The pathophysiologic basis for early clot removal stems from the inflammatory process that accompanies venous thrombosis. Stewart initially proposed four stages for this inflammatory response.1 First, thrombus forms in the veins, with inflammatory cells and platelets becoming activated within this initial thrombus. Second, further neutrophil and platelet activation occurs, generating procoagulant and inflammatory mediators. Third, coagulation occurs on activated platelet phospholipid surfaces, increasing the speed of thrombin and fibrin generation. Finally, leukocytes and platelets layer on top of existing clot, further increasing the thrombotic/inflammatory interplay. Inflammation ultimately leads to the amplification of thrombosis, driven by both tissue factor expression on monocytes and by the exposure of vein wall collagen after endothelial denudation, likely due to cathepsin G release from activated neutrophils.

The above results in leukocyte extravasation into the vein wall, migrating from both the adventitial and luminal membrane. Using a rodent model of stasis-induced venous thrombosis by IVC ligation, we have demonstrated an active vein wall pro-inflammatory response characterized by cellular trafficking, involving early neutrophil extravasation followed by monocyte/macrophage infiltration, occurring as early as 6 hours after thrombus formation begins.3 At 6 hours, an increase in all leukocyte types (except for monocytes) in the vein wall occurs, and by day 2, neutrophils are the predominant cells in the thrombosed vein wall. Although inflammatory cells can be noted at the thrombus/vein wall interface, more leukocytes are recognized in the media and adventitia of the vein wall than at the 6-hour time point. By day 6, neutrophil counts in the vein wall fall to near baseline, while monocyte counts significantly rise and the thrombus/vein wall interface becomes less distinct. FACS analysis and MPO analysis support and extend these observations.

Neutrophils, initially adherent to the endothelium, lead to endothelial disruption, exposing the collagen-rich basement membrane. This leads to further thrombus propagation, followed by leukocyte transendothelial migration and further vein injury. Factors important to leukocyte extravasation include tumor necrosis factor (TNF), the earliest up-regulated selectin (P-selectin), and the adhesion receptor intercellular adhesion molecule-1 (ICAM-1).3,4 In a study evaluating P-selectin and TNF inhibition and their ability to reduce venous thrombosis-induced inflammation, the lowest vein wall neutrophil and total inflammatory cell count early after thrombosis, and the lowest neutrophil and monocyte count later was found in a group given antibodies to TNF plus P-selectin. Other cytokines/chemokines that are also up-regulated in the vein wall include epithelial neutrophil-activating protein-78 (ENA-78), KC, macrophage inflammatory protein-2 (MIP-2), JE/monocyte chemotactic protein-1 (JE/MCP-1), macrophage inflammatory protein 1α (MIP-1α), and interleukin-6 (IL-6). In the rat, cytokine elevations are seen only under conditions of venous thrombosis.2 Levels of ENA-78, TNFα, IL-6, and JE/MCP-1 rise over a 6-day period, while MIP-1α peaks on day 3 after thrombus formation. Additionally, rats passively immunized with neutralizing antibodies to cytokines and adhesion molecules have demonstrated a decrease in neutrophil extravasation into the vein wall with anti-TNF, and a decrease in monocyte/macrophage extravasation with anti-ICAM-1 and anti-TNF.

Although the above factors are pro-inflammatory, we have also noted that the initiation, maintenance, and eventual resolution of phlebitis is dependent on both pro-inflammatory and anti-inflammatory cytokines. Interleukin 10 (IL-10), a naturally occurring anti-inflammatory cytokine produced by inflammatory cells, mast cells, and epithelial cells, has been found elevated in the vein wall after venous thrombosis. In the rodent stasis model of IVC thrombosis, neutralization of endogenous IL-10 increased inflammation, while rIL-10 supplementation decreased inflammation in a time and dose-related fashion.5 Recombinant IL-10 administered at 2.5 μg was found to significantly decrease vein wall total inflammatory cells, neutrophils, and monocytes. At a high dose of 40 μg, IL-10 produced a paradoxical pro-inflammatory response. In a time-dependent fashion, rIL-10 given systemically at the most effective anti-inflammatory dose, 2.5 μg at the time of thrombus induction, was most effective in decreasing inflammation.

Two additional measures of vein wall injury produced by inflammation have been investigated, vein wall permeability to Evans blue given 3 hours prior to vein removal and magnetic resonance venography (MRV) using gadolinium. Gadolinium (Gd) is a non-toxic heavy metal chelate that extravasates into areas of inflammation, as opposed to generalized edema. Gd chelates are para-magnetic heavy metals that decrease the T1 relaxation times of inflammatory foci, resulting in enhancement in areas of inflammation. Enhancement was measured and quantitated in mm². There is essentially no enhancement without thrombosis (1.83±0.40 mm²). In thrombosed IVCs associated with maximal inflammation (IL-10 at 40 mg), Gd enhancement was measured at 32.7±6.2 mm², while in thrombosed IVCs in rats administered rIL-10 at the anti-inflammatory dose of 2.5 mg, enhancement was measured at only 14.7±1.5 mm², p<0.05.6

Inflammation augments thrombosis. Since we had previously noted a correlation between inflammation and venous thrombosis and IL-10 inhibits inflammation, we determined the ability of IL-10 to decrease clot formation. A significant (p<0.05) 18% decrease in gross thrombus weight with rIL-10 administration compared to control was found. We also noted a trend with an 8% decrease in tissue factor production with rIL-10, using flow cytometry. To further examine the mechanism of IL-10’s anti-inflammatory and anti-thrombotic effects, the rodent IVC segment was transfected with an adenovirus-CMV promoter-viral IL-10 (vIL-10) construct to locally express this product. Controls included saline vehicle and the promoter (CMV or RSV)-β galactosidase (βgal) constructs. Successful transfection, confirmed by RT-PCR for the vIL-10 cDNA and suggested by positive X-gal staining in promoter-βgal control rats, resulted in a significant decrease in both total leukocyte count and neutrophil count as well as perithrombotic Gd enhancement (p<0.05). Interestingly, no significant difference in thrombus weight was found, perhaps a reflection of the balance between anti-IL-10 and the pro-inflammatory nature of transfection. Since IL-10 is known to decrease inflammation in part by decreasing cell adhesion molecule expression,7 we also investigated the expression...
of the cell adhesion molecules P- and E-selectin and ICAM-1 by immunohistochemical techniques and cell homogenate ELISA. In the vIL-10 transfected rats, a reduction in the expression of all of these molecules as compared with the control promoter and saline groups was found.

Studies in the rat have been supplemented by evaluation of IVC thrombosis in a primate model. Baboons pretreated with two different antibodies to P-selectin or saline exhibited significantly less thrombus than control animals along with a decrease in inflammation. Using a P- and E-selectin peptide antagonist approach, a similar but even more striking response has been found, with thrombosis much more frequent in IVC segments from control animals as opposed to IVC segments from animals pretreated with the selectin antagonist. These primate studies support the notion that initial leukocyte adhesion is important for thrombus formation and its amplification.

Does the same inflammatory response noted in the animal studies also occur in clinical deep venous thrombosis (DVT)? We have developed a technique to evaluate inflammation in the vein wall noninvasively, using gadolinium (Gd) administered during magnetic resonance venography (MRV). The same enhancement noted in rats and primates has been seen clinically, and the presence or absence of Gd-enhancement defined a DVT less than or greater than 14 days old. Additionally, we have noted that clinical patient vein walls demonstrate an acute increase in inflammatory cells during superficial thrombophlebitis and positive immunohistochemical staining for IL-8 and other chemokines. This suggests that thrombotic inflammation is similar in multiple species, including man.

As inflammation augments thrombosis and is likely involved in vein wall damage leading to the syndrome of chronic venous insufficiency, removal of the thrombus or blockade of the detrimental inflammatory response appears indicated, and, thus, the scientific basis for early clot removal is established.

References

2. Downing LJ, Strieter RM, KadeII AM. Neutrophils are the initial cell type identified in deep venous thrombosis-induced vein wall inflammation, ASAO J. 1996;42: M677-A662.
7. Mulligan MS, Jones ML, Vaporsylan AA. Protective effects of IL-4 and IL-10 against immune complex induced lung injury, J Immunology. 1993;151:5666-5674.

DISCUSSION

DR. CRAIG: That was a great talk. I had a question, perhaps naive, about the precursor of the thrombotic event, and I wondered if you had any experience. Is there anybody working on possible viral mediation for this inflammatory precursor? In other words, could someone catch a cold in their vein valve and lead to a thrombotic event? And second, it also related to the precursor. Is denudation a precursor there and could you just discuss the whole events surrounding the beginning of the thrombotic process?

DR. WAKEFIELD: Virchow's Triad states that you have to have three factors in order to have thrombosis, I think probably if you have two you will get a thrombotic response. For example, in our model where we are producing pure stasis, with the stasis you get vein wall dilatation, and I'm sure with that you end up losing endothelial cell contact, with exposure of subendothelial collagen, and then you get a little bit of thrombin formation. Once you get a little bit of thrombin, that thrombin can really rev up the whole system because thrombin can stimulate cytokine production, cause up-regulation of P-selectin and E-selectin, cause up-regulation of the stable adhesion molecules that then eventually lead to a further inflammatory cell extravasation, and can up-regulate platelets and activate them. So I think all it takes is a little bit of something to stimulate the system to really rev it up, and probably you just need two of the three components. You don't have to be hypercoagulable. You just have to have stasis and injury, I think, in order to initiate the process.

DR. GLOVICZKI: I just had two clinical questions. First, is the inflammatory response in superficial veins different than deep veins? The second, if deep vein thrombosis is then deep vein thrombophlebitis or not?

DR. WAKEFIELD: I think it's the same response. I think it's just that in the deep veins you don't see it. In the superficial veins you see it. So people have recognized it for years. Obviously I haven't had the opportunity to look at a deep vein in a patient in the same way I have looked at superficial veins, but I can tell you that the noninvasive Gadolinium response with magnetic resonance venography is exactly the same that you see in animals as you see in patients. The inflammatory response will last for about ten days to two weeks, and then the Gadolinium extravasation diminishes in the same time course that you see it decline in the primate experiments. So I think it's the same process.

DR. COMEROTA: It appears that some patients can have thrombosis of the greater saphenous system. You can see the clotted vein with very little inflammatory response. In this situation you can strip that vein easily, and the process is over and done with, whereas others have a marked inflammatory response, which has been well characterized. Those with thrombosis without inflammation represent the minority, and those with an inflammatory response the majority. When we've operated on deep vein thrombosis, frequently there is not that edematous inflammation around the deep veins when they're thrombosed. So while I think that there is an inflammatory response, I don't think it's the same in everyone, at least from a clinical perspective.

DR. WAKEFIELD: I think there are gradations for individual patients because not everybody, for example, will resolve their thrombus at the same rate, and you see some patients who at two or three weeks by noninvasive imaging will look like they still have a subacute thrombosis and others will look like they have more of a chronic thrombosis.

DR. HULL: You've identified very succinctly the importance of the inflammation process with leukocytes. What evidence is there, and I'm asking since I don't know, with regards to unfractionated heparin versus low molecular weight heparin? Is one superior to the
other?

DR. WAKEFIELD: I can answer this question with one rat study that we have done, and we have others ongoing. When we looked at standard unfractionated heparin compared to Fragmin, which is the low molecular weight heparin that we looked at, Fragmin at low doses, nonanticoagulant doses, was the best compared to even higher doses of Fragmin or compared to unfractionated heparin for eliminating neutrophil extravasation and for a functional test that we used to evaluate wall integrity. So it appeared that Fragmin at nonanticoagulant doses that do not prolong the anti-factor Xa level is markedly anti-inflammatory. I wonder from this, although it's a big leap, whether or not some of the improvement in mortality rate that has been seen with low molecular weight heparin compared to standard heparin in protocols for venous thrombosis treatment has something to do with the anti-inflammatory effect of low molecular weight heparin compared to standard unfractionated heparin.

DR. BURNAND: I enjoyed your presentation very much indeed. Obviously I thought the baboon model bore greater relationship to human thrombus than the other model. What we've noticed when you ligate everything and you don't have flow going out of the vena cava is that you get a clot that's totally different from organized thrombus. You don't get the sort of nice streaming that you showed, and I was interested to hear that you say that. How do you explain the differences that we've found? And a very simple question, what happens when you deplete the animal of leukocytes? What does that do to the thrombus?

DR. WAKEFIELD: I can tell you that we've used an antibody against monocytes, and we have seen that the thrombus is twice as large as it is when you have not inhibited monocytes. So this is very much in line with what your lab has been showing, that monocytes appear very important for the subsequent resolution of the thrombus over time. We have not performed experiments involving neutrophil depletion.

DR. GONZAGA: Excellent, Dr. Wakefield. Because of the pro-inflammatory and subsequent inflammatory reaction involved in the pathophysiology of venous thrombus formation, do oral anti-inflammatory agents e.g., aspirin, have a role in DVT prevention or recurrence?

DR. WAKEFIELD: It's been taught that anti-platelet agents are not very useful for preventing thrombosis, but I think there is a role of platelets in deep venous thrombosis. I do not think that certainly you're going to get the same anti-thrombotic effect with an anti-platelet agent for venous thrombosis prevention, for example, and that's been well shown, but I do not think platelets are as innocuous a player in DVT as people have thought in the past. As our P-selectin work demonstrates and other work that has been performed using P-selectin receptor antagonists, you can actually show an improvement in various animal injury models. For example, in ischemia reperfusion injury in the liver, in animals where inflammatory cell localization is independent of P-selectin, interventions against P-selectin are still hepatoprotective. This suggests a platelet-mediated effect of the P-selectin inhibition. So I think the platelets are important. As far as should we be using anti-inflammatory agents in patients who have deep venous thrombosis, I think the answer is probably yes. I don't have any randomized control data, though, to answer that question. Certainly, heparin or low-molecular-weight heparin demonstrate some anti-inflammatory effect.

CAN VALVES BE PRESERVED?

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The question of preservation of venous valves is critical in the lower limb below the common femoral vein (CFV) level and is of no demonstrated importance in the veins from the common femoral through the iliac vein and inferior vena cava. The literature on both major and minor maladies due to venous insufficiency has demonstrated the critical importance of both primary and secondary reflux in the thigh and calf, revealing this to be the dominant pathophysiologic problem. Furthermore, reflux in any of the three systems of the limb veins, superficial, perforator, and deep, may be sufficient to cause severe venous problems. In the proximal veins from the CFV through the iliac veins and the inferior vena cava, valves have no recognized physiologic role, but obstruction in these veins may cause severe complications unless it is very well collateralized. The worst physiologic combination in the lower limb veins occurs when proximal obstruction occurs together with distal reflux.

In primary disease there is only reflux, but in post-thrombotic secondary disease both obstruction and reflux are present. Prospective studies demonstrate the great propensity for the initially obstructed veins of DVT to recanalize and to subsequently develop reflux. These studies are ongoing, but it is clear that at least half of the thrombosed limbs develop reflux in the involved segments, and many develop reflux in segments not originally known to have been thrombosed. The natural history data of DVT is accumulating through duplex scan studies which record reflux very well, but it remains possible that significant amounts of more subtle obstructive changes persist in these veins undetected by the ultrasound studies.

The natural history studies also show that up to half of the originally thrombosed veins become recanalized and recover competence by duplex scan criteria. The question of whether this competence is due to preserved normally functioning valves, or whether another mechanism for retaining competence exists, requires an answer. Can retained intraluminal thrombotic masses, or synechiae and strands, produce enough resistance to retrograde flow to simulate competence in these segments? If such masses were present, wouldn't they be obvious on sonography of the distal veins? If the competence is truly due to recovery of normal function by the valves in the originally thrombosed vein, the challenge is to learn what factors cause these particular valves to recover while valves in other segments become scarred and destroyed.

It has been shown experimentally and proven clinically that early thrombolysis of intraluminal thrombosis can yield patent veins that have competent valves, proven by both duplex scan and descending venography, and substantiated by clinical status of the patient. This established fact raises questions such as how long can a thrombus be present and still yield a competent valve after thrombolysis, and are there local or other factors that influence this result other than time?

The ability of thrombectomy to result in a competent valve where
thrombus was present prior to the operation has been studied in Sweden with post-thrombectomy descending venograms which show valvular competence to have been preserved in the thigh veins in the late follow-up at five years. Whether there is a critical time during which surgical thrombectomy can produce this result, or whether there are other factors that are operative, remains unknown.

There are classic studies of the origin of venous thrombosis which show thrombus beginning deep in the vein sinus suggesting that the valve area is highly thrombogenic, probably due to flow factors. In contrast, other studies indicate the valve cusp itself is highly resistant to thrombosis and is prone to remain free of attached thrombus when the adjacent endothelium becomes involved with the thrombus. This suggests the motion of the valve cusp may resist attachment of the thrombus to its endothelium, a finding which could work to preserve valve function.

In primary disease, the valves actually shrink and gradually atrophy over time, perhaps to the point of disappearance. It appears from longitudinal studies that primary reflux disease is a progressive phenomenon during life, but the factors that govern its progress are unknown. There is the possibility that proximal valve reflux contributes to this progression through a process of retrograde dilation of the vein, raising the potential that correction of proximal reflux could forestall the progressive course of distal reflux. Some evidence for this is seen in reports of regression of saphenous dilation after repair of the uppermost valve near the sapheno-femoral junction. In the deep veins, the persistence of good to excellent clinical results for 10-20 years after proximal valve repair also supports this possibility.

The fact that the venous valve can be preserved is established. The fact that venous reflux is the most important physiologic problem in clinical chronic venous disease is also established. The challenge for the future is to identify the elements that cause progressive reflux in both primary and secondary disease and to learn to modify those factors in a favorable direction. Basic studies that lead to better understanding of the venous endothelium and the degenerative changes in the venous wall, in addition to improvements in our knowledge of the effect of thrombosis upon the venous surface, are the most likely areas that will produce progress.

**DISCUSSION**

**DR. COMEROTA:** That’s a very compelling argument regarding many facets of venous disease. I would like to ask Gene Strandness to address one issue that snuck in here. I don’t know if Gene picked up or not. There was one patient that was treated, Gene, in whom the duplex showed competent valves, but the descending phlebogram showed that they were not. I just wonder, which one do you believe.

**DR. KISTNER:** Let me interpret that for a minute. The segment was competent. The individual valves in the superficial femoral vein showed reflux until we got to the competent popliteal valve.

**DR. COMEROTA:** We have on a couple of occasions demonstrated differences between descending phlebograms and what we found in the vascular laboratory. When we looked at physiologic studies, they essentially agreed with the duplex. We now have a dichotomy of what we see on the descending phlebogram and what we saw with our physiologic studies and the duplex. Gene, do you have any thoughts on that?

**DR. STRANDNESS:** I think Dr. Kistner explained it. With duplex you’re looking at reflux by segment. You’re not looking at any individual valve. So you could have a valve, for example, in the superficial femoral vein that might be incompetent and one below it would be competent. So by duplex that segment would appear to be competent.

**DR. KISTNER:** Yes, I think that’s the finding, Gene. Let me ask you, suppose you had permanent thrombosis or blockage of that distal segment and you have an absence of competent valves above that. Will that appear competent? I suggest that could appear competent by duplex even when the valves are actually destroyed. What do you say about that?

**DR. STRANDNESS:** I’m not sure about that. I’d have to think about it. It’s a good question. I don’t really have an answer without thinking about it.

**DR. HASANIYA:** How do you explain that when the whole segment is involved with deep vein thrombosis that certain valves will continue to be competent while other valves will lose competence though they are all subject to the same pathology?

**DR. KISTNER:** I can’t explain it. I think that’s something we need to investigate. The thing that I was fascinated to find out was whether a truly demonstrated thrombosis was lysed by treatment could result in a fully functional valve? I am convinced from this case and a few others -- we’ve studied three cases this way -- that the valve can truly be preserved. I look at the continued mobility of the valve cusp. Even though there’s thrombus around the wall, maybe that process allows several days to get rid of the thrombus before the leaflets become fixed.

**DR. RUTHERFORD:** There’s a point that you touched upon that I think deserves emphasis. In regard to the ability of early clot removal to preserve valves, the focus generally has been on preserving valve function in the involved segment, which is obviously a greater challenge. The delay between onset and treatment is critical, but clearly clot removal has to be done promptly to preserve valves. On the other hand, we tend to overlook the valves downstream, in uninvolved segments. If the clot is not removed early and you have persistent obstruction and high distal pressure, distal valves undergo changes with dilation and ultimately, under the high ambulator pressure below the obstruction, can become secondarily incompetent. I think there’s considerable evidence on this from Gene Strandness’ lab and their serial studies of DVT with duplex scanning which shows that valves below the involved segment progressively become incompetent with time in up to a third of cases. Therefore, I feel that early clot removal may play an important role in also preserving the competence of distal valves, which may be very important functionally.

**DR. BURNAND:** I was going to take up two points, one, the point that you brought up about a single valve being important because one thing that perhaps you and Dr. Strandness, who’s always teaching me things, can explain to me is what segmental reflux below a competent valve means, because I’ve thought that this was a sort of epiphenomenon that wasn’t real because providing you’ve got one competent valve proximally, like you said, that’s probably all you actually need. So is segmental incompetence real or is it just something that we see because if it is true reflux, it has to presumably
reflux through an incompetent perforator coming out of the side of that segment or otherwise it's just "yoyoing" up and down in the isolated segment. The second thing that you brought up was the business about ligating the femoral vein. I caution hard against that. Norman Browse for a spell went through a period of ligating femoral veins and also Vijay Kakkar in London went through a period of ligating femoral veins, and we've got some truly appalling limbs that were left over as a result of that.

DR. COMEROTA: Which femoral vein was it?

DR. BURNAND: The superficial femoral vein just below the profunda, exactly where Bob said he was ligating it. There is something strange because we have people resecting the femoral vein to use as a conduit and they don't seem to get a problem. So there is obviously something different that's going on under different circumstances, and I wonder whether you could tell us what that is.

DR. KISTNER: I have a thought that if all three systems, all axial systems, have become incompetent or thrombosed and all collaterals are incompetent, then ligation of the superficial femoral vein makes no sense. But if there is a competent popliteal-profunda system and/or a retained saphenous system with functional valves, then our studies up to 13 years showed excellent long term results which might have swelling, but not much further in the way of post-thrombotic changes, and no ulcers.

DR. BURNAND: Is the popliteal vein the most important bit of that segment and how can you prevent the thrombus under certain circumstances extending back into the popliteal vein?

DR. KISTNER: Well, I think that one valve in each axial segment is necessary and that may be the popliteal vein, but it may be a valve higher than the popliteal vein. On the segmental reflux, I think that's why it's so key to study our patients thoroughly with the CEAP classification that includes segmental anatomy and segmental reflux and obstruction, and then make the correlations with the clinical course. I don't think we can answer exactly which segmental reflux is going to lead to sequelae at this point.

DR. LABROPoulos: I did a prospective study on deep calf vein thrombosis. So far we have looked at 87 limbs and have a year follow-up. Less than a half of the patients received anticoagulation. The rest of the patients were followed-up with duplex scanning. Only 24 percent of patients developed reflux. Obviously valve function can be preserved in the calf veins regardless of treatment. The femoropopliteal segment is very clear from Dr. Strandness' studies, that only 69 percent of patients that had DVT developed reflux by the end of the first year. A lot of patients did not develop reflux in thrombosed segments. Therefore, valve function can be preserved. Looking at the saphenous vein as one axial pathway, it's very hard to believe that one valve in the saphenous system could preserve the function of the vein. In our study (J Vasc Surg 1997 November issue), we found that in most patients reflux started at below knee segments of the greater saphenous vein. Therefore, if you have a competent valve or competent valves above it, this may not preserve the whole saphenous system. Just to comment on the segmental reflux and the perforating veins. I don't believe that you need to have perforator vein reflux to have reflux in a superficial vein. If you're talking about the greater saphenous vein, for example, there are many tributaries joining the vein. If you have a saphenous segment that's refluxing, you have inflow of blood from the tributaries.

DR. KISTNER: I think I agree with everything you said.

DR. LABROPoulos: I don't think that a single valve could preserve an axial pathway in the greater saphenous system, because most often reflux starts at the below knee segment.

DR. COMEROTA: I think we agree with you, and you have some very fine data to support that.

**Calf Vein DVT: Surveillance and Treatment**

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The danger of clot propagation, pulmonary embolus (PE), and post-thrombotic syndrome is substantial when thrombus involves the iliac or femoral veins, and treatment generally consists of anticoagulation for 3 to 6 months. Less clear are the clinical implications of calf vein deep venous thrombosis (DVT) involving the veins below the knee. Isolated calf vein DVT is estimated to be found in 5% to 33% of all DVT diagnosed. Some have reported significant risk for propagation up to 28% including extension into adjacent crural veins. However, when this is recalculated to include only the significant extension into popliteal or femoral veins, the incidence decreases to 11%. When surveillance duplex scanning alone is used without anticoagulation, Solis reported a proximal propagation rate of 8%.

The direct relationship of isolated calf DVT and pulmonary embolus is controversial. In most series where calf DVT and PE were shown to have a high association, cases were selected by identifying those who presented with PE, and then were subsequently scanned and found to have DVT. The question remains in these reports as to whether a larger, more proximal clot in the femoral or popliteal segment could have embolized before discovery of the calf clot. Obviously, prospective collection of data is critical to accurately study the relationship between PE and calf DVT. Serial duplex scanning of calf DVT and subsequent follow-up to examine the incidence of PE is required.

Post-thrombotic syndrome following calf DVT is believed to occur in 3% to 37% of patients. In one series with follow-up extending to 13 years, there were no ulcers reported. Others claim a high incidence of severe sequelae and physiologic abnormalities in 19%.

Between 1990 and 1995, we examined 58 limbs in 54 patients who were found to have isolated calf DVT by duplex scanning and reported our results. The study consisted of two parts: the first phase with retrospective review of calf DVT and the second phase with prospective acquisition of clinical, imaging, and physiologic data. The first phase was used to examine the rate of clot propagation and pulmonary embolism within 6 months of the DVT, and the second phase consisted of follow-up examination, color-flow duplex scanning, and air plethysmography. Of the 58 limbs with calf DVT, 89%
were symptomatic and 11% were asymptomatic. Since anticoagulation therapy was not controlled, 28 received anticoagulation and 26 did not.

The most common site for isolated calf DVT was the peroneal vein (76%). The second most common location involved the posterior tibial vein (36%). Interestingly, there were no cases of anterior tibial vein involvement.

Rate of clot propagation in entire group was 2 of 49 cases (4%). These cases of propagation occurred within 2 weeks of the diagnosis of DVT. They both occurred in the group who did not receive anticoagulation, and produced an incidence of 8% clot propagation in the untreated group. There were no cases of clinical PE during the surveillance period of calf DVT.

Lysis of thrombi or recanalization occurred in majority by 3 months. At 3 years follow-up, approximately half of all cases had some complaint of swelling, but this was not objectively measurable, and ulceration rare. Interestingly, one third of the group had reflux in venous segments not involved with calf DVT.

In summary, isolated calf vein DVT can be safely managed by duplex scan surveillance without anticoagulation, with a risk for clot propagation in 8%. It is unlikely that isolated calf clot, if properly watched, will produce significant pulmonary emboli or the post-thrombotic syndrome. Duplex scan surveillance should be extended to at least 2 weeks, and preferably 4 weeks to adequately screen for clot extension.

References:

**Calf Vein Thrombosis: Anticoagulation for all?**

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The clinical significance of DVT limited to calf veins is controversial. Although acute DVT can occur anywhere in the deep venous system of the lower extremity, it is well known the majority originate in the infrapopliteal veins or in muscular sinuses. The thrombotic process then subsequently extends into more proximal veins. This is supported by the observation that significant numbers of patients with proximal DVT have coexisting calf vein thrombus. As many as 32% of patients initially diagnosed with calf vein thrombosis show evidence of propagation into proximal veins on subsequent venous duplex studies. The use of anticoagulation, therefore, in patients of calf vein thrombosis may be indicated for any of the following reasons:

1. An adverse natural history with regard to progression to proximal deep vein thrombosis.
2. A risk of pulmonary embolism.
3. The possibility of preventing late abnormal venous hemodynamics associated with isolated calf vein thrombosis.

Pulmonary emboli in patients with DVT apparently limited to the calf has been noted. Moreno-Cabral, et al, found a 33% incidence of clinically "silent" pulmonary emboli by pulmonary arteriography or serial lung scans in patients with calf venous thrombosis. Similarly, Browse and Lea-Thomas also report non-lethal pulmonary emboli in patients with calf vein thrombosis only and concluded that the source of emboli in about 25% of patients with pulmonary emboli was DVT limited to the infrapopliteal deep venous system. Two necropsy studies have reported fatal pulmonary emboli arising from calf vein thrombosis.

In 1997, we reported 105 patients with isolated calf vein thrombosis and various symptoms. Twenty-six percent of these patients had only respiratory symptoms, nine of which (35%) had pulmonary emboli and two died. Seventy-nine patients had only lower extremity complaints and five later developed respiratory symptoms. All five of these patients had pulmonary emboli and none had progression of calf vein thrombosis on repeat duplex scanning. Examination of risk factors revealed that age, gender, prior DVT/PE, obesity, pregnancy, medication, malignancy, smoking, recent surgery or trauma all failed to predict pulmonary emboli. Therefore, it is clear that patients with isolated calf vein thrombosis who do have associated respiratory symptoms have a high prevalence of pulmonary emboli.

Follow-up of patients in our clinic with isolated calf vein thrombosis has revealed a significant incidence of late appearing abnormal venous hemodynamics. Thirty-seven patients who had an isolated calf vein thrombosis documented by duplex scanning between 1989 and 1994 were reexamined. The mean follow-up was 3.4 years after the diagnosis of isolated calf vein thrombosis in 39 extremities. The control group of 17 subjects was also examined with venous hemodynamics studies. In the patients with isolated calf vein thrombosis at follow-up, venous recovery time was abnormal in 23% of the extremities with the isolated calf vein thrombosis and in 9% of extremities without isolated calf vein thrombosis. None of the extremities in the control group had an abnormal venous recovery time (p<0.05). Duplex valve closure times were abnormal at one or more venous segments in 26% of extremities diagnosed with isolated calf vein thrombosis and in only 6% of control extremities.
Follow-up clinical examinations in patients with isolated calf vein thrombosis revealed 35% with reticular veins and 26% with varicose veins and 5.4% with edema and 2.7% with pigmentation and ulcer. It is unclear whether these abnormal hemodynamic sequelae of calf vein thrombosis could have been avoided with the use of anticoagulations.

In summary, anticoagulations for isolated calf vein thrombosis makes sense from several perspectives. It may limit the propagation into the deep venous system. There is a real incidence of pulmonary emboli with calf vein thrombosis and it is possible that anticoagulation may limit abnormal venous hemodynamics that appear late in patients with isolated calf vein thrombosis.

THE ROLE OF FLOW-DIRECTED THROMBOLYTIC THERAPY IN THE TREATMENT OF LOWER EXTREMITY THROMBOSIS: EVALUATING AND TREATING THE ENTIRE LIMB

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PURPOSE
Deep veins in the calf, particularly those converging at the popliteal level, provide important pathways for flow into the femoral system. Thrombosed tibio-popliteal segments, despite patent axial veins can cause acute symptoms and valvular damage related to subsequent chronic venous insufficiency. Often associated with iliofemoral occlusions, unresolved distal venous thrombus can compromise flow, even when proximal vein patency is restored with catheter-directed thrombolysis. Used alone, or in combination with catheter technique, flow-directed therapy promotes purposeful delivery of thrombolytic agents into affected deep veins. When the path of least resistance is the superficial system, intermittent tourniquet compression of the saphenous vein can optimize distal flow in patients undergoing thrombolysis of axial vein thrombosis. Use of this technique can significantly improve deep venous flow to assist large vein patency and reduce venous hypertension.

MATERIALS AND METHODS
Patients presenting with lower extremity DVT, referred for thrombolysis, were evaluated with ascending venography and duplex. Baseline clinical assessment included leg measurements. CEAP classification and hemo-dynamic testing with PPG or APG. Upon determination of sites of deep venous obstruction, the patient was treated with endovascular therapy including one or more of the following: catheter and/or flow-directed lysis, venoplasty and stent(s). Patients with normal iliofemoral segments received flow-directed urokinase or t-PA, whereas patients with distal and proximal thrombosis received simultaneous catheter and flow-directed therapy. Lysis was continued until complete lysis of acute thrombus was achieved and/or acceptable improvement in venous flow was observed venographically. Systemic heparin was used during the procedure. Post-lysis patients were maintained on warfarin and followed with interval duplex, and clinical evaluation

RESULTS
Between March 1989 and August 1999, 116 patients (55M, 61F) received thrombolytic therapy for lower extremity deep venous occlusion. Among the 130 treated limbs (35R, 95L), 73(56%) had an acute clinical presentation, but 54(40%) of this group had evidence of acute thrombus superimposed upon chronic changes. Almost half, 44%(57/130) presented with chronic clinical history and phlebographic changes. The mean age was 49.3 yrs (range 12-90). Flow-directed lysis was given to 35%(42) whereas 88 limbs and 11 IVC were treated with concomitant flow and catheter-directed lytic therapy. Adjunctive balloon diliation and self-expanding metallic stents were used in 79%(50/63) of left limbs, and 64%(16/25) of right limbs. Mortality <30 days was 2(1.7%). Survival, with mean follow-up of 36 mo (range 6 mo-11 years) is 92%. Primary clinical improvement, at three years, in the flow-directed group is 76%(32/42) and 83%(73/88) in the combined group. Complications included: bleeding requiring transfusion (4), MI (1), pulmonary edema (4), site infection (2), hematuria (5), SDH (1). Recurrent DVT occurred in 10.3%(12/130), and one patient had a PE after abdominal surgery. Symptomatic fibrointimal hyperplasia, in stents, occurred in 8(6%) patients.

CONCLUSIONS
An important pattern of DVT, presenting to an endovascular service, is characterized by a relatively young population of productive individuals experiencing the signs and symptoms of acute multi-segmental deep vein thrombosis. The phlebographic pattern, however, reveals a preponderance of patients with acute thrombus superimposed on chronic venous changes, (left>right). Endovascular therapy is an effective and safe approach to restoring a favorable flow pattern, in affected limbs, despite the duration of clinical history. Flow-directed thrombolysis is an effective technique for increasing flow in a limb with hemodynamically significant tibio-popliteal thrombosis.

HEPARIN AND LOW-MOLECULAR WEIGHT HEPARIN THERAPY FOR VENOUS THROMBOEMBOLISM — WILL UNFRACTIONATED HEPARIN SURVIVE?

The Impact of Improved Antithrombotic Therapy!

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Background
Recent methodological improvements in clinical trials and the use of accurate objective testing for the detection of venous thromboembolism have made possible a series of randomized trials to evaluate various treatments for venous thromboembolism. The results of these trials have resolved many of the uncertainties confronted by a clinician in selecting an appropriate course of anticoagulant therapy. These trials have shown that both the intensity of initial heparin treatment and long-term anticoagulant therapy must be sufficient to
prevent unacceptable recurrence rates of venous thromboembolism. Patients with proximal deep vein thrombosis who receive inadequate anticoagulant therapy have a risk of clinically-evident, objectively documented recurrent venous thromboembolism approaching 20% to 25%. The need for therapy with heparin and the importance of monitoring blood levels of the effect of heparin have been established. The importance of achieving adequate heparinization was suggested by a nonrandomized trial in 1972, and randomized trials in the 1980s have confirmed this finding. Furthermore, randomized trials have demonstrated the importance of achieving adequate heparinization early in the course of therapy.

Unfractionated intravenous heparin has provided an effective therapy for more than half a century, but the need to monitor therapy and establish therapeutic levels is a fundamental problem. It is evident that validated heparin protocols are more successful in establishing adequate heparinization than intuitive ordering by the clinician. Even with the best of care using a heparin protocol, however, some patients treated with intravenous heparin will receive subtherapeutic doses. In this context, subtherapy reflects a practical limitation of the use of unfractionated heparin, rather than a poor standard of care. Furthermore, it is recognized that the practical difficulties associated with heparin administration are compounded by the substantive practical difficulties of standardizing APTT testing and the therapeutic range.

Our findings emphasize the confounding effect that initial heparin treatment can have on long-term outcome. In future long-term therapy trials, it is imperative that the initial therapy is of adequate intensity and duration; failure to administer adequate initial treatment may lead to a poor outcome that is falsely attributed to the long-term therapy under evaluation.

A randomized, double-blind trial was conducted comparing the safety and efficacy of intravenous heparin combined with oral anticoagulant versus oral anticoagulant alone in the initial treatment of proximal vein thrombosis. The trial was terminated early because of an unacceptably high incidence of symptomatic extension or recurrence of venous thromboembolism during follow-up in the treatment group of patients receiving only oral anticoagulant. Therefore, it was determined that heparin in addition with oral anticoagulants is required in the initial treatment of patients with proximal vein thrombosis.

Therapy with low-molecular weight heparin, which does not require monitoring and dose finding, is the likely practical solution to these dilemmas. Based on the experience of difficulties achieving adequate therapy with subcutaneous, unfractionated heparin dosing, we administered a low-molecular weight heparin formulation in a single daily dose, rather than splitting the treatment into 2 equal doses. The initial intensity of therapy was thereby maximized. Therapy with low-molecular weight heparin proved to be better than therapy with unfractionated heparin.

**Specific Issues**

1. Unfractionated heparin has been used extensively in the treatment of venous thromboembolism. Recently, various low-molecular weight heparins have been evaluated against unfractionated heparin for treatment in both the hospital and outpatient setting. In a number of countries, the low-molecular weight heparins have replaced unfractionated heparin for the treatment of venous thrombosis. This is because of both the difficulties presented by unfractionated heparin treatment and the demonstrated safety and effectiveness of low-molecular weight heparin therapy.

2. The anticoagulant response to a standard dose of unfractionated heparin varies widely among patients. Furthermore, heparin is poorly absorbed from a subcutaneous site, especially at lower doses. Unless a prescriptive heparin nomogram is used, many patients receive inadequate heparin in the initial 24-48 hours of treatment. Inadequate therapy has been shown to increase the incidence of venous thromboembolism during follow-up.

3. The low-molecular weight heparins are different compounds with distinct pharmacologic properties, and because different regimens have been used in clinical trials, it is inappropriate to make clinical recommendations based on meta-analyses for comparing the effects of low-molecular weight heparin with placebo, unfractionated heparin, or other active agents.

4. In the treatment of established venous thromboembolism, low-molecular weight heparin given by subcutaneous injection has a number of advantages over continuous intravenous unfractionated heparin. It can be given by once- or twice-daily subcutaneous injection, and the antithrombotic response to low-molecular weight heparin is highly correlated with body weight, permitting administration of a fixed dose without laboratory monitoring.

5. A cost-effectiveness analysis indicated that low-molecular weight heparin was cost-effective when compared with continuous intravenous heparin, because monitoring was not necessary and there were fewer complications requiring rehospitalization and treatment. These findings were verified by a sensitivity analysis. It was estimated that 37% of patients on low-molecular weight heparin could have been discharged on day 2, which would have further increased the cost-effectiveness of the low-molecular weight heparin.

6. Evidence is accumulating that low-molecular weight heparin can be used safely for the treatment of acute, sub-massive pulmonary embolism as well. A recent study reported that initial therapy of subcutaneous LMWH is as safe and effective as unfractionated intravenous heparin in acute pulmonary embolism patients. Studies are currently underway to assess the effectiveness and safety of treatment with low-molecular weight heparin for three months compared with standard heparin followed by warfarin therapy.

7. The antithrombotic treatment of segmental venous thrombosis (i.e., calf, femoropopliteal, and iliofemoral) does not differ for either intensity or duration of therapy using either unfractionated heparin or low-molecular weight heparin therapy. The exception to this general therapeutic statement is the patient with calf vein thrombosis who is at high-risk of bleeding. Serial leg testing to detect proximal extension of thrombosis (which occurs in 20-30% of these patients) is an effective strategy. In this context, serial duplex ultrasonography limits anticoagulant therapy to those patients at high risk of pulmonary embolism due to proximal extension; the remaining patients with isolated calf vein thrombosis are at low risk of pulmonary embolism.

8. Thrombolytic therapy for deep vein thrombosis remains highly controversial because of a lack of level A clinical outcome data. Initial antithrombotic therapy data with heparin may have been inadequate given the historical time frame of the thrombolysis studies, and concerns about the risk of bleeding with adjunctive thrombolysis.
9. The clinical deployment of low-molecular weight heparin therapy, which may for certain nations be associated with less bleeding, mandates that clinical investigators reevaluate thrombolysis for adjunctive treatment of deep vein thrombosis immediately prior to low-molecular weight heparin therapy in definitive level A studies.

DISCUSSION

DR. COMEROTA: I think I'd like to limit the discussion on calf DVT to the next mini-symposium. However, Russell, can you summarize for us your conclusion as to what's the outcome of the treatment for DVT in the three segments? I'm not sure I got that from your talk.

DR. HULL: You didn't because I didn't say it. I thought we'd draw it out in the question session.

DR. COMEROTA: Is there a difference in treatment in femoropopliteal versus iliofemoral? We will address the calf DVT next.

DR. HULL: Segmenting thrombosis into iliac deep vein thrombosis, popliteal femoral deep vein thrombosis and calf deep vein thrombosis, is artificial and clinically unhelpful. In Canada and Europe, the majority of patients are treated with low molecular weight heparin and sent home. Before low molecular weight heparin the patients were not sent home because they might deteriorate. Data for low molecular weight heparin in the treatment of proximal deep vein thrombosis or calf deep vein thrombosis shows at least equivalence or superiority, depending on the context versus warfarin. Low molecular weight heparin has been routinely used in Canada for about three years although patients at very high risk of bleeding still receive intravenous heparin, which can be reversed quickly. In numerous countries, unfractionated heparin treatment has been replaced by low molecular weight heparins for the treatment of venous thrombosis. This is both because of the demonstrated safety and effectiveness of low molecular weight heparin therapy and because of the difficulties presented by unfractionated heparin. Subcutaneous low molecular weight heparin has a number of advantages over continuous intravenous unfractionated heparin. It can be self-administered by once or twice daily subcutaneous injection, and the antithrombotic response to low molecular weight heparin is highly correlated with body weight, which permits administration of a fixed dose without need for laboratory monitoring. With more experience, our confidence in low molecular weight heparin is gradually increasing.

DR. COMEROTA: So all DVT is the same and differentiation into venous segments is artificial and unhelpful? Is that your conclusion?

DR. HULL: If you're dealing with antithrombotic therapy. If you're sticking a catheter in for lysis, there are obvious issues of the mechanics of doing that.

DR. COMEROTA: I was attempting to get your opinion regarding the segmental distribution of acute DVT.

DR. HULL: And I said there was no Level A data for lysis yet, but I sure hope we get it.

DR. STRANDNESS: I have a couple questions for you. One that really concerns me most of all is the European attitude towards the detection of DVT. The use of ultrasound only involves looking at two veins, the common femoral and the popliteal. Interestingly, the prevalence of calf vein DVT is in the range of 12 percent. What is your view about the “stop and pop” technique versus doing a complete limb examination. This is very important if we're ever going to deal with the issue of calf vein thrombosis? If you don't look, you won't find it.

DR. HULL: There's good Level A data that's being ignored. So I think your point is particularly poignant because the Europeans just decided they didn't want to look in the calf. That was a decision that they made, and most North American centers that are routine diagnostic imaging centers use the European approach for reasons that it's very cost effective. The technician doesn't have to fuss around in the calf. That's a tragedy because the Oklahoma data shows that if you fuss around in the calf -- and I'm being a little facetious but that's the European view -- you do something very important. You improve the initial detection rate and you decrease the requirements for serial testing to one ultrasound. Now, that's a very important observation. This is Level A. It's in annals. It's recent because the reality is almost nobody does serial testing at all. So one of the tragedies of ultrasound at the moment is we're doing one test and we know we're having patients on lots of aggregate data, yet most diagnostic imaging departments don't realize that one test is not enough. If we went to the Oklahoma approach and just did the one test, we'd be catching more patients. As you pointed out, Gene, and we'd be doing less harm, but the beauty of the Oklahoma approach is you only need one extra test which people probably would do. So it's not two or three. So the serial noninvasive testing issue is a very thorny one, and most people don't comply and we are harming patients.

DR. COMEROTA: To follow up on that comment by Gene, we have over 3,000 noninvasive studies comparing the common femoral vein and popliteal vein compression versus a complete examination. This will be published in the Annals of Vascular Surgery in the first two months of 2000. We found approximately four percent of proximal DVT would have been missed because they were isolated to the superficial femoral vein, obviously all calf DVT would have been missed. Overall, we would have missed 37 percent of all patients with DVT if we used only the common femoral and popliteal vein compression.

DR. RUTHERFORD: I have a comment and a question. Three years ago at this meeting you presented similar data based on the same outcome criteria of pulmonary embolism, death, recurrent DVT and bleeding. At that time I and others pointed out the importance of the other outcome evaluations, specifically those reflecting the post-phlebitic syndrome. You admitted their importance and said this aspect was to be included in future and ongoing studies. So I'm a little disappointed not to hear anything on post-thrombotic sequelae today, although maybe you're going to give us some Level I evidence on that later in the day. Hopefully you will present that because that's one of the things I expected to get out of this meeting. My question is: are there cost effectiveness studies that showed that the added benefits, which we'll concede exist for a low molecular weight heparin, justifies the additional drug costs? You didn't mention them yet, but I'm sure you must have some data on this. Do the savings from ambulatory care outweigh drug costs?

DR. PARTSCH: Also coming to post-thrombotic syndrome, you have mentioned several times that the key issue would be recurrent DVT. As far as I know, there is one randomized controlled study showing that compression stockings are able to reduce the fre-
quency of post-thrombotic syndrome after proximal DVT, but there are no such data concerning the effect of long-term anticoagulation. I wonder how it is possible that in all large series on long-term anticoagulation the authors just looked at recurrent DVT but nobody looked at post-thrombotic syndrome?

DR. COMEROTA: Hugo, would it be incorrect to assume that if you avoided recurrent DVT that you would lessen the risk of a post-thrombotic event in that patient?

DR. PARTSCH: No, it would not. We know from studies, for instance, from Prandoni that recurrent DVT is really the key issue, but we do not have studies showing that long-term anticoagulation is able to decrease the post-thrombotic syndrome. There is one study from Brandjes and co-workers which was able to show this for compression stockings alone (Lancet 1997).

DR. HULL: Graduated pressure support stockings with an ankle pressure of 30 to 40 mmHg are issued routinely in Canada to all patients with acute deep vein thrombosis. There is good evidence that graduated pressure support both controls and prevents the evolution of the post-phlebitic syndrome.

DR. LORD: Several years ago, I asked a similar question. You started your talk by saying that unfractionated heparin was inferior to low molecular weight heparin, but in discussion you conceded then there was one category, namely the high risk surgical patient, for example, aortic surgery or something like that, in whom you wished to give anticoagulation but in whom you may need to reverse this quickly and need a little control. I was just wondering what the current position is. Is that still the case for IV heparin with protocol for the high-risk postoperative surgical patient?

DR. HULL: Yes. We’ve been using low molecular weight heparin routinely in Canada for about three years, and we’re gradually eroding that principle because of the potential for a decreased risk of bleeding, but that caveat still remains pretty globally true because of the reversal issues for the other part of the consultant team that’s involved in the patient. So we’re still honoring the very high-risk patient who we may reverse quickly in giving them IV heparin. Yet the paradox is I’ve showed you some proved safety data, and that safety data may actually be quite real. So our confidence in using low molecular weight heparin is gradually increasing as we get more experience. The experience in Canada now is broad but basically we haven’t hit the wall with an reversal of all patients who died from bleeding with low molecular weight heparin. So that fear is progressively dimishing.

DR. LORD: In the patient I’m referring to, then, what should the ordinary doctor like ourselves --

DR. HULL: We’ve stayed with IV heparin, but we’re close now with a high comfort level with the other part of the team, the surgeon, to taking a gamble if you like. And I’m putting it deliberately as a gamble because we haven’t yet done it in a high number of patients, but because of the increased protection against bleeding, we’re increasingly prepared to take the gamble in the next year or two and we probably will.

DR. LABROPoulos: Russell, what do you think of using D-Dimer as a screen test to exclude DVT or PE and what do you think about the use of spiral CT in detecting pulmonary embolism?

DR. HULL: The D-Dimer test in the future is going to cut down the need for sequential or serial testing by allowing such rapid and sensitive tests as the Eliza assay, to eliminate the diagnosis of deep vein thrombosis and pulmonary embolism in patients in whom the diagnosis is suspected. Spiral CT testing is experimental. PIOPED II, which is an NIH proposal, is undergoing review again, and if the NIH approves funding, there will be a definitive large trial testing the value of spiral CT. If the NIH doesn’t fund it, then we’ll be left with a chaotic mess because the small trials that have been published show results all over the map.

DR. TRIPATHI: I have a comment and I have a question. The comment is that the role of low molecular weight heparin is fairly well established by meta-analysis presented by Leizorovicz in 1997 which shows that there is a decrease in the extension of thrombosis in the iliofemoropopliteal system by 5.8 percent. There is a decrease in the pulmonary embolism rate by 7.8 percent, death in these patients by 11 percent, and bleeding complications by over 50 percent. These are data which includes over 3,000 patients, and it includes the Canadian and the Tasman trial. My question is: Tom Wakefield presented the inflammatory changes in DVT, and he showed that if you can give anti-inflammatory drugs, you can reduce the thrombus load. The model of DVT which he presented was a stasis model where you ligate the vein and produce thrombosis. A vast majority of patients don’t have this stasis type of DVT. They have inflammatory changes which cause endothelial damage and DVT resulting secondary to that. I believe that there may be two different categories of patients, one group that has stasis related DVT and the other group that has endothelial damage related DVT. In patients who have got stasis type of DVT, low molecular weight heparin would suffice by reducing thrombus extension and thrombus load reducing the inflammatory process which is basically the fibrinogen-complement mediated inflammatory change. In the other, endothelial damage related DVT group, anti-inflammatory drugs may have a role. What do you think about that?

DR. HULL: Low molecular weight heparin has both an antithrombotic and anti-inflammatory effect. Aspirin, both an antithrombotic and anti-inflammatory agent has some effect in the prevention of deep vein thrombosis after hip surgery; the risk reduction using aspirin is about 20%. The risk reductions with heparin and low molecular weight heparin are higher and may be as high as 60-70 percent in certain high risk groups. Drugs like aspirin do not have a potent enough effect to be used in isolation and we do not know if they are additive enough in terms of benefit to overcome the increased risk of bleeding.

DR. RUTHERFORD: I thought the evidence presented was pretty convincing for the treatment with low molecular weight heparin of most, if not all calf DVT. There was a time in the past, when we used indirect noninvasive tests of DVT, that were not good for detecting calf DVT, that we excused that by saying, that there’s a low incidence of pulmonary embolus with calf DVT, so it didn’t matter. There was a lot of rationalization there. Now, I think once you’ve detected and visualized a vein clot, even though it propagates in only 10 to 20 percent and has a very small pulmonary embolism rate, because low molecular weight heparin ambulatory treatment has so little risk, it’s very hard to argue against treating all but those with a high risk of bleeding complications. So I stand convinced by that argument.

DR. COMEROTA: When you refer to treatment with low molecular weight heparin, I’m assuming that means conversion to oral anticoagulation with Coumadin. How long should anticoagulation continue?
DR. RUTHERFORD: Yes, in a standard fashion, usually for three
months. I would also agree with the point that was made that if you
have someone with a very high risk of bleeding, let’s say someone
with a brain tumor or recent operation, that those patients with calf
DVT could be monitored closely without anticoagulation.

DR. COMEROTA: Therefore, treatment of most begin with low
molecular weight heparin converted to oral anticoagulation for
two months. Those patients at risk of a complication from antico-
agulation are followed with surveillance duplex examinations. Very
appropriate. Andy, any comments?

DR. CRAGG: Well, I had a lot of thoughts. I may have to
confine it to one or two here. Let me talk from a radiologic standpoint and
just make a comment about some of the things I heard both now and
earlier this morning, that is, ultrasound detection of tibial thrombus
and how accurate it is. I think one of the things when you order tests
in radiology or imaging you think that you send it down and you get
a consistent result. Dealing with ultrasound techs who do, of course,
also all of these exams all over the world, there’s a big variation in
I think, how accurate it is in terms of looking at tibial veins. It’s
not an easy thing to do. Most of them are required in our department
to check off whether they think the tibials are normal, but I’ve got to
tell you, I bet a lot of times they’re guessing.

DR. COMEROTA: That’s a very good point, Andy. Assume you’re
the radiologist on for the day in your hospital. I’m worried that my
patient who has tenderness in the calf might have calf DVT. You and
I would agree that if your venous duplex was negative from the
popliteal and above, we’d be comfortable that there’s no blood clot
in the proximal venous system. I’m now sending this patient to you
with calf tenderness, otherwise healthy, and you don’t see any clot
in the tibial veins. What’s your recommendation to me? Does this
mean that there’s no DVT, or is there DVT which you missed?

Should we bring the patient back in three, four, or five days to repeat
the duplex? Should we do a venogram?

DR. CRAGG: If there is a specific request about the tibial veins,
orally we sort of gloss over them in a report in using general
terms “none seen.” That’s a little different than saying there isn’t
any. So if you were to come to me and hopefully visit me and say this
is a particular patient in whom I’m worried about the calf veins, then
you’re going to have to go back and either scan it yourself or go back
with a technologist and say, “I need you to tell me -- we need to go
down each of these tibial veins.” Most of the time, though, when an
ultrasound tech tells you “I didn’t see any,” what they’re saying is
they looked in the central tibial veins at the confluent with the
popliteal veins and they looked at accessible veins around the ankle
- the posterior tibial. I don’t think it’s necessary that they go down
each peroneal vein, for instance, all the way to the end.

DR. COMEROTA: If you have seen the tibial veins, identifying the
posterior tibial and the peroneal and even the gastro and soleus,
and there’s no clot visualized, can we accept that as true, Gene.

DR. STRANDNESS: Dr. Cragg I can give you a reference to the
American Journal of Roentgenology that compared power Doppler/color
Doppler against venography for calf vein thrombosis. It was
found to be very accurate if it’s properly done. With regard to
venography, a conference sponsored by the NIH several years ago,
concluded that venography was generally poorly done in the United
States. The other thing which is very important is that the technology
and methodology is still evolving. Five years ago there were serious
problems particularly for calf veins but now with the addition of
color and power Doppler, you can look at only the tibial veins,
and the peroneal, but the soleal sinuses and, as Dr. Moneta pointed
out, the gastrocnemius veins as well. This should no longer be a
mystery. We do look at these routinely. If your technologists are not
doing the examinations properly, then they ought to be taught how
to do it properly.

DR. CRAGG: And I couldn’t agree more with you, Gene. I just
think that there’s a difference between that ideal and reality around
the United States.

DR. STRANDNESS: I don’t disagree with that. I think we have to
understand that we can detect calf vein thrombosis.

DR. COMEROTA: Let’s assume that the diagnosis of calf DVT is
reliable. What do you do with that information, Gene.

DR. STRANDNESS: Dr. Brenda Zierler has been looking at our
clinical practice at the University Hospital in Seattle and it’s really
appalling. When we surveyed not only the attending physicians but
the residents as well, up to 25 percent of the residents think that
the calf veins are superficial veins. A cardiac surgeon thought that the
superficial femoral vein was a superficial vein! With this level of
understanding, the treatment will by definition be very poor. We also
found in our survey that one-half of the physicians think that calf vein
thrombosis should not be treated. From an educational standpoint
we’ve got a long way to go.

DR. WAKEFIELD: Ten to twelve years ago, I actually tried in
three patients who had arthroscopy, were young, healthy males
who had calf vein thrombosis to treat with surveillance when that
condition was on the upswing. All three failed, ending up propagat-
ing. So I stopped at that point, and I use low molecular weight
heparin for treatment of calf vein thrombosis.

DR. COMEROTA: And three months of oral anticoagulation after

DR. WAKEFIELD: Well, yes. We were talking yesterday. There
was a recent study in the New England Journal that talked about
the length of time for idiopathic DVT for Coumadin therapy, and it
probably is for more proximal thrombosis longer than the three to
six-month period that we have traditionally been taught. Unfortu-
nately, that study wasn’t segregated into the level of the thrombus
and how long the oral anticoagulant treatment should be given. So
it may be that depending on the level of thrombosis, the length of the
Coumadin therapy will be found to need to vary.

DR. THORPE: Just a comment to what Andy brought up and Dr.
Strandness addressed, it’s even more alarming to me that when you
send a patient down for rule out DVT with ultrasound, the technolo-
gists normally don’t look above the inguinal ligament unless it’s
specifically requested. That’s appalling to me because thrombus is
probably missed at that level, especially if you have common iliac
thrombus where you have flow into a hypogastric. You still have flow
in the common femoral.

DR. COMEROTA: That’s a technologist in the vascular labora-

tory or the radiology department?

DR. THORPE: No. We have a very nice accredited vascular lab
where it’s shared with surgery and radiology and they’re great. But
I have to specifically request that they look in the inguinal area or
above the inguinal ligament because the reality around the United
States is that now, because of a number of articles that have come
out, they do a compression test at the common femoral and the
popliteal level. They don't look below the popliteal very much, and they don't look above the inguinal ligament unless requested. We may be missing thrombus that way. But the question Greg brought up on a very nice slide showed the incidence of reflux in segments that were above the calf and an incidence of some valvular incompetence in both extremities in these patients that you were studying. That brings the question do you think that pre-existing reflux may be a precursor for an element of stasis in patients? That may be a setup for calf vein DVT depending on lifestyle, or on other elements? And one other question that maybe you all could address is that no one ever says what numbers we're talking about because we don't know the epidemiology very well. Ten percent of a huge number like ten million people per year that might have this condition, diagnosed or undiagnosed, may be a huge number, but we're always minimizing it by saying it's only 2 out of 100 or 10 out of 100. What do you think?

DR. MONETA: I have three comments. One, vascular technologists usually work for you, and they'll do whatever you ask. We ask ours to do complete examinations, pelvic veins down all the way to the ankle. They're reasonable people. You tell them what you would like them to do and they'll do it, whenever possible. The second comment concerns why there is reflux in venous segments, that didn't seem to have had thrombus. I don't know if the reflux was pre-existing or developed later. This wasn't a Level I study. Primary reflux may have predisposed to the development of calf vein thrombosis. The patients may also have had some ongoing hypercoagulable state causing small areas of thrombosis. I think you have to keep in mind that from a public health perspective, one-tenth of one percent of a large number can be very important. It's just that when you're dealing with small numbers in terms of percent the importance to an individual practitioner may be lost, but from an overall perspective and a public health perspective, it can still be very important.

DR. LORD: I'm thinking of ambulatory surgery and the big switch toward ambulatory procedures. Is there any evidence that a single dose of low molecular weight heparin is effective in reducing the incidence of calf venous thrombosis?

DR. COMEROTA: For prophylaxis during ambulatory venous surgery?

DR. LORD: Well, a survey of British vascular surgeons showed that some of them thought it was a good idea. About half of them thought it was a good idea for varicose vein operations, but only about a third actually practiced it.

DR. COMEROTA: Well, do you have any information as to what the incidence of DVT even at the calf level is after ambulatory venous surgery?

DR. LORD: No, I don't.

DR. COMEROTA: I think that might be an important denominator to know to get to the heart of your question. Any panelists have any thoughts or information on that? No. Does anybody on the panel or anybody in the audience for that matter give prophylaxis for ambulatory venous surgery? Raise your hand. For DVT prophylaxis during ambulatory venous surgery, for varicose veins, not SEPS, varicose veins. Okay. Very interesting.

DR. LORD: About a third of British vascular surgeons gave anticoagulant prophylaxis and half thought it was a good idea.

DR. CHARLESWORTH: Can I ask Russell Hull, in the case of a symptomatic calf DVT with just an isolated peroneal vein or tibial vein, can you make a logical case for a one-week course of low molecular weight heparin, which we know will be very good in relieving the symptoms, but not proceeding to warfarin?

DR. HULL: An early study with intravenous heparin followed by no long term treatment in symptomatic calf deep vein thrombosis versus intravenous heparin followed by oral anticoagulants showed that a lack of follow up treatment resulted in a 20 percent recurrent thrombosis rate. Logically, patients will have to be followed up with long term anticoagulants. A randomized, double-blind trial was conducted comparing the safety and efficacy of intravenous heparin combined with oral anticoagulant versus oral anticoagulant alone in the initial treatment of proximal-vein thrombosis. The trial was terminated early because of an unacceptably high incidence of symptomatic extension or recurrence of venous thromboembolism during follow-up in the treatment group of patients receiving only oral anticoagulant. Therefore, it was determined that heparin in addition with oral anticoagulants is required in the initial treatment of patients with proximal-vein thrombosis.

DR. COMEROTA: I'm not sure I follow you, Russell. The absence of data doesn't mean segmental distribution and disease severity is unimportant. It means we don't have the data from the Canadian trials or the low molecular weight heparin trials; is that correct?

DR. HULL: I'll rephrase it another way. We have compelling data showing you don't need to, except for in the calf.

DR. COMEROTA: If you're going to anticoagulate everybody?

DR. HULL: Yes.

DR. COMEROTA: I think this slide speaks to the question that was just asked. These data were reported by Lagerstedt from a prospective randomized trial. -- These are Level I data; correct?

DR. HULL: That's what I was referring to.

DR. COMEROTA: This trial used standard unfractionated heparin in patients who had venographically proven isolated calf vein thrombosis randomized for five days to anticoagulation with unfractionated heparin IV alone vs. heparin converted to 3 months of oral anticoagulation. 29 percent of those treated with only 5 days of heparin returned within a year with recurrent venous thromboembolic complications versus those that were treated with oral anticoagulation for three months, who had no recurrent venous thromboembolism. I think that at least addresses the issue of short-term anticoagulation with unfractionated heparin. Whether these data would be altered with lower molecular weight heparin is unknown.

DR. STRANDNESS: I wanted to ask Dr. Hull a question. One of your former colleagues, Jack Hirsh, wrote an editorial in the New England Journal of Medicine which stated that if you had DVT with a reversible risk factor, say an operation, it was not necessary to treat for three to six months. You might get by with six weeks of therapy. It seems to me in the calf vein situation this might be exactly what you're talking about. Dr. Hull, what is your view on the six-week paradigm that Jack suggested in that editorial?

DR. HULL: There is hope that treatment could last for less than three months in somebody with a reversible risk factor, but data are limited. Genetic mutations must also be considered. Twenty percent of patients presenting with deep vein thrombosis in the U.S. and Canada have identifiable genetic mutations. These patients may do poorly even two years after stopping treatment depending on the genetic mutation. A randomized trial looking at home treatment with low molecular weight heparin for three months or low molecu-
lar weight heparin for six days followed by Coumadin is underway. Coumadin has the same frailties as heparin. You have to monitor it. If you get outside the therapeutic range, you'll have recurrences and you will have bleeding if you go above it. In addition to the safety data, quality of life is the key measure. We will determine exactly how many people have the post-phlebitic syndrome. European data are now pointing out that if you ambulate the person early, the thrombotic mass as demonstrated in repeat imaging data, is less and therefore, the post-phlebitic syndrome may be less. With low molecular weight heparin programs, the patients can more readily ambulate even if they are in the hospital. Further, 37% of patients on low molecular weight heparin in our treatment trial could have been discharged on the second day of treatment. The cost-effectiveness of the low molecular weight heparin is demonstrated for both in-hospital and out-of-hospital treatment. In many centers in Canada, up to 70% of patients with deep vein thrombosis are now being treated at home.

DR. ABU-BAKER: Why DVT is localized to one leg, and not in both of them, especially after surgical operation, for example, after appendicitis, cesarean section, total hysterectomy, and abortion? The second question, can the superficial thrombophlebitis produce DVT, and if yes, how?

DR. MONETA: I can take a crack at the second question. Can you have a deep venous thrombosis associated with superficial thrombophlebitis? My understanding of the data is that superficial venous thrombosis can be followed by deep venous thrombosis. Probably 10 to 15 percent, of patients presenting with superficial phlebitis, have a co-existing deep venous thrombosis.

DR. COMEROTA: Aside from the co-existing DVT, have any of the panelists observed a patient with initial superficial, that is greater saphenous or lesser saphenous phlebitis, extend through the perforators and involve segments of the deep system? The second part, to the question, have any observed extension through the saphenofemoral junction and involve the common femoral vein? I've seen the latter, but I have not seen the former.

DR. STRANDNESS: Anyway, I've worried about this, and I've watched greater saphenous thrombophlebitis progress right up to the fossa ovalis, but I've never seen it extend into the common femoral vein. I've been worried about this because what do you do with these patients? I'm sure it happens, but I've never seen it.

DR. KISTNER: I'm sure that we have seen it progress through the saphenofemoral junction and give a highly inflamed very bad common femoral and femoropopliteal thrombosis, but I've never seen it go through perforators.

DR. COMEROTA: The other question that was raised, if people are going to get DVT, especially post-op, why don't they get it in both legs? Why do we see it in only one most of the time?

DR. STRANDNESS: 17 percent of them do.

DR. COMEROTA: But the majority of them do not.

DR. STRANDNESS: I know, but if you look at both legs when you're looking at a patient with DVT, it's not terribly uncommon in the opposite leg, but I agree with you. It's not universal.

DR. COMEROTA: Therefore, the answer is we don't know. Then one other question with all of the experts on the panel. All of you have observed that the anterior tibial vein very rarely is involved with DVT. What is so special about the anterior tibial vein that protects it from deep venous thrombosis?

DR. MONETA: I don't know. The anterior compartment is also the one that's most susceptible to compartment syndrome. Maybe the pressure in that compartment is slightly higher.

DR. COMEROTA: So you think it's something external to the vein rather than intrinsic to the vein?

DR. MONETA: Yes. I can't imagine why it would be intrinsic to the vein.

DR. COMEROTA: In patients with calf DVT should we do hypercoagulable workups? What is the role of compression, Greg?

DR. MONETA: In my practice I do a hypercoagulable workup with the first DVT if there is no identified reason for the DVT. If the patient develops a second venous thrombosis, then a hypercoagulable workup is always done. We treat anyone with any form of lower extremity venous thrombosis with 30 to 40 millimeter gradient compression stockings.

DR. KISTNER: We're very similar. I think we are doing more hypercoagulable panels on patients and just using that as a marker for being more aggressive about following the patient, perhaps treating them at the time, but calf vein elastic stockings for everybody.

DR. HULL: There is hypercoagulable screening in all irrespective of the site for a very practical reason. The proband if you find genetic defects -- and we are in 20 percent of patients and that includes having hip surgery. So idiopathic, obviously you get a better yield, but people who go to surgery still have genetic mutations. Think about public health. I'll give you 15 seconds as a very good reason to screen. I think about Europe, and for those of you European based, there's been a lot of debate about screening before you use a particular drug. Okay. So I'll answer those two questions. The female blood line members of the family are going to be exposed to the oral contraceptive pill and hormonal replacement therapy. If you do that in somebody with a genetic defect like Leiden, you'll knock the risk up 30 to 40-fold.

DR. COMEROTA: Only if you use third generation progesterones though, not if you use some of the others.

DR. HULL: No. That's a separate issue. So let's come back to that in a moment. If you're a female and you wish to take the oral contraceptive pill, in Europe they're now talking about screening because if you have the Leiden gene, which is one of the common ones, your risk on any OCP or HRT is 30 to 40-fold increased if you have the genetic defect and no history of DVT. The first is published. The second is available from our colleagues in the United Kingdom, and that's irrespective of the pill. The third generation progesterone issue is an issue separate to that, and that is it's miasiter than some of the other pills. So that's a degree of risk within the use of OCPs. So basically if you have a young woman who wants to use the OCP and has the Leiden gene, it's absolutely contraindicated to do so, and if you're older, in our range, so to speak, and you are a female and you wish to use HRT, the answer is no. It's contraindicated. So we are actually screening in very large scale and intervening in the public health of many of the family members of the probands.

DR. WAKEFIELD: Russell, would it be reasonable to do a mini screen, to do pro-thrombin 20210A and Factor V Leiden and not do Protein C, Protein S, and all the other tests?

DR. HULL: If you're talking about yield, you're making an excellent point because the yield out of that 20 percent will be 16 percent for those two, but the other four percent are there. So our lab
has bitten the bullet and does everything that we can currently do to give us the 20 percent, which is the remaining four percent that you’d miss.

DR. STRANDNESS: Did I understand you, Dr. Hull, that you screen everybody with DVT? Did you also say that you screen everyone who has a total hip? Are you going to screen our whole population?

DR. HULL: No. I just said we screen all patients who have DVT or PE.

DR. STRANDNESS: Even if a patient has a reversible risk factor like a surgical operation or a total hip, something like that, you would still screen them?

DR. HULL: Yes, because we wish to know the answer to your question as to whether it’s worthwhile. So idiopathic I think you’d agree we screen.

DR. STRANDNESS: But you didn’t say that. You said you screened everybody essentially.

DR. HULL: We do.

DR. COMEROTA: Everybody with DVT or PE?

DR. STRANDNESS: Where is the Level I data?

DR. HULL: We’re trying to generate the Level I data, but obviously we’ll withdraw it from hip patients if we find the yield is low, but the point is it’s not. I suppose the other key point is eight percent of the people in this room, looking at the faces that’s a fair statement, and if you came from the Middle East it’s 20 percent, have the Leiden gene. Staggering, isn’t it? Now, most of us don’t get thrombosis right off the bat or we’d have an army of thrombosis to deal with it, but the Leiden gene is a very common single gene mutation, and it’s made thrombosis the commonest genetic disease which is a real twist in ten years from acquired disease to genetic. So eight percent in this room, twiddle your toes when you’re flying back, whether you go first class or coach.

ILIOFEMORAL DVT – AMBULATORY TREATMENT

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INTRODUCTION
The important question of mobilization and physical activity in the management of DVT is not mentioned in most therapeutic reports including the large randomized trials advocating home-therapy.1,2 For us the term “ambulatory” means that walking should be encouraged and bed-rest should be avoided. This may be done in the hospital or at home.

Three main questions are to be discussed:

1. Can patients with iliofemoral DVT be treated at home?
2. Do patients with iliofemoral DVT need bed rest?
3. What are the benefits from aggressive ambulation with compression?

1. Can Patients With Iliofemoral DVT Be Treated at Home?
The most important undesirable events which may occur during the management of DVT and which are better to be handled in the hospital than at home are:

• death.
• new pulmonary emboli.
• bleeding complications.
• HIT II reaction.

Based on a series of 1,111 consecutive patients with acute DVT, the influence of the following variables on these events was analyzed:

• age.
• localization of DVT.
• previous DVT.
• presence of primary PE.
• presence of malignancy.

The cohort of 1,111 patients which was admitted to the hospital between May 1992 and December 1998 was treated by subcutaneous injections of low-molecular weight heparin (preferably dalteparin, 200 IU/kg body-weight b.i.d.), compression bandages and walking exercises. Major parts of our experience with this regime have been published.3,4

As it is demonstrated in Tab. I an increased risk concerning fatal events, all investigated by autopsy, could be shown for higher age, iliofemoral localization of DVT, and for the presence of malignancy. Three patients died from pulmonary embolism: a 98-year-old man immediately after admission, an 87-year-old lady on day 3 presenting additionally myocardial infarction and a 76-year-old man with additional metastases in the liver. In another 14 cases other causes for a fatal outcome, predominantly malignant disorders, were found.

1,062 patients were investigated by a baseline-V/Q-lung scan which was repeated after 10 days on average. The results are shown in Table II. Most of the pulmonary emboli were clinically completely silent. Very careful interviewing revealed some dyspnoea during walking in about one-third of the patients. Only 6/1,062 patients presented a worsening of pre-existing symptoms or new dyspnoea.

Concerning the occurrence of new pulmonary emboli, although clinically silent in most cases, only the presence or absence of malignancy could be shown to have significant influence (Tab. III).

Bleeding complications (4 major bleedings/1,111 patients) and a HIT II reaction (2 cases) were rare and did not show any correlation with the calculated risks.

From this analysis it may be concluded that DVT-patients with higher age, with iliofemoral thrombosis and with concomitant malignant disorders are not good candidates for home-therapy.

2. Do patients with iliofemoral DVT need bed rest?
In most centers patients with thrombi extending into the pelvic veins are immobilized at least for some days because of the fear of pulmonary embolism.

As can be seen in Tab. II pulmonary embolism is already present at admission in about 50% of the patients with proximal DVT without causing severe symptoms in the majority of cases. The rate of new pulmonary emboli detected by repeated lung-scanning is 7.3% in our patients with iliofemoral DVT and 5.8% in the total
DVT population. This event is significantly lower compared to published data using conventional therapy (Tab. IV). The same is true for fatal pulmonary embolism which was proved by autopsy in 3 patients, all of them admitted because of iliofemoral DVT.

Investigating patients with iliofemoral DVT by MRI scanning, an unexpectedly high rate of thrombi which extend into the common iliac and into the inferior caval vein, may be detected. MRI phlebography performed on 189 patients with proximal DVT revealed parts of the thrombi in the inferior caval vein in 35 patients (18.5%).

The outcome of this group, also treated by compression, walking and dalteparin in 34 patients and by thrombectomy in one 17-year-old boy with venous anomalies was quite favorable (Tab. V and VI).

From these data we may conclude that bed rest is not necessary even in patients with thrombosis extending into the caval vein, at least as long these patients were mobile before admission.

3. What are the benefits from aggressive ambulation with compression?

In a randomized, controlled trial in 45 patients with proximal DVT it could be demonstrated that compression leads to a significantly faster regression of pain and of leg-swelling, and that there is less thrombus progression compared to bed-rest.1 For an optimal outcome immediate acceleration of venous blood-flow by compression and by walking is probably of similar importance like the exact anticoagulation in the first 24 hours.2

CONCLUSION

Our conservative management of symptomatic outpatients with deep vein thrombosis is based on anticoagulation, compression and walking exercises. This regime is independent from localization and morphology of thrombi (floating or not).

Based on an analysis of a total of 1,111 consecutive patients with DVT, 318 extending into the iliofemoral segment (18% reaching into the inferior cava), we recommend to treat such proximal cases, patients older than 70 years and patients with concomitant malignant disorders, preferably in the hospital. All mobile patients are kept “ambulatory” since immediate and intensive walking is considered to improve the outcome.

References


Table 1.—Risk factors for fatal events (up to 6 weeks after admission) in DVT

Table 2.—Incidence of pulmonary embolism (PE) in baseline and repeated lung scan.

Table 3.—Risk factors for new pulmonary emboli (1,062 patients with repeated lung scan).

Table 4.—Comparison of our data concerning the incidence of pulmonary embolism with the literature.
Table 5.—Follow-up of 35 patients (1 months -6 years) with thrombi in the inferior caval vein

| Drop-outs | 2 |
| Follow-up only 1/month | 3 |
| Deaths | 6 |
| - 84 f 3 months at home |
| - 89 f 4 months at home |
| - 54 m 1 year Hypernephroma |
| - 51 m 2.5 years Colon-carcinoma |
| - 70 m 3 years MCI |
| - 88 f 5 years Hypernephroma |

Re-examination 24

Table 6.—Re-examination of 24 patients with cava thrombosis between 4 months and 6 years

<table>
<thead>
<tr>
<th>Readmitted before reinvestigation:</th>
<th>10</th>
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<tr>
<td>contralateral DVT</td>
<td>3</td>
</tr>
<tr>
<td>After 2 months (Marcoumar)</td>
<td></td>
</tr>
<tr>
<td>After 2 years (Marcoumar)</td>
<td></td>
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<tr>
<td>After 5 years (no anticoagulation)</td>
<td></td>
</tr>
<tr>
<td>pulmonary embolism</td>
<td>2</td>
</tr>
<tr>
<td>After 1month (Marcoumar)</td>
<td></td>
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<tr>
<td>Compression</td>
<td>16</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>16</td>
</tr>
<tr>
<td>(11 Marcoumar, 3 LMWH, 2 ASS)</td>
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CATHETER-DIRECTED THROMBOLYSIS FOR SYMPTOMATIC LOWER EXTREMITY DEEP VEIN THROMBOSIS

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ABSTRACT

A national Venous Registry was organized to study catheter-directed thrombolysis (CDT) for the treatment of symptomatic lower extremity deep vein thrombosis (DVT). Between January 1995 and December 1996, 287 patients with lower limb DVT were prospectively treated with CDT. There were 137 (48%) males and 150 (52%) females averaging 47.5 years of age (range: 1-98). Based on symptoms duration, 66% presented with acute DVT (≤10 days), 16% with chronic DVT (>10 days) and 19% with both acute and chronic DVT. From the venograms, Grade I (<50% lysis), Grade II (>50% lysis) or Grade III (complete lysis) were calculated. Based on follow-up duplex scan evaluations, 1-year cumulative primary patencies were derived for different subgroups and compared using life-table methods. Iliofemoral DVT (IFDVT) were present in 221 (71%) and femoral-popliteal DVT (FPDVT) in 79 (25%). Following 7.8 million IU urokinase (range: 0.5–44.0) administered over a mean of 53.4 hours (range: 2.0–147.3), metallic stents were deployed to treat lesions uncovered in 99 iliac veins and 5 femoral veins. Grade III lysis was achieved in 31%, Grade II in 52% and Grade I in 17%. For acute limbs, Grade III lysis occurred in 34% compared to 19% for chronic limbs (p<0.01). Major bleeding complications were reported in 11.5% patients, most often occurring at the puncture site. Two patients died: one fatal PE and one intracranial hemorrhage for a mortality rate of 0.04%. For all limbs, the 1-year primary patency was 60%. Treated IFDVT was more durable than FPDVT (64% versus 47%; p<0.01). Lysis grades were major predictors of patency: for Grade III, Grade II and Grade I lytic outcomes, the 1-year patencies were 79%, 58% and 32% respectively (p<0.001). CDT is safe and effective. Data from the Venous Registry can serve as a guide to judicious patient selection for this potentially effective form of therapy.

SUMMARY

GOALS OF TREATMENT

Elimination of the embolic potential of existing thrombus, restoration of unobstructed flow, prevention of further thrombosis and preservation of venous valve function, are the ideal goals of therapy for acute DVT. Meeting these goals will not only prevent PE but will also minimize the long-term sequelae of venous hypertension and the development of the post-thrombotic syndrome. Multiple treatment options including anticoagulation, surgical venous thrombectomy, and thrombolytic therapy achieve these goals to a variable degree. For instance, while anticoagulation with heparin followed by coumadin therapy is definitely effective in minimizing PE and recurrent thrombotic episodes, it does not prevent the post-thrombotic syndrome. In fact, with anticoagulation alone, restoration of venous patency relies solely upon individual endolytic corrective processes. Furthermore, even with therapeutic heparin anticoagulation, 30-40% of patients will show extension of their DVT and only 20-25% will have venographic evidence of partial thrombolysis. Treatment strategies aimed at eliminating or reducing the risk of PTS should focus on preserving valvular function and eliminating the risk of continued venous obstruction following acute DVT. Surgical removal by means of thrombectomy techniques combined with creation of arteriovenous fistulas have been employed successfully in Europe and the United States but overall such procedures have not been commonly performed. Thrombolytic agents are an attractive form of early therapy because they have the ability to eliminate obstructive thrombus in the deep veins and should therefore help provide protection against the PTS. The perceived benefits of early and rapid recanalization in preserving valve function have been the basis for the use of lytic therapy to treat acute DVT.

THROMBOLYTIC THERAPY: RATIONALE

There is good documentation that systemic thrombolytic therapy is...
superior to heparin anticoagulation alone in achieving early lysis of the deep veins. In a pooled analysis of 13 randomized studies, Comerota and Aldridge found that only 4% of patients treated with heparin had significant or complete lysis, compared to 45% of patients randomized to systemic streptokinase therapy. Furthermore, in the heparin group, as many as 82% had no venographic evidence of lysis or clearly demonstrated thrombus extension, compared to 37% in the streptokinase group. Similarly, in reviewing pooled data from 6 trials judged to have proper randomization, systemic thrombolysis was 3.7 times more effective in producing some degree of lysis than was heparin. From these data, there is objective evidence that systemic thrombolysis is more effective than anticoagulation in promoting early lysis.

Two studies reported late clinical outcome following randomization to either anticoagulation or systemic streptokinase for acute lower limb DVT. Although the follow-up periods in both studies were different, 1.6 years versus 6.5 years, the majority of patients with severe symptoms of the PTS received anticoagulation alone. In both reports, the majority of patients who received streptokinase were free of the PTS. Although both studies suffer from small sample sizes and lack of objective measures to grade the PTS, it can, nonetheless, be suggested that systemic thrombolysis improves anatomic and clinical outcomes when compared to anticoagulation alone. Long-term improved venous hemodynamics and preservation of valvular function have not been well documented following systemic lytic therapy. In a long-term randomized follow-up study, a popliteal venous valve incompetence, measured by direct Doppler examination, was more common in patients randomized to anticoagulation versus systemic streptokinase. Nine percent of patients successfully lysed had an incompetent valve compared with 77% of those who did not lyse. This study, however, has not been published in peer-reviewed journals and still resides in the format of an abstract.

CATHETER-DIRECTED THROMBOLYSIS

Over the past 10 years, catheter-directed thrombolysis techniques have been proved effective in the endovascular treatment of acute limb ischemia secondary to acute native arterial or bypass graft thrombotic occlusions. Delivering thrombolytic agents by means of low-profile infusing catheters and guide wires placed directly into the occlusion under fluoroscopic guidance offers several advantages over systemic lytic therapy. Because highly concentrated plasminogen activators can be delivered directly into the thrombus, treatment duration can be reduced, complete lysis rates improved, and lower incidence of bleeding and other complications associated with systemic therapy can be expected. Second, the technique allows for supplemental endovascular treatment of uncovered hemodynamic lesions by means of balloon angioplasty or stent technique. Similar regional catheter-based lytic treatments have been recently applied towards ilio-femoral DVT. In a series of 25 patients treated with catheter-directed thrombolysis for ilio-femoral DVT by Sembia and Dake, complete lysis was achieved in 18 (72%) patients, swelling was successfully reduced in all but one. Only one patient suffered a bleeding complication of heme-positive stools. After the drug was discontinued, there were no significant adverse sequelae. This initial report suggests that catheter-directed lytic therapy for patients with lower extremity DVT can be effective in achieving significant lysis of clot and may be associated with low complication rates.

This experience stimulated the development of a multicenter venous registry, which was recently closed after enrollment of nearly 500 patients. Completed data with follow-up of at least 6 months were available on nearly 300 patients, 70% of which were IPDVT, as determined by venography. Nearly 40% required a stent in the iliac vein, to relieve an obstruction or a stenosis uncovered after catheter-directed thrombolysis treatment. Significant lysis (> 50%) was achieved in 80% of the limbs and approximately 30% achieved complete lysis. A complete lytic event was more commonly achieved for acute DVT (<10 days) which was present in about 60% of the patients. The lysis grade obtained after lysis and stenting was a major predictor of continued patency. At 6 months, approximately 70% of limbs with significant lysis remained patent, and for acute limbs, when complete lysis was achieved, 90% remained patent. Reflux at follow-up at 6 months was found in less than 30% of those with complete lysis, 45% of those with >50% lysis and over 60% with <50% lysis. There have been only 2 deaths in the entire study (0.4%), one from an intracranial hemorrhage and one of six patients who suffered a PE. The use of the popliteal vein with ultrasound guidance appears to be favored and will likely become the standard access site for most patients.

References:

INTRODUCTION
Pharmacologic dissolution of intravascular thrombi using lytic agents has established itself as a useful adjunct to many forms of revascularization, both surgical and interventional. The most widespread use of thrombolytic therapy has been in the treatment of arterial thrombosis in the lower extremities. Thrombosed native arteries and bypassed grafts can be effectively revascularized with catheter directed infusion therapy using one of several lytic agents. For most interventionalists, urokinase is the lytic agent of choice because of its predictable action and acceptable side effect profile.

We recently published a randomized study reviewing two different protocols for infusion lytic therapy of thrombosed peripheral bypass grafts and native arteries. Two dosing protocols from 50,000 units/hour of urokinase to 250,000 units/hour were found to be equally effective in lysing both acute and chronic thrombi, however, the time to lysis was 20-30 hours requiring overnight infusion and observation in an intensive care setting.¹

We and others have begun examining a variety of new devices and techniques to speed up the lytic process when revascularization is required in a variety of vascular beds. These techniques allow us to rapidly open thrombosed vascular conduits in a single procedure and in some situations, lytic therapy can be used on an outpatient basis.

LYTIC TECHNIQUES
Infusion Therapy
Introduction of a lytic agent through a catheter imbedded in a thrombosed vessel or a bypass graft is an effective means of achieving complete thrombolysis, but one significant limitation is the time it takes for completion of the procedure. This is due in part to the time it takes for the lytic agent to penetrate the thrombus along the length of the occluded segment. To speed up this process we have developed a series of catheters for more effective infusion of lytic therapy. One catheter is a multi side-hole catheter which delivers lytic agent in an even fashion along the length of the infusion segment. Infusion segments vary between 5-20 cm. The catheter has a valve at the tip which allows passage of the catheter over a guide wire but which seals after the removal of the guide wire to allow only side-hole infusion. Another variation of this catheter uses a coaxial design to tailor the length of the infusion segment to the length of the occluded vascular segment. Another device which enhances delivery of the lytic agent to the periphery of the thrombosed vessel is the shape memory, infusion wire which we have developed. This device gradually reforms into a coiled configuration to approximate the vessel wall as lytic therapy progresses. With these devices, coaxial infusions can be performed so that long vascular segments can be treated with infusion therapy.

Pulse Lytic Therapy
Many interventionalists favor pulsed delivery of the lytic agent into the thrombus in order to accelerate the lytic process. With this technique, small boluses of urokinase are delivered in a forceful manner to form jets out of the side holes of an infusion catheter. The side-hole valve tipped infusion catheter we’ve developed allows for more convenient application of this technique since the catheter can be placed over a wire and then used for pulsed lytic therapy without additional tip occluding wires or coaxial devices.

Pharmac-Mechanical Lytic Therapy
Agitation of the thrombus during delivery of the lytic agent may further accelerate the lytic process. We are currently testing the use of the Thrombolytic Brush to effect a combination of pharmacologic and mechanical lysis. The device consists of a soft nylon brush which is rotated at relatively low rpms during the delivery of a lytic agent. The brush agitates thrombus and enhances delivery of the lytic agent to the thrombus. The device is presently approved for use in thrombosed dialysis fistulas and we are currently investigating in pre-clinical studies the use of the device in peripheral arteries and veins. Further development of devices such as these may allow the majority of thrombosed peripheral vessels to be revascularized with lytic therapy in a single sitting. Other devices use a venturi effect from high-pressure saline injection to aspirate thrombus. Different devices may be more beneficial in certain situations than in others.

VENOUS DISEASE
Deep venous thrombosis is a common medical condition with major morbidity for those affected. Acutely, patients may develop painful phlegmasia and chronically a large percentage of patients develop venous stasis problems secondary to valvular dysfunction. Heparin is generally ineffective in preventing the long-term complications of deep venous thrombosis which occur in 50-80% of patients.

Recently, investigators have begun to advocate catheter directed lysis of deep venous thrombosis in order to decrease the acute symptoms and preserve vein patency and valve function. While the long-term clinical efficacy of this technique is not yet established, it has been demonstrated that venous thrombi can be readily lysed using catheter-directed therapy. Disadvantages of this technique however, include relatively cumbersome catheterization from a retrograde approach and the long times associated with lysing venous clots.

Mechanical and pharmac-mechanical thrombolysis may make this procedure more rapid and efficacious. We have recently developed a technique and protocol for antegrade catheterization of the deep venous system in the lower extremity which allows simplified access, better patient tolerance and placement of long coaxial infusion systems. In experimental models, we have demonstrated that venous thrombi can be rapidly dissolved with the Thrombolytic Brush and we anticipate clinical trials with this device in the future. Our goal with lytic therapy and deep venous thrombosis is to provide complete lysis and vein patency in several hours rather than several days.

DIALYSIS ACCESS
The rapid flow through a surgically placed arteriovenous fistula invariably leads to turbulence and pannus formation in the outflow vein near the venous anastomosis. In patients with forearm dialysis access grafts, this often results in narrowing of the outflow vein,
restriction of flow through the fistula and subsequent thrombosis. To preserve patency of the dialysis access after it is thrombosed, it is essential to correct the underlying venous outflow restriction. Recently, many practitioners have found it useful to combine the advantages of thrombolytic therapy and balloon angioplasty in a fluoroscopic suite where the anatomic status of the arterial and venous segments of the fistulas can be accurately determined. In general, access to the radiographic interventional room is more easily obtained than to the standard operating room. In some centers, this has facilitated a shift of patients from traditional operative thrombectomy to fistula revascularization using lytic therapy and angioplasty of the venous outflow. Early results using streptokinase for fistula thrombolysis were disappointing. However, newer developments including the use of urokinase and multiple catheters for more complete fistula lysis have improved the success of the procedure. In general, the acute success in revascularizing thrombosed fistulas exceeds 90% with lytic therapy and angioplasty.  

While lytic therapy can be less invasive than surgical thrombectomy, one disadvantage is the frequent need for overnight hospital admission to complete the lytic procedure. This adds to the cost of the procedure and can inconvenience the physician and the patient because dialysis schedules are often performed on an every-other-day basis. A method for nonsurgical, outpatient revascularization of the thrombosed fistula should provide an attractive alternative to existing methods both from a clinical and a financial standpoint. Recently, techniques for revascularization have been reported using maceration of clots, pulsed spray administration of lytic agent, or embolization of thrombus without use of lytic agents. These techniques high-light a trend toward outpatient management of this clinical problem. With these techniques, successful revascularization has been achieved in 90-95% of patients. Secondary patency for these fistulas averages about 6 months in most series and points out the fact that dialysis fistulas require routine maintenance with repeat procedures in order to maintain their viability. The large number of procedures and the need for repeat procedures suggests that a method for rapidly revascularizing fistulas on an outpatient basis would be very useful.

All revascularization procedures, including surgical thrombectomy, thrombolysis and iatrogenic embolization as described by Trerotola, result in pulmonary embolism to some degree. There is a long clinical history with surgical thrombectomy to suggest that this is relatively well tolerated. With lytic therapy, emboli tend to be small and are generally laced with a lytic agent which should facilitate their dissolution in the pulmonary vascular bed. There is now a large experience with lytic treatment of dialysis access thrombosis and symptomatic pulmonary embolism has not been a significant clinical problem. The technique of Trerotola in which the thrombus occluding the fistula is deliberately emboiled to the lungs without lytic therapy suggests that even larger volumes of thrombus can be well tolerated in most patients. The comments of Dolmatch et al. regarding this technique, however, point out the fact that many dialysis patients have poor cardiopulmonary reserve and care should be exercised in limiting the degree of pulmonary embolism associated with the procedure.

One method for accelerating the lytic procedure involves maceration of the thrombus during delivery of the lytic agent. Mechanical agitation of the thrombus which facilitates mixing of the lytic agent with the thrombus has been shown to rapidly accelerate lysis. This type of mixing can be accomplished in a reproducible and controlled manner with the Thrombolytic Brush. Animal studies suggest that fistula thrombolysis can be accomplished in a matter of minutes without significant pulmonary embolization.

With this technique, short vascular access sheaths are placed into the arterial and venous limbs of the thrombosed fistula. The venous outflow is then studied by diagnostic venography and stenoses in the venous outflow are dilated by balloon angioplasty. 250,000 units of urokinase mixed with 2,000 units of heparin are then delivered in a divided dose into the arterial and venous limbs of the fistula. The Thrombolytic Brush is then introduced and used to gently mix the lytic agent and the thrombus. This agitation usually results in complete lysis of the thrombus in the fistula within several minutes. Follow-up angiography is then performed with additional angioplasty as necessary of either the arterial or venous limbs. The vascular access sheaths are compatible with dialysis tubing and can be left in place for immediate dialysis. The lytic procedure can be completed with in one hour. In this fashion, the interventionalist can complete the procedure in a single sitting without having to move the patient either into another area for short-term lytic infusion or admit the patient to the hospital for overnight lytic infusion. Both of these are impediments to more widespread use of lytic therapy for revascularization of thrombosed fistulas. The simplification of the revascularization procedure fits with the trend toward surveillance and maintenance of dialysis fistulas by repeat outpatient procedures such as lytic therapy or angioplasty. Renal medicine physicians who are largely responsible for the management of dialysis patients find it convenient to schedule patients for this procedure since they can, in general, be treated on a same day outpatient basis without inconveniencing the existing dialysis schedule.

In our practice, this has become the routine standard of care for management of thrombosed dialysis fistulas. Patients can be treated between dialysis sessions without scheduling disruption. In our practice, virtually all dialysis patients with thrombosed access are managed by outpatient accelerated thrombolysis and angioplasty.

References
Intraluminal stents have demonstrated their utility as adjuncts to angioplasty for the treatment of chronic arterial occlusive disease. Their application to the venous circulation has been more limited. We and others have experience with the use of intraluminal stents in a variety of venous applications. These include management of failed angioplasty of the venous outflow in dialysis access fistulas, treatment of superior vena cava syndrome and treatment of chronic pelvic venous occlusion.

Stenting in Conjunction with Dialysis Access Fistula Salvage Intervventional revascularization of the thrombosed dialysis fistula is now a common procedure. Thrombosis or dysfunction is usually due to obstruction of the venous outflow near the venous anastomosis. Regardless of whether a surgical revision or interventional salvage of the thrombosed fistula is undertaken, both techniques exhibit a high recurrence rate in large part related to restenosis of the treated venous outflow segment. In our experience, intraluminal stents have a limited role to play in the salvage of access fistulas. Stents placed in the venous outflow after failed angioplasty can act as a bridge to revision if this cannot be accomplished immediately or if the patient requires immediate dialysis. Stents do not, however, appear to limit restenosis associated with angioplasty and have demonstrated that patency is similar to standard angioplasty. At this time, therefore, there does not appear to be a role for primary stenting as a means to prevent restenosis. Failure of stents in the forearm appears to be a due to a combination of the relatively hostile turbulent flow environment and the smaller caliber of stents in this location.

Superior Vena Cava Syndrome
We have anecdotal experience with the use of intraluminal stents for treatment of superior vena cava syndrome in patients with malignant SVC obstruction. SVC syndrome is a disturbing symptom complex which often occurs in patients with terminal malignancy. In this situation, placement of even relatively smaller caliber stents in the diameter range 8-12 mm usually results in rapid defervescence of the clinical manifestations of SVC syndrome. Patients are quite gratified by this relatively simple technique and stent patency has not generally been an issue because of the limited life expectancy of these patients. For patients with benign obstruction of the superior vena cava, stents may also have a role, however, in this situation adequate caliber is necessary to limit the effects of restenosis. Careful attention to technique is necessary to minimize the important complication of stent misplacement or migration.

Pelvic Venous Stenting
In conjunction with our developing experience with lysis of deep venous thrombosis we have identified a subgroup of patients who appear to benefit from iliac stenting. These are the patients with chronic obstruction of the left iliac vein (May-Thurner Syndrome) who develop acute deep venous thrombosis. Often these are young patients who are active and otherwise healthy. After lytic therapy is accomplished to treat the thrombosis, an underlying stenosis of the common iliac vein is usually uncovered. This can be either a focal stenosis at the confluence of the iliac vein and vena cava or a chronic obstruction of the entire common iliac vein with collateral outflow through the internal iliac vein. These patients do not respond to simple balloon angioplasty even though the initial result may appear favorable. In our experience these patients inevitably rethrombose unless a stent is placed. In this situation we try to place a large stent as possible (12-16 mm diameter). Patients are maintained on anticoagulation for six months after stent placement.

Other causes of chronic venous occlusion including radiation stricture, post-operative stricture or external compression may also respond to intraluminal stenting. In general, the tenants of successful venous stenting are constant regardless of the location. Best results can be expected when the following conditions are met: 1) larger stents, 2) shorter lesions, 3) better inflow, 4) proper anticoagulation.

References

SELECTIVE THROMBECTOMY FOR TREATMENT OF ILIOFEMORAL DVT

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There are data that indicate that early and quick removal of an acute venous thrombus may prevent the destruction of the venous wall and valve, i.e., stop the progress into the post-thrombotic syndrome (PTS).

We, therefore, recommend an aggressive treatment with rapid removal of the occluding thrombus in active patients with acute iliofemoral deep venous thrombosis (DVT).

The first line of treatment should be catheter-directed intra-thrombus thrombolysis with or without adjunct procedures such as angioplasty and stenting. When there are contraindications or failure of thrombolysis, thrombectomy (TE) with a temporary arteriovenous fistula (AVF) is the alternative. Both interventions will be followed by anticoagulation. These aggressive interventions are not justified in chronically ill, bedridden, high-risk, or aged patients, or those with serious intercurrent disease and/or limited life expectancy. In this group of patients these interventions can only be justified for limb salvage in phlegmasia cerulea dolens where conservative treatment does not prevent the development of an acute compartment syndrome with venous gangrene.

THROMBECTOMY
The first TE for iliofemoral venous thrombosis (IFVT) was per-
formed by Lawen in Germany in 1937. Surgery today is performed under intubation anesthesia. Ten cm water PEEP is added during manipulation of the thrombus to prevent perioperative PE. The involved leg and abdomen are prepared. A longitudinal incision is made in the groin to expose the long saphenous vein (LSV), which is followed to its confluence with the common femoral vein (CFV) which is dissected up to the inguinal ligament. The superficial femoral artery 3-4 cm below the femoral bifurcation is prepared for construction of the AVF. Further dissection depends upon the etiology of the IFVT. In primary IFVT with subsequent distal progression of the thrombus, a longitudinal venotomy is made in the CFV and a venous Fogarty TE catheter is passed through the thrombus into the IVC. The balloon is inflated and repeated exercises with the Fogarty catheter are performed until no more thrombotic material is extracted. With the balloon inflated in the common iliac vein a suction catheter is introduced to the level of the internal iliac vein to evacuate thrombi from this vein. Backflow is not a reliable sign of clearance since a proximal valve in the external iliac vein may be present in 25% of cases preventing retrograde flow in a cleared vein. On the other hand, backflow can be excellent from the internal iliac vein and its tributaries despite a remaining occlusion of the common iliac vein. Therefore, an intraoperative completion venogram is mandatory. An alternative is the use of an angioscope which enables removal of residual thrombus material under direct vision. The distal thrombus in the leg is removed by manual massage of the leg starting at the foot. The Fogarty catheter can sometimes be gently advanced in retrograde fashion. The aim is to remove all fresh thrombi from the leg. In IFVT secondary to ascending thrombosis from the calf, the thrombus in the superficial femoral vein (SFV) is often old and adherent to the venous wall and we have already lost the battle of the valves. The objective is to restore patency and preserve valvular function. If iliac patency is established but the thrombus in the femoral vein is too old to remove, then it is preferable to ligate the superficial femoral vein. Recanalization will otherwise lead to valvular incompetence and subsequent reflux. If normal flow in the SFV cannot be re-established, we recommend extending the incision distally and exploring the orifices of the deep femoral branches. These are isolated and venous flow is restored with a small Fogarty catheter. The SFV is ligated. The venotomy is closed with continuous suture and an AVF created using the LSV, anastomosing it end-to-side to the superficial femoral artery. An intraoperative venogram is performed through a catheter inserted in a branch of the AVF. After a satisfactory completion venogram the wound is closed in layers without drainage. If there are signs of iliac vein compression which can occur in about 50% of left-sided IFVT, we recommend intraoperative angioplasty and stenting.

Heparin is continued at least 5 days postoperatively, and warfarin is started the first postop day and continued routinely for 6 months. The patient is ambulant the day after the operation wearing a compression stocking. The patient is usually discharged on the tenth postop day to return after 6 weeks for closure of the fistula. The objectives of a temporary AVF are to increase blood flow in the thrombectomized segment to prevent immediate rethrombosis, to allow time for healing of the endothelium, and to promote development of collaterals in case of incomplete clearance or immediate rethrombosis of the iliac segment. A new percutaneous technique for fistula closure was developed by Endrys in Kuwait. Through a puncture of the femoral artery on the opposite surgically untouched side, a catheter is inserted and positioned at the fistula level. Prior to inflation and release of the balloon or coil, an arteriovenogram can be performed to evaluate the patency of the iliac and caval veins, which is of prognostic value. More than 10% of patients have been shown to have remaining significant stenosis of the iliac vein despite initial successful surgery. A transvenous percutaneous angioplasty with stenting can be performed under the protection of the AVF, which is closed 4 weeks later after repeat arterio-venogram.

"LATE" RESULTS

There are few studies on “long-term” results after TE with AVF. There are 8 studies of clinical results in 521 patients with more than 2 years follow-up where “clinical success” is claimed in 62%. There are 5 studies on iliac vein patency in 247 patients with more than 2 years follow-up showing 82% patency (range 77-88%). There are 5 studies on femoro-popliteal valvular competence in 259 patients with more than 2 years follow-up showing 60% competency (range 36-84%). In the prospective, randomized study from Sweden we found a highly significant difference in the number of asymptomatic patients after 6 months, with 42% in the surgical group versus 7% in the conservatively treated group. At 5 years, 37% of the operated patients were asymptomatic compared with 18% in the conservative group. At 10 years, 54% in the surgical group were basically asymptomatic (class 0-2 new CEAP classification) compared with 23% in the conservative group, however, not a significant difference. Iliac vein patency at 6 months was 76% in the surgical group compared with 35% in the conservative group, demonstrated by venography. This significant difference was upheld after 5 and 10 years with 77% and 77% patency in the surgical group, respectively, versus 30% and 47% in the conservative group, respectively. Femoro-popliteal valvular competence at 6 months was 52% in the surgical group compared with 26% in the conservatively treated group, using descending venography with Valsalva, a significant difference. After 5 years, the patients who underwent TE had significantly lower ambulatory venous pressures, improved venous emptying as shown by plethysmography, and a better calf pump function with less reflux as measured by foot volumetry. Combining the results of all functional tests, 36% of the surgical patients had normal venous function compared with 11% of the conservatively treated group. These differences were not statistically significant due to loss of patients. At 10 years, using duplex scanning, popliteal reflux was found in 32% of the surgical group compared with 67% of the conservative group. Six patients who had a successful TE 10 years before without obstruction of the iliac vein at the time of surgery, were all asymptomatic with patent iliac veins, and 50% had competent popliteal veins. Successful TE seems to be beneficial in the long term.

The treatment of acute iliofemoral DVT should aim at:

- prevention of fatal PE;
- decrease of pain and swelling of the involved leg, trying to stop the development of phlegmasia cerulea dolens, and venous gangrene;
- prevention of the disabling post-thrombotic syndrome by early removal of the blood clot avoiding proximal venous obstruction and preserving normal, functioning valves preventing reflux.
The first choice to accomplish early and quick removal of the thrombus is catheter-directed intra-thrombus thrombolysis. When there are contraindications or failure of thrombolysis, thrombectomy with a temporary AVF is a valid alternative.

References

ALGORITHMS FOR THE TREATMENT OF ACUTE DVT

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Figure 1
Algorithm for the Management of Calf Vein Thrombosis

Figure 2
Iliofemoral DVT

Figure 3
INFRAINGUINAL DVT

Figure 4
Management of Primary Axillo-Subclavian Vein Thrombosis

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DISCUSSION

DR. COMEROTA: We're now going to move to the most extensive form of DVT. Observations from the venous registry and the observations from the quality-of-life outcomes study can serve as a reasonably solid hypothesis that eliminating the clot in the iliofemoral venous system is helpful in our patients and will lead to a more favorable outcome compared to standard anticoagulation. Obviously that needs to be tested in prospective randomized trials. I'd like to invite comments from our expert panelists.

DR. WAKEFIELD: My comment would revolve around the fact that what I think we really need to know is who, when you lyse, you can clear because even in the patients in the registry who had symptoms less than ten days, had no history of prior DVT, and had the best access, the complete lysis rate was only 65 percent. You have shown and others have shown from the data from the '70s that it is in those patients with complete lysis who had the best results. If you don't attain complete lysis, you don't have as good a result. Thus, it seems to me that what we really need is to be able to identify the patient when we see him or her who we expect is going to be able to be lysed completely. That's the person, if you're going to lyse somebody, that you should attempt. If you can't expect that you are going to have complete clearance, then perhaps you should not even...
begin lysis.

DR. COMEROTA: What are your thoughts, Andy? Do you agree? If you can’t get rid of all the clot, should you not even try? Isn’t getting rid of 50 or 75 percent of the clot better than leaving 100 percent of it?

DR. CRAGG: That’s not a yes/no answer. I think some of these patients may have had complete lysis, for instance, of their iliac system and incomplete lysis of their femoral system, and they would automatically go into that Grade II category. I think in terms of swelling, the key item is getting their iliac system open. It sure would be nice to predict who’s not going to do well. I sure can’t do it ahead of time. I’ve got some gut feel after I’ve started, and that’s if you’re not progressing in 12 hours, you’re probably not going to be successful. We tend to slog on on these things for two to three days trying to make a little progress, but I think you’re right in that sense, that what we might learn is when to throw in the towel, not who to pick.

DR. THORPE: Sometimes when the patient comes to you and they’ve had seven days of symptoms or even two days of symptoms, when you do a careful history you find out that actually their symptoms started two or three weeks before. So there is layering of thrombus, the oldest thrombus, then some more recent thrombus where they get that critical mass that makes them swell and hurt and brings them into the doctor’s office. It sort of deludes us to think it’s a relatively acute presentation. By the time they finally figure it out, the thrombus isn’t all that brand new. So when we start the lytic therapy, even with catheter directed technique, we get rid of the brand new clot very quickly. The older clot might take a little bit longer, and in the venous registry there was a learning curve for a lot of people. They weren’t all experienced with catheters, and sometimes therapy could have gone a little longer as opposed to what Andy is saying, and they might have gotten a better result. Would that make a difference in the long run? I don’t think we know.

DR. COMEROTA: Patricia, what do you tell your patients regarding intracranial hemorrhage? Many of these patients are quite young and it’s an identified risk. What do you address this issue?

DR. THORPE: Well, I think it’s a relatively small risk in the younger patients because when you look at the data and the complications in the literature the risk factor that predicts --

DR. COMEROTA: Do you even mention it to them?

DR. THORPE: Oh, yes, I do, because the major risk factor is diastolic hypertension, and this is a young group of people who don’t have hypertension problems yet. I also screen for any seizure disorder because I’ve looked at a number of cases that have gone to court for intracranial bleeding. Seizure disorder, even remote seizure disorder, seems to be related in a number of cases that have had bad outcomes in younger patients, and we don’t know enough. There are not that many patients --

DR. COMEROTA: So you won’t treat anyone who’s had a prior seizure?

DR. THORPE: To tell you the truth, I shy away from anybody who’s had a seizure disorder.

DR. CRAGG: It is worth discussing the use of lytics and intracranial hemorrhage. I always tell them it’s a very remote possibility and it is.

DR. COMEROTA: Do you not treat patients with prior seizure disorders?
phlebitis is that we’ve gotten much better at giving aggressive antithrombotic therapy. I said antithrombotic, not anticoagulant, because anticoagulant we would like to remove and with low molecular weight heparin we have in a sense that we don’t have to anticoagulate monitor. The intracranial bleeding rate is real. I’m a specialists system half the time, the other half of the time a hematologist, and so I think a trial has to be done. Is Abbott going to sponsor the trial?

DR. COMEROTA: I doubt it at the present time because urokinase has been taken off the market in the United States. Gene has a comment for you.

DR. STRANDNESS: We have the data on valve function from the registry. Mark Meissner is preparing the manuscript for publication. I can’t tell you the final details, but it appears that if you achieve complete patency, (removal of the thrombus), it is possible to preserve competence of the venous valve. I think that’s extremely important. Getting back to the issue, if you remove obstruction you preserve valve function, clinically you will do better. It is important to have open veins and good functioning valves. So I think from that standpoint, if nonlytic therapy doesn’t assist in some way to promote thrombosis lysis, it will fall short. The randomized trial with thrombolyis was about to be started, Abbott pulled out of the field. Tony, do you know if there’s a randomized trial?

DR. COMEROTA: I’m not aware of any, no.

DR. STRANDNESS: So this question may not be answered unfortunately.

DR. HULL: I think it will for two reasons if. We go through the history of medicine, we now recognize that you need to give aggressive antithrombotic therapy, and that used to be heparin protocol. It’s now some of the low molecular weight heparin regimens. That allows early ambulation, and some of the low molecular weight heparin regimens may also be safer intrinsically than unfractionated heparin. I’m the glass that’s half full sort of personality. So I think with the improvement in antithrombotic therapy that we’ve achieved and the increased safety margin, that one of the highest priorities now is the lysis trial to resolve the issue because there’s no question that there are patients with very severe thrombosis who may do well for a couple of years who need limb salvage. On the other hand, for the average patient the intracranial bleed is very real, and so if industry won’t sponsor it, it needs to be in an NIH trial, but it needs to be done. All you hear me say is we need the trial to find out who the patients are who require it.

DR. COMEROTA: Russell, what you’re suggesting is similar to what Hugo Partsch has shown us regarding the benefits of ambulation and compression in patients with DVT. Are you using compression? Should we be adding pneumatic compression to the treatment of acute DVT? What do you think about that, Hugo? Will that further help to resolve the clot?

DR. PARTSC'H: I’m hesitating to recommend pneumatic compression because this would be done in the supine position, and you can’t compare this with active ambulation in patients.

DR. COMEROTA: Well, they could sit up. They could sit and have the legs hanging down in a pendent position. That may actually increase venous velocity if you did that.

DR. PARTSC'H: It’s a contraindication if you read the text of the manufacturers.

DR. COMEROTA: But I’m asking you what you’re thinking.

DR. PARTSC'H: In principle if you want to improve flow velocity in patients who are not completely mobile, who are not able to walk two kilometers per day, in very old patients, for instance, such devices could be considered to be used as an adjunctive therapy. One point which has not been mentioned, is that there are some indirect data concerning an anti-inflammatory effect of compression. We heard about the inflammatory changes in deep vein thrombosis and that low molecular weight heparin would be beneficial due to its anti-inflammatory effect. There are new data present which show that compression and also pneumatic compression, is able to exert an anti-inflammatory effect which also would be important, especially in the first days of treatment, additionally to the immediate effect of low-molecular-weight heparin.

DR. ABU-BAKER: I’d like to ask two questions: The first, in selective thrombectomy for the treatment of acute iliofemoral DVT, do you know a non-aggressive method which is ambulatory, aesthetic, functional, and without risk of a pulmonary embolism? The second question is, is there any recommendation of the position of the patient who had acute iliofemoral DVT on the operative table in order to prevent pulmonary emboli?

DR. EKLOF: I can answer the second part of your question. We have them supine. I don’t think it matters too much as we put PEEP pressure on the ventilator during the procedure. Your first question again, Mohammad, was?

DR. ABU-BAKER: The first question is in selective thrombectomy for the treatment of acute iliofemoral DVT do you know, of any non-aggressive method which is ambulatory, aesthetic, functional, and without risk of a pulmonary embolism?

DR. EKLOF: You are forcing me into the battle here with Russell Hull about low molecular weight heparin which is aesthetic. I am very worried about this discussion about low molecular weight heparin. I think we are depriving and excluding patients from an efficient treatment that probably at least will prevent the post-thrombotic syndrome. If you’re going to start to treat every patient with iliofemoral DVT with low molecular weight heparin and send them home, I think this is a big step backwards. I think if you believe in the concept of early removal of the thrombus, we won’t do that with heparin. We know that. So I think we need more information. We need a prospective study comparing catheter-directed thrombolysis and thrombectomy with anticoagulation.

DR. COMEROTA: I also believe that a major problem leading to the confusion and many of the differences of opinion is that the patients who are at risk of the more severe post-thrombotic syndrome are likely to have more extensive DVT’s, with multiple segments involved. The majority of the patients I see with DVT are treated as an outpatient with low molecular weight heparin converted to Coumadin. They are predominantly infrageunal, they’re focal, and much different than the patient with the phlebmasia cerulea dolens who will be incapacitated. Active patients face major disability if the venous system is not reopened. Unfortunately, for the most part that stratification is not available in the current literature. That speaks to issues that are being addressed by Dr. Rutherford.
Dr. Kistner, and others in terms of appropriate classification of patients and stratifying them up front, so that we can all begin to compare similar patients and risks. I think that I have to agree quite enthusiastically with Bo’s answer. Albeit, that those patients that are going to benefit the most are a relatively small group of patients. You may see more of them here in Hawaii than we would see in Philadelphia just by virtue of what it takes to get here.

DR. STRANDNESS: I’m really concerned about one thing, Dr. Hull. At least in the United States, and I can’t comment on Canada, I don’t know of an internist or hematologist who has ever followed a patient with deep venous thrombosis in the long term. They never end up in an internist’s office. They never end up in the hematologist’s office. They end up in the hands of a surgeon to look at the complications of this disease. Furthermore, I think in all the wonderful work that you’ve talked about with regard to all these trials, you’ve only focused really on one issue, and that’s pulmonary embolism and you know that. All those randomized trials have looked at comparable forms of therapy without looking at the leg. You really haven’t done that, and I don’t think a quality of life issue here is going to answer that question unless attention is directed to where the disease starts and what happens to it in the long term.

DR. HULL: We actually have used surveillance and we do follow long term. We have IPG data that we haven’t published which I guess we should and we shall given that prompt, but I’m not a hematologist. I’m actually a systems specialist. So I do follow patients, and quite a few of our colleagues do. So I’ll draw that boundary south of Canada and say that in Canada we do. The problem with the post-thrombotic syndrome is the long-term nature of the follow-up, and it’s not a lack of interest or prospective. It’s a lack of funding. So if you look at the studies that you saw today, that involves an enormous amount of resource, human, kind, wise, people. I don’t think I mentioned the dollars, but the dollars are way beyond $200 million just for some of those trials that were done to get there. So the reason we’re sitting here having -- increasingly my seat is getting hot, but the reason my seat is getting hot is less lack of desire or less lack of willingness to look at the issues. It’s a lack of data. So I’ve taken the position historically for the last 26 years that we need the best trials to show the evidence, and we as a group, including the people here, have been successful doing that. It’s time to do that for thrombolysis. It’s that simple.

DR. RAJU: I hope I’m not piling on. I just wanted to piggyback on Dr. Strandness and the question directed towards Dr. Hull. Your patient population -- you set a very high standard and it’s a source of admiration for me, but at the same time I do want to ask you, you have all these wonderful trials in a well-defined population in Calgary, and the low molecular weight heparin trials in your institution has been going on for at least five or six years. Retrospectively what is the incidence of post-thrombotic syndrome in that population? You have the records.

DR. HULL: We need the funding to do the work. So historically the funding agencies have not been enthusiastic about doing that because they’re actually quite expensive trials. You need a team of people to do it. There are actually people in this room who are discussing the possibility of doing such trials, and indeed there may be interest, but the reason that we’re talking philosophy rather than evidence-based medicine is not a lack of enthusiasm. It reflects the difficulty with the long-term nature of the trial. To give you some idea of the problems, the average Canadian peer review grant goes at the most for three years. So we run into terrible problems when we want the ten-year follow-up. So there are three problems: One is the long-term nature of the disease; the other is the acquisition of the patients and the cost that’s involved is huge; and the third is total lack of interest by the funding agencies to do this up until now, but it might change. What we’ve done is we’ve cut away at the frontier. The frontier is now closing in on thrombolysis and the post-thrombotic syndrome. I think that’s very clear. So that’s why I’m half glass full. I think it will happen.

DR. RAJU: The second question is that I heard you to say early ambulation is likely to prevent post-thrombotic syndrome. Is that based on evidence-based medicine or is it just a hope?

DR. HULL: Well, there are a number of reasons to say that, and I’ll pass the ball to Professor Partsch who directly has observed that, but if you go to low molecular weight heparin, you get a reduction in thrombotic mass which I didn’t mention strongly, but it’s there in all of the repeat venogram data. I alluded to it. So there is a biological or imaging reason why a low molecular weight heparin might be better than unfractionated heparin for the post-thrombotic syndrome. So yes, there is going to early ambulation.

DR. PARTSCH: Coming back to your first question, there are data in the literature showing that after conservative treatment the rate of post-thrombotic syndrome and of ulceration is much lower than we saw in some slides today. There was one slide from Tony Comerota showing 50 percent of venous ulceration ten years after deep vein thrombosis. There is for instance one study published in Circulation, by Franzek from Zurich, Switzerland, looking at cohorts of proximal DVT patients 13 years later. With consequent compression the rate of post-thrombotic syndrome was extremely low. In average the frequency of ulceration after five to ten years is five percent, as it was shown in a large study from Leo Widmer, for instance. So I think there is some overestimation of the complication of severe post-thrombotic syndrome. When there is deep vein thrombosis and you treat it conservatively then the danger of pulmonary embolism is behind you, and the late outcome is obviously much more favorable than it was described until now. Concerning your second question if early ambulation, prevents post-thrombotic syndrome I must say that this is speculation. What we know is that effective early treatment is obviously very important. Russell Hull showed us very convincingly, that the rate of recurrent episodes of DVT can be decreased if in the first phase of early treatment with unfractionated heparin the range of aPTT is prolonged to more than 1.5. If this could not be achieved the recurrence rate in the first months was much higher. From this it is my extrapolation that we should, not only rely on the anticoagulatory effect of heparin, but should also to try to improve the venous flow velocity as soon as possible. If you have a patient coming in walking, the soonest point of time to do that would be just to let him walk with compression and not to put him into bed for several days.

DR. RUTHERFORD: I think we need to concede that, given enough numbers, that anticoagulant therapy will show an improvement in the post-phlebitic syndrome. It is a matter of to what degree. That is it can be expected to the degree that anticoagulant therapy prevents propagation and to the degree it prevents recurrent DVT. We would expect that degree of improvement. Therefore, to make a proper comparison, we’d need a trial comparing anticoagulant...
therapy with thrombolytic therapy, or at least a protocol of early clot removal, because I think we need to keep thrombectomy in our armamentarium because in patients with iliofemoral venous thrombosis, there are a lot of peri-partum cases, post operative cases, post-traumatic cases, and cases with other contraindications. So, if the patient deserves early clot removal and is reasonably healthy, thrombectomy should be included in the armamentarium. Now, if we do a trial I think we need to stratify the cases and include only iliofemoral venous thrombosis in relatively healthy, active people. In whom the development of a post-phlebitic syndrome is a valid issue and not include all the patients including those who are elderly, with significant comorbidities or other factors in whom we wouldn’t even consider as candidates for iliofemoral venous thrombectomy or thrombolysis.

DR. RAJU: Just a quick comment. Regarding the incidence of venous stasis ulceration two to four percent with LMWH, that has been true even for unfractionated heparin over the years; the real question is the incidence of pain and swelling, and that forms the bulk of disabling post-thrombotic syndrome.

DR. PARTSCH: There is one randomized controlled study from Amsterdam which has been mentioned today, and this group showed convincingly that after proximal deep vein thrombosis the rate of swelling and post-thrombotic syndrome, also of minor stages could be reduced to 50 percent, compared with a group of patients without compression.

DR. KISTNER: I direct my question to Gene Strandness and to Bob Rutherford. As we progress to prospective studies and we realize the importance of defining segmental distribution of disease in the chronic phase, do we also have or can we develop an equal classification of the acute disease? We should classify acute disease in a universal fashion just as we classify the chronic in order to make correct correlations later.

DR. COMEROTA: Is that possible, Gene?

DR. STRANDNESS: It should be. I don’t see why it can’t be.

DR. KISTNER: It would require standards for diagnosis.

DR. STRANDNESS: Sure, I think so, and I think the other point is -- Russell talked about it briefly. One of his points is that with low molecular weight heparin it may be possible to get a more rapid resolution of the thrombus load than you do with standard therapy. The other issue I wish you’d just briefly comment on relates to Coumadin therapy which is also very poorly done. The recurrence rate in our study looking at these patients in the long term on Coumadin is very high. So how are you going to get around that problem in the long term? That is another issue with regard to the long-term outcome after any form of therapy.

DR. COMEROTA: But that will be universal, Gene, no matter what therapy those patients have up front, whether it’s lysis, whether it’s thrombectomy, or whether it’s anticoagulation. All of those patients deserve appropriately dosed and duration of oral anticoagulation.

DR. STRANDNESS: I don’t disagree with that, but we’ve been talking about good versus bad with low molecular weight as compared to unfractionated heparin. In our experience long term Coumadin therapy is not well carried out.

DR. RUTHERFORD: To address another aspect of that, we need to have a scoring system based on the factors that are known to affect outcome of DVT in conducting these trials. As I will point out later, in my talk on Friday, Mark Meissner on the AVF adhoc committee on venous outcomes assessment has been working on this aspect, and he’s developing a scoring system including identifiable factors for which there’s evidence that they do affect DVT outcome. With such a scoring system, we can produce an even playing field, or equivalent groups, when we do trials or compare the results of different trials.

DR. TRIPATHI: I have two questions, one for Dr. Raju. We learned during our residency teaching programs that the thrombus in the lumen of the vein gets stuck to the vein wall within about five to ten days, and compression of calf may extend the thrombus or fragment them. If your patients are walking into your clinic with calf vein DVT or popliteal femoral DVT, is compression necessary? Can’t you leave them just on ambulation?

DR. COMEROTA: Where is that shown? That’s a concern that permeates medicine and that’s one reason why manufacturers say that we should not compress legs in patients with DVT. Where is it documented that compressing the leg with DVT causes P.E.? I’ve searched for it but I’ve not been able to find evidence for that concern.

DR. TRIPATHI: I’m sorry, but I haven’t read it, but this is what was taught during our residency.

DR. COMEROTA: Of course. Then one needs to take it the next step. Why does that occur?

DR. TRIPATHI: That’s exactly why I’m asking this question is because there needs to be a study to show --

DR. COMEROTA: No, you stated it as fact, and I wanted to make sure that the statement did not stand as fact.

DR. TRIPATHI: Sure. This is information given to us during our residency program, and that’s what I’m stating.

DR. PARTSCH: I have presented initial data from a randomized controlled study comparing three groups of patients, one with bed rest without compression versus two groups of ambulation with compression. All these patients, had pulmonary lung scan studies in the initial stage and after nine days. There was no significant difference concerning new pulmonary embolism in these groups. It was never proved that compression increases the risk of pulmonary embolism.

DR. TRIPATHI: The other question is for Dr. Eklof. I suppose that the rationale for ligating the superficial femoral vein after iliofemoral thrombectomy is to prevent recurrence in that segment. In how many patients do you get recurrence of thrombosis in the femoro-popliteal venous segment, after ligation of superficial femoral vein?

DR. EKLOF: I can’t answer that question, but the rationale behind doing it, I learned from Bob Kistner with his long-term study of ligation of the superficial femoral vein. As long as you have the profund vein patent and competent, the patients will have no sequela, but if you leave the thrombus in the superficial femoral vein it will recanalize with destruction of the valves and subsequent reflux which will lead to the post-thrombotic syndrome with all its severe sequelae.

DR. TRIPATHI: Why I asked you this question is that we are doing femoral venous thrombectomy without ligating the superficial femoral vein, and we get recurrent thrombosis in about 18 to 20 percent of our patients in the femoro-popliteal venous segment below thrombectomy site and that needs to be looked at.
Venous thromboembolism associated with extended quiet sitting has been known since World War II. Cramped sitting in air raid shelters for prolonged periods during the London Blitz was often followed by cases of PE, not infrequently fatal.

Homans in 1954, was the first who related deep venous thrombosis (DVT) to prolonged air travel. Later when intercontinental flights became more common during the 1960s the incidence probably increased and the problem drew more concern.

The most prominent case of air travel-related DVT was the late former President Richard M. Nixon. In 1974, the last year of his presidential term, he made a long trip to Europe, the Middle East, and the Soviet Union. Early during this trip he developed a DVT of his left leg. He was treated with anticoagulation but continued the trip with recurrent symptoms while in Egypt and Russia. After his resignation in August 1974, he had several serious recurrences and episodes of PE. Hospitalization for treatment prevented him from testifying in the Watergate trial. Despite anticoagulation the thrombus extended into the iliac vein. Surgical ligation of the iliac vein resulted in bleeding complication and shock. The President was in serious condition for several days before he was able to make a full recovery.

Because of the methodological difficulties to study the occurrence, very little is known about the incidence of air flight associated DVT and PE. A 1986 study from London Heathrow airport found that 18% of 61 sudden deaths among long-distance passengers were due to PE. This made PE the most common cause of such death, next to ischemic heart disease. A vast majority of patients develop symptoms during the first 24 hours after the start of the flight. In some cases the first symptoms occur in-flight.

“Virchow’s Triad”: (1) endothelial lesion, (2) venous stasis, and (3) hypercoagulability describes the basic pathophysiology of venous thrombosis. In the pressurized flight cabin a number of factors influence Virchow’s variables. Immobilization, cramped coach position, low air pressure, relative hypoxia, low humidity, and dehydration constitute the most important cabin-related risk factors.

Among the patient-related risk factors, obesity is one of the most common. Chronic heart disease, hormone medication, diabetes mellitus, rheumatoid arthritis, malignancies, chronic renal failure, previous DVT, smoking, and recent trauma or surgery also increase the risk for DVT.

To be able to reduce the risk for flight-related DVT and PE, the traveler must be aware of the possible danger, and the airlines should be responsible for this information. Already with the flight ticket, basic information could be provided giving the traveler an opportunity to discuss with their physician what prophylactic measures should be taken, such as compression stockings. In flight, the general safety information could include advice on appropriate exercise and beverage intake during the flight. Also the airline magazines and in-flight videos could give such information. Further research is needed on the incidence of air travel-related thromboembolism but now, certain precautions that might reduce the risks should be taken.

**London Views**

Kevin Burnand, MD
St. Thomas’ Hospital
London, United Kingdom

There are many anecdotal reports of thrombosis after prolonged air travel, but there have not been any prospective studies. The best study to date comes from the host institution, who showed that 17% of DVTs admitted to Hawaiian hospitals over a six-year period, followed a prolonged airline flight. Dehydration, prolonged immobility combined with flexed dependent limbs, all increased the risk of thrombosis in flight. It is not known if thrombophilia is an important independent risk factor. Airlines should be encouraged to allow prospective studies to be performed on different groups of passengers. We have proposed such a study looking at fibrin degradation products (d-dimer) on departure and arrival, carried out on British Airways customers on long haul flights. Duplex scanning and a thrombophilia screen would be offered to any passenger developing a significant rise in fibrin degradation products. British Airways is considering this proposal at present, but is nervous because of sensitivity that by allowing such a study, they would be recognizing that there is an increased risk of thrombosis during flight. The potential study will be discussed and other evidence reviewed.

**Vienna Views**

Hugo Partsch, MD
Wilhelminens Hospital
Vienna, Austria

**Introduction**

Long sitting, dehydration, and lowered oxygen pressure in the cabin are the most important triggering factors for air-travel thrombosis. However, many patients with DVT are seen in continental Europe also after long journeys in cars and buses, in which prolonged sitting is the decisive trigger for thrombosis.

The “Vienna views” will concentrate on two points:
1. Report of a consensus conference on travel thrombosis,
2. Traveling compared to other risk factors based on a cohort of 543 DVT patients.

**Report of a consensus conference on travel thrombosis**

In May 1995 an Austrian consensus meeting on the subject of travel-related thrombosis was organized in Vienna.
Three main subjects had been discussed:

1. Definition of travel thrombosis
   Travel thrombosis is defined as venous thromboembolism in connection with a long journey (5 hours or longer) in the sitting position (airplane, car, bus, train) in a person without symptoms when the travel was started. The symptoms may occur immediately during or after the journey, up to two weeks later.

2. Risk groups for travel-thrombosis
   In order to be able to give reasonable recommendations three risk groups were defined in analogy to the risk groups in general medical thromboprophylaxis.

3. Recommendations to prevent travel thrombosis
   The recommended measures (Tab. II) depend on the risk-groups defined in Tab. I.

The results of the Vienna consensus meeting have been worked out after long and intense discussions and reflect a sort of minimal agreement between the discussants. However, they have been shown to give useful guidelines for the consultation of patients in everyday practice.

TRAVELING COMPARED TO OTHER RISK FACTORS BASED ON A COHORT OF 543 DVT PATIENTS

All consecutive patients being admitted because of DVT between January 1996 and December 1998 have been analyzed prospectively regarding their individual risk factors as listed in the update of the “Reporting standards in venous disease” document of the Society for Vascular Surgery.

Table III shows the frequency of patients older than 70 years, with a history of VTE and with associated malignant diseases in the total group of 1,111 consecutive patients with DVT between 1992 and 1998.

In a subgroup of patients who were admitted because of DVT between 1996 and 1998 additional risk factors were analyzed (Tab. IV).

7.18% of our patients presented a history of traveling in accordance with the definitions of the above-mentioned Vienna consensus.

Some characteristics of this group of 39 patients are given in Table V.

In our own experience the majority of patients give a history of ground traveling. Dyspnoea as a symptom of pulmonary embolism is seen more frequently than in the whole group of 1,111 DVT patients, in which 30.5% of the patients with scintigraphic PE had symptoms (n.s.). The fact that malignancy was found in 2 cases by active screening underlines the importance also to consider additional risk factors besides the history of traveling.

All mobile patients including two patients who were brought by emergency directly from the airport got firm compression bandages and were encouraged to walk. Anticoagulation was initiated by subcutaneous injections of dalteparin (200 IU/kg body weight) given for a mean period of 11.4 days. Overlapping oral anticoagulation with Marcoumar adapted to reach an INR between 2.0 and 3.0 was administered for at least 3 months.

CONCLUSIONS
A history of recent travel is a risk factor for venous thromboembolism. In contrast to the report from Hawaii, in continental Europe travel thromboses are more frequent after car and bus journeys (70%) than after flights (30%). Proposals concerning definition of risk groups and prevention of travel-thromboses have been made by a Viennese consensus group in 1995. Recommendations of an international task force would be desirable.

References

Table 1.— Risk groups for travel-thrombosis (increased risk if two or more factors are present)

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Medium risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everybody on a travel in sitting position &gt; 5 hours</td>
<td>age &gt;40</td>
<td>previous VTE</td>
</tr>
<tr>
<td>heart failure</td>
<td>malignant disease</td>
<td></td>
</tr>
<tr>
<td>severe varicose veins</td>
<td>Thrombophilia</td>
<td></td>
</tr>
<tr>
<td>chronic venous insufficiency</td>
<td>family-history of VTE</td>
<td></td>
</tr>
<tr>
<td>hormone-intake</td>
<td>plaster on lower extremity</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>recent surgery with increased risk</td>
<td></td>
</tr>
<tr>
<td>pregnancy / postpartum</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2.— Prevention of travel-thrombosis

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Medium risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankle-movement, isometric exercises, repeated walking, step-toes</td>
<td>like in low-risk group plus:</td>
<td>like in low- and medium-risk group plus:</td>
</tr>
<tr>
<td>sufficient fluid intake, no alcoholic drinks (they promote dehydration)</td>
<td>lower leg — compression stockings class I-II</td>
<td>low-molecular-weight heparin (e.g. 5000 IU dalteparin, 40 mg enoxaparin), 2 hours before traveling starts</td>
</tr>
<tr>
<td>restricted use of narcotics and tranquilizers</td>
<td>(daily in round trips)</td>
<td></td>
</tr>
</tbody>
</table>
Table 3.—Age, prior history of DVT and malignancy as risk factors in 1111 patients with DVT

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 70 y</td>
<td>508</td>
<td>46</td>
</tr>
<tr>
<td>Previous VTE</td>
<td>318</td>
<td>29</td>
</tr>
<tr>
<td>Malignancy</td>
<td>201</td>
<td>18</td>
</tr>
</tbody>
</table>

Table 4.—Frequency of additional risk factors in 543 patients with DVT

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immobilization</td>
<td>72</td>
<td>13.3</td>
</tr>
<tr>
<td>(Travel thrombosis)</td>
<td>39</td>
<td>7.18</td>
</tr>
<tr>
<td>Postoperative</td>
<td>23</td>
<td>4.2</td>
</tr>
<tr>
<td>Limb trauma</td>
<td>24</td>
<td>4.4</td>
</tr>
<tr>
<td>Abnormal clotting</td>
<td>52</td>
<td>9.6</td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>39</td>
<td>7.2</td>
</tr>
<tr>
<td>Pregnancy and postpart.</td>
<td>8</td>
<td>1.5</td>
</tr>
<tr>
<td>Obesity</td>
<td>89</td>
<td>16.4</td>
</tr>
</tbody>
</table>

Table 5.—Characteristics of 39 patients with travel thrombosis (7.18 % of consecutive DVT patients admitted between 1996 and 1998).

Mean age: 63.1
Sex: fm 24:15

Localization:
- right: left 41:59 (67.6%)
- iliofemoral 6 (15.4%)
- femoropopliteal 28 (72%)
- lower leg 5 (13%)

Malignancy: 6 known, 2 newly detected (27.5%)

Primary PE (baseline lung scan): 17/36 (48%)
symptomatic (mild dyspnoea): 7/17 (41%)

Repeated lung scan:
- new PE: 2 (asymptomatic)
- improved or normalized: 11
- unchanged: 4

Treatment:
- Compression bandages + walking + dalteparin (Fragmin)
  200 IU/kg/day s.c., mean duration 11.4 days
- Secondary prophylaxis:
  oral anticoagulants (INR 2-3) 32
  dalteparin 5000 IU/day 7
- Air-travel: 11 (28%)
- Car, bus, train: 28 (72%)

SYDNEY VIEWS

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Australia is a large island continent with Sydney the most common entry port for air travellers. Non stop flights between Sydney and Los Angeles take up to fourteen hours and between Sydney and Honolulu nearly nine hours. Singapore, Bangkok, Bombay and Tokyo are similarly remote.

In the twelve month period from July 1997 to June 1998, 14,144,758 Domestic passengers arrived at Sydney Airport and 7,103,471 International passengers landed for a total number of 21,552,661 passengers. About forty passengers with air travel-related venous thrombosis attended St. Vincent’s Hospital Sydney each year. Most of these are international travellers since the majority of Australian domestic flights are relatively short. St. Vincent’s Hospital is an inner city hospital which, I estimate, might treat about one tenth of those affected. By extrapolation, about 400 individuals per year present with a clinical syndrome of venous thromboembolism after arriving in Sydney. The risk of travel related clinically presenting venous thrombosis can thus be derived at about 0.0014% per traveller per international flight. This estimate is based on the number of all passengers including children, infants and younger adults. A more realistic assessment of the risk for adults over 40 might perhaps be three times the global estimate or 0.004% clinically significant venous thromboses per international flight. Non clinical or latent venous thrombosis could be expected to be 25 times this or 0.01% per international flight. Frequent flyers or those with multiple long flights per journey would correspondingly increase the risk.

In 1993 we presented our initial findings in 45 patients (24 females, 21 males) with venous thrombosis related to travel. In 37 cases travel had been by air but in the other 8 travel was restricted to road or train, in each case longer than 8 hours. Thirty five of the 37 air travellers had flown for longer than 8 hours with only 2 flying 4 hours or less. The patients ages ranged from 30 through to 79 with 2 peaks in the age incidence, namely around 30 and at 50-60 years. In 18 patients pulmonary embolism developed or was the initial presentation. Risk factors identified in this group of patients were a previous history of venous thromboembolism (31%), pre-existing varicose veins (20%), systemic lupus erythematosus or other autoimmune disease (11%), pregnancy (3%), and lower limb ischaemia (2%).

Our ability to test for hypercoaguable states then was not as well developed as at present but nevertheless, one or more hypercoaguable factors were detected in 21 patients (47%). These included increased plasma fibrinogen (9%), phospholipid antibody syndrome (5%), antithrombin III deficiency (3%) and polycythemia (2%). We concluded that long distance travel by air or other means does predispose to venous thromboembolism but the risk of venous thromboembolism was small in comparison to the total number of travellers. However, in travellers who are particularly susceptible to venous thrombosis by virtue of pre-existing vascular risk factors or the presence of a procoagulant blood abnormality, the risk is much greater.
Our more recent experience of over 200 patients is summarised elsewhere but procoagulant blood abnormalities were found in about half of those with clinically significant venous thromboembolism related to flight. Protein C activating enzyme deficiency was the most common abnormality.

We recommend that all travellers over 40 should wear elastic support stockings, abstain from alcohol or restrict alcohol consumption, move around the cabin freely, drink plenty of non-alcoholic beverages, try to avoid hip and knee angulation for prolonged periods during the flight and avoid heavy sedation. Those who are known to be at high risk should have low molecular weight heparin before, during and after the flight continuing for 48 hours after resuming normal activities.

**References**


**CHICAGO VIEWS**

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For the most part, modern air transportation is safe. Each year, more than one billion people travel by air worldwide, and the overwhelming majority of them complete their flights safely. The true incidence of in-flight emergencies is unknown, as many airlines either do not keep records of in-flight emergencies or do not make their records public. A recent study at Seattle-Tacoma International Airport reported the incidence of in-flight emergencies to be 1/39,600 passengers. The death rate during flight for the years between 1977 and 1984 was reported as one death per 3.25 million passengers. Of the reported in-flight and post-flight deaths at London-Heathrow airport between 1979 and 1983, pulmonary embolism was the second leading cause of death (18%). Based on the number of reported cases, it may be concluded that venous thromboembolism in air travelers is very rare; however, certain passengers are more at risk depending upon the presence of predisposing risk factors for venous thromboembolism. Venous thromboembolism may develop during or immediately after a flight, or even days later. With the increased volume of air travel during the last decade, the problem has become more important and has been referred to as the "Economy Class Syndrome." Additionally, certain intrinsic risk factors put people at a greater risk for venous thromboembolism. A few genetic abnormalities leading to hypercoagulability and thrombophilia have been associated with thromboembolic disease. The most common inherited predisposing cause of venous thromboembolism is the factor V Leiden mutation, which is present in four to six percent of the general population, and is associated with activated protein C resistance. Heterozygotes for this mutation have a five to tenfold increased risk for venous thromboembolism, while the risk for homozygotes increases by eighty fold. Another mutation, a guanine to adenine nucleotide substitution at nucleotide position 20210 in the prothrombin gene, is associated with higher prothrombin levels and a greater risk for venous thromboembolism. In one study, carriers of this allele had a 2.8-fold increased risk for venous thromboembolism compared with persons homozygous for the allele. Also, hyperhomocysteinemia, caused by a mutated 5-methyltetrahydrofolate reductase (MTHFR), is linked to venous thromboembolism. A mutated MTHFR allele, when it is associated with elevated plasma homocysteine levels, is a confirmed risk factor for a thromboembolic event. To date, there have been no reported studies indicating the percent of air travelers with a mutated allele who experience a venous thromboembolism after air travel, but such studies are needed to assess the effects of this risk factor.

The occurrence of venous thromboembolism from air travel may arise from certain air cabin-related risk factors which, when superimposed on patient-related risk factors, increase the risk for air travel-related venous thromboembolism. These variables include all of Virchow’s variables: hypercoagulability, stasis, and vascular endothelial damage, and cause dehydration and decreased venous flow velocity. Low cabin humidity of 8-12% increases fluid loss, which leads to dehydration. Inadequate fluid intake, the diuretic effect of alcohol consumption, and the dependency distribution of fluids with swollen feet and legs further exacerbate this condition. At the physiological level, dehydration results in hemococoncentration and increased viscosity.

Furthermore, air travel puts people at risk for DVT because passengers experience mild hypoxia as the airplane ascends. A modern airliner flies at cruising altitudes from about 28,000 ft to 43,000 ft. As altitude increases, the atmospheric pressure decreases from 760 mmHg at sea level (14.7 psi) to 176 mmHg (3.40 psi) at the typical operational level of 35,000 ft. Aircraft are pressurized with atmospheric air by use of compression to avoid problems such as decreased partial pressure of oxygen and expansion of gases within
the passenger’s body. However, aircraft are not pressurized to sea level but to a differential of approximately 8.60 psi. Assuming a flight at 35,000 ft. where the atmospheric pressure is only 3.40 psi, the cabin compressor adds another 8.60 psi. The ambient pressure is 3.40 psi plus 8.60 psi, or 12.0 psi, which is the atmospheric pressure at 5,500 ft. above sea level. Similarly, the cabin pressure at 40,000 ft. is 2.72 psi plus 8.60 psi, or a psi of 11.32, which is equivalent to an altitude of 7,500 ft. Therefore, the partial pressure of oxygen in the cabin is always decreased above a flight level of 22,500 ft.

The alveolar \( P_{O_2} \) of a person with normal lungs is 107 mmHg at sea level, where the atmospheric \( P_{O_2} \) is 159 mmHg. At the 5,000-ft. level simulated by the pressurized aircraft actually flying at 35,000 ft., the atmospheric \( P_{O_2} \) drops to 130 mmHg and the alveolar \( P_{O_2} \) to 76 mmHg. At a simulated cabin pressure of 8,000 ft., the atmospheric \( P_{O_2} \) is 116 mmHg, and the alveolar \( P_{O_2} \) drops to only 59 mmHg. Thus, the decrease in \( P_{O_2} \) as the plane ascends can lead to a hypoxic state for the passengers. However, the vulnerability of a patient to hypoxemia at altitude depends on the alveolar or arterial \( P_{O_2} \) of the patient at sea level and his/her physiological ability to compensate for a decrease in \( P_{O_2} \) as the plane ascends.12

Collected data suggest that hypoxia decreases endothelial cell fibrinolytic activity and may lead to the production of oxygen-derived free radicals, which can release endothelium-derived relaxing factors.13 As a result, decreased fibrinolysis enhances hypercoagulability, relaxation of the venous wall leads to decreased flow velocity and stasis, thus putting passengers at greater risk of developing venous thromboembolism.

Moreover, being immobilized in the coach position itself causes depressed venous flow velocity. Venous thromboembolism arising from sitting in cramped aircraft seats parallels the experience encountered by individuals who tried to escape the bombing of London in 1940 by going into the Underground and sleeping overnight on deck chairs. Simpson reported an association between sitting overnight on deck chairs in air-raid shelters and death from pulmonary embolism. In September/October of 1940 he diagnosed 24 cases, 21 of which had occurred in, or soon after leaving air-raid shelters.14 Wright and Osborn2 showed that venous flow velocity was about halved when a subject sits as opposed to being supine. Although it has not been reported, it can be hypothesized that decreased venous flow velocity while sitting results in venous distension. Coleridge-Smith, et al demonstrated that administration of muscle relaxants to facilitate intubation during an operative procedure under general anesthesia results in venous distension, in addition to the slowing of venous blood flow.15 They proposed that the increased diameter in the deep veins of the legs may lead to endothelial damage, a factor suggested by Virchow that predisposes people to venous thromboembolism. Further evidence to support this theory has been suggested by Comerota who demonstrated electron microscopic cracks in the endothelium following venous distention.16 Similar physiological changes may be occurring in patients after prolonged sitting due to the decrease in venous flow velocity, thus putting passengers at a greater risk for venous thromboembolism. Also, pressure on the calves from the seat will impair venous outflow and exacerbate venous stasis. Decreased circulation due to immobilization and pressure from the seat forces capillary pressure to exceed colloid osmotic pressure, thus causing filtration of fluid from the circulation and swelling of the legs and feet.5

To reduce the risk of the “Economy Class Syndrome”, simple precautions should be taken. First of all, cabin-related risk factors that cause hypercoagulability and stasis can be corrected by frequent leg and body exercises, and regular walks. However, passengers need to be cautious about ambulation on the aircraft due to occasional reports of passengers experiencing injury or death from clear air turbulence. Booking reservations on the aisle seat is suggested, as there is more leg stretch room and it is easier to walk around. Individuals should definitely change their positions frequently and engage in numerous stretching exercises. Smoking (now forbidden on virtually all flights), which causes hypoxia and increases blood viscosity, and excessive alcohol consumption should be avoided. To avoid dehydration, regular nonalcoholic beverages should be consumed (at least 1 liter per 5 hours of flight).5

Patients with intrinsic risk factors should use therapeutic compression stockings to reduce swelling of the legs and increase venous flow velocity. Patients with a history of DVT, chronic disease, malignancy, recent surgery or vascular interventions should consider prophylaxis with low-molecular weight heparin to prevent DVT. Some authors have also advised high-risk passengers to minimize platelet adhesion by taking an aspirin each day for a few days prior to a long flight, unless otherwise contraindicated.17 However, the use of aspirin as a preventative measure is controversial according to the latest consensus guidelines.18

Another way that high-risk patients can reduce the risk of venous thromboembolism during air travel is through the use of a foot pump. An arteriovenous (A-V) impulse system has been designed to simulate a physiological pumping mechanism in the sole of the foot, which is activated by the flattening of the plantar arch on weight-bearing, discovered by Gardner and Fox in 1983. This device has been shown to maintain venous circulation as effectively as does normal walking and its use reduces post-traumatic pain, swelling, and compartment pressures.19 The A-V impulse system exhibits its antithrombotic effect by generating sudden, intermittent increases in venous flow and by producing turbulence in the valve pockets where thrombosis commonly begins. Studies have shown the foot pump to be effective in reducing the incidence of proximal DVT from 32.5% to 5% after total hip replacement; from 23% to 0% after knee replacement; and from 18.7% to 0% in total knee replacement.20 Unfortunately, these devices have not been adopted for use on aircraft to date.

In summary, modern air transportation is safe, but venous thromboembolism is an identified problem associated with long flights and deserves greater attention. Even though a few reported cases of DVT/PE following air travel have occurred in passengers with no previous medical history, certain risk factors are associated with the development of air travel-related venous thromboembolism. For individuals with pre-existing risk factors, long trips in cramped conditions by air do carry a risk of DVT/PE. In the future, physicians should have their patients take an individual risk assessment before long distance travel. Using a risk assessment scale, like that developed by Caprini, et al, physicians can classify passengers as low, moderate, or high in their risk for venous thromboembolism. Those passengers who are low-risk (1 factor) should not use prophylaxis, but should be told to drink enough fluids and occasionally stretch their legs. Passengers who are classified as moderate-risk (2 factors) should use calf-length antiembolism graduated hose at 18-20 mm.
Calf-length hose are sufficient to improve the efficiency of the calf muscle pump. Furthermore, compliance with this length of hose is excellent compared to the long-leg variety. High-risk patients (3-4 factors) should use calf-length antiembolism graduated hose at 30-40 mmHg, in addition to the other measures to decrease stasis and maintain adequate hydration. Patients who are in the highest risk category (5 or more factors) should consider low-molecular weight heparin during the flight. The use of foot pumps in these passengers may be beneficial if this method eventually becomes available.

Further study is needed to elucidate the role of cabin-related risk factors that cause dehydration and decreased venous flow velocity, and how they have a synergistic effect on patient-related factors to increase the risk of venous thromboembolism. To decrease the prevalence of this problem, reasonable and simple measures could be implemented by the airlines. For example, they could make passengers aware of the dangers of dehydration during flight, encourage the consumption of non-alcoholic beverages, and discourage the use of alcoholic beverages. Airlines could also increase the space between passengers to give them more room to stretch their legs during flight. It would also be helpful if they developed brochures on medical conditions which may be exacerbated by air travel in order to educate patients and reduce thrombosis-related problems.

References

one hour. So if this would really be a long distance flight, I would recommend the same what Bo has said, but he could do it on the next day with good compression plus prophylaxis with low molecular weight heparin.

DR. LORD: I was going to make the same point. The answer depends on how long the flight is. If it was just a short flight I’d suggest it’s okay and put on the stocking, but for a long flight within a month of operation, I’d probably give our normal low molecular weight prophylaxis therapy beforehand and keep it going for 48 hours after the flight has concluded.

DR. CAPRINI: I think that’s very important, the length of the flight, and I generally like to see those patients at least a week or ten days postoperatively. So oftentimes I won’t let them fly for that period of time. I would have them all wear the stockings up to a month, and if it’s a flight where they go above 30,000 feet -- if you’re only going to fly back to Berlin, they’re not going to get up past 20,000 or 23,000 feet, but if it’s a longer flight, then I think that you have to take the precautions. I like the idea of giving the low molecular weight heparin, and I like the idea of giving it before they start and continuing it for 48 hours after they’re at their destination.

DR. BURNAND: We have quite a few Arabs who come to London for treatment, and we usually recommend at least two weeks after any form of surgery before they even think of going back. That’s our recommendation, but it’s based on no factual evidence whatsoever. It is a recommendation.

DR. HASANIYA: A very stimulating session. I worked with Dr. Eklof for a year in research, and at one time we thought of arranging a study where you get the consent to scan all passengers in a Boeing 747 before the flight, and then scan everybody after landing. We couldn’t do it, but we thought the best group would be military people where people would be cooperative and compliant. The reason I’m saying that is because I think most people that you can have access to scan would be the pilots or co-pilots because these people, are never seen ambulating in the airplane.

DR. BURNAND: We’ve got those in British Airways. They’ve given us all their pilots as a potential source of guinea pigs, and they don’t ambulate evidently which is surprising.

DR. HASANIYA: But how many pilots have you found in your studies?

DR. EKLOF: We have discussed this, and our next discussant is my friend from the Hawaiian Airlines, Paul Casey. I was in touch with United Airlines’ office in Los Angeles, and they had had four pilots who had DVT, but I think it’s very rare because they are young, strong, healthy guys.

DR. BURNAND: That’s not what the Pilots Association tells us for what it’s worth. Your figure of four is not a surprise, and I gather there are quite a few more pilots with thrombosis. Perhaps we just have unhealthy pilots in British Airways.

DR. CAPRINI: I hate to muddy the waters, but as he began to talk, I was thinking of something that was going to be a difficult issue to address, and that is the problems associated with duplex scanning in the asymptomatic patient and how we’re going to try to get around that in order to answer this question.

DR. BURNAND: I think that’s the real anxiety. That’s why we’re looking at fibrin degradation products and other markers as our main form of assessment, but what we may be looking at is a prothrombotic state without ever proving that passengers definitely have a DVT because I suspect that even if a passenger gets a big rise in fibrin degradation products, we will be able to show very few of them have an actual DVT.

DR. LORD: Just to say that we’ve had one pilot in the 122 patients going to our lab in a three-year period.

MR. CASEY: As Dr. Eklof pointed out, my name is Paul Casey, and I’m the president and CEO of Hawaiian Airlines. And if you think that I feel like Daniel walking into the lion’s den, you would be correct. Very interesting session. You may wonder why the airlines have not done very much about this. Pure and simple, ignorance. I’m the CEO of a major U.S. airline. We fly all over the U.S., West Coast, inter-island, and South Pacific, and this is the first time I have ever been invited to participate in any session like this. The longest flight we have is five and a half hours, but Qantas and British Airways, of course, fly 13, 14, 15-hour flights. Some of the recommendations I saw in the early presentations are simply not practical. You know, improving seat pitch, i.e., the room between seats is economics. It’s driven by sheer economics. The last gentleman, forgive me, made some very practical suggestions, and I guess when you look at those who are at high risk, we would look to the medical fraternity to recommend heparin or whatever else it is that you’re talking about, with non-consumption of alcohol and increased consumption of fluids. Moving around the airplane is a big risk these days. We leave the seat belt sign on all day, all night. Why? Because in clear air turbulence, people hit the roof. They get their necks broken. They get killed or whatever. So moving around the cabin is not a good idea to recommend to people, but I think there are a number of things that we as airlines can do to help prevent this problem, and we need to work with the medical community to find out what those things are. Some airlines, I believe, a number of years ago, maybe SAS, Dr. Eklof, was one used to publish a brochure and had a thing on their in-flight video which talked about squeezing your calf muscles and moving your feet around and drinking lots of fluid, all of which I do because I have worn compression stockings for ten years suffering from varicose veins, which Dr. Eklof is attempting to convince me to get removed. Quite right too, he says. So I find this interesting, and I think although lots of it I don’t understand because it’s designed for doctors and the medical fraternity, it is very common sense stuff. I find that I would like to pursue some kind of study for Hawaiian Airlines with Dr. Eklof and Straub Foundation.

DR. BURNAND: I think that’s very good news, and I think the problem has been to date that the airlines have had a very defensive attitude to looking at DVT. We have examples from Reg who already has his hand in the air. I know Bo has told me a wonderful anecdotal story about an airline that I couldn’t possibly talk about. Bo, do you want to give us your anecdote, and then, Reg, we’ll have yours while he’s still standing at the microphone.

DR. EKLOF: About five years ago we sent a questionnaire to 56 airlines that all landed in Honolulu, and we asked them very simple questions about collaboration and if they were interested to participate in research. That’s when we had our great ideas of this 747 and duplex scanning of the passengers before the flight and within one week after arrival in Honolulu. I had one positive response, and that was from the medical director of Philippines Airlines. He happened to be a doctor at Straub. Then I had one letter from this company that was elegantly described by our moderator where they basically told me not to put your nose into this.
MR. CASEY: If I could add one thing, I think the health of our customers is our business. I would imagine the lawyers get involved in this and cause all sorts of barriers.

DR. LORD: I don't want to name any particular airline, but I can tell you that we've been making representations to them for a joint study between Kevin Burnand and myself. There is also traffic between Australia and Hawaii and Bo and I have had discussions about Honolulu and Sydney. I don't know if Russell Hull is still in the audience, but Calgary might be involved also. We've actually spoken with a lot of airlines. In the case of the particular Australian airline I'm talking about I have been told that this matter has been to board level, and their lawyers have advised them not to get involved, believing the incidence is low. Don't rock the boat.

DR. BURNAND: That was also the British Airways line which is from their marketing people who don't want to see it as a problem. If it was less than one percent, then it was something that they would regard as an act of God and not something they should worry about. So I think before we go anywhere, we've got to have some hard information as to how big the problem is. At the moment you've heard the answers to date, and although the studies look similar in the ones that have been published, they're not by any means hard data. They may be grossly overestimating the problem or underestimating it, but we're very, very glad that you came and we're very, very glad that you're going to finance this big study that Bo is now going to organize.

DR. LOMB: I have been told that one airline has lost a suit for $2 million, settled out of court because they didn't want adverse publicity. A lot of airline antagonism to conducting a study is based on the idea that it's going to put people off flying. I don't think recognition of risk will put anyone off flying. I think the airlines ought to print a little disclaimer on their ticket saying flying is a health hazard or similar and can cause this, that, and the other medical problem, but this won't stop anyone flying. This approach would protect the airlines and help the passengers.

MR. CASEY: I happen to agree with you. It will not stop anyone flying. The world population is flying more and more than ever and will continue to do so.

DR. BERNHARD: I have truly enjoyed this discussion. It seems to me that one of my questions has already been answered by Reg Lord. A couple of good, stiff lawsuits might get the attention of the airlines. Some of the things that may add to the hard science we would like to have, would support the enthusiasm to look a little deeper at a fewer practical questions and define simple preventive measures. Though I presume that no one has been on anticoagulation at the time he got travel DVT, and that's a question that should be clarified. What about the use of elastic stockings? Has anybody developed supposed airline DVT while wearing them? What's the minimum number or do we have any idea of the average number of hours of a flight in travelers who developed DVT. We all assume that the longer the flight, the more likely that DVT will appear. A one-hour flight wouldn't be a problem, whereas a 12-hour flight would. A simple approach might be to question travelers who are considered frequent fliers to find out from that group the incidence of factors suggesting venous insufficiency among these individuals.

DR. CAPRINI: I just wanted to say one thing about that. As Victor described, he described people and lives and incidence in essence, and I think if you take a very global look at this, people get DVT's while they're on Coumadin, if their INR isn't right. People get DVT with compression stockings. Let's say they develop a cancer. There are plenty of people. There are 15 million people in the United States at least that develop a venous ulcer, and there's another 10 or 15 million with various forms of chronic venous insufficiency. That's why I think that an individual risk assessment of every single patient is important. You certainly would do that if you were going to do an operative procedure. Well, why don't you just do the same thing for this? In the vast majority of patients, and I think that the airline CEO picked up on that very quickly, putting on some stockings, drinking some fluids, there's some relatively simple measures for most of us who are in the moderate risk group that would really help to take care of this problem and dramatically lower the incidence. One final thing, if you take 1,000 general surgical patients and you don't use prophylaxis, 30 percent of them will get a clot. You'll only see three and a half percent. If you do something as simple as using pneumatic compression on that whole group, you will cut the incidence from 20 or 25 percent down to less than two or three percent. Just simple measures like that could vastly lower this problem, but of course, we do have to document, that's a problem, but I think it is about human beings and flying is just another thing that they do that puts them at risk.

DR. STRANDNESS: I just have one brief comment. I served in the strategic air command, and I can tell you that bomber pilots in the strategic air command stay up for very long periods of time because they often refuel several times. I wonder if you've ever asked the Air Force surgeon general about any evidence or any information at all about this problem in bomber pilots who may be up for 18 or 20 hours.

DR. BURNAND: One thing I learned from our visit to British Airways is that the medical director who was a Jaguar pilot tells me that air force pilots are now fitted with peep packs which is a little device that fits over the penis which makes it preferable if you're a pilot to be a male as far as I can see. It has a little sponge inside to absorb the urine. So nowadays that isn't a problem, but I don't know whether anyone else wants to comment specifically on the bomber pilots. Service personnel? Any experience from that? Joe, you've done your time in the forces.

DR. CAPRINI: Yes. The one thing I would say is now the B-2 flies out of Wittman Air Force base in Missouri anywhere in the world and they always come back and land there.

DR. BURNAND: Is there a high incidence or is it actually lower because you're dealing again with the fit young men type problem rather than --

DR. CAPRINI: Unless they have ulcerative colitis, like I mentioned earlier, they're probably very low risk.

TRAVELLER'S VENOUS THROMBOEMBOLISM

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M.A. McGrath, R.S.A. Lord

OBJECTIVE

To examine the characteristics of patients who developed venous
thromboembolism after long-distance travel and to look for thrombophilic and other risk factors in this group.

METHODS
Between 1996 to June 1999, 122 patients presented to the vascular laboratory with venous thromboembolism following travel (plane, car, train, coach) within the previous 4 weeks. Sixty four patients (32 females, 32 males) who were treated by us suffered from 71 thromboembolic events including deep venous thrombosis (DVT, 57 events in 51 patients, 80%), pulmonary embolism (PE, 23 events in 22 patients, 33%), and superficial thrombophlebitis (STP, 19 events in 18 patients, 27%). The average flight time was 11.2 hours.

RESULTS
Forty-seven patients were tested for thrombophilic blood abnormalities with 34 (72%) demonstrating an abnormality. Seventeen patients (36%) had one thrombophilic abnormality, 12 patients (25%) had two, 3 patients (6%) had three, and one patient (2%) had 4 thrombophilic abnormalities. The procoagulant abnormalities found are summarised in the following table:

<table>
<thead>
<tr>
<th>Procoagulant abnormalities</th>
<th>Patients tested</th>
<th>Patients positive</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated Protein C Resistance</td>
<td>47</td>
<td>22</td>
<td>47%</td>
</tr>
<tr>
<td>Factor V Leiden mutation</td>
<td>47</td>
<td>16</td>
<td>34%</td>
</tr>
<tr>
<td>- Heterozygous</td>
<td></td>
<td>14</td>
<td>30%</td>
</tr>
<tr>
<td>- Homozygous</td>
<td></td>
<td>2</td>
<td>4%</td>
</tr>
<tr>
<td>MTHFR* gene mutation</td>
<td>34</td>
<td>15</td>
<td>44%</td>
</tr>
<tr>
<td>- Heterozygous**</td>
<td></td>
<td>9</td>
<td>26%</td>
</tr>
<tr>
<td>- Homozygous</td>
<td></td>
<td>6</td>
<td>18%</td>
</tr>
<tr>
<td>Prothrombin gene mutation</td>
<td>37</td>
<td>9</td>
<td>24%</td>
</tr>
<tr>
<td>Protein S Deficiency</td>
<td>43</td>
<td>3</td>
<td>7%</td>
</tr>
<tr>
<td>Protein C Deficiency</td>
<td>42</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td>Antibodies</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ig G Anticardiolipin</td>
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<td>3</td>
<td>6%</td>
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<tr>
<td>Lupus anticoagulants</td>
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<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Antithrombin- III</td>
<td>46</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

Any abnormality | 47 | 34 | 72%

* Methylenetetrahydrofolate reductase
** Possible risk factor

CONCLUSION
Venous thromboembolism is a potential complication of long-distance travel especially when procoagulant blood abnormalities or other risk factors are present.

DISCUSSION

DR. BURNAND: Essentially the message seems to be that 72 percent of the patients have thrombophilia, and that now needs to be proven in prospective studies. Does anyone want to make any comments from the floor or from the panel?

DR. PARTSCH: You said 55 percent were traveling in economy class, and I’m missing the figure. 15 percent in business class?

DR. Parsi: 15 percent, yes.

DR. PARTSCH: How does this compare to the usual distribution between economy class and business class in order to assess the correctness of the term “economy class-syndrome”. One could extrapolate that there were more thrombosis in business-class; right?

DR. Parsi: That’s right. I don’t have the exact figures. We should look it up.

DR. BURNAND: I think that’s a important question and the one that I also wanted to ask, which is what’s your denominator. Again,
The aim of this study was to analyze patients with air travel-related venous thromboembolism (VTE) concerning the occurrence of patient-related and cabin-related risk factors. Twenty-five patients with deep vein thrombosis (DVT) and/or pulmonary embolism (PE) with onset of symptoms during or after prolonged air travel were questioned according to a study protocol while they were still in hospital for treatment and had the details fresh in memory. There were 14 women and 11 men with an age range of 36-79 years. The flight time ranged from 5 to 18 hours. All patients had DVT, and nine (36%) had PE as well. The proximal extension of the thrombus was in tibial vein, five patients; popliteal vein, two patients; superficial femoral vein, three patients; common femoral vein, four patients; greater saphenous vein, four patients; and iliac vein, seven patients. All but two patients (92%) had one or more patient-related risk factors, the mean was three. Obesity was present in 76% of the patients; chronic heart disease in 44%; hormone medication in 40%; other chronic diseases such as diabetes mellitus, rheumatoid arthritis, chronic renal failure, hypercholesterolemia in 32%; history of previous VTE in 28%; malignancy in 28%; smoking in 20%; recent lower limb injury in 16%; and recent surgery in 12%. Only two patients had no known patient-related risk factor. The flight travel itself does not seem to be an important risk factor in healthy individuals. However, when patient-related risk factors are superimposed, there is increasing evidence that cabin-related risk factors such as immobilization, cramped “coach” position, insufficient fluid intake, low humidity, and relative hypoxia contribute to development of VTE. Quiet cramped sitting in the special ambience the pressurized flight cabin implies, results in a large number of rheological and biochemical alterations affecting all three of the variables in Virchow’s triad: hypercoagulability, venous stasis, and vein wall lesion, which constitute the etiologic basis for development of venous thrombosis. To decrease the risks, the information has to be improved so that the passengers well in advance can prepare for prophylaxis if needed. Also, in-flight information about exercises and fluid intake should be improved. Active precautions are described.

DISCUSSION

DR. PADERBERG: I raise the question of multiple long distance flights as opposed to only the last leg. This was just renewed in the presentation from Sydney. Many of these people, much as Richard Nixon did, continued to travel despite onset of symptoms and had traveled on multiple long flights. As Mr. Burnand and Professor Partsch also know, many of us have also traveled on at least two planes to get to Hawaii. So my question is whether or not you looked at that. We recognize that it’s hard to get at; but the last report from Straub did not have this information. I was wondering if you were able to add this information in the update. The second question has to do with something a bit more local which I think is perhaps within the power of Straub and its organization here in Hawaii. As it is quite obvious (since we have all come to the Big Island) not everyone stops at Honolulu and goes to Straub. So ideally one could survey physicians hospitals of the Hawaiian Medical Society to identify those that had onset of treatment for DVT, PE, or various combinations thereof on the other islands. Did you look at that is the other question?

DR. ARFVIDSSON: To begin with the second question, no, we did not. And the first question, we only added different travelers. We didn’t look into every single trip.

DR. BERNHARD: Did you stratify those patients by class of travel?

DR. ARFVIDSSON: No, we didn’t.

DR. BERNHARD: We have been knocking economy travel and I do love to fly in business and first class. On the other hand, it occurred to me that if you’re uncomfortable you’ll move and if you’re comfortable that won’t. So stasis may theoretically be greater in patients who are in business and first class because they’re in much more comfortable seats and less inclined to move their legs.

DR. ARFVIDSSON: I think the suggestions from Vienna and Chicago looked OK. We could well agree with them.

DEEP VEIN THROMBOSIS IN AIRLINE PASSENGERS - THE INCIDENCE OF DEEP VEIN THROMBOSIS AND THE EFFICACY OF ELASTIC COMPRESSION STOCKINGS

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P.D. Coleridge Smith, FRCS, S. Machin, MRC Path.

A prospective study to determine the incidence of deep vein thrombosis in passengers on long haul flights, and to determine the efficacy of elastic compression stockings in reducing this incidence. Two hundred patients over the age of 50, with no past history of venous thromboembolic disease, no co-existing medical problems, and no specific risk factors, undergoing flights of eight hours or more, have been accessed. All patients have undergone Duplex ultrasound imaging two weeks prior to departure. Immediately prior to departure, a repeat Duplex ultrasound scan was carried out, and blood taken for D-dimer and thrombin antithrombin complex (TAT) as markers of a hypercoagulable state and soluble vascular cell adhesions molecule (VCAM-1). All patients completed a pre-travel questionnaire. The patients were randomly allocated to receive or not receive elastic compression stockings. On return, each patient was again scanned, and a further blood sample taken for analysis.

Those patients with high levels of D-dimer, TAT or VCAM-1, underwent a full thrombophilia screen. Those patients with a positive Duplex scan on visit one or two were excluded from the study. Those patients with a positive scan on return were considered to have developed thromboembolic disease, and underwent further investigations.

The results are being analysed on an intention to treat basis. The
study will conclude when 100 patients have been recruited to each group.

DISCUSSION

DR. BURNAND: Can I say we have just done a study with a whole series of custom-built stockings on individual volunteers trying to look at venous velocity and changes, and it didn’t seem to us there was a huge amount of difference between different profiles. So while we’ve been handed down a profile for years from the work of Siegel, I’m not sure that we’ve got any evidence that’s the right profile, but it seems to work. Has anyone got any other thoughts on the stocking pressure profile?

DR. CAPRINI: This isn’t based on Level I data, but any time in our vein clinics that we try to take care of people with true symptoms of venous insufficiency and go below a 30 to 40 product they often fail.

DR. BURNAND: I think there’s a difference between DVT prophylaxis and venous insufficiency. I wouldn’t like the two to get muddled.

DR. HASANIYA: I might have missed a point, but if you look at all the studies, we are listing all these risk factors which we have learned from other conditions of DVT, but yet I don’t think we can blame these risk factors unless we have control patients. Something to consider in future studies.

DR. BURNAND: That’s what we haven’t got. We’re looking at people that have a DVT, and that is the argument in favor of prospective studies which is the argument you’re going to make. Dr. Scurr, I didn’t know whether it was Freudian slip or not, but you went between passengers, patients, and subjects. In the end I wasn’t quite clear which of these groups you have studied. You travelled for people who were interested with an advert in the local papers?

DR. SCURR: Yes. We actually did look for passengers really, some became patients. You’re correct. It’s a Freudian slip. The way we got the passengers was to advertise in the local newspapers. We had a fair amount of national advertising as you probably recall, but of course, the patients are so far away that’s impractical. What we’ve done, in fact, is advertised in the West London area. We’ve also advertised in some large travel agents, and that has been quite effective in getting volunteers into the study, but you’re correct, essentially passengers, not patients.

DR. BURNAND: Two other questions before we move on to questions from the floor. One is the obvious “gobsmacking” percentage of passengers who developed a DVT. Up until now we’ve been working on the fact that the incidence is going to be extremely low, and here you are reporting a 25 percent incidence out of 20 patients that you’ve seen already. I thought it was out of 80 patients, but it’s in fact rather less than that. How can you explain this? Were these very sick people who volunteered for the study?

DR. SCURR: No. They’re not particularly sick. They’re over the age of 50. We will eventually be able to analyze this and see precisely whether there are specific risk factors. What we’ve tried to do is just take the absolutely standard airline passenger, and I’ve made the point, I think, that when we had our original results from DVT studies, nobody believed the incidence. Of course, it may be that really all we’re interested in is the symptomatic patients, but I suspect that we’re able to pick up very small clots with a duplex, and it will be very interesting to see what the thrombophilic studies will show. I think in your own study you will find, and I think you alluded to this, that there were going to be quite a large number of patients who had prothrombotic changes which you weren’t able to demonstrate a DVT, probably because you weren’t looking for it.

DR. BURNAND: But these were duplex positive DVT’s? These weren’t raises in FDP’s or anything else?

DR. SCURR: No. These are purely on duplex. There are four patients that have got positive deep vein thromboses. Admittedly they’re calf veins, and only one of the patients is symptomatic, and that was, in fact, probably due to the superficial thrombophlebitic component.

DR. LORD: Echoing what you said, it’s a staggering percentage. I mean, there are over 300 folks on a 747. That’s about 25 percent of the older passengers.

DR. BURNAND: You have to reduce that by the number over 50, but I would still guess on some of the skinny flights too --

DR. LORD: But those with positive scans must be 20 or 30. I suppose the next question is have you confirmed the accuracy of the duplex in your study?

DR. SCURR: Well, it’s the same people who are doing our duplex scanning for routine clinical practice. We know they’re good. When they get a positive scan it is checked by one of the others, and I accept a degree of observer variation. I mean, I fully appreciate that a study like this is open to some questions, but what the purpose of this was was to try and do a prospective study to try and give some idea of the incidence, which is high. You’re obviously surprised by that. I’m not sure I am surprised by it.

DR. BURNAND: I think we’re surprised by it because of the other figures that we’ve heard bandied about this afternoon. If it was 25 percent I would think you’d have the airlines absolutely hopping up and down and being very anxious about the results.

DR. CAPRINI: Can I look at this another way? There were 21 million passengers that went to Australia in a calendar year to Sydney. Now, 4 out of 30, I don’t know what that is percentage-wise, but that would mean 12 percent of 21 million did not show up in the hospitals. So, I mean, if you look at this incidence of DVT the other way around, it’s very, very high.

DR. BURNAND: I’m sure the incidence is much higher than we think. Have you got the FDP data to back the Duplex Scans up?

DR. SCURR: No, and of course, until we finish this study, this is very premature, and we may not get another DVT for the next six patients and the incidence may come down, but I’m presenting this as the results are today. I suspect the true incidence is quite high. They are asymptomatic. The question is does it matter?

DR. BURNAND: Sure it matters I think is the answer to that.

DR. SOBEH: Obviously from previously what we heard is the incidence of symptomatic patients attended the hospital while most of John Scurr’s patients are asymptomatic. So obviously the true incidence lies between the two figures.

DR. SCURR: I think that’s a fair comment. My experience with symptomatic DVT’s is we see on average two patients a week who get off an airplane with a DVT, and they are symptomatic, swollen leg, sometimes embolism.

DR. PARS: Just out of curiosity, how does VCAM-1 predicts the thrombophilic status?

DR. SCURR: Basically the hematologist who is on this project was given the opportunity of looking specifically at anything that was prothrombotic or may be of a useful indicator, et cetera, and the
three things he came up with were those. I'm not sure how that's going to help. I think the D-Dimer is probably the most useful indicator.

DR. BURNAND: It's interesting that there's a paper coming out from our department at St. Thomas next month in the Brochure on Thrombosis and Haemostasis which shows the VCAM is a very good predictor for DVT. So we'd go along with that.

DR. GUEX: May I suggest since we have three duplex machines in next room that everybody goes to the next room to be checked.

DR. OSMAN: In the rather hard-pressed NHS, I'd be interested to know where you got the funding to do this study.

DR. SCURR: Well, not in the hard-pressed NHS, is the simple answer to that. I've got a research grant which covered the cost of the duplex ultrasound scanning. We got another educational grant for the blood analysis, and the final thing is that one of the local private hospitals has agreed to do the actual screening. So a variety of sources, but not the NHS.

DR. KISTNER: Taking off on Dr. Guex, why don't we conduct an experiment right here. Let's all get a scan here at the meeting, and get one when you get home, and we will have a little experiment. We'll call it the Hawaiian PVS experiment, and invite you to come back to discuss the results. We're offering everyone a scan right here.

COULD PROLONGED AIR TRAVEL BE CAUSALLY ASSOCIATED WITH SUBCLAVIAN VEIN THROMBOEMBOLISM?

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Deep venous thrombosis (DVT) is much less common in the upper extremity than in the lower extremity. Axillosubclavian thrombosis has been reported to represent 1% to 2% of all venous thrombosis. The reported incidence of pulmonary embolism (PE) associated with axillosubclavian DVT has increased over time and ranges from 10% to 30% depending on the diagnostic tests used. "Effort thrombosis" of the subclavian vein (Paget-Schroetter Syndrome, PSS) is a condition commonly seen in young and otherwise healthy individuals, mostly men. This disorder has multiple etiologies. The most common cause is compression of the axillosubclavian vein where it crosses the first rib. This compression is caused by adjacent bones, tendons, and muscles at the thoracic inlet, facilitating venous stasis, thereby contributing to thrombotic events. Thoracic inlet syndrome is present in 80% of patients with PSS. Strenuous, repetitive shoulder-arm exercise is frequently reported prior to PSS. Injury is also an important cause of thoracic inlet syndrome and subsequent axillosubclavian thrombosis.

A number of patient-related risk factors for development of air travel-related DVT have been identified in previous reports. Very few air travelers suffering from DVT seem to be devoid of such factors. Increasing indications suggest that there is a relationship between prolonged air flight and lower limb DVT and subsequent PE. However, if this relationship is causal or not, is yet to be determined. When it comes to a possible causal association between air flight and upper extremity DVT, the issue is probably even more obscure. However, a number of the cabin-related risk factors may also affect the rheological and biochemical circumstances in the upper extremity. The pressurized air flight cabin represents a special ambience where passengers often are immobilized in cramped positions for a long time subjected to low air pressure with relative hypoxia and low humidity, which may cause dehydration, hemocoagulation, and subsequently a hypercoaguable state. This may, super-imposed to patient-related risk factors, play a role in precipitating venous thrombotic events.

Normally, hypoxia leads to increased pulmonary ventilation. However, immobility, drowsiness, or even sleeping might hinder proper respiration. This results in decreased oxygen saturation. The low air pressure and the relative hypoxia also reduce the endothelial fibrinolytic activity.

During a three-year-period, five patients with subclavian vein thrombosis were found having performed a prolonged flight in connection with or just before the onset of symptoms. All patients were examined with duplex scan and venography. One patient with PE as well was also examined with ventilation perfusion scan and pulmonary angiography. All patients had risk factors for DVT. Two patients had suffered clavicular fracture and a third had had a shoulder injury and DVT. One patient had atrial fibrillation and lung cancer. The last patient had a subclavian stenosis of unknown origin. Two of the patients suffered from PSS and in both cases, swimming was the most likely triggering factor.

It is not possible to draw any firm conclusions from this small and retrospective case study but the aim of this study was to draw attention to the possible causal relationship between prolonged air flight and subclavian thrombosis. However, further research is needed to settle this issue.

DISCUSSION

DR. BURNAND: I think one of the important things in the cramped seats you talk about is the fact that you lay on your arm for prolonged periods, particularly when you go to sleep. So if you've got an abnormality, this probably adds to it. This is obviously a much rarer problem than lower extremity DVT.

DR. LORD: I only wanted to say that on the long flight over I was observing my fellow passengers and no doubt they were observing me too, because I was thinking about the paper, and what I did notice is that almost all their movements are less than you would think. I don't know if it's a cultural thing or what, but they're not moving their arms much. They don't breathe very deeply. So five patients doesn't make a swallow in the summer or whatever, but nevertheless, it could be a genuine link.

DR. PARTSCH: As somebody has mentioned, a study coming from Innsbruck, Austria showed an increased frequency of cerebral sinus thrombosis after air-flights too. So this would fit very nicely to your study concerning atypical localization of thrombosis.

DR. ABU-BAKER: Why is the incidence of DVT higher in the lower limb compared to the upper limb? Is there a relationship between the valves and the length of the inferior cava system that can be the cause of this DVT?

DR. BURNAND: Do you want to make a hypothesis as to why upper extremity DVT is less common than lower? He says it's due
to the valves.

DR. TERUYA: Yes. I think that’s probably true, and I think also there is venous pooling in your lower extremities is probably much more significant during air flight than in the upper extremity.

DR. BURNAND: I think we’re going to try to pull this together for the last ten minutes or so. I’ve got some things written down that I’d like to sort of discuss with the audience and the panel. First of all, I suppose the simplest thing is not to fly. That’s an option that you all have, but I can’t see many people given the offer of a lovely week in Hawaii choosing this unless you’re going to come by boat and that is going to take a rather long time. We’ve had very little discussion on the seats that are available. Now, one of the big things that British Airways said was that they’re changing the style of their seats, yet the CEO of Hawaiian Airlines says tough luck, chaps. We’re going to have to put up with these rotten seats forever. Can I have some comments from the panel about the airline seats? Do you not think we could come up with a better design for airline seats? My original thoughts were that we ought to have 747s turn into those Japanese hotels where you go to sleep inside a box, but I’m told that when passengers were approached by Virgin, they said it was too clausrophobic. Bo, what about the seats? Do you think we’ve got the answer altogether in the seats?

DR. EKLOF: I usually sleep when I fly. So I do all the wrong things you shouldn’t do. The Swiss study about the changes in the popliteal vein enhances the importance of pressure from the seat against the popliteal space.

DR. BURNAND: Hugo, do you think we should be doing things to improve seat design and do you think seats are important? Is it the only way to fly in seats?

DR. PARTSCH: In these business class seats they are quite comfortable now.

DR. BURNAND: They’re even better in first class, I can tell you.

DR. PARTSCH: But what you still have is the upright position with the stasis.

DR. BURNAND: Not in first class. You get to lie right down now. That’s one of the advantages of first class. Couldn’t they think about designing the aircraft differently? Is the CEO still here from Hawaiian? Can we get you back to the microphone for just a minute because I’m really keen on discussing airline seats in greater detail.

DR. LORD: While he’s coming, I try not to fly economy, but when I do, I realize there’s a giant conspiracy against the big man, just another manifestation of the midgets taking over the world. I think the passengers should be stratified by height. I see little people sitting in great big seats, and I can barely get into my seat.

DR. BURNAND: Upgrades for all the big guys. Is that what it is?

DR. CAPRINI: I think it’s really important. I know United has done two things. They’ve now actually installed in their 757s a roomier forward section of economy class. There’s more room for frequent fliers, and in first class now in the 777s they’ve got beds. I think that’s a great move.

DR. BURNAND: Would you like to respond to that because you said commercially there was no hope for us in getting more room in seating. You’ve got to keep bottoms on seats in order to get the dollars into the airline.

MR. CASEY: I need to correct your comment. You were referring, I believe, to the design of the seat. I believe a lot can be done to design the seat.

DR. BURNAND: I’d like you to address specifically the design of the seat, if you could, with us.

MR. CASEY: Right. First of all, seat manufacturers design seats and airlines buy them, and they buy them based on the best deal they can get. So we don’t design the seats, nor actually do we design the interior of the airplane.

DR. BURNAND: That’s a cop out, if I’m allowed to say that. MR. CASEY: Well, you can say that. The space between seats is an economic issue. The design of a seat -- I mean, the price for this seat versus this seat versus another seat is about the same. So if there can be some work done with seat manufacturers to design a seat that will not cause this problem, we’d be happy to buy them. Most airlines would, I believe.

DR. BURNAND: So your point was the room between the seats and the number that you need to get in, not the design of the seats, and you’re prepared to pay a bit more if you could come up with a better designed seat.

MR. CASEY: Correct.

DR. BURNAND: Are there any other points that you want to bring to our attention having listened to the talks today that commercially make sense? Are you amazed at the 25 percent incidence of DVT that they’re getting in the Middlesex?

MR. CASEY: I am amazed, but most of the previous presentations talked about people that had a predisposition to some kind of illness or they’re overweight or whatever because everybody in this room is nice and slim so they don’t have a problem. What I am struck by is there are many things that airlines can do. They can use their in-flight video. They can use their in-flight magazine. You can put a brochure together to address some basic things and not scare the hell out of people because as soon as you scare the hell out of people, the lawyers step in and will stop you from doing it. That’s a big problem, the legal aspect.

DR. CAPRINI: Before he leaves the microphone, I just wanted to ask a question because one of the things that’s been bantered about, and we’ve been one of those that’s been bantering about it, is the use of a compression pump of some sort, a foot pump or a calf pump. Is that feasible in the airlines, let’s say, as a pilot program in business and first class or are we talking about something that just is not feasible?

MR. CASEY: You know, I have no idea what a calf pump would look like, what it would weigh or how you would use it, but we’re willing to look at anything that’s commercially feasible. Making a buck in the airline business is tough.

DR. CAPRINI: Because there are a lot of people in this room who have shown quite elegantly in some cases that the dependent limb, if it’s compressed either with a stocking or with a pneumatic device or both, you can get quite a flow out of that leg. So it seems to me that we’re going in the direction of foot compression instead of providing beds to everyone on the airplane.

MR. CASEY: Yes. I think you really need to separate it into two categories, those that have some sort of predisposition and those people need to be gotten to way in advance. And by and large it’s going to have to come from the medical community.

DR. BURNAND: Could we come back to talk about that now specifically because that’s the next thing I wanted to dwell on, particularly with the panel members and audience. If you’ve now got someone who’s going to go on a long airline flight and they were
over 50, and I’ll include John Scurr in on this as well, would you recommend that they went out and got a thrombophilia screen before they went? If they could spend 30 pounds ($50) to get a thrombophilia screen, which is about what it costs at St. Thomas, would you recommend it?

DR. PARTSCH: We shouldn’t lose the basis of common sense. Flying is an everyday situation today.

DR. BURNAND: 25 percent DVT.

DR. PARTSCH: 80 percent of our travel thrombosis occurs after car driving. We have a Vienna opera where a performance may take five hours or more. Do you have to screen all these people before they go to the opera or before they do long car driving? I mean, this would be unrealistic.

DR. BURNAND: I’m not sure whether that’s important or not.

DR. CAPRINI: I think one thing is very important, and I’m biased about this, but this risk factor assessment, either the one that we develop or someone else develops. I think that everybody that’s over the age of 50 should sit down and we ought to check off the boxes as to how many risk factors they have. And if they don’t have many risk factors, then we don’t worry about them, but if they have a bunch of risk factors, then we have to individualize how those patients are handled.

DR. BURNAND: But what do you say to the airlines when they say this is not a major risk for a fit healthy person. It’s only if you’ve got a thrombophilia that you’re really at risk. That is what seems to be coming out of the presentations that we’ve heard today.

DR. CAPRINI: I wouldn’t agree with that. You’ve got other things like obesity, previous history of surgery, hormones, varicose veins. He still has his varicose veins. I mean, these numbers add up very quickly. You’d be surprised how often you can get into the high risk category if you just take a look at all these factors.

DR. LORD: Kevin, I don’t think we should recommend anything drastic until we clarify if that study can be repeated. The 25 percent has really rocked me on the panel. If that’s true, then all the other things follow.

DR. BURNAND: No, I agree. We need some better bigger prospective studies which I think has definitely come out of today’s work.

DR. ABU-BAKER: We have heard about all the risk factors with flying. What are your recommendations to avoid coach-class DVT today?

DR. BURNAND: I think that’s a point that Joe has been making repeatedly over the course of today.

DR. CAPRINI: Take low molecular weight heparin. Make sure you get into 30 to 40 millimeter stocking. Make sure you take deep breaths, drink lots of fluids, get a bulkhead seat, move your legs around. I mean, all of these things, until we get hard data, they just make sense.

DR. MARCUSON: Would it be so terrible if you actually put the price up in coach class and had a bit more room?

MR. CASEY: I would be delighted to charge more and give people more room. The problem is people won’t pay more.

DR. BURNAND: I thought that was the commercial answer.

MR. CASEY: It’s not a commercial answer. It’s reality.

DR. SCURR: One point, when you go abroad, if you go to Africa you take malaria prophylaxis. You have your injections. So why not just have an injection of subcutaneous heparin and wear elastic stockings? I was just going to direct one question at Hugo Partsch because I seem to recall that the Austrian physicians at one stage were all taking subcutaneous heparin. Do you remember that, Hugo, or can you comment on that?

DR. PARTSCH: We recommend it only for the higher risk group as we define it for people with high risk.

DR. BURNAND: It seems to me that we recognize the fact that thrombophilia is a major risk factor, yet no one on the panel wants to provide screening for thrombophilia. I think personally they’re wrong, and I think that in years to come we all will get a thrombophilia screen done. I certainly would be very happy to get my thrombophilia screen done at some point because I think it’s going to be important and I think it will be popular. We now go on to the fact of prophylaxis and whether we can suggest any additional measures outside of the straightforward ones, about wearing stockings. Should we be taking some form of pharmacological prophylaxis, and it seems to me that you’re only recommending that from the panel for high-risk patients. Is that correct? Pharmacological treatment only for high-risk patients? Would you recommend heparin in any shape or form for anyone other than high-risk passengers travelling on airline flights? No. What about aspirin as an alternative? Do people take aspirin before they go on a flight? How many people wear compression stockings on an airline flight? (many hands raised.) Well, that’s very interesting, isn’t it? That’s fascinating. That’s the answer maybe. I mean, the real message seems to be that perhaps at least we should educate the airlines to give out anti-embolism stockings which has the advantage that it is a straightforward thing that would cost very little and we should perhaps publicize this. Hugo wants to make one other point.

DR. PARTSCH: I would like to discuss that Class I stockings would not be enough because these stockings are designed for the recumbent patient. In the sitting position these stockings are too weak to decrease the blood-volume of the lower leg to a considerable extent. This can easily be shown by APG, for instance. We have published this recently in Dermatologic Surgery that you need higher pressure and inelastic material if you want to get significant decrease of volume.

DR. SCURR: That’s wrong, Hugo. In fact, nobody in the stocking group got a DVT, zero percent.

DR. BURNAND: But you haven’t got big enough numbers to make any sensible comments on that.

DR. CAPRINI: The one point I was trying to make about that before and I didn’t get it out right was that it doesn’t make sense to put something on the leg which is less than the ambulatory venous pressure, especially in the patient at higher risk the way I categorized it. And, Hugo, if you get a 40 millimeter stocking, that’s higher than the normal ambulatory pressure, and there you have a chance to increase flow out of the leg.

Continues on the next page
A Prospective Evaluation of the Risk for Venous Leg Thrombosis Associated with Prolonged Air Travel: A Pilot Study

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Introduction
Prolonged air travel has been associated with increased risk for venous thromboembolism (VTE) for many years but it has not yet been determined if there is a causal relationship. Numerous reports have appeared on this issue but most are very small series or case reports. Since all published reports are retrospective, very little is known about the incidence of this potentially life-threatening complication.

Every year, more than 6 million travelers arrive at the Honolulu International Airport. Air travel to Hawaii takes at least 5 hours and most passengers have been traveling much longer. Thus, Hawaii is an appropriate place to perform a study on VTE associated with prolonged air travel. Approximately one third of all published cases of air-travel related VTE have been diagnosed in Honolulu, Hawaii.

To learn more about the incidence of this condition, prospective studies are needed. These studies would ideally start with duplex scan screening of air flight passengers before the long flight, and the duplex scan should then be repeated soon after the flight. It would be difficult to accomplish such a study on general passengers, as they will quickly disperse in various directions after the flight. However, in a confined group of travelers this could possibly be accomplished.

Material and Methods
During five days in November 1999, the Third Pacific Vascular Symposium On Venous Disease was held on the island of Hawaii. The meeting contained a group of phlebology minded physicians, some of them with spouses, and a number of representatives from the medical industry, altogether around 250 people. Three companies were demonstrating their latest color flow duplex scanners to the participating physicians. There were also experienced sonographers performing duplex scans on those who wished to be examined.

Stimulated by a presentation by John Scurr of London on travel related VTE on the second day of the meeting it was proposed that as many participants as possible be prospectively examined with leg duplex scan before the return flight. The study could be continued with a repeat duplex scan at the place of residency when the participant returned home. The same evening the idea was hatched a study protocol was adopted, mainly focusing on individual-related risk factors, and the next morning the study was launched. During the following three days, 83 participants were examined with venous duplex scan of both legs, to search for venous thrombosis. The sapheno-femoral junction, the confluence of the deep and common femoral veins, the superficial femoral vein, the popliteal vein as well as the sapheno-popliteal junction, and the calf veins were examined. No pulmonary diagnostics were done. The participants filled out the study protocol.

Results
In the first round of duplex scans, i.e. during the symposium, 83 participants representing 166 legs were scanned with duplex. There were 71% men and 29% women. The mean age was 52 years (range 25-80). Eighty-nine percent were 40 years or older. The age distribution is shown in Table 1. The occurrence of individual-related risk factors associated with deep vein thrombosis (DVT) are shown in Table 2. Sixteen participants were found to have a relevant risk factor, but no participant in this series had more than one risk factor. Thirty-one percent of the travelers reported that they had used in-flight compression stockings. No case of leg DVT was recorded in this duplex scan round.

Repeat duplex scan after the return flight home was planned to be performed within two weeks but because of the low number of scan reports returned after two weeks, the follow up period was extended to four weeks. Within this period, 49 repeat duplex scans were reported. One of these scans revealed a small mural thrombosis in the superficial femoral vein. This thrombosis was not seen on the primary scan. The thrombosis is shown in Figure 1. The participant suffering from this event reported that the thrombosis had given no clinical symptoms. This passenger had no known risk factors for DVT. The repeat scan was performed on the 11th day after the flight home. This was the only evidence of thrombosis seen in the 132 scans, and it was limited to a single focal non-occlusive thrombus. Another duplex scan was performed on the 29th day after the flight home showing that the thrombus had almost vanished. The mean flight time prior to these examinations was nine hours in each direction (range 5-21).

Discussion
This pilot study was based on the fact that a relatively great number of physicians interested in venous disease were gathered for a short period of time in a venue temporarily equipped with three color flow duplex scanners and a number of experienced sonographers. Most of the physicians were expected to arrange a follow up duplex scan for themselves and their spouses after homecoming. Relatively few participants had specific risk factors for thrombotic disease, only 16 of 83, and no one had more than one risk factor. Age is an important risk factor for DVT. The age distribution is detailed in Table 1. The mean age in the present series was only 52 years. In three other studies with patients suffering from air-travel related VTE, the mean age varied from 56 to 63 years.1-3

The first duplex scan round, i.e. the scans performed during the symposium, within one week after arrival by air, served both as an initial post-flight examination and also as a primary screening before the return flight. The average flight time experienced prior to this examination was nine hours.

Forty-nine of 83 participants, (59%) reported the result of a repeat scan upon return home. This second round of scans revealed one mural deep venous lower extremity thrombosis, after two prolonged air flights within one week. This DVT was asymptomatic. This series might be regarded as 132 post-flight duplex scans resulting in one single case of DVT. This result may indicate that the air flight itself may have little impact on the risk for DVT, at least in healthy individuals, and that the thrombosis development associated with prolonged air travel requires other precipitating individual-related risk factors.
It is possible that small asymptomatic DVTs are common. They might be spontaneously lysed at the place or embolized into the lungs and lysed there without clinical symptoms. A thorough duplex scan is needed to detect such small thrombi.

Since the present study was not designed in advance there were no facilities available for blood tests at the venue. A majority, 69% did not use in-flight compression stockings.

An abstract from Scurr et al described a prospective study that will include two hundred passengers 50 years or older without known thromboembolic disease and without specific risk factors for DVT. The passengers will be examined by duplex scan before and after flights of eight hours or more. Blood will also be taken for markers of a hypercoagulable state. The passengers will be randomized to use or not use in-flight compression stockings.

The single conclusion on the incidence of air travel-related venous thrombosis that might be drawn from the present pilot study is that future prospective studies will have to include large samples to establish the magnitude of air travel related VTE. With the reports of a possible relationship between air travel and VTE, passengers need to be properly informed about the risks and advised how to avoid unwanted complications.

Acknowledgement
We acknowledge J. Jerome Guex, Nicos Labropoulos, Darcy Kessler, and Steve Mun for their skillful duplex scanings.

References

Table 1.— Age distribution in 83 long haul flight passengers

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Table 2.— Risk factors associated with development of venous thrombo-embolism in 83 long haul flight passengers

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