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DIAGNOSTIC MERITS OF CURRENT AND POTENTIAL APPLICATIONS OF
SINGLE PHOTON AND POSITRON IMAGING - A PERSPECTIVE

Paul V. Harper

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DIAGNOSTIC MERITS OF CURRENT AND POTENTIAL APPLICATIONS OF SINGLE PHOTON AND POSITRON IMAGING - A PERSPECTIVE

Paul V. Harper*

Abstract

A brief review of the limitations of medical radionuclide imaging techniques in competition with X-ray CAT scanning and ultrasound suggest that the emphasis in this area should be on measurement of the physiologic uptake of tracer materials. Tomography greatly improves the possibilities of quantitation of this uptake - examples using positron and single photon techniques are presented for $^{13}\text{NH}_3$ and ^{201}Tl in the heart.

In my assignment to present a discussion putting medical radionuclide imaging procedures in perspective, the first question I would raise is "What perspective?" A superficial historical review would nominally fulfill this obligation, but would not, I fear, be very constructive. I would appear to be more appropriate to look at the present state of the imaging art from a technical point of view and to attempt to see how this fits with the medical and physiological questions physicians and medical scientists are trying to answer.

As digital technology has progressed explosively during the past few years, the approaches to data storage and display have become progressively refined, and image processing has proceeded from simple smoothing techniques to sophisticated filtering and edge detection procedures. Display matrices have grown from 40 X 40 to 512 X 512 or more. The use of color is with us, but still somewhat controversial.

A tremendous impetus has resulted from the introduction of X-ray transmission CAT scanning in the use of computers to produce reconstructed emission tomographic images one slice at a time or in some configuration with multiple simultaneous slices.

Developments in the area of detector technology include the use of solid state detectors to improve energy resolution in order to reject the effects of scatter more efficiently; the use of thicker detectors or more dense materials such as bismuth germanate; or the use of gas counters which can inexpensively be used to cover large solid angles to produce improved efficiency and to improve angle sampling for reconstruction.

Agents have progressed from the old days of ^{131}I to extensive, though still experimental, use of the short-lived positron emitters, permitting the use of native labels rather than analogues and an increase in the millicurie amounts administered to be safely increased by two orders of magnitude so that the effects of statistical noise have been greatly reduced.

While the majority of medical imaging procedures are still carried out using the Anger camera as the imaging system and some form of $^{99\text{m}}\text{Tc}$ as the agent, the improvement in anatomical delineation and resolution

possible with ultrasound and X-ray CAT scanning is posing a threat to what used to be the standard bread and butter nuclear medicine procedures.

This has led to a changed emphasis in radionuclide imaging. Basically, the localization of a radioactive agent in the body is a physiological or biochemical process and looking at this aspect of the procedure rather than the resultant final distribution one provides unique potentials beyond the capability of simple X-ray and ultrasound visualization. Examples of this are the development and increasing use of tumor specific agents such as ^{67}Ga , ^{111}In and labeled carcinoembryonic antigens, and in functional images where such things as regional uptake rates are mapped.

Probably the major technical development in the past decade, with which the present Symposium is largely concerned, is tomography. In the early days of tomography, extensive studies by D. Kuhl, while often clearly delineating brain tumors, rarely demonstrated lesions not detected by conventional imaging. A major conference on this subject 8 or 10 years ago led to the general conclusion that tomography was probably not worth the effort. In a recent example from our institution, patients with lymphoma were imaged with ^{67}Ga by conventional (Dual 5" scanner) and tomographic (Pho-Con) equipment. The question asked was whether mediastinal localization was present. Three different observers reviewing the study showed clearly that the Pho-Con tomographic images although clearly superior in image quality carried no more diagnostic information. The ROC curves, scoring true positive fraction against false positive fraction were identical for all three observers. Clearly the question being asked was not appropriate for tomographic study. Thus it seems likely that the potential value of tomography must be in some branch of the art other than the standard nuclear medicine, anatomic localization study.

Two factors in recent years have led to a change in this situation. These are the remarkable development of the quantitative methods in connection with cardiac and brain metabolic studies using radioactive tracers. The need for quantitation of uptake immediately placed an emphasis on the removal of the contribution of overlying and underlying activity which make such quantitation difficult or impossible.

In the brain, the ability to quantify regional blood flow, blood volume and metabolism using tomographic methods constitutes a major breakthrough in the study of central nervous system disease, and the development of capabilities to carry out tomographic studies in the heart to demonstrate wall motion, i.e., pumping efficiency of the heart, and regional circulatory disturbances and coronary occlusion with death of patches of heart muscle is providing a major attack on coronary artery disease.

To illustrate this sort of application in greater depth, I propose to discuss in more detail one aspect the problem as it relates to the heart.

In considering of quantification of perfusion scans of the heart, one would like to think that the ultimate goal in performing such a procedure might be to produce a quantitative map of the regional myocardial perfusion. A number of avenues are being followed in pursuit of this goal, and in attempting to determine how close we are to success, it is necessary to

*Professor, Departments of Surgery and Radiology, University of Chicago, and The Franklin McLean Memorial Research Institute (operated by the University of Chicago for the United States Department of Energy under Contract EY-76-C-02-0069), 950 East 59th Street, Chicago, IL. 60637

distinguish two levels of endeavor. The first includes the largely physical set of problems involved in the noninvasive measurement of the amount of tracer in different regions of the myocardium. This involves the radioactivity parameters of the label and the characteristics of the imaging and data processing systems. The second category of problems involves the chemical and biological behavior of the imaging agent, and how well its localization acts as a marker for flow.

Let us first consider some of the agents which have been used for myocardial imaging.

Blood disappearance curves of the potassium analogues are shown in Fig. 1. These materials are

BLOOD DISAPPEARANCE OF POTASSIUM AND ITS ANALOGUES

Fig. 1. Time activity curves are shown for the blood following intravenous injection of the various potassium analogues in the same human subject. In the case of $^{13}\text{NH}_4^+$, this was determined as the volatile component at high pH. The zero time points are assumed as 100% retention in blood compartment.

injected intravenously, pass through the lungs and, except for cesium, are extracted more or less efficiently on the first pass through the various tissues of the body and, of course, the myocardium. The initial distribution thus mirrors the distribution of the cardiac output. Subsequently, the initial distribution becomes altered as the label gradually, over a period of hours, comes into equilibrium in the potassium space in the body to the extent that the agent is a true potassium analogue. This description is a vast oversimplification but accounts for the main features of the distribution of these substances.

The initial fixation of the potassium analogues in tissue implies that in addition to having intact circulation, the tissue is composed of intact metabolically active cells. Thus a fresh infarct or an old avascular scar will appear to have low or absent uptake. An ischemic region appears initially to have

a low uptake since a smaller quantity of tracer is presented to it during the initial bolus and furthermore an ischemic region may have sufficient metabolic disturbance to reduce the uptake still farther. The importance of this factor has been documented in a recent report by Selwyn et al.¹ A degree of ischemia was produced by coronary constriction in an animal model, insufficient to cause metabolic damage. This was clearly demonstrable using a constant infusion of ^{86}K , which looks at perfusion alone, but was not demonstrable by reduction of thallium-201 uptake at 10 minutes until the degree of ischemia was increased sufficiently to produce a metabolic (ECG) change. Consistent with this observation is a further complication in that the localization of the potassium analogues is somewhat diffusion limited so that a region of low perfusion may have a disproportionately high uptake of tracer in the absence of cellular damage.

It is not entirely clear that it is appropriate to include nitrogen-13 ammonia as a potassium analogue, although it has been shown to participate in the Na^+-K^+ ATP-ase pump mechanism. One to two percent of the label is present as NH_3 gas in solution at physiologic pH and could efficiently enter the myocardial tissue by passive diffusion as it apparently does in the brain. It has not yet been established which of these mechanisms or both may be active in the myocardium. The ammonia gas diffusion mechanism, if present, should result in a greater uptake at higher blood pH as in the brain. The only available evidence is for the liver where $^{13}\text{NH}_4^+$ uptake is unaffected by pH, thus supporting pump mechanism (Carter et al.)² The experiments for the myocardium have not yet been carried out.

The behavior of the blood disappearance curve of nitrogen-13 activity appears to differ qualitatively from the other agents (Fig. 1). However, when one looks at the chemically separated ammonia in the blood, this difference disappears. The high tail of the ^{13}N curve is due to the buildup of metabolically fixed ^{13}N as glutamate, glutamine etc. in the circulation. The presence of this high blood level may well hasten the observed redistribution phenomena since glutamate is also extracted by the myocardium. The situation with stress induced uptake defects is further complicated by a changing perfusion pattern as the exercise stress is terminated.

The apparent logical conclusions from all these considerations seems to be that a reasonable measure of perfusion should be obtainable following intravenous administration of one of the potassium analogue tracers if measurements can be made within a few minutes after administration of the tracer so that significant redistribution has not occurred and if there is no significant ischemic damage and if the range of perfusion rates is not excessive.

A number of other substances have been looked at for myocardial imaging, and these deserve some comment.

Labeled glutamate (Lathrop et al.)³ mentioned earlier localizes well in the myocardium. This material is of particular interest since it has been shown that there is a net uptake of glutamate by the heart, unlike any other amino acid and this is enhanced by ischemia (Mudge et al.)⁴

Nitrogen-13 alanine (Phelps)⁵ has been shown incidentally to localize well in the heart. This material is also intimately involved with myocardial nitrogen metabolism. Nitrogen-13 asparagine is concentrated by the canine heart to a remarkable extent (Gelbard et al.)⁶ However, there are equally remarkable species differences (Majumdar et al.)⁷ with much lower uptake in the human. In addition, there are

substantial sex differences and differences associated with whether the subject is in an anabolic or catabolic state.

A number of simple compounds are localized efficiently and are metabolized rapidly. The myocardial uptake of ^{14}C acetate in the baboon at three minutes disappears completely at 18 minutes. This might be a useful flow marker since it is presumably metabolized rapidly and is thus not available to result in redistribution phenomena. ^{14}C -ethanol and methanol exhibit similar behavior.

Labeled fatty acids also appear to fall into this category but with longer time parameters.

It is possible that the rate of disappearance of such materials from the myocardium may be used as measures of myocardial metabolism independent of perfusion.

Studies with these metabolized tracers may produce useful insights but at the present time, the potassium analogues appear to be the agents of choice for estimating perfusion, and of these ^{13}N ammonia and ^{201}Tl have been looked at from the point of view of practicality.

Validation studies with nitrogen-13 ammonia, comparing localization with that of microspheres following left atrial injection, support quite strongly the idea that this substance, in spite of the many theoretical objections, is an excellent marker for flow. It appears to have the identical distribution as that of microspheres administered simultaneously into the left atrium in a pig with a two-hour-old myocardial infarction produced by LAD ligation (Walsh et al).⁸

A more searching study was carried out by Schelbert et al.⁹ A wide variation in myocardial perfusion was produced in a dog model by partial ligation of the LAD or circumflex together with administration of papaverine, over the physiological range of 0-300 ml/100 g/min. Microspheres and $^{13}\text{NH}_3$ were administered into the left atrium. The relationship between flow and uptake was shown to be quite linear with 100% increase in flow corresponding to 70% increase in $^{13}\text{NH}_3$ uptake. The extraction fraction of $^{13}\text{NH}_3$ thus appears to remain relatively constant over this range in the dog under the condition of the experiment.

The techniques for making quantitative in vivo uptake measurements particularly with positron emitters have received great impetus from the development of X-ray CAT scanning and a large variety of configurations have been developed over the past few years. Since the detection probability of a positron annihilation event is independent of depth, the uptake in a deep-seated source may be determined by comparison with a reference standard source on the surface of the body.

In Schelbert's studies the Ortec Emission CAT scanner was used (Phelps et al).¹⁰ This is a single-plane positron emission tomograph based on Ter-Pogossian's original design. Reconstruction using conventional fan beam geometry allows removal of the contributions from overlying and underlying background activity. Normalization to a transmission image corrects for varying attenuation in different regions. Quantitative $^{13}\text{NH}_3$ uptake measurements performed in parallel with the in vitro measurements described above show in general that the relationship between flow and NH_3 uptake is identical except for a vertical offset due to the contribution from small angle scatter in the imaging measurements.

In our own laboratory we have been developing the double camera configuration (Muehlethner et al).¹¹

This device has better resolution and far greater sensitivity than the Ortec machine, but has limited count rate capability. The reconstruction technique is quite different, producing simultaneous longitudinal tomograms and the use of tight energy windows permits elimination of the effects of scatter by a dual window technique.

Quantitative reconstructions have been carried out in phantoms where source activities at different depths matched with the corresponding image count densities.

In vivo studies were carried out in a pig model with an infarct produced by LAD ligation. Quantitative $^{13}\text{NH}_3$ images matched closely the corresponding in vitro measurements following injection of microspheres. Both agents were injected into the left atrium.

In Fig. 2 a clinical study is shown in which conventional images are compared to a tomographic study carried out with this equipment.

Fig. 2. $^{13}\text{NH}_3$ images of heart in a patient with a recent postero-lateral infarct. At a previous bypass operation an apical ventricular tap was used producing the marked apical defect shown in the tomographic images and barely visible in the conventional images.

The quantitation of thallium images at first sight appears to be most difficult. At the principal emission energy of mercury K X-rays, the separation of primary and scattered radiations by pulse height analysis is nearly impossible and the long half-life of 73 hours precludes administration of high activities.

In spite of these difficulties, a practical scheme for partial quantitation of thallium has been devised by Vogel et al.¹²

A special case of coded aperture is used in which seven pinholes produce seven non-overlapping images on a wide field of view camera face. This configuration has the immense advantage that the signal-to-noise ratio problems encountered with other coded aperture systems with overlapping images is completely eliminated. Simultaneous longitudinal tomographic images are produced by an iterative back projection technique which includes an attenuation correction. Lesions not visible in conventional views become clearly visible. Within a slice, the activity is proportional to count density, although comparisons between slices are not at the moment possible. This configuration has the

unique advantage of being potentially portable so that bedside studies can be carried out since patients with acute coronary occlusions ordinarily cannot be moved. Normalized radial count profiles may be generated and compared to normals, and changes during redistribution may be objectively documented.

We are proposing to extend this approach using ^{13}N ammonia as a single photon emitter using a heavy collimator which preserves the geometry of the prototype system, thus making use of the capability of the 10-minute half-life of ^{13}N for sequential and intervention studies. This approach lessens the problems of attenuation and permits an increase of about tenfold in the data rate.

Phenomena which we plan particularly to study with these techniques are the extensive changes in the size of uptake defects associated with fresh infarctions.

Further, it may be possible with quantitative techniques to arrive at some model to describe the changes seen in redistribution and to arrive at meaningful quantitative parameters to describe these phenomena in physiologic terms.

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