A Scintigraphic Sign for Detection of Right-to-Left Shunts

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We evaluated the usefulness of a new scintigraphic sign, a quantum mottling pattern, in diagnosing right-to-left shunt using ^{99m}Tc-MAA particles. The quantum mottling pattern is characterized by random distribution of discrete clumps of radioactivity that are more intense than the general body background. Forty-nine ^{99m}Tc-MAA scintigrams were analyzed retrospectively for presence of a quantum mottling pattern in extrapulmonary soft tissues and brain. This distinctive pattern was observed in every patient (18/18) in whom a right-to-left shunt was confirmed by nonscintigraphic means and was noted only in one patient in whom independent proof of a right-to-left shunt was not available. In contrast, application of conventional criteria yielded a true-positive interpretation for 15/18 patients with right-to-left shunts and a false-positive interpretation for another four patients. Presence of a quantum mottling pattern on ^{99m}Tc-MAA images appears to be a reliable aid for detecting a right-to-left shunt. Use of this sign is likely to improve accuracy of the scintigraphic test in patients with small shunts.

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It is well known that a right-to-left shunt can be detected and quantitated by intravenous administration of radiolabeled macroaggregated albumin (MAA) particles (*1,2,3*). Since particles greater than 10 μm in diameter are trapped in both pulmonary and systemic capillary beds, the ratio of extrapulmonary-to-total-body counts is assumed to reflect that fraction of blood entering the right atrium which is shunted from the right heart to the systemic circulation. When the administered MAA solution contains excessive amounts of unbound radionuclide or labeled MAA fragments less than 10 μm in size, the ratio of extrapulmonary counts to total-body counts will appear abnormally high even in the absence of a true shunt. Large amounts of unbound nuclide (free pertechnetate) can be inferred to have been present in the injectate when significant ^{99m}Tc activity is seen in thyroid, salivary glands and gastric mucosa. But presence of small amounts of free pertechnetate or ^{99m}Tc bound to albumin particles less than 10 μm in size cannot reliably be discerned from inspection of images, even though such radiopharmaceutical impurities may be the cause for abnormally high extrapulmonary activity. Hence, considerable uncertainty can exist regarding presence of a small right-to-left shunt when extrapulmonary ^{99m}Tc activity is less than 15% of total body activity. In situations like this, presence of renal or brain activity is regarded as a pictorial indicator of a shunt (Fig. 1B and C). But renal activity can be due to free pertechnetate and brain activity, when small, may be hard to differentiate from scalp and face activity, also due to circulating pertechnetate. Hence, another pictorial indicator for a right-to-left shunt could be helpful when extrapulmonary activity is relatively low.

We have observed the presence of a distinctive image pattern on the ^{99m}Tc-MAA scintigrams of patients with proven right-to-left shunts. This image pattern consists of a random distribution of minute clumps of activity in soft tissues of the trunk and extremities and even in the brain (Fig. 1C). Because these clumps of activity are discrete and random in their distribution, we have named this pattern "quantum mottling" (QM). To evaluate the reliability of the QM pattern as an indicator of a right-to-left shunt, we retrospectively evaluated all recent ^{99m}Tc-MAA shunt studies performed in patients suspected to have right-to-left shunts and compared scintigraphic findings to nonscintigraphic evidence for the presence or absence of a shunt.

PATIENTS AND METHODS

We reviewed clinical records and scintigraphic data of 49 patients referred to nuclear medicine for evaluation of a possible right-to-left shunt between 1984 and 1991. Seventeen had neurologic symptoms and were suspected of having cerebral infarctions; 16 had proven cardiovascular disease (8 ventricular septal defects, 4 atrial septal defects, 3 patent foramen ovales, 1 patent ductus arteriosus); and 16 had hypoxemia by blood gas determinations. Each of these patients underwent a radionuclide shunt study according to our standard protocol.

Imaging Protocol

MAA was prepared from commercial kits (MediPhysics or Squibb). Each dose of intravenously injected MAA consisted of 50,000–100,000 particles labeled with 4–5 mCi of ^{99m}Tc. Appropriateness of particle size (typically 10–50 μm) and adequate labeling efficiency (>98%) were verified by microscopic evaluation and paper chromatography prior to tracer administration. All tracer injections were into an antecubital vein. Two-minute posterior images of the head, thorax, upper arms, abdomen, pelvis

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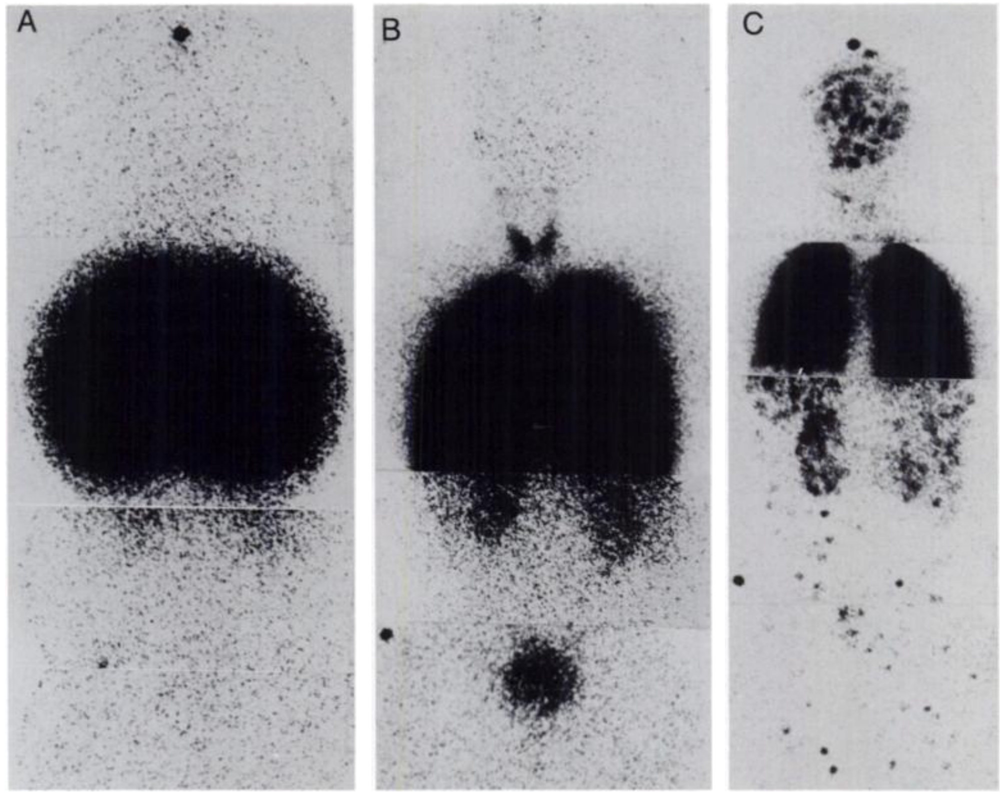

FIGURE 1. Composite total-body images in the posterior projection showing ^{99m}Tc-MAA distribution in three patients. Patient (A) with no evidence of a right-to-left shunt (EPA 2%); patient (B) with no evidence of right-to-left shunt, but evidence of free pertechnetate activity in thyroid, kidney, bladder, cerebral venous sinuses and scalp (EPA 5.5%); patient (C) with ventricular septal defect and right-to-left shunt proven by surgery (EPA 12%): note typical quantum mottling pattern in the brain, kidneys and soft tissues.

and lower extremities were obtained with a large field-of-view scintillation camera (Siemens, Des Plaines, IL) immediately after tracer injection. Images were recorded on film and also stored in an MDS computer. Skin markers were used to ensure that adjacent views were in fact contiguous without gaps or excessive overlap. Skin markers also allowed the computer operator to define two parallel lines at the upper and lower margins of each field-of-view. The counts derived from the area between these two lines were recorded for each image and summed to provide the best estimate of extrapulmonary counts. Lung activity was estimated from the total counts recorded within regions of interest that defined the perimeter of each lung. Like previous investigators who used this technique, we made no attempt to correct for attenuation effects, assuming that attenuation effects were roughly similar in all portions of the body. Extrapulmonary activity (EPA) was computed as the ratio of extrapulmonary counts to total-body counts using the formula:

$$\text{extrapulmonary activity} = \frac{\text{extrapulmonary counts}}{\text{extrapulmonary counts} + \text{pulmonary counts}} \times 100\%.$$

Final diagnoses were based on thorough retrospective review of patient charts with particular focus on clinical information, laboratory studies, blood gas data, nonscintigraphic imaging studies, catheterization results and surgical findings. Clinical evaluation was supplemented by results of contrast echocardiography in 37 patients, cardiac catheterization in seven patients, autopsy findings in four patients, surgery in two patients, Doppler studies in two patients, and cine computed tomography (CT) in one patient. Indications of right-to-left shunting by cardiac catheterization, autopsy, surgery, Doppler and cine CT were regarded as reliable evidence for a right-to-left shunt in 14 cases. Four cases with a very high clinical suspicion of intrapulmonary shunting, including one patient with a positive oxymetry study, were regarded as also having reasonable clinical evidence for the diagnosis of a right-to-left shunt. Hence, a total of 18 cases were accepted as having independent evidence for a right-to-left shunt.

Scintigraphic images were retrospectively analyzed for presence of quantum mottling by three experienced observers who were blinded to the final diagnoses. The scintigraphic study was considered positive for a QM pattern whenever visual inspection of images showed presence of multiple clumps of radioactivity in extrapulmonary sites. Each of these clumps of activity was larger and more intense than the individual dots of activity that constituted the background pattern in the region where the clump occurred. If present, the clumps were always numerous, hence we did not find it necessary to define a lower limit (i.e., 10 or 20) for the number of clumps needed to constitute a valid QM pattern. Finally, the distribution of clumps of activity was always random in any region of the body, although in patients with large shunts the clumps were more numerous in brain and kidney.

RESULTS

Nineteen patients showed a QM pattern in soft tissues; 15 of them had a QM pattern in the brain as well. All 14 patients with extrapulmonary activity over 10% had this pattern and 11 patients were proven to have a right-to-left shunt by other studies. The other three with EPAs > 10% had severe hypoxemia and high clinical suspicion for intrapulmonary shunting. These three were also regarded as having reasonable evidence for a physiologically significant shunt. Four patients with QM patterns had extrapulmonary activity levels of less than 5%, and one had an extrapulmonary activity level of 8%. We have independent ev-

TABLE 1
Interpretation of Right-to-Left Shunt Studies Based on Conventional Criteria

Criterion for positive EPA value	Test positive		Test negative		Sensitivity	Specificity
	TP	FP	TN	FN		
≥5%, no free TcO_4*	15	4	27	3	83%	87%
≥5%	15	14	17	3	83%	55%
≥10%	14	0	31	4	78%	100%

*Original Interpretation
TP = true-positive; FP = false-positive; TN = true-negative; and FN = false-negative.

idence for a shunt in four of these five patients (see Table 3).

Correlation between the final diagnoses (gold standard) and the original scintigraphic diagnoses was 15 TP, 27 TN, 4 FP and 3 FN. Original scintigraphic impressions were based largely on assumption that an extrapulmonary activity of 5% or greater most likely represented a shunt while an extrapulmonary activity value less than 5% most likely was not due to a shunt. The criterion was modified for studies that had extrapulmonary activity values between 5%–10% and that showed obvious evidence of free pertechnetate activity (n = 10). Results of the original interpretation are shown in Table 1. For comparison, Table 1 also shows projected results for interpretations that assume the presence of a shunt for EPA values of ≥5% or ≥10% without adjustments for free pertechnetate.

Table 2 shows a comparison of "truth data" and scintigraphic results obtained by using the presence of a QM pattern as the only criterion indicative of right-to-left shunt. In this group of patients, the presence of a QM pattern is clearly a better indicator of right-to-left shunt than any preselected level of extrapulmonary activity, with or without adjustments for the presence of free pertechnetate. We constructed Table 3 to better understand the relationship between extrapulmonary activity values, visual evidence of free pertechnetate activity and the presence of a QM pattern with respect to various possible diagnostic thresholds for a right-to-left shunt. Group 1 consisted of 20 patients with <5% extrapulmonary activity. Four patients in Group 1 showed a QM pattern. Two of these four were found to have an atrial septal defect (ASD) at catheterization and one had evidence for a patent foramen ovale by color Doppler. All three of these patients with proven right-to-left shunts had extrapulmonary activity sufficiently low (2%, 3%, 3%) to be interpreted as negative by traditional criteria. Yet all three showed a QM pattern on images of the abdomen, lower extremities and brain. For the fourth patient with QM pattern (extrapulmonary activity of 2%), there is no independent proof for a right-to-left shunt other than a positive contrast echo. This hypoxemic patient had abnormal oxymetry suggesting either a pulmonary diffusion problem or a right-to-left shunt.

Group 2 consisted of 15 patients in whom extrapulmonary activity was between 5%–10%. In 11 of these patients, the scintigraphic diagnosis of right-to-left shunt was questionable because much of the extrapulmonary activity was noted in the thyroid or stomach. Only one of these patients showed a QM pattern. This patient had carcinoid syndrome and hypoxemia on blood gas studies. Cardiac catheterization yielded a positive oxymetry study leading to clinical diagnosis of intrapulmonary shunting. Incontrovertible truth data was scant for the remaining 14 patients in this group. Cardiac catheterization and echocardiography studies excluded diagnosis of right-to-left shunt in two patients with extrapulmonary activities of 6.0% and 6.4%; these patients did not show a QM pattern.

Group 3 consisted of 14 patients whose extrapulmonary activity was more than 10%. The scintigraphic images of every patient in this group showed a QM pattern in the extrapulmonary soft tissues and 11 studies showed quantum mottling in the brain parenchyma as well. All 14 of these patients had independent evidence for right-to-left shunt. The shunt was proven in 10 patients (by catheterization in five, by autopsy in three, by cine CT in one, by Doppler in one), and one patient had abnormal oximetry during cardiac catheterization, suggesting intrapulmonary shunting. The other three patients had severe hypoxemia, and were believed to have intrapulmonary shunting on the basis of retrospective clinical assessment.

Whether in Group 1, 2 or 3, every patient with a proven right-to-left shunt also had a QM pattern on scintigraphic study.

TABLE 2
Quantum Mottle as Indicator of Right-to-Left Shunt

	QM+	QM−
shunt (+)	18	0
shunt (−)	1	30

Sensitivity: 100%; specificity: 97%.

Correlation With Echocardiography

Two-dimensional echocardiography with agitated saline was obtained in the standard imaging planes in 36 patients. Among Group 1 patients, only 4 of 17 contrast echo studies were negative. Each of these four patients had an EPA value of 1%. Only 2 of 10 Group 2 patients had negative echo studies with EPA values of 6% and 7%. Among the nine Group 3 patients, one had a negative contrast echo and his EPA was 33%. This patient was shown to have patent ductus arteriosus. Overall, 29 of 36 contrast echo studies were positive for right-to-left shunt.

DISCUSSION

As is so often the case with nuclear medicine studies and many new noninvasive diagnostic studies, validation of study results is very difficult for lack of adequate truth data. We did not have definitive truth data for all of our cases. In 18 patients, nonscintigraphic evidence was sufficient to provide high certainty for the presence of right-to-left shunt. However, in only three of 31 negative cases was there fairly definitive evidence for exclusion of right-to-left shunt. These three patients had extrapulmonary activity values of 3.5%, 6% and 6.4%, and none of their scintigrams had a QM pattern. In the remainder, right-to-left shunt was considered excluded by clinical findings and follow-up.

Contrast echocardiography was not found to be helpful in establishing the presence or absence of a hemodynamically significant right-to-left shunt. The echo study was positive in many patients with very low extrapulmonary activities (13/17 patients with EPAs < 5%) and in over 50% of patients who were considered not to have a shunt by retrospective clinical assessment. It is our impression that a negative-contrast echo result may be valuable for ruling out an intracardiac shunt, but a positive echo study is not a reliable indicator of a hemodynamically significant shunt, even though it may provide clinically important information in patients suspected to have paradoxic embolization.

The standard scintigraphic study for detecting right-to-left shunts is a good diagnostic test, but it is not without its limitations and pitfalls. The level of extrapulmonary activity does not by itself reflect the true magnitude of a right-to-left shunt because the radiopharmaceutical is an imperfect indicator. Lin (*3*) reported that the extraction ratio of MAA particles by lungs was 94%–97% in normal individuals. However, the amount of free pertechnetate and the number of labeled particles less than 10 μm in size is not the same for every preparation, and the latter cannot be assessed reliably before injection. Both free pertechnetate and small or fragmented MAA particles bearing the ^{99m}Tc label pass through the lungs into the systemic circulation. Moreover, some of the ^{99m}Tc-MAA that lodges in the lungs immediately after injection is subject to early metabolism with release of labeled fragments to the circulation. Taplin and McDonald (*6*) demonstrated that MAA particles of 5–25 μ and 10–70 μ in diameter had biologic half-lives of 30 min and 4–6 hr, respectively. Furthermore, rate of fragmentation of particles trapped in the lungs is variable from patient to patient and from kit to kit. Derivation of a correction factor is not realistic. Hence, any delay in imaging extrapulmonary activity may incur errors from redistribution of a fraction of the original pulmonary activity, in addition to errors caused by presence of free pertechnetate and small labeled particles in the injected dose.

Explanation for the presence of a QM pattern in patients with right-to-left shunts is probably related to the small number of MAA particles that embolize to the systemic circulation. Presence of minute, randomly distributed clumps of radioactivity in tissue containing a relatively small number of MAA particles is not an entirely new observation. The same phenomenon has been recognized to occur on perfusion lung images when fewer than 30,000 particles are injected intravenously (*4,5*). Since for safety reasons we limit particle numbers for right-to-left shunt studies to 100,000, the particle numbers available to the systemic circuit are approximately 1,000–15,000 for patients with right-to-left shunts whose magnitude is 1%–15%. Even for large right-to-left shunts (50%), the total number of particles released to the systemic capillary bed would be no more than 50,000. Less than 50,000 particles distributed in perhaps 50 kg of tissue result in an average particle concentration of <1 particle per gram or 0–10 particles per resolution element for the modern gamma camera. Poisson statistics for the distribution of a small number of particles would predict many regions (resolution

TABLE 3
Relationship Between Extrapulmonary Activity, Free Pertechnetate and Quantum Mottle Patterns at Various Diagnostic Thresholds

	EPA	No. of patients	Visual evidence of free TcO4*	QM+	Patients with independent evidence for right-to-left shunt: n	Evidence and/or diagnosis
Group 1 (traditionally negative)	<5%	20	1	4	3	2 ASD (2 cardiac cath) 1 patent foramen ovale (color Doppler) 1 no proof
Group 2 (equivocal)	5%–10%	15	10	1	1	1 carcinoid syndrome and intrapulmonary shunt based on positive oxymetry.
Group 3 (traditionally positive)	>10%	14	4	14	14	8 VSD (3 cardiac cath., 2 autopsy, 2 surgery, 1 Doppler) 1 PFO (autopsy) 1 PDA (cine CT) 1 intrapulmonary shunt (positive oxymetry at cath) 3 high clinical suspicion (1 positive oxymetry)

*Presence of thyroid and/or stomach activity.

elements) with no labeled particles alternating with regions containing a variable (but small) number of particles. Such a distribution of particles would be expected to present a pattern of irregularly distributed hot spots superimposed on a background of diffuse activity caused by the free pertechnetate activity present in the injectate. Similar statistical considerations were applied by Heck et al. (*4*) and Dworkin et al. (*5*) to explain the irregular distribution of radioactivity on scintigraphic images of the lungs in subjects injected with fewer than 30,000 particles. In fact, Heck et al. were able to produce irregular tracer distribution patterns by computer simulations that limited particle numbers relative to the number of resolution elements.

Results of our retrospective study can be used to evaluate reliability of traditional scintigraphic criteria for defining the presence or absence of right-to-left shunt. Tables 1 and 2 provide side-by-side comparisons of the ability of old and new criteria to separate patients with right-to-left shunts from those with no shunts. In this group of patients, reliance on the QM pattern clearly provides a cleaner separation of patients with and without shunts than the traditional criteria. Moreover, for our group of patients, the discriminating power of the QM pattern seems to have been unaffected by the presence of excessive free pertechnetate. If this important observation is confirmed by other series, studies previously considered nondiagnostic due to radiopharmaceutical problems may be interpretable for the presence or absence of a shunt on the basis of a QM pattern, even if the magnitude of the shunt cannot be defined accurately.

Our retrospective review of scintigraphic images disclosed that in one or two cases poor count statistics on analog images made it difficult to determine whether a QM pattern was present in soft tissues and the brain. Therefore, in patients with low extrapulmonary activity, we suggest use of longer exposure times (5 min instead of 2 min) for head and posterior abdomen views to better define the pattern of extrapulmonary activity. A separate long exposure image of the brain may be quite valuable for another reason as well: it would allow better differentiation between a blood-pool pattern (as expected for free pertechnetate) and a parenchymal pattern (as might be seen after ^{99m}Tc-HMPAO administration). Only the latter pattern is indicative of right-to-left shunt.

In summary, we found that in patients with proven right-to-left shunts, traditional ^{99m}Tc-MAA images harbor a previously unrecognized visual indicator for presence of shunt. Retrospective review suggests that the presence of a QM pattern is a reliable guide to presence of right-to-left shunt. This diagnostic sign should facilitate interpretation of the standard ^{99m}Tc-MAA study and may be particularly useful when extrapulmonary ^{99m}Tc activity is <10% or when excess free pertechnetate has raised extrapulmonary activity above 10%. Hopefully, other groups will confirm our observations and strengthen the value of an already useful noninvasive nuclear medicine test.

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