Thrombophilia: Patients Who Clot Too Much

Part 1: Congenital Thrombophilia

by Robert C. Kiser, DO, MSPH

Blood exists in a careful state of equilibrium. We want blood to flow, when it is in arteries, supplying oxygen and nutrients to tissues, or when it is in veins, being returned to the right heart and lungs for re-oxygenation. We also want blood to clot when the circulatory system is opened, to prevent hemorrhage and exsanguination. When blood does not sufficiently clot we describe the condition as “hemophilia,” suggesting a fondness for or excessive tendency toward bleeding. When blood clots excessively the condition is referred to as “thrombophilia.” Just as there are several major and minor hemophilias, several thrombophilias of various levels of severity and etiology have been described.

Virchow’s Triad

Stasis, trauma and hypercoagulable states form the basis of inappropriate clot formation. Frequently two or more of these factors are present before a significant venous thrombosis occurs. Although “unprovoked clots” are most suggestive of a thrombophilia, it is not unusual for a patient with a thrombophilia not to clot until a second “pro-thrombotic” event such as a long plane trip, pregnancy, oral contraceptives, varicose veins, or trauma tip the balance toward clotting.

Genetic vs. Acquired Thrombophilia

Thrombophilias may be either genetic (sometimes called “congenital”) or acquired. “Genetic” means the tendency is inherited and “congenital” means it is present from birth. Congenital thrombophilias have either been shown or are believed to have a genetic basis and often run in familial pedigrees (although sporadic mutations are also possible). Acquired thrombophilias develop over the course of a lifetime and are believed to be associated with specific disease states and/or autoantibodies.

Hypercoagulable State

- Malignancy
- Pregnancy and peri-partum period
- Estrogen therapy
- Trauma or surgery of lower extremity, hip, abdomen or pelvis
- Inflammatory bowel disease
- Nephritic syndrome
- Sepsis
- Thrombophilia

Vascular Wall Injury

- Trauma or surgery
- Venipuncture
- Chemical irritation
- Heart valve disease or replacement
- Atherosclerosis
- Indwelling catheters

Circulatory Stasis

- Atrial fibrillation
- Left ventricular dysfunction
- Immobility or paralysis
- Venous insufficiency or varicose veins
- Venous obstruction from tumor, obesity or pregnancy

Source: Bayer Schering Pharma AG

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Sclerotherapy: A Brief History

by Rory C. Byrne, MD

Sklerosis: from the Greek, a hardening or induration of a tissue or part.

Therapeia: from the Greek, treatment of disease or disorder as by some remedial or restorative process.

Sclerotherapy is a somewhat broad-based term to describe the medical technique of introducing medication into a vein for the purpose of shutting down and eliminating it. Typically this is done to alleviate concomitant symptoms, such as pain, heaviness, aching, cramps, itching or burning, or alternately purely for cosmetic purposes. Sometimes referred to as injection sclerotherapy or compression sclerotherapy, this technique was originally developed for the treatment of varicose veins but later evolved into the treatment of choice for “spider veins” or telangiectasia. More recently the value of this technique in the treatment of the larger varicose veins has been recognized anew.

While varicose veins have almost certainly existed since man initially stood up, the first historical documentation thereof dates to the writings on papyrus scrolls by the ancient physician Ebers in the year 1550 BC. Since that time several major discoveries or inventions have led to the many refinements that bring us to the present day techniques.

Certainly, sclerotherapy has at times been used as an alternative to surgery which was initially very primitive and later simply not as effective as one would have hoped. Presently, sclerotherapy and surgery coexist as complimentary modes of treating the total vein problem.

The first documented treatment of venous disease was found in the historical annals around 400 BC in the form of offerings to the gods as supplication seeking relief. Hippocrates, around 460 BC, wrote of introducing “a slender instrument of iron” through multiple punctures into the veins to induce thrombosis. This concept of inserting a foreign substance into the vein was most likely the precursor to sclerotherapy itself.

Great things evolved from these unlikely beginnings. Events that changed the procedure dramatically include the first injection of distilled plantain water via an enema syringe into a branch of the crural vein by Sigismund Esholtz in the mid-1600’s.

The introduction of a lachrymal syringe by Anel in 1713 led to the development of the hypodermic syringe by Rynd in 1845 and its subsequent modification by Pravaz. At this point experimentation with many varied types of medication resulted, including absolute alcohol (1840), ferric chloride (1851), iodine (1906), mercury (1920), sodium morrhuate (1930), sodium tetradecyl sulfate (1946), polidocanol (1966).

Compression therapy was recognized early on as an important adjunct starting first with Hippocrates, then the use of leather straps by Roman soldiers, plaster bandages and ultimately the mechanically-engineered graduated-pressure compression stockings of today.

The 1970’s saw the refinement of ultrasound as a medical tool that gave rise to applications in the treatment of venous disease. The use of duplex ultrasound in conjunction with the development of thick foam-like medications (some now the consistency of toothpaste) allowed the skilled physician to place by injection, with great precision, measured doses of sclerosant medications directly into the incompetent or refluxing vein.

Sclerotherapy has, in many ways, evolved enormously yet in other ways has changed little. Today it is unquestionably the treatment of choice for “spider veins” in the legs. It is also used to treat veins in the face, arms, back, breasts and other areas. And recently, the use of ultrasound and foam has opened up fantastic possibilities in the treatment of varicose veins, perforator veins and in some cases even the great saphenous vein.

The San Diego Study: A Look at Chronic Vein Disease in a Diverse Population

Which segments of the population are more prone to chronic vein disease – which sex, age and ethnicity? A four-year study by the researchers at the University of California, San Diego attempted to find that out. Their article, “Chronic Venous Disease in an Ethnically Diverse Population – The San Diego Population Study,” was published in 2003 in the American Journal of Epidemiology.

According to the researchers, chronic venous disease causes significant morbidity in diverse populations around the world, but disease definitions had not been uniform and little information was available concerning ethnic differences. They decided to study a diverse population for venous disease utilizing physical examination, duplex ultrasonography, and clinical history. The population for the study was randomly selected from current and retired employees of the University of California, San Diego. Selection was made within strata defined by age (40-49, 50-59, 60-69, and 70-79), sex and ethnicity (African American, Asian, Hispanic, non-Hispanic white and other).

Data from 2,211 participants was analyzed. The average age was 59.9 years for the men and 59.2 years for the women. The research was supported by grants from the National Institutes of Health – National Heart, Lung, and Blood Institute and the National Institutes of Health General Clinical Research Center Program.

According to the article, “in multivariable models, moderate venous disease was independently related to age, a family history of venous disease, previous hernia surgery, and normotension in both sexes. In men, current walking, the absence of cardiovascular disease, and not moving after sitting were also predictive, while in women, additional predictors were weight, number of births, oophorectomy, flat feet, and not sitting. For severe disease, age, family history of venous disease, waist circumference, and flat feet were predictive in both sexes. In men, occupation as a laborer, cigarette smoking, and normotension were also independently associated with severe venous disease, while in women additional significant and independent predictors were hours standing, history of leg injury, number of births, and cardiovascular disease, while African-American ethnicity was protective. Multiple other postulated risk factors for venous disease were not significant in multivariable analysis in this population.”

The researchers concluded that the prevalence of both visible (81.0 percent) and functional (27.9 percent) venous disease makes chronic venous disease the most prevalent vascular disease. In general, the study found that women had more superficial functional disease whereas men had more deep functional disease. Venous disease increased with age, and non-Hispanic Whites had more disease than did
CVR at the ACP 25th Annual Congress

by Alejandro Arnez, MD

In the five months since its creation, the research department of the Center for Vein Restoration (CVR) has produced several papers contributing to the scientific community, including being published in the journal Phlebology (Royal Society of Medicine Press) and the Journal of Vascular Surgery. We were proud to be selected to present the abstract “Vein Diameter and Venous Insufficiency in the Mid-Thigh Great Saphenous Vein: A Retrospective Cohort Analysis” at the American College of Phlebology (ACP) 25th Annual Congress in Los Angeles in November, 2011. The article is based on the Engelhorn et al. abstract titled, “Relationship between reflux and greater saphenous vein diameter”. The objective of the study was to assess a correlation between venous insufficiency and vein diameter and also to establish the predictive effect of vein diameter on the provability of venous insufficiency in the mid-thigh great saphenous vein. At the end of the analysis of 527 patients (697 limbs) we concluded that diameter could be used as a tool of prediction for venous insufficiency. At the mid thigh an 8 mm in diameter vein has an 81% probability of demonstrating venous insufficiency with 51% accuracy. These findings may be useful in creating a rapid screening for venous insufficiency and in deciding whether more extensive testing is recommended.

The opportunity to present our research to the ACP delegation was a great chance to show the potential for research that CVR holds. We also had the privilege to speak with the current President of the ACP, John Mauriello, MD, FACP, who showed a strong interest in establishing future projects with our organization. It also was delightful to rub shoulders with and discuss phlebology topics with such luminaries as Joseph Caprini, Nick Morrison, Dave Centani and Marlin Schul.

It was heart-warming to see that Center for Vein Restoration remains at the cutting edge of technology use as well as in its use of protocols and practice guidelines. The conference was like a hugely expanded Center for Vein Restoration Journal Club meeting, and like the journal club, the conference highlighted the latest updates in medicine and phlebology to provide the very best patient care.

This conference not only demonstrated where we are, but also where we could be heading. The fact that topics such as endovenous heat-induced thrombosis, perforator veins and so many more are still under study gives our department the opportunity to showcase the quality of our research and helps validate our efforts as a leader in evidence-based vein care.

The San Diego Study: A Look at Chronic Vein Disease in a Diverse Population

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Hispanics, African Americans, or Asians. Visible and functional disease were closely linked, and both were strongly associated with edema and thrombotic events.

“Although some risk factors for venous disease such as age, family history of venous disease, and findings suggestive of ligamentous laxity (hernia surgery, flat feet) are immutable, others can be modified, such as weight, physical activity, and cigarette smoking,” they wrote. “Overall, these data provide modest support for the potential of behavioral risk factor modification to prevent chronic venous disease.”

A copy of the complete study is available for download at: http://aje.oxfordjournals.org/content/158/5/448.short

Prothrombin 20210A/G

Prothrombin 20210 A/G is the second most common genetic thrombophilia. It results in a substitution of Adenosine for Guanine at the 20210 locus. This single base pair substitution results in mutated prothrombin that creates too much clotting. Prothrombin, (Factor II), is necessary for fibrin production to make blood clots. The mutated form of prothrombin results in excessive clotting (beyond the amount required for hemostasis), which can result in extensive venous thrombosis. Prothrombin 20210 A/G is not known to cause extensive arterial clotting. Although the mutation may slightly increase Factor II, the only definitive test for the mutation is “Prothrombin Nucleotide 20210 G/A Gene Mutation (Factor II).” The risk of VTE in someone with Prothrombin 20210 A/G mutation is twice normal.4

Too Much Factor VIII

Factor VIII excess is believed to have a genetic basis, however a specific locus or loci have not been elucidated.5 When Factor VIII, or von Willebrand’s Factor, is too low we call the condition hemophilia minor or von Willebrand’s syndrome. When the factor is excessively active or abundant, which has only recently been recognized, a hypercoagulable state results. Because the exact mutations resulting in elevated Factor VIII are not defined at present, Factor VIII levels must be drawn.

Antithrombin III Deficiency

Antithrombin III is a potent inhibitor of thrombin and factor Xa. It is an autosomal dominant disorder that is usually seen in the heterozygous form, the homozgyous form being usually incompatible with life.6 Antithrombin III deficiency results in VTE, most commonly in the third decade of life. Treatment is generally with warfarin, low-molecular weight heparin (LMWH) or antithrombin infusion. LMWH is complicated by heparin being dependent on antithrombin III for its anticoagulant activity. Therefore this is a disorder in which factor Xa activity levels should be carefully monitored if LMWH is used, to assure that the patient is adequately anticoagulated. The estimated risk of VTE in a person with antithrombin III deficiency is up to 50%.

Dysfibrinogenemia

Dysfibrinogenemia is a rare condition in which the fibrin molecule is made in a form that is abnormal. 50% of such patients have a bleeding disorder, 10% have a thrombophilia—and the other 40% are asymptomatic.7

Darwinian Medicine Perspective

The genetic thrombophilias may have had an adaptive advantage at one time. In particular the heterozygous genotype that has a lower risk of fatal thromboembolism may have had increased survival value. If our ancestors were injured by a wild animal or a battle they were more likely to survive to reproduce if they did not exsanguinate. The increased risk of a DVT may have been a relatively small price to pay for the additional protection against bleeding to death, particularly given an active lifestyle of hunting, gathering, or horticulture that did not encourage venous stasis. In today’s developed world, exsanguination risk is relatively diminished (although still a risk of trauma and warfare). Our modern tendency toward a sedentary lifestyle however, has uncovered the risk of increased and inappropriate clotting, which under some circumstances may lead to DVT and PE. As with many genetic illnesses, what is now a disadvantage may have had a survival advantage in earlier times and under different circumstances.

Beyond Laboratory Testing: Risk Assessment

A positive result on a screening or diagnostic test may give rise to the clinician’s heightened awareness of and hence prophylaxis against risk of venous thromboembolism (VTE). The full battery of tests, however, is quite expensive (~$1,500), time consuming, requires large volumes of blood, and does not take into consideration unknown factors not yet elucidated. To rapidly screen for risk of venous thromboembolism, Joseph Caprini, MD, has devised a validated Risk Assessment Model for VTE.8 The Caprini Risk Assessment Model (C-RAM) looks at historical and current risk factors, including genetics/family history and generates a numerical score. The utility of the C-RAM has been validated across several surgical populations.9,10 Although a full discussion of the Caprini Risk Assessment Model is beyond the scope of this paper, it is freely available from the University of Michigan website at http://www.med.umich.edu/cclinical/images/VTE-Risk-Assessment.pdf.

Part 2 of this article, on Acquired Thrombophilia, will appear in the next edition of Venous Review.

References:
2 Ibid.
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With the turn of the New Year comes the annual tradition of making resolutions. Many involve health – quitting smoking, losing weight, getting more exercise and eating right tend to top the list. But, for many people their resolution is to finally address their varicose veins. They've suffered with symptoms of pain, swelling, fatigue and perhaps even ulcers for a while now and it's time to get help.

Our resolution as a health organization is to continue to strive for excellence in caring for these patients – who are also often your patients, whom you’ve referred to us. We understand, as a provider of elective treatment, that reliability and excellent customer service are key priorities we strive to maintain and deliver at all times. In fact, we are continually inspired and are guided by the words of Mahatma Gandhi:

“A customer is the most important visitor on our premises. They are not dependent on us. We are dependent on them. They are not an interruption in our work. They are the purpose of it. They are not an outsider in our business. They are a part of it. We are not doing them a favor by serving them. They are doing us a favor by giving us an opportunity to do so.”

We invite you in this New Year to visit one of our centers, meet our team, and discover our passion for excellent patient care for yourself. We have 16 locations across Maryland, Washington, DC, Northern Virginia and Michigan and we welcome you at any time to the center closest to you or your patients.

Until then we wish you and yours a happy and healthy New Year and we hope you find the articles in this newsletter informative and helpful.

Regards,
Robert C. Kiser, DO, MSPH
Editor