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The Fibrinolytic Effects of Intermittent Pneumatic Compression

Mechanism of Enhanced Fibrinolysis

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Background and Objectives
Intermittent pneumatic compression (IPC) is an effective form of deep vein thrombosis prophylaxis for general surgery patients. The antithrombotic effect of IPC is thought to be the result of increased venous velocity and stimulation of endogenous fibrinolysis. However, the mechanism of enhanced fibrinolytic activity and the relative effects on normal and postthrombotic veins have not been defined. The purposes of this study are 1) to quantify changes in fibrinolytic activity with IPC; 2) to study the mechanism of fibrinolytic enhancement with IPC; and 3) to evaluate whether postthrombotic patients have the same capacity for fibrinolytic enhancement with IPC as do normal subjects.

Methods
Twelve volunteers (6 normal and 6 postthrombotic) had 5 IPC devices applied for 120 minutes in random fashion, 1 per week x 5 weeks. The devices included single-chamber, sequential, foot, calf, and long-leg compression. Subjects had an indwelling antecubital venous cannula placed for blood drawn at baseline, 60, 120, and 180 minutes after IPC devices were applied. Global fibrinolytic activity (euglobulin fraction, fibrin plate assay), tissue plasminogen activator (tPA) antigen (Ag) and activity (Act), plasminogen activator inhibitor-1 (PAI-1) Ag and Act, alpha-2-antiplasmin-plasmin complexes, and von Willebrand factor (vWF) antigen were assayed.

Results
A striking elevation in fibrinolytic activity was noted at 180 minutes with all devices in normal subjects and postthrombotic patients ($p = 0.01–0.0001$); however, baseline and stimulated fibrinolytic activity was attenuated in postthrombotic patients (<0.03). The tPA-Act increased only in normal subjects ($3.8 \pm 1.9\%$) ($p = 0.057$), despite a decrease in plasma tPA-Ag, which was observed in both normal subjects ($-12.4 \pm 3.8\%$) ($p = 0.009$) and patients ($-17.2 \pm 3.1\%$) ($p = 0.001$). PAI-1-Ag decreased in both normal subjects ($-13.4 \pm 3.8\%$) ($p = 0.007$) and patients ($-12.0 \pm 3.1\%$) ($p = 0.013$) with a marked

reduction in PAI-1-Act in both normal subjects ($p = 0.003$) and patients ($p = 0.004$). There were no changes in vWF, and alpha-2-antiplasmin-plasmin complexes increased only in postthrombotic patients ($p = 0.021$).

Conclusions

Stimulation of endogenous fibrinolytic activity occurs after IPC, both in normal subjects and postthrombotic patients; however, baseline and overall fibrinolytic response in postthrombotic patients is reduced. The mechanism of increased fibrinolytic activity is likely because of a reduction in PAI-1, with a resulting increase of tPA activity.

Prophylaxis for deep venous thrombosis (DVT) is mandatory for patients at moderate and high risk for venous thromboembolic complications.[1-3] Intermittent pneumatic compression (IPC) is an effective mechanical method of DVT prophylaxis.[1-3] Because IPC stimulates fibrinolytic activity, its antithrombotic action appears to be due to more than just a mechanical effect on blood flow.[4-6] Intermittent pneumatic compression potentially affects two of the three limbs of Virchow's triad by increasing venous blood flow velocity, thereby reducing stasis, and stimulating fibrinolytic activity, thereby altering hypercoagulability.

Endogenous or stimulated fibrinolysis is the result of activation of plasminogen to plasmin by one of two endogenous plasminogen activators, tissue plasminogen activator (tPA) and urokinase type plasminogen activator (uPA). This activation sequence is balanced by inactivation (binding with inhibitors), especially of tPA by the rapid acting inhibitor, plasminogen activator inhibitor-1 (PAI-1).[7] The degree of endogenous fibrinolysis can be measured and the components of the fibrinolytic system can be quantified, thereby allowing one to study the mechanism of fibrinolytic response to a given stimulus.

Surgical patients at risk of having postoperative DVT develop and those who have suffered venous thrombotic complications have measurably reduced fibrinolytic activity.[8,9] In addition, patients with an inadequate augmentation of fibrinolytic activity with IPC are most likely to have postoperative DVT develop.[5]

It appears that there is a link between development of DVT and endogenous fibrinolytic activity, and understanding this aspect of the patients' endogenous regulatory systems is increasingly important, especially in light of the multiple options for DVT prophylaxis. Because patients with postoperative DVT have depressed endogenous fibrinolytic activity[8,9] and patients with postthrombotic venous disease are at high risk of DVT after surgical procedures,[2] it would be of value to know if the mechanisms of enhanced fibrinolysis with IPC are operative in these patients and whether it is quantifiably different from that in normal subjects.

The purposes of this study are to quantify the enhanced fibrinolytic activity with IPC, to clarify the mechanisms of fibrinolytic enhancement with IPC; and to evaluate whether postthrombotic patients have the same capacity for fibrinolytic enhancement with IPC as do normal subjects.

MATERIALS AND METHODS

Subjects

Twelve volunteers of 2 distinct groups were studied. The first consisted of six healthy subjects (4 men, 2 women; mean age, 46 years; range, 25–68 years) with no history or physical findings of venous or arterial disease (normal subjects). Routine venous duplex examinations were performed to exclude the presence of asymptomatic DVT or evidence of previously undetected chronic venous disease.

The second group consisted of six subjects (4 men, 2 women; mean age, 48 years; range, 31–66 years) with a history of proximal DVT treated with long-term anticoagulation and venous duplex evidence of recanalization and thickened walls of their veins (postthrombotic patients).

Devices

Five IPC devices were studied in random sequence; these included thigh length sequential compression (SCD; Kendal Health Care Products Company, Mansfield, MA), TSQ; calf-length sequential compression (SCD Kendal Health Care Products Company, Mansfield, MA), CSQ; thigh-length single-chamber compression (DVT, 30 Flowtron; Huntleigh Health Care, Malapan, NJ), TSC; calf-length single-chamber compression (Huntleigh Health Care, Malapan, NJ), CSC; and the foot pump (Plexipulse; NuTech, San Antonio, TX), FP.

Subjects were studied in the Clinical Research Center

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of Temple University Hospital, and each had five IPC devices applied in random fashion, one per week x five weeks. Each subject was studied at the same time of day to avoid confounding results by the known diurnal variations in fibrinolytic activity.[10] After resting in the supine position with the head of the bed elevated for a minimum of 15 minutes, each compression device was applied for a period of 120 minutes, as per manufacturer's instructions. An indwelling catheter was placed in an antecubital vein, and blood samples were drawn without application of a tourniquet. Blood samples were collected into one-tenth volume of 3.8% sodium citrate at the following intervals: baseline (after rest period but before compression), 60 minutes, 120 minutes, and 180 minutes after the start of IPC. For measurement of tPA activity, blood samples were collected into one-tenth volume of acidified buffered citrate (0.45 M trisodium citrate to which citric acid was added to pH 4.3). The acid pH prevents the ongoing in vitro inactivation of tPA by complex formation with PAI-1. Plasma was harvested by centrifugation at 2500*g* for 20 minutes within 30 minutes of collection and stored in aliquots at −80 C.

Assays

Fibrin-Plate Assay

The overall fibrinolytic activity was assessed by measuring the fibrinolytic activity of the euglobulin fraction of plasma on a fibrin plate.[11,12] These were performed on blood samples drawn at baseline and at 180 minutes. The zone of fibrinolysis was quantified by comparison to a known standard using streptokinase.

Tissue Plasminogen Activator and Plasminogen Activator Inhibitor-1

The plasma samples were assessed for tPA and PAI-1 antigens using enzyme-linked immunosorbent assays from American Diagnostica, Inc (Greenwich, CT). The tPA activity and PAI-1 activity were measured using a commercially available kit from American Diagnostica (Greenwich, CT).

Plasmin Alpha-2-Antiplasmin Complex

Circulating plasmin is rapidly bound by its inhibitor alpha-2-antiplasmin. To assess whether IPC results in plasmin generation, plasma levels of plasmin alpha-2-antiplasmin complexes were measured using an enzyme immunoassay from Behringwerke AG, Germany.

von Willebrand Factor

von Willebrand factor (vWF-Ag) was measured as a marker of endothelial stimulation. It was measured using a sandwich enzyme-linked immunosorbent assay from Diagnostica Stago (Seine, France). The protocol was approved by the Institutional Review Board of Temple University Health Sciences Center, and each subject signed an informed consent.

Statistical Analysis

Analyses of mean differences in the various protein measurements among devices, time points, and samples were performed using general linear models. Devices and time points were treated as with-person (repeated measures) factors. Probability values reported for those factors are based on the Huynh–Feldt adjustment.[13] Differences from baseline over time and percent change from baseline were analyzed for each device and each group. Changes in the measured parameters were quantitated and reported for each group and each compression device. To detect changes in tPA, PAI-1, alpha-2-antiplasmin-plasmin complexes, and vWF, the endpoint was defined as the mean levels observed at 120 and 180 minutes and reported as percent change from baseline (mean ± standard error of the mean).

RESULTS

Fibrinolytic activity, measured by fibrin-plate assay, was reduced significantly at baseline in postthrombotic subjects compared with that of normal subjects ($p < 0.01$). Intermittent pneumatic compression increased fibrinolytic activity, both in normal subjects and postthrombotics ($p = 0.01–0.001$) (Table 1). The IPC-stimulated fibrinolytic activity in postthrombotics was equivalent to the baseline fibrinolytic activity of normal subjects.

Plasma levels of the measured proteins of the fibrinolytic system during IPC with each device are shown in Figures 1 through 6. Analyses of the data using linear models indicated that there were significant changes over time in plasma levels of tPA antigen ($p = 0.001$), tPA activity ($p = 0.005$), PAI-1 antigen ($p = 0.0001$), and PAI-1 activity ($p = 0.0007$) but not vWF or alpha-2-antiplasmin complexes. Changes in plasma fibrinolytic activity and vWF during IPC are reported as percent change from baseline in Table 2.

There were no differences observed between compression devices either for the fibrin-plate assay or any of the other measurements. Although patients with postthrombotic venous disease had higher levels of vWF at baseline ($p = 0.07$), vWF factor showed no change during IPC in either group (Fig. 2, Table 2).

The tPA antigen decreased over time with IPC in both normal subjects ($p < 0.009$) and postthrombotics ($p < 0.001$). Despite the drop in tPA-Ag, tPA activity increased in both normal subjects and postthrombotics, achieving significance only in normal subjects ($p < 0.038$).

Plasminogen activator inhibitor antigen decreased with IPC in normal subjects ($p < 0.001$) and postthrombotics

Table 1. FIBRIN-PLATE ASSAY AT BASELINE AND 180 MINUTES FOR EACH OF FIVE COMPRESSION DEVICES*

	FP	CSQ	CSC	TSQ	TSC
Normals					
Baseline	62.6 ± 2.6	71.9 ± 4.0	61.3 ± 3.1	73.0 ± 3.4	66.8 ± 2.8
180 min	91.3 ± 3.7	106.8 ± 6.5	145.1 ± 13.7	113.6 ± 11.9	104.50 ± 2.8
p	<0.001	<0.001	0.003	0.01	<0.001
Postthrombotic patients					
Baseline	28.2 ± 0.8	28.3 ± 0.6	28.6 ± 0.9	26.6 ± 1.0	29.2 ± 1.1
180 min	61.4 ± 3.7	62.7 ± 3.0	64.3 ± 3.7	64.6 ± 4.0	63.8 ± 3.9
p	<0.001	<0.001	<0.001	<0.001	0.001

FP = foot pump; CSQ = calf sequential; CSC = calf single chamber; TSQ = thigh sequential; TSC = thigh single chamber.
* Values are given as SU/mL (streptokinase units per milliliter; mean ± SEM). Comparison of patients *vs.* normals for each device at baseline and 180 min: $p < 0.01$ and $p < 0.01$, respectively.

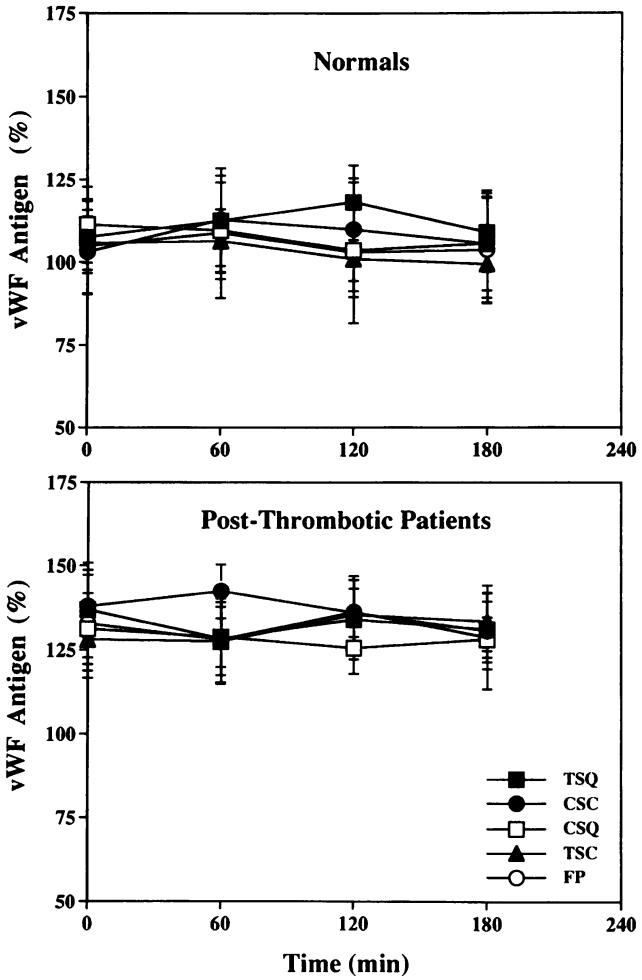

Figure 1. Plasma levels of von Willebrand factor during intermittent pneumatic compression with each of five compression devices in normal subjects (top) and postthrombotic patients (bottom). Shown are mean + standard error of the mean (n = 6). FP = foot pump, CSQ = calf sequential, CSC = calf single chamber, TSQ = thigh sequential, TSC = thigh single chamber.

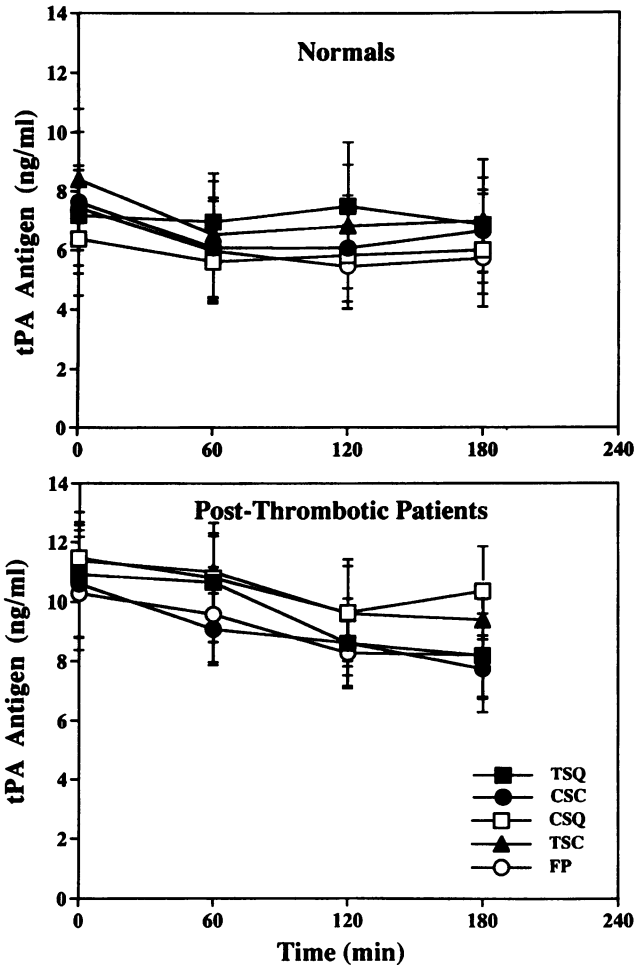

Figure 2. Plasma levels of tissue plasminogen activator antigen during intermittent pneumatic compression with each of five compression devices in normal subjects (top) and postthrombotic patients (bottom). Shown are mean + standard error of the mean (n = 6). FP = foot pump, CSQ = calf sequential, CSC = calf single chamber, TSQ = thigh sequential, TSC = thigh single chamber.

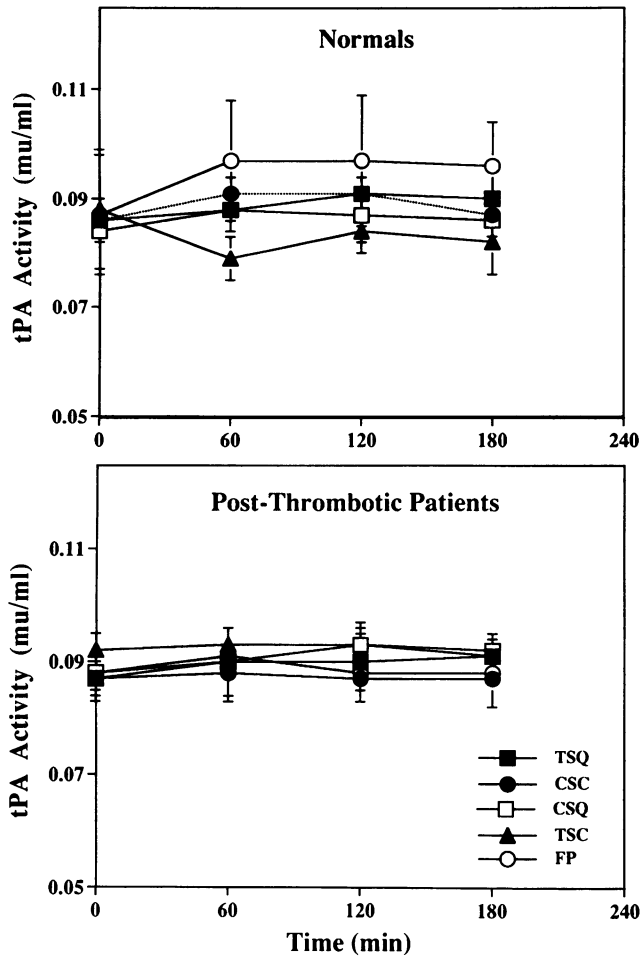

Figure 3. Plasma levels of tissue plasminogen activator activity during intermittent pneumatic compression with each of five compression devices in normal subjects (top) and postthrombotic patients (bottom). Shown are mean + standard error of the mean (n = 6). FP = foot pump, CSQ = calf sequential, CSC = calf single chamber, TSQ = thigh sequential, TSC = thigh single chamber.

($p < 0.013$) and was accompanied by a reduction in PAI-1 activity in normal subjects ($p < 0.003$) and postthrombotic patients ($p < 0.004$).

Changes in alpha 2-antiplasmin-plasmin complexes diverged between the two subject groups. An increase was observed in postthrombotic patients ($p = 0.021$), whereas in normal subjects, there was no significant change, although the mean levels at endpoint were lower than at baseline (Table 2). The difference between normal subjects and postthrombotic patients was significant ($p = 0.014$).

DISCUSSION

Vascular endothelium plays an important antithrombotic role by a number of separate but interrelated mechanisms, including regulation of fibrinolysis, inhibition of procoagulant proteins, and production of thromboregulatory compounds.[14] Stimulation of the vascular endothelium by IPC of the extremities may alter the homeostatic interactions of a number of these pathways,[14-16] although the focus of this report is the alteration of fibrinolytic activity.

The relation of endogenous fibrinolytic activity to postoperative DVT has been studied. Before specific measures of the components of the fibrinolytic system, the preoperative euglobulin lysis time was shown to be a predictor of postoperative DVT.[9] During the postoperative period, a transient fall in fibrinolytic activity commonly is observed.[8,17,18]

Intermittent pneumatic compression has been shown to stimulate endogenous fibrinolytic activity in a number of previous studies and can reduce or eliminate the postoperative depression in fibrinolytic activity.[4-6,19] Although the

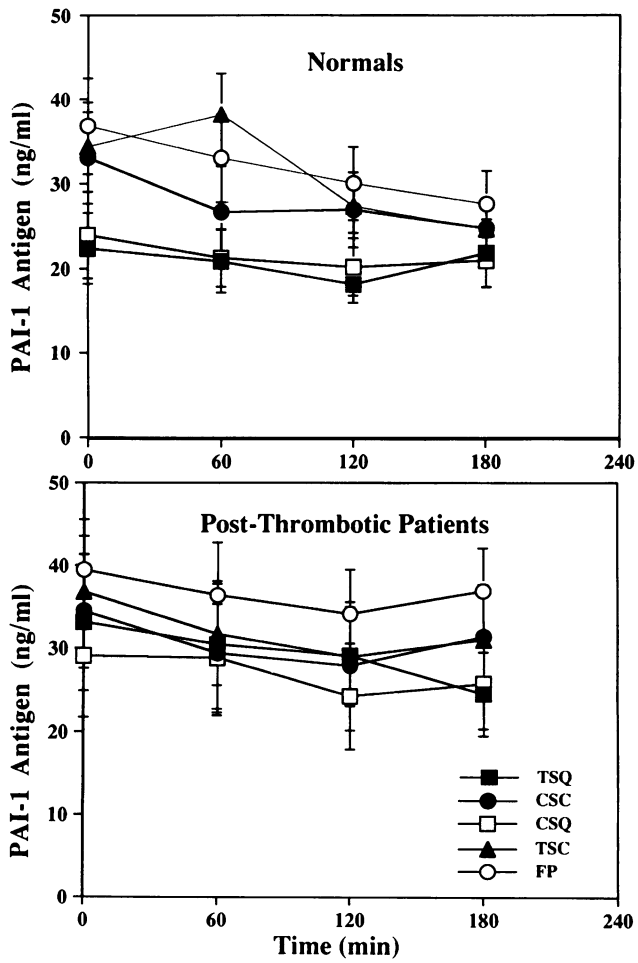

Figure 4. Plasma levels of plasminogen activator inhibitor-1-antigen during intermittent pneumatic compression with each of five compression devices in normal subjects (top) and postthrombotic patients (bottom). Shown are mean + standard error of the mean (n = 6). FP = foot pump, CSQ = calf sequential, CSC = calf single chamber, TSQ = thigh sequential, TSC = thigh single chamber.

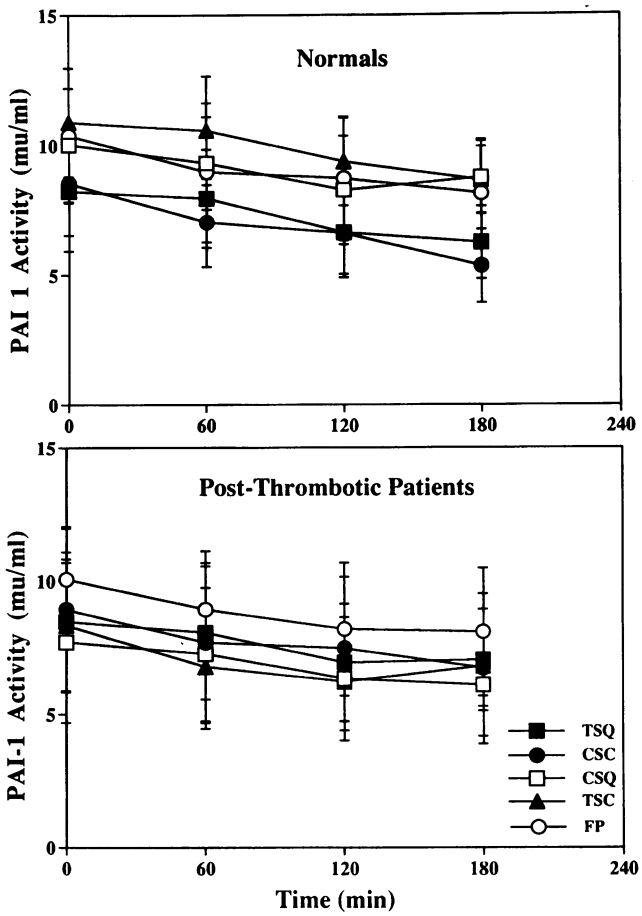

Figure 5. Plasma levels of plasminogen activator inhibitor-1 during intermittent pneumatic compression with each of five compression devices in normal subjects (top) and postthrombotic patients (bottom). Shown are mean + standard error of the mean (n = 6). FP = foot pump, CSQ = calf sequential, CSC = calf single chamber, TSQ = thigh sequential, TSC = thigh single chamber.

mechanism of enhanced fibrinolytic activity with IPC has not been clarified previously, it generally has been considered that tPA release from endothelial cells was stimulated by IPC.[4,5] This presumed mechanism of action has led to expressions of concern that IPC may be thrombogenic due to depletion of intravascular plasminogen activator.[20]

Our data show that IPC stimulates endogenous fibrinolytic activity in both normal subjects and postthrombotic patients. Not surprisingly, postthrombotic patients have significantly reduced baseline fibrinolytic activity, and when stimulated by IPC, increased their fibrinolytic activity to levels observed in normal subjects at baseline. This may be related to chronic endothelial dysfunction.

The increase in fibrinolytic activity is not because of an increase of tPA being released from endothelial cells into the circulation. There was no increase in tPA antigen with compression, nor was there any change in vWF, another marker for endothelial secretion.

The main finding in this study is that IPC enhanced plasma fibrinolytic activity associated with a decrease in plasma tPA antigen, PAI-1 antigen, and PAI-1 activity, but with an increase in tPA activity. The tPA activity in blood is regulated by the specific fast-acting inhibitor, PAI-1. The tPA antigen levels reflect both free tPA plus tPA bound to PAI-1 and thus do not represent only active tPA. Therefore, tPA activity was measured directly in this study. Intermittent pneumatic compression caused a decrease in PAI-1 antigen with a corresponding decline in PAI-1 activity (Table 2). The observed reduction in PAI-1 and the drop in tPA-Ag may be related to an increased clearance of PAI-1 and PAI-1-tPA complexes. Because most of the circulating tPA is bound to PAI-1, clearance of these complexes would result in a reduction in tPA-Ag. The remaining unbound tPA then may have greater relative activity.

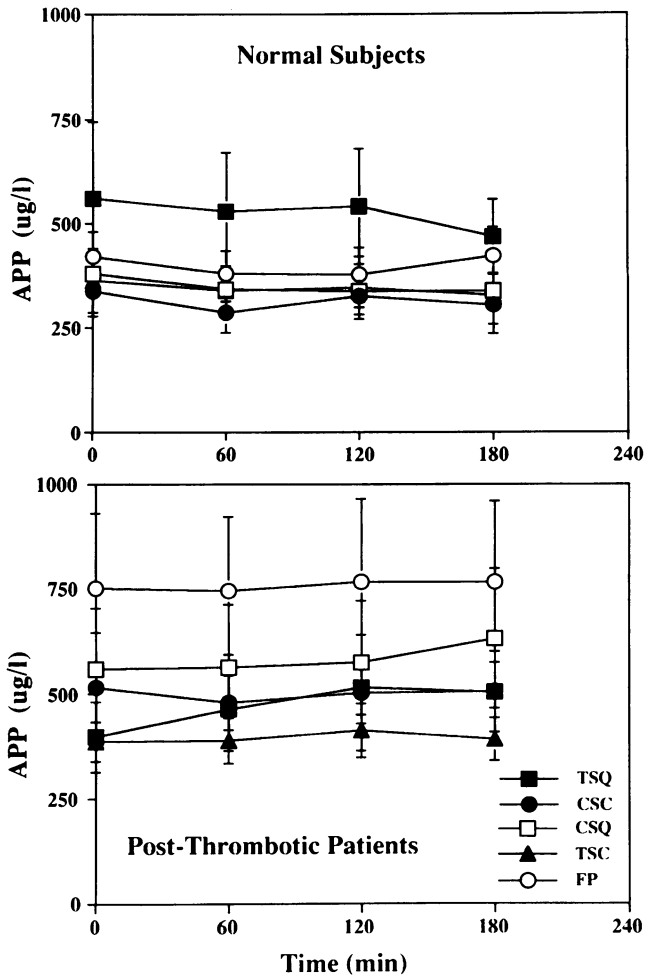

Figure 6. Plasma levels of alpha-2-antiplasmin-plasmin complexes during intermittent pneumatic compression with each of five compression devices in normal subjects (top) and postthrombotic patients (bottom). Shown are mean + standard error of the mean (n = 6). FP = foot pump, CSQ = calf sequential, CSC = calf single chamber, TSQ = thigh sequential, TSC = thigh single chamber.

Table 2. CHANGES IN PLASMA FIBRINOLYTIC SYSTEM AND vWF DURING INTERMITTENT PNEUMATIC COMPRESSION: BASELINE, ENDPOINT AND PERCENT CHANGE TO ENDPOINT BY GROUP*

	Group	Baseline	Endpoint	% Change	p
von Willebrand Factor (%)	Normal	106.5 ± 4.9	104.4 ± 5.9	−1.6 ± 2.3	NS
	Post-thrombotic	133.3 ± 5.1	130.3 ± 4.4	0.5 ± 2.3	NS
t-PA antigen (ng/mL)	Normal	7.4 ± 0.8	6.4 ± 0.7	−12.4 ± 3.8	0.009
	Post-thrombotic	10.9 ± 1.0	8.8 ± 1.0	−17.2 ± 3.1	0.001
t-PA activity (mU/mL)	Normal	0.086 ± 0.002	0.088 ± 0.002	3.8 ± 1.0	0.038
	Post-thrombotic	0.088 ± 0.001	0.089 ± 0.001	2.2 ± 1.3	NS
PAI-1 antigen (ng/mL)	Normal	30.1 ± 2.4	24.1 ± 1.6	−13.4 ± 3.8	0.007
	Post-thrombotic	34.6 ± 3.0	29.9 ± 2.4	−12.0 ± 3.1	0.013
PAI-1 activity (mU/mL)	Normal	9.6 ± 1.0	7.4 ± 0.7	−18.4 ± 3.2	0.003
	Post-thrombotic	8.7 ± 1.1	6.9 ± 0.9	−17.0 ± 5.3	0.004
α_2-plasmin-antiplasmin complexes (μg/L)	Normal	411.7 ± 43.7	370 ± 31.5	−5.4 ± 3.0	NS
	Post-thrombotic	521.6 ± 70.1	560 ± 73.9	9.8 ± 4.3	0.021

NS = not significant.
* Shown are the changes (mean ± SEM for five devices) from baseline to the endpoint. The endpoint was defined as the mean of the levels observed at 120 and 180 min in each study.

Given the relative excess of PAI-1 over tPA in the circulation, enhanced clearance of PAI-1 and tPA-PAI-1 complexes may by itself not be an adequate explanation for the net increase in tPA activity. We postulate that, overall, there may be an alteration in the balance between plasma tPA and PAI-1 activities induced by IPC, and this may be related to a differential secretion of tPA and PAI-1 from endothelial cells, with the net effect favoring expression of tPA activity. The effects induced by IPC may be analogous to the diurnal changes observed in the activities of these plasma proteins.[21] In normal subjects, there is an increase in tPA activity in the evening with substantial decreases in the plasma levels of PAI-1 activity, tPA-PAI-1 complex, and total tPA.[21] It has been suggested that both PAI-1 secretion and tPA secretion are increased in the morning, but PAI-1 secretion decreases more during the day, resulting in higher levels of active tPA in the evening.[21] Thus, it is conceivable that a similar differential effect on the endothelial secretion of tPA and PAI-1 may be induced by IPC with a relative increase in tPA secretion leading to enhanced fibrinolytic activity. Interestingly, we found no significant change in plasma vWF, a protein also secreted from endothelial cells, suggesting that the effect of IPC on endothelial tPA secretion is relatively subtle and that IPC does induce a nonspecific perturbation of the endothelium. Relatively small increases in tPA secretion may be responsible for enhanced fibrinolytic activity in the face of altered regulation by PAI-1. If this were indeed the case, tPA activity is more a function of the PAI-1 activity than the total tPA in circulation.[21] This also explains the observed increased fibrinolytic activity and increased tPA activity despite a modest fall in tPA-Ag.

Although many factors are know to stimulate release of PAI-1, conditions associated with its clearance from the circulation are not well defined. The observations of this study are supported by the findings of Jacobs et al.,[6] who reported that sequential gradient IPC produced shortened euglobulin lysis times associated with a reduction of PAI-1. Additional indirect evidence supporting these data is that increased PAI-1 is responsible for the association between reduced endogenous fibrinolysis and DVT.[22] The variation in PAI-1 levels rather than tPA is thought to be responsible for the diurnal variation of fibrinolytic activity and correlate with myocardial infarction.[10]

Although we believe that the predominant mechanism of fibrinolytic enhancement by IPC is reduction of PAI-1, the increased fibrinolytic activity may not be solely due to changes in tPA. After a variety of stimuli, endothelial cells preferentially synthesize and release another plasminogen activator, uPA, which typically activates plasminogen in the fluid phase and down regulates tPA.[14] The PAI-1 binds to uPA as well, and a reduction in PAI-1 may result in increased uPA activity. Although we did not measure uPA, it is possible that it contributed to overall fibrinolytic activity after IPC, and this might explain the marked increase in overall fibrinolytic activity compared to the modest elevation of tPA-Act. Moreover, it is conceivable that IPC induces changes in other plasma and endothelial mechanisms that contribute to its antithrombotic effect. Recent studies from our laboratory indicate that IPC induces an increase in plasma levels of tissue factor pathway inhibitor, the major physiologic inhibitor of the tissue factor-dependent pathway of blood coagulation.[23]

Prostacycline production was not studied in these pa-

tients; however, it too may play a direct role in fibrinolysis by stimulating the production of tPA,[24] and IPC has been shown to increase the production of prostacycline.[25]

We did not find any differences between the various compression devices with respect to measured changes in plasma. The limited number of subjects in this study probably was insufficient to show the differences between the devices.[26]

In summary, IPC stimulates fibrinolytic activity in normal subjects and postthrombotic patients; however, the overall fibrinolytic activity is attenuated in postthrombotic patients. We propose that the increase in fibrinolytic activity is related to a reduction in PAI-1 levels associated with a resulting increase in tPA activity. These findings underscore the important role of PAI-1 in regulating the endogenous fibrinolytic system.

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Discussion

DR. JAMES O. MENZOIAN (Boston, Massachusetts): This represents another fine piece of work by Dr. Comerota and his associates.

Over the years, he has been trying to educate us especially in the area of deep venous thrombosis and prophylaxis against deep venous thrombosis.

It is well established that intermittent pneumatic compression is efficacious in decreasing the incidence of deep venous thrombosis, and presumably by two mechanisms. One is increasing venous flow as measured by Duplex scans of the popliteal vein and femoral vein, and also by enhancing fibrinolysis. Today's study by Dr. Comerota shows us that the mechanism by which it enhances fibrinolysis is by a reduction in the amount of plasminogen activator inhibitor. I have a few questions, if I may, Dr. Comerota.

First, you showed in your subjects that the lytic activity was enhanced both in the healthy subjects and in those subjects with post-thrombotic syndrome, yet quantitatively there was less of a response in those subjects with post-thrombotic syndrome. Could you comment on the mechanism by which that could be, and does that have any clinical significance?

Second, the effect of intermittent pneumatic compression seemed to be fairly selective because it inhibited the plasminogen activator inhibitor, but it did not have any effect on the release of von Willebrand factor. Could you comment on that specificity of intermittent pneumatic compression?

Third, after initiation of intermittent pneumatic compression, when did this onset of fibrinolysis manifest itself and how long