by increasing the production of red blood cells (through erythropoietin).[12] Sports-men and -women take advantage of this phenomenon by training at high altitudes in order to benefit from a greater potential to carry oxygen in the blood when they return to normoxic, normobaric circumstances.

At sea level, erythrocytosis that is not due to an intrinsic problem in the bone marrow (secondary erythrocytosis) is, in most cases, acquired (congenital causes are rare and will not be discussed here). Acquired erythrocytosis can be caused by exogenous erythropoietin use or by pathological erythropoietin production by certain tumors (e.g. parathyroid carcinoma/adenomas, hepatocellular carcinoma, renal cell cancer, pheochromocytoma), but is generally a result of conditions that lead to hypoxia. Obvious examples are smoking and lung disease, but congenital heart disease with right-to-left cardiopulmonary shunts also leads to increased erythropoietin production.[13]

An increased risk of venous and arterial thrombosis in relation to primary erythrocytosis has been well described. However, the mechanisms are complex and being debated[14] and a direct relation between the hematocrit level and the risk of venous thrombosis is not clearly present in these conditions. An old study from 1978 found a striking correlation between hematocrit level and thrombosis in patients with polycythemia vera,[15] but this correlation was not confirmed in a recent study in which no such relation could be demonstrated.[16]

With respect to the association of venous thrombosis with hematocrit in the general population, data are scarce and inconclusive. Vaya *et al.* performed a case-control study in 109 patients with a first deep vein thrombosis, without thrombophilia, and 121 healthy controls. They reported that the percentage of cases with a hematocrit above 45% was higher in cases than in controls, i.e. 43% *versus* 27%. The association was attenuated when several other factors were included in a multivariate model.[17] In one other population-based study (the LITE study, a cohort study in subjects above 45 years of age), no relation between high hematocrit levels and risk of venous thrombosis was demonstrated, but the authors used a relatively low cut-off level for the hematocrit (43.5%).[18]

The strengths of the new study by Braekkan and colleagues are that it is large, prospective, and carried out in a general population with a high response rate, a long follow-up, and well-validated venous thrombotic events.[2] We may, therefore, assume that the link found between high hematocrit and risk of venous thrombosis is real, but again, the important issue is to decide whether or not the relation is causal or explained by other diseases.

Various studies into a causal association have been performed in patients with polycythemia vera, but as several complex mechanisms play a role in this disease, these studies should not be used as a model to extrapolate the relationship between high hematocrit and venous thrombosis in the general population. Otherwise, there are only a few experimental studies that have examined a direct effect of red blood cell mass on thrombotic mechanisms. The hypothesis that platelet activation plays a role has been tested in two *in vitro* studies by the same group of researchers; both studies suggest that red blood cells amplify platelet reactivity.[19,20] A direct relationship between levels of hematocrit and thrombin generation has only been described *in vitro*, in a small experimental study of blood samples from five participants. Hematocrit was artificially increased in these samples by centrifugation. It is questionable whether such artificially increased hematocrit levels reflect the complicated mechanism of

increased levels of hematocrit *in vivo*.[21]

Other arguments for a direct causal relation are more circumstantial or hypothetical: low hematocrit is associated with a risk of bleeding, which is corrected by transfusion;[22] increased viscosity of the blood may lead to increased exposure of platelets and coagulation factors to endothelium and, therefore, increased interaction and activation.

An alternative explanation for the relation between increased levels of hematocrit and the risk of venous thrombosis would be the presence of conditions or factors that increase in parallel, but independently, both hematocrit levels and the risk of venous thrombosis, such as smoking, lung disease, or heart disease. Considering that 37% of the cases with venous thrombosis in the study by Braekkan and colleagues were smokers at the time of the thrombosis, and that some medical condition was present in 22%, these factors can be expected to have influenced the results. To determine the effect of hematocrit levels independently of these factors, the data need to be adjusted for such confounders. The authors appropriately addressed this issue in their discussion, but they could not overcome the problem since data on medical conditions in the reference group were lacking. With respect to smoking, the authors were probably not able to fully remove the confounding effect, since smoking was rather roughly classified. So, unfortunately, this study does not exclude the possibility that the relationship that was found between high hematocrit levels and venous thrombosis could be explained by the presence of other conditions. This issue should, therefore, be the focus of studies in the future.

If the relationship is found to hold true in further research, more questions and challenges arise. Why is the association more pronounced in men than in women? What are the clinical consequences? Do we need to screen all patients with venous thrombosis for high hematocrit levels, or should we be aware of an increased risk of venous thrombosis in all subjects in whom we find a high hematocrit? And if we do so, what are the possibilities for treatment or prevention? Do high levels of hematocrit interact with other risk factors for venous thrombosis and, therefore, increase the risk of venous thrombosis even more? Could it indeed explain part of the link between arterial and venous thrombosis, as the authors suggest?

In conclusion, Brækkan and colleagues have performed an interesting, large-scale study into the relation between high levels of hematocrit and the risk of venous thrombosis. They convincingly demonstrated a dose-response relation between level of hematocrit and risk of venous thrombosis. However, questions remain on the causal interpretation and the clinical consequences of their results.

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