Recurrence of venous thromboembolism and its prevention
Paolo Prandoni (Padua, Italy)

Iliac vein outflow obstruction in ‘primary’ chronic venous disease
Seshadri Raju (Flowood, MS, USA)

Pelviperineal venous insufficiency and varicose veins of the lower limbs

Skin necrosis as a complication of compression in the treatment of venous disease and in prevention of venous thromboembolism
Michel Perrin (Chassieu, France)

Towards a better understanding of lymph circulation
Olivier Stücker, Catherine Pons-Himbert, Elisabeth Laemmel (Paris, France)
AIMS AND SCOPE

Phlebolymphology is an international scientific journal entirely devoted to venous and lymphatic diseases.

The aim of Phlebolymphology is to provide doctors with updated information on phlebology and lymphology written by well-known international specialists.

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Dear Readers,

This new issue of Phlebolymphology includes contributions from world leaders in the field, and demonstrates once more the fascinating variety of our discipline. In this issue you will find:

**Paolo PRANDONI** from the University of Padua is one of the world’s top authorities in clinical research on venous thromboembolism, and he has published several landmark articles in this field. In his current article he discusses the ways in which recurrences of venous thromboembolism can be prevented. This is a problem of very high practical interest for doctors, as recurrent episodes of venous thrombosis are among the deciding risk factors in the development of postthrombotic syndrome.

**Seshadri RAJU,** from Jackson, Mississippi, is one of the great pioneers in the treatment of proximal outflow obstructions by venous stenting. He discusses the “permissive role” of pelvic obstructions in the development of venous reflux in the distal vein segments, which may lead to leg ulceration.

**Edgar BALIAN** and his team, from France, point to the connections between pelviperineal reflux and varicose veins of the limbs. Their article describes the clinical signs, imaging, and treatment options with interventional radiology.

An interesting review of the published data concerning skin defects after compression therapy comes from **Michel PERRIN**, Lyon. His article suggests that it may be assumed that such side effects occur more frequently than reported.

**Olivier STÜCKER** and his coworkers from the University in Paris provide an overview on the physiology and pathology of the lymphatic system, and discuss some important issues regarding pharmacologic effects, especially on lymphatic vasomotion.

A report from **Reagan QUAN** from the Walter Reed Army Medical Center in Washington DC, who won the last Servier-sponsored American Venous Forum fellowship, completes this issue of Phlebolymphology. He visited some colleagues working at some Paris-based institutions, and was not only impressed by the good food, but also by the fact that the French angiologists performed their own ultrasound.

Enjoy your reading!

Hugo Partsch, MD
Recurrence of venous thromboembolism and its prevention

Keywords: deep vein thrombosis, pulmonary embolism, venous thromboembolism, anticoagulation, thrombophilia, heparin, warfarin.

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ABSTRACT

The risk of recurrent venous thromboembolism (VTE) approaches 40% in all patients after 10 years of follow-up. This risk is higher in patients with permanent risk factors for thrombosis, such as active cancer, prolonged immobilization because of disease, and antiphospholipid antibody syndrome; in patients with idiopathic presentation; and in carriers of several thrombophilic abnormalities, including carriers of AT, protein C or S, increased factor VIII, hyperhomocysteinemia, homozygous carriers of factor V Leiden or prothrombin G20210A variant, and carriers of multiple abnormalities. Patients with permanent risk factors for thrombosis should receive indefinite anticoagulation, consisting of subtherapeutic doses of low-molecular-weight heparin (LMWH) in cancer patients, and oral anticoagulants in all other conditions. Patients with idiopathic VTE, including carriers of thrombophilia, should receive 6 to 12 months of anticoagulation. The decision to discontinue anticoagulation after this period, or to go on with conventional or less intense warfarin treatment, should be individually tailored and balanced against the hemorrhagic risk.

INTRODUCTION

Ten years ago we published the results of a prospective cohort study dealing with the long-term follow-up of more than 300 patients after their first episode of deep venous thrombosis (DVT) of the lower extremities, alone or associated with clinically symptomatic pulmonary embolism (PE).1 All of them had received short anticoagulation treatment, ranging from 3 to 6 months. The cumulative incidence of recurrent thromboembolism was approximately 20% after two years, 25% after five years, and 30% after eight years. Overall, this risk was considerably higher than previously thought. Among the investigated risk factors for recurrences, those associated with the highest hazard ratio were idiopathic presentation, malignancy, and thrombophilia. As a consequence of this and other similar observations,2-9 in the last 10 years there has been an increasing tendency to prolong anticoagulation, adjusting it to individual risk profiles.10,11
Ten years later, we published the results of a new prospective cohort study, dealing with the long-term follow-up of more than 1600 patients with a first episode of DVT and/or PE recruited at several centers in Italy.\textsuperscript{12} We excluded from the evaluation patients with active cancer, as well as all those with an indication for indefinite anticoagulation. The analysis started at the time of coumarin discontinuation. Surprisingly enough, in spite of the exclusion of patients with active cancer, the cumulative incidence of recurrent VTE was even higher than that reported 10 years earlier, approaching 30\% after 5 years, 35\% after 8 years, and then increasing to 40\% after 10 years (Figure 1). As expected, the recurrence risk was twice as high in patients with idiopathic thrombosis as in those with secondary thrombosis. Much work therefore remains to be done in order to improve the long-term prognosis of patients with acute VTE, especially those with idiopathic thromboembolism.

According to the results of recent randomized clinical trials and prospective cohort studies, LMWH in full doses for the first month, followed by a dose ranging from 50\% to 100\% of the initial regimen, potentially provides a more effective antithrombotic regimen in cancer patients with venous thrombosis than conventional treatment, and is not associated with an increased hemorrhagic risk.\textsuperscript{15-18} In addition, anticoagulation by LMWH is easier to administer, more convenient and flexible, and not influenced by nutrition problems or liver impairment. Thus, the long-term administration of LMWH should now be considered the treatment of choice in patients with metastatic disease and in those with conditions limiting the use of oral anticoagulants.\textsuperscript{10,11} Conventional oral anticoagulants are still the treatment of choice in medical conditions other than neoplastic diseases.\textsuperscript{14}

Other conditions associated with a particularly high risk of recurrent VTE and which therefore require indefinite anticoagulation are multiple (especially if idiopathic) VTE episodes,\textsuperscript{19} the insertion of a permanent vena caval filter (whenever anticoagulation is not contraindicated),\textsuperscript{20} and antiphospholipid antibody syndrome.\textsuperscript{10,11} As compared with control subjects, carriers of antiphospholipid antibody syndrome have a higher risk of recurrence,\textsuperscript{21-23} and a higher risk of death.\textsuperscript{23} It is unclear whether\textsuperscript{20} or not\textsuperscript{25,26} these subjects require anticoagulation regimens that are more intensive than usual (ie, that produce an international normalized ratio [INR] higher than 3.0). The latest international guidelines advise against the routine adoption of intensive anticoagulation regimens.\textsuperscript{10,11}

2. Idiopathic presentation

Prospective cohort, population-based, and randomized clinical trials of recent years,\textsuperscript{1,5,8,12,18,24,27-34} have shown that the most important advance in risk assessment of recurrent VTE after cessation of anticoagulant therapy is probably the recognition that patients whose thrombosis is provoked by a major reversible risk factor, such as surgery or major trauma, have a low risk of recurrence, whereas this risk is higher when thrombosis is provoked by a minor reversible risk factor, such as minor leg trauma, estrogen therapy, pregnancy or puerperium, or prolonged air travel, and is particularly high in patients with an idiopathic episode of VTE.

Accordingly, patients with major transient risk factors, such as major trauma or surgery, should be given 12 weeks of anticoagulant therapy.\textsuperscript{10,11,34} This period can be halved in those patients in whom DVT is confined to the

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Cumulative incidence of recurrent VTE in patients with DVT and/or PE.}
\end{figure}

\section*{RISK FACTORS OF RECURRENT THROMBOEMBOLISM}

1. Persistent acquired risk factors

Patients with active cancer, especially those with metastatic malignancy and those undergoing chemotherapy, carry a particularly high risk of recurrent VTE after discontinuation of anticoagulation,\textsuperscript{13} and so do patients with chronic diseases requiring prolonged immobilization.\textsuperscript{14} Although there is no conclusive evidence from randomized clinical trials, both patient categories should be treated with long-term anticoagulation.
calf vein system. A longer duration may be considered on a case-by-case basis in patients with minor transient risk factors, such as minor trauma, long air travel, pregnancy, puerperium, or hormonal therapy. When a thrombotic episode arises during pregnancy, it should be managed with full-dose LMWH for at least three months, bearing in mind that the treatment should not be discontinued before the end of pregnancy, and should always be extended to cover the first six weeks after delivery. Patients presenting with a first episode of idiopathic VTE should be offered 6 to 12 months of anticoagulation. Although it has recently been reported that prolonging anticoagulation may offer better protection than confining it to the first 6 months, it is generally believed that prolonging anticoagulation is of little value, as it simply delays the date of VTE recurrence while increasing the rate of major bleeding. The annual incidence of major bleeding during long-term anticoagulation is 1.5–2.0%. Moreover, the ‘case-fatality rate’ of an episode of major bleeding is 2 to 3 times as high as it is in patients who develop recurrent VTE.

Debate surrounds the use of low-dose warfarin to improve the benefit-to-risk ratio of prolonging anticoagulation. In a recent double-blind, randomized trial, Ridker et al convincingly demonstrated that low-intensity warfarin prophylaxis, using a targeted INR of 1.5 to 2.0, is superior to placebo in preventing recurrent venous thromboembolism in patients with idiopathic VTE who have previously been treated for at least three months with warfarin at the conventional dosage, and is not associated with increased hemorrhagic risk. However, in a randomized, double-blind trial of similar size, Kearon et al found that low-intensity warfarin (INR, 1.5 to 1.9) was significantly less effective than conventional-intensity warfarin for extended prevention of recurrent thromboembolism in patients with idiopathic VTE, without significant differences in the rate of bleeding complications. Therefore, in patients who require prolonged anticoagulation, a conventional warfarin regimen remains the first-choice treatment. However, a low-intensity regimen can be considered in particular situations, depending on individual judgment.

To optimize the long-term treatment of VTE, new strategies and new drugs are currently under investigation. In a recent prospective cohort study, we have shown that the persistence of residual thrombosis after an episode of proximal DVT, as detected by repeated ultrasonography, is an independent risk factor for recurrent thromboembolism. Veins were considered as recanalized in the case of a vein diameter <2.0 mm in a single determination, or <3.0 mm in two consecutive determinations in patients with DVT. Among 313 consecutive patients with proximal DVT, who were followed up prospectively for up to six years after a three- to six-month period of anticoagulation, those with persistent venous obstruction were at a significantly higher risk of recurrence (RR=2.4), after adjustment for thrombophilia and spontaneous clinical presentation. A similar prognostic value of the resolution of the thrombus was observed by Piovella et al in 179 patients with a symptomatic first episode of DVT, and in 104 patients with DVT occurring after hip replacement surgery serially monitored by ultrasonography over a period of 12 months. In this regard, the results of a recent prospective study by Young et al are particularly intriguing. In follow-up over several years of a cohort of 316 patients with acute DVT, they found a statistically significant higher risk of death in patients with residual thrombus on follow-up ultrasound than in those with earlier vein recanalization (RR=2.8). Although the majority of deaths were due to malignancy, there was a trend towards increased vascular death in the patients with residual thrombus on follow-up ultrasound (RR=4.1). Two recent reviews of clinical trials comparing regimens of anticoagulant therapy, in which ascending phlebography had been used as a tool to assess thrombus evolution, showed an important inverse correlation between thrombus regression and recurrent VTE.

Strategies that include such an assessment of thrombotic burden are intuitively attractive, since a patient can potentially be managed based on the individual course of the thrombotic disease, rather than by broad guidelines alone.

Following the demonstration that a marker of a thrombotic tendency (D-dimer) can be helpful in risk stratification, and thus ultimately in guiding therapy, in individual patients with DVT, Palareti et al performed D-dimer testing one month after the discontinuation of anticoagulation in consecutive patients with a first idiopathic VTE who had received a vitamin K antagonist for at least 3 months. Patients with normal D-dimer level did not resume anticoagulation, whereas those with an abnormal D-dimer level were randomly assigned either to resume or to discontinue treatment. Among patients who stopped anticoagulation, the adjusted hazard ratio for recurrent VTE among those with an abnormal D-dimer level, as compared with those with a normal D-
Finally, new categories of drugs are emerging, which have the potential to simplify the long-term treatment of patients with VTE by obviating the need for periodic laboratory monitoring, while being associated with a favorable benefit-to-risk ratio. They include compounds that inhibit factor Xa, such as idraparinux, rivaroxaban and apixaban, and compounds that inhibit thrombin, such as ximelagatran and dabigatran etexilate. While ximelagatran, a highly effective drug, 33 has been withdrawn from the market owing to its potential liver toxicity, the efficacy and safety of the other preparations are currently being assessed by properly controlled investigations. 46

In summary, the optimal long-term treatment for patients with idiopathic VTE remains to be determined. The decision to discontinue anticoagulation after the first 6 to 12 months, or to continue with conventional or less intensive warfarin treatment, should be individually tailored and balanced against the hemorrhagic risks. Criteria in support of prolonging anticoagulation are the severity of the initial episode, combined thrombophilic abnormalities (see later), suspected malignant disease, positive family history, residual vein thrombosis on ultrasound tests, lack of contraindications to long-term anticoagulation, and (last but not least) patient preference. Conversely, criteria in support of discontinuing anticoagulation are thrombus location in the calf vein system, relative contraindications to anticoagulation (such as very old age, liver or renal failure, peptic ulcer), earlier vein recanalization, D-dimer negativity and, once again, patient preference. Correctly informed patients should play a pivotal role in making such an important decision concerning their lives.

3. Inherited thrombophilia
It is unclear whether or to what extent carriers of inherited thrombophilia are at higher risk of recurrent VTE. It is generally accepted, although not conclusively demonstrated, that carriers of AT, protein C and S, 1,47,48 carriers of hyperhomocysteinemia, 49,50 carriers of increased levels of factor VIII or IX, 51-53 carriers of multiple abnormalities, 6,12 homozygous carriers of factor V Leiden or prothrombin G20210A variant and heterozygous carriers of both mutations 54,55 have a recurrence risk that is higher than that of control subjects. Whether heterozygous carriers of factor V Leiden or prothrombin G20210A variant are also at higher risk of recurrence is controversial, as there are data 7,12,56-61 and against this association. 6,8,24,31,54,55,62-64 Discrepancies among studies may be related to differences in selection of the inception cohort, length of follow-up, initial treatment of the acute thrombotic disorder, duration of treatment, and changes in general management of thrombotic patients. 45 As a consequence, it is virtually unknown whether detection of these abnormalities, which are highly prevalent in Western countries, has the potential to identify a subgroup of patients who might benefit from the adoption of individually adjusted prevention strategies following their first thrombotic episode. 10,11 Over recent years a good number of prospective cohort and randomized clinical trials have reported data on the long-term outcome of heterozygous carriers of either mutation after discontinuing anticoagulation. We therefore undertook the first systematic review and meta-analysis of available prospective investigations. 66 Our meta-analysis indicates that the heterozygous carriage of FVL confers an increased (by about 40%) risk of VTE recurrence, while the risk conferred by the heterozygous carriage of PTM is lower and of uncertain interpretation, as it depends on the method used for its estimation, and ranges between 20% (using the Mantel-Haenszel fixed-effects model) and 36% (using the Der Simonian and Laird random effects model, which takes into greater account the inter-study variability). 66

According to the latest international guidelines, carriers of whichever thrombophilia who have a thrombotic episode in conjunction with a promptly detectable transient risk factor for thrombosis should receive short-term (3 to 6 months) anticoagulation. Heterozygous carriers of factor V Leiden or prothrombin G20210A variant who develop an idiopathic VTE episode should be regarded as noncarriers. Carriers of multiple abnormalities, carriers of AT, protein C or S, increased factor VIII or IX, hyperhomocysteinemia, homozygous carriers of factor V Leiden or prothrombin G20210A variant and heterozygous carriers of both mutations.
should receive a 6- to 12-month course of anticoagulation.\textsuperscript{10,11} According to the results of a recent controlled, randomized clinical trial, homocysteine lowering by B-vitamin supplementation does not help prevent recurrent venous thrombosis.\textsuperscript{67} As patients with thrombophilic defects who belong to thrombophilic families are more likely to have recurrences than are unselected patients with thrombophilic defects,\textsuperscript{65} this consideration should be taken into account when deciding the duration of anticoagulant therapy following the first thrombotic episode. Further prospective studies addressing the role of thrombophilia in determining the risk of recurrent VTE are indicated, as are randomized studies addressing the benefit-to-risk ratio of prolonging anticoagulation in carriers of thrombophilic abnormalities. Meanwhile, clinical judgment on a case-by-case basis should be used when administering long-term anticoagulation to carriers of whichever thrombophilic abnormality after the first thrombotic episode.

4. Other factors

In a prospective study conducted in Austria, patients with clinically symptomatic PE were found to be associated with a much higher risk of recurrent events than those with symptomatic DVT not associated with PE.\textsuperscript{27} These findings, however, have not been confirmed by a prospective cohort investigation recently carried out at our institution in a much wider series of patients.\textsuperscript{12} In our study, the rate of recurrent VTE was significantly higher in patients with proximal DVT (alone or associated with clinically symptomatic PE) than in those with PE alone at presentation (Figure 2). Accordingly, there seems to be no reason to systematically adopt a longer duration of anticoagulation in patients with PE than in those with DVT. Our results are consistent with data from a randomized, controlled clinical trial, which failed to show an appreciable advantage from prolonging anticoagulation beyond three months both in the subgroup of patients with idiopathic PE and in the subgroup of patients with secondary PE.\textsuperscript{30} Interestingly, in both the Austrian and Italian cohorts, patients with clinically symptomatic PE were at a higher risk of recurrent PE than those with DVT alone.\textsuperscript{12,27} As PE is potentially more dangerous than DVT alone, long-term anticoagulation may be considered in selected patients with idiopathic PE, at least in those presenting with life-threatening manifestations.\textsuperscript{14}

Recently, an unexpected association has been reported between male sex and recurrent VTE, especially in patients with idiopathic VTE.\textsuperscript{68} The are recent literature data for\textsuperscript{5,6,8,69-73} and against\textsuperscript{1,2,4,7,74-76} this association. In a prospective study recently conducted in Italy in a broad cohort of patients, we could only find a slight and nonsignificant increase in the risk of recurrent VTE in men (Figure 3).\textsuperscript{12} Even when the analysis was confined to patients with idiopathic VTE, we could not show significant differences between men and women in this regard. Even if we assume that women have a slightly lower recurrence rate than men, the 35% recurrence rate we observed after 10 years of follow-up, as compared with 40% in males, means that this difference is of virtually no clinical relevance. Therefore, based on current evidence, we think that sex should not be regarded as a qualifying factor in deciding the duration of oral anticoagulant therapy after the first episode of thrombosis.

Other predictive factors of VTE recurrence are the location of DVT and the patient’s age. As clearly shown by several investigations, patients with isolated calf DVT have a
lower risk of recurrent VTE than patients in whom thrombosis involves the popliteal or more proximal veins.3,29 Accordingly, patients with isolated calf vein thrombosis, except for selected cases, should not receive anticoagulation for longer than 12 weeks when the clinical presentation is idiopathic, or for longer than 6 weeks when the thrombotic episode is triggered by transient risk factors.10,11 Finally, old age, which has long been regarded as a risk factor for venous thrombosis,5 has recently been identified as a predictor of recurrent VTE.12 Thus, the common practice of administering less intensive or shorter term anticoagulation to old patients, because of the fear of hemorrhagic complications, should be reconsidered.77

CONCLUSIONS

The risk of recurrent thromboembolism after an episode of VTE is high, and approaches 40% of all patients after 10 years of follow-up. The risk of recurrent VTE is higher in patients with active cancer, prolonged immobilization because of disease, antiphospholipid antibody syndrome, multiple VTE episodes, and the application of a permanent vena caval filter. If there are no contraindications, patients with permanent risk factors for thrombosis should receive indefinite anticoagulation, consisting of subtherapeutic doses of LMWH in patients with cancer, and vitamin K antagonists in all other conditions. The risk of recurrent VTE is definitely higher in patients with idiopathic DVT than in those with secondary DVT. While in the latter group (including carriers of thrombophilic abnormalities) a short duration of anticoagulation (except for pregnant women, requiring full-dose LMWH throughout pregnancy and for the first six weeks after delivery) is all that is needed, patients with idiopathic VTE, including heterozygous carriers of factor V Leiden or prothrombin mutation, should receive 6 to 12 months of anticoagulation. The decision to discontinue anticoagulation after this period, or to continue with conventional or less intensive warfarin treatment should be individually tailored and balanced against the hemorrhagic risks. It remains to be established whether assessing residual vein thrombosis and/or D-dimer values can help define the optimal duration of anticoagulation. Carriers of multiple abnormalities, carriers of AT, protein C or S, increased factor VIII, hyperhomocysteinemia, homozygous carriers of factor V Leiden or prothrombin G20210A variant and heterozygous carriers of both mutations who develop an episode of idiopathic VTE should receive on average a 6- to 12-month course of anticoagulation. Administration of long-term anticoagulation will depend on case-by-case clinical judgment. Patients with proximal DVT are at a higher risk of recurrent VTE than those with isolated calf DVT. Patients with proximal DVT, alone or associated with PE, are at a higher risk of recurrent VTE than those with PE alone. However, patients with clinically symptomatic PE are at higher risk of recurrent PE than those with DVT alone. The risk of recurrent VTE increases with age, and does not substantially differ between men and women. Women of childbearing age are at higher risk of recurrent VTE when they are given hormonal treatment or become pregnant. Hormonal compounds should no longer be administered. While post-partum anticoagulation is recommended in all women with previous VTE, only those in whom the previous episode was triggered by hormonal compounds or developed during pregnancy.78-80 Accordingly, hormonal treatment should be strongly discouraged in women with previous VTE. Whenever hormonal treatment is deemed to be necessary, the concomitant administration of oral anticoagulants should be considered. Postpartum anticoagulation is recommended in all women with previous VTE.81 While the systematic use throughout pregnancy of compression hosiery is recommended in all women with previous VTE, antenatal thromboprophylaxis with LMWH should be offered whenever the previous episode was idiopathic or was pregnancy- or estrogen-related, in carriers of thrombophilia, if there is a family history of thrombosis, if there are additional risk factors (such as obesity), and in women with multiple previous VTE episodes.81

Poor quality of vitamin K antagonists may or may not be an additional risk factor for recurrent VTE.82,83 Interestingly, a family history of VTE does not segregate patients into high- or low-risk categories, and is not suitable to identify patients at increased risk of recurrent VTE.84 Obesity, which is a well-known risk factor for venous thrombosis,85,86 does not seem to increase the risk of recurrent VTE.87 Finally, it has recently been reported that a number of simple laboratory tests, such as determination of activated partial thromboplastin time88 and global coagulation assays measuring thrombin generation,89-90 can help identify patients at a lower or higher risk of recurrent VTE. However, these findings need confirmation.

Women who had their first episode of thromboembolism while of childbearing age are at higher risk of recurrence when they are given hormonal treatment or become pregnant. This risk is particularly high in women in whom the first episode was triggered by hormonal compounds or developed during pregnancy.78-80 Accordingly, hormonal treatment should be strongly discouraged in women with previous VTE. Whenever hormonal treatment is deemed to be necessary, the concomitant administration of oral anticoagulants should be considered. Postpartum anticoagulation is recommended in all women with previous VTE.81 While the systematic use throughout pregnancy of compression hosiery is recommended in all women with previous VTE, antenatal thromboprophylaxis with LMWH should be offered whenever the previous episode was idiopathic or was pregnancy- or estrogen-related, in carriers of thrombophilia, if there is a family history of thrombosis, if there are additional risk factors (such as obesity), and in women with multiple previous VTE episodes.81

Poor quality of vitamin K antagonists may or may not be an additional risk factor for recurrent VTE.82,83 Interestingly, a family history of VTE does not segregate patients into high- or low-risk categories, and is not suitable to identify patients at increased risk of recurrent VTE.84 Obesity, which is a well-known risk factor for venous thrombosis,85,86 does not seem to increase the risk of recurrent VTE.87 Finally, it has recently been reported that a number of simple laboratory tests, such as determination of activated partial thromboplastin time88 and global coagulation assays measuring thrombin generation,89-90 can help identify patients at a lower or higher risk of recurrent VTE. However, these findings need confirmation.
was idiopathic or was pregnancy- or estrogen-related require antenatal prophylaxis with LMWH, as do carriers of thrombophilia, women with a family history of thrombosis, those with additional risk factors, and those with multiple previous VTE episodes.

REFERENCES


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Iliac vein outflow obstruction in ‘primary’ chronic venous disease

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ABSTRACT

The nonthrombotic iliac vein lesion (NIVL) was first described in 1908. Since then, it has become clear that the lesion is present in over half the general population in silent form. A clinical syndrome variously known as May-Thurner syndrome, Cockett syndrome, or “iliac vein compression syndrome”, caused by NIVL, is thought to be a rare form of chronic venous disease (CVD). However, with liberal use of intravascular ultrasound (IVUS), the lesion is found in over 90% of highly symptomatic CVD cases, with a very broad clinical and demographic spectrum. Silent NIVL in the general population may play a permissive role in the development of CVD. Venous stenting of NIVL provides excellent clinical relief including healing of stasis ulceration even when the associated reflux is left uncorrected. Liberal use of IVUS is recommended in CVD cases with significant symptoms of swelling, pain, or stasis skin changes.

Chronic venous disease (CVD) is also more frequent on the left side. McMurrich in 1908 was the first to demonstrate an intrinsic web-like lesion obstructing the lumen of the left iliac vein at the arterial crossover point. Numerous autopsy studies since have confirmed the presence of such intraluminal lesions in a surprisingly high 20% to 30% of unselected cadavers. The morphology of the lesion can vary from a thin membrane to “ridges, velums, chords spurs, or bridges”; “quilted” wall adhesions, and even total occlusion. There is general agreement that the lesion is not postthrombotic but controversy persists whether it is ontogenic or traumatic from pulsations of the overlying artery. It is also clear from autopsy studies that extrinsic compression of the vein by the crossing artery occurs even more often than the presence of intrinsic webs and membranes. Recent data from magnetic resonance (MR) imaging suggest that the combined incidence of intrinsic and extrinsic lesions in the general population could be as high as 66%. Some confusion regarding the underlying pathology has arisen from use of the traditional nomenclature “iliac compression syndrome”, Cockett syndrome, and May-Thurner syndrome, which are often used synonymously. Since modern imaging
modalities cannot distinguish between extrinsic and intrinsic lesions with adequate reliability, it is suggested that the term nonthrombotic iliac vein lesion (NIVL) be used to be inclusive of both types of lesions.

**Diagnosis**

Venographic features of NIVL are quite variable and often subtle (Figure 1). Extensive contrast studies by Lea Thomas and colleagues3-6 half a century ago established that the diagnostic sensitivity of venography for NIVL is only on the order of about 50%. Concurrent use of intravascular ultrasound (IVUS) with venography has confirmed the poor sensitivity of the latter in our own experience.8 This derives from obscuration of the lesion in frontal projections becoming evident only in lateral or oblique projections (Figure 2). Even with multiplane venography, some lesions can be missed. Since IVUS has a diagnostic sensitivity of >90% and is free of radiation, it has become the diagnostic standard in NIVL.

Liberal use of IVUS in CVD patients has also provided a broader demographic spectrum for NIVL than the traditional concept.9 IVUS lesions occur in both sexes and all age groups; lesions are found both on the left and right side. A new finding was the occurrence of the lesion at distal arterial crossover points (Figure 3). NIVL has a very high prevalence in symptomatic CVD: over 90% of “primary” patients with significant symptoms of pain, swelling, or venous stasis skin changes will be found to have NIVL by IVUS examination.

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**Is NIVL pathogenic?**

Ever since its first description, controversy has surrounded NIVL with regard to its pathologic import, because the lesion appears to be largely silent in the overwhelming majority of the population in which it is found. In fact, some have argued that the lesion be considered a ‘normal’ anatomical variant because of its quiescence and high prevalence.7 On the other hand, NIVL is undeniably
Causative of pathology in several subsets of patients. Cockett and colleagues highlighted NIVL as a cause of clinical acute iliac vein thrombosis.10 Hundreds of well-documented cases of this type have appeared in the literature since. In a large registry11 of patients with acute iliac vein thromboses, NIVL-like lesions are detected in about one-third or more of patients after catheter-directed thrombolysis. Stent placement to correct such lesions after successful clot lysis is now standard practice. Cockett and colleagues also described a chronic form of disease caused by NIVL presenting with leg pain and swelling.3 They popularized the notion that this form of the disease was prone to affect the left lower limb of young women, even though their clinical series included older patients, men, and involvement of the right leg as well. The notion that NIVL is pathogenic at least in some patients is now readily accepted,12,13 but the relationship between the symptomatic lesions in patients and the asymptomatic ones in the general population has remained obscure.

**NIVL as a permissive lesion**

One way to reconcile these apparent contradictions is to view NIVL as a permissive lesion.9 A permissive lesion is one that is generally silent until an additional pathology or sequel is superimposed and triggers symptoms. Numerous permissive lesions are known to play a role in human pathology. A well-known example is patent foramen ovale, which has a population incidence similar to that of NIVL (20% to 30%), but remains silent except occasionally when passage of a paradoxical embolus takes place. Some other examples include gastroesophageal reflux disease and asthma, ureteric reflux and pyelonephritis, cricopharyngeal spasm and Zenker’s diverticulum, Helicobacter and peptic ulceration, obesity and diabetes, diabetes and neuropathy, middle lobe syndrome and pneumonia, carotid stenosis, and transient ischemic attacks. A general principle in treating many of these complex pathologies is to address the permissive lesion first, which alone may remit symptoms. In nonresponders, the secondary pathology may need to be addressed in sequence.

NIVL displays many of these characteristics of a permissive lesion. Despite its high incidence in the general population, it remains largely silent. We hypothesize that additional pathologies or sequelae such as trauma, cellulitis, distal thrombosis, lymphatic exhaustion, or reflux may render the extremity symptomatic. In the elderly, atherosclerosis of the overlying artery, venosclerosis, decreasing mobility, and leg dependency or other comorbid conditions predisposing to pedal edema may be contributory factors in symptom expression. In some cases no such secondary aggravating factors are apparent and symptom expression may simply be related to further progression of the stenotic lesion or to another as yet obscure cause.

**Results of stenting to correct NIVL**

Venous stenting is safe and the morbidity is minor.14 “Primary” CVD cases enjoy extraordinary stent patency (Figure 4). Clinical results are excellent as well, as shown in Figures 5 to 8. Long-term data (unpublished) extending the follow-up to 9 years show no major decline in the survival curves. A remarkable finding was that the thera-
Nonthrombotic iliac vein lesion (NIVL)

Phlebolymphology.

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Nonthrombotic iliac vein lesion (NIVL) therapeutic response to stent placement was excellent even when associated reflux, 30% of which was ‘axial’, was left uncorrected. Results in this subset were no different from the NIVL subset without reflux (Figures 5 to 8). Remarkably, 67% of ulcers healed (cumulative) in response to stenting alone, despite the presence of uncorrected residual reflux (Figure 7). More than other manifestations of CVD, stasis ulcer is thought to be a product of reflux. These results support the notion that NIVL is a permissive lesion.

Current approach to ‘primary’ CVD patients

IVUS is recommended in patients with significant symptoms of swelling, pain (VAS>5/10), or stasis skin changes after conventional forms of therapy have failed. NIVL with significant lumen stenosis (>60%) will be found in a great many of these ‘primary’ CVD patients, and can be stented at the same session. In selected cases, laser ablation of the saphenous vein can be combined with stent placement. These are percutaneous procedures carried out on an outpatient basis (23-hour admission). Symptoms will ameliorate in most patients. In the minority where adequate relief is not achieved, additional open procedures such as veno-venous bypass or valve reconstruction may be considered. Prior stent placement does not preclude subsequent open procedures.

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Investigation and treatment of pelvic venous insufficiency (PVI) in women to date has primarily involved its most familiar clinical presentation, ie, pelvic congestion syndrome (PCS) accurately described by Hobbs. For the last few years, more attention has focused on involvement of PVI in the pathogenesis of primary varicose veins or recurring varicosities of the lower limbs. This finding has been confirmed by a national epidemiologic survey that evaluated the potential incidence of pelvic pain of venous origin in a targeted population of women, and its possible association with lower limb varicosities.

While advances in the recognition of PCS have been made as the result of findings of laparoscopy and phlebography, currently its relationship with superficial varices of the lower limbs has been further elucidated by non-invasive imaging methods, primarily Doppler ultrasonography.

Treatment of this condition by interventional radiology procedures is an effective therapeutic alternative in ruling out pelvic varicosities, and complements surgical disconnection of incontinent anastomoses (sites of leakage), which supply varicose veins of the lower limbs.

**CLINICAL PRESENTATION**

PVI seems to be the most appropriate term to describe the hemodynamic findings in this disease and fits the description of its different clinical manifestations. Depending on the territory mainly involved, such manifestations predominate in the pelvis or the lower limbs: in PCS and/or varicose veins of the lower limbs.

The principal specialists involved in management of this condition, ie, gynecologists, vascular surgeons, and angiologists, should therefore be aware of PVI when they examine women presenting with pelvic pain and/or atypical or recurring varicose veins of the lower limbs, and should order the required tests, in particular, Doppler ultrasonography.
Pelvic congestion syndrome

PCS is characterized by chronic pain (of more than 6 months duration) manifest by pelvic heaviness, exacerbated by the standing position, and its presence at the end of the day and during the premenstrual period. Dysmenorrhea, dyspareunia, post-coital pain and dysuria are frequently present. Such pain is refractory to analgesics. Sometimes, hematuria associated with left low back pain is observed, suggesting tight extrinsic compression of the left renal vein between the aorta and the superior mesenteric artery, the so-called “nutcracker phenomenon.”

Examination may reveal a retroverted uterus combined with varicose veins of the lower limbs, suggesting superficial venous insufficiency (SVI), hemorrhoids, vulvar and gluteal varicosities.

Varicose veins of the lower limbs

Lower limb varicosities can be manifest in three forms: perineal and/or gluteal varicosities, specific for SVI, territories of the long or short saphenous veins, and recurrence following invasive treatment. In these two populations, which often overlap, there is an increased incidence of multiparous women; and a family history of venous disease, gynecological disorders and surgery. Emotional disorders are often observed in such patients.

SCHEMATIC DESCRIPTION AND ANATOMICAL CHARACTERIZATION OF THE PELVIC VENOUS SYSTEM IN WOMEN

Anatomical characteristics

This complex and incompletely systematized network of intersecting veins centered around the uterus comprises many interconnected plexuses. The very dense collecting network is located as a shunt in the femoral iliocaval system, and disease in one plexus can affect another.

The paucity or total absence of venous valves allows two-directional blood flow. Another essential feature of the pelvic venous system is its ability to adapt to certain conditions, in particular pregnancy (Figure 1). The physiological changes that it produces can become abnormal and continue after childbirth.

Anatomical description

The pelvic venous system consists of visceral and parietal networks.

- The visceral network: is highly variable, forms avalvular venous plexuses, with abundant interconnecting utero-ovarian, uterovaginal, vesicovaginal, vesical and rectal anastomoses, which are partly drained by the visceroperineal venous trunk into the avalvular internal iliac vein, and partly into the ovarian veins. Lastly, an accessory pedicle, the vein of the round ligament, connects to the utero-ovarian system on one side and on the other with the superficial epigastric vein or the external iliac vein or both (Figure 2);

- The parietal network is systematized, but nonetheless has many anatomical variants. Generally, the veins follow a pathway very similar to that of the arteries. This network consists of the superior gluteal, inferior gluteal, lateral sacral, iliolumbar, obturator, and internal pudendal veins (Figure 3).
Pelvi-perineal venous insufficiency

The gluteal-ischiatic network:
- The gluteal vein, which drains the sacral plexus, anastomoses with the external circumflex iliac vein, a collateral of the internal saphenous vein.
- The ischiatic vein, which drains the posterior compartment of the thigh, empties into the internal pudendal vein and anastomoses with the deep femoral vein, its perforating veins and with the internal saphenous vein.

These two veins can anastomose with each other.

The internal pudendal venous network:
- It anastomoses with the long saphenous vein and with the external pudendal vein via the network of the superficial and deep dorsal veins of the clitoris, or directly by anastomosis between the internal pudendal and the external pudendal veins in the labia majora (which gives rise to vulvar varicosities during pregnancy).

These veins combine to form the anterior branch of the internal iliac vein, which is a single vein in 50% of cases, double in 36%, and plexiform in 14% (Figure 3).

These two networks are drained by three collecting veins: the internal iliac vein, which with the external iliac vein forms the common iliac vein, and arises from the inferior vena cava, the ovarian veins, which on the left side end in the renal vein in 99% of cases (a single vein in 79% of cases) and in the vena cava in 1%; and on the right side end in the inferior vena cava in 98% of cases (a single vein in 78% of cases) and in the renal vein in 2%, the superior rectal vein, which joins the inferior mesenteric vein.

The intra/extra-pelvic anastomoses with the lower limbs (Figure 4).

There are two connecting networks, the gluteal-ischiatic and the internal pudendal venous.
• The internal pudendal vein forms an anastomosis with the perineal veins of the visceroperineal trunk (anterior branch) and the obturator branch.

**PATHOPHYSIOLOGY**

The ovarian veins, which drain in a vertical direction, frequently have valves (48% on the right side, 62% on the left) at their ends (84% on the right side, 77% on the left) and normally at the mouth of each branch.

The hypogastric veins, which drain in a horizontal direction, most often do not have valves and communicate largely between each other by different venous plexuses of the pelvis. Thus, they form a unique network that is physiologically incontinent.

The perineal, labial and clitoral superficial veins have valves, which prevent a reflux from the pelvis to the lower limbs.⁶

Some anatomical, hemodynamic and hormonal conditions, which can occur concomitantly, may, as a result of the excessive pressure they produce, generate or exacerbate venous disease with venous insufficiency, which causes varicosities of the lower limbs and/or pelvic varicocoeles.

• The nutcracker syndrome: there is a variable degree of compression of the left renal vein in its pathway between the superior mesenteric artery and the aorta. Evaluation of the impact of this effect is difficult because it varies depending on the patient’s position, respiration, and is very likely enhanced by the standing position. It can have a specific clinical expression associating pelvic congestion syndrome with left flank pain and microscopic hematuria (nutcracker syndrome).⁴

• The natural very high blood flow in the renal veins;

• Pregnancy generates major hemodynamic changes: very high blood flow in arteries, and thus in the uterine veins (60 times normal), and compression of the major large veins which can produce pelvic and perineal vein dilation. These veins can become varicose and progress after childbirth. They produce venous reflux and varicosities in the superficial network of the perineum, vulva, and lower limbs. This risk increases with subsequent pregnancies.

These circumstances produce almost constant dilation of the left ovarian vein and increased blood flow into the uterine veins. Generally, the right ovarian vein is subject only to pregnancy-related changes, and often serves as a shunt, relieving the effects of incontinence of the left ovarian vein.

The effects of incontinence of the left ovarian vein can be compared with those of the long saphenous vein, because of its biomechanical consequences: the height of the column of blood is increased by the high blood flow in the renal vein.

• This incontinence becomes permanent in the uterine veins, which are dilated during pregnancy. Extension to the vaginal veins and then to the perineal veins occurs as a logical consequence

• Extension to other anastomoses of the uterine veins and a possible direct impact on the arch of the long saphenous vein are explained by the concept of very high blood flow. If indeed one of the pathways of physiological drainage is this arch, pregnancy or incontinence of the ovarian vein will divert blood flow towards this downward drainage.

• The long saphenous vein is not always able to accept this increased blood flow. This can then result in incontinence of the underlying long saphenous vein at the saphenofemoral junction. This abnormality is frequent and may account for at least 15% of cases of incontinence of the long saphenous vein.

• Another mechanism for incontinence of the saphenous veins can be the increased blood flow into the posterior communicating vein, the natural drainage pathway of the perineal veins.

• Subsequently, incontinence occurs below the area where it empties into the long saphenous vein, or even incontinence of the communicating vein and then of the short saphenous vein.

**INVESTIGATIONS**

**Computed tomographic scan and magnetic resonance imaging**

Computed tomographic (CT)-scan and magnetic resonance imaging (MRI) are rarely proposed as first-line methods for diagnosis of PVI.³ Yet, they do have an essential part to play in the assessment of abdominal-pelvic pain. In this context, they can detect ovarian vein incontinence and varicocele, which can be asymptomatic (Figure 5).⁸ They can rule out other major causes of pelvic pain, eg, fibroids, endometriosis, adenomyosis, an ovarian mass, and disorders of the lumbar spine.
MRI with injection of gadolinium has advantages over CT-scan: there is no associated radiation, it identifies the direction of blood flow, and has increased sensitivity and specificity (Figure 6).

**Figure 5. CT-scan: coronal reformatting (multiplanar reconstruction images): dilation of the ovarian vein and left para-uterine varicosities.**

**Figure 6. T2 Fat Sat axial MRI: left para-uterine varicocele.**

**Doppler ultrasound**

Doppler ultrasound (Duplex scanning) is the first-line method of investigation in suspected PVI. Venous examination of the lower limbs (with a linear transducer of at least 7.5 MHz) is carried out prior to, or concomitantly with, examination of the pelvis when there are varicosities. The examination is performed opposite the anatomic zones and seeks to detect reflux, which if longer than 1s signifies incontinence. It is necessary to establish mapping of abnormalities and to assess the relative impact of pelvic hemodynamic abnormalities. In female patients who do not undergo surgery, varicosities are classified as saphenous or non-saphenous. When there is saphenous vein involvement, it is essential to define involvement of the saphenofemoral junction in the case of the long saphenous vein, and participation of the posterior communicating vein in incontinence of the short saphenous vein. The absence of involvement of the saphenofemoral junction, as well as incontinence of the posterior communicating vein, are findings in support of participation of the posterior communicating vein or of pelvic varices in this process. For nonsaphenous varicosities, pelvic origin is the conclusion in the case of gluteal and/or perineal varicosities.

Examination of patients presenting with varicose vein recurrence after surgery or effective sclerotherapy is extremely complicated and requires excellent knowledge of varicose venous disease. Features that suggest PVI may include the absence of a neo-arch, the stump of the arch or of an incontinent perforating vein, and the existence of veins of abdominal origin (superficial circumflex, superficial epigastric vein) or subinguinal origin (external...
pudendal vein, posterior communicating vein), emptying into the incontinent superficial venous network.9−11

In a recent article, possible involvement of two sites of systemic leakage were found, one opposite the inguinal orifice (where the leak may be attributable to the vein of the round ligament) and the other opposite the superficial aponeurosis of the perineum (where the leak may be attributable to branches of the internal pudendal vein).6

Examination of the abdomen (with a 5.3 or 5.2 MHz transducer depending on body weight) requires preparation: the patient must be fasting and have had a residue-free diet.

The ovarian veins (Figure 7):

- On the left side, the vein is identified as a compressible hypoechoic image, emptying into the renal vein seen on cross-section. The examination is then continued with longitudinal sections. The vein then ascends along the anterior aspect of the psoas muscle, from inward to outward, crossing the ureter at L4-L5 and then anterior to the iliac axis, practically opposite the arterial bifurcation.

- It is considered pathological when there is reflux that lasts longer than two seconds, and when venous diameter is greater than 8 mm. Reflux is sought after compression of the upper part of the inferior vena cava, in the standing position. When observed, it very frequently occurs spontaneously:

- On the right side, the right ovarian vein rarely empties into the renal vein. It is more difficult than the left ovarian vein to identify strictly.12 When pathological, it meets the same criteria as on the left.

- The left renal vein, the iliocaval veins: and the “nutcracker syndrome” should systematically be sought, but the evaluation is best performed by phlebography4 (Figure 8). Moreover, it is appropriate to look for Cockett’s syndrome or sequelae of iliac vein thrombosis.

Endocavitary examination (Figure 9) requires use of a 5 to 7.5 MHz endocavitary transducer. Its primary use is in visualizing the lateral uterine and lateral vaginal venousplexuses, the adnexal veins and the transuterine venous passages. Venous formations appear as anechoic cords, more or less dilated. A diameter greater than 8 mm, a

Figure 7. Doppler ultrasonography of pelvic varicosities, upper panel: dilation of the ovarian vein, mesoaortic compression.
Sinuous appearance, and an abundance of veins are the features most often referred to when speaking of PVI. Venous stasis with reduced blood flow rate and the absence of change related to respiration should also be sought to posit PVI. Most of the time, a Valsalva maneuver (or compression of the vena cava) produces a reflux without it being systematically considered abnormal.

**Phlebography**

As the reference imaging method of the pelvic veins, phlebography should be performed only after confirmation by Doppler ultrasound of utero-ovarian vein incontinence, uterine varicosities, and as the first step in a therapeutic procedure.

After prior consultation with an anesthesiologist, which is essential, this test is generally performed under local anesthesia, with/without placement of a urinary catheter. It confirms the diagnosis and provides all information necessary for treatment: anatomy, degree of valvulation, and of dilation of the four major venous trunks involved, direction of blood flow. It is also useful to detect communicating vessels.

Two approaches are possible: brachial or femoral.

After inserting a 4/5 French Desilet, the patency and abnormalities of the major collecting vessels, the iliac vein, vena cava and left renal vein, are checked. Then, the ovarian veins opposite and the internal iliac major veins are partly opacified during a Valsalva maneuver. The diameter of the veins, the size of varicoceles, the degree of stasis of the contrast medium, and points of leakage are assessed, which will allow treatment to be adapted.

Catheters and guidewires used are as follows:

- By the femoral approach: a Cobra 1.2 for the left utero-ovarian vein and the internal iliac veins and a Simmons 1.2 for the right ovarian vein;
- By the brachial approach: a multipurpose catheter, a Picard catheter of appropriate length (125 cm);
- Hydrophilic guidewires: 0.35 from 135 to 230 cm;
- The author's personal variation: opacification with an occlusion balloon catheter to better assess the extent of the varicoceles and enhance demonstration of points of leakage.
ENDOVASCULAR TREATMENT: EMBOLIZATION

Embolization is performed subsequent to phlebography but is not always complete in a single phase. This procedure starts by treating the incontinent ovarian veins and then the points of leakage.

Endovenous navigation runs into some difficulties, in particular, in relation to the hypogastric veins, with tortuous varicosities, valves, collateral branches, venous compliance that varies with position, and respiratory time. This is to be taken into account in adjustment of coil diameter, which should be overvalued by 1-2 mm.

Materials for embolization: To inject the veins, the same catheters are used as for phlebography, sometimes a 3F coaxial catheter for the right ovarian vein.

Materials differ depending on the areas to be embolized:
• Sclerotherapy agents (Aetoxysclerol) for venous networks and taking the collateral vessels into account, with a 30% dextrose/water solution.
• Coils for occlusion of the large venous vessels, most often these two materials are used in combination.
• More rarely, a polymerizing agent (Histoacryl) mixed with ultrafluid Lipiodol is used.

Embolization starts with the left utero-ovarian vein (Figures 10 and 11).

Four to five coils 8 to 15 mm in diameter over 4 to 20 cm in length are released; either into the main collateral veins, or at the origin of the vein (promontory). Some operators in addition use sclerotherapy agents between the coils. The collaterals identified along the main venous axis are occluded by the smallest coils (3-5 mm). The right ovarian vein is systematically embolized by some authors, while this is done by other clinicians only if this vein is incontinent. In the hypogastric veins, some clinicians treat only incontinent collaterals, with coils and sclerotherapy agents, while others perform sclerosis of the hypogastric veins en masse (Figures 12 and 13).

Author’s personal variation: the sclerotherapy agent (4-8 cc 3% Aetoxysclerol foam) is injected under protection of a balloon catheter kept inflated for 5 minutes, then is supplemented by release of coils before deflation.

Post-procedure therapy: Antibiotics are not systematically prescribed, analgesics, and anti-inflammatory agents in principle are given for 5 days.

Serious treatment-related complications are rare: migration of the embolization material. In the post-therapy period, the following manifestations may be observed: pelvic heaviness and pain, left low back pain, fever. These symptoms can be controlled perfectly with treatment and rapidly regress.

Figures 10 and 11. Phlebography prior to embolization: incontinence of the ovarian vein and left para-uterine varicosities. Repeat phlebography after embolization.
Immediate technical results: A 95% to 100% success rate for embolization of the ovarian veins in the majority of studies, but lower success rates for leakage points dependent on the hypogastric veins: 85%.\(^2\)

Clinical results: It is difficult to classify results according to baseline clinical criteria: PCS and/or concomitant perineal varices and/or varicosities of the lower limbs. The majority of publications in particular involve PCS. They only amount to a few hundred cases and results do not necessarily appear better when the two ovarian veins are systematically occluded.\(^4,14-16\) The results reported in this context in particular are expressed in terms of symptom improvement and are around 70%, in a follow-up period ranging from 6 to 22 months. Clinical improvement occurs only 3 to 4 weeks after the start of therapy. In the setting of veins that flow back to the lower limbs, the more complete the treatment, the better the results. Only one (large) study reported an 90% improvement in symptoms.\(^2\)

Doppler ultrasound is the basic method of investigation of PVI and its consequences in the lower limbs. It is an essential procedure prior to phlebography, which should only be performed with intent to treat. Embolization has been shown to be an effective, low-risk procedure to rule out involvement of the ovarian veins. In the hypogastric veins and their pathological branches, the procedures for embolization and the materials used can be improved. The clinical results of this new therapeutic procedure remain to be evaluated by multicenter studies.

**CONCLUSION**

Some primary varicosities of the lower limbs and some varicose vein recurrences can arise from pelvic venous insufficiency. Therefore, it is important to look for PVI (pelvic congestion syndrome) in an interview with the patient, and in the case of suggestive signs, to order appropriate tests.

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REFERENCES

Skin necrosis as a complication of compression in the treatment of venous disease and in prevention of venous thromboembolism

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BACKGROUND

The main concern with compression treatment for chronic venous disease of the lower limb remains compliance, which is difficult to assess depending on the clinical status. Complications like skin allergic reaction and eczema, and nerve palsy, have been reported, but the most severe is skin necrosis in diabetics or patients with peripheral arterial disease of the lower limbs. There is a consensus for contraindicating compression in patients whose ankle/brachial index (ABI) is less than 0.6, but the arterial disease is not always identified. Diabetes also carries a potential risk of skin wound, but few data are available.

LITERATURE REVIEW

A literature search for skin necrosis related to compression identified several articles, including the Scottish survey. The aim of this survey was to review the experience of Scottish surgeons over the past five years concerning skin necrosis induced or aggravated by compression of the lower limb. All 154 consultants in general surgery asked to complete a questionnaire did so. One third of them reported at least one case of damage induced by compression, and 20% more than one. The replies are shown in Table I.

| Keywords: bandages (and contraindications), diabetes mellitus, leg ulcer, skin ulcer, thromboembolism, vascular disease, varicose vein (and surgery). |

<table>
<thead>
<tr>
<th>No. of surgeons (%)</th>
<th>No. of cases</th>
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<tr>
<td>Ulcer/necrosis due to compression bandages</td>
<td>29 (19)</td>
</tr>
<tr>
<td>Elastic stockings</td>
<td>16 (10)</td>
</tr>
<tr>
<td>Stockings used to prevent thromboembolism</td>
<td>17 (11)</td>
</tr>
<tr>
<td>Total</td>
<td>62 (40)</td>
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Table I. Compression damage.
Damage necessitated reconstructive arterial surgery in 7 cases and amputation in 12 (12/147 = 8.2%). Other cases of amputation have been reported in the litterature (Figure 1).

Our personal experience includes two diabetic patients who presented severe skin necrosis, related in both cases to stockings prescribed for thromboembolism prevention.

The Scottish survey does not, of course, give the prevalence of this complication, but the question of under- and overreporting arises. Like the authors, I think the number was underestimated, for several reasons.

- The survey was retrospective and depended on recollection.
- The cause of this kind of damage often remains unrecognized.
- The survey was limited to consultant general surgeons, and excluded vascular surgeons, dermatologists, and angiologists.
- Eighty percent of patients with leg ulcers in the UK over this period were managed entirely in the community.

**OTHER CIRCUMSTANCE OF SKIN ULCERATION RELATED TO COMPRESSION**

Skin ulceration after inappropriate postoperative compression after varicose vein surgery has also been described in patient without arterial disease or diabetes, but this complication is very infrequent (Figures 2 and 3).^8^

**CAUSE**

Several causes of this complication can be identified:

- Compression is usually prescribed and applied by unspecialized therapists, and this may be harmful when using compression bandages.
- When compression is used to treat leg ulcers, between 20% and 30% of patients have impaired arterial blood supply in the ulcerated leg. This association is frequent in elderly patients; it has been estimated that up to 50% of patients over 80 years with leg ulceration also have a significant arterial disease.~9~
• Arterial investigation is not systematically undertaken before prescription of compression, and it is well known that clinical examination is unreliable or difficult in patients with edema or ulcerated legs.

**RECOMMENDATIONS FOR ALLEVIATING THIS COMPLICATION**

Ultrasound investigation including ABI measurement should be mandatory before the use of any kind of compression.

The manufacturer’s warnings are often neglected. We suggest highlighting the warning, as has been done on cigarette packs. In patients with an ABI <0.7, other treatment should be considered:

• prevention of thromboembolic risk by prescribing anticoagulation or mobilizing devices,
• improvement of chronic venous disease by drugs or interventional treatment according to the clinical status of the patient.

To prevent postoperative compression complication after varicose vein surgery, the compression must be assessed by the surgeon and the patient informed that any postoperative persistent pain needs to be identified.

**COMMENT BY PROFESSOR HUGO PARTSCH:**

*Beware of sustained compression!*

An effective treatment always carries the risk of side effects. The margin between benefit and risk of compression therapy is determined by the pressure and the material of the compression device. Strong compression bandages with a resting pressure in the range of 40-60 mm Hg are successfully used in the treatment of venous leg ulcers, a disease that mainly involves elderly patients. Due to the reduction in edema the interface pressure of the bandages will drop instantly to a pressure range that is well tolerated in most cases. Unless distal pulses of good volume can be felt, Doppler pressures should be measured. If the arterial brachial pressure index is between 0.6 and 0.9 we recommend bandages with reduced compression (~20 mm Hg) and close surveillance of the patients. Inelastic short stretch bandages exert a massage effect during walking, which will reduce swelling and increase the blood flow. In a similar way intermittent pneumatic pressure machines have been shown to increase arterial blood flow and to reveal beneficial clinical effects even in patients with symptomatic arterial occlusive disease.

On the other hand, elastic material maintaining a constantly high resting pressure independent of body position exerts much lower pressure peaks during movement. Skin damage has been reported even with light thromboprophylactic stockings. Incorrect fitting and lack of daily surveillance seem to be the most important flaws in patient care in these cases.

Patient-related risk factors that have to be considered are not only age and arteriosclerosis but also sensory loss, eg, due to diabetic neuropathy. Sometimes the pain level associated with leg ulcers can be so severe that the occurrence of pressure sores caused by the compression device may not be recognized.

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Towards a better understanding of lymph circulation

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Keywords: lymphatics, valves, pump, physiology.

SUMMARY

The lymphatic system was for years considered an “accessory” system and was neglected in comparison with the vascular system, which appeared much more crucial. In the last decade, researchers have become interested in lymphatic function since many diseases seem to interact with it (cancer, inflammation, infection, auto-immunity). The lymphatic system is harder to study than its vascular counterpart as its vessels are ill-defined, almost invisible. Intravital microscopy alone correctly visualizes these structures, thus shedding light on their function and quantifying their movements. This paper focuses on lymph anatomy and physiology, summarizes research trends, and considers lymph diseases and the latest treatments, particularly of cancer.

INTRODUCTION

The circulations of both blood and lymph are involved in cardiovascular function. Blood circulation is a closed circuit, but many exchanges occur at the venular and capillary levels between blood tissue and perfused organs. Fluid and proteins can cross from one compartment to another. The lymph circulation returns the lost fluid to the general circulation.

Two etiologies can be distinguished in lymph disease: excess fluid in the interstitial due to changes in permeability, and impaired draining of fluid by the lymphatics.

Lymphedema results from fluid accumulation in the interstitial compartment of the extravascular space. Although frequently encountered in medical practice, its prevalence is not well established, because we lack a precise definition, treatment varies, and affected populations are poorly defined. The prevalence rate of lymphedema in women treated for breast cancer has been reported as 11% and 25%. Lymphedema is not well understood as the...
mechanisms responsible for normal lymph flow are still unclear. Despite the importance of the lymphatic system in fluid and macromolecule exchange, our understanding of it lags far behind that of the vascular system, partly because it is difficult to study such tiny and thin vessels.

Lymph vessels are found in all tissues save those with a low level of exchanges, as bone and cartilage and the particular case of the central nervous system. The lymphatic system plays an important role in lipid absorption as in the intestinal tract where it is particularly developed. It is also involved in immune reactions. Lymph vessels carry immune factors and cells (lymphocytes) to the tissues and lymph nodes, and act as filters and reservoirs for white blood cells and tumor cells. However, the most important function of lymph vessels is to maintain fluid and macromolecule balance and oncotic pressure. Plasma filters into the interstitial space from blood through the capillaries. Much is reabsorbed by tissue cells or blood, but not all because of osmotic forces resulting from protein extravasation. Lymph vessels drain this excess fluid to venous blood to avoid edema. Proteins that leak out of capillaries into the interstitial space return to the blood through the permeable lymph vessels, thus ensuring homeostasis. Otherwise, if the blood osmotic pressure falls, fluid imbalance and its consequences will ensue. Because of the role of lymph vessels, lymphedema is often associated with venous disease and cancer. Fluid accumulation in tissues also causes fibrosis, chronic inflammation, and tissue changes.

The lymphatic system can be considered as an organ in its own right, as recent research work has demonstrated lymphangiogenic factors, specific lymphatic markers, and lymphatic endothelial cells (which differ from vascular endothelial cells). The idea of a specific organ is confirmed by the fact that lymph sacs are already present in 6- to 7-week-old human embryos, sprouting from embryonic veins.

**PHYSIOLOGY OF THE LYMPHATIC SYSTEM**

**Functional anatomy**

The lymphatic system is composed of capillaries, collecting vessels, lymph nodes, trunks and ducts, each part with a specific anatomy and role. Lymph vessels can anatomically be divided in 2 parts, initial lymphatics and collecting lymphatics. The initial lymphatics are located in tissues close to blood microvessels. Even intravital microscopy, which reveals microvessels and red blood cells, cannot distinguish initial lymphatics, whose size (10 µm to 60 µm diameter) has hampered investigations. By injection of microspheres into the arterioles, combined with histological techniques, Schmid-Schönbein has recently found that the initial lymphatics have a wall of loose, flattened, overlapping endothelial cells that are depleted in adhesion molecules as VE-catheters. Anchoring filaments bind the endothelial cells tightly to surrounding tissues. The discontinuity of the basal lamina allows macromolecules and cells to reach the lymph. Schmid-Schönbein suggested that the initial lymphatics contain endothelial microvalves (Figure 1), which allow the fluid to enter but not leave the interstitium. Initial lymphatics are not contractile, but lymph formation in them requires periodic expansion and compression of surrounding tissues. During expansion, the interstitial fluid can enter the lymphatics through the endothelial microvalves, because the intralymphatic pressure is lower than the interstitial fluid pressure. Compression of surrounding tissues forces the lymph towards the collecting lymphatics, whose smooth muscle can spontaneously contract. The valve-containing part of a lymph vessel and the adjacent portion of the vessel before the next valve form a functional unit called the lymphangion, which is able to contract or expand. Lymphangions are clearly seen by intravital microscopy of the rat mesentery circulation, close to the microvascular system and around lipid cells (Figure 2). They show spontaneous contractions and their valves can be easily seen in Figure 3.

Collecting lymphatics drain initial lymphatics toward the nodes. Pre- and postnodal lymphatics can be distinguished. Lymph nodes crossed by collecting lymphatics are organized in clusters and play an important part in the exchange between lymph and blood. White
Physiology of lymphatic vessels

As the lymph vessels are not replete with fluid, they are protected from hydrostatic problems during gravitational stress, unlike veins. The lymphatic system includes lymph (circulating fluid), vessels (parallel to veins), nodes along collecting vessels, and isolated nodules in the intestinal wall and specialized organs (as tonsils, thymus, and spleen). Unlike the vascular system, the lymphatic system is not a closed circuit.

Pump activity

The lymphatic system has all the anatomic components required for active pumping of the interstitial fluid. For years, the lymphatic system was considered as a passive pump and excited limited interest. In recent decades, studies have demonstrated the pumping activity of the lymphatics. To work, a pump needs a pressure and volume difference, and this can be generated by the contractility of the vessels or by changes in external pressure. The initial lymphatics have two valve systems: endothelial microvalves and classical intralymphatic valves. This two-valve system provides a mechanism for unidirectional flow during compression and expansion of the initial lymphatics. These compression and expansion movements depend on muscle contraction, breathing movements (particularly inspiration), arterial pulsations, postural changes, and skin tension. Lymph flows at around 125 mL/h, and this rate may be increased 10-fold during exercise.

Lymphangions can act as a pump when actively transporting lymph against a pressure gradient, or as a conduit when passively transporting lymph down a pressure gradient as described by Quick and Gashev. These authors compare the lymphangion to a ventricle. Transmural pressure is an important hydrodynamic factor for the contractility of lymphangions. It modulates the strength and frequency of contractions. Zhang et al described a motion wave propagation from one lymphangion to the next due to a pacemaker site at the inlet side in the valve in each lymphangion. The flow is related to the pressure changes between two lymphangions and stimulates a new contraction. Quick and Gashev suggest that the response of endothelium to wall tension and shear stress close to the inlet valve site could be one of the mechanisms responsible for lymphatic motion.

The conducting lymphatics contain smooth muscle that contracts at a rate of 1 to 15 cycles per minute, in phase opposition: one lymphangion contracts when the next dilates, so one is empty when the next is full.
Lymphatics have a low internal pressure (several mm Hg), but are very sensitive to pressure gradient, which has an influence in edema, for example. Other factors may interfere with pump activity. For example, the pump is only active at low oxygen tension (25-40 mmHg). Conversely, a high level of oxygen inhibits the frequency and amplitude of the contractions.

The lymphatic system is active, but some authors suggest that whether it is active or passive depends on the environment. In some diseases, where a substantial fluid drainage is needed, the lymphatics dilate and lose their contractile activity. Using mathematical models, Quick et al.\(^\text{11}\) have demonstrated a pressure gradient along lymphatics with an excess pressure in the surrounding tissues. In this case, drainage is better if the vessels are dilated rather than spontaneously contracting.

The lymphatic system is highly adaptable, and sensitive to small internal or external pressure differences. Embryologically, lymphatic endothelial cells can be distinguished from vascular endothelial cells, and have specific receptors, suggesting they also have a specific pharmacological role.

**PHARMACOLOGY OF THE LYMPHATIC SYSTEM**

As the lymphatic system was compared to the vascular system, vasoactive drugs have been tested on lymphatics, but we know that receptors on lymphatic endothelial cells differ from those on vascular endothelial cells. Some vasoactive agents can regulate the activity of the lymphatics. Several agents, particularly cardiovascular drugs, have been tested in vitro (bovine isolated lymphatics) and in animals (sheep, rat). It was shown that lymphangions are sensitive to vasoactive drugs as nitric oxide (NO) donors,\(^\text{15,16}\) prostaglandins, and thromboxane.\(^\text{17}\) Vasodilators as NO tend to diminish the force and frequency of lymphatic pumping. Vasoconstrictors, as thromboxane, seem to have the opposite effect.

Using intravital microscopy on rat mesenteric lymphatics, adrenergic drugs were tested on lymphatic activity. The receptor antagonists alpha 1 (prazosin) and alpha 2 (yohimbine) do not modify the diameter or contractile activity of lymphatics, suggesting that there is no adrenergic tone in lymphatics. Norepinephrine and phenylephrine increase the frequency of contractions and decrease the diameter. These experiments indicate that lymphatic function can be increased through alpha-1 but not alpha-2 adrenoreceptors.\(^\text{18}\)

Bradykinin increases the frequency, strength, and duration of contractions of initial lymphatics.\(^\text{19,20}\) Its effect on mesenteric lymph vessels of the rat can be visualized using intravital microscopy (Figure 4).

**Figure 4. Effect of bradykinin on lymphatic contractions.**

Against the backdrop of the recent interest in lymphatics and the demonstration that the lymphatic system is a system apart and different from the vascular system, with specific lymphatic endothelial cells, Ohhashi\(^\text{21}\) has reviewed new pharmacological research on lymphatics. For example, the generation of endogenous NO and reactive oxygen radicals (ROR) from lymphatic endothelial cells, and the activation of ATP-sensitive potassium channels (KATP), were shown to play a role in the regulation of lymph transport. NO released from these endothelial cells (through the constitutive NO synthase) inhibits rhythm and amplitude of the pump activity. ATP induces dilation and also inhibits lymphatic pump activity. Acetylcholine provokes relaxation of the lymph vessels through the release of NO and has negative chronotropic and inotropic effects on the pump. Endothelin increases lymphatic vasomotion involving calcium.

Because of the role of lymphatics in tumor metastases, Ohhashi also mentions substances released by tumor cells, as NO and derivatives, which reduce pump activity. Exuded macrophages present in the lymph vessels or nodes, when they are activated by bacterial lipopolysaccharides, release NO and vasodilating...
prostaglandins, thereby decreasing pump activity. Edema is one of the consequences of low pump activity.

LYMPHATIC SYSTEM IN DISEASE

Damage to the lymphatic system can cause lymphedema. Primary lymphedema is an inherited condition, which can appear in different parts of the body and at different ages. More common is secondary lymphedema, which can be due to inflammation, invasion of bacteria or parasites, occlusion after surgery, or irradiation of tumors. This is the clinical manifestation of an imbalance of forces at the capillary wall. Edema is an excess accumulation in the interstitial space of fluid that has not been reabsorbed by capillaries or taken up by lymphatics. It can occur because of obstructions, lymphatic insufficiency, increased protein permeability, inflammation, and reduction in plasma proteins. In humans, benzopyrones (coumarin, oxerutins, and diosmin), flavonoids, and ruscus extract are used to treat high-protein edema. They reduce swelling and pain, and improve healing and oxygenation. Benzopyrones increase the number of macrophages, which lyse excess proteins, and improve pumping by collecting lymphatics.22

The lymphatic system has a major role in immune defense.23 The lymph vessels and nodes transport antibodies, lymphocytes, but also bacteria. The lymphatic system plays a major role in all diseases involving an inflammatory process (rheumatoid arthritis, lupus, scleroderma). In AIDS, HIV can be propagated through the lymph vessels, which could be a target for antiviral medication. The lymphatic system also interacts with digestion, helping reabsorption of fat, and its dysfunction can lead to malnutrition, ascites, and obesity.

As seen above, the lymphatic system is of importance in many diseases of different organs (liver, heart, kidney, stomach, blood) and different causes (virus, bacteria, hemorrhagic shock, organ transplantation, autoimmunity). In most cases, the clinical sign is edema.

ROLE OF THE LYMPHATIC SYSTEM IN SPREAD OF CANCER

The lymphatics play a crucial role in the dissemination of solid tumors, particularly of the breast, lung, colon, and prostate.9 Tumor cells are transported through lymph vessels into lymph nodes and are then disseminated to other nodes and organs. Tumor cells themselves induce lymphangiogenesis by secreting substances that trigger the proliferation of lymph vessels. The lymphatic system itself may also be the site of cancer, such as lymphoma, which is due to the transformation of lymphocytes.

CONCLUSION

Following years during which the lymphatic system was neglected, new work has shown that it plays a central role or is implicated in inflammation, cancer, transplant rejection, and lymphedema. This renewed research interest has already led to advances in prevention and treatment, such as an anti-VEGFR-3 antibody, which inhibits lymphatic regeneration, and gene or gene-product therapy of lymphedema.24

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REFERENCES


The Servier Traveling Fellowship was established for postgraduate vascular physicians or surgeons. It is designed to help further understanding between European and American physicians in the treatment of venous diseases. Following the completion of my Vascular Surgery Fellowship at Walter Reed Army Medical Center in Washington, DC, I was afforded a once-in-a-lifetime opportunity. As a result of my research on Repair of Military Venous Trauma and Thromboembolic Events, much to my delight I was awarded the Servier Traveling Fellowship. This award allowed me to travel abroad and gain a better understanding of treatment of venous diseases from European physicians.

My starting point was Istanbul, Turkey, where I presented my research at the European Venous Forum. This meeting included a dinner at an outdoor fish restaurant following a sunset boat trip along the Marmara Sea, which separates the European and Asiatic halves of Istanbul. I also visited ancient landmarks such as the Blue Mosque, the underground cisterns, and the Hagia Sophia (a church built during the crusades and later converted into a mosque).

After this insightful meeting, I traveled to Paris. On my first day, Servier sponsored a guided chauffeured tour of Paris. We visited the courtyard of Louis XIV, Notre Dame Cathedral, Napoleon’s tomb, had lunch at the Louvre, and, of course, visited the Eiffel Tower. I also learned a little bit of history from the tour guide at each site that we visited.
That evening, I traveled by train to the city of Marseille, which is on the Mediterranean Sea. I met Professor Yves Alimi and Dr. Olivier Hartung at the university-based Phlebolymphology. The following day, I met with Dr. Françoise Pitsch and we visited the Servier Research Laboratory. I learned of the many basic science research projects that are ongoing for future drug development. Unfortunately, I can’t discuss this proprietary information. In the afternoon, I met with Dr. Jean-Luc Gérard, who works as a phlebologist and angiologist in private practice. He demonstrated the combined use of a 1024 nm laser and actetaxol foam sclerotherapy for the treatment of venous varicosities in an outpatient setting. Dr. Gérard emphasized the importance of duplex ultrasound in the diagnosis and treatment of venous diseases. He performs all of his own ultrasound and is exceptionally skilled at it. This will become one of my goals as I enter medical practice.

On the third day, I was with Dr. Christian Lebard of the Clinique Monceau. This clinic located in Paris is the original site of the construction of the Statue of Liberty. In contrast to office-based laser treatment of varicose veins, Dr. Lebard prefers to use radiofrequency ablation in conjunction with sclerotherapy in the operating room. He explained its advantages and demonstrated the use of the ClosureFast™ on three patients. That evening, I traveled to Lyon by train.

In Lyon, Drs. Philippe Nicolini and Michel Perrin were my hosts for a dinner. Lyon is known as the food capital of France. We ate at a local restaurant called ‘Le Bouchon’. Being adventurous, I had the regional specialty of Tablier de Sapeur (breaded, fried omentum). It tasted wonderful and I slept well that night. The next morning I went to the Clinique du Grand Large, a private practice hospital. The day was focused on endovascular recanalization of iliofemoral thrombosis, and iliac vein stenting for the treatment of May-Thurner syndrome with Dr. Nicolini.
Hôpital Nord, and we went for dinner. The restaurant was situated at the mouth of the city harbor and the view was spectacular. Looking north there were the moored ships and edge of the city, and to the south was the Mediterranean Sea.

The next morning, I started my day with bedside teaching rounds with Dr Hartung and his surgical house officers. After the rounds, I went to the operating room. The three cases of pelvic congestion syndrome were treated by endovascular embolization of the ovarian vein, using coil-foam-coil “sandwich” technique.

This was my first trip to Europe and I am very fortunate to have had this opportunity. I will take what I have learned from this experience and incorporate it into my own surgical practice. In France, most of the physicians I worked with performed their own ultrasound. But, more importantly, they were extremely skilled at ultrasound-guided surgical techniques. This has motivated me to continue to develop my own ultrasound skills in the operating room and in the vascular lab. Additionally, my experience of venous diseases has been broadened. I have gained an appreciation of the complexity of diseases such as pelvic congestion syndrome and iliocaval thrombosis. Lastly, I have developed a better understanding of and improved communication with vascular physicians and surgeons abroad.

This was a very rewarding experience. Not only did I get to work with new colleagues, but I have also made new friends. I feel that my experience and contacts have brought us closer together as members of a global medical community.

I would like to thank Dr Françoise Pitsch and Dr Michel Perrin for their assistance and companionship during this exchange. I am grateful to Servier and to the American and European Venous Forum for offering this lifetime opportunity to foster my interest in the treatment of venous diseases.
CONGRESS

Congress and conference calendar

**LX**th International French-Language Angiology Meeting

This congress will be held in Paris (France) from January 11 to 12, 2008.
- **For further information, please contact:**
  - President: Prof A. V. Saveliev
  - Organizing secretariat: Prof Kirienko
  - 8, Leninski prosp
  - Moscow, Russia
  - Tel/Fax: +7 495 236 02 49
  - E-mail: phlebo-union@bk.ru
  - Web site: www.phlebo-union.ru

**XXXII**nd Angiology Meeting

This congress will be held in Praha (Czech Republic) from February 21 to 23, 2008.
- **For further information, please contact:**
  - President: Dr Karel Roztocil
  - Organizing secretariat: AMCA – Eva Uhrova
  - Academic and Medical Conference Agency
  - Ujezd 40
  - 118 01 Praha 1, Czech Republic
  - Tel: +420 257 007 629 / 731 496 060
  - Fax: +420 257 007 622
  - E-mail: amca@amca.cz
  - Web site: www.angiologie.cz

**III**nd Congress of Surgeons

This congress will be held in Moscow (Russia) from February 21 to 24, 2008.
- **For further information, please contact:**
  - President: Prof A. V. Saveliev
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  - Moscow, Russia
  - Tel/Fax: +7 495 236 02 49
  - E-mail: phlebo-union@bk.ru
  - Web site: www.phlebo-union.ru

**XLII**nd Congress of the French College of Vascular Pathology

This congress will be held in Paris (France) from March 12 to 14, 2008.
- **For further information, please contact:**
  - President: Dr Michel Vayssairat
  - Organizing secretariat: Pascal Priollet
  - Nex & Com
  - 159 rue de Silly
  - 92100 Boulogne-Billancourt, France
  - Tel: +33 1 46 43 33 06
  - Fax: +33 1 46 43 33 24
  - E-mail: s.garafoli@nex-com.com
IXth INTERNATIONAL CONGRESS OF PHLEBOLOGY

This congress will be held in Bologna (Italy) from April 4 to 5, 2008.

For further information, please contact:
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Web site: www.valet.it / congresso@valet.it

VIth INTERNATIONAL CONGRESS OF CENTRAL EUROPEAN VASCULAR FORUM

This congress will be held in Bratislava (Slovak Republic) from May 16 to 18, 2008.

For further information, please contact:
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Lidicka 43/66
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XXXth CHARING CROSS INTERNATIONAL SYMPOSIUM

This congress will be held in London (Imperial College, UK) from April 12 to 15, 2008.

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LIVth SPANISH ANGIOLOGY MEETING (XV NATIONAL CONGRESS DEL CAPÍTULO ESPAÑOL PHLEBOLOGY / XI NATIONAL CONGRESS CAPÍTULO DE DIAGNÓSTICO VASCULAR NO INVASIVO DE LA SEACV / IV NATIONAL CONGRESS DEL CAPÍTULO DE ENDOVASCULAR SURGERY DE LA SEACV)

This congress will be held in Barcelona (Spain) from May 29 to 31, 2008.

For further information, please contact:
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**SPRING CONGRESS OF THE SWISS PHLEBOLOGY SOCIETY**

This congress will be held in Switzerland from May 31 to June 1, 2008.

*For further information, please contact:
No additional information for the moment.*

**WACHAUER VENENSYMPOSIUM**

This congress will be held in Melk (Austria) from June 6 to 8, 2008.

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**XXIVTH WORLD CONGRESS OF THE INTERNATIONAL UNION OF ANGIOLOGY (IUA)**

This congress will be held in Buenos Aires (Argentina) from April 21 to 25, 2010.

*For further information, please contact:
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**XVIITH WORLD MEETING OF THE UNION INTERNATIONALE DE PHLEBOLOGIE (UIP)**

This congress will be held in the principality of Monaco from August 31 to September 4, 2009.

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