A randomized, blinded trial comparing the hemostatic effects of pentastarch versus hetastarch

Ronald G. Strauss, Beverly J. Pennell, and David C. Stump

BACKGROUND: HES solutions provide a sterile, alternative colloidal fluid to albumin solutions and/or plasma in the management of patients who need plasma volume expansion. Solutions of HES are widely accepted internationally but are used only modestly in the United States, largely because of concerns over hemostasis.

STUDY DESIGN AND METHODS: A randomized, blinded, two-arm trial comparing the hemostatic effects of pentastarch versus hetastarch when infused in the clinically relevant dose of 90 g of HES dissolved in 1.5 L of saline was conducted. Multiple studies of fibrin clot formation, fibrinogen/fibrinolysis, and platelet (PLT) functions were performed before and on multiple occasions for 70 days following HES infusion.

RESULTS: Several significant abnormalities of hemostasis assay results occurred following HES infusions, with hetastarch causing significantly greater abnormalities than pentastarch. Individual clotting proteins and blood PLTs fell modestly because of plasma volume expansion and hemodilution. A fall in excess of that caused by hemodilution was demonstrated for von Willebrand factor antigen plus its associated FVIII and ristocetin cofactor activities. The partial thromboplastin time was prolonged, whereas the thrombin time was shortened. Plt function abnormalities were seen in most subjects to a modest degree. Studies of fibrinolysis were normal.

CONCLUSIONS: Solutions of hetastarch produce significant abnormalities of some hemostasis laboratory results when infused at clinically relevant doses, but it is unlikely that the modest hemostatic abnormalities produced at these doses per se would lead to clinical bleeding. Hetastarch causes greater hemostatic abnormalities than pentastarch, and because both HES solutions have comparable plasma volume-expanding effects, it is reasonable to prefer pentastarch as a plasma volume expander.

Solutions of HES provide a sterile, alternative colloidal fluid to albumin solutions and/or plasma for critically ill patients who need plasma volume expansion,[1-5] for patients who are undergoing therapeutic plasma exchange,[6-8] for use in priming solutions for cardiopulmonary bypass circuits,[9-11] and during postoperative care, including cardiac surgery.[12-16] HES is a complex polysaccharide that consists of glucose units, connected primarily by α-1 to α-4 glycosidic linkages with α-1 to α-6 linkages serving as branch points, to which hydroxyethyl groups are attached. A wide variety of HES molecules can be prepared from amylopectin by reaction with ethylene oxide under alkaline conditions to attach hydroxyethyl groups to carbon atoms C2, C3, and/or C6.[17] The presence of hydroxyethyl groups retards hydrolysis of the starch molecules by plasma amylase, and as a result, HES circulates in the bloodstream following infusion longer than does underivatized starch, thus functioning as an osmotic plasma volume-expanding agent. The number of hydroxyethyl groups attached to each glucose unit within the starch polymers and their sites of attachment (i.e., C2:C6 ratio) greatly affect the metabolism and, consequently, the size of HES molecules circulating in the bloodstream, which, in turn, determines the biologic properties of different HES solutions.[17-19]

ABBREVIATIONS: BT = bleeding time; MW = molecular weight; PLT = platelet; PT = prothrombin time; PTT = partial thromboplastin time; RCoF = ristocetin cofactor; TT = thrombin time; vWA = von Willebrand antigen.

From the University of Iowa DeGowin Blood Center and the Department of Pathology, University of Iowa Hospitals and Clinics, Iowa City, Iowa; and the University of Vermont College of Medicine, and Human Genome Sciences, Burlington, Vermont.

Address reprint requests to: Ronald G. Strauss, MD, Department of Pathology, C250 GH, University of Iowa College of Medicine, Iowa City, IA 52242-1182; e-mail: ronald-strauss@uiowa.edu.

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Distinguished by differing molecular weight (MW) and the extent and pattern of hydroxyethylation, a wide variety of HES preparations are available internationally—each exhibiting relatively different properties that permit application in diverse clinical situations.[17] Only two major varieties of HES are available in the United States: hetastarch and pentastarch. The weight average MW of hetastarch—the higher MW variety—varies depending on the manufacturer, but it is approximately 450,000 to 670,000, with a number average MW of 71,000. The weight average MW is defined as the sum of the number of molecules at each MW times their mass divided by the total weight of the molecules, whereas the number average MW is the numerical average of the individual MWs present.[1] For hetastarch, the molar substitution is 0.7 (i.e., 70 molecules of hydroxyethyl moiety are present for every 100 glucose units contained in the HES), with some glucose units containing more than one hydroxyethyl moiety. Pentastarch has a lower MW than hetastarch (weight average MW = 264,000, number average MW = 63,000) and a lesser extent of hydroxyethylation (molar substitution = 0.45). Therefore, for a few hours following infusion, pentastarch exerts an acceptable plasma volume-expanding effect but has a much quicker terminal elimination from the blood than hetastarch and, consequently, exhibits fewer adverse effects, particularly abnormalities of hemostasis.[17,20]

Solutions of HES are widely accepted as albumin and plasma substitutes internationally but are used only modestly in the United States. Currently, hetastarch is the only HES preparation approved by the FDA for plasma volume expansion or replacement. Pentastarch is approved for use only during leukapheresis; however, it has been reported to be quite effective as a plasma and albumin substitute,[1] and internationally, HES solutions with properties similar to pentastarch are commonly used for plasma volume expansion.[17] Presumably, pentastarch is used "off-label" (without stated FDA approval) in the United States as a plasma and albumin substitute because of its advantages over hetastarch, particularly its more rapid terminal elimination from the bloodstream and lesser effects on hemostasis.[1,17,20]

A major impediment to more widespread use of HES solutions in the United States is concern over hemostatic abnormalities[17,21-24] and clinical bleeding,[24-28] the latter occurring usually only with relatively large doses (>1.5 L). One preparation of hetastarch (Hespan, B. Braun McGaw, Irvine, CA) has been reported to alter hemostasis by decreasing the concentration of most clotting proteins via its expected effect of hemodilution secondary to plasma volume expansion, by lowering levels of vWF:Ag and, consequently, its associated FVIII molecules, by altering the structure of fibrin clots, and by modestly diminishing platelet (PLT) functions.[17,24] Another preparation of hetastarch (Hextend, Abbott Laboratories, North Chicago, IL, and BioTime, Berkeley, CA) is formulated in a lactated electrolyte solution and, because of added calcium, is purported to exert fewer adverse hemostatic effects when used at recommended doses,[29] a presumption that needs more extensive study in patient trials before it will gain widespread acceptance. In preliminary studies, one preparation of pentastarch (Pentaspan, B. Braun McGaw) has been reported to be nearly devoid of effects on hemostasis—other than the transient slight decrease in clotting protein levels expected because of hemodilution.[20] However, more definitive comparative data of the hetastarch and pentastarch solutions available in the United States are limited, and the two preparations have not been investigated in a randomized, blinded, head-to-head study. Accordingly, we conducted such a study to provide data for physicians using HES solutions for plasma volume expansion—information that will be particularly useful if pentastarch gains FDA approval for this use.

MATERIALS AND METHODS

Experimental design

A randomized, blinded, two-arm trial was approved by The University of Iowa Human Studies Committee, and

TABLE 1. Assays of clotting proteins and functions[20-22,30-45]

Assay	Normal result or range
PT	10 to 13 seconds
PTT	22 to 33 seconds
TT*	14 to 20 seconds
BT	2.5 to 9.5 minutes
Fibrinogen	150 to 500 mg per dL
FVIII activity	50 to 200 percent
vWA	60 to 160 percent
RCoF activity†	50 to 200 percent
Urokinase-activated clot lysis time	38 to 46 seconds
D-dimer	<0.2 mg per mL
α-2 antiplasmin	75 to 125 percent
Euglobulin fibrinolytic activity	<5 IU per mL
Tissue plasminogen activator	<4 to 20 ng per mL
Urine plasminogen activator	<1 to 5 ng per mL
Plasminogen activator inhibitor	<6 IU per mL
Plasminogen	75 to 125 percent
Plt adhesion	>78 percent
Clot retraction	40 to 94 percent
Plt aggregation	Increase in light
Collagen	Transmission comparable to controls
Epinephrine	Transmission comparable to controls
ADP	Transmission comparable to controls

* Thrombin time.
† Ristocetin cofactor.

TABLE 2. Results (mean ± SEM) of standard plasma clotting times and fibrinogen following pentastarch or hetastarch infusions

	PT (sec)		PTT (sec)		TT (sec)		Fib (mg/dL)	
Time	Pentastarch	Hetastarch	Pentastarch	Hetastarch	Pentastarch	Hetastarch	Pentastarch	Hetastarch
Preinfusion	12 ± 0.2	12 ± 0.3	26 ± 0.8	27 ± 0.8	17 ± 0.6	17 ± 0.4	268 ± 17	240 ± 16
2 Hours	13 ± 0.3	13 ± 0.5	32 ± 1.4	37 ± 3.4	13 ± 0.4	13 ± 0.5	210 ± 13	184 ± 10
Day 1	13 ± 0.3	12 ± 0.4	28 ± 0.7*	35 ± 1.9	16 ± 0.3*	13 ± 0.3	253 ± 16	207 ± 12
Day 2	12 ± 0.3	12 ± 0.3	30 ± 1.1	33 ± 0.9	16 ± 0.5*	13 ± 0.3	279 ± 17	227 ± 11
Day 3	12 ± 0.2	12 ± 0.3	28 ± 0.7*	32 ± 1.1	16 ± 0.3*	14 ± 0.3	225 ± 17	216 ± 14
Day 7	12 ± 0.1	12 ± 0.3	27 ± 0.7*	31 ± 1.2	16 ± 0.3*	14 ± 0.2	232 ± 7	207 ± 15
Day 14	12 ± 0.2	12 ± 0.3	28 ± 0.8	29 ± 1.1	16 ± 0.2*	14 ± 0.4	250 ± 17	228 ± 28
Day 21	12 ± 0.1	12 ± 0.3	27 ± 0.9	29 ± 0.9	16 ± 0.4	15 ± 0.5	282 ± 20*	207 ± 10
Day 70	12 ± 0.2	12 ± 0.3	29 ± 0.7*	28 ± 0.7	17 ± 0.4	15 ± 0.3	256 ± 11	226 ± 18

* Significant different ($p < 0.05$) between pentastarch and hetastarch.

each subject provided written consent. Twenty-four healthy adults were randomly assigned to receive 90 g of HES dissolved in 1.5 L of saline infused intravenously either as hetastarch (1.5 L of 6% Hespan) or as pentastarch (0.9 L of 10% Pentaspan plus 0.6 L isotonic NaCl). This dose was selected because the dose of 6-percent hetastarch not to be exceeded in 24 hours, as recommended by the manufacturer, is 1.5 L. An identical dose of pentastarch, by weight, was given. Hextend was not approved by the FDA at the time that this study was conducted and was not evaluated. All subjects had a negative personal and family history for bleeding and had taken no medications, including aspirin, for at least 1 week prior to admission. Prestudy prothrombin times (PT), partial thromboplastin times (PTT), and bleeding times (BT) were normal.

Subjects were admitted to the Clinical Research Center the day before the HES infusion for medical evaluation and baseline laboratory studies. An IV catheter was placed to ensure optimal access for accurate infusions and free-flowing blood sampling. Solutions of either hetastarch or pentastarch plus NaCl were infused over exactly 2 hours (i.e., from 0 to 2 h) via an infusion pump placed behind a curtain for blinding of subjects and laboratory staff. Blood samples for coagulation studies were drawn immediately before the HES infusion (0 h) and immediately afterward (2 hours) and subsequently at 24 hours and on Days 2, 3, 7, 14, 21, and 70 following initiation of the infusion. As noted in the text, additional samples were drawn at more frequent intervals for other tests such as blood counts.

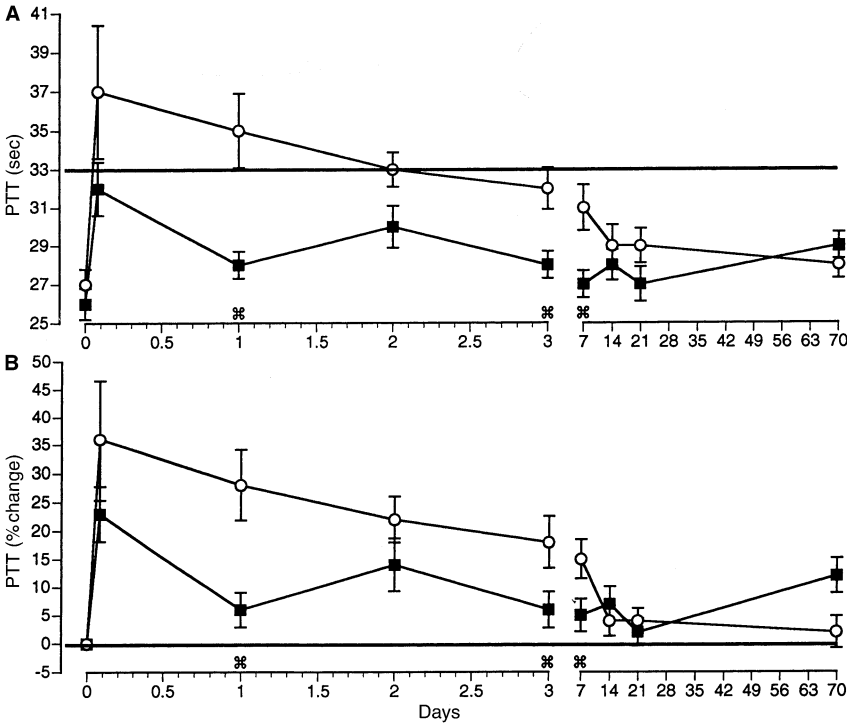

Fig. 1. Results of PTT following pentastarch (■, n = 12) or hetastarch (○, n = 12) infusion. (A) Results expressed in seconds to form a clot, and (B) results expressed as percentage change from the preinfusion value. The horizontal lines at 33 seconds (A) and 0 percent (B) indicate normal values and provide points of reference for postinfusion results. ⌘ P < 0.05 pentastarch versus hetastarch.

Clotting and hemostasis assays

Blood samples were drawn before and at timed intervals after either hetastarch or pentastarch solutions were infused. The assays performed, their abbreviations, and their normal ranges are presented in Table 1.[20-22,30-45] Every assay listed was performed on blood samples obtained before HES infusions (0 h) and afterward at 2 and 24 hours and Days 21 and 70 postinfusion. In addition, selected assays were performed more frequently. For example, additional assays performed on Days 2, 3, 7, and

14 were PT, PTT, thrombin time (TT), fibrinogen, FVIII, von Willebrand antigen (vWA), ristocetin cofactor (RCoF) avtivity, and BT—the last only if BT or PLT function studies performed earlier were abnormal, not if earlier results were normal. In addition, PLT function studies (adhesion, aggregation, and clot retraction) were repeated on Days 2, 3 and 7 only if they were abnormal when studied at earlier times. Additional assays of fibrinolysis (urokinase-activated clot lysis time, α-2 antiplasmin, D-dimer, euglobulin fibrinolytic activity, tissue-type plasminogen activator, urokinase-type plasminogen activator, plasminogen activator inhibitor, and plasminogen) were performed on Days 2 and 3 if earlier test results were abnormal.

Statistical analysis

The primary objective of the study was to detect differences of ≥50 percent in results of clotting assays following infusion of hetastarch (Hespan) versus pentastarch (Pentaspan). For example, if a clotting protein fell by 30 percent from the baseline level following infusion of hetastarch, it was important to detect and demonstrate the significance of a lesser fall of either 15 percent or a greater fall of 45 percent following pentastarch infusion. Based on our earlier studies,[20-22] a sample size of 12 subjects per group was judged to provide an adequate number. All statistical analyses were performed with statistical software (Statistical Analysis System v. 6.06, SAS, Cary, NC). Results of the statistical tests were deemed significant if the two-tailed probability (p value) was ≤0.05.

RESULTS

Clinical response to HES infusions

Heart rate, respiratory rate, and systolic and diastolic blood pressures were measured immediately before and after the HES infusions and at 24 hours postinfusion. Vital signs were stable, and there were no clinically significant changes (deviations) from preinfusion values or differences between pentastarch and hetastarch groups. The maximum deviations from baseline (mean values) following pentastarch versus hetastarch, respectively, for heart rate were −2.6 versus 2.4 beats per minute, for respirations were −0.7 versus 0.4 breaths per minute, for systolic blood pressure were 2.4 versus −2.9 mmHg, and for diastolic blood pressure were −2.6 versus −7.1 mmHg. There were no significant differences between pentastarch and hetastarch groups in the number of adverse clinical events that might be attributed to HES, although more events were reported for hetastarch. Following pentastarch infusions, two subjects complained of headache. Following hetastarch, four subjects complained of headache, and three complained of urticaria.

Blood Hb was measured immediately before infusion (0 h), immediately following infusion, at 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours after infusion, and on Days 2, 3, 5, 7, 9, 11, and 14 after infusion, and then weekly through Day 70. The maximum fall (% deviation from the value measured immediately before infusion [0 h]) for Hb values in subjects given pentastarch versus hetastarch, respectively, was −15.4 and −15.9 percent at 2 hours (immediately after infusion), with later values fairly rapidly increasing toward the baseline. Significant differences ($p < 0.05$) between groups in the percentage fall of Hb values from baseline were found at 8 hours (−6.3% vs. −13.8%) and 24 hours (−0.5% vs. −6.1%) after infusion for pentastarch versus hetastarch, respectively. The fall in Hb values during the first 3 days after infusion was ascribed to hemodilution, largely because of the plasma volume-expanding effects of HES—rather than to blood drawn for laboratory testing—and changes of this magnitude in in-

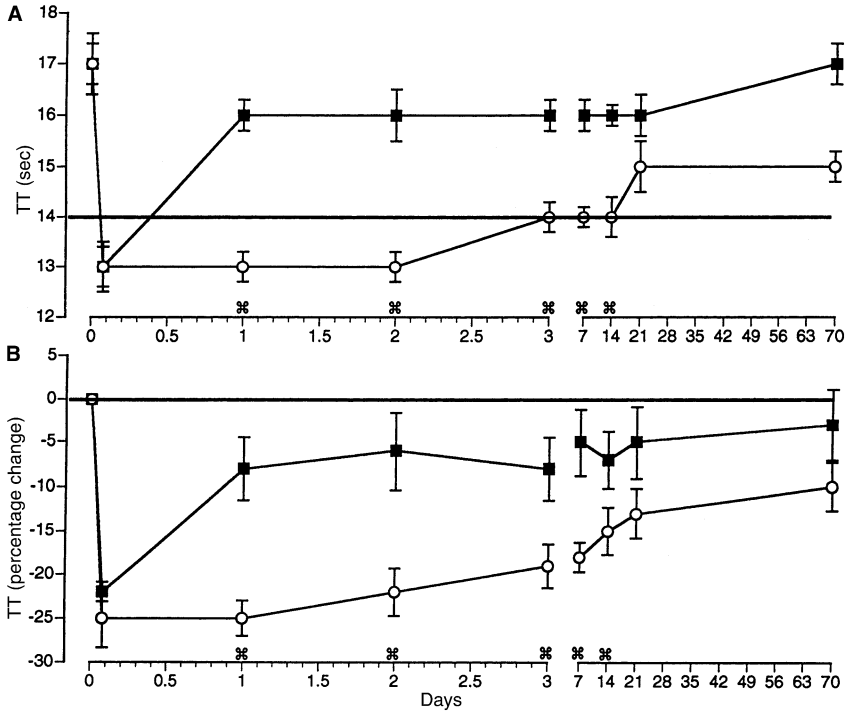

Fig. 2. Results of TT following either pentastarch (■, n = 12) or hetastarch (○, n = 12) infusions. (A) Results expressed in seconds to form a clot, and (B) results expressed as a percentage change from the preinfusion value. The horizontal lines at 14 seconds (A) and 0 percent (B) indicate normal values and provide points of reference for postinfusion results. ⌘ P < 0.05 pentastarch versus hetastarch.

TABLE 3. Results (mean ± SEM) of clotting FVIII, vWA, and RCoF following pentastarch or hetastarch infusions

	FVIII activity (%)		vWA (%)		RcoF activity (%)	
Time	Pentastarch	Hetastarch	Pentastarch	Hetastarch	Pentastarch	Hetastarch
Preinfusion	140 ± 18	103 ± 8	144 ± 28	100 ± 14	103 ± 12	99 ± 10
2 Hours	85 ± 8	55 ± 6	75 ± 11*	44 ± 6	85 ± 10*	54 ± 8
Day 1	116 ± 18*	53 ± 6	96 ± 28*	33 ± 5	84 ± 8*	43 ± 7
Day 2	140 ± 27*	66 ± 6	110 ± 21	36 ± 4	119 ± 13*	59 ± 11
Day 3	117 ± 7*	65 ± 6	103 ± 15*	34 ± 4	92 ± 7*	65 ± 10
Day 7	108 ± 10	87 ± 9	100 ± 13*	47 ± 5	107 ± 12	81 ± 11
Day 14	111 ± 8	95 ± 8	99 ± 11	69 ± 10	106 ± 12	88 ± 12
Day 21	125 ± 9	108 ± 7	105 ± 13	92 ± 11	113 ± 15	92 ± 12
Day 70	113 ± 6	122 ± 15	117 ± 14	113 ± 17	96 ± 9	113 ± 10

* Significant difference ($p < 0.05$) between pentastarch and hetastarch.

dividual clotting proteins measured during the first 3 days, likewise, were ascribed to effects of hemodilution. Accordingly, deviations from baseline values of a magnitude of greater than 16 percent likely are due to a mechanism, evoked by HES, that is independent of (not explained by) hemodilution alone.[21,22]

Clotting times and hemostatic proteins

Compared with the preinfusion value, the PT significantly increased ($p < 0.05$) immediately following infusion but remained in the normal range, and no differences were detected between the pentastarch and hetastarch groups (Table 2). Likewise, the PTT increased ($p < 0.05$) after infusion, but the effects were significantly greater for hetastarch (Table 2 and Fig. 1). The PTT was increased outside of the normal range for only hetastarch and remained prolonged for 2 days postinfusion, with hetastarch exerting a significantly greater ($p < 0.05$) effect than pentastarch up to 7 days postinfusion (Table 2 and Fig. 1). The TT decreased ($p < 0.05$) immediately following infusion, with greater shortening in hetastarch versus pentastarch recipients (Table 2 and Fig. 2). The shortened TT returned to normal within 1 day following pentastarch infusion, whereas it took 3 days to become normal following hetastarch infusion, with hetastarch values being significantly ($p < 0.05$) shorter than pentastarch for 14 days postinfusion (Table 2 and Fig. 2).

Plasma fibrinogen levels fell ($p < 0.05$) modestly 24 hours after infusion, but there were no significant differences between pentastarch versus hetastarch recipients (Table 2). The maximum fall from preinfusion fibrinogen values was 21 percent for pentastarch versus 23 percent for hetastarch immediately following infusion—a fall only slightly greater than the 16-percent fall expected for hemodilution. In contrast, the effects on FVIII, vWA, and RCoF activity greatly exceeded those ascribed simply to hemodilution (Table 3 and Figs. 3-5). Following pentastarch infusion, FVIII activity fell 37 percent from the preinfusion value ($p < 0.05$), but recovered quickly and returned to baseline by Day 2 (Fig. 3). In contrast, following hetastarch infusion, FVIII activity fell 47 percent from

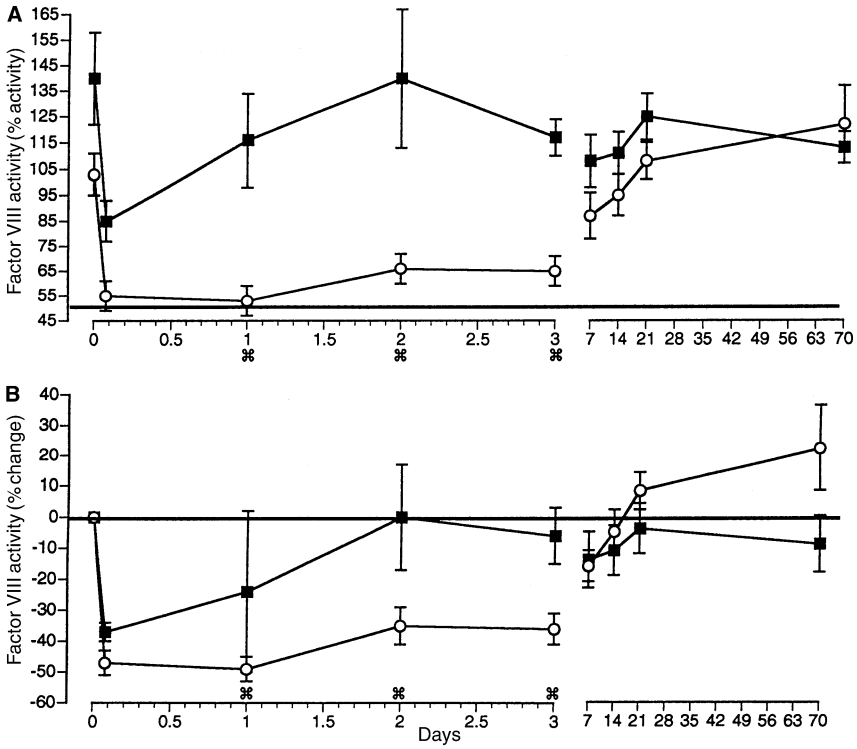

Fig. 3. Results of FVIII activity following either pentastarch (■, n = 12) or hetastarch (○, n = 12) infusions. (A) Results expressed as percentage of normal activity, and (B) results expressed as percentage change from the preinfusion value. The horizontal line at 50 percent activity (A) and 0 percent (B) indicate normal values and provide points of reference for postinfusion results. P < 0.05 pentastarch versus hetastarch.

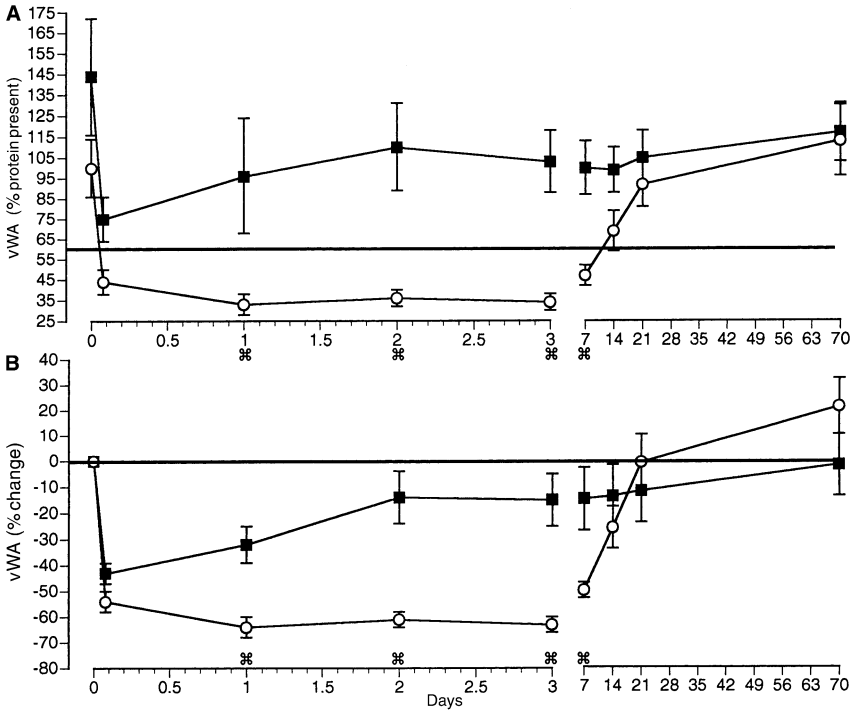

Fig. 4. Results of vWA following either pentastarch (■, n = 12) or hetastarch (○, n = 12) infusions. (A) Results expressed as the percent of a normal quantity of protein present, and (b) results expressed as a percentage change from the preinfusion value. The horizontal lines at 60-percent protein present (A) and 0 percent (B) indicate normal values and provide points of reference for postinfusion results. ⌘ P < 0.05 pentastarch versus hetastarch.

the preinfusion value ($p < 0.05$) and did not recover until between Days 7 and 14, with values significantly below ($p < 0.05$) those of pentastarch recipients until between Days 3 and 7 (Fig. 3). Somewhat similar results were seen for vWA antigen (Fig. 4) and RCoF activity (Fig. 5), but the effects of both pentastarch and hetastarch were most pronounced on vWA (Table 3 and Fig. 4). The maximum fall of vWA from the preinfusion value was 43 percent for pentastarch immediately following infusion and 64 percent for hetastarch 1 day after infusion. Values for vWA returned nearly to the baseline at 2 days after infusion for pentastarch, but took between 14 and 21 days following hetastarch, with hetastarch values being significantly lower ($p < 0.05$) than pentastarch for at least 7 days postinfusion (Table 3 and Fig. 4). Interestingly, pentastarch exerted almost no affect on RCoF activity, as a measure of vWA function, in contrast to the marked and prolonged decrease in activity following hetastarch infusion (Table 3 and Fig. 5).

Because of the known incorporation of HES molecules into polymerizing fibrin strands,[23] an effect reported to alter clot structure[23] and to shorten thrombin and reptilase clotting times and to accelerate clot lysis times,[22] several factors involved in fibrinogen and fibrinolysis were measured following pentastarch and hetastarch infusions (Table 4). With only occasional exceptions, the results after infusion were either unchanged from preinfusion baseline values or were similar to changes expected due to hemodilution. Thus, there was no indication of abnormal fibrinogen or fibrin lytic activity evoked by either pentastarch or hetastarch infusions.

PLT counts and functions

There were no clinically significant changes in PLT counts following either pentastarch or hetastarch infusions (Table 5). Immediately following infusion, the PLT count fell from the preinfusion value by 13 percent in pentastarch and by 24 percent in hetastarch recipients, respectively, but this difference was not significant ($p > 0.05$), and at no time after infusion did the mean blood PLT count fall to less than 200×10^9 per L for either group. The BT increased significantly ($p < 0.05$) following infusion of either pentastarch or hetastarch when preinfusion values were compared with those measured immediately following infusion (Table 5). The maximum lengthening of the BT occurred at 2 hours, with an increase from the preinfusion value of 49 percent following pentastarch versus 59 percent for hetastarch. For hetastarch, the value exceeded the normal range, but there was no difference between groups. The BT quickly returned to normal by 1 day after infusion. Plt adhesion decreased significantly ($p < 0.05$) from the preinfusion value immediately following infusion in both pentastarch and hetastarch recipients (Table 5). The maximal decrease in adhesion from baseline was 25 percent following pentastarch versus 23 percent for hetastarch ($p > 0.05$)—values that were out of the normal range, but reverted to normal within 1 day after infusion. Clot retraction values remained within the normal range and did not differ between groups (Table 5), but interestingly, increased significantly ($p < 0.05$) immediately following infusion for both pentastarch (23% change from baseline) and hetastarch (20% change from baseline).

Plt aggregation appeared to be more adversely affected by hetastarch than pentastarch, but interpretation of aggregation curves is quite subjective and is difficult to quantitate. Because baseline PLT aggregation results were not completely normal in all subjects—despite normal PLT counts, normal BT, and normal results of all other hemostatic assays—only 12 pentastarch recipients and 10 hetastarch recipients were considered evaluable. Hetastarch

decreased PLT aggregation in 100 percent of recipients immediately following infusion, with a correction in 50 percent of recipients within 1 day after infusion, and correction in 90 percent of recipients within 2 days (Table 5). By comparison, pentastarch decreased after aggregation in only 58 percent of recipients immediately following infusion, with nearly one half of these abnormal results judged to differ only minimally from normal controls. Plt aggregation quickly returned to normal following pentastarch infusion; that is, only 10 percent of recipients exhibited decreased aggregation 1 day after infusion, and none were abnormal at 2 days. Nearly all decreased PLT aggregation responses in both of the HES groups were detected with epinephrine as the agonist; only occasionally were decreased responses detected with collagen or ADP as agonists.

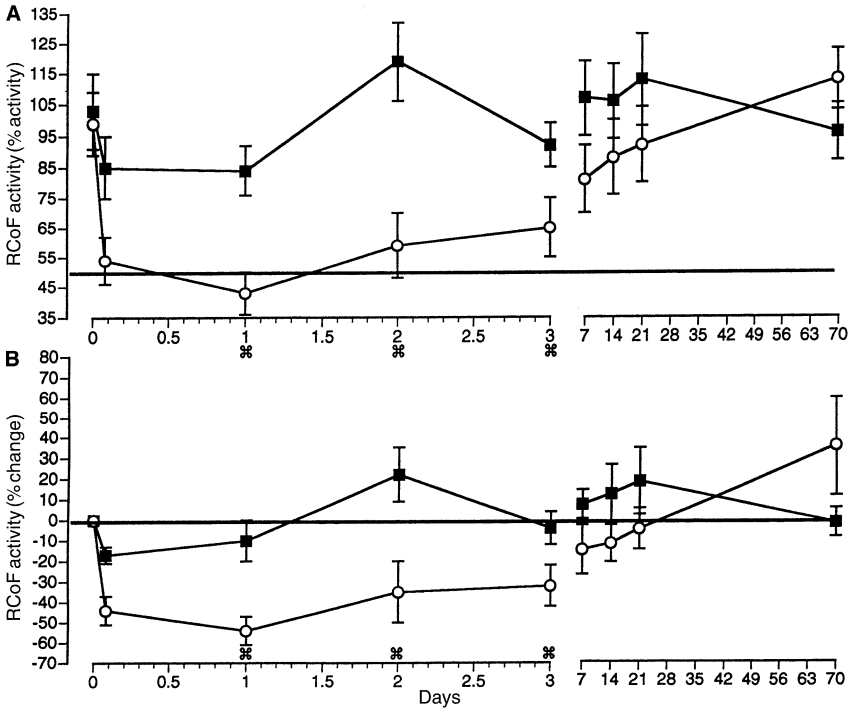

Fig. 5. Results of RCoF activity following either pentastarch (■, n = 12) or hetastarch (○, n = 12) infusions. (A) Results expressed as percent activity, and (B) results expressed as percentage change from the preinfusion value. The horizontal lines at 50-percent activity (A) and 0 percent (B) indicate normal values and provide points of reference for postinfusion results. ⌘ P < 0.05 pentastarch versus hetastarch.

DISCUSSION

We demonstrated several abnormalities of hemostasis laboratory assays following the infusion of HES solutions, hetastarch or pentastarch, into normal subjects at clinically relevant dosage. Many effects were significantly greater following hetastarch versus pentastarch infusions. However, it is unlikely that the hemostatic abnormalities produced at the dose infused would lead to clinical bleeding in patients without other concomitant clotting problems.[24]

Immediately following infusion of either HES solution, individual clotting proteins and blood PLT counts fell by approximately 20 percent from the preinfusion values, an effect explained largely by expected plasma volume expansion with consequent hemodilution.[1,21,22,24] An additional postinfusion fall in vWA plus its associated FVIII and RCoF activities was of much greater

TABLE 4. Results (mean ± SEM) of fibrinogen and fibrinolysis studies following pentastarch and hetastarch infusions*

	Urokinase-activated clot time (sec)		Euglobulin (IU/mL) fibrinolytic activity		Plasminogen (%)	
Time	Pentastarch	Hetastarch	Pentastarch	Hetastarch	Pentastarch	Hetastarch
Preinfusion	22 ± 0.7	23 ± 0.8	0.4 ± 0.1	0.2 ± 0.0	98 ± 2	105 ± 3
2 Hours	20 ± 0.8	21 ± 0.5	0.3 ± 0.0	0.3 ± 0.1	80 ± 3	87 ± 4
Day 1	21 ± 0.7	23 ± 0.9	0.4 ± 0.1	0.3 ± 0.0	97 ± 3	89 ± 3
Day 21	21 ± 0.8	23 ± 0.8	0.3 ± 0.0	0.3 ± 0.1	101 ± 2	90 ± 2
Day 70	22 ± 0.7	22 ± 0.6	0.4 ± 0.1	0.3 ± 0.0	98 ± 2	101 ± 3
	Tissue plasminogen activator (ng/mL)		Urine plasminogen activator (ng/mL)		α-2 antiplasmin (%)	
Time	Pentastarch	Hetastarch	Pentastarch	Hetastarch	Pentastarch	Hetastarch
Preinfusion	23 ± 15	23 ± 21	8 ± 1.0	2.2 ± 0.3	101 ± 5	107 ± 7
2 Hours	13 ± 7	12 ± 11	7 ± 0.8	1.6 ± 0.3	76 ± 7	82 ± 6
Day 1	22 ± 13	16 ± 14	8 ± 1.3	2.1 ± 0.3	102 ± 4	90 ± 5
Day 21	24 ± 15	22 ± 20	8 ± 1.4	2.0 ± 0.3	103 ± 6	106 ± 5
Day 70	27 ± 18	22 ± 20	9 ± 1.4	2.0 ± 0.4	106 ± 5	116 ± 5

* There were no significant differences ($p < 0.05$) between groups for any test.

TABLE 5. Results (mean ± SEM) of blood PLT counts and PLT function studies following pentastarch or hetastarch infusions*

	PLT count (10^9/L)		BT (min)		PLT adhesion (%)		Clot retraction (%)		PLT aggregation Percentages of recipients with decreased responses	
Time	Pentastarch	Hetastarch	Pentastarch	Hetastarch	Pentastarch	Hetastarch	Pentastarch	Hetastarch	Pentastarch	Hetastarch
Preinfusion	247 ± 15	223 ± 15	5.7 ± 0.4	7.0 ± 0.7	87 ± 6	82 ± 5	54 ± 4	63 ± 4	0	0
2 Hours	215 ± 13	200 ± 11	8.3 ± 0.6	11.2 ± 1.8	65 ± 8	63 ± 7	63 ± 4	73 ± 2	58	100
Day 1	247 ± 14	221 ± 14	6.5 ± 0.5	7.0 ± 1.1	86 ± 6	79 ± 7	61 ± 4	69 ± 2	10	50
Day 2	265 ± 12	243 ± 14	NT	NT	NT	NT	NT	NT	NT	10
Day 7	273 ± 15	237 ± 17	NT	NT	NT	NT	NT	NT	NT	NT
Day 14	272 ± 9	233 ± 16	NT	NT	NT	NT	NT	NT	NT	NT
Day 21	271 ± 12	222 ± 15	7.4 ± 0.6	8.5 ± 0.8	93 ± 2	82 ± 10	59 ± 4	65 ± 5	0	0
Day 70	258 ± 14	234 ± 15	6.3 ± 0.5	6.3 ± 0.5	88 ± 3	95 ± 1	58 ± 4	59 ± 4	16	20

* There were no significant differences ($p < 0.05$) between groups for PLT counts, BTs, PLT adhesion, or clot retraction.

magnitude than could be explained simply by hemodilution. This finding has been also demonstrated following dextran infusions and is postulated to be due to accelerated clearance of vWA via its binding in vivo to dextran and/or HES molecules, although other undefined mechanisms may also contribute.[17,21,24] The effects on vWA can be severe enough, particularly following hetastarch infusion, to mimic vWD.[17,24,27] The TT was shortened, consistent with incorporation of HES molecules into the polymerizing clot,[22,23] but the results of several assays assessing fibrinogen and fibrinolysis were affected minimally, or not at all, following infusions of either hetastarch or pentastarch. Plt counts fell only slightly, but BT values were significantly prolonged to suggest a modest qualitative PLT defect. Prolonged BT values quickly reverted to normal and were actually out of the normal range in only hetastarch recipients. Hetastarch induced abnormal PLT aggregation in all subjects, but the clinical importance, if any, was questionable because defective aggregation was not seen with all agonists and results began to revert to normal within 1 day after infusion. Pentastarch exerted fewer effects on BT and PLT aggregation results than did hetastarch.

Solutions of HES have appeal as an alternative colloidal fluid to albumin solutions and plasma in the management of patients who need restoration, expansion, or replacement of plasma proteins.[1,17] HES solutions are relatively inexpensive, pose no risk of transmitting donor infections that rarely follow blood component transfusions, require no pretransfusion compatibility considerations, and are readily available and stored without refrigeration. Hetastarch and pentastarch have nearly comparable plasma volume-expanding effects when given in similar dosage.[1,17] However, a relatively small quantity of hetastarch will remain in the blood stream for weeks because of the number and the intramolecular position of hydroxyethyl groups—a situation not found with pentastarch because it contains fewer and more favorably placed hydroxyethyl groups.[1,17-19] It is the prolonged circulation of these highly hydroxyethylated HES molecules—unfortunately, too few in number to exert meaningful plasma volume expansion—that likely cause the more pronounced adverse effects of hetastarch on hemostasis.[17-19]

Therefore, it is reasonable to prefer pentastarch (relatively low MW and hydroxyethylation) over hetastarch (relatively high MW and hydroxyethylation) as a plasma volume-replacement or -expansion solution, providing that one always remains cognizant of the fact that formulations of either pentastarch or hetastarch that appear at first glance to have similar MW and molar substitution values may not actually be the same when the number and placement of hydroxyethyl groups within glucose molecules (i.e., C2:C6 ratio) are considered.[17,19] This knowledge will be particularly relevant if pentastarch solutions gain approval from the FDA for use in plasma volume replacement and/or expansion.

REFERENCES

1. Quon CY. Clinical pharmacokinetics and pharmacodynamics of colloidal plasma volume expanders. J Cardiothorac Anesth 1988;2:13-23.
2. Lazrove S, Waxman K, Shippy C, Shoemaker WC. Hemodynamic, blood volume, and oxygen transport responses to albumin and hydroxyethyl starch infusions in critically ill postoperative patients. Crit Care Med 1980;8:302-6.
3. Rackow EC, Falk JL, Fein IA, et al. Fluid resuscitation in circulatory shock: a comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. Crit Care Med 1983;11:839-50.
4. Shatney CH, Deepika K, Militello PR, et al. Efficacy of hetastarch in the resuscitation of patients with multisystem trauma and shock. Arch Surg 1983;118:804-9.
5. Rackow EC, Mecher C, Astiz ME, et al. Effects of pen-

tastarch and albumin infusion on cardiorespiratory function and coagulation in patients with severe sepsis and systemic hypoperfusion. Crit Care Med 1989;17:394-8.
6. Brecher ME, Owen HG, Bandarenko N. Alternatives to albumin: starch replacement for plasma exchange. J Clin Apheresis 1997;12:146-53.
7. Rock G, Sutton DM, Freedman J, Nair RC. Pentastarch instead of albumin as replacement fluid for therapeutic plasma exchange. The Canadian Apheresis Group. J Clin Apheresis 1997;12:165-9.
8. Goss GA, Weinstein R. Pentastarch as partial replacement fluid for therapeutic plasma exchange: effect on plasma proteins, adverse events during treatment, and serum ionized calcium. J Clin Apheresis 1999;14:114-21.
9. Sade RM, Crawford FA Jr, Dearing JP, Stroud M. Hydroxyethyl starch in priming fluid for cardiopulmonary bypass. J Thorac Cardiovasc Surg 1982;84:35-8.
10. Sade RM, Stroud MR, Carwford FA Jr, et al. A prospective randomized study of hydroxyethyl starch, albumin, and lactated Ringer's solution as priming fluid for cardiopulmonary bypass. J Thorac Cardiovasc Surg 1985;89:713-22.
11. London MJ, Franks M, Verrier ED, et al. The safety and efficacy of ten percent pentastarch as a cardiopulmonary bypass priming solution. A randomized clinical trial. J Thorac Cardiovasc Surg 1992;104:284-96.
12. Diehl JT, Lester JL III, Cosgrove DM. Clinical comparison of hetastarch and albumin in postoperative cardiac patients. Ann Thorac Surg 1982;34:674-9.
13. Moggio RA, Rha CC, Somberg ED, et al. Hemodynamic comparison of albumin and hydroxyethyl starch in postoperative cardiac surgery patients. Crit Care Med 1983;11: 943-5.
14. Munsch CM, MacIntyre E, Machin SJ, et al. Hydroxyethyl starch: an alternative to plasma for postoperative expansion after cardiac surgery. Br J Surg 1988;75:675-8.
15. London MJ, Ho JS, Triedman JK, et al. A randomized clinical trial of 10% pentastarch (low molecular weight hydroxyethyl starch) versus 5% albumin for plasma volume expansion after cardiac operations. J Thorac Cardiovasc Surg 1989;97:785-97.
16. Mastroianni L, Low HB, Rollman J, et al. A comparison of 10% pentastarch and 5% albumin in patients undergoing open-heart surgery. J Clin Pharmacol 1994;34:34-40.
17. Treib J, Baron JF, Grauer MT, Strauss RG. An international view of hydroxyethyl starches. Intensive Care Med 1999;25:258-68.
18. Treib J, Haass A, Pindur G, et al. All medium starches are not the same: influence of the degree of hydroxyethyl substitution of hydroxyethyl starch on plasma volume, hemorrheologic conditions, and coagulation. Transfusion 1996;36:450-5.
19. Treib J, Haass A, Pindur G, et al. HES 200/0.5 is not HES 200/0.5. Influence of the C2/C6 hydroxyethylation ratio of hydroxyethyl starch (HES) on hemorheology, coagulation and elimination kinetics. Thromb Haemost 1995;74: 1452-6.
20. Strauss RG, Stansfield C, Henriksen RA, Villhauer PJ. Pentastarch may cause fewer effects on coagulation than hetastarch. Transfusion 1988;28:257-60.
21. Stump DC, Strauss RG, Henriksen RA, et al. Effects of hydroxyethyl starch on blood coagulation, particularly factor VIII. Transfusion 1985;25:349-54.
22. Strauss RG, Stump DC, Henriksen RA, Saunders R. Effects of hydroxyethyl starch on fibrinogen, fibrin clot formation, and fibrinolysis. Transfusion 1985;25:230-4.
23. Carr ME Jr. Effect of hydroxyethyl starch on the structure of thrombin- and reptilase-induced fibrin gels. J Lab Clin Med 1986;108:556-61.
24. Strauss RG. Volume replacement and coagulation: a comparative review. J Cardiothorac Anesth 1988;2:24-32.
25. Cope JT, Banks D, Mauney MC, et al. Intraoperative hetastarch infusion impairs hemostasis after cardiac operations. Ann Thorac Surg 1997;63:78-83.
26. Trumble ER Muizelaar JP, Myseros JS, et al. Coagulopathy with the use of hetastarch in the treatment of vasospasm. J Neurosurg 1995;82:44-7.
27. Lockwood DN, Bullen C, Machin SJ. A severe coagulopathy following volume replacement with hydroxyethyl starch in a Jehovah's Witness. Anaesthesia 1988;43:391-3.
28. Chang JC, Gross HM, Jang NS. Disseminated intravascular coagulation due to intravenous administration of hetastarch. Am J Med Sci 1990;300:301-3.
29. Bick RL. Evaluation of a new hydroxyethyl starch preparation (Hextend™) on selected coagulation parameters. Clin Appl Thromb Hemost 1995;1:215-9.
30. Harker LA, Slichter SJ. The bleeding time as a screening test for evaluation of platelet function. N Engl J Med 1972;287:155-9.
31. Rizza CR, Walke W. One stage prothrombin time techniques. In: Bang NU, Beller FK, Deutsch E, et al., eds. Thrombosis and bleeding disorders: therapy and methods. New York: Academic Press, 1971:92-4.
32. Babson AL, Babson SR. Comparative evaluation of a partial thromboplastin reagent containing a non-settling, particulate activator. Am J Clin Pathol 1974;62:856-60.
33. Hardisty RM, MacPherson JC. A one-stage factor VIII (antihemophilic globulin) assay and its use on venous and capillary plasma. Thromb Diath Haemorrh 1962;7:215-29.
34. Laurell CB. Quantitative estimation of proteins by electrophoresis in agarose gel containing antibodies. Anal Biochem 1966;15:45-52.
35. Zimmerman TS, Hoyer LW, Dickson L, Edgington TS. Determination of the von Willebrand's disease antigen (factor VIII-related antigen) in plasma by quantitative immunoelectrophoresis. J Lab Clin Med 1975;86:152-9.
36. Allain JP, Cooper HA, Wagner RH, Brinkhous KM. Platelets fixed with paraformaldehyde: a new reagent for assay of von Willebrand factor and platelet aggregating factor. J Lab Clin Med 1975;85:318-28.

37. Astrup T, Müllertz S. Fibrin plate method for estimating fibrinolytic activity. Arch Biochem 1952;40:346-51.
38. Vermylen C, DeVreker RA, Verstraete M. A rapid enzymatic method for assay of fibrinogen fibrin polymerization time (FPT test). Clin Chim Acta 1963;8:418-24.
39. Juhan-Vague I, Moerman B, De Cock F, et al. Plasma levels of a specific inhibitor of tissue-type plasminogen activator (and urokinase) in normal and pathological conditions. Thromb Res 1984;33:523-30.
40. Holvoet P, Cleemput H, Collen D. Assay of human tissue-type plasminogen activator (t-PA) with an enzyme-linked immunosorbent assay (ELISA) based on three murine monoclonal antibodies to t-PA. Thromb Haemost 1985;54: 684-7.
41. Darras V, Thienpont M, Stump DC, Collen D. Measurement of urokinase-type plasminogen activator (u-PA) with an enzyme-linked immunosorbent assay (ELISA) based on three murine monoclonal antibodies. Thromb Haemost 1986;56:411-4.
42. Merskey C, Lalezari P, Johnson AJ. A rapid, simple, sensitive method for measuring fibrinolytic split products in human serum. Exp Biol Med 1969;131:871-5.
43. Edy J, De Cock F, Collen D. Inhibition of plasmin by normal and antiplasmin-depleted human plasma. Thromb Res 1976;8:513-8.
44. Ranby M, Norrman B, Wallen P. A sensitive assay for tissue plasminogen activator. Thromb Res 1982;27:743-9.
45. Wiman B, Mellbring G, Ranby M. Plasminogen activator release during venous stasis and exercise as determined by a new specific assay. Clin Chim Acta 1983;127:279-88.