## INVITED COMMENTARY

# Regarding "Coagulation and fibrinolysis in patients undergoing operation for ruptured and nonruptured infrarenal abdominal aortic aneurysms"

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The rupture of an abdominal aortic aneurysm is associated with death in the vast majority of patients in whom it occurs. One of the most eye-opening demonstrations of the lethality of the problem is the population-based report from Malmö in which 88% of the patients with ruptured aortic aneurysms died, most of whom did not survive to reach the hospital.[1] Lowering the rate of mortality would require the development of a screening program to identify individuals with aortic aneurysms so that elective repair could be performed before rupture. The reality of such an approach is uncertain, and the cost effectiveness is questionable. As such, the institution of global methods to identify and repair the great number of asymptomatic aneurysms is a matter of public policy and poorly controllable by the vascular practitioner.

By contrast, vascular surgeons have the potential to alter patient survival rates for those patients who arrive at the hospital alive. Anecdotally, it appears that intraoperative mortality rate has, indeed, decreased over time, but the chance of surviving to discharge remains only one in two for these patients.[2] Vascular surgeons and anesthesiologists have become remarkably effective at getting patients with ruptured aneurysms through the operation itself, but the perioperative mortality rate remains depressingly high. Thrombotic complications predominate during the early postoperative period, including myocardial infarction, lower extremity and intestinal ischemia, stroke, and venous thromboembolism. The frequency of these events must be limited if a decrease in the in-hospital mortality rate is to be achieved.

The work of Adam and colleagues sheds light on possible mechanisms to explain the increased incidence of thrombotic events in patients who undergo repair of ruptured aortic aneurysms. The crux of their work is based on the assumption that thrombotic events occur as a result of an imbalance between thrombogenesis (thrombin generation vs natural anticoagulant pathways) and endogenous thrombolysis (plasminogen activation vs plasminogen activator inhibition and antiplasmin activity). Elucidation of these mechanisms provides critical information that can be used to design treatments directed at the prevention of intravascular thrombosis, thereby decreasing the rate of associated perioperative thrombotic complications. In this regard, it is likely that similar mechanisms underlie the pathophysiology of thrombotic events after many peripheral vascular procedures, as well as major operative procedures in general.

There are two major findings of this study, both of which relate to the development of a hypercoagulable state before and during the repair of ruptured aneurysms. First, the investigators detected markers of intense thrombin generation in these patients, with elevation of thrombin-antithrombin complexes and prothrombin fragments 1 and 2. Second, reduced endogenous tissue plasminogen activator (t-PA) activity was seen, explainable by marked elevations in plasminogen activator inhibitor (PAI). The PAI activity was high enough to account for the diminished t-PA activity in spite of an increase in the levels of circulating t-PA antigen. This apparent paradox is easily understood when one considers that total t-PA antigen measures both unbound (active) t-PA as well as

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the inactive t-PA bound to inhibitors such as PAI-1. In fact, the importance of measuring t-PA activity rather than antigen underlies apparent contradictions between this study and a previous investigation of our own, where elevations in t-PA antigen were thought to account for an increased incidence of bleeding after supraceliac aortic cross clamping.

It is important to note that the present study compared the levels of markers of coagulation and fibrinolysis in patients with ruptured versus elective aneurysm repair. Interesting findings are revealed when the levels in the elective group are compared with the normal range. For instance, even the group of patients who underwent elective aneurysm repair manifested mild elevations in prothrombin fragments 1 and 2, indicative of ongoing thrombin generation. t-PA and PAI were, however, within the range of normal before, during, and after operation. These findings suggest that a procoagulant state is present at baseline in patients with aneurysms, primarily related to increased thrombin generation. This contention, however, may be spurious, related to an increase in prothrombin fragments in blood drawn from the arterial lines of patients with aneurysms rather than the potentially less traumatic venous sticks used for determining the normal range. Nevertheless, it corroborates previous work from a variety of investigators, documenting significant coagulation derangements in patients with abdominal aortic aneurysms.[3,4]

There are some potential limitations of the authors' work. There exist unavoidable demographic, anatomic, and pharmacologic differences in patients with ruptured versus non-ruptured aneurysms. For instance, the patients with ruptured aneurysms may be older, with an increased frequency of coexistent medical illnesses. As well, these patients have larger aneurysms with a greater amount of potentially thrombogenic surface area exposed to blood flow. Lastly, the pharmacologic profile implemented in patients with ruptured and non-ruptured aneurysms is quite different, most importantly with respect to the use of heparin, but also with regard to vasoactive agents, such as epinephrine and dopamine—agents that can have significant effects on coagulation, platelet function, and endothelial physiology.

Despite these potential drawbacks, the present work represents a carefully designed and well-executed study of coagulation and fibrinolytic derangements in patients with ruptured aortic aneurysms. Although the observations must be corroborated by subsequent, larger studies, a major value of the present study resides in the fact that it will generate cognizance of these hemostatic derangements. Clinical results can only be improved through the acquisition of sound research data gained from investigations such as this. Novel techniques and strategies are, of necessity, formulated and implemented on the basis of fundamental research. It is incumbent on us to assure a continuing supply of well-trained vascular surgeons with education sufficient to critique research studies and, in many cases, design and conduct investigations themselves. Training of academically inclined vascular surgeons will ensure adequate growth in the fund of knowledge relating to vascular disease and, ultimately, bring about great improvements in patient care and clinical outcome.

REFERENCES

1. Bengtsson H, Bergqvist D. Ruptured abdominal aortic aneurysm: a population-based study. J Vasc Surg 1993;18: 74-80.
2. Ouriel K, Geary K, Green RM, Fiore W, Geary JE, DeWeese JA. Factors determining survival after ruptured aortic aneurysm: the hospital, the surgeon, and the patient. J Vasc Surg 1990;11:493-6.
3. Illig KA, Green RM, Ouriel K, Riggs PN, Bartos S, Whorf R, et al. Primary fibrinolysis during supraceliac aortic clamping. J Vasc Surg 1997;25:244-54.
4. Gibney EJ, Bouchier-Hayes D. Coagulopathy and abdominal aortic aneurysm. Eur J Vasc Surg 1990;4:557-62.

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Please see related article by Adam et al on pages 641-50.