Stroke rate is markedly reduced after carotid endarterectomy by avoidance of protamine

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Purpose: **Postoperative neurologic injury remains a significant risk of carotid endarterectomy. Mechanisms include embolization of debris and formation of thrombus on the newly endarterectomized surface. We hypothesized that the risk of postoperative neurologic injury would be lower in those patients who did not receive protamine for reversal of heparin anticoagulation.**

Methods: **We reviewed 348 consecutive primary carotid endarterectomies performed since January 1, 1986, to determine the relationship between surgical outcomes and reversal of heparin anticoagulation. Patients undergoing additional simultaneous cardiovascular procedures were excluded. One hundred ninety-three patients received protamine after completion of the endarterectomy. The remaining 155 patients did not receive any protamine.**

Results: **All patients in both groups survived to discharge. There were no strokes in those patients who did not receive any protamine; however, the stroke rate in the protamine group was 2.6% (5 of 193), $p < 0.045$. The incidence of hematoma requiring reexploration was 1.0% (2 of 193) and 1.9% (3 of 155) in the protamine and no-protamine groups, respectively (p = NS). Intraoperative shunting was used more frequently in the no-protamine group (84% vs 67%, $p < 0.001$), and patch angioplasty was performed more frequently in the protamine group (35% vs 15%, $p < 0.001$). However, neither shunting nor patching significantly influenced stroke rates.**

Conclusions: **We conclude that carotid endarterectomy without reversal of heparin anticoagulation is associated with a reduced postoperative stroke rate without a significant increase in morbidity rates. (J VASC SURG 1995;22:264-70.)**

Cerebrovascular disease remains the third leading cause of death in the United States, accounting for 500,000 strokes a year.[1] Because half of all strokes are attributed to carotid artery bifurcation disease, carotid endarterectomy (CEA) has become the most common peripheral vascular operation performed in the United States. Despite significant improvements in patient selection and perioperative management, however, postoperative stroke remains a potentially devastating complication for 2% to 4% of patients undergoing CEA.[1-3]

The most likely mechanism of perioperative stroke is cerebral embolization of platelet aggregates and thrombi from the operative site. In a recent review of more than 3000 CEAs, Riles et al.[4] attributed almost half of the perioperative strokes to thromboembolic events, one half of which were identified in the operating room or recovery room. Several strategies for minimizing stroke after CEA have evolved. Foremost among them is a meticulous technique that minimizes manipulation of the artery during dissection and achieves smooth margins at the endarterectomy site. Two of the most common techniques used at the University of Virginia include intraoperative shunting to maintain perfusion pressures distal to the occluding clamps[5] and patch angioplasty to avoid compromising the vascular lumen.[6,7]

Until recently all the senior authors administered protamine to reverse administration of systemic heparin on completion of the endarterectomy. However, after a major stroke occurred in a patient after a routine CEA in 1991, one senior author began to

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withhold protamine administration in an effort to prolong the period of heparin anticoagulation and reduce the risk of thrombus formation and embolization during the immediate postoperative period. Avoidance of protamine has now become routine for all the senior authors after CEA. Since that time there have been no strokes in patients who did not receive protamine. This study was undertaken to test the hypothesis that avoidance of protamine during CEA reduces the postoperative stroke rate.

METHODS

We reviewed the medical records of all patients undergoing primary CEA at the University of Virginia since January 1, 1986. All patients undergoing concomitant cardiovascular procedures were excluded because of differences in anticoagulation protocol. All operations were performed by one of three faculty members of the Section of Vascular Surgery. Preoperative variables recorded were age, sex, symptomatic status, operative status (elective vs urgent/emergency), and degree of contralateral obstruction (as determined by preoperative angiography results). Intraoperative variables included route of anesthesia delivery, use of a shunt, and use of patch angioplasty. After operation, a neurologic deficit was defined as a new unilateral sensory or motor deficit attributable to the operative side that persisted for greater than 24 hours. Focal deficits lasting less than 24 hours were listed as transient ischemic attacks (TIAs). Focal sensory deficits attributable to mandibular nerve injury or hypoglossal nerve injury were not included as deficits. Postoperative neck hematomas were classified as those requiring reexploration.

Standard operative procedure included the administration of 100 U/kg heparin intravenously after dissection of the carotid artery. Activated clotting times were not monitored. All senior authors followed the endarterectomy technique described by Thompson and Talkington.[8] Use of patch angioplasty and intraoperative shunting varied according to the senior surgeon's preference. Intraoperative stump pressures were occasionally recorded by two surgeons to identify patients requiring intraoperative shunting. The third author routinely performed shunting on all of his patients. Both on-table angiography and Doppler scanning were occasionally used. Before July 1991 administration of protamine sulfate in 1 mg/kg doses was routine. However, after a stroke occurred during an uncomplicated CEA, one of the senior authors routinely began to withhold protamine administration. This approach has now become routine for all three senior authors. After operation all patients were admitted to the surgical intensive care unit for hourly neurologic and cardiovascular monitoring and treatment before being transferred to a routine surgical bed. Systemic blood pressure was maintained above 120 mm Hg with careful administration of intravenous crystalloid and kept below 160 mm Hg with either intravenous nitroprusside or hydralazine. All patients received aspirin before operation and continued to receive aspirin after operation. No patients received heparin or protamine after operation. All patients had Jackson-Pratt drains (Baxter Healthcare, Inc., Deerfield, Ill.) placed that were removed on postoperative day 1.

Statistics. Differences between groups of patients were compared by use of normal approximation of proportions. Groups were considered significantly different if $p < 0.05$. A log linear analysis with shunting, patching, and administration of protamine was used to predict the best model of stroke.

RESULTS

All 348 patients survived to discharge. The perioperative stroke rate was 1.4% (5/348), and the TIA rate was 1.4% (5 of 348). All five patients with stroke were found to have neurologic deficits apparent on awakening from general anesthesia, which necessitated emergency reexploration. The clinical course of all five patients who had a stroke after endarterectomy is summarized in Table I. Four of the five patients were found to have thrombosis at the endarterectomy site without evidence of technical flaws such as intimal flaps, stenoses, or kinking. The remaining patient had no identifiable cause of stroke. There were no delayed-onset strokes. Five patients required reexploration for neck hematomas (1.4%). All patients were neurologically intact before and after reexploration. One patient had development of bleeding on postoperative day 1 associated with a significant period of systolic hypertension. The remaining hematomas were diagnosed within the first few hours after surgery. Two patients underwent reexploration immediately in the operating room after bleeding and vigorous coughing were noticed on extubation. The other patients were taken back to the operating room from the postoperative unit and underwent exploration under local anesthesia. Hematomas occurred in 2.2% (2 of 90) of patients undergoing patch angioplasty, one with Gore-tex* (1/62) and the other with facial vein (1/28) for hematoma rates of 1.6% and 3.6% for the two patch

*Gore-tex is a trademark of W.L. Gore & Associates, Elkton, Md.

Table I. Preoperative indications, extent of disease, postoperative deficits, and treatment of all patients have perioperative stroke after CEA

Patient	*History*	*Preoperative arteriogram*	*Shunted/patched*	*Postoperative deficits*	*Onset of deficit/diagnostic test obtained*	*Findings at reexploration*	*Procedure*
1	R-sided TIAs	Moderate L stenosis	Yes/no	No R arm movement	In postoperative unit/none	Small thrombi in CCA, none in I CA, no technical flaws	Primary closure
2	L amaurosis, weak on R	L stenosis >90%	Yes/no	R hemiparesis/speech hestanoy	In postoperative unit/A gram >CCA occlusion	Large thrombus in CCA/ICA, no technical flaws	Thrombectomy, PFGE angioplasty
3	R facial paresthesias	L ulcerated plaques	Yes/no	R hemiparesis	In postoperative unit/A gram >ICA occlusion	Thrombus, no technical flaws	Thrombectomy, primary closure
4	R-sided TIAs	Bilateral ulcerated plaques	Yes/no	R leg weak	In OR/on-table A-gram > clean	No thrombus, no technical flaws	Primary closure
5	Asymptomatic pod 6 L CEA	Bilateral 90% stenosis	Yes/no	L leg weak	In OR/none	Complete ICA thrombosis, no technical flaws	Thrombectomy and PTFE angioplasty

R, Right; *L*, left; *CCA*, common carotid artery; *A-gram*, arteriogram; *OR*, operating room; *pod 6*, postoperative day 6.

materials, respectively ($p = 0.58$). No patient required transfusion of blood products after operation.

Regarding intraoperative reversal of heparin anticoagulation, 193 patients received protamine, and 155 patients did not receive protamine. Table II displays the demographic, intraoperative, and postoperative variables for all patients undergoing CEA either with or without protamine administration. There were no significant differences between the two groups in terms of urgent or emergency need for surgery, anesthetic delivery, or contralateral disease. However, patients who received protamine were slightly younger, had fewer symptoms, and were more likely to be women. There were differences in surgical technique as well; patients receiving protamine were more likely to have undergone intraoperative patch angioplasty with polytetrafluoroethylene (PTFE) patches and less likely to have undergone shunting than those patients not receiving protamine.

Table III documents the postoperative outcomes for all patients on the basis of whether they received protamine. There were no significant differences in rates of reexploration for hematoma or TIAs. Most striking, however, was the observation that all five strokes occurred in those patients who received protamine. By approximation of proportions, the use of protamine was associated with a significantly higher perioperative stroke rate when compared with patients who did not receive protamine. Table IV illustrates that neither shunting nor patch angioplasty itself was associated with an increased risk of stroke. Similarly, the stroke rate did not differ among the three senior authors. Log linear analysis of the data in Table V revealed that the combination of shunting, no patching, and protamine administration was the best predictor of stroke.

DISCUSSION

CEA has been widely performed for decades. Recently, well-organized, prospective randomized trials have reported the efficacy of CEA over medical therapy for patients with symptoms.[9,10] New data seem to suggest that selected symptom-free patients may benefit from CEA as well.[11] These findings may well lead to an even greater use of CEA for the treatment of cerebrovascular disease. The stroke council of the American Heart Association recommends that the combined morbidity and mortality rate after CEA for patients with and without symptoms should not exceed 5% and 3%, respectively.[12] Fortunately, most active vascular surgeons who routinely perform CEA can report similarly low morbidity and mortality rates. Nevertheless, as more symptom-free patients undergo CEA, efforts must continue to reduce the risk of perioperative stroke.

In our study we found an overall stroke rate of 1.4% with no deaths, consistent with results of larger series on CEA morbidity and death.[13] Even in those patients who received protamine, the stroke rate was still an acceptably low 2.6%. However, as we expected, we found a 0% stroke rate in those patients

Table II. Demographic, preoperative, and postoperative data for patients undergoing CEA either with or without protamine administration, *p* values by approximation of proportions

	No protamine (n = 155)	*Protamine (n = 193)*	*p Values*
Average age (yrs.)	68.8	65.9	$p < 0.03$
Men (%)	70.3	59.1	$p < 0.001$
Preoperative symptoms (%)	85.2	75.1	$p = 0.021$
Operative classification (%)			
Elective	94.8	95.9	NS
Urgent/emergency	5.2	4.1	NS
Contralateral disease (%)			
Stenosis >90%	9.0	10.9	NS
Total occlusion	9.7	6.2	NS
Anesthesia (%)			
General	97.4	99.0	NS
Local	2.6	1.0	NS
Patch angioplasty (%)			
PTFE	6.5	26.9	$p = 0.000$
Facial vein	6.5	6.2	NS
Other vein	1.9	1.0	NS
Shunted during operation (%)	83.9	69.0	$p < 0.001$

Table III. Comparison of postoperative outcomes after CEA with and without protamine, *p* values by approximation of proportions

Clinical outcomes (%)	*No protamine (n = 155)*	*Protamine (n = 193)*	*p values*
Perioperative stroke	0.0 (0/155)	2.6 (5/193)	$p = 0.045$
TIA	1.9 (3/155)	1.0 (2/193)	$p = 0.480$
Hematoma requiring reexploration	1.9 (3/155)	1.0 (2/193)	$p = 0.480$

Table IV. Stroke rate as determined by use of shunts, patch angioplasty, and individual surgeons, *p* values by approximation of proportions

	Shunt	*No shunt*	*Patch*	*No patch*	*Author 1*	*Author 2*	*Author 3*
	n = 260	*n = 88*	*n = 90*	*n = 258*	*(n = 243)*	*(n = 61)*	*(n = 44)*
Stroke rate	1.9%	0%	0%	1.9%	1.2%	1.6%	2.2%
p Value	NS, $p = 0.194$		NS, $p = 0.184$			NS, $p > 0.60$	

Table V. Stroke rates as determined by use of protamine, shunts, and patch angioplasty

	Not patched		*Patched*	
	Shunted	*Not shunted*	*Shunted*	*Not shunted*
Protamine	6.1% (*n* = 82)	0% (*n* = 45)	0% (*n* = 48)	0% (*n* = 18)
No protamine	0% (*n* = 116)	0% (*n* = 16)	0% (*n* = 14)	0% (*n* = 9)

who did not receive protamine at the completion of the endarterectomy, a difference that was statistically significant. Although the combined neurologic events rate (cerebrovascular accident and TIA) were not significantly different between the two groups, we strongly believe that the reduction in morbidity associated with stroke versus TIAs is a better endpoint for clinical outcomes after CEA. Furthermore, this reduction in stroke rate was not associated with any significant increase in morbidity related to wound hematomas. Our hematoma rate of 1.9% is the lowest reported in a series of patients not receiving protamine. Previous reports of patients undergoing CEA without protamine cite reexploration rates for hematoma of 4.5% to 6.5%,[14,15] this latter study also routinely drained patients who did

not receive protamine. Hematoma rates for patients receiving protamine range from 1.9% to 2.5%.[15-17]

Other differences between the protamine and no-protamine groups were found. The patients receiving no protamine were slightly older, more likely to have symptoms, and less likely to be men. One could argue that the first two differences make the 0% stroke rate for the no-protamine group even more significant. Perhaps more important, however, there were differences in intraoperative technique between the groups. The patients receiving protamine were less likely to undergo shunting and more likely to have undergone patch angioplasty with PTFE.

Did these differences in technique account for the different stroke rates between the protamine and no-protamine groups? We do not believe so for several reasons. First, Table IV shows, by the same statistical analysis as was used in Table III, that regardless of protamine administration, patients who underwent shunting did not have a statistically different stroke rate compared with patients who did not undergo shunting. The same observation was made when the issue of whether patients underwent patch angioplasty was examined. Second, the mechanism of stroke in four of five patients clearly was acute thrombosis on the basis of the operative findings at the time of reexploration. There were no technical flaws identified in any of the endarterectomies. Table V indicates that all strokes occurred in patients who underwent shunting, did not undergo patch angioplasty, and received protamine. More important, shunting and avoidance of patch angioplasty were not associated with any strokes as long as protamine was not given. We conclude that the patient undergoing CEA with intraoperative shunting and no patch angioplasty may have a higher thrombogenic potential but that avoiding reversal of heparin anticoagulation with protamine significantly decreases these patients' risk of stroke.

Heparin has many mechanisms of action beyond anticoagulation that could potentially minimize stroke in a postendarterectomy environment. Heparin is a strongly charged glycosaminoglycan that displays a high protein binding potential. Heparin binding proteins have been identified on platelets, endothelial cells, monocytes, and neutrophils.[18] Potentially beneficial effects include decreased platelet adhesion to collagen,[19] decreased platelet activation and thromboxane release,[20] and decreased endothelial release of endothelin-1.[21] During the postischemic phase of reperfusion, heparin may also benefit neuronal cell survival by increasing plasma superoxide dismutase activity and reducing free radical injury.[22] Endothelial damage from ischemia and reperfusion may be minimized by several antiinflammatory effects of heparin including attenuation of tumor necrosis factor–induced endothelial toxicity after ischemia and reperfusion,[23] antagonism of histamine and bradykinin,[24] and inhibition of complement activation.[25] Given these beneficial effects of heparin, it is logical to hypothesize that reversal of heparin with protamine in the thrombogenic environment of the postendarterectomy carotid artery could increase the potential for stroke by increasing the chance of thrombus formation, embolization, and endothelial injury. In addition protamine has been shown to directly injure canine coronary artery endothelial cells[26] and is associated with well-described, potentially lethal anaphylactic reactions.[27]

Could these strokes have been prevented? As already mentioned, on-table completion studies were only occasionally performed. On-table angiography or ultrasonography has been recommended as a means to detect clinically significant defects in the freshly endarterectomized artery.[28] However, we believe that routine use of such imaging modalities may incur unnecessary cost and risk to the patient. Furthermore, the ability of such procedures to reduce perioperative stroke rates has been challenged by a recent review by Jain et al.[29] They found a cumulative stroke rate of 2.0% in 10 series of patients receiving completion angiography compared with a 2.2% stroke rate in 430 of their own patients who did *not* receive any completion studies. No evidence of technical flaws such as intimal flaps were found in any of our patients undergoing reexploration for new neurologic deficits. Therefore we do not believe that these strokes could have been prevented by any intraoperative radiographic studies.

In conclusion, we recognize the limitations of this study as those related to any single-institution, retrospective review of an operative procedure with several surgeon-dependent techniques. The relatively small number of patients and the infrequent occurrence of postoperative stroke limits the statistical analysis. Nevertheless, we have performed 155 CEAs without the use of protamine and have not encountered any postoperative strokes, compared with a 2.6% stroke rate in those patients who did receive protamine. We believe this difference is real but concede that larger numbers of patients from multiple institutions are needed to strengthen our argument. As more patients undergo CEA, reduction of the already low risk of perioperative stroke must be pursued. Avoidance of protamine is a simple, safe

technique that has made the practice of CEA at the University of Virginia safer.

REFERENCES

1. McDowell FH, Caplan LR, eds. Cerebrovascular survey report 1985. For the National Institute of Neurological and Communicative disorders and stroke, National Institutes of Health. Bethesda: Public Health Service.
2. Mohr JP, Caplan LR, Melski JW, et al. The Harvard Cooperative Stroke Registry: a prospective registry. Neurology 1978;28:754-62.
3. Ernst CB, Rutkow IM, Cleveland RJ, et al. Vascular surgery in the United States. J VASC SURG 1987;6:611-21.
4. Riles TS, Imparato AM, Jacobowitz GR, et al. The cause of perioperative stroke after carotid endarterectomy. J VASC SURG 1994;206-16.
5. Boysen G. Cerebral hemodynamics in carotid surgery. Acta Neurol Scand 1973;52:1-84.
6. Hertzer NR, Beven EG, O'Hara PJ, Krajewski LP. A prospective study of vein patch angioplasty during carotid endarterectomy. Am Surg 1987;206:628-35.
7. Eikelboom BC, Ackerstaff RGA, Hoeneveld H, Ludwig JW, Teeuwen C, Vermeulen FEE, Welten RJT. Benefits of carotid patching: a randomized study. J VASC SURG 1988;7:240-7.
8. Thompson JE, Talkington CM. Carotid endarterectomy. In: Warlow C, Morris PJ, eds. Transient ischemic attacks. New York: Marcel Dekker, 1982:253-82.
9. North American Symptomatic Carotid Endarterectomy Trial Collaborator. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade stenosis. N Engl J Med 1991;325:445-53.
10. European Carotid Surgery Trialist's Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. Lancet 1991;337:1255-66.
11. Hobson RW II, Weiss DG, Fields WS, et al. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. N Engl J Med 1993;328:221-7.
12. Beebe UG, Clagett GP, DeWeese JA, et al. Assessing risk associated with carotid endarterectomy. Stroke 1989;20: 314-5.
13. Hertzer NR. Presidential address: carotid endarterectomy—a crisis in confidence. J VASC SURG 1988;7:611-9.
14. Oller DW, Welch H. Complications of carotid endarterectomy: a military hospital experience. Am Surg J 1986; 52:479-84.
15. Treiman RL, Cossman DV, Foran RF, Levin PM, Cohen JL, Wagner WH. The influence of neutralizing heparin after carotid endarterectomy on postoperative stroke and wound hematoma. J VASC SURG 1990;12:440-6.
16. Welling RE, Ramadas HS, Gansmuller KJ. Cervical wound hematoma after carotid endarterectomy. Ann Vasc Surg 1989;3:229-31.
17. Kunkel JM, Gomez ER, Spebar MJ, et al. Wound hematomas after carotid endarterectomy. Am J Surg 1984;148:844-7.
18. Lindahl U, Lidholt K, Spillmann D, Kjellen L. More to "heparin" than anticoagulation. Thrombosis Res 1994;75:1-32.
19. Heiden D, Mielke CH, Rodvien R. Impairment by heparin of primary hemostasis and platelet (14C)5-hydroxytryptamine release. Br J Haemotol 1977;36:427-36.
20. Fernandez F, Hnuyen P, Van Ryn J, Ofosu FA, Hirsh J, Buchanan MR. Hemorrhagic doses of heparin and other glycosaminoglycans induce a platelet defect. Thromb Res 1986;43:491-5.
21. Reantragoon S, Arrigo LM, Rosenfeld L. Heparin lowers endothelin-I levels in cultured endothelial cells [Abstract]. FASEB J 1994;8:A616.
22. Oyanagui Y, Sato S. Heparin, a potent releasing agent of extracellular superoxide dismutase (EC-SOD), suppresses ischemic paw oedema in mice. Free Radic Res Commum 199;9:87-99.
23. Karisson K, Marklund SL. Extracellular superoxide dismutase in the vascular system of mammals. Biochem J 1988;255: 223-8.
24. Carr J. The anti-inflammatory action of heparin: heparin as an antagonist to histamine, bradykinin, and prostaglandin E. Thromb Res 1979;16:507-16.
25. Rent R, Nyirman R, Fiedel BA, Gewurz H. Potentiation of C1 esterase inhibitor activity by heparin. Clin Exp Immunol 1976;23:264-71.
26. Wakefield TW, Hinshaw DB, Burger JM, Burkel WE, Stanley JC. Protamine-induced reductions of endothelial cell ATP. Surgery 1989;106:378-85.
27. Cormack JG, Levy JH. Adverse reactions to protamine. Coronary Artery Dis 1993;4:420-5.
28. Dilley RB, Bernstein EF. A comparison of B-mode real-time imaging and arteriography in the intra-operative assessment of CE. J VASC SURG 1986;4:457-63.
29. Jain KM, Simoni EJ, Munn JS. Routine completion study during carotid endarterectomy is not necessary. Am J Surg 1994;168:163-7.

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DISCUSSION

Dr. Bertram L. Smith (Dallas, Texas). This is an interesting study that attempts to analyze one of the causative factors of stroke after CEA. Although the authors agree that the sources of perioperative stroke are multiple, namely cerebral ischemia, embolization that occurs during operation, and thrombus formation at the endarterectomy site, the specific cause studied, in retrospect, is the effect of neutralization of heparin by protamine sulfate given at the completion of endarteretomy: patients who received no protamine had no strokes versus 2% to 6% of patients receiving protamine.

Although it is well known that the heparin-protamine complex may cause numerous physiologic changes such as leukopenia, thrombocytopenia, complement activation,

and pulmonary vasoconstriction, especially when the protamine is given rapidly, it is less clear whether protamine causes increased platelet adhesiveness and thrombosis of endarterectomized surfaces when combined with heparin. Moreover it is undocumented in this series that any of the known physiologic sequelae of heparin-protamine interaction occurred in those patients who had perioperative stroke. Therefore it is difficult to credit the absence of protamine to the absence of stroke in this series.

Also there are other variables including carotid artery patching and shunting that may have had some bearing on postoperative results.

It is interesting, however, that no strokes occurred in those patients who received no protamine. Obviously further investigation is needed.

It has been shown by several studies that thromboxane is the primary mediator of the pulmonary vasoconstrictive thrombocytopenic reaction that occurs in up to 5% to 15% of patients receiving protamine heparin reversal. Blocking thromboxane synthetase will diminish the physiologic reaction that occurs.

Because all your patients were receiving aspirin, what caused the "breakthrough thrombosis" that occurred in those patients who had stroke?

Because the patients who had stroke had neurologic deficits on awakening from anesthesia, how do you exclude intraoperative embolization as a cause?

How many hematomas occurred that did not require exploration? Do you believe that residual blood in the wound increases the risk of late synthetic patch infection?

Dr. Michael C. Mauney. With regard to your first question about the mechanism of thrombosis, given that patients were receiving aspirin, despite inhibition of thromboxane production, there must have been enough stimulus for platelet activation, either from the injured endothelial surface or possibly decreased synthesis of the antiplatelet prostaglandin prostacyclin. Even though we did not document the presence of any systemic effects of the heparin-protamine complex you summarized, they do not necessarily have to be present for the prothrombotic effects we cite to occur. With regard to the mechanism of stroke, all patients with new neurologic deficits underwent immediate reexploration. Partial or complete thrbombosis at the endarterectomy site was found in four of the patients without any evidence of intimal flaps, kinks, or arterial lumen compromise We cannot rule out thromboembolism from excessive dissection, clamp placement and removal, or shunt insertion as a cause of stroke in the other patient. With regard to your third question, we were not able to thoroughly determine the presence or absence of mild hematomas not requiring reexploration because of the retrospective nature of the study and lack of documentation in some cases. Our impression is that withholding protamine is not associated with any higher incidence of minor hematomas. Of course we are concerned about any hematoma in the presence of synthetic patches and have been fortunae not to have seen this problem so far.