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Do Blood Constituents in Varicose Veins Differ From the Systemic Blood Constituents?

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WHAT THIS PAPER ADDS

This study is one of the first to compare blood constituents in varicose veins with systemic blood. In varicose veins there are increased levels of inflammatory markers, indicators of endothelial damage, and increased procoagulant activity. These findings support the assumption that the constitution of blood in varicose veins differs from that of systemic blood. This is the consequence of changes of blood flow and deterioration of hemodynamic forces, which could be involved in progression and complications of varicose veins.

Objective: Varicose veins represent one of the most frequent vascular diseases and are in most cases benign. However, advanced disease is frequently associated with complications such as chronic venous insufficiency and superficial vein thrombosis. The pathogenic mechanisms are not well understood. Besides increased venous pressure, it is suggested that local blood constituents trigger various mechanisms responsible for the progression of the disease and its complications.

Design: The aim of this study was to investigate the changes in the blood in varicose veins and to compare them with the systemic markers of inflammation and endothelial damage.

Materials and methods: Forty patients with primary varicose veins were included in the study. Most patients were class C2. Blood samples were taken from the leg from the tortuous and dilated varicose tributaries of the great saphenous vein and from the cubital vein.

Results: The values of basic hematologic tests were comparable between blood samples (varicose vs. systemic). In varicose veins, the following parameters were significantly increased in comparison with systemic blood: hsCRP (3.12 ± 2.18 mg/L vs. 2.04 ± 2.21 mg/L, $p = .04$), IL-6 (3.54 ± 2.59 pg/mL vs. 2.25 ± 1.27 pg/mL, $p = .008$), vWF ($118.4 \pm 27\%$ vs. $83.2 \pm 22\%$, $p < .05$). D-dimer, in samples taken from the leg varicose veins, was also significantly higher than in the systemic blood (104.3 ± 9.3 ng/mL vs. 89.5 ± 8.3 ng/mL, $p = .039$).

Conclusions: Some inflammatory markers and indicators of endothelial dysfunction are increased in varicose vein blood. This is most probably the consequence of deteriorated blood flow in dilated and tortuous superficial veins, and increased venous pressure. Damage to the venous wall, which causes a chronic inflammatory response, together with the procoagulant properties of local blood may promote further progression of the disease and thrombotic complications.

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INTRODUCTION

Varicose veins are dilated, tortuous, and elongated veins especially affecting the superficial veins of the lower limbs. The disease is one of the most frequent manifestations of vascular pathology.[1] In developed countries, the prevalence of chronic venous disease is about 40–60% in females and 15–30% in males,[2] and the annual incidence is 2.6% in women and 1.9% in men.[3] The prevalence of varicose veins varies from 2% to 56% in men and 1% to 60% in women.[4]

According to the etiology, primary and secondary forms should be distinguished, with the latter usually occurring as consequence of deep vein thrombosis. The exact cause of the primary varicosities is not yet completely understood, but various theories of primary varicose vein pathophysiology exist. As early as in the seventeenth century, Sir William Harvey postulated that varicose veins develop as a consequence of central valvular incompetence related to valve atrophy. This could cause venous hypertension, which

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damages the peripheral venous valves and results in the propagation of the disease.[5] This theory from the seventeenth century was later substituted with primary vein wall weakness theories, which state that varicose veins develop from an inherited defect in vein wall integrity. Varicose veins exhibit proliferation of collagen matrix with disruption and distortion of muscle fibers. Primary vein wall weakness can also lead to valvular incompetence and venous hypertension.[6] The data also indicate that deterioration of venous endothelial function could be involved in the pathogenesis of varicose veins, which is predominantly a consequence of decreased bioavailability of nitric oxide (NO).[7] Nitric oxide is an important cellular signaling molecule and a potent vasodilator, which inhibits platelet adherence and aggregation and reduces the adherence of leukocytes to the endothelium. It has also been shown to inhibit proliferation of vascular smooth muscle cells. Thus the deterioration of vessel wall homeostasis caused by decreased bioavailability of NO results in changes in vascular tone and platelet adhesion, and finally morphologic deterioration of the vascular wall.

Progression of deterioration of the venous wall and valves leads to various clinically significant complications, such as chronic venous insufficiency including venous ulcers, thrombophlebitis, and an impact on the deep venous system. In addition to turbulent blood flow in tortuous veins and venous hypertension, local blood changes in varicose veins including increased thrombotic potential and inflammation are most likely involved in the development of complications. Therefore, impaired venous drainage of the lower extremities determines a cascade of pathologic events leading to chronic venous insufficiency. One of the theories suggests that the venous hypertension causes red blood cell extravasation and local iron overload that could generate free radicals and iron dependent inflammation. One of the studies showed that iron deposits in varicose veins and tissue oxidative state measured by proton induced X-ray emission spectroscopy correlate with iron deposition, and this is related to oxidative stress, which could influence the progression of chronic venous disease.[8] However, the role of local changes in blood constituents in disease progression and development of complications in varicose veins has not been fully elucidated. Therefore, the aim of this study was to compare the levels of markers of inflammation and of coagulation/fibrinolysis in varicose veins with systemic levels (the blood taken from cubital veins).

PATIENTS AND METHODS

The study population consisted of 40 patients with primary varicose veins that were scheduled for outpatient sclerotherapy.

The clinical characteristics of the patients included in the study are presented in Table 1. Although patients of both sexes were recruited, there were only four males. Most patients had increased body mass index, and in most there was a family history of varicose veins. BMI $>$ 30 kg/m^2 defined obesity. Dyslipidemia was defined as total cholesterol $>$ 4.5 mmol/L, LDL cholesterol $>$ 4.5 mmol, LDL cholesterol $>$ 3.0 mmol/L, and /or triglycerides $>$ 2 mmol/L.

Table 1. Clinical characteristics and the presence of risk factors in 40 subjects with varicose veins.

Parameter	
Age, years	54.2 $\pm$ 11.3
Sex, male	4 (10%)
Arterial hypertension	16 (40%)
Mean systolic BP, mmHg	131.5 $\pm$ 12.7
Mean diastolic BP, mmHg	83.4 $\pm$ 7.6
BMI, kg/m^2	29.7 $\pm$ 4.6
Diabetes mellitus	4 (10%)
Positive family history	34 (85%)
Hyperlipidemia	8 (20%)
Smoking	15 (37.5%)

Data are expressed as mean $\pm$ standard deviation (SD) for continuous variables and as numbers (*N*) and percentages (%) for categorical variables.

The diagnosis of primary varicose veins was performed by clinical examination and bilateral venous duplex ultrasound scanning. Both the superficial and deep venous systems were examined.

Ultrasound examination of the deep veins was performed in patients lying in the supine position with head elevation of 15° to 30°. All examinations followed a standard protocol, both legs were scanned. Transverse and longitudinal imaging was done with a 10 MHz linear array probe (Vivid 7, GE Medical Systems). The leg was flexed at the knee and the hip was externally rotated to allow the best exposure of the junction of the common, deep, and superficial femoral veins as well as the popliteal fossa. The probe was held both transverse and perpendicular to the skin surface. The examination was started as proximally as possible, ideally at the inguinal ligament. The common femoral vein and artery were identified first, then the great saphenous vein emptying into the common femoral vein was scanned and the examination proceeded distally to the junction of the common femoral, superficial femoral, and deep femoral veins. Finally, the probe was placed in the popliteal fossa for visualization of the popliteal vein and artery and the proximal calf veins. Compressibility was assessed in the transverse plane, while the presence of venous flow and valvular reflux were measured in the longitudinal plane.

Investigation of the superficial venous system was performed in the standing position, because in this position veins become fully distended and the identification of reflux was most reliable. Different transducer positions were used with both longitudinal and transverse views. Examination started in the groin, where compressibility and reflux of sapheno-femoral junction and its tributaries and their reflux were registered. The diameter of the great saphenous vein in the thigh was measured, if reflux was present. Further, the course of the great and small saphenous veins from the knee to the ankle was examined by B mode scan of branches and perforating veins. Examination of the posterior tibial perforating vein and sapheno-popliteal junction compressibility, flow, and reflux were recorded.