Imaging of Vascular Injury With $^{99m}$Tc-Labeled Monoclonal Antiplatelet Antibody S12

Preliminary Experience in Human Percutaneous Transluminal Angioplasty

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Background. To evaluate the in vivo safety, biodistribution, and diagnostic accuracy of a monoclonal Fab' antibody (S12) that is specific for the platelet membrane glycoprotein (GMP-140) expressed during platelet activation at vascular injury sites, 11 peripheral percutaneous transluminal angioplasty (PTA) patients (age, 61±8 years) with severe vascular disease had serial $^{99m}$Tc S12 radionuclide imaging at 5 and 90 minutes, 4–6 hours, and 20–24 hours after a total of 23 angiographically successful PTA procedures. No acute allergic reactions or hematologic toxicity occurred.

Methods and Results. The average PTA percent angiographic diameter stenosis (DS) at all 23 sites decreased from 85±12% to 12±1%, with a mean before-to-after–PTA change of 73±14% (p <0.01). The mean radionuclide image–derived ratio of $^{99m}$Tc S12 activity in PTA versus contralateral non-PTA arterial segments for all angioplasty sites was 1.6±0.5. Vascular $^{99m}$Tc S12 antibody activity was qualitatively evident in the majority (78%) of PTA sites at 4–6 hours after injection. $^{99m}$Tc S12 target-to-background (muscle) ratio equaled 2.3±0.6 at PTA sites. Nine PTA sites (39%) had residual $^{99m}$Tc S12 activity at 24 hours after injection (mean PTA site–to–contralateral artery ratio, 1.5±0.4). The mean vascular $^{99m}$Tc S12 activity ratios in 10 procedurally complicated (defined as extensive dilation [>2 cm] or grade I or greater arterial dissection) and 13 uncomplicated PTA segments were 1.9±0.5 versus 1.2±0.1, respectively (p<0.01). The associated before-to-after–PTA angiographic improvement was significantly less in procedurally complicated PTA sites (66±12% versus 80±12% DS; p<0.01).

Conclusions. $^{99m}$Tc S12 activity is significantly increased at angiographically patent PTA sites that are procedurally complicated and are associated with less significant before-to-after–PTA angiographic improvement. $^{99m}$Tc S12 monoclonal Fab' antibody imaging permits noninvasive identification of local vascular platelet activation resulting from angioplasty balloon injury in humans. (Circulation 1992;85:1354–1363)

Key Words • percutaneous transluminal angioplasty • radionuclide imaging • monoclonal antibodies • platelets • restenosis

Percutaneous transluminal angioplasty (PTA) is a proven alternative to surgical revascularization for the treatment of atherosclerotic vascular disease. Despite a high initial success rate, there is an unpredictable early (6-month) restenosis rate of between 30% and 50%.1–3 Platelet-derived growth factor (PDGF) is a two-polypeptide chain protein secreted from platelet $\alpha$-granules after their activation by endothelial injury.4–7 Binding of PDGF and other growth factors to local receptors induces smooth muscle cell migration and intimal proliferation predisposing to postangioplasty restenosis.8–10 Recent technical advances in monoclonal antibody preparation techniques have permitted development of radionuclide-labeled tracers with specificity for components of the atherosclerotic plaque and related thrombus, including translocated platelet granular surface membrane antigens.11–13 The hybridoma-produced monoclonal Fab' antibody S12 (or anti-PADGEM) has high in vitro14–16 and in vivo17–20 specificity for GMP-140, the platelet membrane glycoprotein expressed acutely during PDGF release from platelet $\alpha$-granules.

The goal of the current study was to extend experimental studies11,14–19,21 by evaluating the safety, biodistribution, angiographic correlates, and preliminary diagnostic accuracy of ($^{99m}$Tc) monoclonal Fab' S12 antibody imaging as an in vivo marker of local platelet activation after balloon angioplasty in patients with severe atherosclerotic disease.
Methods

Patient Population

The patient population was drawn from the University of Texas Health Science Center teaching hospitals (Medical Center Hospital, Audie L. Murphy Veterans Administration Hospital) in San Antonio. Eleven patients aged 61±8 years (10 men and one woman) with severe peripheral vascular disease producing rest pain (n=8) and/or tissue loss (n=8) gave informed consent to participate in this study. All patients were evaluated by an experienced interventional radiologist (J.C.P. or F.J.R.) before angioplasty. The distribution of 23 angioplasty sites was iliac (n=2), superficial femoral (n=6), profunda femoral (n=1), popliteal (n=5), and tibial-peroneal (n=9) arteries.

Angiography

All diagnostic studies and angioplasty procedures were performed using a digital subtraction angiography system (General Electric LUA or Philips DVI) with a 9-in. field image intensifier and 512×512 image matrix. Unzoomed images were formatted with grading of masked and unmasked x-rays.

Intravenous nitroglycerin (400 μg) was given to ensure maximal vasodilatation before angiography. All patients received heparin (5,000 U intravascularly) during angioplasty and by continuous infusion for 24–48 hours after the angioplasty procedure. Coumadin (n=3) and urokinase (n=2) were coadministered in selected patients for clinical reasons. Three patients had received aspirin within 1 week of the PTA procedure.

Angiographic percent luminal diameter stenosis (DS) severity was graded before and after the procedure at each angioplasty site by two experienced radiologists blinded to the experimental protocol. The mean pre-PTA to post-PTA percent change in stenosis severity was calculated (percent delta stenosis). Procedurally complicated PTA was prospectively defined as either dilation of an extensive (>2 cm) arterial segment or grade I or greater intimal dissection. This occurred at 10 PTA sites. Angiographic PTA success, present in all studies, was prospectively defined as a ≥30% decrease in the pre-PTA luminal percent DS to a residual postangioplasty luminal percent DS of 50% or less.

Side Effects and Safety Monitoring

Patients with previous exposure to monoclonal antibodies or mouse protein (i.e., animal laboratory technicians) were prospectively excluded from these studies. All patients underwent a detailed history and physical examination, including evaluation of vital signs and baseline hematologic and biochemical blood analysis.

For 1 hour after injection, each patient underwent serial monitoring of vital signs and repeated questioning for symptoms of local or systemic allergic reaction. A postinjection physical examination and evaluation of hematologic and biochemical parameters were performed at 24 hours. All patients remained hospitalized for at least 5 days after antibody injection and underwent serial evaluation of hematologic and biochemical parameters.

99mTc Monoclonal Antibody Preparation

The Fab’ fragment was prepared from hybridoma-produced IgG by pepsin digestion followed by reduction of the F[ab’]2 with diithothreitol. The purified S12 Fab’antibody fragment was labeled with 99mTc using the two-vial “kit” method of Pak et al.21 One milliliter of TC04 (20-40 mCi/ml) was eluted from a 99mTc/99Mo generator and transferred into a lypophilized vial containing 12.5 mg 2-glucarate and 150 mg stannous chloride. After incubation at room temperature for 2 minutes, 400 μl 99mTc was mixed with 400 μl Fab’.

The final specific activity was 20 mCi/mg and the protein concentration was 1 mg/ml in the labeling solution. The incorporation of 99mTc was quantitated by gel filtration-high-performance liquid chromatography equipped with radiometric detector and instant thin-layer chromatography (ITLC, Gelman Sciences). Preparations with labeling efficiency of >90% were used.

99mTc S12 Radionuclide Imaging Protocol

99mTc S12 Fab’ monoclonal antibody (15 mCi) was injected via an upper extremity vein followed by a 10-ml saline flush. All doses were evaluated by a radiation calibration system before administration. Imaging of the injection site confirmed no infiltrated doses. A 99mTc marker was used to locate the level of the knee before image acquisition (10 seconds) and was then removed. Efforts were made to minimize patient motion. All patients were well hydrated and encouraged to void before and after imaging. In selected patients, an oval-shaped lead shield was used to attenuate secondary activity in the bladder and/or gonads.

99mTc S12 Fab’ injection was performed within 24 hours after angioplasty. Radionuclide imaging was performed with a large field-of-view planar gamma camera (Scintorinix Co.) equipped with a high-resolution collimator. Images were acquired without the use of a zoom function into a 129×129-byte computer matrix.

Image acquisition time was 2, 5, 10, and 10 minutes per view at 5 minutes, 90 minutes, 4–6 hours, and 20–24 hours after injection, respectively. Anterior and posterior images of the pelvis and leg above and below the knee were obtained. All images were acquired by a nuclear medicine technologist with previous experience using 99mTc S12 in an animal angioplasty model.17,18,22

All scintigraphic data were viewed with the aid of a Medasys Pinnacle imaging computer (Ann Arbor, Mich.). Image regions of interest (ROIs) were placed by consensus of two blinded observers and guided by the angiographic location of angioplasty sites in pre-PTA studies in the balloon-dilated and contralateral unoperated arterial segments at the arteriotomy site and in the adjacent muscle (background). Early visualization of arterial blood pool assisted in subsequent assignment of ROIs at angioplasty and contralateral artery sites and by correlation of radionuclide images with pre-PTA digital subtraction angiography studies.

Statistical Analysis

Mean group values±1 SD are used in all tables and figures. After performance of a Wilk-Shapiro test of normality, mean±1 SD values of parametric and nonparametric data for continuous angiographic, radionuclide image–derived, and toxicity data were statistically
were decreased bladder (0.7 brachial) 24 hours perceptible activity.

suggestive, the sites puncture 23 patients.

were noted injection. Activity at arteriotomy sites were present in seven of 11 studies (six femoral, one brachial) but was only slightly increased above background activity.

compared using a two-tailed t test. A significance level of p<0.05 was required to reject the null hypothesis. Statistics were performed using commercially available software (R/S-1, Bolt Baranek-Newman, Cambridge, Mass.).

Results

Qualitative Image Analysis

As summarized in Figure 1, the biodistribution of 99mTc S12 5 minutes after injection demonstrated significant blood pool activity that gradually decreased by 90 minutes. Local 99mTc S12 activity visualization at angioplasty sites was optimal at 4–6 hours after injection. Regional accumulation of 99mTc S12 antibody activity, distinct from blood pool and background, was qualitatively evident in 18 of 23 (78%) angioplasty sites. Two iliac angioplasty sites (one common and one external) were not well visualized because of significant adjacent bladder activity despite the use of a catheter to enhance renovesicular activity excretion in one patient. In addition to this, one popliteal, one tibial–peroneal, and one common femoral site did not demonstrate increased local 99mTc S12 activity despite low background counts. Residual activity was still noted in nine of 23 angioplasty sites (39%) at 20–24 hours after injection. Activity distinct from blood pool was noted at arteriotomy puncture sites (femoral, six; brachial, one) in seven of 11 patients.

Secondary activity was greatest in the kidney and bladder, the sites of antibody excretion blood pool clearance. Additional variable secondary activity was noted in the spleen and liver up to 4–6 hours after injection. Vertebral and iliac bone marrow activity was observed in five of 11 patients beyond 90 minutes after injection. Minimal background activity was noted in soft tissue and muscle adjacent to arterial PTA segments. Secondary counts did not interfere with local vascular 99mTc S12 visualization in the majority (91%) of arterial injury sites.

Quantitative Image Analysis

Regional antibody clearance kinetics. In addition to initial 99mTc S12 antibody binding to GMP-140 platelet sites, the early (<6 hours) and late (6–24 hours) clearance rates of 99mTc S12 activity may also contribute to regional vascular differences in activity after radiotracer injection.

The overall 0–24-hour postinjection clearance half-time for 99mTc S12 activity in angioplasty sites, contralateral arteries, and background muscle averaged 208±9, 205±10, and 220±21 minutes, respectively (p=NS). The early (5 minutes to 4–6 hours) clearance half-time for 99mTc S12 activity averaged 57±9, 56±10, and 67±22 minutes in the same ROIs (p=NS). The most significant change in regional activity occurred between the 5- and 90-minute image sets, with 72±5%, 75±6%, and 68±13% of initial activity clearing over this time interval in these ROIs. The percent of original (5 minutes after injection) activity that had cleared by 4–6 hours after injection was 94±3%, 94±2%, and 90±7% in PTA sites, contralateral arteries, and background muscle, respectively (Figures 2A and 2B). Overall clearance rates did not differ significantly between complicated and uncomplicated angioplasty sites (209±6 versus 199±12 minutes; p=NS; Figure 2C).

99mTc S12 activity in angioplasty sites. Angiographic data in procedurally complicated and uncomplicated sites are summarized in Figure 3 (also see Table 1). Two patients had extensive >2-cm dilatation, and four patients experienced intimal dissection. The mean 99mTc S12 activity ratio was higher in 18 qualitatively visualized angioplasty sites at or below the level of the inguinal ligament (1.7±0.5 versus 1.1±0.1; p<0.05). The 4–6-hour postinjection 99mTc S12 activity ratio averaged 1.6±0.5 for all 23 sites, ranging from 1.0 in an uncomplicated external iliac artery site (adjacent to the bladder) activity to 2.9 in an extensive popliteal–tibial–peroneal artery angioplasty site that required multiple prolonged inflations (see Figure 4). Nine angioplasty sites (four complicated and five uncomplicated) with persistently visible 20–24-hour postinjection 99mTc S12 activity had a mean 99mTc S12 activity ratio of 1.5±0.4 (see Figure 5), including a value of 2.0 at one superficial femoral site with grade I dissection and at another complex angioplasty of a 6-cm popliteal artery–vein graft anastomosis.

The 4–6-hour 99mTc S12 activity ratios in 10 procedurally complicated and 13 uncomplicated sites were 1.9±0.5 and 1.2±0.1, respectively (p<0.01; see Figure 6). The 4–6-hour target-to-background (muscle) ratio was 2.3±0.6 and 4.4±1.7 at all 23 angioplasty and seven visible arteriotomy sites, respectively.

There was no significant linear or nonlinear correlation between the pre- or post-PTA percent DS and the quantitative 4–6-hour 99mTc S12 activity ratio when all PTA sites were analyzed. Two patients with multiple extensive angioplasty dilatations in three superficial femoral artery sites, one tibial–peroneal–popliteal site, and one popliteal artery site had markedly increased 99mTc S12 activity ratios (2.3±0.4) despite an excellent angiographic result and no angiographically visible
thrombus. In these sites, the average postangioplasty percent stenosis (10%) and average percent change in DS (71±7%) during PTA did not differ from other sites and supported a successful angiographic result (see Figure 7). These patients did not differ clinically from the other patients; both received heparin during and after the angioplasty procedure. The extensive balloon dilation of arterial segments (four serial lesions over 16 cm in one and one continuous site of 6 cm in the other) may have contributed to rheological disturbances predisposing platelet activation despite angiographic PTA success in these patients.

Coumadin and urokinase were administered to three patients (one received coumadin only, and two received coumadin and urokinase). The mean 4–6-hour S12 injury ratio in these patients (five sites) was 1.4±0.3. Of interest, all three patients exhibited 24-hour S12 activity in at least one angioplasty site (mean activity ratio, 1.5±0.5). The $^{99m}$Tc S12 activity ratio in this subset of three patients (five PTA sites) receiving coumadin/urokinase was not significantly different from that observed in the other patients.

Initially, distal perfusion was improved by angioplasty in association with restoration of pulses, improved skin temperature, and angiographic runoff in all patients. Four patients with advanced distal vascular disease subsequently proceeded to limited amputation because of tissue loss or revascularization associated with recurrent severe rest pain at 13±6 days after angioplasty. Two patients required subsequent distal arterial embolectomy. The 4–6-hour and 24-hour $^{99m}$Tc S12 activity ratios were not correlated with the occurrence of these complications.

**Acute Toxicity Evaluation**

Monitoring of vital signs before and during the first hour after injection demonstrated no significant change

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**Figure 2.** Graphs show $^{99m}$Tc S12 Fab' activity clearance curves derived from angioplasty (PTA) and contralateral (non-PTA) site regions of interest, with (panel A) and without (panel B) background subtraction. There was no difference in S12 activity clearance from PTA versus non-PTA sites and no difference in S12 clearance from procedurally complicated versus uncomplicated PTA sites (panel C).

**Figure 3.** Bar graph of results in $^{99m}$Tc S12 study population. Patients are subgrouped according to presence or absence of complicated percutaneous transluminal angioplasty (PTA): 13 patients without and 10 patients with procedurally complicated PTA had no significant difference in preangioplasty (89±12% vs. 80±9%) or postangioplasty (10±11% vs. 18±15%) lesion severity. However, there was a significant difference in pre- to postangioplasty percent delta stenosis, which was significantly greater in the procedurally uncomplicated subgroup (80±12% vs. 66±12%; p<0.02). Procedurally, complications were prospectively defined as extensive (>2 cm) arterial segment dilation or post-PTA intimal dissection grade 1 or greater.
in systolic blood pressure (145±24 to 146±17 mm Hg; p=NS), diastolic blood pressure (81±16 to 78±14 mm Hg; p=NS), heart rate (78±9 to 78±10 beats per minute; p=NS), respiratory rate (20±3 to 19±4 per minute; p=NS), or temperature (98.2±1 to 98.4±1°F; p=NS). (See Table 2.)

There was no evidence of local urticaria or hypersensitivity reaction after 99mTc S12 injection. There were no systemic complaints attributable to an allergic reaction. One patient noted a transient dry cough while supine for several minutes after injection without associated auscultatory evidence of bronchospasm.

Analysis of blood biochemistry and hematologic data indicated no significant derangements from the preinjection state after 99mTc S12 injection. Prothrombin time was 13.1±4.4 seconds before injection and 13.6±2.2 seconds after injection (p=NS). Partial thromboplastin time was 33.5±9.7 seconds before injection and 35.9±13.5 seconds after injection (p=NS). Bleeding time was 3.6±1.8 minutes before injection and 4.3±2.7 minutes after injection (p=NS). There was no significant change in the quantitative platelet count from the pre- to postinjection (24–72-hour) time points (397±131 to 408±154×10³/mm³; p=NS).

**Discussion**

The current clinical study confirms previous 111In-labeled platelet imaging studies23–26 and extends our experimental observations7,22 by demonstrating significantly increased local 99mTc-labeled monoclonal S12 Fab' antibody activity at sites of angioplasty-induced vascular injury in human atherosclerotic arteries. The presumed mechanism of this increase is S12 antibody binding to the translocated α-granule membrane glycoprotein (GMP-140) expressed at the surface of activated platelets in vascular balloon injury sites.15,16

Significant 99mTc S12 activity was observed despite angiographic patency and in the absence of visible thrombus, particularly in complex angioplasty sites and at sites with a suboptimal pre- to postangioplasty percent diameter stenosis reduction. Residual postangioplasty turbulence and increased shear stress associated with a suboptimal procedural result are known to contribute to local platelet activation.23,24,27 Arterial damage and resulting changes in vascular shear rate can affect platelet activation in patients.28,29 Significantly increased thrombus formation occurs in association with increasing shear stress in deep arterial injury models30 and an ex vivo swine arterial model.31 Two patients who required extensive areas of dilation with a satisfactory angiographic result and no evidence of dissection demonstrated markedly increased local 99mTc S12 activity at five angioplasty sites. Increased local vascular 99mTc S12 binding at these sites may have been predisposed by individual biological and/or local rheological factors.

The comparability of 99mTc S12 activity clearance kinetics between the angioplastied and unoperated contralateral vascular ROIs implies that the greatest con-

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**Table 1. Summary of Clinical, Angiographic, and Radionuclide Data**

<table>
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<tr>
<th>Patient</th>
<th>Indication</th>
<th>Age (yr)</th>
<th>Drugs</th>
<th>PTA site</th>
<th>Stenosis (%)</th>
<th>Complication</th>
<th>Pre</th>
<th>Post</th>
<th>Delta</th>
<th>4–6 hours</th>
<th>24 hours</th>
<th>Target to BKGD ratio</th>
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PTA, percutaneous transluminal angioplasty; BKGD, background activity; Hep, heparin; UK, urokinase; Cou, coumadin; TL, tissue loss; L, left; RP, rest pain; SFA, superficial femoral artery; R, right; CL, claudication.

**Notes:** 1. Data are expressed as mean ± SD unless otherwise indicated. 2. *P* values were determined using Student's *t*-test. 3. *P* values were determined using the paired *t*-test. 4. *P* values were determined using the unpaired *t*-test. 5. *P* values were determined using the Mann-Whitney U test. 6. *P* values were determined using the Fisher's exact test. 7. *P* values were determined using the chi-square test. 8. *P* values were determined using the Kruskal-Wallis test.
FIGURE 4. Top panel: Angiograph of a 61-year-old man undergoing complex angioplasty for rest pain and tissue loss in the right popliteal-tibial-peroneal artery trifurcation demonstrates excellent angioplasty result with reduction of percent diameter stenosis from 90% to 10%. Bottom panel: Corresponding 4-hour $^{99m}$Tc S12 antibody images from this patient demonstrates intense focal uptake with injury ratio of 2.0 at the complex angioplasty site and minimal activity in the contralateral unoperated artery.
FIGURE 5. Bar graph shows 99mTc S12 activity in radiouclide images at visualized and nonvisualized percutaneous transluminal angioplasty (PTA) sites at 4–6 hours after injection. Qualitatively visible angioplasty sites had significantly greater S12 activity ratios (1.7±0.5 vs. 1.1±0.1). Residual activity was still present in nine of 18 sites at 20–24 hours after injection (1.5±0.4). Continued 99mTc S12 activity implies sustained S12–GMP-140 binding at angioplasty site.

Previous Platelet Imaging Studies

Radionuclide imaging of 111In-labeled autologous platelets was the first diagnostic approach used to visualize vascular platelet activity after peripheral angioplasty24,25 and acute coronary thrombosis.26 These studies were compromised by the need to remove platelets for labeling followed by reinfusion, high nonspecific blood pool background activity, and the requirement for thrombus to incorporate newly labeled platelets at the time of injection.

Initial studies with radiolabeled monoclonal antibodies specific for the platelet plasma membrane glycoprotein IIb–IIIa complex in a venous thrombus model12 were also limited by high nonspecific blood pool background originating from both activated and inactivated circulating platelets. A new group of highly specific monoclonal antibodies (AC1.2, P256, S12) identifies the α-granule membrane protein GMP-140, also known as PADGEM protein, which is expressed after platelet activation.11,14–19 Radiolabeled S12/anti-PADGEM antibody imaging has the advantages of low blood pool activity and rapid blood pool clearance, with in vivo 2-hour target-to-background ratios averaging 3:1.11,17

The labeled monoclonal antibody used in the current study, 99mTc S12, has previously demonstrated significantly increased uptake at angioplasty sites in atherosclerotic rabbit aortas when injected within 15 minutes of balloon injury.17 Immunohistopathological studies of S12 binding to activated platelets from angioplasty injury sites demonstrate high (22:1) in vivo specificity compared with nonrelevant antibodies. Angioplasty site uptake of 99mTc S12 decreases significantly by 1 week after balloon injury,22 when activated platelets are histologically absent and neointimal proliferative vascular repair response is underway.4,7

Safety Evaluation

Another than the need for intravenous injection, the gamma camera imaging technique used is totally noninvasive, with radiation exposure similar to other routine diagnostic scans. Dosimetry studies in the rabbit, supported by biodistribution data in the current clinical study, indicate that the kidney is the critical organ (0.0885 mGy/MBq; 0.327 radian/mCi). The sustained 20–24-hour activity observed in the kidneys and bladder reflects the fact that the urine is the primary route of Fab’ antibody excretion. Frequent voiding or the placement of a urethral catheter should decrease the radiation burden to the bladder.

As with the administration of any murine monoclonal antibody, a risk of allergic reaction exists. However, the potential for such reaction is reduced by the use of small Fab’ fragments for imaging. Extensive toxicity studies, including rechallenge of rabbits with second doses of antibody, have failed to demonstrate any hypersensitivity reactions (Centocor, data on file). No local urticarial or hypersensitivity reactions occurred after 99mTc S12 injection, and patients did not complain of local injection site discomfort. Vital signs (see Table 2) were unchanged from preinjection levels during 1 hour of monitoring after injection.

Detailed analysis of blood biochemistry and hematologic data indicated no significant derangements from preinjection levels. In particular, platelet inhibitory,
FIGURE 7. Left panel: Digital subtraction angiogram of a 55-year-old man undergoing percutaneous transluminal angioplasty (PTA) for rest pain and tissue loss. Before angioplasty, serial focal lesions were observed in the left superficial femoral artery and left tibial peroneal popliteal artery (70–85% diameter stenosis). After angioplasty, a residual stenosis of 10% was observed at each of the four angioplasty sites. Bottom panel: Corresponding 4-hour 99mTc S12 antibody images demonstrate discrete areas of increased activity at each of the four angioplasty sites. 99mTc S12 activity ratio equaled 1.9, 2.3, 2.3, and 2.9, respectively, a mean increase of 135 (±50%) in comparison with the contralateral unoperated artery.

anticoagulant, or procoagulant activity was not noted after 99mTc S12 injection. Rabbit studies have also demonstrated that the administration of S12 antibody does not significantly affect or inhibit the ex vivo platelet aggregation reaction induced by 20 mM ADP (Cento- cor, Inc., data on file).
Clinical Implications

The release of PDGF from the platelet α-granule is postulated to predispose to smooth muscle cell hyperproliferative restenosis. New technical and pharmacological approaches designed to take advantage of the growing basic understanding of the role of local growth factor secretion in the biology of vascular injury and the pathogenesis of postangioplasty restenosis have been difficult to evaluate because a simple noninvasive in vivo measure of local platelet activation has been lacking.

The current study demonstrates for the first time in humans that a platelet membrane–targeted, specific monoclonal antibody, when radiolabeled for noninvasive imaging, can safely identify the majority (78%) of recent angioplasty injury sites in 91% of patients studied (10 of 11) without significant image degradation or loss of specificity caused by blood pool activity. The observed association of higher local 99mTc S12 activity at angiographically patent but procedurally complicated angioplasty sites correlates with previous basic studies of quantitative platelet deposition at sites of increased vascular turbulence and abnormal rheology.

The mechanisms and rates of postangioplasty restenosis in the peripheral and coronary beds are comparable. Our initial clinical experience with 99mTc S12 imaging of a coronary angioplasty patient as well as nonimaging flow cytometric data confirming augmented platelet GMP-140 expression in the coronary effluent of angioplasty patients and unstable angina patients supports the possible extension of these peripheral vascular studies to the setting of coronary angioplasty and acute ischemic coronary syndromes. The widely postulated and experimentally supported hypothesis that local thrombosis and growth factor release are important mediators of hyperproliferative restenosis may now be evaluable in humans by using longitudinal angiographic and S12 scintigraphic studies.

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References

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Table 2. Safety Monitoring

<table>
<thead>
<tr>
<th>Vital signs</th>
<th>Before S12</th>
<th>After S12</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>145±24</td>
<td>146±17</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>81±16</td>
<td>78±14</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>78±0.9</td>
<td>78±10</td>
<td>NS</td>
</tr>
<tr>
<td>Respiration rate (min⁻¹)</td>
<td>20±3</td>
<td>19±4</td>
<td>NS</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>98.2±1</td>
<td>98.4±1°</td>
<td>NS</td>
</tr>
</tbody>
</table>

Blood

| Prothrombin time (sec)                           | 13.1±1.4   | 13.6±2    | NS  |
| Partial prothrombin time (sec)                  | 33.5±9.7   | 35.9±13.5 | NS  |
| Bleeding time (min)                              | 3.6±1.8    | 4.3±2.7   | NS  |
| Platelets (1,000/mm³)                            | 397±131    | 408±154   | NS  |


Imaging of vascular injury with 99mTc-labeled monoclonal antiplatelet antibody S12. 
Preliminary experience in human percutaneous transluminal angioplasty.
D D Miller, F J Rivera, O J Garcia, J C Palmaz, H J Berger and H F Weisman

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