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BASIC RESEARCH STUDIES

From the Midwestern Vascular Surgical Society

Activation of fibrinolytic pathways is associated with duration of supraceliac aortic cross-clamping

Benjamin E. Haithcock, MD,[a] Alexander D. Shepard, MD,[a] Sundra B. K. Raman, MD,[a,b] Mark F. Conrad, MD,[a] Keshav Pandurangi, MD,[a] and **Nervin H. Fanous, MD,[a]** *Detroit, Mich*

Purpose: **The cause of the coagulopathy seen with supraceliac aortic cross-clamping (SC AXC) is unclear. SC AXC for 30 minutes results in both clotting factor consumption and activation of fibrinolytic pathways. This study was undertaken to define the hemostatic alterations that occur with longer intervals of SC AXC.**

Methods: **Seven pigs underwent SC AXC for 60 minutes. Five pigs that underwent infrarenal aortic cross-clamping (IR AXC) for 60 minutes and 11 pigs that underwent SC AXC for 30 minutes served as controls. No heparin was used. Blood samples were drawn at baseline, 5 minutes before release of the aortic clamp, and 5, 30, and 60 minutes after unclamping. Prothrombin time, partial thromboplastin time, platelet count, and fibrinogen concentration were measured as basic tests of hemostatic function. Thrombin-antithrombin complexes were used to detect the presence of intravascular thrombosis. Fibrinolytic pathway activation was assessed with levels of tissue plasminogen activator antigen and tissue plasminogen activator activity, plasminogen activator inhibitor-1 activity, and α2-antiplasmin activity. Statistical analysis was performed with the Student *t* test and repeated measures of analysis of variance.**

Results: **Prothrombin time, partial thromboplastin time, and platelet count did not differ between groups at any time. Fibrinogen concentration decreased 5 minutes ($P = .005$) and 30 minutes ($P = .006$) after unclamping in both SC AXC groups, but did not change in the IR AXC group. Thrombin-antithrombin complexes increased in both SC AXC groups, but were not significantly greater than in the IR AXC group. SC AXC for both 30 and 60 minutes produced a significant increase in tissue plasminogen activator antigen during clamping and 5 minutes after clamping. This increase persisted for 30 and 60 minutes after clamp release in the 60-minute SC AXC group. Tissue plasminogen activator activity, however, increased only in the 60-min SC AXC group during clamping ($P = .02$), and 5 minutes ($P = .05$) and 30 minutes ($P = .06$) after unclamping, compared with both control groups.**

Conclusions: **Thirty and 60 minutes of SC AXC results in similar degrees of intravascular thrombosis and fibrinogen depletion. Although SC AXC for both 30 and 60 minutes leads to activation of fibrinolytic pathways, only 60 minutes of SC AXC actually induces a fibrinolytic state. Fibrinolysis appears to be an important component of the coagulopathy associated with SC AXC, and is related to the duration of aortic clamping. (J Vasc Surg 2004;40:325-33.)**

Clinical Relevance: **The coagulopathy frequently associated with thoracoabdominal aortic aneurysm repair is thought to revolt visceral ischemia-reperfusion. The nature of this coagulopathy is controversial. The current study demonstrates that the major hemostatic alteration associated with supraceliac aortic cross-clamping is activation of fibrinolytic pathways. The magnitude of this fibrinolytic response is directly related to the duration of supraceliac aortic occlusion. Future efforts to treat this coagulopathy may well include judicious use of autofibrinolytic agents.**

Aortic cross-clamping proximal to the celiac trunk is frequently necessary during complex procedures on the thoracoabdominal aorta. Excessive bleeding is common during these procedures, and can be a source of significant morbidity and mortality. As many as 25% of early deaths after thoracoabdominal aneurysm (TAAA) repair result from bleeding complications.[1,2] Bleeding is also thought to be a significant contributor to multisystem organ dysfunction, which is the most common cause of perioperative death after TAAA repair. In most cases this bleeding is the result of a diffuse coagulopathy that is thought to be related to visceral ischemia-reperfusion.[3-5]

The nature of this coagulopathy is unclear, and there are only limited studies in the literature. In the late 1980s Cohen et al[3] suggested that the cause was disseminated intravascular coagulation (DIC). Using a canine model, they showed that 60 and 90 minutes of supraceliac aortic cross-clamping (SC AXC) was associated with a decrease in platelet count and fibrinogen concentration, and prolonga-

From the Department of Surgery, Division of Vascular Surgery[a] and Department of Pathology,[b] Henry Ford Hospital.

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Reprint requests: Alexander D. Shepard, MD, Division of Vascular Surgery, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202 (e-mail: ashepar2@hfhs.org).

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tion of prothrombin time (PT) and partial thromboplastin time (PTT).[3] These hemostatic alterations were prevented with continuous arterial perfusion of the superior mesenteric artery (SMA) during prolonged cross-clamping.[4] This work has been criticized because of lack of specificity of the studies used to document DIC. Nearly a decade later, Illig et al[5] published a study that suggested that SC AXC induces primary fibrinolysis. Using a population of patients undergoing elective aortic reconstruction, they demonstrated elevated levels of tissue plasminogen activator (t-PA) and reduced levels of α2-antiplasmin (α2-AP) in patients undergoing SC AXC. However, only t-PA antigen (t-PA Ag) was measured in this study, and not t-PA activity; recent data have proved that elevated t-PA Ag levels alone can be misleading in determining the presence of fibrinolysis, because t-PA Ag reflects both active and inactive forms of t-PA.[6-8]

Previous work in our laboratory has demonstrated that SC AXC for 30 minutes results in both intravascular thrombosis with factor (primarily fibrinogen) consumption and activation of fibrinolytic pathways.[9,10] Although SC AXC for 30 minutes did activate fibrinolysis, as determined by a marked increase in t-PA Ag, it did not induce a fibrinolytic state; t-PA activity levels remained normal. The current study was undertaken to determine whether longer intervals of supraceliac aortic occlusion would lead to more pronounced factor consumption, more significant fibrinolysis, or both.

METHODS

Market pigs weighing 25 to 35 kg were used for the study. A porcine model was chosen because of the known similarities of its coagulation physiology with that in human beings.[11,12] Pigs were tested for von Willebrand disease before selection for study. Animals were sedated, and underwent general endotracheal anesthesia with 1% to 2% isoflurane. A right neck cutdown was performed for placement of monitoring and sampling catheters. A pulmonary artery catheter was placed through the jugular vein and advanced under fluoroscopy into the correct position. This catheter was used to ensure optimal hemodynamics during the experiment. An arterial line was placed in the carotid artery. Warming blankets and warmed intravenous fluids were used to maintain normothermia. Lactated Ringer solution was infused at a rate of 5 to 10 mL/kg/hr to keep the animals hydrated. Intermittent boluses were used as necessary to maintain hemodynamic stability. Other monitoring included pulse oximetry and continuous electrocardiography.

Each pig underwent a midline celiotomy. Before dissection, a Foley catheter was inserted into the bladder to help in monitoring volume status. The aorta was then dissected and controlled above the celiac trunk, just below the renal arteries and above the aortic trifurcation. During aortic clamping the aorta was occluded proximally at the designated clamp site and distally just above the trifurcation. Seven pigs underwent SC AXC for 60 minutes. Control groups consisted of 5 pigs that underwent infrarenal aortic cross-clamping (IR AXC) for 60 minutes and 11 pigs that underwent SC AXC for 30 minutes. After unclamping, the animals were observed for 1 hour. No heparin was used. Blood samples were obtained from the arterial line before cross-clamping as baseline measurements, 5 minutes before cross-clamp release, and 5, 30, and 60 minutes after cross-clamp release. Blood samples were immediately transported to the hematopathology laboratory for processing. After the last blood sample was drawn, animals were sacrificed according to institutional protocol.

Blood samples were collected in tubes containing 0.5 mL of 0.5 mol/L citrate buffer, pH 4.3 (Stabilyte; Biopool International), 0.5 mL of 0.11 mol/L sodium citrate (BD Vacutainer), and 15% (K3) ethylenediamine tetra-acetic acid (BD Vacutainer). Plasma was isolated within 30 to 60 minutes by means of centrifugation at 1500 $\times g$ for 15 minutes, aliquoted, and frozen at $-30°C$. Before freezing the citrated aliquots for the specialized assays, samples were screened for basic coagulation tests including PT, PTT, and fibrinogen concentration. Platelet count and hematocrit were determined with a Coulter AcT8 (Coulter Corp). The sodium- citrated samples were used to measure thrombin-antithrombin complexes (TAT) with the Enzygnost TAT microenzyme immunoassay (Dade Behring). An enzyme-linked immunosorbent assay (TintElize t-PA; Biopool International) was used for quantitative determination of t-PA Ag. Assessment of t-PA activity and plasminogen activator inhibitor-1 activity (PAI-1) was accomplished with a chromogenic assay (Spectrolyze/fibrin; Biopool International). α2-AP activity was measured with the STA-Stachrom Antiplasmin chromogenic assay (Diagnostica Stago).

All results are expressed as mean ± SEM. A repeated measures analysis of variance (ANOVA) model was used to test for any significant differences over time in each of the three groups. When there were statistically significant overall time differences ($P < .05$), pairwise comparisons were used to determine where the significant time differences were via paired testing. When significant group by time interactions were observed, the Student *t* test was performed to look for differences at each time point between groups. For all pairwise comparisons, the Hochberg method was used to adjust *P* values for multiple comparisons. The package used for statistical analysis was SAS (SAS Institute Inc).

This experiment was approved by the Henry Ford Hospital Care of Experimental Animals Committee, and conformed with the *Guide for the Care and Use of Laboratory Animals.*

RESULTS

A summary of the data analysis from this study is presented in the Table.

Basic coagulation test. There was no significant change in PTT or platelet count from baseline in any of the study groups. PT was prolonged in the 30- minute SC AXC group just after unclamping ($P = .005$), and remained prolonged 30 and 60 minutes after unclamping ($P = .005$,

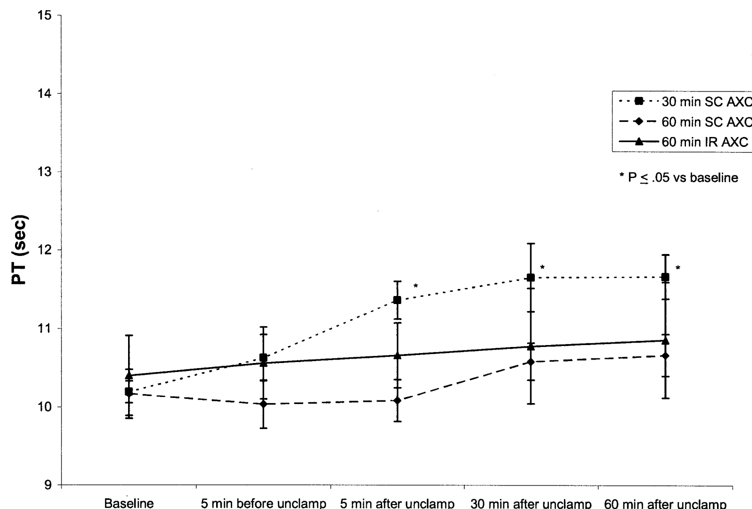

Fig 1. Prothrombin time *(PT)* in the 30- minute and 60-minute supraceliac aortic cross-clamping groups *(SC AXC)* and the 60-minute infrarenal aortic cross clamping group *(IR AXC)*.

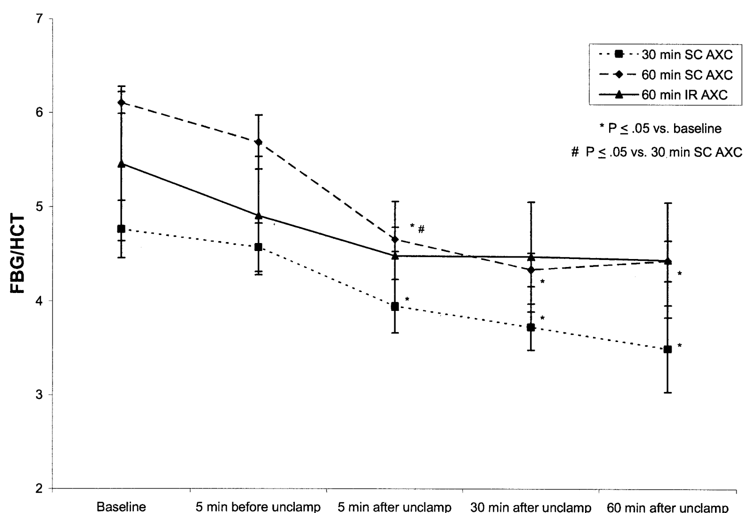

Fig 2. Fibrinogen *(FBG)* levels in the 30-minute and 60-minute supraceliac aortic cross-clamping groups *(SC AXC)* and the 60-minute infrarenal aortic cross clamping group *(IR AXC)*. Fibrinogen concentration was corrected for dilution with hematocrit *(HCT)*.

ANOVA; Fig 1). However, when compared with the other two groups at *t* testing, these changes were not significant.

There was a significant decrease in fibrinogen concentration (corrected for dilution) in both the 30-minute ($P <$ .001, ANOVA) and 60-minute ($P < .001$, ANOVA) SC AXC groups (Fig 2). This decrease began just after unclamping, and continued throughout the remainder of the experiment in both groups. The decrease in fibrinogen concentration was greater in the 60-minute SC AXC group compared with the 30-minute SC AXC group ($P = .03$) only at 5 minutes after unclamping. There was no change in fibrinogen concentration in the IR AXC group.

Markers of thrombosis. TAT complexes increased in both SC AXC groups during the period of aortic clamping, and returned to baseline after clamp release; however, these changes did not reach statistical significance ($P < .18$; Fig 3). There was no change in TAT levels from baseline in the IR AXC group.

Markers of fibrinolysis. There was a significant increase in t-PA Ag levels during the period of aortic clamping in both SC AXC groups ($P < .001$, ANOVA; Fig 4). t-PA Ag levels remained significantly elevated 30 and 60 minutes after clamp release ($P = .034$) with 60 minutes of SC AXC. In the 30-minute SC AXC group t-PA Ag levels

Data analysis (Δ from baseline)

	PTT		PLT		PT		FBG	
	Mean ± SD	P	*Mean ± SD*	P	*Mean ± SD*	P	*Mean ± SD*	P
60-Min SC AXC								
5 Min before unclamping	–0.67 ± 3.50	≥.29	–0.52 ± 0.51	≥.73	–0.13 ± 0.45	≥.06	–0.35 ± 0.53	>.05
5 Min after unclamping	–0.83 ± 2.14	≥.29	1.38 ± 4.27	≥.73	–0.08 ± 0.38	≥.06	–0.43 ± 2.44	<.01
30 Min after unclamping	0.00 ± 2.97	≥.29	1.09 ± 4.46	≥.73	0.42 ± 0.47	≥.06	–0.75 ± 2.13	<.01
60 Min after unclamping	–1.83 ± 3.31	≥.29	0.88 ± 4.92	≥.73	0.50 ± 0.46	≥.06	–0.66 ± 2.10	<.01
30-Min SC AXC								
5 Min before unclamping	0.60 ± 2.91	≥.12	1.28 ± 0.41	≥.05	0.18 ± 0.58	≥.05	–0.19 ± 0.36	>.05
5 Min after unclamping	1.70 ± 3.37	≥.12	0.94 ± 0.3	≥.05	1.02 ± 0.52	<.01	–0.87 ± 0.38	<.01
30 Min after unclamping	2.80 ± 3.29	≥.12	1.35 ± 0.43	≥.05	1.38 ± 1.36	<.01	–1.01 ± 0.37	<.01
60 Min after unclamping	1.00 ± 2.83	≥.12	1.16 ± 0.37	≥.05	1.15 ± 0.89	<.01	–1.12 ± 0.87	<.01
60-Min IR AXC								
5 Min before unclamping	–0.60 ± 0.55	≥.72	4.43 ± 2.56	≥.06	0.16 ± 0.27	≥.44	2.3 ± 2.28	>.05
5 Min after unclamping	–0.60 ± 1.14	≥.72	4.28 ± 2.47	≥.06	0.26 ± 0.46	≥.44	2.1 ± 2.08	>.05
30 Min after unclamping	0.00 ± 3.16	≥.72	4.00 ± 2.31	≥.06	0.38 ± 0.79	≥.44	2.1 ± 2.07	>.05
60 Min after unclamping	–0.40 ± 2.51	≥.72	4.05 ± 2.34	≥.06	0.46 ± 0.82	≥.44	2.1 ± 2.03	>.05

SC AXC, Supraceliac aortic cross-clamping; *IR AXC,* infrarenal aortic cross-clamping.

rapidly returned to baseline with unclamping. There was no change in t-PA Ag levels in the IR AXC group at any time point.

To determine whether this increase in t-PA Ag was associated with a fibrinolytic state, t-PA activity was also measured. In the 60-minute SC AXC group, t-PA activity increased during the period of aortic occlusion, remained elevated 5 minutes after clamp release (P = .012), and decreased toward baseline by 30 minutes after unclamping (Fig 5). There was no significant change in t-PA activity from baseline in either the 30-minute SC AXC group or the IR AXC group.

A non-significant decrease in PAI-1 levels occurred in both SC AXC groups up to 30 minutes after clamp release (Fig 6). By 60 minutes after unclamping, PAI-1 had increased above baseline in both SC AXC groups, but this change was only significant in the 30-minute SC AXC group ($P < .001$, ANOVA). In comparison with the 60-minute SC AXC group, this rise was not significant at t testing. There was no significant change in PAI-1 levels in the IR AXC group. α2-AP activity levels decreased from baseline 5 and 30 minutes after unclamping in both SC AXC groups ($P < .01$, ANOVA), but returned toward baseline 60 minutes after cross-clamp release (Fig 7). There was no significant change in the IR group.

DISCUSSION

The nature of the coagulopathy associated with SC AXC remains controversial. While most authorities agree that intravascular thrombosis with factor consumption or depletion, so called DIC, has an important role,[3,4,13] others believe that fibrinolysis is the major culprit.[2,5] The evidence that fibrinolysis occurs with SC AXC is limited. In a series of 33 patients undergoing TAAA repair Godet et al[2] noted severe bleeding complications in 8 patients; these patients had significantly higher levels of t-PA and lower levels of α2-AP both during the period of SC AXC and shortly after restoration of visceral perfusion, compared with the 25 patients who did not bleed. Illig et al[5] demonstrated similar changes in a group of patients undergoing elective abdominal aortic reconstruction. A previous study from our laboratory documented the presence of both factor consumption and increased t-PA Ag levels with 30 minutes of supraceliac aortic occlusion. t-PA activity, however, did not increase, which suggests that normal regulatory mechanisms (PAI-1 inactivation, hepatic clearance) are capable of controlling the fibrinolytic pathway activation resulting from SC AXC for 30 minutes.[9] The current study was designed to document the hemostatic alterations that occur with longer durations of supraceliac aortic occlusion.

SC AXC for both 30 and 60 minutes led to significant fibrinogen depletion in this study. The cause of this deple-

(Table continued)

TAT		t-PA Ag		t-PA act		PAI-1		α2-AP	
Mean ± SD	P	*Mean ± SD*	P	*Mean ± SD*	P	*Mean ± SD*	P	*Mean ± SD*	P
11.43 ± 17.81	≥.18	9.17 ± 5.36	.03	37.38 ± 29.60	.01	–1.43 ± 5.29	≥.11	0.17 ± 10.61	>.05
14.90 ± 20.67	≥.18	9.37 ± 8.50	>.05	32.25 ± 20.54	.01	–4.33 ± 5.06	≥.11	–17.33 ± 8.57	.01
13.50 ± 19.94	≥.18	8.08 ± 4.91	.03	15.92 ± 20.04	>.05	–0.13 ± 8.21	≥.11	–16.83 ± 7.0	.01
10.60 ± 21.14	≥.18	6.15 ± 3.51	.03	−0.10 ± 4.37	>.05	6.65 ± 9.38	≥.11	–10.33 ± 14.36	>.05
25.04 ± 39.05	≥.16	6.13 ± 2.90	<.01	8.99 ± 14.72	≥.94	–2.16 ± 5.83	≥.05	–4.00 ± 6.06	>.05
30.01 ± 44.13	≥.16	3.26 ± 1.80	>.05	9.86 ± 20.17	≥.94	–4.69 ± 6.62	≥.05	–16.00 ± 4.03	.04
5.75 ± 22.22	≥.16	0.92 ± 2.07	>.05	–3.71 ± 5.31	≥.94	–4.11 ± 5.03	≥.05	–17.3 ± 8.39	.04
8.04 ± 13.12	≥.16	–.22 ± 1.49	>.05	–4.06 ± 8.09	≥.94	4.00 ± 6.49	≥.05	–10.1 ± 14.71	>.05
–1.84 ± 8.66	≥.24	–0.64 ± 1.15	≥.27	–4.12 ± 16.74	≥.17	10.24 ± 7.88	≥.15	–2.8 ± 4.09	≥.09
–2.04 ± 12.98	≥.24	–0.04 ± 1.11	≥.27	–10.52 ± 11.31	≥.17	7.98 ± 13.06	≥.15	–8.4 ± 7.54	≥.09
–9.16 ± 6.25	≥.24	–0.64 ± 1.14	≥.27	–10.34 ± 10.71	≥.17	9.12 ± 11.29	≥.15	–9.00 ± 5.39	≥.09
–3.30 ± 7.09	≥.24	–0.34 ± 1.13	≥.27	–9.12 ± 9.67	≥.17	11.08 ± 13.65	≥.15	–6.6 ± 9.34	≥.09

tion is unclear, but may well be due to factor consumption resulting from clamp-induced intravascular thrombosis. Elevations of TAT in these two groups compared with the IR AXC group lend support to the theory that SC AXC is associated with a greater microvascular clot burden. Efforts to study this point further were hampered by the absence of accurate assays for porcine D-dimers and other coagulation factors. The lack of significant changes in PT, PTT, or platelet count suggests that this factor consumption was not enough to substantially perturb normal clotting function. In our previous study SC AXC for 30 minutes was associated with a small but significant decrease in platelet count and an increase in PTT 30 minutes after unclamping.[9] Our failure to confirm these findings in the current study is unexplained.

In this study SC AXC resulted in activation of fibrinolytic pathways, the intensity of which was directly related to the duration of aortic occlusion. Clamping for 30 minutes led to a significant increase in t-PA Ag, which fell rapidly back to baseline after unclamping. In contrast, supraceliac occlusion for 60 minutes led to markedly elevated levels of t-PA Ag during clamping, which persisted for up to 60 minutes after unclamping. Similar to our previous study, the elevation in t-PA Ag in the 30-minute group was not associated with an increase in t-PA activity. However, the more pronounced elevations in t-PA Ag in the 60-minute group were associated with marked increases in t-PA activity both during and immediately after the period of aortic occlusion. The changes in PAI-1 (the major circulating inhibitor of t-PA) and α2-AP (the major inhibitor of plasmin) activity levels in the SC AXC groups provide confirmatory evidence for stimulation of fibrinolytic pathways. In our study, PAI-1 activity did drop during the period of aortic occlusion in both SC AXC groups, and remained depressed for up to 30 minutes after unclamping, compared with the IR AXC group, in which it actually increased. Although none of these changes were statistically significant, the trend toward lower PAI-1 levels in the SC AXC groups is probably in response to increased t-PA generation. Similarly, α2-AP activity levels also decreased in both SC AXC groups after unclamping, but remained unchanged in the IR AXC group, no doubt in response to increased plasmin generation from increased t-PA release. These changes reflect activation of serum inhibitors designed to hold the fibrinolytic system in check.

Both t-PA Ag and t-PA activity were measured because recent data show that t-PA Ag alone is not an accurate measure of the presence of fibrinolysis. t-PA Ag detects both active (free t-PA) and inactive (bound by serum inhibitors) forms of t-PA, and is thus a marker only for activation of fibrinolytic pathways. t-PA activity, on the other hand, detects only free t-PA, and is thus a more accurate measure of whether a true fibrinolytic state is present.[6-8]

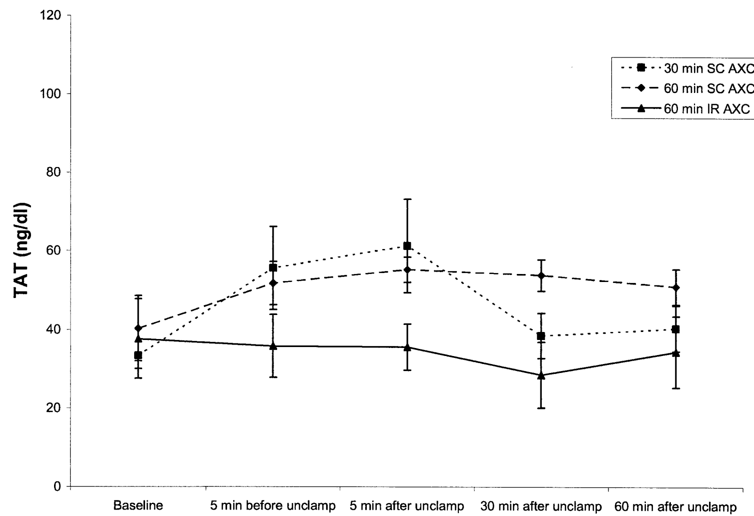

Fig 3. Thrombin-antithrombin complexes *(TAT)* in the 30-minute and 60-minute supraceliac aortic cross-clamping groups *(SC AXC)* and the 60-minute infrarenal aortic cross clamping group *(IR AXC)*.

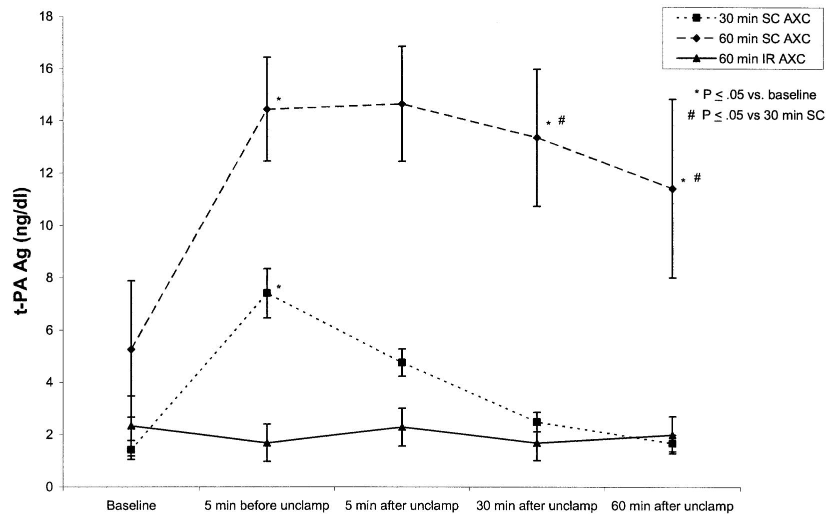

Fig 4. Tissue plasminogen activator antigen *(t-PA Ag)* in the 30-minute and 60-minute supraceliac aortic cross-clamping groups *(SC AXC)* and the 60-minute infrarenal aortic cross clamping group *(IR AXC)*.

The position of the aortic clamp also correlates with the degree of fibrinolytic pathway activation. In this study, IR AXC was associated with no change in t-PA activity, t-PA Ag, or their plasma inhibitors. These findings point to the importance of the liver in regulating the fibrinolytic system. First-pass hepatic clearance of t-PA is as important as serum inhibitors in controlling t-PA activity.[6] SC AXC markedly reduces hepatic perfusion and eliminates this regulatory pathway. In addition, because the liver is a major site for PAI-1 production, hepatic ischemia can also potentially reduce the pool of available serum inhibitors. Illig et al[5] likened the changes attendant with SC AXC to those occurring during the anhepatic phase of liver transplantation. In this setting, enhanced t-PA release and decreased hepatic clearance lead to bleeding complications from unregulated fibrinolysis.[14] The importance of reduced hepatic clearance has been highlighted in studies that compared heterotopic with orthotopic liver transplantation. Elevated t-PA levels common to orthotopic transplantation are not found with heterotopic transplantation when the host liver is not removed.[15] The results of the current study suggest that PAI-1 and other serum inhibitors are adequate to hold the fibrinolytic system in check with supraceliac occlusion of short duration (≤30 minutes); however, with longer periods of SC AXC these compensatory mechanisms are overwhelmed, leading to the presence of a fibrinolytic state.

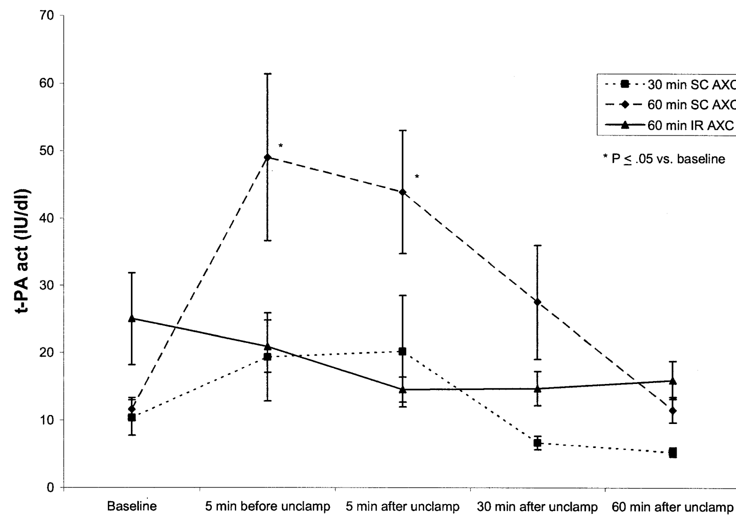

Fig 5. Tissue plasminogen activator activity *(t-PA act)* in the 30-minute and 60-minute supraceliac aortic cross-clamping groups *(SC AXC)* and the 60-minute infrarenal aortic cross clamping group *(IR AXC)*.

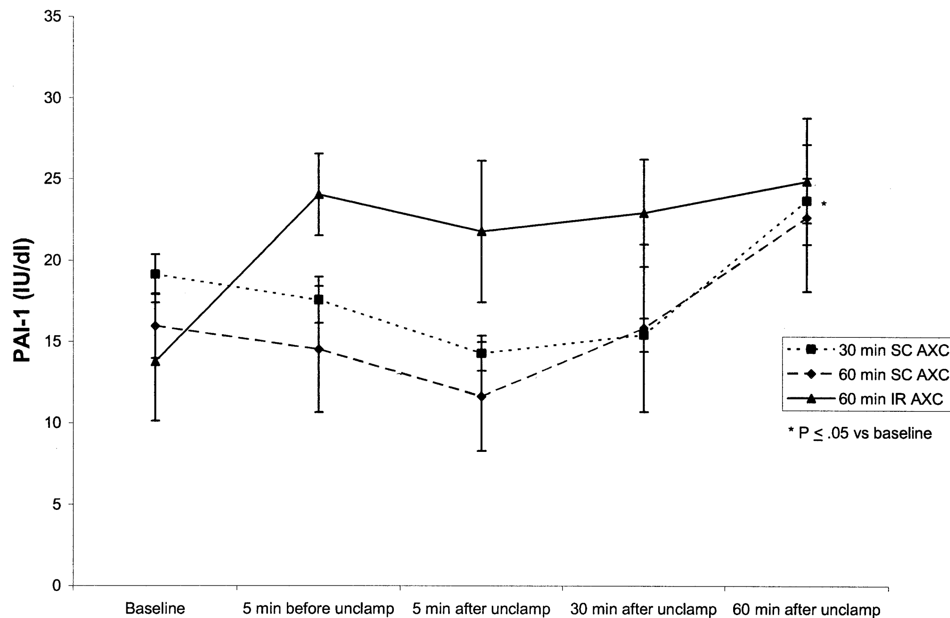

Fig 6. Plasminogen activator inhibitor activity *(PAI-1)* in the 30-minute (min) and 60-minute supraceliac aortic cross-clamping groups *(SC AXC)* and the 60-minute infrarenal aortic cross clamping group *(IR AXC)*.

The mechanism by which SC AXC leads to enhanced t-PA release is not clear. Two possibilities seem likely. The first is that t-PA release occurs with induction of tissue ischemia. Schneiderman et al[16,17] documented that acute ischemia leads to a rapid rise in t-PA activity resulting from the release of stored t-PA in ischemic tissue beds. In addition, they also demonstrated that acute ischemia can increase t-PA gene expression in distant well-perfused tissues, which suggests that non-ischemic tissues may be induced to produce more sustained t-PA levels by humoral mediators released from the ischemic site.[17] The more proximal the site of aortic occlusion and the longer the duration of clamping, the larger the ischemic tissue burden and the greater the production of t-PA. The second possibility is that the presence of intravascular clot leads to an appropriate and protective activation of the fibrinolytic system. So-called secondary fibrinolysis is believed to be the cause of the fibrinolytic changes seen with DIC.[18,19] Which

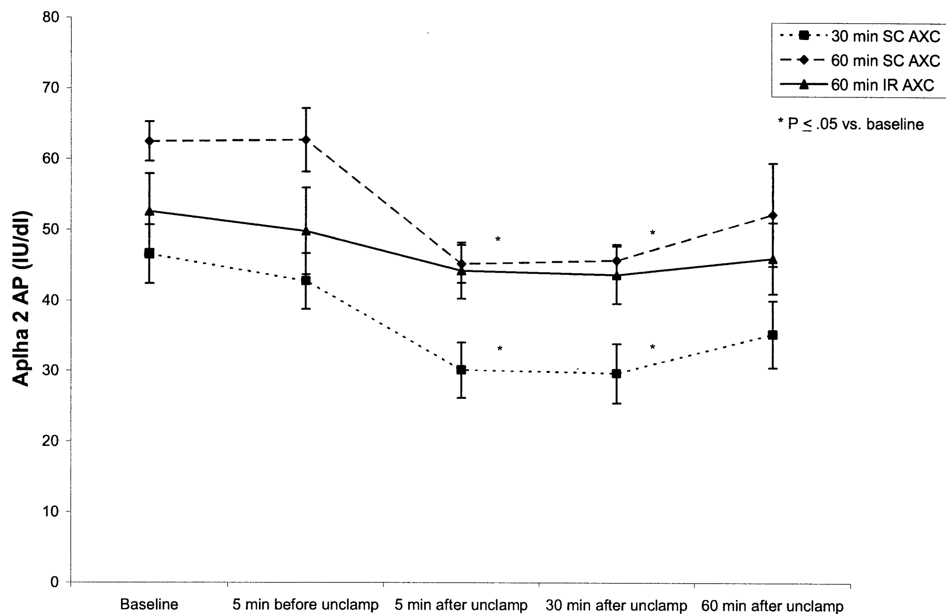

Fig 7. α2-Antiplasmin activity *(α2-AP)* in the 30-minute and 60-minute supraceliac aortic cross-clamping groups *(SC AXC)* and the 60-minute infrarenal aortic cross clamping group *(IR AXC)*.

mechanism is dominant is unclear; both probably have a role in the activation of fibrinolytic pathways with SC AXC. Measurement of D-dimers would have been helpful to answer the question; elevated D-dimers would be expected in the presence of intravascular thrombus. Currently available assays for D-dimers do not have good porcine reactivity. Regardless of cause, t-PA Ag levels rise dramatically with SC AXC in a time-dependent manner.

There are several limitations to this study. A larger sample size would assist in determining whether the trends associated with the various measured factors, such as TAT, PAI-1, or α2-AP, were significant. With the current sample size we only had enough power to detect fairly large differences, as in t-PA activity. Even though there were no obvious bleeding abnormalities with these experiments, this was difficult to quantify. In addition, we used a porcine model to conduct the experiments. The advantage of this model is that the proteins and biochemical factors are not greatly different from those in human beings. In terms of coagulation parameters, factors I, II, XI, XIII, fibrinogen, antithrombin III, TAT, t-PA, PAI-1, and protein C are present at levels near those in human beings. Pigs have higher levels of factors V, VII, VIII, IX, X, and XII than in human beings. Also, D-dimers do not have good porcine reactivity.[12] Despite these limitations for this model, we believe it is adequate to examine hemostatic modifications.

Whether the fibrinolytic pathway activation demonstrated in this study is a primary or secondary phenomenon, the major cause would appear to be visceral ischemia-reperfusion. Svensson et al[20] recognized the importance of minimizing visceral clamp times in the prevention of bleeding complications with TAAA repair. In the late 1980s Cohen et al[4] documented in a canine model that continuous arterial perfusion of the SMA prevented the hemostatic alterations associated with SC AXC. More recently Cambria et al[21] suggested that in-line shunting to the celiac trunk or SMA during TAAA can reduce coagulopathic bleeding complications. We have had some anecdotal success with continuous cold perfusion of the SMA during TAAA repair (similar to the cold renal artery perfusion used for preservation of renal function[20,21]) in reducing the requirement for clotting factors. Regardless of the method used (shortening clamp times, visceral artery perfusion), efforts to minimize the magnitude of visceral ischemia-reperfusion should help to avert the hemostatic aberrations seen with SC AXC. The current data also support the possibility that antifibrinolytic agents, as suggested by Illig et al[5] and discounted by us,[9] may be helpful in treating this coagulopathy.

In conclusion, our data demonstrate that SC AXC results in both intravascular thrombosis and fibrinogen consumption that is not seen with IR AXC. In addition, SC AXC leads to activation of the fibrinolytic system in a time-dependent manner. With short duration of clamping ($\leq$30 minutes), serum inhibitors can compensate and avert induction of a fibrinolytic state. Longer periods (60 minutes) of supraceliac occlusion, however, result in a much greater accumulation of t-PA, which overwhelms regulatory mechanisms and leads to a fibrinolytic state. Whether fibrinolysis in this setting is a primary or secondary (to intravascular thrombosis) phenomenon is unclear. While SC AXC results in both fibrinogen consumption and t-PA release, with longer periods of clamping fibrinolytic activation rather than factor consumption is the predominant

finding. This unregulated fibrinolytic state appears to be the cause of the coagulopathy associated with SC AXC.

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