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 (131I) human serum albumin for the detection of pericardial effusion. In the
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 (99mTc-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 99mTc-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 99mTc-HSA contained impurities such as pertechnetate, hydrolyzed 99mTc, coprecipitated 99mTc, chelated 99mTc, 99mTc associated with polymeric or aggregated albumin, or 99mTc 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 99mTc-labeled red cells by an in vitro method (4) and an in vivo method (5) alleviated most of the problems encountered with 99mTc-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 99mTc-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 99mTc-chelated DTPA-HSA (diethyleneetriaminepentaacetic acid conjugated to human serum albumin) in cardiac imaging. They compared the performance of 99mTc-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 99mTc-DTPA-HSA is comparable to that of contrast angiography. Spleen uptake with 99mTc-DTPA-HSA is lower than that of 99mTc-RBCs. However, in comparison with RBCs, the activity of 99mTc-DTPA-HSA does not remain constant long enough in circulation. It seems the radiopharmaceutical/radioisotope escapes from the vascular space into the extracellular fluid system, contributing to the slightly higher uptake noticed in the liver. However, 99mTc-DTPA-HSA seems to be considerably better than the previous 99mTc-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 11C-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 (62Cu-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 62Zn 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 vascular lumen, 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 62Cu-benzyl-TETA-HSA seems to be stable in vitro in serum (10,11), possibly due to both square planar structure and macrocyclic effect. The 62Cu-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, 62Cu-benzyl-TETA-HSA performs better when compared to other 62Cu radiopharmaceuticals tested (7). The use of 62Cu-benzyl-TETA-HSA as a subtraction agent in conjunction with 62Cu-PTSM (12) in perfusion studies of myocardium and brain is another interesting development that needs further investigation.

Generator-produced radionuclides such as 62Cu 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 \(^{62}\text{Cu}\)-benzyl-TETA-HSA blood-pool imaging and perfusion measurements with generator-produced \(^{82}\text{Rb}\) competitive with single-photon techniques in the near future.

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**REFERENCES**


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