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LITERATURE SURVEY

Radiopharmaceuticals Used in Myocardial Imaging

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CONTENTS

INTRODUCTION

Ischemic and Infarcted Myocardium—To understand fully radiopharmaceutical procedures for diagnostic evaluation of myocardial ischemia and infarction, a basic understanding of the conditions is required. Myocardial ischemia is defined as a reduced blood supply without necrosis, resulting in a reduced supply of oxygen to the myocardium. A myocardial infarction is an area within the myocardium where coagulation necrosis has occurred, or is in the process of occurring, with varied stages of repair or changes in volume.

Both acute and chronic arterial obstruction may cause myocardial infarction; however, arterial occlusion, old or new, is evident in only ~40% of the deaths associated with myocardial infarctions (1–5), the same percentage of arterial occlusions found in patients dying from causes other than myocardial infarctions (6). Occlusion of a single coronary artery in dogs rarely produces transmural infarction (7). The excellent collateral circulation that exists with interconnections of all sizes of arteries, in addition to the arteriolar–capillary plexuses of the myocardium (8), provides the heart with the ability to circumvent, to a certain extent, minor occluded vessels. However, if collateral circulation is compromised from old occlusions, old infarctions, or coronary artery disease, a thrombus producing a major occlusion may be the impetus for acute myocardial infarction (9). The ability to assess accurately the extent of damage from these occlusions, infarctions, and coronary artery diseases, along with the ability to determine the amount of improvement offered by different therapeutic modalities, is essential for improvements in therapy and prevention of acute myocardial infarction.

Approaches to Imaging Myocardial Ischemia and Infarctions—The purpose of identifying myocardial ischemia and acute myocardial infarction is multifold. Most important is identification of the pathological condition. To care for the patient properly, the physician must be as well informed as possible about the patient's condi-

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tion; the physician must determine first if the patient does indeed have an infarction or ischemic zone within the myocardium. Second, the physician must determine if this area is recent or if it constitutes an area where intervention probably would not result in improvement of the condition. Third, the physician must determine if the tissue surrounding the infarction, ischemic at examination, will progressively worsen and further compromise additional tissue. The accurate determination of the volume of the infarction at the time of the initial insult and of the likelihood of this area increasing with time may play a vital role in the choice of the treatment modality. If, by various means, the ischemic area and final volume of the infarction can be reduced, prognosis will be improved.

Two methods have evolved for identification of acute myocardial infarction: identifying that tissue unaffected by the present condition, which gives an indirect determination of the extent of damage (cold spot imaging), and labeling the compromised tissue and imaging it externally, which gives a direct indication of infarcted tissue (hot spot imaging).

Diagnosticians at present utilize one or both of these methods in conjunction with electrocardiograph (ECG) changes and angiographic findings to assess the patient's condition. No single procedure assesses quantitatively and/or qualitatively both myocardial ischemia and acute infarction with a high degree of accuracy.

COLD SPOT IMAGING

Radionuclides as Inorganic Salts—Radionuclides for myocardial imaging generally are injected as the chloride salt in the ionic state. The biological behavior of the radionuclides of potassium, rubidium, cesium, and thallium varies with respect to dosimetry, blood clearance, duration in target organ, and target to nontarget ratios (T/NT). Isotopes of specific elements, such as potassium isotopes, demonstrate the same biological behavior. However, isotopes of a given element will not have the same dosimetry, because each isotope has different decay characteristics. Blood clearance, myocardial uptake, and T/NT ratios of isotopes should remain constant. Potassium analogs (although not in the same group in the periodic table) tend to localize in viable tissues, *e.g.*, the myocardium, to produce cold spot images of the infarcted or ischemic areas.

Potassium—The three isotopes of potassium that have been used in the assessment of myocardial ischemia and acute myocardial infarction are potassium 38, potassium 42, and potassium 43. Most recent research has been with potassium 43 because of better imaging characteristics; however, the high-energy γ-rays of all three isotopes result in poor quality images and excessive patient radiation dosage, limiting their use in the clinical setting on a routine basis.

Early work by Conn and Robertson (10) using potassium 42 assessed the exchange rates of potassium between coronary circulation and the myocardial interstitial fluid and between the interstitial and the intracellular fluid compartments. Sapirstein used potassium 42 in rats (11) and potassium 42 and rubidium 86 in dogs (12) to determine blood flow to specific organs and observed that 4.5 and 2.6% of the cardiac output resulted in coronary blood flow in dogs and rats, respectively. Not until Love and Smith (13) were able to develop a focusing collimator to image the hard γ-rays of potassium 42 was this isotope used to demonstrate zones of myocardial infarctions. Love *et al.* (14) later demonstrated that 71% of the potassium 42 was removed from arterial blood by the myocardium on the first pass.

Because potassium is taken up by other tissues and a small amount is maintained in the blood, low T/NT ratios were a problem. Poe (15) injected the radionuclide directly into the coronary circulation, eliminating the dilution of the radiotracer in body fluids. The results he obtained on first-pass extraction were similar to those of Love and coworkers. Holman *et al.* (16), using the same technique, observed a first-pass extraction rate of only 40%. Intracoronary artery injection, although a common procedure, should be used with caution when injecting electrolytes such as potassium. Intracoronary infusion of potassium alters repolarization and produces fibrillation (17), but no reports of repolarization with tracer quantities have been cited in the literature. Potassium 38 has been proposed as an alternative to potassium 42 and potassium 43 (18). However, with the availability of potassium 43 and suitable imaging equipment, the use of potassium 38 was not pursued (19).

With the availability of potassium 43 and its decreased shielding requirements (compared to potassium 42), decreased patient dose, and improved scanning characteristics, patient trials were initiated in 1971 (20, 21). The noninvasive technique of potassium 43 scanning compared well with traditional contrast angiograms (22–26). By imaging before and after exercise (27, 28), ischemic zones and infarcted myocardial areas were demonstrated (29, 30). This technique provided accurate, noninvasive assessment of patients with false-positive ECG exercise tests (31) and closely correlated with the reduced flow values of microspheres (32). With the use of digital computers (33) and of gated cardiac blood pool scanning (34), potassium 43 produced important diagnostic information not obtainable from other techniques.

Potassium 43 is not without its problems: the dosimetry is higher than with thallium 201 and rubidium 86 (35), the hard γ-emissions are difficult to collimate with equipment in use today, and the distribution changes after ~30 min, resulting in reduced T/NT ratios (36).

Rubidium—Early research on rubidium 86 (37–41) prompted Love and Burch to estimate the rate of myocardial rubidium 86 uptake (42), with and without cardiac disease (43), and to evaluate the effect of varying plasma flow rates on myocardial uptake (44). They concluded that an increased plasma flow rate increased uptake and that a decreased flow rate decreased uptake. Nolting *et al.* (45) and other investigators (46–50) reported the opposite observation, namely, an increase in rubidium 86 extraction at decreased flow rates. However, most reports supported the observation of Love and Burch that the flow rate and uptake parallel each other (44, 51–55). Conn (56, 57) showed that rubidium uptake may depend on factors other than flow rates.

Rubidium 84 was used to evaluate coronary blood flow changes (51, 58–62), but its decay characteristics preclude its use in patients. Ischemic zones and acute myocardial infarctions have been demonstrated with both rubidium 86 (63, 64) and rubidium 82 (65–67), a generator-produced radionuclide (68).

The best isotope of rubidium for scanning is rubidium 81, which has more favorable photon energies, a desirable short half-life, and economic production (69, 70). Berman and coworkers (71–73) reported better sensitivity and specificity when comparing rubidium 81 to stress ECG. Rubidium 81 scans compared favorably with intracoronary myocardial perfusion scintigrams performed with technetium 99m-labeled albumin particles (74). Rubidium 81 scintigrams (75, 76) were used to show perfusion improvement following aortocoronary bypass surgery (77). One cause of misdiagnosis in rubidium 81 perfusion scintigrams was the development of widespread collateral vessels or prior myocardial infarction (78). There is less absorbed dose with rubidium 81 than with thallium 201, with a total body dose estimate of 0.08 mrad/mCi (35), but, like potassium, the high-energy γ-emissions (Table I) are difficult to collimate and image with existing equipment (36).

Cesium—Cesium was first used for infarct imaging by Carr *et al.* (79, 80). Using cesium 131, they visualized myocardial infarctions in dogs and humans. Love *et al.* (81) later showed that only 22% of cesium 134 in arterial blood was removed during one passage through the heart, a value considerably less than that obtained with potassium and rubidium and supportive of earlier work on erythrocytes, which demonstrated that cesium 134 entered red blood cells more slowly than potassium or rubidium (82). Although cesium 131 has demonstrated anterior myocardial infarctions (83), it emits very low energy X-rays, which are not suitable for deeper tissue visualizations (Table I).

Cesium 129 and cesium 134m have energy emissions more suitable for imaging deeper tissues (84–86). Yano *et al.* (87) and Sodd *et al.* (88) prepared cesium 129 as a radiopharmaceutical, and the former investigators imaged patients with coronary disease and normal patients. Cesium 129 was shown to be effective in demonstrating acute myocardial infarction (89) and compared favorably to macroaggregated albumin labeled with technetium 99m (90) in flow studies. Dosimetry calculations for cesium 129 showed that it is comparable to thallium 201 with a whole body dose of 0.17 rad/mCi (35, 91). The whole body dose for cesium 129 might be reduced further by administering Prussian blue orally to inhibit the reabsorption of cesium from the gut. As with potassium and rubidium, cesium 129 emits γ-rays that are not suitable for imaging with existing equipment (Table I). Considering both the γ-ray energy and extraction rate, cesium 129 has little, if any, clinical use (92).

Table I—Radionuclides (Potassium Analogs) Used in Myocardial Imaging [a]

Radionuclide	Major Emissions[b], Mev: Gamma (γ)	Positron (β^+)	Beta (β^-)	Half-Life ($t_{1/2}$)
Potassium 38	2.17 (100%)	2.68	—	7.7 min
Potassium 42	1.524 (18%)	—	3.52	12.35 hr
Potassium 43	0.373 (85%)	—	1.82 (1%)	22.4 hr
	0.619 (81%)	—	1.20 (3%)	
Rubidium 81	0.511 (64%)	1.03	—	4.7 hr
	0.190 (65%)[c]			
Rubidium 82	0.777 (9%)	3.15 (96%)	—	75 sec
Rubidium 84	0.88 (74%)	1.66	0.91	33 days
Rubidium 86	1.078 (8.8%)	—	1.78	18.66 days
Cesium 131	X-rays; 0.029	—	—	9.7 days
Cesium 129	0.375 (48%)	—	—	32.1 hr
	0.416 (25%)			
Cesium 134m	0.128 (14%)	—	0.55	2.9 hr
Thallium 201	0.135 (2%)	—	—	72 hr
	0.167 (8%)			
	X-rays; 0.083 (98%)			

[a] Values taken from "Radiological Health Handbook," rev. ed., Bureau of Radiological Health, Rockville, Md., 1970. [b] Positron and beta particle values are listed as maximum. [c] From daughter krypton 81m.

Thallium 201—Thallium is a metallic element in Group IIIA of the periodic table. Thallium 201 is administered as thallous chloride in the ionic (+1) state. Lebowitz *et al.* (93, 94) produced thallium 201 for biological distribution by irradiating a target of 99.999% pure natural thallium metal (29.5% isotopic abundance of thallium 203) with 31-Mev protons produced by the 152.4-cm Brookhaven cyclotron. The nuclear reaction is $^{203}Tl(p,3n)^{201}Pb$. The lead 201 produced has a half-life of 9.4 hr and is the parent for thallium 201.

Initial interest in the production of thallium 201 as a potential myocardial scanning agent began with work on thallium 199 by Kawana *et al.* (95). The ability of thallium to mimic potassium in the biological system was reported earlier (96–98) and may be due to the fact that the hydrated ionic radius of Tl^+ is between K^+ and Rb^+ in size (94), thus providing thallium 201 with the ability to enter cells through passive diffusion.

Immediately following Lebowitz's production of thallium 201, Bradley-Moore *et al.* (99) reported biodistribution studies in goats demonstrating that >3% of the injected dose localized in normal myocardium. One abnormality of thallium uptake in normal myocardium noted was nonhomogeneous uptake. Strauss *et al.* (100) found the biodistribution to be slightly less in mice, with 2.08% of the dose localized in the normal myocardium in mice. This amount compared to 1.25% for potassium 43 and 1.15% for rubidium 81 in the same 10-min interval.

Dosimetry calculated from goat (99) and rat (35) data did not correlate well, with the estimations from goat data being 20% higher for the kidneys, 40% higher for the heart, and 25% lower for the testes. This variation probably was due, in part, to the metabolic variations of species. Early patient studies (101, 102) confirmed the myocardial uptake of thallium 201 in humans. The later work indicated an effective half-life of 2.3 days and a whole body radiation dose of 162 mrad/mCi. Both reports indicated the feasibility of rapid imaging following injection of thallium 201. Atkins *et al.* (103) later reported a whole body dose of 0.21 rad/mCi following a 1-mCi injection of thallium 201. Thallium 201 has been compared, both in experimental work (104) and in review articles (35, 105, 106), to potassium 43, rubidium 81, and cesium 129. Because the ionic nature and biological properties are similar, the dosimetry (105) and biodistribution (100) of these radionuclides in animals have been analyzed. In general, due to radiation doses and current γ-camera limitations, thallium 201 appears to be the most suitable agent of this group (105).

The ability of thallium 201 to detect and localize myocardial ischemia as a result of coronary artery disease (107–111), cardiomyopathies (112–114), myocardial infarctions (101, 110, 115–117), and angina pectoris (118, 119) is well documented. Myocardial blood flow is the determining factor for initial myocardial uptake with thallium 201. The concentration of thallium 201 during the first few minutes accurately depicts well-perfused tissue

(100, 120, 121). This blood flow dependency seen on initial scans changes in a short time, and redistribution of the radiotracer occurs (122). Initially, tissues with reduced blood flow receive less thallium 201 than well-perfused tissue. Later, ischemic tissue tends to accumulate thallium 201 while well-perfused tissue loses activity (123). Animal studies (122, 123) demonstrated that within 2 hr, the concentration of tracer appeared to equalize between the normal and ischemic areas. Maseri *et al.* (118) studied the effect of redistribution of thallium 201 in patients with angina pectoris and found that the equilibrium of normal and ischemic tissue was complete within 2–4 hr. The redistribution of thallium 201 in patients with coronary artery disease appears to be complete within 4 hr and may vary depending on the extent of the disease (124).

Myocardial infarctions will not accumulate thallium 201 but appear as defects, both in the exercise and resting scintiscans. Ischemic zones surrounding infarctions appear as cold areas on the exercise scintigrams but will accumulate thallium 201 during the resting state (111). The patient, following maximal exercise stress, is injected and imaged immediately (exercise scintigram); in 4 hr, a repeat scintigram (redistribution scintigram) is made. This single-dose technique produces results similar to the double-dose exercise and rest scintigram (124).

Thallium 201 scintigrams have a high sensitivity of infarct identification within 6 hr after onset of symptoms, and optimum diagnostic information is obtained within 24 hr (110). Thallium 201 scans appear to be of little value if performed several days following the onset of symptoms (125), partly because the damage done may be irreversible. In addition, questionable and false-negative scintiscans may be obtained in patients with elevated transaminase levels (110). Ischemic regions may not, in selected cases, result in abnormal thallium 201 scans. If collateral vessels are present, a high incidence of normal-appearing scans may be produced. Rigo *et al.* (126) demonstrated that 35% of the patients with collateral blood flow failed to show stress-induced perfusion defects. Although disagreement exists (127–130), recent experimental work indicates that thallium 201 scans cannot predict the extent of ischemic tissue (131).

Myocardial uptake of thallium 201 may be enhanced or diminished by drugs currently used in the treatment of conditions associated with the heart. Hetzel *et al.* (132) demonstrated an increase in myocardial uptake of thallium 201 with bicarbonate. Hamilton *et al.* (133) produced an increase in the myocardium to background ratio by first injecting dipyridamole. Costin and Zaret (134), by first injecting propranolol, showed a 32% decrease in thallium 201 uptake, a greater reduction than the 11% decrease reported by Hamilton *et al.* (133) for the same drug.

It is difficult to differentiate between ischemic and infarcted areas and almost impossible to determine if an infarct is old or new using thallium 201 alone (135). The utilization of technetium 99m stannous pyrophosphate in conjunction with thallium 201 provides additional information essential in differentiating the ischemic tissue from acute myocardial infarctions in the presence of previously infarcted necrotic tissue (136, 137).

When imaged with current γ-cameras, the low-energy emissions of thallium 201 raise questions concerning which collimator (pinhole, converging, or high resolution) to use. Groch and Lewis (138) reported that a 75-kev converging collimator produced the best line spread function and modulation transfer function; in addition, they noted that the high-resolution collimator may not produce acceptable images unless the thallium 202 contaminant in the commercial thallium 201 is negligible. Nishiyama *et al.* (139) reported increased diagnostic accuracy with the pinhole collimator and poor lesion detectability with the converging collimator. At present, the low-energy high-resolution collimator provides the most information and is the collimator of choice in the clinical setting (108, 110, 115, 122).

Attempts to improve the diagnostic quality of thallium 201 scintiscans using computers have been reported. Graphic representation (140) and ECG synchronization (141) have been attempted to improve lesion detectability. Observer variability (142) and small infarction detection (143) may be improved by utilizing computer manipulation of data and by close attention to exercise techniques (144).

Nitrogen 13—Nitrogen 13, which decays by positron emission (β^+) with a 10-min half-life (145), is the only feasible radionuclide of nitrogen. Uptake studies in dogs (146–148) indicated that ^{13}N-labeled ammonia was cleared rapidly from the blood and localized well in the myocardial tissue, although skeletal muscle, liver, kidney, and brain activity also was noted. In human subjects, researchers indicated rapid clearance from the blood (85% in 1 min), estimated a whole body dose of 5 mrad/mCi assuming uniform distribution (149), and demonstrated ischemic myocardium (150) and cold spot imaging of infarctions (151, 152).

To image the positron emissions, nitrogen 13 requires special equipment that is not available in most hospitals. In addition, the 10-min half-life of nitrogen 13 requires that the production facility and synthesizing equipment be very near the hospital (Table II).

Technetium 99m Complexes—*Macroaggregated Albumin*—Early attempts at myocardial scanning with macroaggregated albumin utilized iodine 131 as the ra-

Table II—Radionuclides Used in Myocardial Imaging [a]

Radionuclide	Major Emissions[b], Mev: Gamma (γ)	Positron (β^+)	Beta (β^-)	Half-Life ($t_{1/2}$)
Nitrogen 13	—	1.2	—	10 min
Gallium 67	0.093 (40%) 0.184 (24%) 0.296 (22%)	—	—	78 hr
Fluorine 18	—	0.635	—	110 min
Technetium 99m	0.140 (90%)	—	—	6.1 hr
Iodine 123	0.159 (83%)	—	—	13.3 hr
Iodine 131	0.364 (82%)	—	0.806	8.05 days
	0.637 (6.8%)	—	0.606	
Xenon 127	0.203 (65%) 0.172 (22%) 0.375 (20%)	—	—	36.4 days
Xenon 133	0.081 (37%)	—	0.346	5.3 days
Krypton 81m	0.190 (65%)	—	—	13 sec
Krypton 85	0.514 (0.41%)	—	0.67	10.8 years
Mercury 197	0.077 (18%)	—	—	65 hr
Mercury 203	0.279 (77%)	—	0.214	46.9 days
Erbium 165	X-rays; 0.050	—	—	10.3 hr

[a] Values taken from "Radiological Health Handbook," rev. ed., Bureau of Radiological Health, Rockville, Md., 1970. [b] Positron and beta particle values are listed as maximum.

diolabel. Quinn *et al.* (153) identified coronary branch occlusions in dogs, and Endo *et al.* (154) demonstrated ischemic zones in patients using macroaggregated albumin. Ashburn *et al.* (155) labeled macroggregated albumin with technetium 99m and iodine 131 and demonstrated bilateral areas of reduced blood flow in patients with coronary artery disease by injecting the ^{99m}Tc-labeled particles into the left coronary artery and ^{131}I-labeled particles into the right coronary artery, utilizing separate or composite images. Currently, only ^{99m}Tc-labeled macroaggregated albumin is used due to the high radiation dose of iodine 131.

Sources of errors utilizing macroaggregated albumin have been characterized (156, 157), and improvements in labeling with technetium 99m have been reported (158). Acute myocardial infarctions have been demonstrated with macroaggregated albumin (159), but care must be taken because variations in uptake with different particle sizes have been reported (160–165). The safety of injecting radiolabeled particles (macroaggregated albumin) into the coronary arteries has been questioned (166–168), but no alterations in myocardial status have been noted. Gould *et al.* (169) observed the behavior of two injections of ^{99m}Tc-labeled macroaggregated albumin, one in the normal state and one following vasodilation. They observed decreased tracer uptake distal to the coronary artery narrowing following vasodilation. This technique has the disadvantage of requiring surgical intervention for intracoronary artery injection and does not accurately reflect regional rates of local myocardial capillary blood flow (170).

Human Serum Albumin—^{99m}Tc-Labeled human serum albumin and computers have been used to produce multiple-gated acquisition images. A complete cardiac cycle, terminating at end systole or end diastole, is recorded for ~800 cardiac cycles (~10 min) following intravenous injection of 20 mCi of ^{99m}Tc-labeled human serum albumin, and the cycles are summed by the computer. By viewing a full cardiac cycle, regional wall motion abnormalities can be observed (171–173). This technique may be valuable in determining the ejection fraction and end diastolic volume in patients with acute myocardial infarction (174), especially inferior wall infarctions (175). Multiple-gated acquisition images do not provide any information concerning the integrity of the myocardial blood supply, the presence of a myocardial infarction, or the age of the lesion.

Radiolabeled Metabolites—*Fatty Acid Analogs*—The normal myocardial tissue readily extracts fatty acids and utilizes them *via* β-oxidation as a source of energy (176–181). In myocardial tissue, oxidation appears to be the major metabolic pathway for fatty acids (182). Bragdon and Gordon (183) showed major uptake of [1-^{14}C]palmitic acid in muscle and liver; by feeding rats carbohydrates, they noted increased radiolabel in the heart. The extraction of [1-^{14}C]palmitate appears to be inversely related to the coronary blood flow; in hypoxic states, alteration in fatty acid metabolism from β-oxidation to triglyceride formation was reported (184).

Evans and coworkers first demonstrated the myocardial uptake of radioiodinated oleic acid in dogs (185) and humans (186, 187) and proposed the use of ^{131}I-labeled oleic acid to demonstrate areas of reduced blood flow or metabolism. They demonstrated maximum uptake of label in the myocardium within 20 min. Low specific activity of the labeled fatty acid and relatively poor physical characteristics of iodine 131 limited its use.

The greatest extraction of radioiodinated fatty acids occurs in the first pass (188), and the activity of radiolabeled oleic acid analogs in the myocardium drops to ~5% at 60 min (189). Oleic acid radioiodinated by double-bond saturation is not extracted as efficiently as natural compounds (190). By terminally labeling hexadecenoic acid with iodine 123, improved imaging characteristics were observed (191, 192). The ω-labeled hexadecenoic acid has a dosimetry estimate of 0.03 rad/mCi, assuming uniform distribution and relatively pure iodine 123 (193). The ω-labeled 16-iodo-9-hexadecenoic acid is metabolized rapidly to iodoacetate and deiodinated (193). The resulting free iodide in the blood (194) increases blood background radioactivity; similar observations were made by Beierwaltes *et al.* (195) with ^{131}I-labeled oleic acid.

With a myocardial half-life of 25 min (196), ^{123}I-labeled hexadecenoic acid demonstrated ischemic defects in patients with coronary artery disease (196) or infarctions (197). The extraction rate of ~70% was comparable to that of potassium 43 (198). Using ^{14}C-labeled oleic acid, Bilheimer *et al.* (199) showed that more fatty acid accumulates in the border and peripheral zones of infarction than in normal cells. Attempts at improvements in formulation (195) and labeling with other radionuclides such as carbon 11 (200, 201), fluorine 18 (202), chlorine 34m and bromine 77 (194), technetium 99m (203–205), and tellurium 123m (206–208) have not significantly improved fatty acids for myocardial scanning.

The most promising of these agents, ^{11}C-labeled palmitic acid (209–211), will not be in routine use in the near future because of the need for specialized equipment (212). The additional problems of specific activity and formulation (213) also must be overcome for fatty acids to provide information not currently obtainable concerning acute myocardial infarctions and accompanying ischemia.

β-Adrenoceptor Blocker Analogs—Jiang *et al.* (214) synthesized tyramine-containing analogs of β-adrenoceptor blockers and, by labeling them with iodine 123, determined their distribution in rats as potential myocardial imaging agents. Of the four compounds synthesized, only one, a derivative of practolol, showed sufficient heart to blood ratios to be promising. The problem encountered was a myocardium to lung ratio of two, insufficient to image changes in myocardial uptake.

Toluidine Blue Analogs—Kang (215) proposed toluidine blue analogs as agents in infarct imaging because unlabeled toluidine blue did not concentrate as well in the infarcted tissue as in the normal tissue. However, using radioactive iodotoluidine blue, no selective uptake by the myocardium was noted by Archer *et al.* (216, 217). Carr *et al.* (218) attempted to increase the T/NT ratio by injecting a loading dose of cold toluidine blue prior to the radioactive compound. They were able to obtain a normal myocardium to blood ratio of 12:1 and an infarct to normal ratio of 0.18 (±0.31):1, which was insufficient for imaging purposes.

Bretylium Analogs—Counsell and coworkers (219–221) synthesized the *ortho-*, *meta-*, and *para*-analogs of bretylium, radioiodinated these compounds with iodine 125 and iodine 131, and reported results in animals, but an

increase in serum glutamic oxaloacetic transaminase levels of patients caused clinical trials to be canceled.

^{13}N-Labeled L-Asparagine—Gelbard *et al.* (222) labeled L-asparagine with nitrogen 13 and injected the purified compound into two dogs to assess organ uptake of the compound. The compound localized in the myocardium (13.7% of the injected dose), with an equal amount in the liver. Maximal uptake appeared within minutes in both organs. ^{13}N-Labeled compounds require special equipment that is not available to most nuclear medicine departments, and no subsequent work has appeared in the literature.

Inert Gas Radionuclides—Although several different radioactive isotopes have been used, the technique is similar. Herd *et al.* (223), using krypton 85, studied myocardial blood flow in dogs. The technique, applied later in humans (224, 225), provided blood flow rates in myocardial tissues. Xenon 133 in solution was used by Ross *et al.* (226) because it has better decay characteristics than krypton 85 (Table I). By injecting xenon 133 following selective coronary arteriography, the myocardial blood flow and washout were recorded.

Today, the technique consists of single- (227–231) or multiple-crystal scintillation cameras (232–234) externally measuring washout curves in different regions of the myocardium following injection of xenon 133 directly into the coronary arteries. Computer analysis determines the rate constants of regional clearance from the heart muscle. No complications have been noted with this technique (235–239), and it correlates well with the flowmeter technique (240, 241). Xenon 127 has been proposed as a replacement for xenon 133. Although improved decay characteristics (Table II) result in improved imaging and dosimetry, its long half-life (36.4 days) may produce storage and disposal problems.

This drawback is not shared by krypton 81m with a half-life of 13 sec and γ-emission of 0.190 Mev (65%), which also has been proposed as a replacement for xenon 133. Produced from rubidium 81 (242–247), the krypton 81m is continuously infused in 5% dextrose into the coronary artery (248–250) directly from the generator.

HOT SPOT IMAGING

Radionuclides as Inorganic Salts—*Gallium 67*—Gallium 67 localizes in inflammatory processes, resulting in a hot spot, an area containing more activity than surrounding tissue. Kramer *et al.* (251) reasoned that, since inflammation accompanies myocardial infarctions, gallium 67 might localize sufficiently to identify acute myocardial infarctions. In patients with gallium 67 localization, the uptake correlated well with conventional techniques such as ECG and angiography, but only 63% of the cases with confirmed acute myocardial infarction showed gallium 67 uptake.

Fluorine 18—Bonte *et al.* (252) first proposed fluorine 18 as a potential infarct-avid agent but demonstrated less uptake than with technetium 99m stannous pyrophosphate in acute myocardial infarction, a result later confirmed by Weber *et al.* (253). Cochavi *et al.* (254), using improved tomography equipment, reevaluated fluorine 18 and determined that, although sufficient uptake for imaging was noted, uptake peaked at 48–72 hr postinfarction. This delay in imaging of 48–72 hr negates the usefulness of the technique for early identification.

Erbium 165—Erbium 165 citrate (255) has been shown to have an affinity for myocardial infarcts in dogs with infarct to normal ratios of 2.5:1 at 2 hr, 12.5:1 at 8 hr, and 108:1 at 24 hr. However, its low-energy photopeak at 0.050 Mev with a half-life of 10 hr may preclude its use with current imaging equipment.

Technetium 99m Complexes—*Tetracycline*—Malek *et al.* (256), working with fluorescent identification of tetracycline in dogs, noted increased uptake of this antibiotic in acute myocardial infarctions. Holman and coworkers (257–259) labeled tetracycline with technetium 99m and attempted to identify acute myocardial infarctions directly *via* hot spot imaging. They observed maximal infarct to normal myocardium ratios of 8.4:1, requiring 24 hr for sufficient blood clearance. In 24 hr, technetium 99m has decayed four half-lives, reducing the photon yield appreciably. With a low photon yield, a 24-hr wait before imaging, and insufficient T/NT ratios, tetracycline was not pursued as an agent in acute myocardial infarction scanning.

Glucoheptonate—Although complete blood clearance of technetium 99m glucoheptonate is not achieved, the clearance is much more rapid than that of tetracycline. Rossman *et al.* (260) detected glucoheptonate uptake shortly after injection in animals, with acceptable infarct to normal ratios of 20:1. In subsequent studies (261–263), infarct to blood ratios were not sufficient to identify acute myocardial infarctions consistently; only one of four patients with documented acute myocardial infarctions showed diagnostic glucoheptonate scans.

Pyrophosphate—Bonte *et al.* (264) first reported the use of technetium 99m stannous pyrophosphate to demonstrate myocardial infarctions in closed-chest dogs. Soon thereafter, Parkey *et al.* (265) observed similar results in human patients. These early studies, followed by clinical trials performed by Holman *et al.* (266), prompted a great deal of research concerning technetium 99m pyrophosphate, currently the most widely used hot spot radiopharmaceutical for myocardial infarct imaging.

The study of Tetalman *et al.* (267), using technetium 99m pyrophosphate in 103 patients, found 68.7% true positives and 92.4% true negatives, compared with the findings of Holman *et al.* (266) of 100% true positives and 80% true negatives. Most published studies indicated true positives and true negatives within this range of values. Tetalman *et al.* (267) also indicated that a negative scan does not rule out the possibility of a recent small (<2.5 cm), subendocardial, myocardial infarct.

The ability to size acute anterior transmural myocardial infarctions in dogs accurately has been reported (268–271). Bruno *et al.* (272) reported the ability to detect infarctions of 1% of the left ventricular mass in dogs. Other experimental work with the canine model appears less encouraging. Zaret *et al.* (273) found more uptake in the border zones of acute infarctions, while Marcus *et al.* (274) discouraged the utilization of the intensity of technetium 99m pyrophosphate images for infarct sizing. Technetium 99m pyrophosphate is sequestered in bone as well as damaged myocardium, providing excellent landmarks for locating the myocardium and infarcted tissue. However, this potentially limits its ability to define the extent of the in-

farction due to labeling of the sternum and rib cage. Although pyrophosphate is a superior imaging agent, there are cases where the borders of the infarct are totally obscured by overlying bone.

In patients with inferior infarction (275) and subendocardial infarction (276, 277), the estimation of infarct size by a scintigram does not correlate well with enzyme levels. Massie *et al.* (276) reported only a 32% discrete uptake in patients with nontransmural infarction, compared with 84% of patients with a transmural infarction. The difficulty in determining the size of inferior, as well as subendocardial, infarctions has been reported (278).

The flow-dependent uptake of technetium 99m pyrophosphate (272–274, 279, 280) may limit its ability to provide accurate assessment of acute myocardial infarction size. The amount of radioactivity is inversely related to the extent of infarction after permanent occlusion and is directly related to the extent of infarction after transient occlusion (272).

The ability of technetium 99m pyrophosphate to localize in myocardial tissues following acute myocardial infarction is well documented (264–267, 281); however, other conditions also may result in myocardial uptake. Both diffuse and localized uptake have been reported with subendocardial and transmural portions of the left ventricle (267, 282–284) or the right ventricle (285). Technetium 99m pyrophosphate also will localize in old myocardial infarctions (282, 286–290), old myocardial infarctions with or without ventricular aneurysm (282, 286, 291, 292), subclinical necrosis of the myocardium (291), carcinoma invasion of the left ventricle (293), myocardial contusions (294–296), valvular calcification (297, 298), stable angina pectoris (283, 292, 299), unstable angina pectoris (267, 283, 292, 300), primary cardiomyopathy, and congestive heart failure (301, 302). In addition, technetium 99m pyrophosphate also accumulates in the myocardium following coronary artery bypass graft surgery (303), in high-energy cardioversion (304, 305), in benign and malignant breast lesions in females (306, 307), in experimental viral mild pericarditis (308), and in several cases of unknown etiology (309).

Experimentally infarcted myocardium has the potential of accumulating technetium 99m pyrophosphate within 12 hr following myocardial insult (264, 265). Because of this observation, initial patient scintigrams are obtained 12–24 hr postinfarction. In cases where the 12–24-hr postinfarct scintigram is negative, a second scintigram at 48–72 hr is recommended if acute infarction is strongly suspected (310). With the necessity for early detection and intervention, a technetium 99m pyrophosphate scintigram may be performed as early as 4 hr following the suspected injury (311). However, this approach results in a decrease in sensitivity. Images of the myocardium are usually taken 2 hr following injection of the radiopharmaceutical but may be taken as early as 90 min postinjection. If uptake is not localized, followup imaging should be done at 4 hr to allow time for blood clearance.

The mechanism of localization of technetium 99m pyrophosphate in the myocardium is unclear. Bonte and coworkers (264, 312) postulated that the phenomenon of calcium localization within the mitochondria reported by D'Agostino (313) and later by D'Agostino and Chiga (314) was the mechanism of localization. Shen and Jennings (315, 316) discussed accumulation of calcium as an index of irreversible myocardial cell damage resulting from ischemia. Dewanjee and coworkers (317, 318) proposed that the uptake of technetium 99m pyrophosphate could be due to the formation of polynuclear complexes with denatured macromolecules rather than to the formation of calcium phosphate complexes. These investigators reported most of the technetium 99m pyrophosphate activity to be associated with macromolecules rather than nuclei, mitochondria, and microsomes.

Methylene Diphosphonate—Following the success of pyrophosphate as a myocardial agent, virtually all bone agents have been used in an attempt to image acute myocardial infarctions. As with pyrophosphate, these agents have the disadvantage of bone uptake with varying degrees of infarct to bone ratios as well as infarct to normal myocardium ratios. Technetium 99m methylene diphosphonate has a greater affinity for infarcted myocardium, but its bone uptake is too high to prove useful. The infarct to normal ratio (27.9:1) exceeds most reports of pyrophosphate, but the infarct to bone ratio (0.4:1) does not allow sufficient visualization of myocardial damage that may lie beneath the ribs (319).

Polyphosphate—Polyphosphate studies in animals (320) and humans (321–323) showed good infarct to bone ratios, but optimum images were obtained 2–3 days postinfarction (323), delaying treatment.

Diphosphonate—Technetium 99m disphosphonate, although taken up by infarcted tissue, accumulates unevenly, preventing accurate assessment (324).

Ethylenediaminetetramethylenephosphonic Acid—Holman *et al.* (325), labeling ethylenediaminetetramethylenephosphonic acid with either indium 113m or technetium 99m, found the agents to be specific for infarcts. The infarct to normal ratio was 50% of published technetium 99m pyrophosphate values. Dewanjee and Kahn (326) reported good infarct to normal ratios with ethylenediaminetetramethylenephosphonic acid (40–50:1) but high bone uptake (50–57% of the injected dose).

Imidodiphosphonate—Preliminary work on rabbits (327) indicates that imidodiphosphonate labeled with technetium 99m has a greater infarct to normal ratio than pyrophosphate (14:1 at 1 hr and 33:1 at 6 hr). Subsequent work on rats (328) and preliminary work on 50 patients (329) indicated improved uptake over pyrophosphate, although in-depth studies have not been completed.

Radiolabeled Metabolites—*Mercurials*—Carr *et al.* (330) first demonstrated hot spot imaging of acute myocardial infarctions with ^{203}Hg-labeled chlormerodrin[1] and reported 16 infarct to normal ratios greater than 15%. The initial study in dogs (330), later repeated in humans (331), was promising, but limited equipment hindered diagnostic effectiveness. Gorten *et al.* (332) also demonstrated the propensity of ^{203}Hg-labeled chlormerodrin to localize in acute myocardial infarctions of swine. Malek *et al.* (333), using mercury 197 and mercury 203 labeling, produced a series of radiolabeled difluorescinylmercury and mono- and bis-hydroxymercurifluorescein derivatives. After improving the specific activity (334), they reported T/NT ratios of 20–77% (335). Subsequent work confirmed the

[1] Neohydrin.

infarct avidity of mercury-radiolabeled fluorescein derivatives but with varying T/NT ratios (336–338).

Recent work on structure–activity relationships of phthaleins (339) and fluoresceins (340, 341) has shown that diiodohydroxymercurifluorescein has almost six times the avidity of technetium 99m pyrophosphate for acute myocardial infarctions. ^{203}Hg-Labeled hydroxymercurifluorescein has a T/NT ratio of 51.5(±13.5):1 and an infarct to blood ratio of 22.1(±8.1):1. Although less than the fluorescein derivatives, the ratios of the phthalein derivatives were higher than those of technetium 99m pyrophosphate, with ratios of 20.7–34.1:1 and 12.1–20.1:1, respectively (339). The structure requirements are a polycyclic organic moiety and a hydroxymercury group, with the latter (mercury 203 and mercury 197) structural requirement being more important.

The mercury-labeled compounds are hampered by poor decay characteristics (Table II) and higher absorbed radiation doses than ^{99m}Tc-labeled compounds.

Cardiac Myosin-Specific Antibodies (Fab′)$_2$—Khaw *et al.* (342) showed that myocardial uptake in acute myocardial infarction tissue, resulting in a hot spot image with ^{131}I-labeled Ab(Fab′)$_2$, was the result of antigen-antibody reactions rather than a nonspecific sequestration of proteins (343). Ab(Fab′)$_2$ uptake is very specific and inversely related to blood flow (344). Imaging must be delayed at least 48 hr following intravenous injection (345). Khaw *et al.* (346) reduced the delay in imaging by injecting the radiopharmaceutical directly into the main left coronary artery in dogs. Localization in infarcted tissue occurred within 30 min, resulting in a T/NT ratio of 34.3(±1.5):1.

Khaw *et al.* (347) recently reported formation of a bifunctional chelate labeled with Ab(Fab′)$_2$, which was labeled with gallium 68. The bifunctional chelating agent diethylenetriaminepentaacetic acid was used and tested in dogs with reported T/NT ratios as high as 100:1.

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