Discussion Session II

DR. GRAOR: I would like to start this discussion period by asking Dr. Comerota if he has any experience combining anticoagulation or lytic therapy with surgical removal of thrombi in patients with phlegmasia cerulea dolens, venous gangrene, or massive iliofemoral deep vein thrombosis. If so, what have the results been?

DR. COMEROTA: I have no experience in combining lytic therapy with operative removal, but I have used fibrinolysis in patients with phlegmasia and venous gangrene. Clearly 50% of patients with venous gangrene have an underlying malignancy, and the mortality of this condition is high—averaging 50% [1]. Death from venous gangrene is essentially an extension of the thrombotic process, and we've found that lytic therapy has arrested the extension of the gangrenous process in a small number of patients.

DR. GRAOR: In your experience, what does it take to save a venous valve that has a thrombus wrapped around it? Can the clot be lysed within 5 to 7 days and have the venous architecture remain normal?

DR. COMEROTA: I think Jeffery's data, presented at the Second International Vascular Symposium in London [2], are the most convincing that we have to date. When evaluating long-term venous hemodynamics, its key is to analyze the patients in terms of whether they had lysis or not, instead of whether they had lytic or anticoagulation therapy. The reason I consider this appropriate is because of reports in the literature that thrombolytic therapy is of no value and gives no better results than anticoagulation therapy. The reason I consider this appropriate is because of reports in the literature that thrombolytic therapy is of no value and gives no better results than anticoagulation therapy. The reason I consider this appropriate is because of reports in the literature that thrombolytic therapy is of no value and gives no better results than anticoagulation therapy. The reason I consider this appropriate is because of reports in the literature that thrombolytic therapy is of no value and gives no better results than anticoagulation therapy. The reason I consider this appropriate is because of reports in the literature that thrombolytic therapy is of no value and gives no better results than anticoagulation therapy. The reason I consider this appropriate is because of reports in the literature that thrombolytic therapy is of no value and gives no better results than anticoagulation therapy.

DR. KATZEN: Let's say you are giving a patient continuous thrombolytic therapy and are monitoring fibrinogen levels. The patient's fibrinogen drops below 40–50 mg/dL, and he's starting to develop minor bleeding complications around the venipuncture sites. Is it appropriate to maintain the infusion and give fresh frozen plasma, as opposed to stopping the infusion altogether?

DR. SASAHARA: The problem with transfusing the patient in that situation is that you don't know how much it will change the degree of lytic state. As long as the patient is bleeding only superficially from the puncture site, I would just do mechanical compression. If that failed, I would simply soak the pledget in Amicar, then apply. That stops the bleeding immediately and completely. Tony, what do you think?

DR. COMEROTA: I know we've had a long discussion about the importance of fibrinogen and monitoring. All of us are familiar with the classic articles showing no correlation between laboratory data and the ability to predict complications or therapeutic efficacy. I think we must realize the complications we are dealing with, as well as the mechanisms behind bleeding, when we administer lytic therapy.

There are two reasons why patients bleed: clot lysis and underlying coagulopathy. With lytic therapy, we should expect our patients to bleed at puncture sites. That is nuisance bleeding, which is easily controlled and shouldn't really be considered a complication. The patients we need to worry about are those who develop intracranial bleeding, which is almost uniformly fatal during lytic therapy. We also need to be concerned about massive bleeds, which are associated with a high rate of transfusion and a high morbidity, if not mortality. The question is, can those patients at risk be identified?

In reviewing the literature, I have found that most patients who had intracranial bleeding during lytic therapy had a low fibrinogen level. In our experience with streptokinase, we've found that intrarterial infusion causes fibrinogen to plummet, compared with the more gradual decline during sys-
Dr. Bettmann: I can give you some data on "effort" thrombosis, which we have recently collected. In upper extremity thrombosis, the incidence of effort thrombosis, or thrombosis without an underlying cause, was about 10%. I think it is clear that in patients with an obvious cause, such as an indwelling venous line or a pacemaker, the primary aim is to remove the irritant.

Patients with effort thrombosis received a variety of treatments, ranging from heparin alone, to heparin plus thrombolytic therapy, to thrombolytic therapy, heparin, and angioplasty. At 1-year follow-up, all 8 patients had minimal recurrent or persistent symptoms, such as occasional swelling and pain, that did not appear to be related to treatment.

I don't think these data are conclusive, but I do think they indicate that in the upper extremity, a postphlebitic type of syndrome is less likely to occur, perhaps because of the development of collaterals or the different movement of the arm. Also, resolution of symptoms is perhaps not related to the particular treatment given.

Dr. Sasahara: Did you find clearing of thrombi on a repeat venogram in patients on heparin therapy? I ask because we've done some work with fastball pitchers who had effort thrombosis that was treated with heparin and Coumadin. Repeat venography showed that the subclavian axillary veins never recanalized, they collateralized, and the patients also lost their fastball. After we began using lytic therapy, virtually all the clots dissolved without collaterization, and patency was established. The lack of recanalization seen with conventional anticoagulants is why I think lytic therapy is the treatment of choice for patients with effort thrombosis.

Dr. Bettmann: In our study, we had no fastball pitchers—but we did have a quarterback. Our follow-up studies showed surprisingly little correlation between symptoms and recanalization. I think only 1 of the 8 patients had complete recanalization, and that may have been due to timing of therapy. That patient had no thrombolysis. All of the others had varying degrees of residual venous occlusion.

Dr. Graor: This might be a bit of a complicated question, too, because if you are dealing with effort thrombosis, you may be dealing with an entity of thoracic outlet syndrome; therefore, symptoms may or may not be related to venous thrombosis.

I think most of us realize that venous insufficiency in the upper extremity, with subclavian or axillary subclavian vein thrombosis, is uncommon. We've tried to lyse about 180 patients who had upper extremity thrombosis, of which 82 were cathe-
ter-related and the remainder were effort. We had poor clot lysis in the patients with effort thrombosis unless the clot was very fresh. I don’t recall ever seeing a clot clear up in response to heparin therapy. The patients collateralized very nicely, and I think the symptoms were related not to thrombosis, but to nerve compression or some such in the thoracic outlet.

DR. COMEROTA: These observations illustrate the importance of finding the underlying cause of the problem, whether you are doing an arterial or venous lytic process. Patients with subclavian vein thrombosis or effort vein thrombosis are usually young, and I would thoroughly agree with the lack of recanalization and development of collaterals. A high percentage of these patients will become symptomatic over the long term. We have been able, though, to lyse most patients whom we treat since they present rather acutely. I don’t think we should stop short of full treatment, and we also ought to treat the underlying problem whenever we can define it.

The majority of patients with thoracic outlet syndrome do not need surgery—that’s tenet number one. But once a complication develops and is diagnosed, first rib resection is indicated. Often you will see marked narrowing of the subclavian as it crosses over the first rib. Complete removal of the first rib, generally through the transaxillary approach, will give the most total decompression.

DR. GARDINER: Dr. Katzen, what has been your experience in treating effort thrombosis? Are you treating it systemically or with cathether infusion, and do you see any difference between the two?

DR. KATZEN: Our experience has been the same concerning heparin. We have had several patients in whom we hesitated to give streptokinase. They improved dramatically in response to anticoagulation, but have since collateralized.

We have had limited experience in probably 7 or 8 patients who had thrombosis related to indwelling lines or the like and had underlying stenosis. We generally infuse them directly with catheters and then perform angioplasty if there is a concomitant problem, which there universally is either because of the device or resulting stenosis. About 8 cases were reported in the Journal of Vascular Surgery earlier this past year, with reasonably good 6-month results from lysis and angioplasty, using direct infusion of a low, not a systemic, dose [3].

DR. GRAOR: It is quite convenient to use the same catheter stick being used for whatever else you are doing. Just infuse from there, or run a catheter right up to the thrombus.

DR. MCNAMARA: In patients who have significant pulmonary emboli—that is, bilateral emboli—and are candidates for thrombolysis, where do you put the catheter? Is it appropriate to use two catheters?

DR. GRAOR: We have been using the catheter in the pulmonary artery, and when the big embolus is on one side, we leave it there. I’m not convinced that there is any difference if you take that pulmonary artery catheter back into the superior vena cava or to the inferior vena cava and infuse from there. In comparing patients we infuse centrally vs. those we infuse from an arm vein, I have never been able to show a more rapid resolution of the clot. Maybe someone has had another experience.

DR. SASAHARA: No, I think that’s right. In 70% of pulmonary embolisms, the patient will have bilateral involvement. Unless you are going to do a pulmonary angiogram or are doing research, there is really no reason to leave the pulmonary artery catheter in. The lung is different from the legs, because there is always new activator being pumped around the clot by the right heart, which you don’t have in the leg. Early studies have shown no significant difference in degree of clot lysis and resolution in pulmonary embolism when comparing catheter or systemic infusion; also, you give the same dose. In routine clinical practice, I would just remove the catheter because it is another source for oozing.

DR. GRAOR: One point about that, though: Removing the catheter from the groin may not be such a smart idea, because you leave a hole in a vein. In our series we actually substituted a Swan-Ganz catheter through a sheath, which allowed us to monitor pulmonary arterial pressure. This was a side benefit, but it also plugged the hole so there was no bleeding.

DR. SASAHARA: I guess it’s a difference in approach. I never use the leg. I always use the arm. I get uncomfortable putting a catheter in from the femoral, particularly in patients who develop pulmonary embolism after a hip replacement, since proximal vein thrombosis is common.

DR. KATZEN: A catheter is an advantage in determining the end of therapy—if you are going to use it. I think most of us who have left it in recognize that there is no difference. But perhaps you are going to bring the patient back down in 10 hours and do another angio—
I wanted to ask Bob another question. The one intervention regarding massive pulmonary emboli that hasn’t been mentioned is the concept of breaking up clot, and the big saddle embolus. I really have very limited experience. One or 2 patients presented with a saddle and were acutely ill, so we just elected to go ahead and see if we could break it up, with the idea of increasing the surface area and improving pulmonary physiology. I am not sure whether we have done the right thing. Have you had any experience with that?

DR. GRAOR: During lytic therapy, I have had inadvertent experience where a clot has shattered and gone distally. I can remember two cases clearly—one where the patient got much worse, and the other where the patient did much better. What’s your experience?

DR. CORSON: In some of our cases, the patient is really in acute cardiac distress, secondary to right heart decompensation. Most of those have responded within the first hour or 2 of high-dose lytic therapy.

I wanted to add one other thing about pulmonary emboli. We have had a few patients with massive pulmonary emboli, who have had no evidence of lysis after 24 hours. Several of those patients have since died of right heart failure. If a patient has a very high right heart pressure during the right heart catheterization, and the left ventricle and the output are down, then you know the right heart is decompensating. If the patient has had elevated pulmonary pressures for a long time, he generally will die of right heart failure. There is a group of patients who probably ought to have surgery if lytic therapy doesn’t work, before they actually develop right heart failure. The ability to determine output would be very useful in those patients.

DR. SASAHRARA: I would like to respond to Barry’s question about breaking up clots. Unless the patient has unstable cardiopulmonary status, I think it is better just to leave the saddle embolus alone. Clots dissolve in the same fashion as an ice cube melts, and therefore you want to keep bathing the clot with new activator, which is best accomplished in the very large vessels. If you start fragmenting the thrombus, sending it distally to the smaller vessels where there is a tendency for a more complete occlusion, the activator is not going to bathe the whole clot. You may end up with less clot lysis. If the clot accidently breaks up during therapy, you don’t have any choice, but unless the patient is unstable, it is better to leave the clot alone. Unstable patients may regain cardiopulmonary stability if the clot is pushed more distally, where there is less cross-sectional area obstruction.

DR. GRAOR: Yes. The other thing, too, is if it does fragment and go distally, you run a higher risk of infarcting lung tissue than you do with a proximal clot.

DR. CORSON: Art., which pulmonary emboli would you treat with thrombolytic therapy?

DR. SASAHRARA: If you weren’t concerned with cost, I would use thrombolytic therapy in all patients with pulmonary embolism, simply because the vast majority, if not all, have clots in the deep venous system. I think you always end up with residual thromboemboli if you treat with anticoagulant. But these days, on a cost-benefit basis, we’ve compromised and said that in patients with more than one lobar artery involvement—which is about 18–20% of total pulmonary blood flow—we can consider thrombolytic therapy. For less involvement than that, we would tend to go with heparin.

Theoretically, however, since you have both lung and deep venous thrombosis involvement, you can make a case that if they cost the same, and if the morbidity is much less, thrombolytic therapy should be used on everybody.

DR. GARDINER: Would you use a fixed dose? We’ve used thrombolytic therapy for pulmonary emboli only in patients who are acutely threatened, and have not been terribly secure with the data for venous thrombosis all the way. Would you use a fixed dose and fixed time?

DR. SASAHRARA: Yes. For that I would simply use the standard dose, such as 2,000 U/lb for the loading and hourly maintenance doses of urokinase, or 250,000 units as a loading dose, and 100,000 U/h as a maintenance dose for streptokinase.

References
1. Cranley JJ (1975) Vascular surgery: Peripheral venous disease, vol 2. Harper and Row, Hagerstown, MD, pp 47–57
2. Jeffery P, Immelman E, Amoore J (1986) Treatment of deep vein thrombosis with heparin or streptokinase: Long-term venous function assessment. Proc. 2nd Int Vascular Symp, London
3. Drury EM, Trout HH II, Giordand JM, Hicks WR (1985) Lytic therapy in the treatment of axillary and subclavian vein thrombosis. J Vase Surg 2:821–827