Thrombus-Specific Imaging: Approaching the Elusive Goal

The importance of developing a thrombus-specific imaging method is a goal of undisputed clinical importance. Whereas thrombus formation after vascular injury is cardinal in hemostasis, it is also the cause of unwanted effects due to occlusions and emboli in the arterial and venous circulation. Early detection and treatment of pathological intravascular thrombosis is effective. The high incidence of side effects from thrombolytic therapy, however, necessitates accurate identification of patients who will not benefit from such treatment.

A noninvasive, rapid and specific method for thrombus detection which will also enable monitoring thrombus dissolution is therefore highly desirable. Such a method should preferably allow imaging of arterial and venous thrombi of various ages and help determine whether a thrombus is still amenable to thrombolytic therapy. This topic has been reviewed intensively, including mesenteric ischemia and thrombolysis (1-6).

The search for thrombus-specific imaging agents began two decades ago when radiiodinated fibrinogen was first evaluated (7). Since then, a plethora of thrombus imaging agents have been described, including agents that are incorporated into thrombi and agents that bind to components of previously formed thrombi (7-29).

Radiolabeled platelets (8) and antiplatelet antibodies will bind to forming thrombi (14,15,19), antifibrin antibodies (16,20-23), anti-activated platelet antibodies (24,25) and active or inactivated tissue type plasminogen activator (t-PA) (26-28) will bind to formed, older thrombi.

Theoretically, agents targeted to forming thrombi should be suitable for imaging fresh propagating thrombi. In addition, an agent may show preferential binding to a thrombus type based on the abundance of that specific factor in either arterial or venous thrombi. Thus, radiolabeled platelets or antiplatelet antibodies will display higher affinity for arterial thrombi that are rich in platelets, while venous preformed thrombi will probably be better imaged with agents that bind to fibrin, antifibrin antibodies or by native or inactivated t-PA.

Although venous thrombosis and embolism occur frequently, resulting in a high incidence of morbidity and mortality, arterial thrombosis is of greater concern. Thrombus formation on atherosclerotic plaques may result in complete occlusion of coronary arteries, leading to critical and often fatal infarction. Although imaging arterial thrombosis is of great importance, little success has been achieved to date (14,15,29-31). This disappointing situation may have resulted from the use of compounds with inadequate thrombus-to-blood ratios and small-size arterial thrombi, particularly in the coronary circulation.

The greatest success has been achieved in imaging venous thrombosis with monoclonal antifibrin antibodies. The reports in the literature include antibodies that react with the NH$_2$ group on the alpha (32) or beta terminus (16,33-34), on the D-domain of the noncrosslinked fibrin (35), on the fibrin D-domain after plasmin digestion (36) or on cross-linked D-domain regions (37). In the current issue of the Journal, Bautovich et al. report human studies using an antifibrin antibody directed against crosslinked human fibrin dimer (38). Bautovich et al. offer convincing evidence of the safety, feasibility and efficacy of the monoclonal antifibrin antibody method. By using a Fab’ fragment preparation labeled with $^{99m}$Tc, thrombus imaging was accomplished 2-6 hr after injection, a significant improvement over previously reported compounds that required 6-24 hr of preparation before successful imaging. Moreover, this method demonstrated pulmonary emboli. False-negative


scans might have resulted from epiphelization of thrombi due to the long interval between the thrombophlebitis-confirming studies (IPG, contrast venography) and scintigraphy. Nevertheless, the antifibrin antibody method deserves large scale clinical trials.

Other preliminary studies indicate that an alternative for the use of antibodies may soon become practical. Small peptides with platelet affinity labeled with $^{99m}$Tc become incorporated into thrombi (39, 40). These small peptides with specific amino acid sequences are more advantageous than complex, large molecular weight antibodies or fragments since they can be produced synthetically and are therefore less expensive. They are minimally antigenic and there is little danger of viral contamination, resulting in less stringent procedural requirements. Finally, blood clearance of peptides is fast when compared to antibodies. In the future, these preparations may replace many of the antibody methods. Correlative studies with antibodies and peptides will determine the outcome of this prediction.

The results of the studies of Bautovich et al. clearly indicate that similar efforts towards developing methods for arterial thrombus imaging should be made (31, 41).

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REFERENCES