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EDITORIAL
Cardiac Blood-Pool Tracers

Today, cardiac imaging can be performed with a scintillation camera on line with a computer by single-photon emission computed tomography (SPECT) or by positron emission tomography (PET) using suitable radiopharmaceuticals. While PET blood-pool imaging is not a common procedure, the enhanced resolution of PET and its ability to provide tomographic delineation of the cardiac structures has the potential to improve the quality of diagnostic information that can be gleaned from this study.

Blood-pool imaging began in 1958 (*1*) with radioiodinated (^{131}I) human serum albumin for the detection of pericardial effusion. In the

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early 1970s, first-pass and equilibrium gated blood-pool imaging were developed to measure regional and global ventricular function. These procedures required radiopharmaceuticals that could provide a high photon flux with an acceptable radiation burden to permit recording of several million events in an acceptable interval of time. Technetium-99m-labeled human serum albumin (^{99m}Tc-HSA), an agent introduced by McAfee et al. in 1964 (*2*) as a blood-pool tracer for placental imaging, was initially selected for this task.

Although ^{99m}Tc-albumin was widely used, it was far from an ideal compound: there were a number of problems associated with its preparation, quality control, and stability in vivo. Due to poor analytical techniques in the separation of the end product, labeled ^{99m}Tc-HSA contained impurities such as pertechnetate, hydrolyzed ^{99m}Tc, coprecipitated ^{99m}Tc, chelated ^{99m}Tc, ^{99m}Tc associated with polymeric or aggregated albumin, or ^{99m}Tc weakly bound to albumin (nonspecific binding), depending on the method of preparation (*3*). Technetium-99m-HSA also leaks out of the vascular compartment to equilibrate with the total-body albumin space. The high concentration of labeled albumin in the liver, caused by the large albumin space, may interfere with visualization of the inferior wall of the cardiac blood pool. In addition, the lungs have a larger albumin space than red cell volume, contributing to the lower target/background activity seen with albumin imaging.

The introduction of ^{99m}Tc-labeled red cells by an in vitro method (*4*) and an in vivo method (*5*) alleviated most of the problems encountered with ^{99m}Tc-HSA. The labeling procedure is based on the observation that the reduced technetium ion cannot move in or out of the red cell, while pertechnetate can diffuse freely in and out of the red cell. Labeled ^{99m}Tc-RBCs are prepared by reducing the pertechnetate ion inside the cell with a reducing agent such as stannous ion, already present in the cell. Technetium-99m-labeled red cells maintain a higher concentration in the vascular space. The liver has a relatively small red cell volume and, hence, does not usually interfere with visualization of the inferior wall. The spleen, however, has a high hematocrit and is frequently the site of the highest red cell concentration.

Nishimura et al. (*6*) reported recently on the use of ^{99m}Tc-chelated DTPA-HSA (diethylenetriaminepentaacetic acid conjugated to human serum albumin) in cardiac imaging. They compared the performance of ^{99m}Tc-DTPA-HSA with in vivo labeled RBCs and found that both labels offer similar results for the determination of ventricular function. They demonstrated that the ejection fraction of the left ventricle obtained with ^{99m}Tc-DTPA-HSA is comparable to that of contrast angiography. Spleen uptake with ^{99m}Tc-DTPA-HSA is lower than that of ^{99m}Tc-RBCs. However in comparison with RBCs, the activity of ^{99m}Tc-DTPA-HSA does not remain constant long enough in circulation. It seems the radiopharmaceutical/radionuclide escapes from the vascular space into the extracellular fluid system, contributing to the slightly higher uptake noticed in the liver. However, ^{99m}Tc-DTPA-HSA seems to be considerably better than the previous ^{99m}Tc-Sn-HSA preparations used in the early days of cardiac imaging.

Cardiac imaging can now also be performed using PET. In the past, the major red cell label was ^{11}C-labeled carbon monoxide. Following inhalation, this agent binds to hemoglobin, forming carboxyhemoglobin. While this is an excellent red cell label, it suffers from gradual dissociation from the red cell and requires the use of an on-site cyclotron to manufacture the radionuclide. In this issue of the *Journal*, Mathias et al. (*7*) report on the use of the positron-emitting radionuclide copper-62 (^{62}Cu-benzyl-TETA-HSA) for blood-pool imaging with PET.

Copper-62, a positron-emitting nuclide with a half-life of 9.7 min, is obtained from a ^{62}Zn generator (half-life of Zn is 9.2 hr) (*8*). Copper is found in both serum albumin and ceruloplasmin in plasma. However, to form a stable protein bound complex that will remain in the vasculature, the copper must be complexed with a protein through a ligand. Copper forms stable square planar complexes (see Ref. 11) with four coordination sites (*9*). The new biologic tracer ^{62}Cu-benzyl-TETA-HSA seems to be stable in vitro in serum (*10,11*), possibly due to both square planar structure and macrocylic effect. The ^{62}Cu-benzyl-TETA-HSA complex stays in the blood pool in an appreciable quantity even after 1 hr (*7*). With PET, this is sufficient to record high quality blood-pool images. The tomographic nature of PET imaging overcomes the potential problems from radiotracer uptake in the lungs, liver, and spleen (*7*), which would contribute to the background activity if the data were recorded with planar techniques. As a blood-pool tracer, ^{62}Cu-benzyl-TETA-HSA performs better when compared to other ^{62}Cu radiopharmaceuticals tested (*7*). The use of ^{62}Cu-benzyl-TETA-HSA as a subtraction agent in conjunction with ^{62}Cu-PTSM (*12*) in perfusion studies of myocardium and brain is another interesting development that needs further investigation.

Generator-produced radionuclides such as ^{62}Cu have certain obvious advantages for institutions where PET cameras are available but not medical cyclotrons. Zinc-62/Copper-62 generators, though not ideal because of the parent's half-life (9.2 hr, productive life 1 to 2 days), create an opportunity for non-cyclotron based PET centers to offer the major measurements required for evaluation of the heart with two

generator systems. The combination of available radiopharmaceuticals and high-resolution imaging devices will make ^{62}Cu-benzyl-TETA-HSA blood-pool imaging and perfusion measurements with generator-produced ^{82}Rb competitive with single-photon techniques in the near future.

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