111-Indium Platelet Imaging, Doppler Spectral Analysis and Angiography Compared in Patients with Transient Cerebral Ischaemia


SUMMARY We have evaluated carotid gamma imaging using 111Indium-labelled platelets in the diagnosis of carotid artery disease and measured the accumulation of labelled platelets on endarterectomy specimens.

Autologous 111In labelled platelets were injected in 25 patients with TIA. Gamma images were then taken daily and independently interpreted by two observers. Carotid endarterectomy was performed in 11 patients allowing measurement of the radioactivity on the operative specimen. These results were compared to the findings on angiography and Doppler spectral analysis.

All endarterectomy specimens accumulated platelets with the most active equivalent to platelets from 1.8 ml blood. Atheromatous ulcers were more active than stenoses with mean (± sem) activities of 1.12 ± 0.37 and 0.38 ± 0.10 respectively. These radioactivity levels were at the threshold of gamma camera resolution in a theoretical model. Both observers agreed that 22 of the 50 carotid bifurcations showed platelet accumulation on gamma imaging. Of the 12 atheromatous ulcers demonstrated by angiography 11 were visualized, but only five of ten stenoses greater than 80% were detected. As Doppler identified all stenoses only one angiographically diseased carotid was not detected by combining ultrasound with platelet scanning.

Atherosclerotic arteries accumulate 111In platelets and the more thrombogenic ulcerated plaques are identified more frequently than stenoses. Long-term follow-up is required to establish the clinical relevance of platelet deposition.

MANY PATIENTS suffer transient ischaemic attacks (TIA) or stroke as a consequence of extracranial carotid artery disease. These symptoms may be caused by either a high grade stenosis disturbing cerebral blood flow or an ulcerated plaque stimulating thrombotic cerebral embolism. As stenoses may also cause emboli, prophylaxis against stroke depends on first establishing the pathophysiology in each individual, although surgical intervention is often advocated for stenoses and drug therapy for other lesions. Angiography is usually used for the diagnosis of operable lesions in patients with TIA but may miss up to 40 percent of atherosclerotic ulcers and is not without risk. Doppler ultrasound is reliable for haemodynamically significant stenoses but not for non-stenotic lesions. Furthermore, conventional investigations cannot detect thrombus deposition and embolisation although evidence for the role of these processes is found on examination of surgical specimens.

Indium (111In) labelled platelets have recently been detected in diseased carotids by gamma imaging. We were attracted by the possibility that the embolic causes of TIA evaluated by 111In platelet techniques may be distinguished from the haemodynamic causes which are detectable by doppler ultrasound. Hence we studied the deposition of autologous 111In-labelled platelets on diseased carotid arteries in patients in whom angiography and doppler ultrasound examination were also performed so that platelet uptake could be related to the type of lesion. We also measured the radioactivity on endarterectomy specimens to investigate whether the activity found could be reliably detected by a gamma camera or quantitated by external counting.

Patients and Methods

Twenty-five patients with a clinical diagnosis of unilateral TIA gave informed consent and entered the study. A TIA was defined as either amaurosis fugax or a focal neurological deficit, referable to the carotid artery territory and with complete resolution within 24 hours. There were 19 men and 6 women with a mean age of 60 years. All but 2 patients had suffered a TIA within one month of entry and 11 were receiving prophylactic aspirin therapy. All patients were assessed by 111In platelet study and Doppler spectral analysis. When angiography was also performed (18 patients) 111In platelet investigations were delayed for 48 hours to prevent artefacts arising from arterial puncture or injection of contrast medium.

111In Platelet Studies

Autologous platelets were labelled with 5.55–7.4 MBq (150–200 μCi) of 111In oxine by a method described previously. Four hours after injection of the labelled platelets anterior neck images were obtained over a 10 minute period using a Searle LFOV gamma camera fitted with a medium energy parallel hole collimator and utilizing both 111In energy peaks. Patients were seated and imaged erect to reduce venous filling and background radioactivity in the neck. Images were...
repeated at 24 hour intervals up to a maximum of 5 days. An on-line DEC PDP 11/40 computer was used to store the information enabling each patient's images to be displayed sequentially at the end of the study period. These were interpreted independently by a physicist and a clinician without knowledge of clinical details or other investigations. Any increase in activity at either carotid bifurcation with respect to the surrounding tissue was considered to represent \(^{111}\)In-platelet deposition and was reported positive (fig. 1). Thus each observer reported a total of 50 bifurcations in 25 patients, but only the physicist's opinion was used in subsequent clinical comparisons.

Eleven patients underwent carotid endarterectomy 48 hours after platelet labelling. The surgical specimens were retrieved and after washing to remove blood containing labelled platelets, their radioactivity was counted in a scintillation well crystal. A 5 ml blood sample, taken at surgery was simultaneously counted. Platelet deposition (specimen activity) was expressed as a ratio of emissions from the endarterectomy specimens over those from 1 ml of blood, thus avoiding the need to correct radioactivity counts for variation in injected dose and isotopic decay.

Ultrasonic Examination

A real time spectrum analyser (Spectroscribe) linked to directional dopplers (Sonicaid BV 380) was used to analyse sonagrams of the common carotid, internal carotid and supra-orbital arteries. Lesions in the internal carotid were classified as stenoses only if considered haemodynamically significant.

Angiography

Biplanar angiography was carried out in 18 patients and assessed independently with internal carotid lesions classified as either stenosis, if narrowing was greater than 80% of the luminal diameter, or atheromatosus ulcer/plaque. No attempt was made to distinguish ulcerated from non-ulcerated lesions and minimal atheroma or slight intimal irregularity were reported as normal.

Theoretical Study

A phantom was constructed to represent the neck region (fig. 2). The activities used to simulate the major vessels and soft tissues were calculated from blood samples in the clinical study and computer analysis of images in 20 patients with peripheral arterial disease. The average activity of blood at 48 hours after injection was 370 Bq/ml and the average neck tissue activity was 56% that of the carotid region. To represent labelled platelet deposition a range of \(^{111}\)In activities (185, 370, 925, 1850 and 3700 Bq) based on endarterectomy specimen activities (maximum 851 Bq) were introduced into the phantom in a tapered tube as shown. The phantom was imaged with and then without each level of added “lesion” activity. These images were then viewed by our physicist who, after being shown a reference image without activity, was required to pronounce on subsequent images presented randomly and on a varying number of occasions, whether additional activity was present.

Results

Measurable platelet deposition was found on all eleven endarterectomy specimens with a mean (± SEM) specimen activity of 0.65 ± 0.19 (table 1). In two cases discrete plaques could be isolated from the attached intima and were found to contain 90% of the total specimen activity (fig. 3). The mean activity in
the 4 ulcerated plaques of 1.12 ± 0.37 exceeded that of 0.38 ± 0.10 in the 7 stenotic lesions. The two observer’s interpretations of the gamma images of these 11 lesions agreed in 9 cases. The two lesions in which there was failure to agree had similar low activities of 0.33 and 0.46. The maximum specimen activity found was 1.8, equivalent to 851 Bq.

In the phantom study added activities of 1850 Bq and 3700 Bq were consistently detected whereas activities of 925 Bq were reported positive on half the occasions they were displayed. Added activities of 370 Bq or less were not identified.

Interpretations of the 25 patient’s images (table 2) showed significant accord between observers (Chi square \( p < 0.001 \)) with agreement in 38 of the 50 bifurcations. Our physicist (observer 1) reported 16 lesions on the symptomatic side and ten on the asymptomatic side (table 1). When the physicists reports were compared to the findings in the 18 patients who had angiography (table 3), 11 of 12 atheromatous ulcers were noted \( ^{111} \text{In} \) scan positive but only 5 out of 10 stenoses giving an overall sensitivity of 73% and specificity of 61%.

Doppler ultrasound examination in these 18 patients demonstrated all 10 stenotic lesions but performed very poorly with ulcerated plaques giving an overall 64% sensitivity and 61% specificity. When combined, ultrasound and imaging identified 22 of 23 lesions but recorded 6 positives in carotids reported to be angiographically normal.

**Discussion**

Labelled platelets were deposited during the 48 hours preceding endarterectomy on every surgical specimen, implying a continuous turnover of platelets. However, not all these lesions were identified by external gamma imaging. The theoretical study using a phantom established that the levels of radioactivity found on endarterectomy specimens were at the limit of gamma camera resolution. Consequently, only the most thrombogenic lesions would have accumulated sufficient labelled platelets to be detected. The finding that ulcers and plaques imaged more frequently than stenoses is explained by the greater accumulation of labelled platelets found on endarterectomy specimens in these patients.

Radiolabelled platelet imaging allows the dynamic process of carotid thrombosis to be studied in vivo.
Since platelets will be deposited whenever the thrombogenic subintima is exposed, $^{111}$In platelet uptake could occur in an angiographically normal vessel with endothelial disease. Without follow-up information on untreated patients, we can only speculate on the significance of these minimally diseased but thrombogenic carotids. Furthermore, as platelet turnover is occurring continuously, and imaging takes only 10 minutes in each 24 hours, a negative result implies only that activity during imaging was below the necessary threshold for detection. Nevertheless, when the results of imaging and spectral analysis were compared to angiographic findings in the same patients a similar overall sensitivity and specificity was noted. The imaging detected more ulcerated plaques and spectral analysis demonstrated hemodynamically significant stenoses. Combining the two investigations diagnosed all but one of the angiographic lesions but six further angiographically unremarkable bifurcations would have been identified. The single atheromatous plaque that was not identified by $^{111}$In platelets was in a patient taking aspirin. Aspirin however did not prevent imaging in all patients so treated, although this is a selected group in that these patients were referred for investigation due to continued TIA despite anti-platelet therapy. In order to test the influence of platelet-inhibitory drugs it would be necessary both to randomize therapy and quantitate the rate of platelet deposition in the diseased carotid. The endarterectomy specimen could be used for this only if the surgery can be prevented from disturbing the luminal surface during the operation. We believe that the carotid lesions that imaged strongly but had low specimen counts may have been traumatized by suction during removal.

In a previous study interpretation of images was performed by an observer with access to clinical information. Such knowledge would not assist the interpretation of the images by our criteria but might bias an observer towards the symptomatic side. Platelet deposition contributes only a small proportion of the total radioactivity in the neck due to high background activity. Hence it has been suggested that subtraction studies may be used to enhance images. Using $^{99m}$Tc labelled albumin for background subtraction the clarity of images in our study was not improved. As we are limited by the capabilities of existing gamma cameras only the more thrombogenic lesions are likely to be imaged. As the significance of a thrombogenic lesion is unknown, long term follow-up of patients with positive images is required to establish whether detectable $^{111}$In platelet deposition is related to subsequent clinical events.

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**References**

THE DIAGNOSIS of acute thrombotic or embolic processes in major arteries at the base of the brain may have therapeutic significance. In many cases of acute cerebral infarction, angiography is considered to be not indicated and commonly is deferred until there is clinical improvement. The ability to suggest the presence of major intracranial arterial occlusion on initial CT scan therefore is of clinical importance.

Demonstration of intravascular clots on CT scan is well known in large aneurysms and in venous sinususes.1-4 Yock5 demonstrated the possibility of CT diagnosis of chronic calcified emboli. No reports of the visualization of acute arterial thrombotic or thromboembolic occlusions are available. This report concerns eight instances of this phenomenon.

Patients and Methods

During a prospective study for evaluating the effectiveness of clinical diagnosis of ischemic cerebral disease6 one of the patients was found to have a high density visualization of the middle cerebral artery on the non-contrast scan. Angiography proved that the finding represented occlusion presumed to be due to thrombosis of the artery. A subsequent retrospective review of the CT scans of 735 patients with cerebral ischemia disclosed seven other cases including one of the posterior cerebral artery. Three of the eight patients were submitted to angiography confirming obstruction of the artery.

Case 1

A 41 year old right-handed physician presented at another hospital with a four day history of left-sided headache followed by sudden onset of aphasia and weakness of his right upper extremity. Five hours after onset of symptoms angiography revealed a left internal carotid occlusion (possibly due to dissection) and an unsuccessful attempt was made to reopen the artery. The patient suffered a series of epileptic seizures after surgery.

The patient was transferred to our institution the following day. Neurological examination revealed a left Horner's syndrome, right homonymous hemianopsia, complete right hemiplegia and total aphasia.

Computed tomography revealed a large area of low density in the territory of the left middle cerebral artery. The left middle cerebral artery was visualized on the non-contrast scan as a high density structure and was suspected to contain thrombus (fig. 1A). Subsequent angiography revealed abrupt occlusion of the origin of the middle cerebral artery with a rounded edge suggesting a middle cerebral artery embolus (fig. 1B and 1C).

The patient was treated with Dexamethasone and volume expanders. He remained densely aphasic and hemiplegic during his five days stay at this hospital.

Case 2

A 43 year old man with a history of migraine beginning in adolescence consulted an osteopath for neck...
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