Teaching Editorial

Clinical Uses of Radiolabeled Platelets

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Platelets were first successfully radiolabeled in 1953 (*1*). At that time, investigators were primarily interested in developing a technique to accurately measure platelet lifespan in both normal and thrombocytopenic patients. Studies using platelets labeled with ^{51}Cr have shown shortened platelet survival times in a number of diseases including idiopathic thrombocytopenic purpura (*2*), coronary artery disease (*3,4*), and diabetes mellitus (*5*). More recently, labels such as ^{111}In have been developed that allow in vivo imaging of platelets (*6*). Indium-111 platelets are being used to better understand the pathophysiology of atherosclerosis, thrombophlebitis, pulmonary embolism and clotting disorders, and to improve the clinical diagnosis of these diseases.

PLATELET ANATOMY AND PHYSIOLOGY

Platelets are formed in the bone marrow by megakaryocytes, large multinucleated cells which form demarcation zones enclosing a small quantity of cytoplasm. Eventually the platelet splits off from the megakaryocyte and is released into the circulation.

Platelets are small disc-shaped cells averaging 3 × 1 micron in size. Although they do not have a nucleus, they are anatomically complex cells that contain a large number of organelles. Functionally, platelets are capable of phagocytosis, chemotaxis, and the sponge-like transport of blood clotting factors. Most importantly, platelets have the ability to change shape on contact with foreign materials or subendothelial surfaces stimulating release of substances involved in hemostasis, leading to vascular smooth muscle contraction, adherence of platelets, and coagulation of blood.

Platelets are one of the three major systems that account for hemostasis, the other two being smooth muscle contraction and the blood coagulation system. None of these systems, by themselves, can bring about hemostasis.

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Hemostasis can be divided into five steps: 1) platelet adhesion to the periphery of a wound; 2) localized vasoconstriction; 3) platelet plug formation; 4) reinforcement of the platelet plug with fibrin; and 5) removal of the clot through the fibrinolytic system.

An important control over hemostasis is provided by prostaglandins and their derivatives (*7,8*). When platelets are "activated" and aggregate, they metabolize the prostaglandin precursor arachidonic acid into intermediate products, endoperoxidases. A similar process occurs in the blood vessel wall. In the platelet, the endoperoxidases are metabolized to thromboxane A_2, one of the most potent vasoconstrictors known. In the vessel wall, however, the endoperoxidase intermediates are converted into a different substance, prostacyclin. Prostacyclin, a powerful vasodilator, counteracts the vasoconstrictive effects of thromboxane. Thromboxane and prostacyclin also have opposing effects on platelet aggregation; thromboxane promotes aggregation whereas prostacyclin inhibits it. Many drugs, such as aspirin, which decrease platelet aggregation, do so by inhibiting cyclo-oxygenases. This activity blocks the conversion of arachidonic acid to endoperoxidase, thereby reducing thromboxane A_2 levels.

LABELING CONSIDERATIONS

Ideally, we would like to label platelets in vivo, similar to the red cell labeling method with [^{99m}Tc]pertechnetate. However, in vivo techniques are not possible for two reasons. First, the labeling agents are indiscriminate and label all cell types in the blood to a variable degree. Second, agents such as ^{111}In oxine have a higher affinity for plasma transferrin than for platelets, leading to a low labeling efficiency when platelets are labeled in the presence of plasma (*6*). For these reasons, platelets must be isolated from the blood prior to labeling.

Blood Collection

A large bore needle, at least 19 gauge, must be used with a plastic or siliconized glass syringe to reduce the trauma of blood collection (*4,9*). The first milliliter of blood collected should be discarded since it will contain a large quantity of plasmin and fibrinogen. After withdrawal, the syringe should

be gently rotated to mix the anticoagulant with the blood.

Choice of Anticoagulant

The anticoagulant used in the collecting syringe is critical. ACD has a clear superiority over other anticoagulants. In a study comparing ACD to EDTA, the percentage recovery of ^{51}Cr labeled platelets transfused into normal recipients was 62% when ACD was used as the anticoagulant but averaged only 27% with EDTA (*10*). In addition, platelets anticoagulated with EDTA quickly disappeared from the circulation and sequestered in the liver for several hours before eventually reentering the circulation.

Studies have also indicated that the recovery of labeled platelets is higher if the pH of the anticoagulant is somewhat acidic (*11*). The increased recovery is not related to an effect on platelet survival, but rather to a decrease in platelet adhesiveness and aggregation which allows the cells to be centrifuged and resuspended without clumping. One part ACD to 6 parts blood is usually adequate to obtain a pH of 6.5 (*7*).

Cell Separation

Platelets are separated from other blood cells and plasma in two centrifugation steps. The first centrifugation produces platelet-rich-plasma (PRP). Centrifugation of the PRP forms a platelet pellet, plus platelet-poor-plasma (PPP).

Centrifugation forces can be expressed in two ways: 1) as a separate G force and time in minutes (150 G for 10 min); or 2) as G force × minutes (1500 G-min). Thus a slow spin for a longer duration (150 G × 10 min) or a fast spin for shorter times (1500 G × 1 min) would be equivalent (*9*).

The duration of centrifugation may affect the age of harvested platelets (*12*). Young platelets are more adhesive than older platelets. Consequently, with longer centrifugation times, the younger platelets may be sedimented out of the PRP.

Studies of ideal centrifugation conditions for producing PRP have found the best compromise is 1750–2700 G-min. At higher forces, too many platelets are lost; lower forces result in too much red cell contamination. Optimal conditions for the production of the platelet pellet are less definitive, but 10,000–20,000 G-min appears optimal.

RADIOLABELING TECHNIQUES

Sodium [^{51}Cr]chromate is the usual label used for platelet survival studies. Its abundance of gamma emissions is too low (9%, 320 keV) to allow practical external imaging; therefore, studies with chromium labeled platelets must be performed on blood samples in vitro.

The labeling technique for ^{51}Cr has been standardized (*13*). In vivo studies of ^{51}Cr labeled platelets have indicated normal survival characteristics and a biodistribution similar to that of ^{111}In oxine (*14*) (see Biodistribution Section).

Because of its physical characteristics, ^{111}In is superior to ^{51}Cr as a platelet labeling agent. Indium-111 has two gamma photons in high abundance (90%, 173 keV and 94%, 247 keV), which allows scintillation camera imaging. Another advantage is ^{111}In's 2.8 day half-life, which is considerably shorter than the 27-day half-life of ^{51}Cr.

Oxine (8-hydroxyquinoline) is a lipophilic chelating agent that combines with ^{111}In to form 3:1 complexes having no net charge. Used as a bacteriostatic agent in antiseptics, oxine is toxic in high doses. The safety factor for human labeled cell studies is large, however.

Since the ^{111}In oxine complex is lipophilic, it readily penetrates the platelet cell membrane. Once inside the cell, the indium-oxine complex quickly dissociates and the oxine rapidly leaves the cell with the indium remaining intracellularly bound (a typical labeling technique is shown in Table 1).

Thakur, et al. (*6*) developed the first technique for labeling platelets with ^{111}In oxine. In his technique the ^{111}In oxine was incubated with the platelets in a plasma-free environment. Thakur felt that, to ensure a high labeling efficiency, it was important to remove all the plasma from the platelet button before exposing it to indium-oxine, since indium binds preferentially and with high avidity to transferrin in the plasma.

Although labeling in plasma does reduce labeling efficiencies, some investigators have obtained reasonable yields of 27–67% (*9*). The disadvantage of the lower labeling efficiency may be offset by improved platelet function when platelets are labeled in plasma. Some studies have indicated that morphologic changes occur in blood cells within 10 min of removal from plasma (*15*), and platelets labeled outside of plasma may have decreased ability to aggregate (*16*). However, other studies have found excellent platelet function with platelets labeled in a plasma-free environment (*14*). When high labeling efficiency is necessary, such as with a low number of platelets, labeling in a nonplasma medium is probably best. However, when labeling efficiency is unimportant and viability is a prime concern, labeling in plasma may be the better technique (*9*).

QUALITY CONTROL

Because platelets undergo a tremendous amount of physical and chemical manipulation during labeling, it is important to perform quality control studies on each patient preparation. Unlike indium-labeled leukocytes, with which few tests of function can be quickly and easily performed, platelet viability studies can be performed in almost all laboratories.

First, labeling efficiency and the activity in a post-labeling plasma wash should be measured (*9*). Normally, less than 10% of the radioactivity is removed with washing. An abnormality in the labeling efficiency or wash indicates a significant labeling problem. A low labeling efficiency and high loss of label with washing can indicate either severe mechanical trauma to the platelets with fragmentation of the cells, or inhibition of the normal uptake of ^{111}In. Inhibition of uptake may result from mistakes in preparation of the labeling solution, including errors in chelate concentration, pH, temperature, or osmolality.

Following labeling, the cell suspension should be examined with a phase contrast microscope for platelet aggregates and cell fragmentation. If aggregates of cells or fragments are seen, the preparation should not be administered (*9*).

Platelet counts should also be performed on the labeled cells to be sure the platelet yield in the preparation is adequate. Pro-

cedures using low numbers of platelets may not yield accurate results.

Using an aggregometer, the ability of the platelets to aggregate in vitro can be measured. The labeled cells' response is compared to those obtained using platelet-rich-plasma from the same donor. An aggregometer consists of a light source and detector. The amount of light transmitted through the platelet suspension is measured while aggregation-stimulating agents, such as ADP and collagen are added. Generally, following the addition of the aggregation agent, a marked increase in the percent of light transmitted is seen. This increase indicates primary aggregation. If platelets are damaged, the lag time until aggregation occurs following a stimulation may be delayed, or aggregation may not occur at all. Keep in mind that similar findings may be seen in patients taking antiplatelet drugs (*9*).

BIODISTRIBUTION, RADIATION EFFECTS, AND DOSIMETRY

Other than the peripheral blood, the primary site of platelet pooling is the spleen (*14*). Studies indicate that between 25 and 50% of injected platelets are found in the spleen. Differences in the percentage of splenic activity measured in these studies may be related to differences in labeling methods or variations in the techniques used to quantitate splenic uptake. Pooled platelets are not irreversibly sequestered in the spleen; they are freely exchangeable with the circulating pool. Some investigators have found the liver and lung to be sites of platelet pooling, as well.

Senescent platelets are destroyed by the reticuloendothelial system of the liver and spleen. Platelets damaged by the labeling process are also removed by these organs.

The radiation dose to an individual platelet among 7.5×10^9 ^{111}In labeled platelets separated from 30 cc of whole blood is 12,900 rads/mCi (*17*). This dose is considerably higher than the 1,480 rads delivered to a neutrophil under similar labeling conditions. The surprising high radiation dose to the platelet is related to its relatively small mass (less than a third of the size of a neutrophil) and its longer life span.

Platelets, because they lack nuclei, are highly radioresistant. Studies have indicated normal survival times and function of platelets after radiation doses as large as 50,000–70,000 rads, and, since the cells are post-mitotic, oncogenesis is not a problem. The total body dose from a ^{111}In labeled platelet study is 0.6 rads/mCi, and the highest organ dose is to the spleen, 33.5 rad/mCi.

PLATELET SURVIVAL STUDIES

One of the most common uses of labeled platelets is to measure platelet life span. In normals, the survival curve is usually linear since, as random labels, ^{51}Cr and ^{111}In tag platelets of all ages (*7*). Assuming no damage occurs to the platelets during labeling, the disappearance of platelets from the circulation should be related to their destruction on the basis of age by the reticuloendothelial system (*14*). When radioactivity is plotted versus time, the point at which the straight line representing radioactivity intersects the x (time) axis is the platelet life span (*7*). A linear survival curve argues against ongoing platelet loss in the peripheral vasculature. Platelet life span calculated with linear plots using both ^{111}In- and ^{51}Cr-labeled cells is approximately 9 days (*14*).

Normal survival curves often deviate from the ideal in two ways. First, a plateau is frequently seen in the early part of the curve from 1–48 hr (*14*). Although the cause of the plateau is unknown, it may be related to reversible liver sequestration, as seen when EDTA is used as an anticoagulant, or to a gradual fall in platelet-transit times through the spleen with a net shift of platelets out of the splenic pool. Finally, it may be related to the failure of older platelets to take up the label.

At 7–8 days, the curve again often departs from linearity, forming a prolonged tail (*14*). This pattern appears to be more common with ^{51}Cr-labeled platelets than with ^{111}In-labeled cells and may be related to preferential labeling of younger platelets when low concentrations of chromium are used (*7*).

When platelets are diminished by pathologic processes, other curve shapes are seen. One way to look at these pathologic processes is to use a "hit" model. Each incident in which the platelet is affected by a pathologic condition is called a

TABLE 1. Cell Separation and Labeling with ^{111}In Oxine

50 ml whole blood + ACD (6:1 V/V)

1
- a. Centrifuge at 180 × G for 15 min
- b. Remove supernatant
- c. Discard red cells and white cells

Platelet-rich plasma

2
- a. Centrifuge at 1,800 × G for 7 min
- b. Withdraw and save PPP
- c. Wash with 4 ml ACD:saline to remove contaminating plasma
- d. Centrifuge at 1,800 × G for 7 min
- e. Discard wash solution

Platelet Button

3
- a. Add ^{111}In oxine
- b. Incubate 20 min at room temperature
- c. Centrifuge at 1,800 × G for 7 min
- d. Withdraw supernatant

Labeled Platelets

4
- a. Wash with 4 ml PPP from step 2b to remove loosely bound ^{111}In
- b. Centrifuge at 1,800 × G for 7 min
- c. Withdraw supernatant
- d. Resuspend in 4 ml citrated plasma*

Labeled Platelet Injectate

*Prepared by: 18 ml whole blood + 2 ml 3.8% sodium citrate; centrifuge 180G × 15 min; remove supernatant and recentrifuge 1,800G × 7 min; remove supernatant.
Reprinted with permission (*7*).

"hit." The shape of the survival curve is dependent on the number of hits required to kill the platelet. If only a single hit is necessary, the disappearance becomes random and the curve is exponential. If multiple hits are necessary, the curve is curvilinear and represents a complex function of destruction superimposed on age-dependent removal.

Platelet survival is diminished in a number of pathologic conditions including idiopathic thrombocytopenic purpura (ITP), prosthetic heart valves, arterial grafts, peripheral vascular disease, coronary artery disease, Eisenminger's syndrome, primary pulmonary hypertension, diabetes mellitus, hepatic cirrhosis, hyperlipidemia, and renal transplantation (*14*).

In diseases such as ITP, elution of ^{51}Cr has been observed secondary to platelet-antibody interaction. In these patients, indium appears to give a more accurate survival measurement (*14*).

IMAGING TECHNIQUE

Depending on the area of the body being imaged, a large field camera may be preferred over a standard field camera. A medium energy collimator should be used with both photopeaks (173 and 247 keV) selected with 20% energy windows. Images should be acquired for 5–10 min each. Unfortunately, there are few counts in most body regions where platelet deposition may occur, which provide very low count images. This is, in fact, beneficial because body background is low and abnormal ^{111}In platelet accumulation may be readily evident. Images, especially those of the head and neck or extremities, will require increased time and sufficient intensity settings to obtain adequate film density.

DEEP VENOUS THROMBOSIS

One of the areas in which platelets show the greatest potential is in diagnosing deep venous thrombosis (DVT). Studies with animals have shown excellent results with thrombus/blood ratios of 20:1–50:1 (*6,18,19*). Studies in humans have also given excellent results, yielding a sensitivity of 95% and a specificity of 100% (*20*) (Fig. 1).

The following potential problems are associated with platelet imaging of deep venous thrombosis (*21,22*):

1. In dogs, high dose heparin therapy has prevented visualization of thrombi with indium-labeled platelets. When the heparin was neutralized with protamine sulfate, thrombi became visible within 40 min. Contrary to findings in animal studies, heparin does not appear to have a significant effect on the diagnosis of DVT in humans. The reason for this is not clear. It may be that the uptake seen in humans in the presence of heparin is not related to platelet accumulation on the clot, but rather to uptake at the sites of endothelial injury associated with the thrombi. Also, heparin can potentiate platelet aggregation by neutralizing the effects of prostacyclin (*23*).

2. Uptake of ^{111}In platelets is dependent on thrombus age. As the age increases, less deposition is seen. This aging is related to thrombi becoming more red (i.e., predominantly fibrin with entrapped red cells without the white platelet layers). Although the age at which thrombi would not take up significant numbers of platelets is not known, it has been

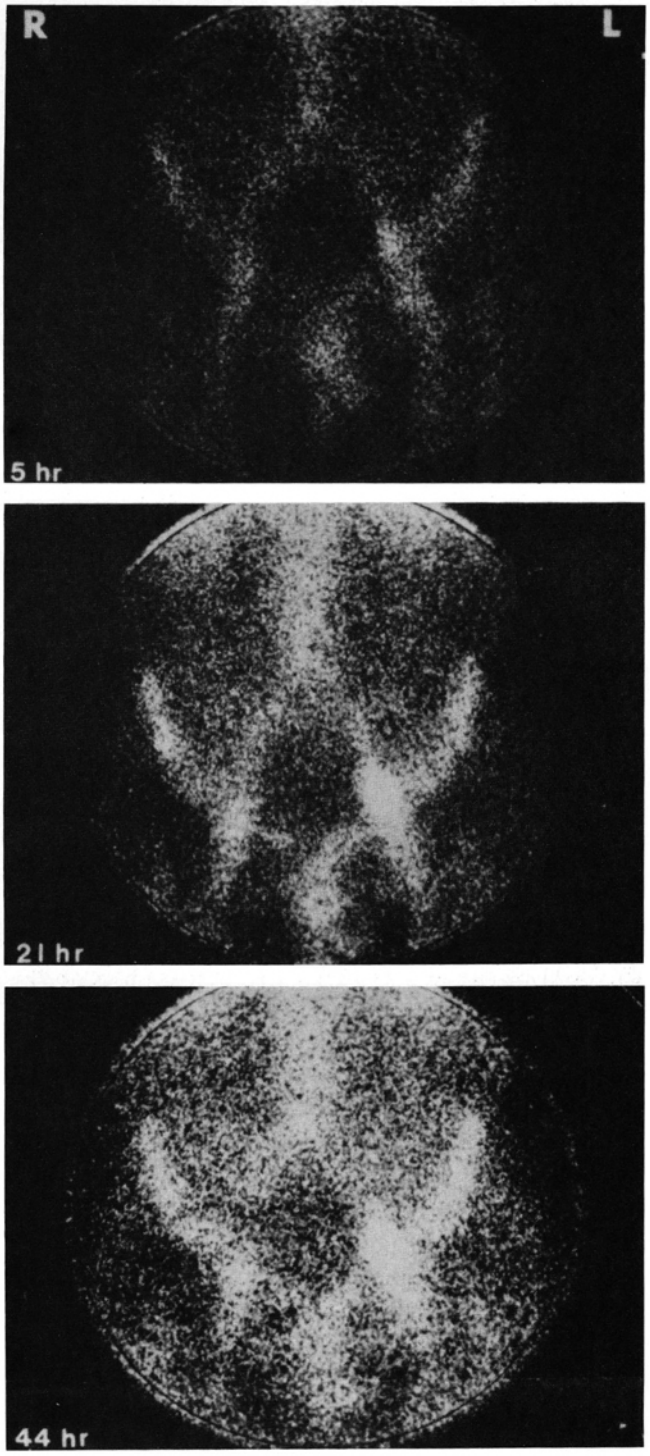

FIG. 1. Indium-111 platelets imaged over the pelvis of a 49-yr-old man with shortness of breath and chest pain. The patient had an episode of left-sided thrombophlebitis 1.5 yr earlier. The images show progressive increased platelet uptake over the left iliofemoral region indicating acute thrombophlebitis. A V/Q scan showed high probability (*23*).

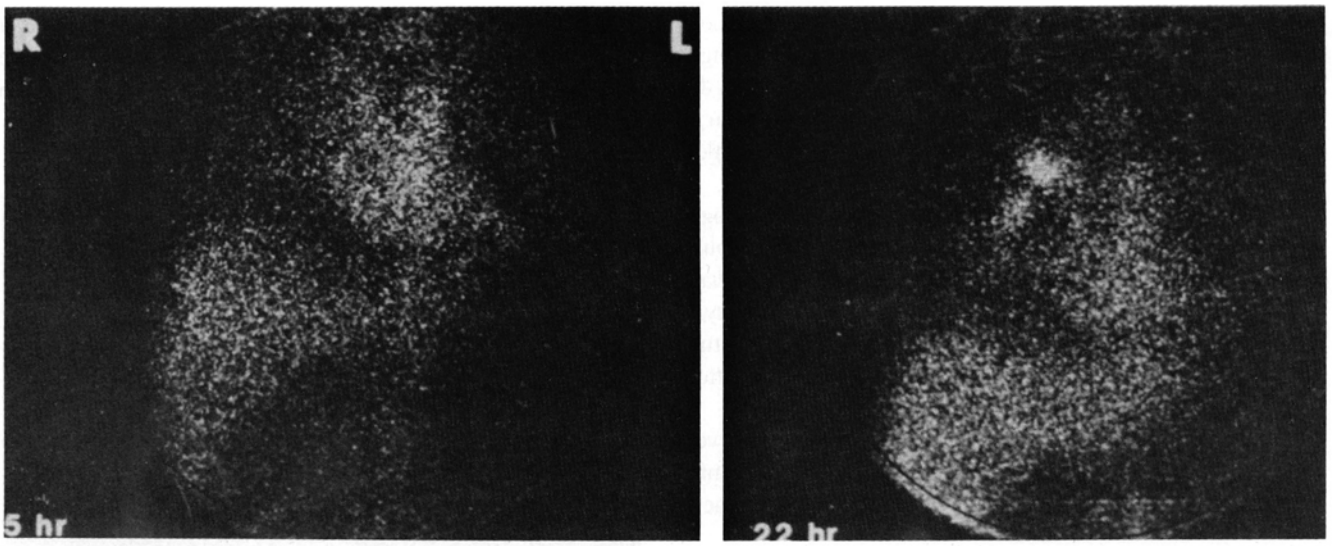

FIG. 2. A 27-yr-old man, status-post renal transplant, with superficial thrombophlebitis. The chest image at 5 hr is normal, but at 22 hr, two areas of ^{111}In platelet accumulation are seen in the right hilar region. A V/Q scan showed mismatched segmental perfusion defects in the right upper and lower lobes (*23*).

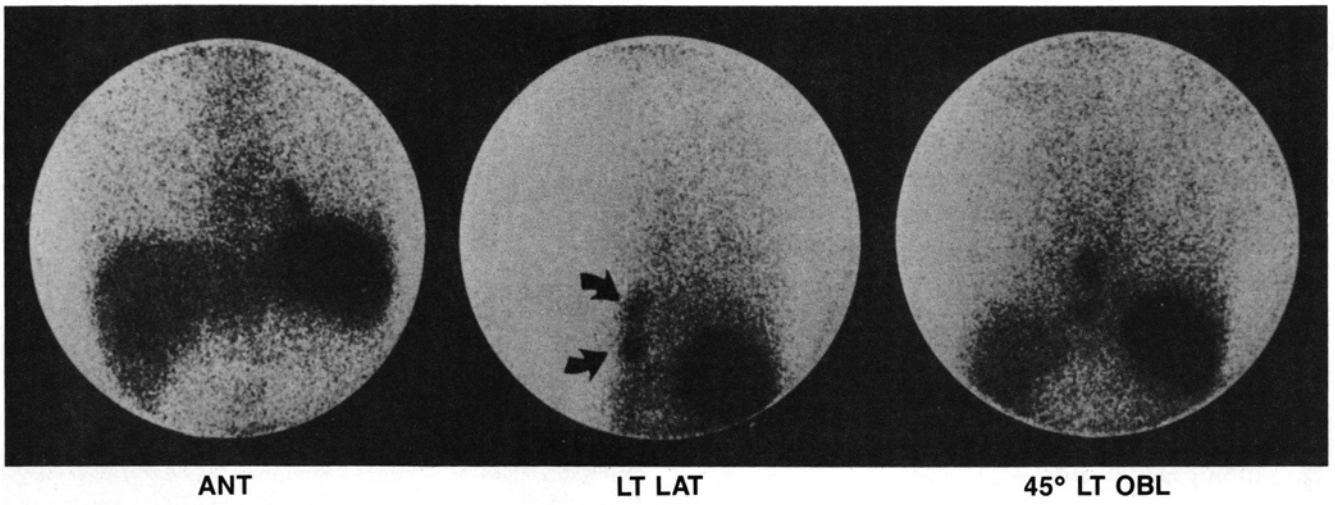

FIG. 3. Indium-111 platelet scan over the chest 4 days post-injection shows uptake in a left ventricular mural thrombus. Patient had undergone an anterolateral infarct. (Reproduced with permission of Dewanjee MK. Cardiac and vascular imaging with labeled platelets and leukocytes. *Semin Nucl Med* 1984;15:154–87.)

estimated at 3–5 days post formation.

3. The older the thrombus, the longer the delay in imaging necessary to visualize the clot. In some cases, delayed imaging from 24–48 hr is necessary.

PULMONARY EMBOLISM

There have been few studies looking at the efficiency of ^{111}In platelets in pulmonary embolism in humans (*23–26*). Thus far, results have been disappointing. In one study, only one patient out of eleven with pulmonary emboli was successfully diagnosed with ^{111}In platelets (*23*) (Fig. 2). This appears to be related to heparin therapy. Unlike deep venous thrombosis, heparin does appear to prevent embolus visualization in humans. It also appears that, although the age of the thrombus itself is not important, the amount of time the thrombus has been in the lung is important. With aging, platelet adherence to the emboli becomes diminished or absent. Another potential problem is that large emboli which cause complete occlusion of arteries may be falsely negative since they are not exposed to labeled platelets in the circulating blood.

THROMBI IN OTHER LOCATIONS

Left ventricular thrombi occur in 50% of patients with left ventricular aneurysms. Contrast ventriculography, the gold

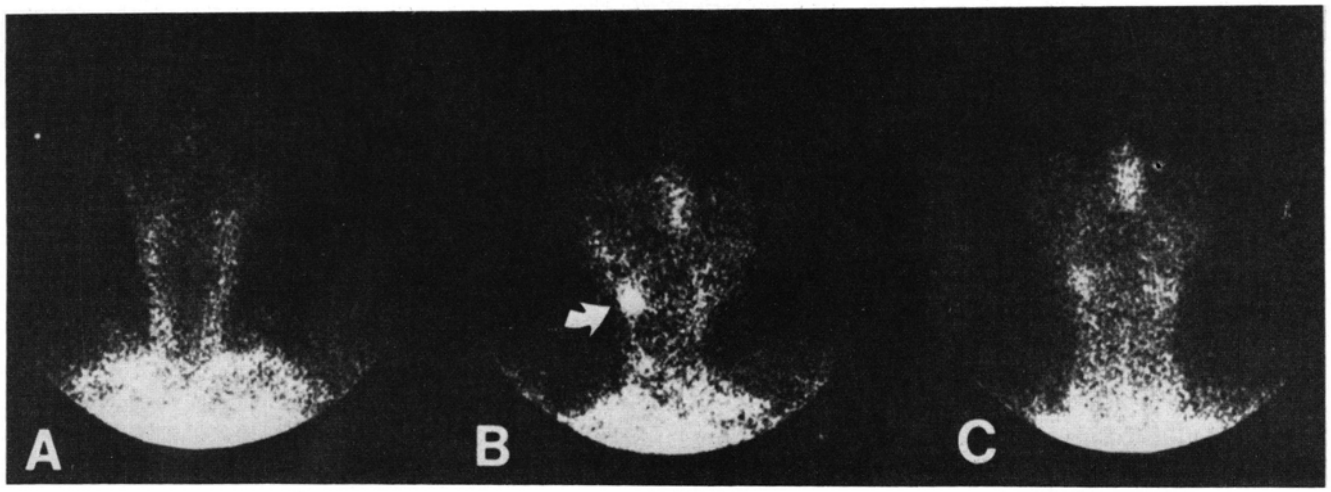

FIG. 4. Indium-111 platelet images over the head and neck. (A) Normal. (B) Uptake (arrow) in right carotid bifurcation in a stroke patient. (C) Mild increased uptake in right bifurcation in a patient with amaurosis fugax (*33*).

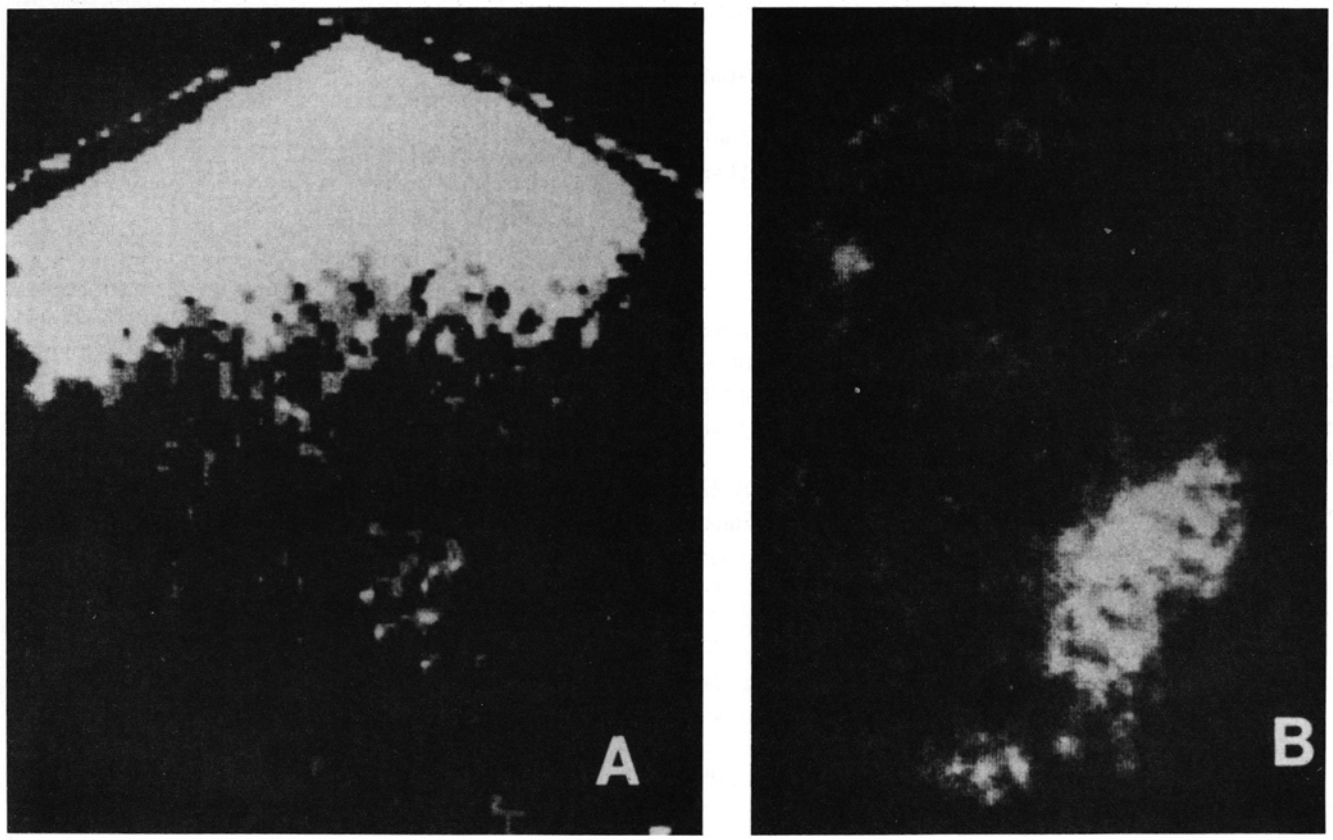

FIG. 5. Indium-111 platelet studies in two patients with renal transplants. (A) Normal graft (graft: opposite fossa ratio 1.2:1). (B) Acutely rejecting transplant (graft: opposite renal fossa ratio 3.5:1) (*35*).

standard, identifies less than 50% of these patients (*27*). Platelets have a higher sensitivity (70%) for ventricular thrombi (*28,29*). Specificity is even better at 100% (Fig. 3). The cases that are missed appear to be related to chronic aneurysms with older thrombi which are less active. Also, many of these patients are on antiplatelet and anticoagulation therapy which can also decrease sensitivity. Indium-111 platelets have also been used to identify renal vein thrombosis (*30*), sagittal sinus thrombosis (*22*) and pelvic vein thrombosis (*31*).

ATHEROSCLEROSIS

The association between atherosclerotic involvement of the

internal carotid artery and cerebral ischemia and infarction is well known (*32*). Fibrin-platelet thrombi are frequently found adhering to plaques at endarterectomy. In addition, platelet emboli have been found in retinal vessels during amaurosis fugax. For these reasons, ^{111}In platelet scintigraphy would appear to be an attractive technique for diagnosing cerebrovascular disease. However, results have thus far been disappointing. Sensitivity for angiographically proven disease averages only 50% (*32–34*) and, platelet deposition is seen in as many as 25% of normals (Fig. 4).

The following are a number of possible explanations for the low sensitivity of platelet studies compared to contrast angiography (*7,22*):

1. The formation of platelet thrombi on plaques may be less important than other factors in the pathogenesis of cerebrovascular disease.
2. Platelet deposition may be occurring in foci too small to detect.
3. Contrast angiography looks at anatomy, not pathophysiology. The fact that there is a lesion present anatomically does not indicate that platelets are actively accumulating and being embolized.
4. The presence of platelets on plaques may be very transient.
5. Antiplatelet and anticoagulation therapy may have some effect on uptake, although most studies have indicated that they do not.

RENAL TRANSPLANT REJECTION

There are a variety of causes of renal failure following renal transplantation, the most important of which are acute tubular necrosis (ATN) and rejection. Since platelets are involved in both cellular and humoral rejection but not in ATN, they can be used to diagnose acute rejection.

Results using ^{111}In platelets to differentiate ATN from acute rejection have been excellent (*35,36*). Comparing the transplant/background activity ratio of the transplant to the opposite renal fossa, ratios of < 1.5 are found in ATN and in normals, whereas in rejection, ratios > 1.5 are seen (Fig. 5). In patients whose antirejection therapy is successful, the ratio usually falls below 1.5. Occasionally, the ^{111}In uptake can lag behind the clinical onset of rejection. Also, ^{111}In platelet imaging does not appear to be of benefit in cases of chronic rejection.

Indium-111 platelet studies have also been used successfully to diagnose rejection of pancreas transplants (*37*).

MISCELLANEOUS CONDITIONS

Platelets may be useful in diagnosing sites of intermittent gastrointestinal hemorrhage (*38*). The platelets appear to adhere at sites of known hemorrhage even after cessation of active bleeding. Platelets have also been used to measure splenic function, blood flow, and platelet transit time (*39*) as well as to detect accessory spleens (*40*).

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