Pulmonary Edema After Aneurysm Surgery Is Modified by Mannitol

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Abdominal aortic aneurysmectomy (AAA) results in thromboxane (Tx)A_2 generation, a rise in mean pulmonary artery pressure (MPAP), leukopenia, and noncardiogenic pulmonary edema. This study tests whether mannitol, a hydroxyl radical scavenger, modifies these events. Patients received mannitol 0.2 g/kg (n = 14) or saline (n = 12) intravenously before infrarenal aortic clamping. With saline, 30 minutes after clamping, plasma TxB_2 levels rose from 124 to 290 pg/mL ($p < 0.01$), and MPAP rose from 19 to 27 mmHg ($p < 0.01$). Aortic clamp release led to further increases in plasma TxB_2 to 378 pg/mL ($p < 0.01$) and MPAP to 34 mmHg ($p < 0.01$). The white blood count (WBC) fell from 9800 to 4400/mm^3 ($p < 0.01$). Four to eight hours after surgery, physiologic shunting ($\dot{Q}$[sc]S[xsc]/$\dot{Q}$[sc]T[xsc]) rose from 9% to 20% ($p < 0.01$) and peak inspiratory pressure (PIP) increased from 22 to 32 cmH_2O ($p < 0.01$). Chest radiography demonstrated pulmonary edema while the pulmonary wedge pressure was 12 mmHg, excluding left ventricular failure. By 24 hours pulmonary edema resolved and the PIP and P_aO_2 returned to baseline. Mannitol treatment relative to saline, during and after aortic clamping reduced plasma TxB_2 levels to 155 and 198 pg/mL, respectively ($p < 0.01$); MPAP to 21 and 26 mmHg ($p < 0.01$); minimized the decline in WBC to 5850/mm^3 ($p < 0.01$), and the postoperative rise in $\dot{Q}$[sc]S[xsc]/$\dot{Q}$[sc]T[xsc] to 12%, and PIP to 28 cmH_2O (both $p < 0.01$). Chest radiography showed no pulmonary edema. Finally *in vitro* studies documented that mannitol 1 to 10^{-4}M, but not dextrose, in a dose-dependent manner inhibited Tx synthesis by ADP-activated platelets. These data indicate that mannitol maintains pulmonary function after AAA by limiting ischemia-induced thromboxane synthesis.

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REPERFUSION OF ISCHEMIC tissue during abdominal aortic aneurysmectomy (AAA) results in thromboxane (Tx) generation with subsequent pulmonary hypertension and later nonhydrostatic or increased permeability pulmonary edema.[1] Studies in experimental animals have demonstrated that this ischemia-induced lung injury is dependent, in large part, on Tx and neutrophils.[2-4] Thromboxane is an important mediator of this event because inhibition of Tx synthesis or the blockade of Tx receptors[3] prevents pulmonary edema. Although cyclooxygenase inhibitors will limit Tx synthesis and may prevent the lung injury, their clinical application is limited because of the potential of these drugs to aggravate renal failure.[5]

Current evidence also suggests that other potentially toxic agents, such as oxygen-free radicals (OFR), are generated on ischemia and reperfusion.[6] Thus a number of studies document the protective effect of free-radical antagonists and scavengers not only in limiting the local injury after myocardial, intestinal, or renal ischemia[7-9] but also in limiting the pulmonary injury following lower torso ischemia.[10] Further the hydroxyl radical scavenger mannitol[11] has proved effective in reducing pulmonary injury after bilateral hindlimb ischemia in rats.[12] This study was designed to test the ability of mannitol to modify the lung injury in humans following AAA.

Materials and Methods

An open, randomized series of 26 consecutive patients undergoing elective infrarenal abdominal aortic aneurysmectomy and reconstruction with a tube graft formed the study group. Before surgery all patients had arterial and flow-directed 7 French pulmonary arterial catheters (Ab-

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bott Critical Care Catheters, N. Chicago, IL) inserted. General anesthesia was used after intramuscular premedication with 0.04 mg/kg medazolam or 0.14 mg/kg morphine sulphate. All patients were paralyzed and mechanically ventilated. They were maintained with fentanyl, oxygen, and nitrous oxide. After induction of anesthesia, crystalloid was infused to maintain a high PAWP between 10 and 12 mmHg, a technique shown to prevent large fluctuations in cardiac output during surgery.[13] Each patient received 5000 μ heparin intravenously just before application of the aortic cross clamp. An average of 0.5 units of packed red cells was transfused during aortic clamping. The remaining blood, including cell-saver blood (Autotrans, Electromedics Inc., Englewood, CO), was given at the time of wound closure through a 40μ Pall filter (Pall Corp., Glenn Cove, NY). After operation patients were gradually weaned from the ventilator and all were extubated by 24 hours.

Patients were randomized to receive 0.2 g/kg mannitol (Abbott Laboratories, N. Chicago, IL) (n = 14) or a similar volume (30 mL) of normal saline (n = 12) intravenously as a short infusion just before application of the aortic crossclamp. Measurements were conducted at the following time periods: (1) before operation; (2) 10 minutes after induction of anesthesia and intubation; (3) 30 minutes after skin incision; (4) 30 minutes after aortic clamping; (5) just before declamping; (6) 3 minutes after clamp removal; (7) at wound closure; (8) hourly for 24 hours after operation.

Hemodynamics

Several variables were monitored. Central venous pressure (CVP), mean pulmonary arterial pressure (MPAP), pulmonary arterial wedge pressure (PAWP), and mean arterial pressure (MAP) were measured with strain-gauge transducers (Trantec, Model 800, Bentley Trantec, Anasco, Puerto Rico). The values were taken at end-exhalation. Pulse rate was counted from the arterial wave form. Cardiac output (CO) measurements were performed in triplicate using the thermodilution technique.

Hematology

Platelet and white blood cell counts were assayed on arterial blood using phase microscopy.

Prostanoids

Plasma concentrations of TxB_2 and 6-ketoprostaglandin(PG)$F_{1\alpha}$, the stable hydrolysis products of TxA_2 and prostacyclin, respectively, were measured with a double radioimmunoassay[14,15] using an antibody whose cross-reactivity with heterologous prostanoids was less than 1%. Blood was drawn into tubes containing ethylene diamine tetracetic acid and aspirin. The blood was centrifuged at 1500 × g for 20 minutes and the plasma was separated and stored at −20 C until assayed.

Pulmonary Function

Mixed venous and arterial blood samples were analyzed for PO_2, PCO_2, and pH using Clark and Severinghaus electrodes (Instrumentation Laboratory, Model 813, Lexington, MA). Hemoglobin and percentage of saturation were measured spectrophotometrically (Instrumentation Laboratory, Model 282) and the physiological shunt fraction ($\dot{Q}$[sc]S[xsc]/$\dot{Q}$[sc]T[xsc]) was calculated from the Berggren equation.[16] Peak inspiratory pressure was measured at the end of an inspiratory pause while the patient was mechanically ventilated.

Chest Radiography

Radiographs were taken before operation, 4 to 8 hours and 24 hours after operation. All postoperative films were portable and anterioposterior exposures were taken in inspiration with the patient sitting. The x-ray films were interpreted in a blinded fashion by a single roentgenologist (R.P.). The films were assessed with regard to fixed radiologic criteria for edema and each film was assigned a score of 0 to 4 with a grade of zero being normal.

To test the ability of mannitol to inhibit Tx synthesis, an *in vitro* study was conducted. Forty-five mL of blood were obtained from normal human volunteers (n = 14) who had not taken aspirin or other cyclooxygenase inhibitors for ten days. The blood was anticoagulated with 5mL 3.8% sodium citrate and centrifuged at 180 × g for five minutes. Platelet-rich plasma (PRP) was carefully aspirated without disturbing the lower erythrocyte layer and divided into two aliquots. One aliquot was incubated for 30 minutes at 37 C with 0.2 mL mannitol, 1 to 10^{-4} M (n = 7), or dextrose 1 to 10^{-4} M (n = 7), while the other aliquot from the same subject was incubated at 37 with 0.2 mL saline. A platelet count was performed. Duplicate 450 μl samples of treated PRP were activated in a lumiaggregometer (Chronolog Corp., Havertown, PA) with 50 μl 1.0mM adenosine diphosphate (Calbiochem-Behring Corp., La Jolla, CA). After one minute 10 μg of ibuprofen (Upjohn Co., Kalamazoo, MI) was added to stop prostanoid synthesis. The PRP was centrifuged and the supernatant frozen for later assay of TxB_2.

Investigations using human subjects were conducted in conformity with the principles embodied in the Helsinki declaration of 1975, and were approved by the Brigham and Women's Hospital and Harvard Medical School Institutional Review Boards for Human Research.

Data are presented as mean ± standard error in tables and figures. Statistical analysis used an analysis of variance, paired and unpaired t tests, and linear regression. When multiple comparisons were performed, the Bon-

TABLE 1. *Patient Profiles*

Patient Data	Untreated	Mannitol
Number	12	14
Age	73 ± 3	74 ± 6
Sex		
Male	6	9
Female	6	5
Preoperative disease		
Hypertension	5	9
Myocardial ischemia	6	10
Obstructive pulmonary	8	9
Body weight (kg)	74 ± 10	71 ± 12
Aortic cross clamp time (min)	61 ± 15	58 ± 16

* Values are mean ± standard error.

ferroni procedure was applied.[17] Significant difference was accepted if $p < 0.05$.

Results

Patients treated with saline or mannitol were similar with respect to age, sex, body weight, past medical history, and aortic crossclamp time (Table 1). In saline-treated patients, TxB_2 rose from preoperative values of 124 ± 24 pg/mL to 290 ± 68 pg/mL ($p < 0.01$) 30 minutes after aortic occlusion (Fig. 1). At this time there were also increases in MAP from 85 ± 5 to 103 ± 4 mmHg ($p < 0.01$), MPAP from 19 ± 2 to 27 ± 4 mmHg ($p < 0.01$; Fig. 2), and PAWP from 12 ± 2 to 15 ± 2 mmHg ($p < 0.01$). The CO fell from 6.3 ± 0.4 to 3.9 ± 0.8 L/min ($p < 0.01$; Fig. 3). Immediately after aortic occlusion sodium nitroprusside 10 to 30 μg/min was infused into 8 of 12 patients treated with saline. This lowered systemic blood pressure to 88 ± 4 mmHg. At this point CO and MPAP were unchanged. After 30 minutes MPAP had decreased to preclamping levels. In addition white blood cell counts fell from a baseline value of 9800 ± 890/mm^3 to 7600 ± 900/mm^3 ($p < 0.01$; Fig. 4) and platelets fell from 294 ± 25 to 214 ± 43 × 10^3/mm^3 ($p < 0.01$). Hematocrit decreased from preoperative values of 36 ± 4 to 31 ± 3% ($p < 0.01$) due largely to the crystalloid infusion (Table 2).

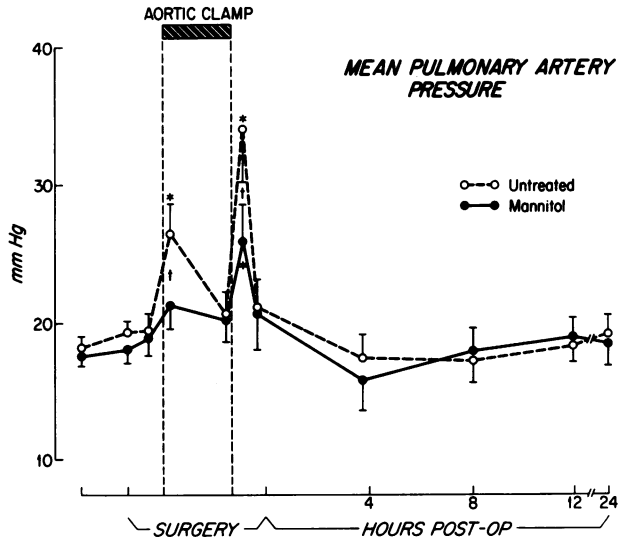

FIG. 2. Mean pulmonary artery pressure rose with aortic clamping and with clamp removal. These increases were blunted by treatment with mannitol before aortic occlusion. Asterisks and daggers refer to significance relative to baseline and between groups, respectively.

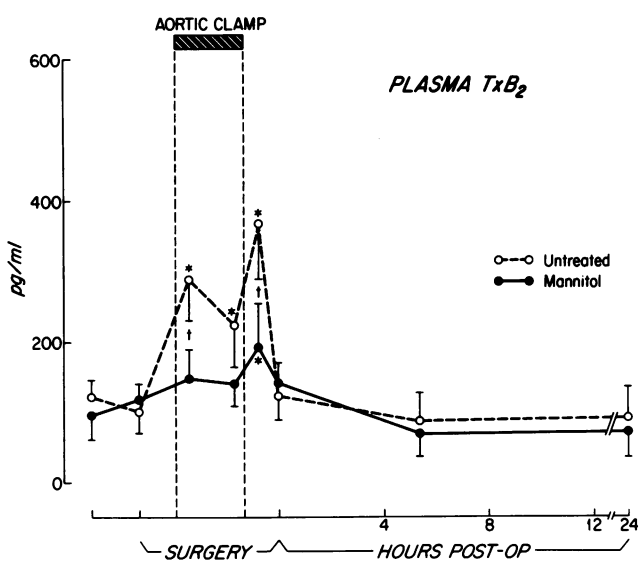

FIG. 1. Aortic crossclamping and clamp removal led to transient increases in plasma TxB_2 levels. Mannitol did not alter baseline plasma TxB_2 levels but reduced ischemia-induced TxB_2 synthesis. Asterisks and daggers refer to significance relative to baseline and between groups, respectively.

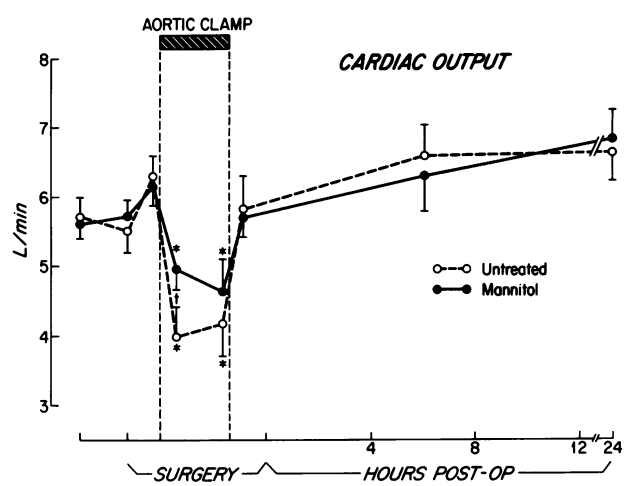

FIG. 3. Cardiac output fell with application of the aortic crossclamp and returned to normal after surgery. Mannitol reduced the magnitude of the fall in cardiac output during aortic occlusion. Asterisks and daggers refer to significance relative to baseline and between groups, respectively.

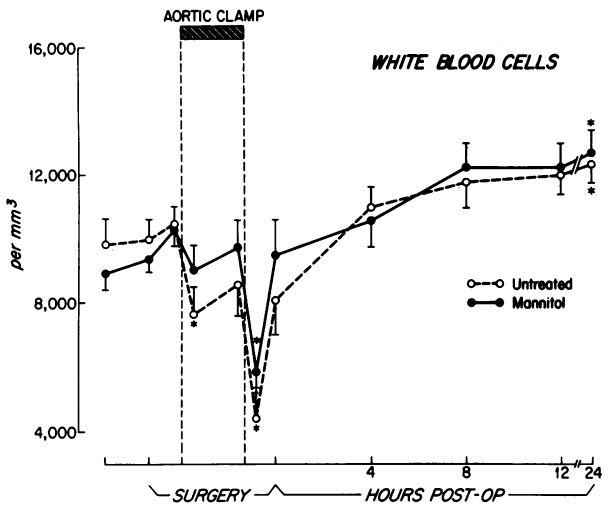

FIG. 4. Transient leukopenia occurred with aortic occlusion and with clamp removal. Mannitol prevented the clamp-induced leukopenia but only attenuated the fall in WBC counts on declamping. Asterisks and daggers refer to significance relative to baseline and between groups, respectively.

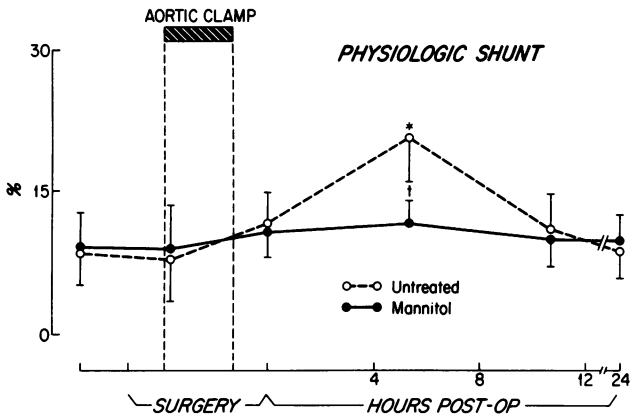

FIG. 5. Postoperative pulmonary dysfunction was manifested by an increase in physiologic shunt four to eight hours after surgery. Mannitol maintained oxygenation. Asterisks and daggers refer to significance relative to baseline and between groups, respectively.

Removal of the aortic crossclamp restored full perfusion to the lower torso. This led to a further increase in TxB_2 levels to 378 ± 105 pg/mL, ($p < 0.01$; Fig. 1) and MPAP to 34 ± 4 mmHg, ($p < 0.01$; Fig. 2). Within 30 minutes of declamping, plasma TxB_2, MPAP and CO had returned to pre-crossclamping levels. MAP and PAWP were not significantly altered during reperfusion. White blood cell and platelet counts fell further during the first ten minutes of reperfusion to 4400 ± 620/mm^3 and 125 ± 13 × 10^3/mm^3, respectively (both $p < 0.01$). The hematocrit was unchanged.

Pulmonary dysfunction occurred in all patients 4 to 8 hours after surgery. This dysfunction was manifested by increases in $\dot{Q}$[sc]S[xsc]/$\dot{Q}$[sc]T[xsc] from 9 ± 2 to 20 ± 6% ($p < 0.01$; Fig. 5) and PIP from 22 ± 2 to 32 ± 2 cm H_2O ($p < 0.01$; Fig. 6). Pulmonary edema was noted in all patients who had chest radiographs 4 to 8 hours after operation: one grade 1, four grade 2, three grade 3, and two grade 4. At this time PAWP was 12 ± 2 mmHg and CO 6.5 ± 0.5 L/min.

Nine of the 14 patients receiving mannitol required a short sodium nitroprusside infusion after aortic occlusion. As in the saline-treated group, MAP was the only variable affected during the infusion. Mannitol treatment before crossclamp application reduced the rise during aortic occlusion and declamping of plasma TxB_2 to 155 ± 55 pg/mL and 198 ± 75 pg/mL, respectively (both $p < 0.01$ relative to saline treatment; Fig. 1); MPAP to 21 ± 2 and 26 ± 3 mmHg respectively, (both $p < 0.01$; Fig. 2). In addition mannitol lessened the decline in CO to 4.9 ± 0.4

TABLE 2. *Fluid Balance*

	Saline	Mannitol
Estimated blood loss	1.7 ± 0.6	1.8 ± 0.2
Intraoperative fluid		
Autologous blood	1.2 ± 0.4	2.0 ± 0.3†
Homologous blood	0.4 ± 0.2	0.5 ± 0.3
Crystalloid	6.4 ± 1.3	6.0 ± 1.4
Colloid‡	0.8 ± 0.3	1.0 ± 0.4
Urine output	0.8 ± 0.1	0.7 ± 0.1
Postoperative fluid		
Crystalloid	4.5 ± 1.2	3.9 ± 1.6
Colloid‡	0.2 ± 0.1	0.3 ± 0.1
Urine output	4.3 ± 1.3	4.2 ± 1.6
Weight gain at 24 hours (kgs)	6.4 ± 0.8	6.6 ± 1.3

* All measurements are in litres unless otherwise stated.
† This value was significantly ($p < 0.05$) higher than the saline group.
‡ These solutions included: salt poor albumin, fresh frozen plasma and plasmanate.

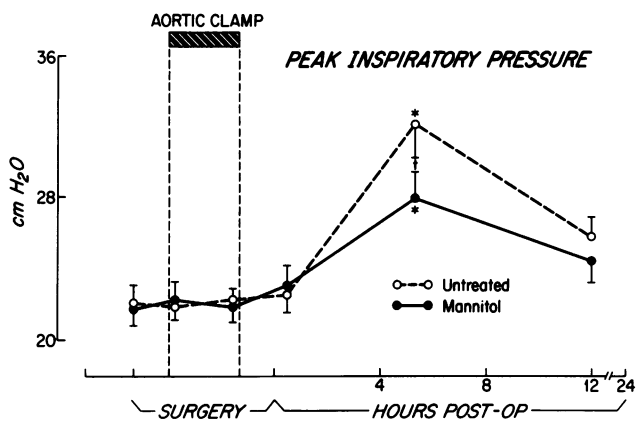

FIG. 6. Decreased postoperative lung compliance was indicated four to eight hours after surgery by an increase in peak inspiratory pressure. Mannitol reduced the ventilation pressures during the period of respiratory dysfunction. Asterists and daggers refer to significance relative to baseline and between groups, respectively.

L/min, ($p < 0.01$; Fig. 3), and white blood cell count to $5850 \pm 460/mm^3$ ($p < 0.01$) on declamping (Fig. 4). The postoperative rise in $\dot{Q}$[sc]S[xsc]/$\dot{Q}$[sc]T[xsc] and PIP was reduced to $12 \pm 2\%$ and 28 ± 2 cmH_2O, respectively (both $p < 0.01$; Figs. 5 and 6). Chest radiography revealed no pulmonary edema in the 11 patients who had chest radiographs four to eight hours after operation (n=11)

In vitro incubation of mannitol in a range of 1 to 10^{-4} M with PRP prevented TxB_2 synthesis in a dose-dependent manner. An equiosmolar solution of dextrose in a similar concentration range was ineffective in preventing Tx synthesis (Fig. 7).

Discussion

This study confirms recent observations that the reperfusion of ischemic tissue during AAA leads to intraoperative pulmonary hypertension, postoperative shunting, increased inspiratory pressure, and pulmonary edema.[1] In animal studies the injury is associated with the entrapment of neutrophils in pulmonary capillaries.[18] Pulmonary edema, although often due to cardiac failure and increased hydrostatic pressure in the pulmonary microvasculature,[19] has been increasingly associated with increased microvascular permeability in settings such as complement activation, aspiration, and oxygen toxicity.[20-22] The noncardiogenic nature of the pulmonary edema following lower torso ischemia and reperfusion was documented in a previous patient study[1] and was again noted here by the finding that PAWP was within normal limits before and during the time that edema was noted. The relationship between lower torso ischemia and increased pulmonary microvascular permeability has also been studied in sheep using the chronic lung lymph fistula preparation with an inflated left atrial balloon.[3] Reperfusion after two hours of bilateral hindlimb tourniquet ischemia led to a sustained increase in lung lymph flow and an increase in the lymph/plasma (L/P) protein ratio, changes that document increased permeability.

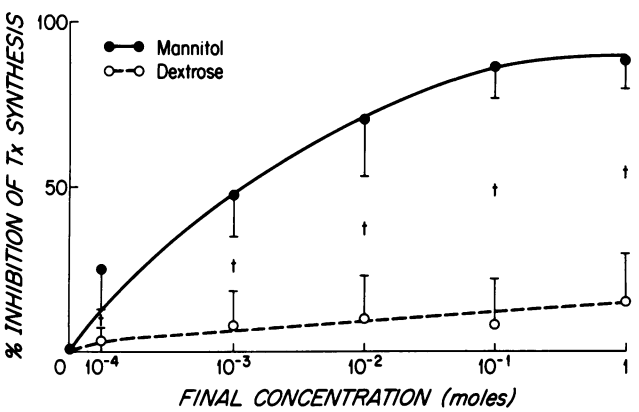

FIG. 7. Mannitol inhibited Tx production by ADP-stimulated platelets in a dose-dependent manner. An equiosmolar solution of dextrose was ineffective. Daggers refer to significance between groups.

In these sheep studies, pulmonary endothelial injury with increased permeability occurred immediately on reperfusion. In the present study pulmonary edema accumulated slowly, its rate of appearance being determined by the imbalance in transvascular fluid efflux and lymphatic clearance. This is probably the reason for the delay in respiratory dysfunction, the rise in $\dot{Q}$[sc]s[xsc]/$\dot{Q}$[sc]t[xsc] and PIP being noted only after four to eight hours (Figs. 5 and 6).

Mannitol's effectiveness in preventing the ischemia-induced lung injury in this setting is most likely due to its ability to decrease ischemia-induced Tx synthesis (Fig. 7). Tx appears to be the central mediator involved. The increase in plasma TxB_2 temporally correlates with the observed pulmonary hypertension in this study, while the increase in lung lymph TxB_2 in animal studies correlates with the increase in pulmonary microvascular permeability.[3] In addition inhibition of Tx synthesis or blockade of Tx receptors prevents the pulmonary hypertension, transient leukopenia, lung leukosequestration, and increase in lung microvascular permeability following lower torso ischemia.[3] Finally infusion of a Tx mimic has been shown to lead to increased permeability in the lungs.

Mannitol inhibits Tx synthesis, as evidenced by the findings in this study of a dose-dependent lowering of Tx production by ADP-stimulated platelets (Fig. 7). This effect may be direct or indirect by the scavenging of free radicals required for Tx synthesis.[24] Thus mannitol is a known scavenger of the OH radical[11] generated with reperfusion of ischemic tissue.[25] In addition mannitol, by scavenging oxygen-free radicals, can prevent their stimulating arachidonic acid breakdown that will lead to a general increase in eicosanoid synthesis. Thus, in addition to a rise in TxB_2 after ischemia, we have reported a rise in plasma leukotriene B_4.[26]

Oxygen-free radicals have been implicated as a cause of the local damage following ischemia in a number of tissues.[6-9] They may also mediate, in part, the pulmonary injury following remote ischemia.[10] This thesis is consistent with the beneficial effects of mannitol, as is the animal studies showing that allopurinol, and superoxide dismutase with catalase, protect sheep from lung injury after hindlimb ischemia.[10] The interpretation of the effects of the free radical scavengers is obscured by the ability of SOD to also inhibit Tx synthesis.[27] Dispite these considerations, the fact that a Tx-receptor antagonist prevents an experimental increase in pulmonary permeability after ischemia is strong evidence against the intermediary role of free radicals. It is possible, however, that the final injurious pathway after the presumed Tx activation of neutrophilis is their release of these vasotoxins. Thus mannitol

inhibits the ischemia-induced neutrophil oxidative burst and consequent H_2O_2 production.[12]

The importance of white blood cells in this setting is emphasized by the protection afforded by rendering animals neutropenic before ischemia.[4] Animal studies indicate that the transient leukopenia on reperfusion and neutrophil activation is Tx dependent.[28] We believe that the subsequent entrapment of PMN in the lungs is also Tx dependent. Thus inhibition of Tx synthesis or blockade of Tx receptors not only prevents leukopenia and the oxidative burst of the neutrophil but also abolishes later pulmonary leukosequestration.[3] In rats subjected to bilateral hindlimb ischemia, mannitol reduces Tx synthesis, PMN activation, lung leukosequestration, and pulmonary injury (unpublished data). The present study suggests that by limiting the rise in Tx, mannitol can moderate the fall in circulating white blood cells (Fig. 4).

Although an osmotic control solution was not infused in this study, the observed effects of mannitol are unlikely to be due to hyperosmolarity or an intraoperative diuresis because urine output and weight gain were the same for the study and control group (Tables 1 and 2). Further in rats equiosmolar sugar solutions have proved ineffective during ischemia, in contrast to mannitol in inhibiting Tx synthesis (Fig. 7).

The lung injury following abdominal aortic aneurysmectomy is prevented by mannitol, probably by its ability to inhibit ischemia-induced Tx synthesis.

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