In-111 Platelet Scintigraphy: Carotid Atherosclerosis and Stroke

An association between atherosclerosis of the internal carotid artery and ischemia or infarction of the ipsilateral cerebral hemisphere has been demonstrated by numerous radiographic and pathologic studies. The precise mechanism by which carotid atherosclerosis causes these problems, however, remains unclear. Several observations suggest that fibrin-platelet thrombi form on atherosclerotic plaques in the neck arteries and then embolize distally into the intracranial circulation. Platelet emboli have been observed in retinal vessels during attacks of transient monocular blindness (*1,2*) and platelet thrombi have been found adhering to atherosclerotic plaques removed during carotid endarterectomy for cerebral ischemia (*3,4*). Unfortunately, platelet embolization does not adequately explain a variety of clinical and pathological findings in patients with cerebrovascular disease (*5*). Furthermore, several recent studies have shown that fresh intraplaque hemorrhage, rather than adherent platelet thrombus, is the most common finding in atherosclerotic plaques from patients with recent hemispheric ischemia or infarction (*6,7*). These later data suggest that a sudden increase in the size of the plaque, causing a sudden decrease in blood flow, may be critical in producing symptoms of cerebral ischemia. It is obvious from even this brief discussion that our understanding of the role of platelets in the pathogenesis of ischemic cerebrovascular disease is far from complete.

The development of a technique to radiolabel platelets with In-111 made it possible to study platelets in vivo by gamma scintigraphy (*8*). Several groups of investigators have applied this technique to the study of carotid atherosclerosis. In general, they have found that In-111 platelets accumulate at about half of arteriographically abnormal sites in the carotid arteries and at approximately one-quarter of arteriographically normal sites (*9–15*). In our series of 100 patients, we found no correlation between the scintigraphic findings and the previous or subsequent occurrence of transient ischemic attacks or cerebral infarction (*13*). Furthermore, there was no relation between scintigraphic results and the degree of arteriographic stenosis, the presence of arteriographic ulceration, or the use of anticoagulant or antiplatelet drugs, alone or in combination. This failure of In-111 platelet scintigraphy to correlate with the clinical, arteriographic, or pharmacological factors expected to be associated with platelet deposition has several possible explanations. It may be that factors other than the simple formation of platelet thrombi in the cervical carotid arteries are of primary importance in the pathogenesis of stroke. Alternatively, In-111 platelet scintigraphy may not be sensitive enough to detect some small but potentially harmful platelet thrombi.

In an attempt to improve the sensitivity of In-111 platelet scintigraphy, we and others have used an additional radiotracer for the circulating blood pool, either Tc-99m red blood cells (RBCs) or Tc-99m albumin (*16–25*). This technique improves sensitivity by permitting subtraction of the radioactivity due to labeled platelets still circulating in the blood, and provides a measure of quantification by relating local platelet deposition to the platelet concentration in the adjacent circulating blood pool. It is based on the use of a vascular reference region where no platelet deposition is present. The ratio of In-111 to Tc-99m counts in the reference region is multiplied by the Tc-99m counts in the region of interest to calculate the In-111 counts attributable to circulating blood platelets in the region of interest. This calculated value for In-111 in the blood pool is then subtracted from the total In-111 counts in the region of interest to determine the excess In-111 counts that are due to local platelet deposition. The excess In-111 counts may then be divided by the calculated value for In-111 in the blood pool within the region of interest, thus expressing local platelet deposition relative to platelet concentration in the blood and providing a scintigraphic thrombus-to-blood ratio.

In the application of this technique, two basic assumptions are made. First, both radionuclides must be accurate tracers for their respective functions. Indium-111 platelets fulfill this requirement well; they distribute in the circulating platelet pool and maintain function with no apprecia-

ble loss of the radiolabel. Technetium-99m RBCs and Tc-99m albumin are suitable blood-pool tracers, although they do suffer from some disadvantages. Free Tc-99m that is injected with the radiotracer—or that dissociates from the radiotracer in vivo—will distribute into extravascular tissue and cause errors in the blood-pool calculation. Any incorporation of labeled RBCs or albumin into a thrombus will cause overestimation of the blood pool within the region of interest, and consequent underestimation of the amount of platelet deposition. Second, the radioactivity from these two radionuclides must be measured accurately. This requires uniform response for the entire field of view for the gamma camera or correction for any nonuniformity. The reference region and region of interest should be of the same size, shape, and tissue depth. This will ensure that counting geometry and relative attenuation will be the same for both radionuclides in both regions. Some correction must be made for both Compton scatter from In-111 into the Tc-99m photopeak and the overlap between the 173-keV photopeak of In-111 and the 140-keV photopeak of Tc-99m. This is usually accomplished by recording only the 247-keV photopeak of In-111 and by measuring Compton scatter in the Tc-99m energy window before administering the Tc-99m radiotracer, then subtracting this amount from the Tc-99m counts. Alternatively, the fraction of counts due to Compton scatter in the Tc-99m energy window can be reduced by administering a dose of Tc-99m several times that of In-111.

Since the gamma camera portrays three-dimensional structures as two-dimensional images, this technique actually determines excess platelet deposition relative to blood for the entire volume of tissue within the region of interest, not just for the vessel under study. Overestimation of intravascular platelet deposition can result from deposition of platelets in extravascular sites, such as the bone marrow. Such errors can be minimized by performing a correction for this extravascular tissue background or by including similar extravascular tissue sites in the reference region. Future application of single photon emission computerized tomography to dual-radiotracer scintigraphy would help to reduce these errors further.

The accuracy of this method depends on the appropriate choice of a reference region. As noted above, it should resemble the thrombus region of interest in size, shape, and tissue depth. This is best accomplished by choosing a portion of contiguous or contralateral vessel. A further requirement for the reference region is the absence of In-111 platelet deposition. While this requirement may be easy to satisfy in experimental models, it can produce difficulties in clinical studies when a diffuse vascular process such as atherosclerosis is present. In this case, a vessel that is rarely involved by the disease (such as the brachial artery or pulmonary artery) can be used. An alternative approach is to use the vascular region with the minimum ratio of In-111 to Tc-99m, since this will represent an area with minimal or absent In-111 platelet deposition (*17*). Caution must be exercised with this latter approach to ensure that there are statistically adequate counts in the regions sampled. Any In-111 platelet deposition in the reference region will produce falsely low values for the scintigraphic ratio and may mask the effect of antithrombotic drugs if the drug reduces the rate of platelet uptake in both reference and thrombus regions.

Although a direct measurement of In-111 radioactivity in the thrombus is not made with this technique, the thrombus-to-blood ratio in the region of interest is accurately determined by expressing the scintigraphically measured radioactivity of the thrombus relative to the adjacent blood pool. This scintigraphic thrombus-to-blood ratio depends on the volume of blood within the region of interest. For vessels of similar size this volume will be the same. As long as this condition is fulfilled, the scintigraphic ratio will be directly proportional to the thrombus-to-blood ratio measured in vitro (*20*). The scintigraphic measurement can therefore be used to make reliable quantitative comparisons of intravascular platelet deposition in vessels of similar size. Comparisons among vessels of different sizes will not be valid. This technique is thus well suited to in vivo study of platelet deposition in vessels of similar size in different subjects, and is especially well suited for sequential studies on the same vessel in the same subject, such as before and after pharmacologic intervention. Since the concentration of In-111 platelets circulating in the blood will vary, depending on the initial amount of splenic sequestration and the subsequent rate of platelet destruction, thrombi with the same amount of In-111 platelet deposition may have different scintigraphic ratios, and a stable thrombus will increase its ratio as In-111 platelets are cleared from the circulation. A measurement of platelet deposition that is independent of the circulating concentration of In-111 platelets can be derived by multiplying the scintigraphic ratio by the percent injected dose of In-111 in 1 ml of blood drawn concurrently (*20*).

This technique provides a measurement of the amount of platelet deposition that has occurred since In-111 platelets were injected. The measurement can be used to calculate the rate of platelet accumulation in a region. Determination of actual thrombus mass or volume is not possible, due to the variable incorporation of blood elements other than platelets into the thrombus and the presence of thrombus formed before injection of In-111 platelets.

In this issue of the *Journal*, Isaka and his colleagues report the application of this dual-radiotracer method to the study of 12 normal subjects and 25 patients with carotid atherosclerosis (*26*). They found the scintigraphic ratio to be increased in 19 of 34 arteriographically abnormal sites and in one of 16 arteriographically normal sites. Furthermore, the ratio was higher when ulceration was present and when the degree of arteriographic stenosis was greater than 50%. This latter finding was not an artifact of decreased local blood pool produced by the stenosis, since blood-pool values were similar in all carotid arteries regardless of the degree of stenosis. Conventional visual interpretation of the images resulted in detection of only 13 of 34 arteriographically abnormal sites when equivocal regions were counted as negative. Based on this, the authors conclude that the dual-radiotracer technique increases the sensitivity of In-111 platelet scintigraphy for detecting carotid atherosclerosis. However, if visually equivocal regions are counted as positive, the sensitivity of visual analysis rises to 22/34, and there is no clear advantage to the dual-radiotracer technique. We have studied 28 patients with the dual-radiotracer technique and find no improvement in sensitivity for detecting carotid atherosclerosis. Goldman et al. have recently reported similar negative results (*15*). The explanation for this failure of the dual-radiotracer technique to improve sensitivity in this setting is not clear. It may be due to poor counting statistics from the carotid arteries, and the propagation of this statistical error by the arithmetic operations involved in calculating the scintigraphic ratio. Alternatively, the results may simply reflect the absence of platelet deposition in a substantial number of patients. Mural platelet thrombi were not found in any of the 16 patients from our series of 28 who subsequently underwent carotid endarterectomy. All had had negative dual-radiotracer scintigraphy preoperatively.

Although In-111 platelet scintigraphy has been shown to be useful for detecting deep-vein thrombosis, intraventricular thrombi, and acute renal transplant rejection (*27*), its value in the clinical investigation of carotid artery disease still remains to be established. Since the importance of platelet deposition in the carotid arteries is uncertain, merely demonstrating an association with carotid atherosclerosis serves little purpose. There are other simpler and more sensitive noninvasive techniques available to detect carotid atherosclerosis, although the clinical value of the information obtained from these tests is still unknown. In order for In-111 platelet scintigraphy to be of clinical value, a correlation between the scintigraphic results and some important clinical parameter must be established. Along these lines, it would be useful to make further quantitative studies with the dual-radiotracer technique, correlating the rate of platelet deposition in the carotid arteries with the subsequent occurrence of cerebral ischemia or infarction and the response to drug therapy.

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