The effect of external pneumatic compression on regional fibrinolysis in a prospective randomized trial

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Introduction: External pneumatic compression devices (EPC) prevent deep venous thrombosis (DVT) by reducing lower extremity venous stasis. Early studies suggested they also enhance fibrinolytic activity; however, in a recent study, EPC had no effect on systemic fibrinolysis in patients undergoing abdominal surgery. The hypothesis of this study was that EPCs enhance regional fibrinolysis in these subjects.

Methods: Forty-five patients (44 male, one female; mean age, 67 years) undergoing major abdominal surgery (35 bowel procedures, 10 aortic reconstructions) were prospectively randomized to one of three groups for DVT prophylaxis: subcutaneous heparin injections (HEP), thigh-length sequential EPC devices (EPC), or both (HEP+EPC). Prophylaxis was begun immediately before surgical incision and continued until postoperative day 5 or patient discharge. Venous blood samples were collected from the common femoral vein for measurement of regional fibrinolysis after induction of anesthesia but before initiation of prophylaxis, and on postoperative days 1, 3, and 5. A baseline sample was collected the day before surgery. Fibrinolysis was quantified with measurement of the activities of tissue plasminogen activator (tPA; the activator of fibrinolysis) and its inhibitor plasminogen activator inhibitor-1 (PAI-1) with amidolytic technique.

Results: tPA activity in all groups was normal at baseline; baseline PAI-1 activity was elevated. Within each prophylaxis group, no significant changes occurred in either tPA or PAI-1 activities after induction of anesthesia or after surgery compared with before surgery (P > .05, analysis of variance with repeated measures). No changes occurred between postoperative samples and after anesthesia within each group. No significant enhancement of fibrinolysis, manifested as either increased tPA activity or decreased PAI-1 activity, occurred in either EPC group compared with the HEP group at any time point (P > .05, analysis of variance with repeated measures). No differences were noted when surgery was performed for malignant disease versus nonmalignant disease.

Conclusion: In this study, enhanced regional fibrinolysis in the lower extremities could not be detected with the use of EPCs, as measured with tPA and PAI-1 activity in common femoral venous blood samples. EPC devices do not appear to prevent DVT with fibrinolytic enhancement; effective and safe prophylaxis is provided only when the devices are used in a manner that reduces lower extremity venous stasis. (J Vasc Surg 2002;36:953-8.)

The efficacy of external pneumatic compression (EPC) devices in prevention of lower extremity deep venous thrombosis (DVT) is well established. When used properly, these devices reduce the incidence of lower extremity DVT to that found with low-dose anticoagulation therapy.1-9 The primary mechanism by which EPC devices prevent DVT is reduction of lower extremity venous stasis. This has been shown as increased venous flow velocities in major lower extremity veins obtained with duplex ultrasound scan8-12 and with increased lower extremity venous flow shown with plethysmography.6

External pneumatic compression devices are also believed to enhance endogenous fibrinolysis, the system by which the body lyses excess or inappropriately formed thrombus.13 This belief originated from studies in which tourniquet-induced compression of arm veins resulted in increased plasma fibrinolytic activity. It was presumed that venous compression resulted in the increased synthesis or secretion of profibrinolytic factors from the venous endothelium.14,15 Because EPC devices also compress endothelium, investigators concluded that they must also increase fibrinolysis. Early clinical studies showed that EPC devices increased fibrinolysis in healthy volunteers and surgical patients and prevented the reduction in fibrinolysis (“fibrinolytic shutdown”) that normally follows surgery.2,16-19

However, the techniques available to measure fibrinolytic activity at the time these studies were published were crude and nonspecific because of the lack of understanding of the enzymatic mechanism of fibrinolysis. Moreover, it was not understood that numerous variables, including age, time of day, and the presence of diseases such as atherosclerosis and cancer,20,21 affect fibrinolysis, and therefore, no attempts were made to control these variables. Closer inspection of the results of many of the studies shows inconsistencies and conflicting data.
Patient characteristics

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<th>HEP</th>
<th>EPC</th>
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<td>Atherosclerosis*</td>
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<td>2 (12.5%)</td>
<td>4 (26.7%)</td>
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* Atherosclerosis was defined as patient-reported history of coronary artery disease (CAD), myocardial infarction, or peripheral arterial occlusive disease, electrocardiographic evidence of CAD, or revascularization for CAD, peripheral arterial occlusive disease, or carotid artery disease.

More recent studies in which the rate-limiting enzymes of fibrinolysis are measured have generally not confirmed the original findings. A study conducted in our laboratory found no effect of EPC devices on systemic fibrinolytic activity, measured from antecubital venous samples. However, any increase in fibrinolysis produced by EPC might not be measurable in the systemic circulation because of dilution and hepatic clearance of fibrinolytic factors. The hypothesis of this study was therefore that EPC devices enhance regional fibrinolytic activity in the lower extremity to which they are applied.

METHODS

Forty-five patients (44 males, one female; mean age, 67 years) undergoing major abdominal surgery were randomized to one of three groups for DVT prophylaxis: 1, unfractionated heparin injections given subcutaneously at a dose of 5000 units twice a day (HEP); 2, thigh-length sequential pneumatic compression device (EPC; Kendall Health Care, Manchester, Miss); or 3, combination of both methods (HEP+EPC). The surgical procedures that were performed are listed in the Table; these included 10 abdominal aortic aneurysm repairs, 25 resections for malignant disease, and 10 miscellaneous laparotomies (nine bowel resections/lysis of adhesions, one splenectomy). Patients undergoing aortic reconstruction were given systemic doses of heparin during the surgical procedure, which were reversed at the end of the procedure with protamine. The protocol was approved by the Institutional Review Board, and all subjects gave informed consent before participation.

A venous duplex ultrasound scan was performed before enrollment in the study to exclude the presence of preexisting venous disease, and a second ultrasound scan was performed on postoperative day 5 or before discharge to exclude the development of DVT. Those patients with a history or ultrasound scan evidence of venous thromboembolic disease, or a requirement for systemic anticoagulation therapy, were excluded. Ultrasound scans were performed from the confluence of the tibial veins to the iliac veins; calf veins were not routinely scanned because calf vein DVT were not considered clinically significant. The criteria for a positive ultrasound scan have been previously reported.

DVT prophylaxis was initiated in the operating room after induction of anesthesia and continued until postoperative day 5 or discharge. In the event that a postoperative ultrasound scan identified a proximal DVT, the patient was withdrawn from the study and treated for DVT with standard methods. The decision for method of treatment was left to the discretion of the patient’s regular physician.

Fibrinolysis was quantified with measurement of the biologic activities of tissue plasminogen activator (tPA, the activator of fibrinolysis) and its inhibitor plasminogen activator inhibitor-1 (PAI-1). For measurement of regional fibrinolytic activity, samples were collected from the common femoral vein on the day before surgery, after induction of anesthesia but before initiation of prophylaxis, and on postoperative days 1, 3, and 5. All samples were collected between 7:00 am and 11:00 am to eliminate the known diurnal variations in fibrinolysis. All subjects in the EPC and EPC+HEP groups wore EPC devices on both lower extremities, and all sampling was performed from the same extremity in each patient. The choice of extremity was determined randomly. To ensure maximum compliance with the study protocol, a study coordinator monitored the devices twice daily to ensure that they remained on the patient. The nursing staff in the intensive care units and on the wards were inserviced regarding the study protocol and the need for the patients to wear the devices at all times. No attempts were made to control ambulation in any of the subjects; it was assumed this would be similar among the groups given the similarity of the surgical procedures.

For determination of tPA activity, blood was first collected into 130 mmol/L sodium citrate anticoagulant (9:1 volume) and immediately acidified with addition of 0.5 mmol/L sodium acetate, pH 4.2 (2:1 volume), to prevent the ongoing in vitro inactivation of tPA by complex formation with PAI-1. Samples for measurement of PAI-1 activity were collected into a 5-mL syringe containing modified Files solution (1 mL acid citrate dextrose solution, 80 μL acetylsalicylic acid solution, 10 μL prostaglandin E1) to minimize in vitro platelet activation (final dilution, 1:5). Samples were maintained at 4°C until centrifugation at 10,000g for 20 minutes. Platelet-poor plasma was stored at −80°C until assays were performed.
The activity levels of tPA and PAI-1 were measured with amidolytic methodology. Assays were performed in duplicate, and interassay variability was less than 5%. tPA activity was expressed in international units (IU/mL) assessed against the Second International Standard for tPA from the National Institute for Biological Standards and Control. PAI-1 activity was expressed in arbitrary units (AU/mL); 1 arbitrary unit of inhibitor equals the amount that inhibits 1 international unit of tPA/mL plasma.

Values for tPA activity were combined for subjects in each group at each time point. Values for PAI-1 activity were treated similarly. All data were expressed as the mean ± standard error of the mean. The activity levels of tPA and PAI-1 were analyzed with analysis of variance for a two-factor experiment with repeated measures on one factor (time). The two factors were patient group (HEP, EPC, HEP+EPC) and time (five time points: before surgery, after anesthesia, and postoperative days 1, 3, and 5). Ages of the three patient groups were compared with one-way analysis of variance. Association between the prevalence of atherosclerosis and patient groups, and between surgical procedures and patient groups, was assessed with the Fisher exact test. All tests were assessed at the .05 level of significance.

RESULTS

Subjects and procedures. Forty-five subjects participated in this study and were divided equally among the three treatment groups. Mean age, prevalence of atherosclerosis, and frequencies of surgical procedures for each group are summarized in the Table. There were no significant differences in age among the three groups (P = .96). The prevalence of atherosclerosis was similar among the three groups (P = .99). Association between surgical procedures and patient groups was not significant (frequencies of each of the three major types of procedures were similar among the groups; P = .50). No subject had signs or symptoms of venous thromboembolism develop during the study. Venous duplex ultrasound scans were performed on 81% of the subjects after surgery; no proximal DVT were identified.

tPA activity. tPA activities in the three groups were normal before surgery (1.16 ± 0.24 IU/mL to 1.65 ± 0.31 IU/mL; Fig 1). tPA activities among the three patient groups were not statistically different at any time point (group main effect, P = .83; group by time interaction, P = .29). In addition, the difference between any two time points was not statistically different in any of the groups (time main effect, P = .29).

PAI-1 activity. Mean PAI-1 activities of the three groups (19.2 ± 3.4 AU/mL to 24.4 ± 1.7 AU/mL; Fig 2) were elevated compared with age-matched and gender-matched healthy subjects at baseline. PAI-1 activities among the three groups were not statistically different at any time point (group main effect, P = .41; group by time interaction, P = .87). In addition, the difference between any two time points was not statistically different in any of the patient groups (time main effect, P = .57).

Effect of malignant disease on fibrinolysis and EPC devices. Fifty-seven percent of subjects (25 of 45) in this study underwent laparotomy for treatment of malignant disease. Because of this, and because of the known influence of malignant disease on fibrinolysis, the data were reanalyzed, taking into account of the presence or absence of malignant disease. Subjects who underwent abdominal cancer procedures were similarly distributed among the three groups (P = .50; Table). There was higher regional tPA activity in subjects without malignant disease compared with those with malignant disease (1.76 ± 0.14 IU/mL without malignant disease; 1.10 ± 0.23 IU/mL with malignant disease; P = .02). There were no significant differences in PAI-1 activities between the subjects with malignant disease and those without (19.6 ± 1.9 AU/mL without malignant disease; 25.6 ± 1.8 AU/mL with malignant disease; P = .06).

DISCUSSION

In 1972, Hills et al showed that application of a pneumatic compression device to the legs of patients undergoing surgery for nonmalignant disease prevented the development of postoperative DVT, and in subjects with malignant disease, there was no benefit. This finding led Allenby et al to speculate that the coagulation system in the two groups might be different and that the EPC device might be affecting it. At the same time, venous occlusion with a tourniquet on the arm was shown to increase fibrinolysis in the veins distal to the tourniquet. If tourniquet compression produced increased fibrinolysis, it seemed logical that intermittent compression would also increase fibrinolysis. Until this time, EPC devices had been shown to increase lower extremity venous flow, and this was
thought to be the mechanism by which they prevented the development of DVT.

Allenby et al\textsuperscript{14} measured euglobulin clot lysis times (ECLT; a crude measure of global fibrinolysis) in surgical patients treated with EPC devices. Subjects undergoing surgery for nonmalignant disease had decreased ECLTs (increased fibrinolysis), whereas those with malignant disease and control subjects not treated with pneumatic compression had increased ECLT. Allenby et al\textsuperscript{14} proposed that enhancement of fibrinolysis by increased secretion of fibrinolytic factors from vein walls was the primary mechanism by which EPC devices prevent DVT and, because the effect appeared to be systemic, suggested that in the future it might be possible to provide DVT prophylaxis in the legs by application of these devices to the arms. A later paper provided evidence that EPC applied to the arms resulted in increased fibrinolytic activity measured in the common femoral vein.\textsuperscript{15}

Soon thereafter, Salzman, McManama, and Shapiro\textsuperscript{17} showed that EPC protected against postoperative fibrinolytic shutdown in patients undergoing neurological procedures, and Inada et al\textsuperscript{18} found similar results in patients undergoing surgical procedures for malignant disease. Caprini et al\textsuperscript{19} showed reduced postoperative fibrinolytic shutdown with EPC devices in patients undergoing orthopedic or neurological procedures, although in patients undergoing abdominal surgery the devices had no effect.

None of these early studies, however, used techniques in which the specific enzymatic components of fibrinolysis were measured, and many variables (time of day, age, atherosclerosis) now known to affect fibrinolytic activity were not controlled. The results must therefore be viewed with caution. Tarnay et al\textsuperscript{16} did measure fibrinolytic activity in the arms and legs (femoral vein sampling) of healthy volunteers in a more controlled study and found that fibrinolytic activity in the legs increased by 22% after 1 hour of pumping. Systemic activity measured from the arms, however, increased only 6% and barely achieved statistical significance.

In our laboratory, studies were performed on both healthy volunteers and surgical patients, with measurement of tPA and PAI-1 activities on antecubital venous samples to quantify systemic fibrinolysis. We were unable to show an effect of EPC devices on systemic fibrinolysis in either group. In healthy volunteer subjects, neither a thigh-length sequential, calf-length sequential, or arteriovenous foot pump produced statistically significant increases in tPA activity or decreases in PAI-1 activity during a 3-hour pumping period (unpublished data). In subjects undergoing abdominal surgery, EPC devices produced no changes in systemic tPA or PAI-1 and did not prevent postoperative fibrinolytic shutdown.\textsuperscript{27}

It is possible that EPC devices produce an increase in tPA secretion from lower extremity veins when applied there, but the effect is not measurable from the systemic circulation because of dilution and the hepatic clearance of tPA.\textsuperscript{41} In this study, we measured fibrinolytic activity on venous samples collected from the common femoral veins of legs pumped with a thigh-length sequential compression device, presuming that this would provide the most direct method of assessing the effects of EPC devices on secretion of fibrinolytic factors from vein wall endothelium. However, we were again unable to show any effect of the EPC device on postoperative fibrinolysis, manifested as either increased tPA activity or decreased PAI-1 activity. Neither the presence of atherosclerosis or malignant disease affected these results.

The results of other recent studies addressing the effects of EPC devices on fibrinolysis have also been conflicting. Comerota et al\textsuperscript{28} studied systemic (antecubital) fibrinolytic activity in healthy volunteers treated with five different pneumatic compression devices. They found small (18%) but significant decreases in PAI-1 activity and increases in tPA activity (4%) with all devices. Jacobs et al showed decreased PAI-1 antigen levels in the inferior vena cava of healthy volunteers after a 4-hour compression period, but no changes occurred after a second period of compression.\textsuperscript{29} Christen et al\textsuperscript{24} found no changes in either tPA or PAI-1 antigen levels measured from the antecubital vein in healthy volunteers after pumping with a sequential leg device and a foot pump. Kosir et al\textsuperscript{26} evaluated tPA and PAI-1 antigen levels in patients undergoing general surgical procedures treated with either heparin or EPC devices. They found increases in both measurements in patients treated with both methods of DVT prophylaxis, making it difficult to draw conclusions regarding the effect of EPC on fibrinolysis.

Review of the original suppositions on which the theory of enhanced fibrinolysis with EPC is based raises additional questions regarding its validity. Placement of a tourniquet on the forearm for 15 to 30 minutes was observed to produce elevated levels of tPA in the arm distal to the tourniquet, and this was presumed to result from increased endothelial secretion.\textsuperscript{42} However, recent data and computer modeling of the kinetics of tPA metabolism show that the increased levels of tPA associated with venous occlusion result from trapping of tPA distal to the tourniquet and that the basal rate of secretion of tPA remains unchanged.\textsuperscript{44,45} Because EPC devices compress intermittently, no trapping of tPA occurs. Early studies suggested that increased blood flow resulting in higher than normal shear stress values might also be associated with increased secretion of tPA from venous endothelium. However, it was later shown that this only occurs at shear stress rates associated with arterial flow.\textsuperscript{44,45} Evidence that compression of the venous endothelium results in changes in levels of PAI-1 is also lacking. Recent data show that PAI-1 secretion from venous endothelium is low and not physiologically important and that PAI-1 secretion occurs primarily from the liver.\textsuperscript{46,47} Studies involving catecholamine injection have shown increases in forearm tPA activity but no changes in PAI-1.\textsuperscript{47,48} When all of the evidence is considered, enhancement of either regional or systemic fibrinolysis from intermittent compression seems unlikely.

In this study, baseline tPA activity was within the normal range for subjects of this age group, but baseline
PAI-1 activity was markedly elevated. The most likely explanation for this elevation is the high incidence rate of atherosclerotic disease in the study population. Seventy-five percent of the subjects had evidence of atherosclerosis in the coronary, carotid, or peripheral circulations. There is considerable evidence that atherosclerosis is associated with elevations of PAI-1 activity.20,21

The presence of malignant disease is also known to affect endogenous fibrinolysis.35,36 Malignant disease has been associated with elevations of urokinase plasminogen activator,36 thrombin-antithrombin complex, and pro-thrombin fragment 1+2.35 In a previous study, we found a significant correlation between the presence of malignant disease and tPA activity,27 similar to that found here. Most importantly, EPC devices did not produce a greater increase in fibrinolysis in subjects with nonmalignant disease compared with those with malignant disease. The presence of malignant disease resulting in impaired fibrinolysis did not “mask” any effect of EPC devices on endogenous fibrinolysis in this study. In conclusion, EPC devices do not increase endogenous fibrinolytic activity either systemically or in the extremity to which they are applied, at least through increased tPA activity or decreased PAI-1 activity. It is possible that they produce an anticoagulant state through a different mechanism. However, until more information regarding these alternative mechanisms of anticoagulation is provided, effective and safe DVT prophylaxis with EPC devices can be assured only in the setting of enhanced venous flow velocities.

REFERENCES

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