

# Choosing a Radiopharmaceutical for Cardiac Blood Pool Imaging

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*Technetium-99m HSA, in vitro Tc-99m RBCs, and in vivo Tc-99m RBCs are clinically useful for cardiac blood pool imaging. The characteristics of each of these radiopharmaceuticals are described and some advantages and disadvantages of each are indicated. A table of considerations is presented for choosing a radiopharmaceutical for cardiac blood pool imaging. Each institution should consider all known factors before deciding which radiopharmaceutical will best fulfill its own particular needs.*

Use of dynamic imaging of the cardiac blood pool to analyze regional myocardial motion and to calculate the ejection fraction has increased rapidly over the past several years. Fundamental to this procedure is the use of a suitable radiopharmaceutical that achieves reproducibly steady and high blood pool concentrations. Radiopharmaceuticals that have been deemed suitable and have been widely used for this purpose include Tc-99m human serum albumin (HSA), in vitro labeled Tc-99m red blood cells (RBCs), and in vivo labeled Tc-99m RBCs. The purpose of this article is to describe and compare these radiopharmaceuticals and to discuss some considerations in choosing a radiopharmaceutical for cardiac blood pool imaging.

**Tc-99m HSA:** Both unit-dose and multi-dose HSA kits for labeling with Tc-99m are commercially available in the United States. The vials contain a lyophilized mixture of HSA and stannous tartrate. Preparation is relatively fast and easy, simply adding sterile water for injection and [<sup>99m</sup>Tc] sodium pertechnetate to the vials and allowing to incubate for 20 min (1). Labeling efficiencies obtained are 90% to 99% (1-4).

Although Tc-99m HSA is a blood pool agent, there is a slow leakage from the vascular space (1-5) and some kidney filtration, particularly in the presence of certain renal diseases (5). Reported blood pool disappearance half-times have ranged from 5-30 min in dogs (4) to 4.7 hr in man (5). Approximately 82% of the injected activity remains in the blood after 30 min, 60% after 2 hr, and 45% after 4 hr (1,3).

Adverse (allergic) reactions reported with the use of Tc-99m HSA have involved such symptoms as flushing,

respiratory difficulty, rapid pulse, rash, and high temperature. Although the estimated incidence of adverse reactions with Tc-99m HSA in 1978 was only 18-89/100,000 patient administrations, the risk of developing adverse reactions with Tc-99m HSA is 1-2 orders of magnitude greater than is the risk with other radiopharmaceuticals (6).

Some advantages of Tc-99m HSA include its FDA approval, commercial availability, ease in preparation, and single venipuncture. Some disadvantages include vascular leakage and relatively high risk of adverse reactions.

**In Vitro Tc-99m RBCs:** In vitro Tc-99m RBCs represent another suitable blood pool agent. Unlike labeled HSA, labeled RBCs do not leak from the vascular space. However, the labeling procedure may damage the RBCs with resultant extraction by the spleen (7). In vitro Tc-99m RBCs provide a relatively stable blood pool concentration with 95% remaining in the blood pool at 30 min (7). Reported blood pool disappearance half-times in man range from 17 to 29 hr (5,8).

Originally, in vitro Tc-99m RBCs were prepared by the addition of [<sup>99m</sup>Tc] sodium pertechnetate to a sample of patient blood incubated with stannous salt. The technetium is reduced and bound mainly to the protein moiety of the RBCs with preferential binding to the beta chain of the globin (9). Greater than 98% labeling was observed using 0.28 µg tin/2 ml blood (10).

To overcome some of the potential problems inherent in the above labeling method (e.g., air oxidation of the stannous ions, low labeling efficiencies, difficulty in maintaining sterility and apyrogenicity), investigators at Brookhaven National Laboratory developed a labeling kit (11). The kit consists of a vacutainer containing a lyophilized mixture of tin, sodium citrate, and dextrose. Patient blood is withdrawn into the vacutainer where it mixes with the tin. The tube is centrifuged, and the RBCs are removed and added to a vial containing [<sup>99m</sup>Tc] sodium pertechnetate. The labeled RBCs are diluted to a proper hematocrit and are ready for patient administration. Labeling efficiencies are consistently about 97% but are lowered by the presence of excess carrier Tc-99 (11).

At the time of this writing, in vitro labeling of RBCs with Tc-99m has not received FDA approval.

Some advantages of in vitro Tc-99m RBCs include consistent and high labeling efficiencies, relatively

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slow blood pool clearance, high cardiac-to-background ratios, and determination of labeling efficiency before patient administration. Some disadvantages include personnel time and equipment needed for preparation, risk of RBC damage or contamination, necessity of using a large gauge needle, and investigational status.

**In Vivo Tc-99m RBCs:** It has long been known that pertechnetate administered after a stannous-containing bone scan may label RBCs in vivo and result in potentially false negative brain scans (12). Pavel et al. (13) have turned adversity to fortune by purposely making use of this phenomenon to label RBCs in vivo for cardiac blood pool studies. In vivo Tc-99m RBCs provide a stable blood concentration, with greater than 95% remaining in the blood pool at 1 hr (13) and greater than 90% at 4 hr (14). In vivo Tc-99m RBCs have a blood pool disappearance half-time of 18 to 20 hr (15, 16).

Although many stannous compounds permit RBC labeling (16, 17), stannous pyrophosphate has been most widely used and, at the time of this writing, is the only FDA-approved agent for in vivo labeling of Tc-99m RBCs.

The labeling procedure is relatively simple. A lyophilized vial of stannous pyrophosphate is reconstituted with normal saline, and all or part of the solution is injected intravenously. After a brief waiting period, [<sup>99m</sup>Tc] sodium pertechnetate is injected. The stannous ion reduces the technetium and allows it to label the RBCs.

This labeling process is not instantaneous, but rather time-dependent, having a half-time of about 1.5 min (18). Adequate labeling, therefore, requires 3.5 to 10 min (14, 15, 19, 20). Because of this time dependence, some technetium may diffuse into extracellular fluid before it can be labeled (18). Consequently, although labeling efficiencies are high, the cardiac blood pool-to-background ratio is lower than with in vitro Tc-99m RBCs (18, 21). Reported labeling efficiencies generally range from 89% to 98% (13, 14, 20, 22, 23) although Mallinckrodt

(19) still indicates an unusually low labeling efficiency of 76% found in one earlier report (21).

The two injections should be made by direct venipuncture (19) as the use of heparin and heparinized catheter systems has been implicated in subnormal labeling efficiencies (21, 24). The labeling is not affected by the presence of excess carrier Tc-99 (16).

In this method of labeling Tc-99m RBCs in vivo, three important questions arise. The first question is simply, "what is the optimum amount of stannous pyrophosphate to be injected?" The answer is more confusing that it may first appear. "Stannous pyrophosphate" is a convenient term applied to the contents of the vial, which actually consists of a mixture of stannous chloride and sodium pyrophosphate (14, 19). Various literature references report dosages as mg of stannous pyrophosphate, stannous chloride, or stannous ion (Sn<sup>+2</sup>). Furthermore, the dosage of stannous pyrophosphate may be based on weight or blood volume, evoking even more confusion. Table 1 compares a number of recommended dosages and their equivalent values. From this information, it appears that the optimal adult dosage of stannous pyrophosphate is 5 to 15.4 mg. Of the available products on the market, Mallinckrodt's TechneScan<sup>®</sup> PYP<sup>®</sup> has the most tin, enough for one to three patient doses per vial, while formulations from the other manufacturers have tin enough for only one patient per vial.

A second question is, "What is the optimal waiting time between the stannous pyrophosphate injection and the pertechnetate injection?" This question can be answered by citing values from the literature: the recommended waiting time is approximately 20 to 30 min (13, 14, 18-22) although 10 to 15 min may be sufficient (16).

The third question is, "What is the period of time required after stannous pyrophosphate administration until the secondary RBC labeling effects are gone?" As mentioned previously, performance of a pertechnetate scan (e.g., brain, thyroid, etc.) subsequent to stannous

**TABLE 1. Comparison of Recommended Tin Dosages for In Vivo Tc-99m RBC Labeling\***

Reference	Stannous pyrophosphate (mg)	Stannous chloride (mg)	Stannous ion (mg)	Stannous pyrophosphate/ blood volume (μg/ml)	Stannous ion/ blood volume (μg/ml)	Stannous pyrophosphate/ body weight (μg/kg)	Stannous ion/ body weight (μg/kg)
10	5	1.1	0.7	1	0.14†	71	10
13	14	3.1	1.9	2.8	0.56	200†	27
14	7.2	1.6	1.0	1.43†	0.2	102	14.3
16	5	1.1	0.7	1	0.14	71	10†
19	5-15.4†	1.1-3.4	0.7-2.1	1-3	0.14-0.42	71-220	10-30
22	5-10	1.1-2.2	0.7-1.4	1-2	0.14-0.28	71-142	10-20†
27	14-29	3-6	2-4	2.9-5.7	0.4-0.8†	203-406	29-57

\*Comparative data assume a standard man weighing 70 kg with a blood volume of 5,000 ml.

†Values reported in the literature.

**TABLE 2. Factors to Consider in Choosing a Radiopharmaceutical for Cardiac Blood Pool Imaging**

Factors		Tc-99m HSA	In Vitro Tc-99m RBCs	In Vivo Tc-99m RBCs
FDA approval	Minimal amount of paperwork, consent, etc.	Yes	No	Yes
Availability	Acquisition	Commercial	Brookhaven National Laboratory	Commercial
Preparation: Personnel time	Time and money, scheduling	Short	Modest	Short
Additional equipment	Space, budget	None	Centrifuge	None
Length of time	Scheduling	~ 30 min	~ 30 min	~ 30 min
Labeling efficiency	Minimal free pertechnetate biodistribution	> 90%	> 97%, essentially 100% if washed	> 90%
Tc-99 carrier effect	Reduction in labeling efficiency	Negligible	Significant	Negligible
Cardiac blood pool-to-background ratio	Imaging detail	Adequate	Very high	High
Blood pool concentration	Imaging detail, prolonged or delayed imaging	Fairly steady; some vascular leakage	Very steady; some splenic uptake	Very steady
Secondary labeling effects	Interference with subsequent pertechnetate scans	Negligible	Negligible	Significant
Number of venipunctures	Patient discomfort	1	2	2
Needle gauge	Patient discomfort, injection in patients with "bad veins"	Can be small	20 g	Can be small
Volume of injection	Injection as bolus	Can be < 1 ml	> 3 ml	Can be < 1 ml
Bolus injection	Concurrent first-pass study	Relatively easy	Relatively difficult	Relatively easy
Risk of microbial contamination/ sepsis	Patient morbidity or mortality	Very low	Low, but greater than with the other agents	Very low
Risk of hemolyzing and/or damaging RBCs	Altered biodistribution, splenic uptake	No	Yes	No
Risk of allergic reactions	Patient morbidity or mortality	Low, but greater than with other radiopharmaceuticals	Very low	Very low
Determination of labeling efficiency before patient administration	Avoid injection of defective radiopharmaceuticals	Yes	Yes	No
Affected by heparin	Reduction in labeling efficiency and image quality	No	No	Yes
Cost	Budget	Modest	—	Modest

complex administration may result in labeled RBCs (12). This question, therefore, relates to the waiting time required after stannous complex administration to avoid secondary RBC labeling with pertechnetate. Secondary RBC labeling, as with primary RBC labeling, is dependent on the blood concentration of stannous ion. Excess tin is cleared from the blood by a combination of bone uptake and urinary excretion (17). Secondary labeling effects diminish fairly rapidly during the first few hours and then continue to diminish at a slower rate (14). To avoid secondary labeling effects, pertechnetate scans should not be performed within 6 to 14 days after administration of a stannous complex (13,14,25,26).

A second method of obtaining in vivo Tc-99m RBCs is being investigated by Patel et al. (23). Encapsulated stannous chloride, 100 to 200 mg, is given orally and pertechnetate is injected about 2 hr later. Almost 1,000 times the intravenous dosage is required because tin is slowly and somewhat erratically absorbed from the gastrointestinal tract. Nonetheless, labeling efficiencies as high as 95% have been reported (23).

Some advantages of in vivo Tc-99m RBCs include FDA approval, steady blood pool concentrations, minimal personnel time, use of small gauge needles and ability to inject a bolus. Some disadvantages include a somewhat lower cardiac blood pool-to-background ratio, lack of

determination of labeling efficiency before patient administration, decreased labeling in the presence of heparin or infiltration of the stannous pyrophosphate injection, and secondary labeling effects.

### Comparative Studies

Several studies have been published comparing the three radiopharmaceuticals. Atkins et al. (5) compared Tc-99m HSA and in vitro Tc-99m RBCs and found that in vitro Tc-99m RBCs had a higher cardiac blood pool-to-background ratio and resulted in clearly superior cardiac blood pool imaging. In a comparison of Tc-99m HSA and in vivo Tc-99m RBCs, Thrall et al. (2) found a higher cardiac blood pool-to-background ratio and greater cardiac blood-pool activity levels with in vivo Tc-99m RBCs. Three comparisons (16,18,21) of in vitro and in vivo Tc-99m RBCs found higher cardiac blood pool-to-background ratios and better subjective images with in vitro Tc-99m RBCs, but the differences were not great. The images were satisfactory with both agents and virtually identical ejection fractions were obtained.

### Conclusion

Although all three radiopharmaceuticals are clinically useful for cardiac blood pool imaging, comparative studies indicate that Tc-99m RBCs are superior to Tc-99m HSA. Both in vitro and in vivo Tc-99m RBCs give high quality diagnostic studies.

Table 2 lists a number of factors to consider before choosing a radiopharmaceutical for cardiac blood pool imaging. Each institution should consider all known factors before making its decision.

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