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PHLEBOLYMPHOLOGY

Hugo Partsch

Dear Readers,

*In this new issue, **Christine Biron-Andréani** from Montpellier presents an excellent review on the clinically very important issue of the thromboembolic risk in the postpartum period. Based on recommendations from the Royal College of Obstetricians and Gynaecologists, categories of very high, high, and intermediate risk are defined and prenatal and postnatal prophylaxis with low-molecular-weight heparin is suggested to be given for a period of time that should be adjusted to the risk group.*

*An interesting overview on modern advancements in stent technologies including drug-eluting, biodegradable, and covered stents is presented by **Nabil Chakfé** and his group from Strasbourg, concentrating on stenting of superficial femoral arteries and iliac veins. The article not only discusses technical aspects, but also important questions of indications and outcome, and contains an updated reference list which will be helpful for those readers who are interested in obtaining more details.*

*Interesting first results from a Russian randomized multicenter study guided by **Vadim Bogachev**, Moscow, are presented which demonstrate, after endovenous procedures on varicose veins, improved VCSS and quality of life outcomes in the group taking 2 tablets of MPFF* 2 weeks before and 4 weeks after the procedure, compared with compression. This indication is certainly a model of considerable clinical relevance.*

*Superficial vein thrombosis is the "little sister" in the unfriendly family of venous thromboembolism. **Denis Clément** from Ghent summarizes in his contribution the evidence that this little sister is far less harmless than previously thought, and provides an excellent review about modern therapy. The cost-effectiveness discussion regarding routine therapy with fondaparinux is mentioned and—unlike in most other publications—suggestions are also made for the management of such patients after the acute event.*

Veins constitute important components of our complex vascular organ system and are not simply passive conduits serving blood transport. The vein wall comprises several tissues and owns its own richly developed microvascular system, including the vena venarum, *which can be the focus of thrombotic and inflammatory processes, a fact that has been ignored widely in clinical practice. The article written by **Stephan Nees**, Munich, and coworkers, containing some very informative illustrations, should not only arouse the curiosity of* Phlebolymphology *readers, but should also help them to understand that the vena venarum system plays an important role in the development of many forms of venous disease. Venous thrombotic events and the transition to a postthrombotic syndrome are good examples.*

Only in recent years has it become clear that the postcapillary venules in all organ systems play a key role in the induction of hemostatic reactions and in the genesis of inflammatory cell activities and edema. Only recently has attention been directed to the vessel wall and its interaction with inflammation, hypercoagulabity and immune responses. The article by Nees et al offers considerable new detail in this respect.

The second part of this presentation, to be published in the next issue of this journal, will concentrate on therapeutic consequences of these basic research results.

Enjoy reading this issue!

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Venous thromboembolic risk in postpartum

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ABSTRACT

In 2010, venous thromboembolism (VTE) was the third leading cause of mortality among pregnant women in France accounting for 0.95 deaths per 100 000 deliveries; one-third of the deaths were considered to be avoidable. The highest risk period is postpartum and the increased risk persists for 6 weeks postpartum. During this period, the risk of pulmonary embolism is higher than the risk of deep vein thrombosis. Risk factors differ in the antepartum and postpartum period, but both clinical and genetic risk factors are important for predicting VTE during pregnancy and postpartum. Recent data indicate that 50% of postpartum women had two or more risk factors and that interactions between these risk factors are important; obesity, in particular, warrants consideration. VTE risk assessment should therefore be performed and repeated in every pregnant woman. This has been highlighted in the guidelines of the Royal College of Obstetricians and Gynaecologists. With better identification of postpartum risk factors, health care providers may be able to reduce the rate of maternal deaths resulting from pulmonary embolism.

INTRODUCTION

Pregnant women have a four- to fivefold increased risk of symptomatic venous thromboembolism (VTE) compared with nonpregnant women, with an estimated incidence of one to two per 1000 pregnancies.[1-5]

In developed countries, pulmonary embolism remains one of the most common causes of maternal mortality: VTE accounts for 1.1 deaths per 100 000 deliveries.[6] In France, VTE is the third leading cause of mortality among pregnant women accounting for 0.95 deaths per 100 000 deliveries. In the 2010 *Bulletin Epidémiologique Français*, one-third of the deaths were considered avoidable. The prevalence and the severity of this condition warrants careful management including the identification of risk factors.

Epidemiologic research assessing potential VTE risk factors in pregnant women has some limitations, such as the grouping of antenatal and postnatal VTE, despite potential different levels of risk and different risk factors. The objective of this article is to review the literature focusing on postpartumVTE risk.

Keywords:
postpartum; venous thromboembolism

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INCIDENCE AND MORTALITY OF POSTPARTUM-ASSOCIATED VTE

Postpartum is the highest risk period

Historically, the last trimester and immediate postpartum were considered the highest risk periods for deep vein thrombosis (DVT) and pulmonary embolism (PE). However, more recent studies have shed further light on these data. Symptomatic VTE is estimated to occur antepartum (from conception to delivery or to 40 weeks) in 5 to 12 per 10000 pregnancies, with events equally distributed throughout all three trimesters.[7] Postpartum (6 weeks) VTE is estimated in 3 to 7 per 10000 deliveries.[8] Compared with age-matched, nonpregnant women, this translates into a per-day risk that is increased seven- to tenfold for antepartum VTE and 35-fold for postpartum VTE.[1,2] In a meta-analysis of 14 studies (1966-1998), the estimated relative distribution of 100 DVT events was 0.23 per day during pregnancy and 0.82 per day in the postpartum period.[7] More recently, Pomp *et al* reported a fivefold increased risk during pregnancy and a 60-fold increased risk during the first 3 months after delivery compared with nonpregnant women.[5]

What is the duration of the postpartum risk?

The prothrombotic changes associated with pregnancy do not revert completely to normal until several weeks after delivery. Clinical data suggest the persistence of an increased risk for up to 6 weeks postpartum with an odds ratio (OR) of 84 (95% CI, 31.7-222.6).[5] Most cases occurred during the first 4 weeks postpartum (95%): with 18%, 42%, 20%, and 15% in the first, second, third, and fourth weeks, respectively. The risk remained increased up to 3 months postpartum (OR, 8.9; 95% CI 1.7-48.1). After the third month, the OR was 0.3 (95% CI, 0.1-1.4). In a Norwegian study, most VTE occurred during the 6 week postpartum period (49.3%). The incidence then dropped rapidly to 1.8%.[3] In a study by Morris et al, rates approached background levels after the fourth week postpartum.[9]

Risk of pulmonary embolism higher than deep vein thrombosis in postpartum

In the case-control study of Pomp et al, the risk for both PE and DVT was increased, with a relative risk of 34.4 and 72.6, respectively.[5] In the meta-analysis by Ray et al, two-thirds of DVT events occurred antepartum,[7] while 43% to 60% of PE events occurred postpartum in two others studies.[8,10] More recently, Heit et al, using the Rochester registry, found that PE was relatively uncommon during pregnancy versus postpartum (10.6 vs 159.7 events per 100000 women-years).[2] In a hospital-based case control study and a registry-based case-control study, Jacobsen found PE more common after delivery (0.22 vs 0.006 per 1000 deliveries).[3,11] In a large Australian cohort, Morris et al reported similar results: PE was most frequent postpartum (61.3%) with a rate of 0.45 per 1000 births.[9]

WHAT ARE THE RISK FACTORS FOR VTE POSTPARTUM? HOW SHOULD THEY BE MANAGED?

Factors previously reported to increase the risk of postnatal VTE include age >35 years, operative delivery, blood group A, hypertension, and postpartum bleeding.[8] More recent data have confirmed and extended our

Risk factor	Adjusted odds ratio (aOR) (95% CI)
Postpartum	
Non-emergency caesarean delivery	1.3 (0.7-2.2)
Emergency caesarean delivery	2.7 (1.8-4.1)
Postpartum infection	
- after vaginal delivery	20.2 (6.4-63.5)
- after caesarean delivery	6.2 (2.4-16.2)
Immobilization	
- BMI < 25 kg/m^2	10.8 (4.0-28.8)
- BMI < 25 kg/m^2	40.1 (8.0-201.5)
Postpartum bleeding	4.1 (2.3-7.3)
Postpartum bleeding with surgery	12.0 (3.9-36.9)
Fetal growth restriction (< 2.5 percentile)	3.8 (1.4-10.2)
Preeclampsia	3.1 (1.8-5.3)
Pre-pregnancy BMI > 25 kg/m^2	2.4 (1.7-3.3)
Smoking (10-30 cigarettes per day)	3.4 (2.0-5.5)
Smoking (5-9 cigarettes per day)	2.0 (1.1-3.7)
Antepartum	
Immobilization	
- BMI < 25 kg/m^2	7.7 (3.2-19.0)
- BMI < 25 kg/m^2	62.3 (11.5-337)
Weight gain < 7 kg	1.7 (1.1-2.6)
Pre-pregnancy BMI > 25 kg/m^2	1.8 (1.3-2.4)
Smoking (10-30 cigarettes per day)	2.1 (1.3-3.4)
Spontaneous twins	2.6 (1.1-6.2)
Assisted reproductive technology	4.3 (2.0-9.4)

Table I. *Risk factors for ante- and postpartum venous thromboembolism (VTE)[11]*
Abbreviations: BMI, body mass index; CI, confidence interval

knowledge of VTE risk factors during this period. In an Australian registry, stillbirth (aOR 5.97), lupus (aOR 8.83), and transfusion (aOR 8.84) were most strongly associated with PE in postpartum.[9] Age ≥ 40 years (aOR 1.67), parity ≥3 (aOR 1.49), pregnancy hypertension (aOR 2.06), and preterm livebirth (aOR 2.18) were also associated.[9]

A large, well-conducted Norwegian case-control study compared 559 women with pregnancy-associated VTE with 1229 controls. The study used the same group of cases as reported in a previous population-based registry study,[3] but a different control group to allow investigation of other risk factors. The authors reported a number of new complex risk factors and different ante- and postpartum risk factors *(Table I)*.[11] Of particular interest was the fact that 50% of postpartum women had two or more risk factors and 50% had no or only one risk factor.

Previous VTE

The most important individual risk factor for VTE is a personal history of thrombosis,[6] particularly when unprovoked or associated with oral contraceptive use or VTE in pregnancy. Few studies have analysed separately the ante- and postpartum periods. Two large retrospective cohorts reported a very high risk of recurrence during the postpartum period.[12,13] Pabinger et al found that 4 of 65 women (6.1%) who had not received thromboprophylaxis experienced VTE compared with 5 of 73 women (6.9%) who had received prophylaxis.[13] In a cohort of 88 women with a previous episode of VTE who became pregnant at least once without receiving antithrombotic prophylaxis, 120 puerperium periods without prophylaxis were recorded with a postpartum VTE recurrence rate of 8.3%.[12]

All published guidelines, including American, British, Australian, and French are in favor of thromboprophylaxis, usually for 6 weeks postpartum in case of previous VTE, regardless of the mode of delivery.

Hereditary thrombophilia

Thrombophilia is present in 20% to 50% of women who experience VTE during pregnancy.[14] Patients are generally categorized into the following groups: pregnant women with thrombophilia and previous VTE, and pregnant women with thrombophilia, no previous VTE but a family history of VTE. More recently, a new category has been introduced of pregnant women with thrombophilia, no previous VTE and no family history. Again, few studies have analyzed the ante- and postpartum periods separately.

Pregnant women with thombophilia and previous VTE

Data regarding thrombophilia and the risk of recurrent VTE specifically during postpartum are inconsistent. De Stefano et al found that inherited thrombophilia, mainly factor V Leiden (FVL) and prothrombin gene G20210A factor II (FII) polymorphisms, was not associated with a statistically significant increased risk.[12] As previously discussed, guidelines recommend that all women with a previous VTE event receive postpartum thromboprophylaxis whether or not they have thrombophilia.

Pregnant women with thrombophilia, no previous VTE with or without a family history of VTE

The risk associated with thrombophilic defects varies considerably both between defects and also between studies, probably reflecting differences in methodology (*Table II*). However, there is consensus that heterozygous FVL or FII polymorphisms are weakly thrombophilic and antithrombin (AT) deficiency (type I) is strongly thrombophilic.

Thrombophilia was not considered in the Norwegian study nor in the Australian registry.[9,11] However, recently Jacobsen et al published a specific case-control study on the risk of venous thrombosis among carriers of FVL and FII.[15] Among 559 women with a first VTE during pregnancy or within 14 weeks postpartum, and

Thrombophilic defect	Pregnancy	Antepartum	Postpartum
AT, PC or PS deficiency	4.1 (1.7-8.3)	1.2 (0.3-4.2)	3.0 (1.3-6.7)
AT type I	15-50 (range)	0-40	11-28
FVL heterozygous	2.1 (0.7-4.9)	0.4 (0.1-2.4)	1.7 (0.7-4.3)
FII heterozygous	2.3 (0.8-5.3)	0.5 (0.1-2.6)	1.9 (0.7-4.7)
FVL homozygous or compound heterozygous	1.8-15.8 (range)	0-5	1-10

Table II. *Estimated absolute risk of pregnancy-associated venous thromboembolism in different thrombophilic defects in women with a first degree family history. Abbreviations: AT, antithrombin; FII, prothrombin gene G 20210 A; FVL, factor V Leiden; PC, protein C; PS, protein S.*

1229 controls, 313 cases and 353 controls could be investigated for thrombophilia screening. The ORs for FVL and FII were 4.2 (95% CI, 2.4-7.4) and 10.2 (95% CI 2.1-49.8), respectively. The authors estimated that pregnancy-associated VTE occurred in 1.1/1000 non-carriers, 5.4/1000 FVL heterozygotes, and 9.4/1000 FII heterozygotes. The number of pregnant women to be screened and the number needed to be provided with prophylaxis was 2015 and 157, respectively, for FVL and FII. Heit et al also estimated that the absolute risk is very low arguing against prophylaxis in the absence of a personal or family history of VTE and weak thrombophilia.[2] However, when a positive family history is present, the absolute risk is higher with an incidence of 2% to 3%, two-thirds in postpartum.[16] In a multicenter family study, Martinelli et al found no VTE during pregnancy, whereas in the postpartum period VTE occurred in 1.8% 1.5%, 1% and 0.4% in double carriers, FVL, FII, and noncarriers, respectively.[17] In the European Prospective Cohort on Thrombophilia (EPCOT), the highest incidence was associated with AT deficiency or combined defects and the lowest incidence with FVL.[18] In a retrospective family cohort study with AT, protein C (PC) or protein S (PS) deficiencies, the frequency of pregnancy-associated VTE was 7% (12/162), two thirds in postpartum (8/12); five cases were in AT-deficient women.[19] In a review, the estimated incidence of a first VTE in carriers of various thrombophilic defects in postpartum was 3% (1.3-6.7) for AT, PC, or PS deficiencies, 1.7% (0.7%-4.3%) for FVL, and 1.9% (0.7%-4.7%) for FII.[16] Individuals with AT deficiency have historically been regarded to be at very high risk of thrombosis, particularly during pregnancy.[16]

Management and guidelines

While all guidelines recommend 6 weeks postpartum prophylaxis in pregnant women at high risk of VTE, there is debate as to the optimal duration of prophylaxis in women considered at intermediate risk of VTE. As clinical data suggest that the highest risk lies in the first week postpartum, a minimum of 7 days thromboprophylaxis is usually recommended; the duration can be extended to 6 weeks depending on the number of concomitant risk factors. The Royal College of Obstetricians and Gynecologists (RCOG) guidelines for thromboprophylaxis is presented in *Table III and Figure 1*.[20] In this guideline, asymptomatic weak thrombophilia is managed with 7 days of thromboprophylaxis in the absence of other risk factors, or 6 weeks of thromboprophylaxis if a family history or other risk factors are present.

The 9th American College of Chest Physicians (ACCP) guidelines suggest postpartum clinical surveillance rather than pharmacologic prophylaxis (grade 2C) for FVL or FII heterozygous pregnant women without a family or personal history.[21] The Practice Bulletin of the American College of Obstetricians and Gynecologists has similar recommendations.[22] Lussana et al in the Italian recommendations suggest clinical surveillance in women at low risk, including those with any thrombophilia without previous VTE and without a positive family history of VTE.[23]

Risk	History	Prophylaxis
Very high	Previous VTE on long-term warfarin Antithrombin deficiency Antiphospholipid syndrome with previous VTE	*Recommend* antenatal high dose LMWH and at least 6 weeks postnatal LMWH
High	Previous recurrent, estrogen-provoked (pill or pregnancy) or unprovoked VTE Previous VTE + thrombophilia Previous VTE + family history Asymptomatic thrombophilia (combined defects, homozygous FVL)	*Recommend* antenatal and at least 6 weeks postnatal prophylactic LMWH
Intermediate	Single previous VTE associated with transient risk factor no longer present without thrombophilia, family history or other risk factors Asymptomatic thrombophilia (except antithrombin, combined defects, homozygous FVL)	*Consider* antenatal LMWH (but not routinely recommended) *Recommend* 6 weeks postnatal prophylactic LMWH *Recommend* 7 days (or 6 weeks if family history or other risk factors) postnatal prophylactic LMWH

Table III. *Guidelines for thromboprophylaxis in women with previous VTE and/or thrombophilia from the Royal College of Obstetricians and Gynecologists*[20]
Abbreviations: FVL, Factor V Leiden; LMWH, low molecular weight heparin; VTE, venous thromboembolism.

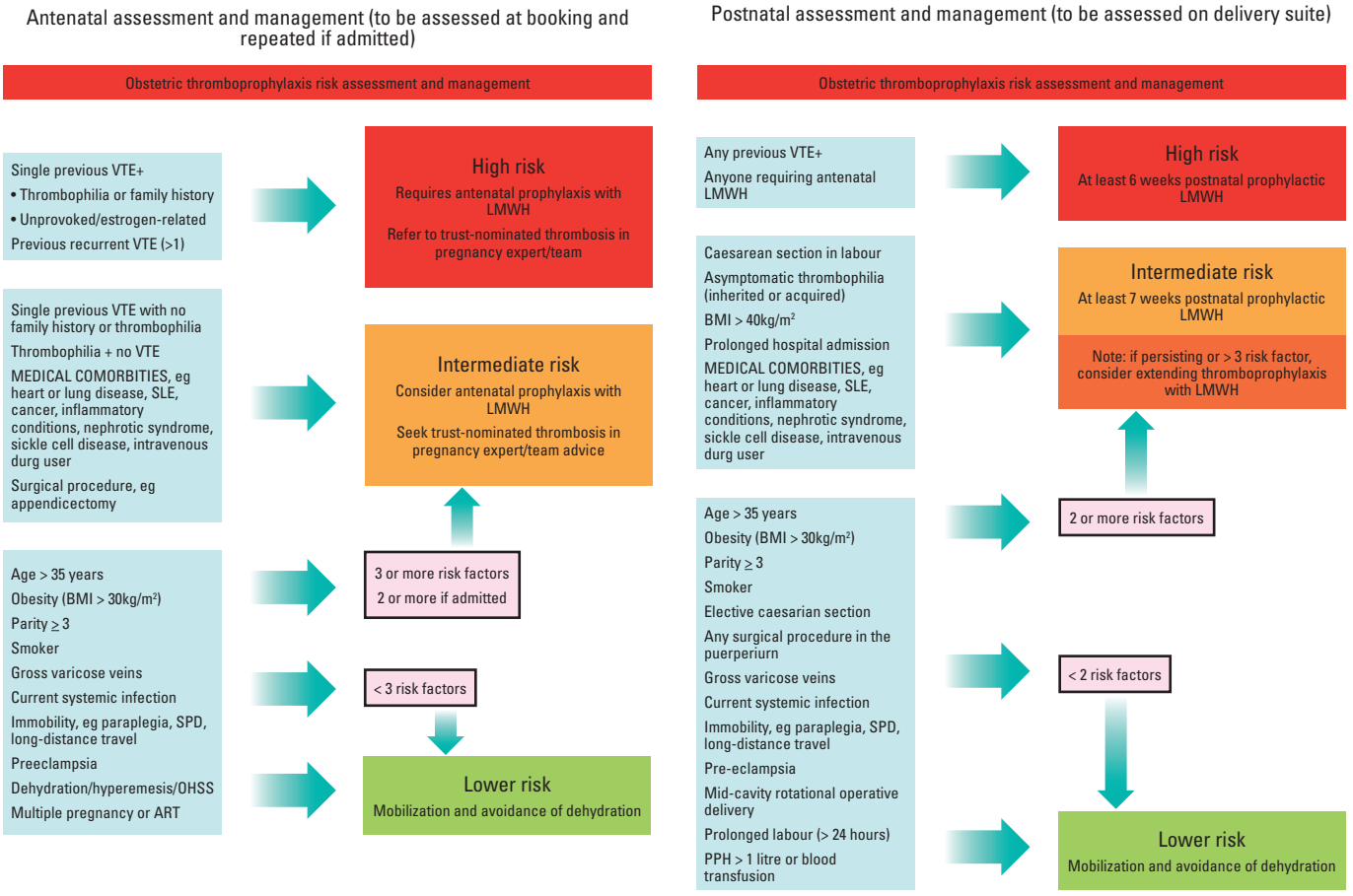

Figure 1. *Obstetric thromboprophylaxis risk assessment and management from the Green-top Guidelines No. 37a, 2009, Royal College of Obstetricians and Gynecologists*[20]

Several studies have reported that usual prophylactic dosage regimens are not fully effective during the postpartum period.[13] How to identify these women at higher risk remains a challenge.

Can we identify new biological risk factors?

Established family risk factors cannot be detected in many families with a clustering of VTE. Individuals who have a first-degree relative with a history of VTE are at increased risk of VTE almost independent of known heritable risk factors, which suggests that there are unknown genetic risk factors.[24] Recently, genome-wide association studies on VTE have been published.[25] This approach has been used to investigate genetic causes of pregnancy-related VTE. Using the Norwegian hospital case-control study,[26] Dahm et al found new associations between single nucleotide polymorphisms (SNPs): seventeen SNPs were found to be associated, and one SNP belonging to the gene encoding P-selectin was associated with postpartum VTE. These results need to be confirmed in further studies.

Antiphospholipid syndrome (APS)

Antiphospholipid syndrome is defined by venous or arterial thrombosis and/or specific pregnancy complications with persistently positive tests for antiphospholipid antibodies. It is common for such women to be on long-term anticoagulation after a first thrombotic event because of an increased risk of recurrence. These women receive antenatal therapeutic doses of low molecular weight heparin (LMWH) (those on warfarin convert to LMWH before 6 weeks of pregnancy) until after delivery and then switch back to oral anticoagulants. However, the optimal management of such women for the prevention of recurrent thrombosis is difficult as there is a lack of trials of women with APS during pregnancy and prior thrombosis. In the Bauersachs et al study of 28 women, two thrombotic events occurred postpartum despite treatment, highlighting the very increased risk.[27] These women require close management with collaboration between different experts including a haematologist.

Women not on anticoagulants should start LMWH as soon as possible in the first trimester, which should be continued for at least 6 weeks after delivery. Recently, the first report of the European Registry on Obstetric Antiphopsholipid Syndrome (EUROAPS) was published.[28] In the presence of antiphospholipid antibodies alone, without APS, RCOG suggests LMWH for 7 days postpartum.

Caesarean delivery

The association between caesarean delivery and VTE was previously confounded by many independent VTE risk factors. In the Australian registry, caesarean section carried an increased risk regardless of whether it was performed in the presence (aOR 3.7) or absence (aOR 3.11) of labor after adjustment.[9] The point estimate risk for caesarean section during labor was higher than without labor, but this could have been due to chance (*P*=0.46). In the Norwegian study, uncomplicated caesarean delivery was not associated with an increased risk after adjustment for complications.[11] On the other hand, postpartum infection after vaginal delivery remained a stronger risk factor than postoperative infection after any type of caesarean section.

High body mass index / immobilization

Antepartum immobilization, defined as strict bed rest for at least 1 week, was the strongest risk factor for both ante- and postpartum VTE in the Jacobsen study.[11] The importance of immobilization as a risk factor for VTE has been poorly investigated during pregnancy. The effect of immobilization is modified by body mass index (BMI), which has a multiplicative effect with an aOR of 40.1 (immobilization and BMI >25kg/m^2). Obesity is a well known risk factor for VTE both in the general population and during pregnancy[11] and warrants particular consideration because of its increasing prevalence.

Smoking

Most studies have not found a significant association with smoking. However, Jacobsen et al reported an association of smoking with ante- and postpartum VTE (5-9 and 10-30 cigarettes/day prior or during pregnancy).[11]

CONCLUSION

Postpartum is the highest risk period for VTE. There are differences in antepartum and postpartum risk factors and both clinical and genetic risk factors are important for predicting VTE during pregnancy and postpartum. Recent data have shown that it is important to systematically assess individual VTE risk, taking into account all risk factors, both antenatal and postnatal. VTE risk assessment should be performed and repeated in every pregnant woman. By improving identification of postpartum risk factors, health care providers may be able to reduce the rate of maternal deaths resulting from PE.

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Advances in stent technology for femoral artery lesions and use of stents for venous pathology

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ABSTRACT

Endovascular surgery with femoral superficial artery stent implantation was first conducted over 20 years ago. However, the first experiments with steel stents were relatively disappointing. A notable advance was the development of nitinol stents, which led to an initial improvement in clinical outcomes, but a relatively high rate of fractures. A better understanding of the biomechanics of the superficial femoral artery and technological developments have led to a second generation of nitinol stents with improved flexibility, and thereby fewer fractures. The phenomenon of restenosis related to neointimal hyperplasia has also led to the development of new concepts in stents including: drug-eluting, biodegradable, and covered stents. These technologies are of use for treating the more complex lesions of the superficial femoral artery, but also extend the endovascular indications of stents to venous pathology, such as vein compression syndrome in the upper or lower deep veins with deep vein thrombosis, and postthrombotic syndrome of the lower legs.

INTRODUCTION

Peripheral arterial disease is a manifestation of systemic atherosclerosis and its prevalence increases with age. Remarkable technological advances in the past decade, along with patient preference, have shifted revascularization strategies from traditional open surgical approaches toward lower morbidity percutaneous endovascular treatments.[1,2] Although the superficial femoral artery (SFA) is the artery most commonly affected by atherosclerosis, it has nevertheless many particularities compared with other arteries in the human body. Indeed, the SFA is the longest artery in the human body, and has two major points of flexion: hip and knee. During movement, the SFA is exposed to various stresses,[3] which is a major reason for the high restenosis rate observed after angioplasty, with or without stenting.[4] Better knowledge of the biomechanics of the SFA and technological developments have led to the introduction of new stents, with better results. These arterial endovascular techniques have also been applied to extrinsic compression of the deep veins, as well as for postthrombotic syndrome.

Keywords:
deep vein thrombosis; iliac vein compression syndrome; Paget Schroetter syndrome; postthrombotic syndrome; stent

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STENT EVOLUTION FOR SUPERFICIAL FEMORAL ARTERY LESIONS

The first stent was developed by Hans Wallsten, a Swedish engineer, in Lausanne. It consisted of a self-expandable intravascular coil, first of metal wires, which were subsequently covered with a polyester fabric. The stent could be bare or covered with a silicone or polyurethane lining. Deployment tools were also designed and manufactured to allow percutaneous introduction and correct coil deployment. The first results were quite satisfactory: easy to implant in large vessels; perfect stability of the coil when deployed in the ascending aorta without major histological changes in the aortic wall; and progressive growth of the endothelial cell lining from both extremities, covering progressively the whole metallic or polyester mesh. After a year of extensive animal studies, the device became known as a stent rather than a coil, and clinical trials were carried out. Extravascular applications were also started in urology and the gastrointestinal tract with promising results, but the real market of stents was atherosclerotic vessels. At this time, the main issues with stents appeared in small vessels, as a result of acute occlusion of the vessel by early thrombosis on the foreign material, and late progressive narrowing of lumen size by in-stent tissue in-growth. The first studies with the Wallstent™ showed re-occlusion rates of up to 70% at 3 years in the SFA,[5] and stenting indications were limited to residual stenosis or dissection.[6,7]

A major advance occurred with the introduction of nitinol stents. Nitinol is an alloy of nickel and titanium, with two essential properties: shape memory, and elasticity.[8,9] The SIROCCO study compared a rapamycin-coated stent with a bare nitinol stent to combat in-stent restenosis in the SFA.[10] The study demonstrated good efficacy of the uncoated stent in the control group, with comparable patency rates between groups. The SIROCCO II study also showed for the first time acceptable levels of in-stent restenosis with rates of 17.9% in the nitinol group, and 20.7% in the rapamycin-coated-stent group, a non-significant difference[11]. Since this accidental discovery, industry and the scientific community have heavily invested in the development of nitinol stents, and obtained acceptable patency rates: 75% and 66% for 1-year and 3-year primary patency, respectively, for stenosis, and 73% and 64% for 1-year and 3-year primary patency, respectively, for occlusion[4]. The first generation of nitinol stents presented a relatively high fracture rate, around 24% in SIROCCO II, leading to the development of a second generation of nitinol stents. The newer generation of nitinol stents demonstrated greater flexibility with lower fracture rates, and were produced in lengths of up to 20 cm. They not only improved outcomes compared with angioplasty alone, but could also treat longer and greater numbers of lesions, particularly in the context of critical limb ischemia.[12]

Drug-eluting stents were developed to prevent in-stent restenosis. Restenosis is mainly due to neointimal proliferation of smooth muscle cells. The use of various pharmacological methods to inhibit the proliferation of smooth muscle cells led to the concept of drug-eluting stent, which not only keep the artery open, but also act as a pharmacological platform. The stent is capable of delivering a pharmacological agent in situ, in contact with the arterial wall, and thus inhibiting restenosis at the initiation of the process. Drug-eluting stents combine three components: the pharmacological agent, the drug delivery system (usually a polymer), and the bare metal stent. Major meta-analyses of randomized controlled trials from interventional cardiology have shown that the use of drug-eluting stents for coronary artery disease has resulted in decreased in-stent restenosis and reintervention rates compared with bare metal stents.[13-15]

While the use of drug-eluting stents is well known in coronary pathology, it may be more complex in lower limb arteries. Indeed, peripheral lesions are often longer and more calcified than coronary lesions, and the biological response of peripheral arteries to the endovascular treatment appears to be different from coronary arteries. The SIROCCO investigators provided objective evidence of the safety and efficacy of drug-eluting stents in patients with critical limb ischemia, but without a significant difference in terms of restenosis between drug-eluting stents and bare stents.[10-11] The STRIDES trial (Superficial femoral artery TReatment with Drug-Eluting Stents)[16] was a propective, non-randomized, single-arm, multicenter controlled trial designed to evaluate the safety and performance of an everolimus-eluting self-expandable stent, in above-knee femoropopliteal de novo or restenotic lesions up to 17 cm in length. The primary end point was in-stent restenosis in the superficial femoral artery at 6 months. Secondary end points included angiographic measurements of the change in vessel lumen diameter between time of stent placement and 12 months, restenosis at 12 months, as

well as 5 years of clinical follow-up to track resolution of peripheral arterial disease symptoms, limb salvage, and patient survival. One hundred and four patients were enrolled in 11 European investigative centers. The patients had severe peripheral vascular disease with a mean lesion length of 9 ± 4.3 cm. Ninety-nine percent of patients were available for 12-month follow-up, including duplex imaging in 90% and angiography in 83%. Clinical improvement was achieved in 80% of patients. Primary patency (freedom from ≥ 50% in-stent restenosis) was 94% at 6 months, and 68% at 12 months. Radiographic examination of 122 implanted devices at 12 months revealed no evidence of stent fracture. The authors concluded that the everolimus-eluting self-expanding nitinol stent could be safely and successfully implanted in patients with severe peripheral arterial disease, with favorable outcomes and clinical improvements observed in the majority of patients. Neointimal hyperplasia appeared to be inhibited and patency enhanced during the first 6 months. The effect was not sustained, however, as primary patency decreased to 68% by 12 months. Further improvements in the performance of drug-eluting stents will require the development of nonthrombogenic absorbable polymeric coating matrices with suitable degradation profiles, and a low inflammatory tissue response during polymer degradation to allow for a quick and complete stent endothelialization.

Another notable development was the evolution of bioabsorbable stents. The history of absorbable stents dates back to the mid-1980s. Since then, a number of international research groups have evaluated absorbable stent designs, but most have only reached preclinical evaluation. Interest in the development of biodegradable stents is based on the idea of decreasing in-stent restenosis by limiting the time of implantation of a metallic material, foreign to the arterial wall.[17] Although current highly successful stent technology is based on permanent metallic stent platforms, there is clinical consensus that stents are only required during the vascular healing period after stent implantation. Unlike permanent bare-metal stents and drug-eluting stents, which are both associated with long-term constrictive vascular remodeling, absorbable stents could be completely replaced by tissue, and may even allow positive vascular remodeling. Unlike permanent stents, a further advantage of absorbable stents is that they will not interfere with advanced imaging techniques (magnetic resonance imaging compatibility) and vascular surgery. However, the fact that absorbable stents cannot yet be found in clinical practice, and clinical testing is limited, is largely because of the inferior mechanical properties of degradable polymers compared with permanent metallic stent materials. Two main types of biodegradable stents are currently available: metal and polymer. As a result of their thickness and lack of radial force, biodegradable polymer stents are not good candidates for peripheral arterial disease. In fact, clinical experience with absorbable vascular stents is very limited and is insufficient to assess the efficacy and the safety of biodegradable stents in peripheral arterial disease. Major technical improvements will be necessary before biodegradable stents can be used with acceptable results.[18,19]

Covered stents were first used to treat vascular perforations, and to exclude aneurysms, but have subsequently been used for the prevention of in-stent restenosis. The aim is to prevent the vascular wall cells responsible for restenosis from proliferating through the mesh of the stent by covering the stent with a membrane.[17] The first results obtained with polyethylene-terephthalate-covered stents were not very encouraging. Other results with polytetrafluoroethylene-covered stents were more satisfactory. The theoretical benefit of the expanded polytetrafluoroethylene-covered nitinol stent graft is that in-growth of tissue between the stent struts, which plagues SFA stents, is prevented. However, edge restenosis may not be avoided, and concerns about stent thrombosis must be addressed. A randomized prospective study evaluated 100 limbs in 86 patients with peripheral arterial disease due to stenosis or occlusion of the SFA.[20] These patients had been treated by prosthetic femoropopliteal bypass or angioplasty with insertion of a polyethylene-terephthalate-covered stent. The stent graft group demonstrated a primary patency of 72%, 63%, 63%, and 59% with a secondary patency of 83%, 74%, 74%, and 74% at 12, 24, 36, and 48 months, respectively. No difference was found between groups. The contoured edge heparin bond Viabahn™ endoprosthesis has been compared with nitinol stent placement in TASC II C and D femoro-popliteal lesions. Despite significant early failures, Viabahn™ endoprosthesis treatment may be durable in patients who do not have early failure, and Viabahn™ stent-graft assisted subintimal recanalization is an acceptable alternative to vein bypass in selected patients with severe SFA disease.[21,22] However, potential disadvantages of using self-expanding endoprostheses

include the sheath size needed for these large-caliber systems (≥ 7 or 8 Fr), the occlusion of side branches, a nonspecific systemic vascular wall reaction, and their high cost. Due to the relatively low radial force of the endoprostheses, particularly when used in recurrent stenoses and occlusions, it is important to create an adequate lumen to allow the prosthesis to be introduced and expanded. However, Viabahn™ endoprostheses up to 25 cm long are available in Europe and just recently the device diameter has been downsized to 6 Fr for 5 mm and 6 mm endoprostheses.

USE OF STENTS FOR VENOUS PATHOLOGY

Iliac vein compression syndrome is the symptomatic compression of the left common iliac vein between the right common iliac artery and the vertebrae.[23] This compression may cause left lower extremity deep vein thrombosis or chronic symptoms of venous hypertension without thrombosis such as edema, leg heaviness, varicose veins, skin pigmentation, and ulceration. Iliocaval obstructive disease was traditionally treated by surgical techniques that could be very invasive. Unlike obstructive arterial lesions, where endovascular procedures are now part of routine therapy, stenosis or occlusions of large caliber veins are not currently treated by endovascular surgery. The poor performance of many surgical techniques for the treatment of iliocaval obstructive disease led to a disinterest in surgery for the treatment of these lesions that prevailed until 2000. More recently, endovascular techniques have transformed the treatment of both acute and chronic iliocaval obstructive lesions. Balloon dilation alone or completed by stenting of the venous stenosis is used in the treatment of acute thrombosis in addition to iliac thrombolytic treatment or surgical thrombectomy. Stents are also now used in the treatment of primitive (Cockett or May-Thurner syndrome) or secondary (post-thrombotic) iliac stenosis or occlusion.[24,25] Apart from neoplasic obstructions, endovascular treatment for iliac vein compression syndrome has become, in little more than 10 years, the technique of choice and represents a new and minimally invasive way to treat occlusive iliocaval lesions.

Venous endovascular surgery requires the use of guide wires. In patients with acute deep vein thrombosis (<15 days), a venous thrombectomy combined with the creation of an arteriovenous fistula can provide good immediate and long-term results.[26] However, when thrombolysis is induced via multiperforated catheters, residual stenosis lesions are frequent and are a cause of early rethrombosis. Mickley et al showed that residual stenosis led to rethrombosis in 73% of cases, while only in 13% after stenting.[27] Rates of primary and secondary patency in the long term (60 months) were 72% and 88%, respectively. Thus, angioplasty combined with stenting should be systematically performed during a venous thrombectomy in all patients with obstructive lesions.

Chronic lesions have a considerable impact on patients' quality of life and are very disabling. Medical treatment, mainly venous elastic restraint, is not always sufficient to enable patients to lead normal lives. Several teams have reported good results with patency rates of stented segments of around 90% at 24 months. Raju et al presented results for 304 limbs with iliac vein compression syndrome and reported a stent patency rate at 24 months of 90%.[28] The median degree of swelling and pain were significantly reduced, and the ulcer healing rate was 62%. Hartung et al reported similar mid-term results after endovascular treatment.[29] The stent patency rate at 36 months was 90%, and thrombotic occlusion occurred in 5% of limbs. Stents for stenosis of the left iliac vein can therefore enhance treatment of long-term chronic swelling and ulcers of the lower extremities, but can also prevent recurrence of secondary complications.[30] In fact, iliac vein stent placement is a safe and effective method for improving the patient's quality of life. The choice of the stent and its positioning are crucial. Stents must be self-expanding, because of the crushing risk of balloon expandable stents. Iliac stents must be at least 60 mm long and 16 mm in diameter in order to extend past both sides of the lesion and to prevent their migration. Raju et al showed that stents should be placed across the iliocava confluence and that this positioning does not induce a risk of right common iliac vein thrombosis. Compared with the experience of placing stents in other areas, such as the femoral artery and subclavian vein, the long-term patency of an iliac vein stent is considerably higher. Possible reasons are the relatively immobile position of the pelvic stents compared with the freely mobile femoral artery or subclavian vein, as well as the lack of compression, contraction, torsion and flexion from bony structures or muscular motion. In addition, the length of the stenosis is much shorter than in a femoral artery, which is associated with arteriosclerosis.

Upper extremity deep vein thrombosis occurs frequently and can cause considerable morbidity, including pulmonary embolism in one-third of cases.[31] Thrombosis is most often observed in the axillary or subclavian veins. Primary deep vein thrombosis is rare, and is known as effort thrombosis (Paget-Schroetter syndrome) or idiopathic thrombosis. Idiopathic thrombosis may by suggestive of cancer (lung cancer or lymphoma). The prevalence of hypercoagulability in these patients is variable, but other risk factors such as a personal or family history of deep vein thrombosis should be sought. Secondary deep vein thrombosis is more frequent and mostly observed in patients with a central catheter, pacemaker, or cancer. Axillary or subclavian vein thrombosis may be asymptomatic, but patients may complain of discomfort in the shoulder or neck, swelling of the arm, dizziness or dyspnea in case of obstruction of the superior vena cava.

The traditional method of treating malignant central venous obstruction is radiotherapy and chemotherapy, which is effective in 90% of cases; surgery is rarely indicated. A clinical response to chemotherapy and radiotherapy is seen after one week, but there is a 20% recurrence rate, even after the use of the total permissible dose of radiation. The high recurrence rate is due to progression of disease, postradiation fibrosis, or complicating thrombosis. Due to the relatively long latent period between medical treatment and clinical response and the high rate of recurrence, endovascular management with venous stenting should be initiated early and may be considered a firstline intervention. Balloon veinoplasty with stent placement provides nearly instantaneous symptomatic relief with a low risk of side effects and high long-term patency. Nagata et al reported primary and secondary patency rates of 88% and 95%, respectively, for malignant superior vena cava syndrome.[32] Stenting of benign stenosis or obstruction is undertaken less frequently than stenting in the setting of malignancy, although the number of cases is increasing. Obstruction in the setting of catheter-related stenosis or chronic thrombosis may be improved or relieved by removal of the catheter, but this may not be an option in patients with tenuous venous access or catheter dependence. Balloon angioplasty is the mainstay of treatment, and stent placement is reserved for patients in whom angioplasty has failed due to elastic recoil or restenosis of the vessel. Benign obstructions are frequently difficult to treat successfully with venoplasty alone and may require multiple reinterventions and eventual stent placement to maintain venous patency. Studies have shown a 24-month primary patency of about 90%, with a 16% reintervention rate.[33-35] Data for upper extremity deep vein stenting are lacking.

CONCLUSION

The advent of new stent technology, with its potential to overcome in-stent restenosis as the major limitation of conventional bare metal stents, has had a very large influence on clinical practice in vascular intervention. However, initial enthusiasm about drug-eluting stents has been replaced by discussion about their risks in terms of incomplete endothelialization, as well as hypersensitivity reactions to the polymer coating. Clinically, these potential complications following drug-eluting stent implantation are observed as subacute or late stent thrombosis. Whether or not thrombosis is more frequent with drug-eluting stents than with bare metal stents is still the subject of scientific debate. However, it is clear that there is a great demand for improved and possibly degradable drug-eluting stent coatings with higher biocompatibility and improved pharmacological action compared with first generation drug-eluting stents. Novel approaches currently being pursued encompass the use of polymer-free or biocompatible, absorbable, polymeric, drug-eluting stent coatings together with the promotion of vascular healing by the application of alternative active agents. Ultimately, fully absorbable stents or absorbable drug-eluting stents based on degradable polymers may replace permanent stents due to their inherent advantages over permanent implants, and their options for bulk incorporation of drugs. Although the feasibility of absorbable polymer stents has already been established, important issues, such as long-term fatigue resistance and absorption behavior until complete disappearance, will have to be addressed in future studies before they enter routine clinical use. Endovascular treatment of peripheral arterial disease continues to evolve, with expectations of improvements in safety and long-term durability with newer technologies ranging from local drug delivery to bioabsorbable stents. Percutaneous procedures will continue to replace open surgery as well as venous open surgery, especially for iliac vein compression syndrome.

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Can Micronized Purified Flavonoid Fraction* (MPFF) improve outcomes of lower extremity varicose vein endovenous treatment? First results from the DECISION study

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ABSTRACT

Aim: To evaluate whether the addition of Micronized Purified Flavonoid Fraction (MPFF*) to patients undergoing endovenous treatment (EVT) for varicose veins of the lower extremities improves postoperative symptoms and signs of chronic venous disease (CVD) and patient quality of life (QOL).

Methods. A total of 230 patients with CVD CEAP class C2-4sEpAsPr and with at least three CVD-related symptoms were randomly assigned to either the MPFF group (n=126) or the control group (n=104). Patients in the MPFF group received MPFF tablets, 1000 mg daily for 2 weeks before and 4 weeks after EVT. Patients in the control group received standard compression therapy. Venous Clinical Severity Scoring (VCSS) was used to assess postprocedural outcomes and the 14-item ChronIc Venous dIsease QOL Questionnaire (CIVIQ-14) was used pre- and postoperatively to assess patient QOL. A Darvall questionnaire modified for Russian was used to measure patient expectactions and posttreatment satisfaction.

Results. VCSS was significantly decreased at 2 weeks after EVT in the MPFF group ($P<0.00001$), but not in the control group ($P=0.15$). The reduction in VCSS in the MPFF group was also markedly greater than the control group 4 weeks after EVT, although this did not reach statistical significance. Patients' QOL was significantly improved in both groups ($P<0.00001$) at 4 weeks with a stronger trend observed in the MPFF group. Physicians' overall satisfaction regarding the use of MPFF was significantly greater at 4 weeks than at 2 weeks after EVT ($P=0.000018$). Patients receiving MPFF expressed significantly greater satisfaction compared with the control group (95% vs 82%, $P<0.0001$).

**Also registered as Ardium®, Alvenor®, Arvenum® 500, Capiven®, Daflon 500 mg®, Detralex®, Elatec®, Flebotropin®, Variton®, and Venitol®.*

Conclusion. MPFF is of benefit for routine use in combination with varicose vein EVT due to its vein-specific pharmacological protection.

INTRODUCTION

Current endovenous treatments for refluxing varicose veins include ultrasound-guided sclerotherapy (liquid or foam), endovenous laser ablation (EVLA), and radiofrequency ablation (RFA). In recent years, these minimally invasive endovenous procedures have gained popularity in the treatment of superficial venous reflux. The perceived advantages of endovenous therapy include reduced postoperative pain, high vein occlusion rates, and early return to work and normal activities. In the present protocol, we will focus on ultrasound-guided foam sclerotherapy (UGFS), EVLA, and RFA, which are increasingly used for vein ablation all over the world.[1,2]

Endovenous procedures have also led to major changes in the standards of varicose vein treatment in Russia. However, permanent improvements in technology aimed at enhancing the capacity, efficacy, and safety of varicose vein treatment requires a constant modernization of basic equipment (lasers and radiofrequency generators) and disposables (fibers, catheters, etc). Such steadily escalating costs of varicose vein treatments limit the availability of these new techniques for patients, especially in countries with developing economics and an imperfect system of health care insurance.

The mechanism of endovascular obliteration of varicose veins is universal and based on thermal or chemical damage to the vessel wall, primarily to its endothelial layer. As a result, a process of thrombus formation is induced, which should ideally lead to the complete obliteration and fibrous transformation of the diseased vein.[3,4] The weak element of endovenous technology is the inability to fully control the depth of damage to the vein wall and the course of the thrombotic process, as well as the possible occurrence of paravasal reactions. These late reactions are most often manifested by intradermal and subcutaneous hemorrhages, hematomas and skin depigmentation, and may be associated with lower limb pain and edema. Much more rarely, necrosis and skin burn, deep vein thrombosis, thrombophlebitis, damage to nerves, as well as to lymphatic collectors and great vessels may be produced by endovenous procedures.[5]

Finally, the inflammatory process that accompanies thermal and chemical ablation has not been clearly elucidated, but there is a body of evidence to suggest that this inflammation is involved in the ablation process, and may in turn lead to post-procedure complications in the case of "hyperinflammation."[3,4]

Micronized Purified Flavonoid Fraction (MPFF) consists of 90% diosmin and 10% other flavonoids expressed as hesperidin, diosmetin, linarin, and isorhoifolin, The benefits of MPFF as part of the pharmacological post-operative recovery of patients with varicose veins who have undergone phlebectomy have been evaluated in two trials.[6-9] In both studies, MPFF helped attenuate pain, decrease postoperative hematomas and accelerate their resorption. It was also associated with an increase in exercise tolerance in the early postoperative period.

The main aim of minimally invasive procedures is to avoid reflux and limit hypertension, which are central to chronic venous disease (CVD) progression. In an animal model of acute venous hypertension, MPFF has been shown to reduce reflux through pressurized veins.[10] It is the only available venoactive drug known to modify the chain of events leading to chronic venous hypertension.[11] MPFF therefore possesses the most appropriate profile to be associated with endovenous procedures for reinforcing the effect of such techniques on vein ablation and for decreasing venous hypertension, with beneficial effects on clinical severity, symptoms, and quality of life.[12]

Most postprocedure complications are probably the result of 'hyperinflammation' in the injured vein. MPFF is likely to be of use in limiting such post-intervention complications as a result of its vein-specific anti-inflammatory action.[11,12] Despite inconsistent evidence, the combination of compression therapy with invasive techniques is often promoted. To our knowledge, there are no published studies on the use of venoactive drugs after an intervention and no recommendations for such an association in current guidelines. The results of this study should fill the gap.

OBJECTIVE

The objective of the DECISION study (Observational stuDy among patiEnts with variCose veins of the lower limbs undergoIng endovenouS ablatIon alOne or in assocIatioN with venoactive drugs) was to evaluate the benefits of adjunctive MPFF with endovenous ablation of varicose veins.

MATERIAL AND METHODS

This was a randomized, nonblinded trial comparing two groups of patients: a control group (endoluminal vein ablation with standard postprocedure treatment) and the MPFF group (endoluminal vein ablation with standard postprocedure treatment plus MPFF, two tablets daily, from the day of intervention to the follow-up visit).

The study end points were as follows:

- Assessment of clinical disease severity with VCSS.[13-15]
- Assessment of changes in quality of life (QOL) using CIVIQ-14[16,17] with a score ranging from 0 for poor QOL to 100 for very good QOL.
- Evaluation of patients' overall expectations and satisfaction with adjunctive MPFF treatment using Darvall's questionnaire modified for Russian.[18]
- Evaluation of investigators' overall satisfaction with adjunctive MPFF treatment using a five-point scale.

Adults of any race could be included in the study if they met the following inclusion criteria: aged between 30 and 60 years; symptomatic (pain, itching, tingling, cramps, restless legs, sensation of swelling, heaviness) primary varicose veins with a single lower limb to be treated; diagnosis of venous disease according to the clinical, etiological, anatomical, pathophysiological (CEAP) classification – C2 with or without complications (±C3, ±C4), Ep (primary VV), P_R (with reflux), anatomically located at the short saphenous vein (SSV), and/or the great saphenous vein (GSV), and/or perforators; and presence of venous reflux confirmed by duplex ultrasonography (measured in upright position at 3 cm below the saphenofemoral junction and after the Valsalva maneuver with the patient standing on the contralateral limb). Patients were also required to have no known allergy to anesthetics or sclerosing agents (for foam sclerotherapy), taken no phlebotropic agent during the 4 weeks before selection, no expected pregnancy in the 2 months following (for women), given their written informed consent and to be available for follow-up visits.

The exclusion criteria were as follows: phlebotropic treatment in the 4 weeks before selection; history of alcohol or drug abuse; known history of allergy or intolerance to diosmin or any other phlebotropic agent and to sclerosing agents (in the case of foam sclertherapy); asymptomatic varicose veins; secondary varicose veins; angiodysplasia; neoplasia; presence of lower-limb lymphedema; diabetes mellitus; connective tissue disorders including rheumatoid arthritis; blood disorders; arterial disease (ankle-brachial index <0.9); any concomitant active disease that may interfere with the results (particularly inflammatory and/or infectious disease); previous deep venous thrombosis (less than 1 year prior to study); recent superficial venous thrombophlebitis (less than 3 months prior to study); obesity with body mass index (BMI) >30 kg/m^2; inability to walk; predictable poor compliance with treatment; participation in another clinical trial during the previous 3 months; pregnant or breastfeeding women, or women wishing to become pregnant; and unavailability for follow-up visits.

A total of four visits were planned during the study. The pre-intervention visit at which point patients were included in the study, took place 2 weeks before the endovascular procedure. The second visit was the day of operation and was followed by two further visits at 2 and 4 weeks after the procedure.

Once included, patients were randomly allocated to either MPFF or the control group, and the choice of endovenous procedure was made after discussion with the investigator. Endovenous procedures proposed to patients included UGFS, EVLA, or RFA. These procedures could be performed in isolation or in association, depending on the position, diameter and length of the vein to be ablated. The investigations schedule is presented in *Table I*.

	Day -15	Day 0 (operation)	Day +15	Day +30
Social and demographic characteristics	+			
Medical history	+			
CEAP classification	+		+	+
Duplex examination of lower limbs, and features of the diseased vein	+		+	+
Choice of endovenous procedure (UGFS, EVLA, RFA)	+			
Randomization	+			
VCSS scoring	+		+	+
Quality of life assessment with CIVIQ-14	+		+	+
Assessment of patients' expectations and satisfaction (Darvall's questionnaire modified for Russian)	+			+
Assessment of investigators' satisfaction			+	+
Assessment of adverse events			+	+

Table I. *DECISION investigation schedule*

Statistical analysis

Patient characteristics

Groups were compared at baseline using the Student's t-test and Fisher's exact test when appropriate; the complementary Mann-Whitney test was used for quantitative variables, and the chi-square test for sex ratio.

End points

Between-group comparisons for changes in VCSS scores and in health-related quality of life scores were made using two-way analysis of variance with repeated measures of variance to compare scores before and after treatment.

Overall evaluation

Fisher's exact test for between-group comparisons (with or without MPFF) of the investigators' treatment assessment.

For all tests, the level of statistical significance was set at 5%.

RESULTS

DECISION was carried out in eight clinical centers in the Russian Federation from January to September 2011. The study included 230 patients who gave informed consent for participation in the study.

Flow chart and choice of endovenous procedure

Randomization was performed at Day -15 before the intervention using sealed envelopes. A total of 126 patients were assigned to the MPFF group and 104 to the control group. UGFS was used in 98 patients, EVLA in 128, and RFA in 46. The vast majority of patients (n=228) underwent a combination of two endovascular procedures.

EVLA was performed using certified diode lasers with wavelengths from 940 to 1560 nm. The mean levels of laser exposure in the MPFF and control groups were 18.2 ± 5.8 and 18.3 ± 5.9, respectively (P=0.93), and spent energy was -2904 ± 1692 and 2427 ± 1361 J (P=0.28), respectively. RFA was performed using the VNUS Closure system (Covidien, USA) at the standard mode. The type of endovenous procedure performed was equally distributed between groups with no statistically significant differences. The DECISION flow diagram is presented in *Figure 1*.

Patient characteristics at baseline

A total of 230 patients (52 men and 178 women) aged from 20 to 62 years (mean age 43.1 ± 10.7 years), assigned C2-4s,Ep,As, Pr of the CEAP classification, with indications for endovascular treatment of varicose veins were enrolled in the study. Characteristics of patients were as follows: mean weight 72.6 ± 13.8 kg;

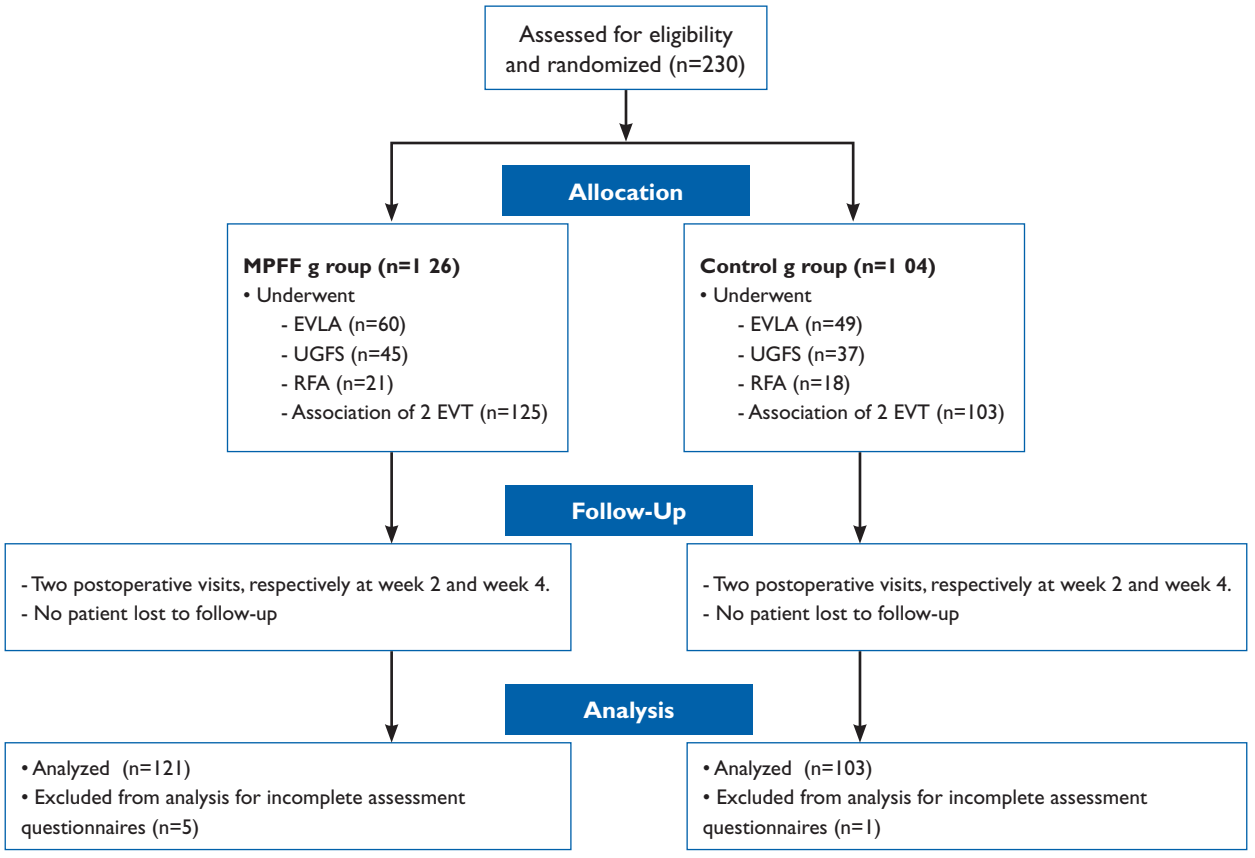

Figure 1. *DECISION study flow diagram.*

	Total population n=230	MPFF group n=126	Control group n=104	*P*-value between groups
Age (years)	43.1 ± 10.7	43.1 ± 10.9	43.2 ± 10.5	NS
Male/female (%)	23/77	22/78	24/76	NS
BMI (kg/m^2)	25.3 ± 4.2	25.5 ± 4.0	25.1 ± 4.3	NS
Superficial reflux (n, %)	227 (99%)	125 (99.2%)	102 (98.1%)	NS
Deep reflux (n, %)	14 (6%)	8 (6.4%)	6 (5.8)	NS
Perforator reflux (n, %)	56 (25%)	32 (25.4%)	24 (23.1%)	NS
Family history of CVD (n, %)	165 (71.8%)	92 (73.0%)	71 (68.3%)	NS
Personal history of deep vein thrombosis (n, %)	13 (5.7%)	7 (5.6%)	6 (5.8%)	NS
Hours spent daily in a standing position	5.5 ± 3.0	5.9 ± 2.9	5.2 ± 2.9	<0.045
Hours spent daily in a sitting position	5.7 ± 2.7	6.1 ± 2.6	5.3 ± 2.8	<0.040
Lack of regular exercise (n, %)	150 (65%)	39 (31%)	39 (38%)	0.25
Hours spent weekly lifting heavy loads	5.3 ± 7.6	6.2 ± 2.1	4.0 ± 1.5	0.44
Current smoker (n, %)	47 (20%)	26 (20.6%)	21 (20.2%)	NS
Past smoker (n, %)	29 (13%)	12 (9.5%)	17 (16.4%)	0.11
Previous childbirth (n=178) (n, %)	154 (86%)	85 (67.5%)	69 (66.4%)	NS
Hormonal contraception (n, %)	9 (5%)	7 (5.6%)	2 (1.9%)	0.17
Hormone replacement therapy (n, %)	4 (2%)	3 (2.4%)	1 (1.0%)	0.43

Table II. *Patients characteristics of the DECISION population at baseline.*

mean height 169.5 ± 8.3 cm; and mean BMI 25.3 ± 4.2 kg/m^2. Groups did not differ significantly in age, sex, BMI, nature and extent of the venous refluxes, and underlying risk factors. The only difference was that patients in the MPFF group spent more time in a sitting position (P<0.040), and less time in a standing position (P<0.045) compared with the control group.

The ultrasound study revealed severe superficial reflux in 227 patients (196 patients in the GSV, 31 patients in the SSV). Retrograde blood flow through the deep and perforating veins was detected in 14 and 56 observed patients, respectively. Clinical and investigational characteristics, as well as history and risk factors for CVD of patients enrolled in the study are presented in *Table II*.

VCSS scores

The baseline average VCSS values in patients randomized to the MPFF and control groups were 4.2 ± 2.1 and 4.0 ± 2.1, respectively (P=0.55), indicating no significant differences between groups. The difference between pre-operative and postoperative VCSS scores at week 2 was statistically significant between groups in favor of MPFF (P<0.00001 in the MPFF group vs P=0.15 in the control group). (*Figure 2*).

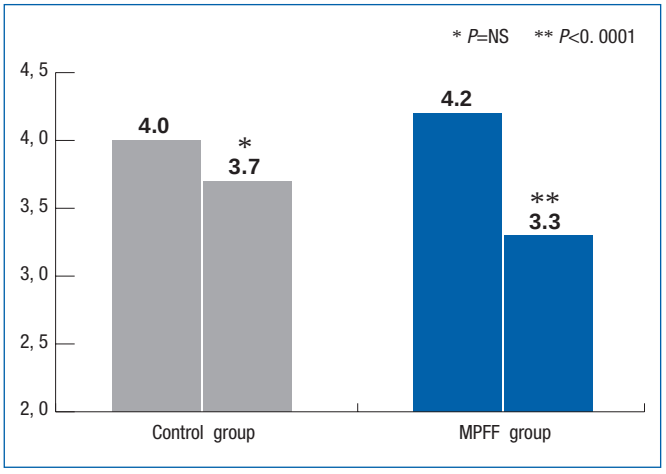

Figure 2. *Changes in VCSS scores between the preoperative visit and week 2 postoperative visit. Comparison between MPFF and control groups.*

The reduction in VCSS score during the first 2 weeks after the endovenous procedure was significantly greater in the MPFF group compared with the control group. At 4 weeks after the procedure, the reduction in VCSS score in the MPFF group was also markedly higher than in the control group, although the result was not statistically significant. These findings suggest that MPFF is associated with a decrease in the severity of CVD, ie, positive changes in the disease course.

Quality of life changes

A significant increase in the global index score (GIS) was observed within the first 2 weeks after the endovenous procedure both in the MPFF group (P<0.00001) and in the control group (P=0.00022), corresponding to an improvement in patient quality of life. Similar results were observed at week 4 with a significant increase in GIS in both groups (P<0.00001).

Despite a trend throughout the follow-up period for a higher GIS in the MPFF group compared with the control group, this did not reach statistical significance (*Figure 3*).

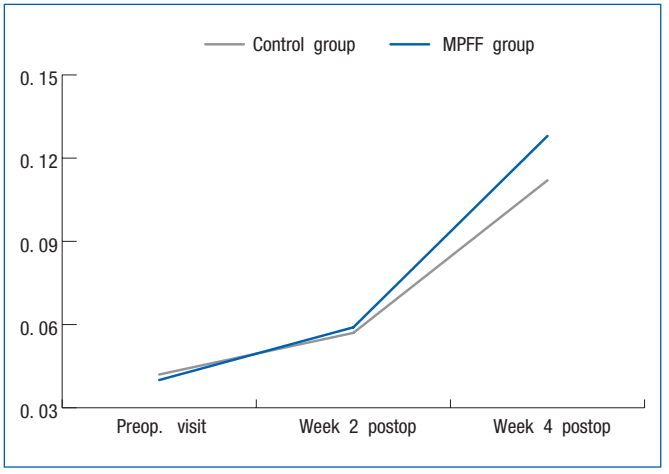

Figure 3. *Changes in the CIVIQ-14 GIS during the DECISION study.*

Treatment outcomes

Complete obliteration of varicose veins was achieved in 207 patients, and partial obliteration in 15 patients. The remaining 8 patients did not complete all the questionnaires.

Overall patient expectation and satisfaction

Before the treatment, 87% of MPFF patients and 91% of patients in the control group expected a decrease in their CVD specific symptoms, venous edema, aesthetic improvement of legs, and the possibility of wearing light clothes, etc. The overall satisfaction of patients receiving MPFF was significantly higher compared with the control group (95% vs 82%, P<0.0001).

Overall physician satisfaction

The overall physician satisfaction regarding the use of MPFF was significantly higher at week 4 than week 2 (P=0.000018). Globally, the investigators were fully satisfied with adjunctive MPFF in the perioperative period after endovenous procedures for varicose veins and considered this drug as appropriate for use in daily practice.

Adverse events

No adverse events were reported in the MPFF group.

CONCLUSION

The present study demonstrates the possibility of improving the results of varicose vein endovenous procedures by administration of MPFF in the perioperative period. This can abolish the consequences of vascular wall damage and prepare paravasal structures, particluarly the microvasculature, to the operating trauma, making the disease course over the postoperative period more comfortable and predictable.

This article presents only the essentials of the DECISION study, which also addressed such critical problems as the assessment of changes in individual CVD symptoms using visual analog scales, the analysis of patient expectations and satisfaction with treatment outcomes, as well as morphometry of the obliterated varicose vein. Further discussion of these important issues that open new prospects for contemporary phlebology, requires a separate article, which will be published soon.

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Superficial vein thrombosis: more dangerous than anticipated

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ABSTRACT

Physicians were once taught that superficial venous thrombosis is a rather benign condition. However, more recent information suggests that in quite a number of cases this thrombosis may be complicated by pulmonary embolism. Diverse mechanisms play a role in its development, but it is most frequently linked to varicose veins. Diagnosis is clinical, but ultrasound visualization of the venous segment is essential for the initiation of adequate management. Compression and mobilisation are the cornerstones of treatment. For a short segment thrombosis, nonsteroidal anti-inflammatory drugs exert a proven favorable effect. For longer segments, low molecular weight heparins are preferred. In case of extensive thrombosis, fondaparinux is usually the first-line treatment. Information on the effect of the newer anticoagulant drugs for the treatment of superficial venous thrombosis is lacking. Physicians are advised to adapt their views on superficial vein thrombosis according to this new information.

INTRODUCTION

Superficial vein thrombosis (SVT) of the lower limbs is considered by most clinicians to be a rather innocent entity. However, recent information indicates that SVT has a high prevalence and is quite often accompanied by pulmonary embolism, putting the patient at immediate risk.[1] Essential aspects of this new information will be summarised in the present review.

DEFINITION

SVT is a clinical entity well known by experts in venous disease and most physicians in general. It presents as an acute clinical condition characterized by a painful, warm and erythematous cutaneous area following the course of a peripheral vein, which often takes on the external aspect of a cord-like structure. It occurs most frequently in the lower limbs, but with increased use of intravenous catheters and injections in the arm, its prevalence in upper limbs has increased sharply.

Thrombus formation in SVT is largely due to an inflammatory process in the venous wall. It typically occurs in varicose veins (primary thrombosis), but can occur in nonvaricose veins, where both thrombosis and inflammation play a role. The thrombus adheres better to the wall of superficial veins than

Keywords:
Anticoagulant drugs; Calisto; compression; fondaparinux; heparin; pulmonary embolism; thrombophlebitis; varicose veins

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deep vein thrombosis making it less serious; however, SVT is complicated by pulmonary embolism in at least one-third of cases.[2,3]

Thrombosis is probably a better name for the entity than thrombophlebitis as infection is rarely involved; as a consequence and contrary to common belief, in most patients antibiotics are not necessary. The typical clinical context (*Table I*) is that of lower limb varicose veins. In many cases, the likelihood of thrombosis developing is increased by immobilization, for example in patients with heart failure, and in chronic conditions due to pulmonary or malignant disease or postsurgery. Upper limb venous thrombosis is now recognized to be occurring more and more frequently following an increase in the use of procedures that cause trauma to the arm veins. Alterations in coagulation status also increase the risk of thrombosis developing.

- Varicose veins
- Prolonged bed immobilization
- Cancer
- Pregnancy
- Oral contraceptives
- Intravenous injections and catheters
- Presence of risk factors (see epidemiology) such as age (more than 60 years), obesity, thrombophilia, arterial disease causing slowing of the circulation…

Table I. *Most frequent causes of acute superficial thrombosis.*

PREVALENCE AND RISK OF SVT

The exact incidence of SVT in not known. It is estimated to be two to three times more frequent than deep vein thrombosis. In many cases, SVT is a mild condition that resolves spontaneously. As a consequence the patient does not seek medical assistance or treatment, and it can be assumed that the prevalence is much higher than actually documented. There is therefore a need for new studies on the prevalence and complications of SVT. It is estimated that 20%–33% of SVT cases, almost one-third, are complicated by asymptomatic pulmonary embolism, while 2%–13% are associated with life-threatening symptomatic pulmonary embolism.[4–6] Although these data require further confirmation and documentation, they indicate that SVT is far from a benign entity.

DIAGNOSIS

The diagnosis of SVT is primarily clinical, based on the presence of redness and tenderness along the vein, which is often transformed into an easily identifiable palpable cord. There is often some local or regional edema of the surrounding tissues. In most cases there is no edema of the whole leg as long as the deep venous system is not involved, although there are exceptions to this rule. When SVT is extensive, it is often very painful. During recovery, the inflammation and thrombus often resolve. Recanalization usually occurs after a few months. In cases where there is no recanalization, this may lead to a hardening of the tissues often accompanied by pigmentation.

Ultrasound color flow examination is mandatory to determine the precise location and extent of the SVT. During the healing phase it is also useful for documenting the degree of recanalization. The status of the deep venous system should also be evaluated, and the distance of the SVT to junctions measured. When there is an acute greater saphenous vein thrombosis, ultrasound shows a characteristic increased cross-sectional diameter with homogenous echolucent intraluminal material and lack of compressibility.[7] It is recommended that both legs be examined in all patients.

MANAGEMENT

In all patients, but particularly in cases of nonvaricose SVT, a full clinical examination is necessary and attention should be focused on specific causes. Thrombophilia and cancer need to be excluded as SVT can be among the first signs of another, as yet undiagnosed disease. In a retrospective analysis of 140 consecutive patients, an association of SVT and malignancy was found in 18 (12.9%) patients.[8]

In the acute phase of SVT, several options for treatment are available, although there are not many strong recommendations, based on proven information, on the best action to take.[9] The most important message that physicians should be aware of is that SVT is not a benign disease.

The following steps should be considered in the treatment of acute SVT:

- Compression
- Mobilization
- Pharmacological treatment

Compression

There is a general consensus that compression is helpful in relieving symptoms and may contribute to healing of the thrombotic process.[10] Fixed compression, used as the only treatment, has been shown to improve duplex findings in 81% of patients.[11] Both bandages and graduated elastic compression stockings can be used; in extensive cases, both types of compression may be applied. It is recommended that the compression bandage should exceed the thrombosed section by at least 10 cm. Compression should be applied for at least 2 weeks, but in varicose patients, it should be continued as a chronic treatment.

Mobilization

The concept of mobilisation has changed the treatment of SVT entirely. A long-held belief was that patients in the acute phase of thrombosis should rest and avoid any movement of the leg. The reasoning was understandable and largely consisted of helping the thrombus to stabilize and avoid the danger of having loose material embolized into the circulation. Current views differ quite fundamentally. It is now considered that bed rest favors the progression of thrombus formation, largely in the direction of the deep venous system. The general consensus is therefore that patients should walk regularly and avoid prolonged periods in bed, seated, or even standing.

Although there are no well-controlled studies proving the validity of this approach, clinical experience shows beneficial effects including a clear improvement in patient quality of life that resembles the favorable effects of training in patients with peripheral arterial disease and even coronary ischemia.

Pharmacological treatment

Anticoagulation remains the pharmacological treatment of choice. Treatment will differ according to the length of the thrombosis, which should be determined by ultrasonic examination, performed by well-trained technicians with plenty of experience. As a general rule, the following steps are advised.

If the length of the thrombosis is 5 cm or less, treatment is with nonsteroidal anti-inflammatory drugs (NSAIDs). These can be given locally or systemically[12] and reduce pain and most likely perivenous inflammation. In a large, double-blind study comparing NSAIDs, low molecular weight heparin (LMWH) and placebo in 427 patients with documented acute superficial vein thrombosis, NSAIDs (in this case Tenoxicam) significantly reduced the risk of thrombosis extension at the level of the superficial vein at day 12, with no major bleeding.[13] However, there was no change in the incidence of deep venous thrombosis. NSAID should not be given in addition to anticoagulants.[12] In contrast to arterial thrombosis, there is no proven argument in favor of antiplatelet drugs for this indication.[12]

If the length of the thrombosis is up to 10 cm (as judged by ultrasound examination), regular anticoagulant therapy is indicated, including LMWH, unfractionated heparin (UFH), and vitamin K antagonists. LMWH can be given as either a prophylactic or therapeutic dose.[14] In the above-mentioned double-blind study,[13] LMWH also significantly improved the course of SVT. The Cochrane Database Review Group confirmed a positive effect compared with placebo after analysis of 24 studies in 2469 patients, but underlined the rather poor methodological quality of several studies.[9] The Cochrane group suggested using an intermediate dose of LMWH for at least 1 month.[9] During the early days, this treatment also helps in bridging toward use of oral antivitamin K drugs. An international normalized ratio (INR) of 2.5 should be aimed for.

In cases of extensive thrombosis (longer than 10 cm), especially when several other risk factors are present, there is grade B recommendation, evidence level 2,[15] to start fondaparinux, largely based on the findings of the Calisto study.[16] Calisto was a double-blind, multicenter study where fondaparinux (2.5 mg/day) and placebo were compared in 3002 patients. The primary efficacy outcome was a composite of death, symptomatic deep vein thrombosis and extension/recurrence of SVT. The outcome at Day 47 was 0.9% in the fondaparinux-treated patients and 5.9% in the placebo group ($P<0.001$). The efficacy of fondaparinux was also demonstrated in every component of the composite outcome except for death, which was extremely low in the whole study. These results are quite convincing even if there may be some discussion on the cost-effectiveness.[17]

Clinical experience and a few clinical papers have reported an improvement in local signs and symptoms after applying topical drugs such as diclofenac, ibuprofen and other gels. Their effect is often well accepted and appreciated by patients, although local irritation or allergy can occur. However, none of these studies has

convincingly demonstrated a decrease in the incidence of deep vein thrombosis or extension of the SVT.

There is a great expectation that newer classes of anticoagulant drugs will be tested for this indication. To date, the limited information available concerns deep vein thrombosis.

Surgical treatment

Surgery is rarely indicated for acute SVT. Excision of the involved vein can be performed when symptoms persist after 2 or more weeks of intensive medical treatment (see above). If there are concerns for further extension of the thrombosis, ligation of the vein and eventually excision can be considered, although there is not much support for this type of treatment and almost no well-controlled, randomized studies.

Treatment of a thrombosed venous segment in the chronic phase[10]

Compression and mobilization remain the basic aspects of treatment in the chronic phase, controlling conditions for the patient both at home and at work. Standing immobile for long periods of time is generally accepted to be a provoking factor for venous insufficiency. Ad hoc advice should be given, involving both the physician and manager at the work place. Some drugs have been proven in well-controlled studies to relieve symptoms and heal skin lesions.[18] Further research will continue to develop new drugs to treat this important and highly prevalent entity.

In contrast to the acute phase, there are ample indications for surgical treatment in the chronic phase, including stripping and ligation. For smaller vein segments, foam sclerotherapy is likely to be safe and beneficial when performed with ultrasound guidance. However, in all cases, it is important to respect the advice on mobilisation and compression as detailed above. A focus on epidemiology will help determine which patients are at risk and require more intensive management, with clear guidance on mobilization and eventually compression.[19,20]

CONCLUSIONS

SVT has been considered by many in the medical world to be an innocent entity without significant consequences. However, a recent review of previously published data has pointed toward a high prevalence of pulmonary emboli associated with this condition. It should also be recognized that in most cases SVT leads to some degree of venous insufficiency, not only causing symptoms and incapacity to work, but also creating the background for stasis, new episodes of thrombosis, and skin changes including venous ulcers.

Essential pillars in the treatment of acute SVT are compression, mobilization, and anticoagulation. Several studies, published in high-quality journals, have shown the beneficial effects of both old and newer anticoagulant drugs. After relief of the symptoms and signs associated with the acute phase, great care should be taken in the chronic phase, where venous insufficiency can develop and lead to symptoms, work incapacity, and skin changes. An understanding of the epidemiology of SVT is useful to determine which patients are at increased risk. The information provided in this review will hopefully focus readers' attention on the often widely underestimated relationship that exists between the peripheral vascular system and the heart.[21]

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Critical role of the vasa venarum in the pathogenesis of chronic venous disease. Part I: malperfused venules as pathogenetic hot spots

This is the first of the 2 chapters that make up the "critical role of the vasa venarum in the pathogenesis of CVD." These chapters will be published consecutively in Phlebolymphology.

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ABSTRACT

A new concept for the pathogenesis of venous disease is presented in which the numerous postcapillary venules of the "vasa venarum" play a key pathogenetic role. These tiny veins consist of a highly specialized endothelium, reinforced by an adventitial network of pericytes. Local accumulation of inflammatory mediators induces contraction of the endothelial cells, rapidly leading to an increase in vessel permeability with subsequent efflux of plasma into the interstitium. This triggers the prothrombogenic and proinflammatory potential of the adventitial pericytes, which rapidly express high concentrations of tissue factor. Local accumulation of thrombin results in the formation of fibrin cuffs around neighboring blood and lymph vessels and thrombosis in collecting veins downstream. The subsequent draining of the vasa venarum results in luminal blood in larger downstream veins also becoming involved in the pathogenetic processes. Early systematic prophylaxis is important to prevent disease progression and limit restrictions to patient quality of life (see part II).

INTRODUCTION

Until recently, a convincing concept to explain the pathogenesis of the primary, idiopathic form of venous disease associated with acute thrombosis and the postthrombotic syndrome, and frequently leading to secondary chronic venous insufficiency (CVI) was missing. In particular, the link between gravity-dependent, adverse perfusion conditions in the legs during upright posture and the induction of the chronic inflammatory and microthrombotic processes associated with venous disease and CVI[1, 2] was still unclear. However, a consistent pathogenetic model of this disorder, based on progress in basic medical research, must be viewed as a prime prerequisite for rational therapeutic measures.

The circulatory system finds its greatest histological and functional manifestation and specialization in the microcirculatory beds within organs. This truism also applies to the vein walls, which are characterized by a very well developed nutritive system, the "vasa venarum."[3] Venules by far outnumber arterioles in these microvascular networks.[4] They drain via small collecting veins into the lumen of the appropriate saphenous vein, so that the perfusion of the vasa venarum in all large leg veins depends not least on the prevailing transmural pressure differences, which, depending on posture, eg standing or sitting, can be very high in humans.

Reduced perfusion in microvascular systems may trigger acute inflammatory processes,[5] in which the postcapillary venules play a seminal role by virtue of their recruitment of blood immune defense mechanisms.[6-8] A highly specific thrombotic occlusion of these tiny veins has been regarded for some time as the first reliable sign of impending organ rejection.[9-11] Apparently, and for reasons not yet understood, the postcapillary venules also play a central role in the induction of thrombotic processes.

The aim of the present review is to summarize recent relevant findings on the cellular and hemostatic properties of postcapillary venules, explaining the key elements in the pathogenesis of primary and secondary venous disease, with a particular emphasis on the unique and newly recognized functional features of the constituent venule cell types (endothelial cells and pericytes). Current therapeutic approaches will be critically reviewed and relevant perspectives will be outlined in a separate publication (Part II).

THE COMPLEX VENOUS SYSTEM OF THE LEGS IN HEALTH AND IN CVI

Influence of some physical parameters

When standing still, blood accumulates in the thin-walled leg veins and the abdominal vena cava under the influence of the hydrostatic pressure exerted by the vertical fluid column. Blood flow velocity is slow, and slows even further if venous tone decreases, as during warm weather, resulting in further venous pooling in the lower extremities. The ratio between endothelial surface area and blood volume, a parameter characterizing the contact of blood with the embracing endothelium, is also correspondingly low (*Figure 1*). The increased hydrostatic pressure, highest

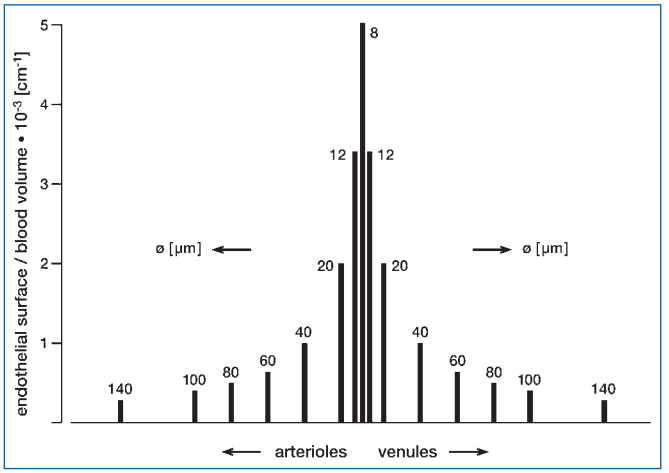

Figure 1: Blood endothelial contact in the various vascular regions of the circulation (ratio of endothelial surface area to blood volume). The contact between blood and endothelium is 5000 times higher in the capillaries than in the large arterioles (arteries) or venules (veins). Diameters are plotted from published data,[48] assuming that the blood vessels are cylindric. The values in italics above/beside the columns indicate the diameters (in micrometers) of each vessel type.

in the feet, increases plasma water filtration from capillaries into the surrounding interstitium, causing edematous expansion of the dependent extravascular space (hydrostatic edema), impairment of substance exchange. Manifest edema in the lower extremities may result. Under these conditions, "auxiliary" mechanisms provide important support for the return of blood to the heart. These include the pulse wave in the arteries accompanying the large veins, and rhythmic pressure changes in the abdomen accompanying respiration. As soon as locomotion starts, the contraction of the leg muscles, particularly those of the calves, together with the vein valves, constitute the "muscle pump" (*Figure 2*). This plays a major role in supporting circulatory performance during physical effort, especially in the upright position.

When the delicate mechanisms transporting blood in the veins back to the heart against gravity fail, elevated transmural pressure in the leg veins may result. This is even more likely when the vein valves become incompetent, and reflux of venous blood and hence ambulatory venous hypertension occur. Although the above-mentioned hydrostatic and hydrodynamic consequences of upright posture[12] are generally believed to be an important prerequisite in the pathogenesis of venous disease, the mechanisms leading to valve incompetence, vein wall sclerosis, thrombosis, severe

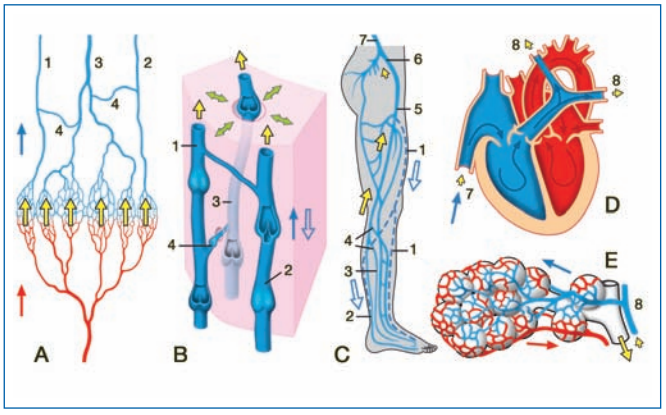

Figure 2: The venous vascular bed from the leg to the lung: consequences for the plasma concentrations of short-lived antithrombogenic mediators of endothelial origin (heavily-outlined yellow arrows). A) The skin and the various leg organs (muscle, bone etc) all possess their own microcirculatory systems, with an endothelium producing large amounts of short-lived inhibitors of platelets and coagulation factors that are released into the venous blood (large yellow arrows). 1, 2: Superficial veins (1: greater and 2: lesser saphenous veins). 3: Deep leg vein (eg peroneal vein). 4: perforating veins. Red or blue arrow: arterial or venous blood flow, respectively. B) Morphological details of the veins and their valves at the level of the calf (1, 2: superficial veins; 3: deep vein: also shown: perforating veins). In the case of valve insufficiency, the direction of venous flow can be reversed (open blue arrow). The green double-ended arrows indicate the effect of the (calf) muscle pump, the smaller yellow arrows indicate the now lower autacoid concentrations. C) The concentration of the endothelial inhibitors decreases further in the course of the long flow path to the lung via the deep and superficial leg veins, the common femoral vein (5), the internal iliac vein (6), the inferior vena cava (7) and the right side of the heart (D) and the pulmonary artery (8). Once in the arterial limb of the pulmonary microcirculation (E) the concentration of the inhibitors is restituted.

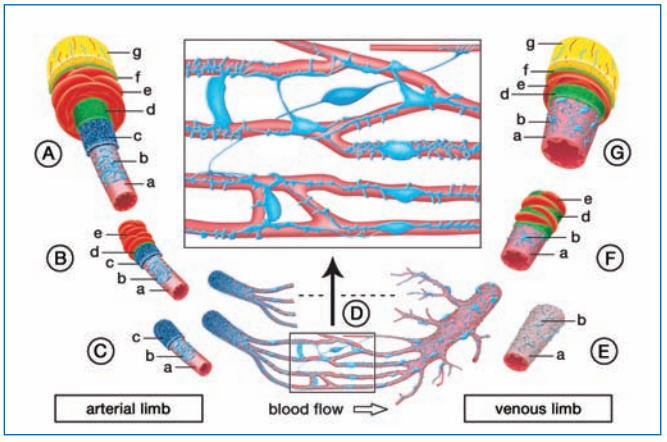

Figure 3: Bizarre shaped and interconnected pericytes as companion cells in all blood vessels. In the capillary beds the pericytes (blue) lie immediately at the endothelial tube (pink) on its adventitial side. Their extensions make contact with neighboring and even more distant terminal vascular beds (see enlargement in the inset). Each capillary bed is supplied by a precapillary arteriole, the endothelial tube of which is enveloped by a particularly dense layer of pericytes embedded in the self-synthesized extracellular matrix (ECM, dark blue). The larger, feed arterioles consist of the intimal double layer of endothelium and pericytes plus an outer layer of vascular smooth muscle (red). The smooth musculature continues upstream in a large artery, where it is much thicker and constitutes the media of these vessels. Big arteries also have an adventitia (yellow) containing a well-developed network of nutritive microvessels (vasa vasorum) that penetrate deep into the media. The right-hand diagram shows that the venous limb of the circulation is constructed similarly, although the pericytes of the venules and larger veins here form a looser, larger meshed net and do not synthesize a continuous extracellular matrix. A large artery, B feed arteriole, C precapillary arterioles, D capillary bed, E postcapillary venules, F collecting venule, G large vein; a endothelial tube, b pericytes, c extracellular matrix (the "cocoon"of the pericytes), d internal elastic membrane, e smooth muscle cells (media), f external elastic membrane, g adventitia with vasa vasorum or vasa venarum, respectively.

inflammation and ulcers are not clear. The following new insights into cell and tissue architecture of the complex venous wall, in association with the hemostatic and inflammatory consequences of the upright position, may contribute to a better understanding.

New insights into the histology and hemostatic properties of the venous system of the legs

Flowing blood is only able to fulfill its numerous transport and distribution functions as long as it is fluid. On the other hand, at sites of vessel injury it must rapidly solidify to prevent blood loss. The solution to this apparent functional paradox is found in the complex structure of the blood vessel intima that generally consists of two types of tissue with contrasting functions.[13-15]

A luminal coat of healthy endothelium prevents thrombosis

Vascular endothelium covers the intimal surface of all blood vessels (*Figure 3*) and is thus the actual blood container of the body. This contact surface with the blood is normally characterized not only by platelet- and coagulation-inhibiting activities (anti-aggregatory and anticoagulant activities), but can also develop profibrinolytic activity and thus even dissolve already formed fibrin thrombi (*Figure 4*).[13,15-19] The corresponding biochemical processes are bolstered by typical release products of activated platelets, and also depend on the availability of certain plasma proteins of hepatic

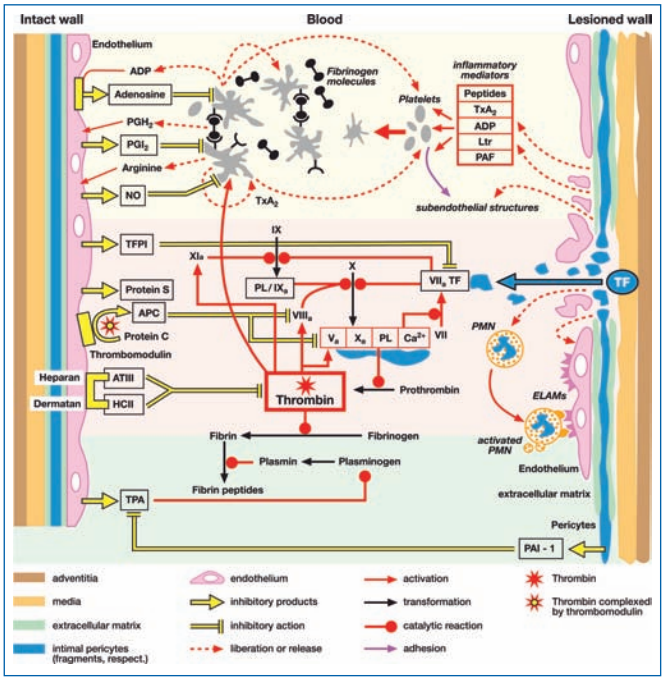

Figure 4: A survey of the most important antithrombogenic and prothrombogenic activities at the interface between the blood and the vessel wall. The thrombotic potential of blood is mainly determined by the behavior of the platelets (shown in the uppermost segment of the diagram on a pale yellow background), the coagulation system (middle segment on a pale pink background), and the fibrinolysis system (lower segment, pale green background). Healthy endothelium (left-hand side of the diagram) is consistently antithrombotic and, in the context of its anti-aggregatory activity, synthesizes platelet-inhibiting autacoids such as adenosine, prostacyclin (PGI_2) and nitric oxide (NO), especially when activated platelets release substances that can serve as precursors, eg adenosine diphosphate (ADP), prostaglandin H_2 (PGH_2) and arginine, respectively. In the context of its anti-coagulatory activity the endothelium releases tissue factor pathway inhibitor (TFPI) and protein S. In addition, endothelial thrombomodulin can bind thrombin and, in so doing, causes the latter to refold. Thrombin now expresses antocoagulant activity and activates protein C (APC). The binding of antithrombin III (ATIII) to proteoglycans in the glycocalyx, together with participation of heparin cofactor II (HCII), enhances ATIII's anticoagulant potency 1000-fold. Finally, healthy endothelium has a profibrinolytic effect by releasing tissue-type plasminogen activator (TPA). Under inflammatory conditions plasminogen activator inhibitor 1 (PAI-1) is released by the subendothelial pericytes.[49] Damage to the endothelium (right-hand side of the diagram) results in the release of numerous inflammatory mediators—diverse peptides, thromboxane A_2 (TxA_2), ADP, leukotrienes (Ltr), and platelet activating factor (PAF) from the activated pericytes or necrotic tissue—and the blood makes contact with tissue factor (TF) expressed on the surface of pericytes (or on microparticles released by the latter).

origin such as protein C, antithrombin III, and heparin cofactor II. Healthy endothelium — acting as a complex boundary catalyst continuously inhibiting or removing proaggregatory and procoagulant molecules and lysing fibrin — thus counteracts the formation of thrombi in the circulation. For geometrical reasons, the smaller the vessel, the higher the ratio between intimal surface area and blood volume. This contact between endothelial cells and the blood, and thus the antithrombotic and anti-inflammatory potency of the endothelium, will therefore be most intimate in the terminal vessels of organ microcirculatory systems (*Figures 1 and 2*).

Subendothelial pericytes strongly express procoagulant activity

In the nutritive microvessels of the vein wall, interconnected pericytes and their extracellular matrix form a sort of adventitial coat (*Figures 3C-E*), which is particularly well developed in the arterial limb of the

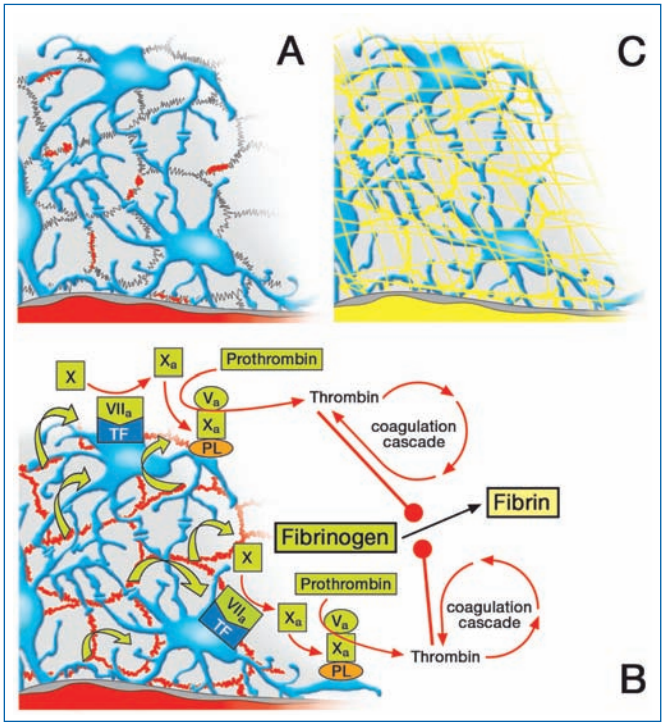

Figure 5: Valvular origin of venous thrombosis (view from the abluminal surface of the intimal coat of a valve). A) Acute effect on endothelial permeability: endothelial clefts become leaky (small red areas). B) The plasmatic zymogens of the coagulatory system are extravasating into the interstitium (green arrows). The subendothelial pericytes unfold extremely high concentrations of tissue factor (TF) and prothrombinase (phospholipids PL, Va, Xa, Ca^{++}), thus promptly initiating coagulation. C) The final result is envelopment of the respective vessel in a fibrin cuff that firmly anchors the fibrin thrombus that can also intrude into the lumen of the parent vessel.

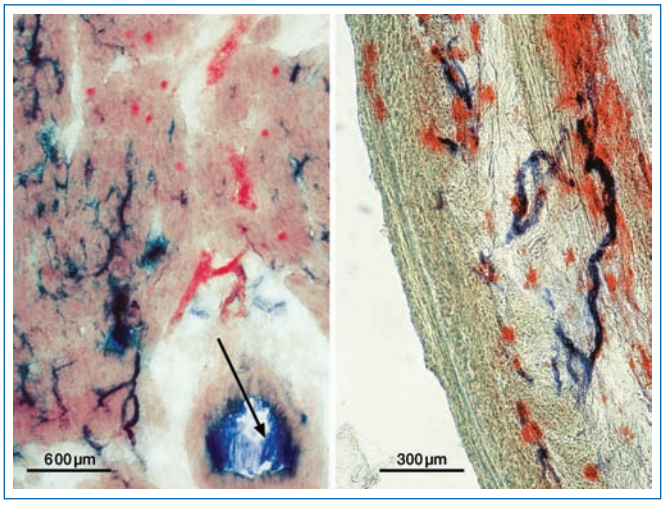

Figure 6: Similarity of coronary microvasculature in human left ventricular myocardium (left) and the vasa venarum of the saphenous vein wall (right). Specific demonstration of alkaline phosphatase on the pericyte tube of arterioles (blue), and dipeptidylaminopeptidase IV in the endothelial tube of postcapillary venules (red) by application of enzyme histochemical staining techniques. In addition, the arrow in the left figure identifies a sectioned branch of a larger coronary artery. The blue staining shows that alkaline phosphatase is also expressed also in the intima (here partly desquamated), indicating the presence of subendothelial pericytes (see *Figure 3*).

respective microvascular systems.[20] A net-like tissue of pericytes is also located in the subendothelium of the intima of larger arteries and veins (*Figures 3A, 5 and left micrograph in Figure 6*). All venous pericytes contain large amounts of tissue factor,[15] which can be rapidly recruited to the cell surface under acute inflammatory conditions,[21] eg in a fresh wound. No other cell types in the vessel wall or blood (besides activated monocytes) express this inducer molecule of nearly all clinically relevant thrombotic processes.[22,23] Tissue factor, together with factor VIIa, activates factor X,[15] as well as further membrane components that assemble the activated factors Xa and Va to form the prothrombinase complex (*Figures 3 and 5*), which in turn rapidly catalyzes the proteolytic conversion of prothrombin to thrombin.[24] Immediately after injury, exposed pericytes in the intima, nutritive vessels, and microvascular networks of adjacent connective or parenchymal tissue all contribute to local thrombin formation and hence to the normally rapid initiation of hemostasis. Thrombin concentrations in blood as low as 1 nM (0.1 U/ml) produce fibrin clots that are turbid and composed of thick, loosely-woven fibrin strands.[25] In parallel, immediate activation of platelets produces increasing numbers of aggregates, which recruit the entire coagulatory cascade to the rapidly enlarging surface area of this "white thrombus."[26] Thus, after a lag phase of 2-6 minutes, the generation of thrombin in the local environment of a thrombus can build up concentrations of between 100-500 nM.[25] Release products from the platelets (eg platelet activating factor [PAF], see *Figures 4, 7*) in turn activate polymorphonuclear granulocytes (PMN),[27] which immediately ensure an effective immune defense in the injured area.[28] The final result of these processes is a highly organized "red thrombus". All the activators that diffuse into the passing blood are rapidly inactivated due to their metabolic, thermal or chemical instability.[13] Serpins in the plasma specifically contribute to the rapid removal of procoagulatory and profibrinolytic factors.[29]

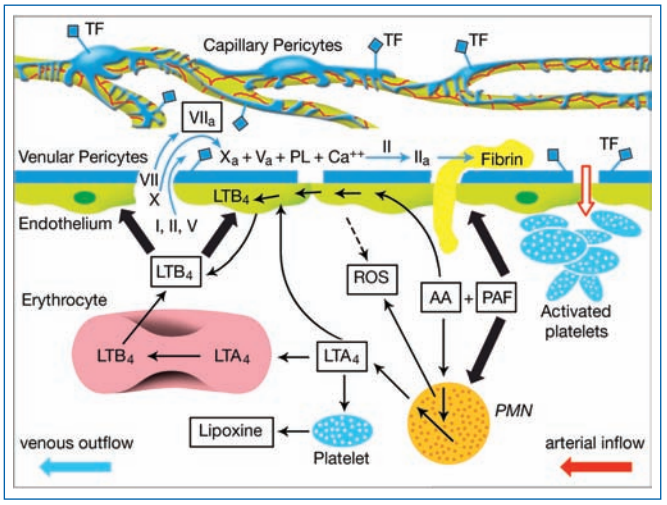

Figure 7: Scheme of the proposed cellular and biochemical mechanisms responsible for breakdown of the venular endothelial barrier, formation of fibrin cuffs, and the thread of venulo-thrombosis. Locally released inflammatory mediators activate the arteriolar endothelium, resulting in the adhesion/aggregation of platelets. Platelet activating factor (PAF) released from these platelets further activates the arteriolar endothelium as well as incoming neutrophils (PMN). The latter promptly synthesize leukotriene LTA_4 from arachidonic acid (AA) (also released by the platelets). The LTA_4 is metabolized by erythrocytes and endothelial cells to LTB_4, which in turn activates, via specific receptors, the postcapillary venular endothelium. Via complex signal cascades this results, among other enzyme systems, in activation of the myosin light chain kinase (MLCK), contraction of the venular endothelial cells, and widening of the intercellular junctions and hence breakdown of the blood-myocardium barrier. Plasma now flowing into the subendothelial space encounters the activated pericytes. The latter initiate activation of the coagulatory cascade and a rapid formation of fibrin cuffs, which can grow into the lumen of the parent vessel.

Prothrombotic processes in a wound terminate themselves once hemostasis is achieved

An important prerequisite for the physiological occlusion of wounds is that the antithrombogenic factors secreted continuously by the endothelial cells into the blood are evanescent, and thus disappear rapidly from the blood at the site of injury. This allows the autocatalytic prothrombogenic processes to proceed at that site, whilst their concentrations in the intact circulatory system are kept at a sufficient concentration by continuous endothelial re-synthesis. The contraction of integral contractile proteins released from aggregating platelets results in a retraction of the thrombus, whereby the latter becomes firm and extremely dense and thus prevents the contact of any further coagulation zymogens with the pericytes located outside the vessel. In this manner, the fulminant, self-reinforcing hemostatic process at the site of an injury is stifled as soon as its goal is achieved, whilst the remaining intact and perfused vascular bed remains free of thrombi.

INDUCTION OF VENOUS THROMBOSIS AND VENOUS DISEASE

The previously described ingenious principle of hemostasis functions well at sites of tissue or organ injury and never spontaneously in a well perfused and healthy vascular bed. Under adverse perfusion conditions, as may occur in leg veins during upright stance, intravasal thrombotic processes can be initiated without mechanical damage, and the prothrombotic mediators accumulating in the venous blood are not inactivated with the necessary efficiency (see next section). In this context, the nutritive microvascular system within the vessel walls, particularly in the large veins (vasa venarum), appears to play a key role (although this is not yet widely recognized).

Involvement of the vasa venarum

The vasa venarum[3] in the vein wall correspond to the nutritive microvessels of the arterial wall, the vasa vasorum.[30] In the saphenous vein, they are characterized by numerous postcapillary venules that stain highly specifically for dipeptidyl aminopeptidase IV, similarly to the smallest veins of the coronary microvasculature (*Figure 6*). In contrast, the arterioles of both microvascular systems stain selectively for alkaline phosphatase.[31] This histological similarity is not surprising, as from an evolutionary point of view the heart is also a blood vessel, albeit with a specialized musculature in its wall. Indeed, some authors regard the coronary microvasculature as the "vasa vasorum of the myocardium,"[32] and the numerous studies on the regulation of coronary blood flow and vessel density in the literature can therefore be regarded as meaningful models for the microvasculature of the arterial or venous walls.

The site at which the vena venarum of the leg veins drain into the lumen of the respective vein deserves special attention. In a recent article, Crotty describes the structure and function of the venous valve agger (a crescent-shaped fibroelastic sleeve, spanning the vein wall at the base of every vein valve): *"The agger forms part of a complex that, in conjunction with its dedicated musculature, a reversible transmural pressure gradient and physiological turbulence in the valve sinuses, positively facilitates drainage from the local segment of the vasa venarum network when venous tone is normal. However, when venous tone is elevated the agger pumps and sucks blood from the lumen of the vein to perfuse the vasa venarum network."*[33] Crotty concludes that disturbed agger function underlies the formation of varicose veins. Other authors also report direct entry of the vena venarum into the venous lumen.[34] However, regardless of whether the blood from the vena venarum passes directly into the lumen of the large parent vein, or if it first enters a tributary, drainage of the wall venules into the lumen of the main vein proceeds within a few seconds and will allow reflux of venous blood into the vena venarum network, particularly during walking. As will be discussed in the next section, such reflux may trigger pathophysiological processes that disturb homeostasis in the vein wall and culminate in manifest venous disease under adverse, initially purely physical conditions.

Reflux, inflammation and thrombosis

Reflux is accompanied by hypoxia and local ischemia, which together rapidly activate blood platelets and PMNs.[5,35-37] Both cell types cooperate metabolically. Thus, PAF released from platelets[27] stimulates the PMN to increase the synthesis and release of leukotriene A_4 (LTA_4), which is the precursor for LTB_4 synthesis and release by erythrocytes and endothelial cells (*Figure 7*). Using an in vitro model of the human coronary postcapillary venular wall, we have recently shown that this leukotriene elicits a rapid and specific contraction of the respective, highly specialized endothelium, which would most likely result in the breakdown of the venular barrier in situ.[27] Very similar results have been obtained in studies on the mesenteric microvasculature in situ.[38]

All these findings are consistent with the generally accepted concept that postcapillary venules play a key role in the recruitment of leukocytes, in plasma exudation and hence in the genesis of inflammatory edema.[6-8] At this point the pericytes come into play.[20] These cells accompany and envelop the postcapillary venules (*Figure 3*). Their direct contact with plasma coagulation factors initiates the coagulation processes described above (*Figure 4*) and results in the frequently observed fibrin cuffs that surround the microvessels in the later stages of CVI,[20,39,40] and which can also be recognized in the subendothelium of larger veins of CVI patients. Tissue coagulation processes are always accompanied by acute inflammatory reactions, involving in particular the complement system, monocytes and PMN. The risk is that these processes spread into the venular lumina, reinforce themselves autocatalytically, with the resultant thrombi extending into the lumen of the parent large leg veins. The stability of the highly structured thrombi and the evanescence of endothelial inhibitors, which are advantageous in the case of perforating injury, may now represent a serious disadvantage by creating permanent obstruction in more and more terminal vessels of the vein wall (or adjacent leg organs) and ultimately even in the larger vein. A similar mechanism is likely to take place in the subendothelial pericytes in the region of vein valves (*Figure 5*) making the latter fibrotic and incompetent. This could explain the postulated valvular origin of venous thrombosis.[41]

For purely geometrical reasons (*Figure 1*), the refluxing blood flowing back and forth within the larger leg veins is generally in contact with relatively little endothelium. As a result the concentration of the short-lived inhibitors from the endothelium can become critical (*Figure 2*). Thrombosis in the deep leg veins[42] may thus result in an even greater delay in the return of venous blood to the heart and to the pulmonary circulation, where the enormous total surface area of the lung capillaries normally delivers adequate amounts of anticoagulatory and anti-inflammatory mediators to the mixed venous blood (*Figure 2*). Such thrombi in the deep leg veins can extend further downstream and, in the worst case, tear loose and cause a potentially fatal pulmonary embolus.[43]

Postthrombotic syndrome

The remodeling of the walls and functional loss of valves in the larger veins, leading to rarefication of the nutrient vessel networks, sclerosis and varicosis, becomes understandable in the context of the spreading microthrombotic and inflammatory processes described above, and the consequent breakdown of the venular barrier between the blood and vein wall connective tissue. Pericytes are generally characterized by profibrotic activities.[20] A correspondingly altered wall structure is frequently seen in the leg veins of patients suffering from "postthrombotic syndrome".[44] The spectrum of symptoms is further complicated by the fact that the microcirculation in the skin, muscles, and bones also contains numerous venules, which will react similarly under conditions of reflux and obstruction and become pathophysiologically important disease foci. This spread of microcirculatory dysfunction and self-reinforcing processes thus represents a vicious circle, which is the basis for the typical progression of the later stages of CVI.

Orthopedic surgery predisposes to deep vein thrombosis

An acute predisposition for such events is created, in particular, by orthopedic surgery (especially hip and knee replacements), which is accompanied by a high risk of thrombosis, despite postoperative anticoagulation.[45-47] Under these circumstances there is a massive, iatrogenically caused influx of pericyte fragments (microparticles) from the red bone marrow, via the numerous small veins that drain venous blood from the central vein in the main leg bones into the deep leg veins. With their high tissue factor content and prothrombinase activity, these particles constitute an extremely effective foci for the formation of fibrin thrombi, culminating in rampant thrombosis, and in the longer term, to secondary venous disease.

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December 2013	ANNUAL MEETING OF THE AUSTRIAN SOCITETY OF PHLEBOLOGY	Austria	Vienna
December 2013	4th LISBON INTERNATIONAL FORUM ON VASCULAR DISEASES	Portugal	Lisbon
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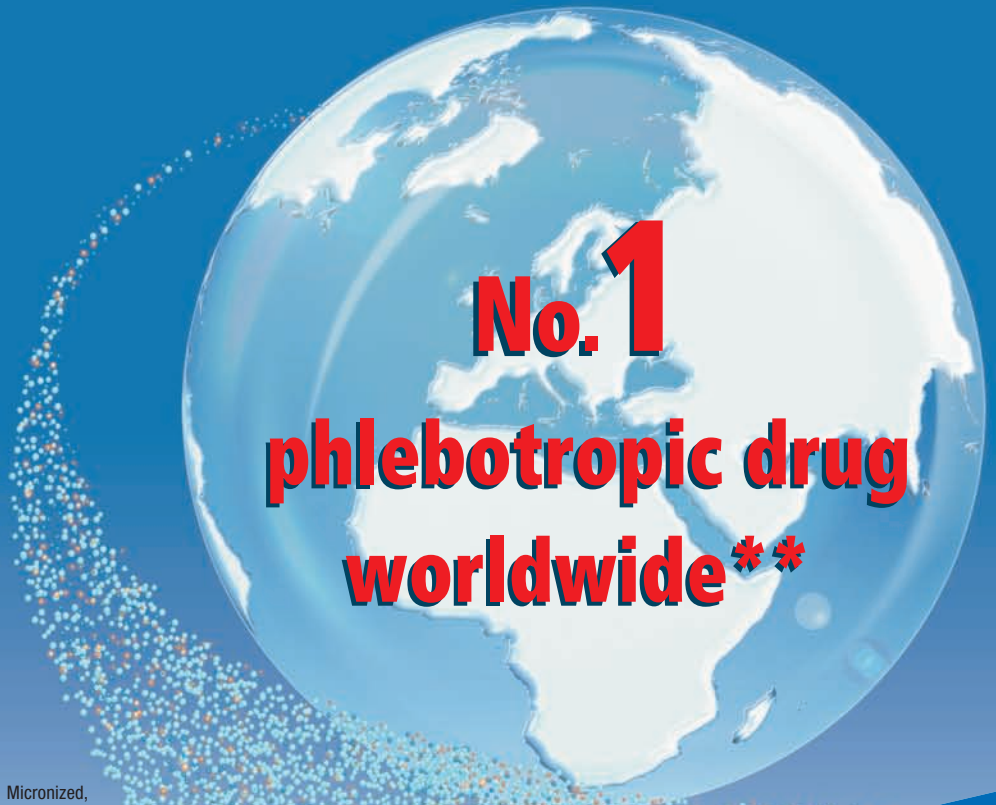

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