knowing if mechanisms are available to reverse the action of this peptide. Could the persistent post-CPB elevation of the clotting times have been a result of moderate hypothermia and/or postbypass hemodilution of clotting factors?

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Reference

Reply
Thank you for the opportunity to reply to DeAnda and colleagues. We are pleased that such detailed interest was given to our work1 since we believe that alternative anticoagulants to heparin are needed and can be developed. The abstract has a typographical error as found by DeAnda et al in that the ACT values are given for 90 minutes postpump, not 30 minutes. Thank you for pointing this out. Fig 2 is correct, as is the remainder of the article.

Initial studies on the synthetic thrombin inhibitor DuP 714 revealed the half-life to be <30 minutes following bolus administration in two animal models.2 In our study of CPB as stated in the first paragraph of “Methods,” the half-life of a single injection of the inhibitor was approximately 15 minutes. Thus, because of the short half-life, a bolus-plus-infusion regimen was required. With the dose studied, blood levels were significantly reduced although not completely eliminated within 30 minutes after CPB as determined by the ACT, other clotting assays, and a specific biochemical assay for the thrombin inhibitor. Hypothermia and hemodilution probably did not play a major role in the ACT elevation.

It is not established whether the ACT response is a true measure of anticoagulation/bleeding risk when drugs other than heparin are used. In our study, the template bleeding time in the inhibitor-treated animals (lower dose) was not significantly different from that for heparin during and after CPB (Fig 1).1 Moreover, the blood loss, even in the higher dosed group, was lower than that from heparin, suggesting that elevated ACT levels may not correlate with excess bleeding. All animals were physiologically more stable than heparin-treated animals throughout the surgical period. Therefore, we stated that a neutralizing agent should not be required.

A more optimal dosing regimen for this inhibitor may be found in future studies. An ACT value <600 seconds may be adequate during CPB with this inhibitor as we have seen with other anticoagulants such as low molecular weight heparin. Our own unpublished pilot data suggest that a lower infusion rate of this peptide could be adequate with ACT values near 350 seconds on pump and 150 seconds 30 minutes postpump. However, if after all investigations have been made it is deemed that clinically acceptable post-CPB blood levels of this inhibitor cannot be quickly achieved, a neutralizing agent should be used. At this time several ideas are under investigation, such as the use of antibodies, hemofiltration, and fresh-frozen plasma or the equivalent.

Our primary objective in publishing this article was to increase the awareness of the developments in the field of anticoagulation for cardiovascular surgery. Future studies by others as well as by us are surely needed to define optimal dosing and other issues of these new drugs, but the direction seems promising.

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References

Atrial Natriuretic Peptide Secretion in Right Ventricular Infarction

To the Editor:
Yasuda and colleagues1 clarify a great deal about atrial natriuretic peptide (ANP) secretion in acute right ventricular infarction. Their discussion can be amplified, however, because of the similarity in hemodynamics between acute right ventricular infarction and constrictive pericarditis.2 The authors correctly note that stretch rather than pressure is the immediate stimulus for ANP production but do not continue that part of the discussion. We demonstrated that in constrictive pericarditis, as in cardiac tamponade,4 despite extremely high central pressures, ANP secretion remains quite low but rises acutely upon relief of cardiac compression in both conditions.5,6 Dilation of an acutely infarcted right ventricle within a presumably normal pericardium produces “constrictive” hemodynamics, presumably tightening the pericardium on the heart, thereby preventing further stretch and consequently, expression of ANP.

It would have been worthwhile also to document absence or presence of increased pericardial fluid as a precondition for considering that other pericardial factor. Even without clinical tamponade, any excess pericardial fluid from minimal effusions to large effusions couples the heart and pericardium such that respiration-associated physiological effects are exaggerated when measured by sensitive techniques.5,6 Presumably paralleling another kind of pericardium-associated resistance to stretch. However, the principal point remains the corresponding hemodynamics of acute right ventricular infarction and constrictive pericarditis, which may account for at least some of the ANP depression in the authors’ URP group.

These remarks are not meant in criticism but rather to amplify the authors’ excellent report.

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Atrial natriuretic peptide secretion in right ventricular infarction.
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