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COMPARATIVE MYOCARDIAL DISTRIBUTION PATTERNS AFTER
INTRACORONARY INJECTION OF CESIUM AND LABELED PARTICLES

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KEY WORDS

Myocardial scanning, coronary blood flow, regional blood flow, radioactive cesium, radioactive particles.

ABSTRACT

To determine if soluble indicators could replace labeled macroaggregates for myocardial scanning after coronary artery injection, simultaneous coronary artery or left atrial injections of cesium-131 and several technetium-99m labeled suspensions were made in dogs. Only very small particles ($< 35\mu$) showed uniform distribution comparable to cesium.. Perfusion defects and vascular beds were more discretely outlined with particles after atrial injection, but with arterial injection particle distribution determined by in vitro analysis often was markedly irregular. No significant differences were found in vivo. Ionic radiopharmaceuticals, e.g., Cs-129, can be used as a safe substitute for macroaggregates for intracoronary administration.

Following coronary arterial injection, radioactive particles can be used in the measurement of regional myocardial blood flow (1). In conjunction with scintiscanning this method has been used successfully in man to localize sites of myocardial infarction in vivo (2,3). If the particle size is small, the size range well controlled and the number administered kept at low levels, injections can be made without detectable alterations in flow or function (4). However, excessive vascular blockade with particles is a potential hazard, especially in the presence of coronary artery disease, and safer radiopharmaceuticals would be desirable for clinical application.

Soluble substances which are highly extracted by the myocardium would seem preferable to particles. The potassium analogs, rubidium-86 and cesium-131, have been explored as myocardial scan agents (5,6), but the gamma energies of these radionuclides are not optimal for imaging. Now potassium-43 and cesium-129, with energies similar to iodine-131, can be produced in clinically useful amounts and have been shown to yield satisfactory myocardial scans after intravenous injection (7,8).

To explore the possibility of substituting a soluble tracer for labeled particles, a study was undertaken in dogs to determine if comparable regional myocardial flow patterns could be obtained with ionic cesium-131 and four different particulate preparations labeled with technetium-99m.

MATERIALS AND METHODS

Mongrel dogs (15-20 kg.) were anesthetized with pentobarbital, 25 mg/kg. After intubation with a cuffed endotracheal tube ventilation was

maintained by an intermittent positive pressure respirator. The left chest was surgically opened to expose the left atrium and/or anterior descending coronary artery. Injections were made in one of three ways: into the left atrium in normal dogs, into the left atrium after ligation of the anterior descending artery, or directly in the anterior descending artery. Atrial injections were made via a small gauge needle. For intracoronary injections a special number 27 needle with attached tubing was inserted into the artery near its origin. To produce ischemic lesions the artery was tied distal to the first main branch. Propranolol (4-5 mg) was sometimes required to reduce myocardial irritability and prevent ventricular fibrillation. A left lateral heart scan was performed in vivo with the chest open. A 3-inch rectilinear scanner with a high sensitivity 3-inch focus collimator recorded the scans. A high resolution collimator was occasionally used for better definition in vitro. At termination of the study, animals were sacrificed with intravenous potassium chloride. The hearts were immediately removed, washed, and scanned in the anterior and left lateral projections. Multiple full thickness tissue sections weighing approximately 1 gram were taken and counted in a well scintillation counter with dual spectrometers. Scanning was excluded in some of the normal animals.

In all experiments involving scanning, approximately 1.0 mCi of carrier-free $^{131}\text{CsCl}$ was mixed and injected with 1-3 mCi of one of the following $^{99\text{m}}\text{Tc}$ labeled particle suspensions: macroaggregates of albumin (MAA) with no particles greater than 40 microns maximum diameter*, sulfide-MAA

*Modification of method of Stern, H.S., et al., Int. J. Appl. Radiat. 16: 283, 1965.

(10-100 micron diameter)** , anion exchange resin (10-100 microns diameter, 14.9×10^6 particles/gm)*** and microfine anion exchange resin (35 micron maximum diameter with 60% greater than 10 microns, 7.2×10^9 particles/gm)†. These low density resin spheres bind technetium efficiently and can be easily counted microscopically. From 93 to 430 mg of the larger resin microspheres or about 130 mg of the small resin microspheres were injected in each experiment. The resin spheres were suspended in normal saline and subjected to ultrasound to assure complete dispersion. If in vitro counts alone were to be obtained, the radioactivity was reduced by a factor of 10.

For the intra-arterial studies the test material in a total volume of approximately 0.5 cc was injected rapidly but not as a bolus and the needle and tubing were subsequently flushed with normal saline. The intra-atrial injections were made rapidly with the test suspensions mixed with 1.5-5.0 cc normal saline or venous blood after which the needle and syringe were flushed with 1.0 cc of atrial blood.

In the ischemic series electrocardiographic monitoring was done with standard limb leads and an epicardial electrode inserted into the region of probable ischemia.

RESULTS

Intra-atrial Injections: Normal Hearts

The results for left ventricular distribution are summarized in Table 1. Each group represents 3 dogs with from five to seven myocardial

← TABLE 1

** Modification of method of Cragin, M.D., et al., J. Nucl. Med., 10:621, 1969.

*** J.T. Baker Ion Exchange Resin CGA-541, 200-400 mesh.

† J.T. Baker Ion Exchange Resin MFA-6, microfine.

samples counted in each. Cesium always serves as the reference and each cesium value is normalized to the highest sample count which is given the arbitrary value of 1.00. Technetium values are similarly normalized to the technetium count found in the sample serving as the cesium standard.

Although the numbers of observations in each group of experiments seen in Table 1 are too small for meaningful statistical analysis, it is obvious that the values for cesium in the twelve animals are reasonably reproducible and fall within a relatively small range as is manifested by the overall mean and standard deviation of $.96 \pm .03$. In contrast much greater variation in the means and standard deviations is found with the particles. The single exception is the ultrafine microspheres which yield results almost identical to cesium. Regardless of the in vitro results, scans obtained with these two radionuclides in normal dogs are comparable.

Intra-atrial Injections: Coronary Occlusion

Only the MAA, sulfide-MAA and larger resin microspheres were used in this part of the study. The results in 9 dogs are shown by scattergrams with regression lines in Fig. 1. The best correlation is apparent with cesium and the small MAA (1A) but with the sulfide-MAA (1B) and microspheres (1C) the wide scatter of the technetium values produces much more variation. Although there are a number of exceptions, in the ischemic areas there is a tendency for greater flow reductions to be found with the particles than with cesium. This finding is supported by the scans which show more discrete and complete ischemic deficits with technetium (Fig. 2). In some of these animals, the ECG failed to show changes of ischemia or infarction indicating good collateral circulation.

← FIG. 1

← FIG. 2

Intra-arterial Injections:

Direct intracoronary arterial injections were made in 7 animals using cesium and either MAA, sulfide MAA or the large resin microspheres. The highly variable results obtained by in vitro analysis are not amenable to meaningful tabulation; however, based on multiple sample counts (6-15 per animal), the ratio of technetium to cesium is an inverse one. In the proximal portion of the vascular bed supplied by the injected artery, relative technetium concentrations often greatly exceed cesium but more peripherally the reverse is found with cesium predominating over technetium. On the scans the technetium particles appear to be more discretely localized. In contrast, the perfusion pattern with cesium is consistently larger and in most scans there is demonstrable cesium uptake throughout the entire myocardium (Fig. 3). In some of the post mortem scans the technetium pattern is very irregular (Fig. 4) and confirms the varied results obtained by tissue counting.

← FIG. 3

← FIG. 4

DISCUSSION

In vivo scans using cesium and any of the technetium labeled particles were qualitatively similar following left atrial injection. The in vitro scans and the direct tissue counts show definite differences. The primary difference is the more generalized and homogenous distribution of the cesium. Some localized differences were anticipated. Assuming adequate mixing in the blood during administration, the ionic cesium and particulate technetium reach the coronary vascular bed in proportion to blood flow but the methods of extraction and retention are different. Cesium is removed from the blood similar to potassium by rapid equilibration with

the extracellular fluid and subsequent incorporation into cells. Normally, the extraction of cesium on a single circulation in anesthetized dogs is only 20-25% (9,10). The remainder is free to move to adjacent areas by arteriolar-capillary anastomoses and be similarly cleared or to return to the general circulation where it can eventually be extracted during recirculation to the myocardium, the skeletal muscle, the liver or other tissues. Particle clearance by the coronary arteriolar capillary network is strictly mechanical and approaches maximal efficiency as particles exceed 10μ in diameter (11). The larger particles will be trapped farther upstream than will the smaller ones, and any particles under capillary size will be ultimately removed by the reticuloendothelial system. The difference in extraction efficiency, the lack of recirculation and the more central deposition of the larger particles probably combine to produce the more discrete ischemic defects and localized distribution patterns found with the technetium particles.

In explaining the localized irregularities of particle distribution, which were most evident with the sulfide macroaggregates and the large resin spheres, at least three variables must be considered. First, the particles because of their size, shape and density may be subject to different physical forces which result in uneven mixing or which favor intravascular streaming. Laminar flow would be a particular problem during direct arterial injection. Second, clumping may have occasionally occurred before or during injection. This would result in increased deposition in the larger vessels more centrally in the perfusion bed. The third point is an extension of the second and is related to the relatively

exaggerated radionuclide content of the larger particles. Size inequality plus low absolute numbers of particles could be a major source of error because the statistical reliability of an observation increases with the number of particles in the sampling unit. Buckberg et al. (11) have shown that 400 uniform radioactive particles per unit sample is the lower limit necessary for statistically significant measurements. In the work presented in this paper calculations show that between 500 and 1000 particles per gram of myocardium could be obtained with the doses of sulfide macroaggregates and large resin spheres used. However, this amount frequently caused electrocardiographic abnormalities, eg. premature ventricular contractions or T wave changes. These particles were not of uniform size and differed in diameter by as much as a factor of 10. Inasmuch as the radionuclide is thought to be evenly distributed throughout the particles used, the amount of radioactivity in a 100μ particle could be up to a thousand-fold the amount in a 10μ particle. It is apparent that very large counting errors could result using these two indicators in the numbers described but that the use of larger numbers of them could adversely affect myocardial blood flow and function. No electrocardiographic abnormalities were noted with the ultrafine resin microspheres even though they were given in numbers up to a thousand times greater. In addition more consistent results were obtained with them. It was originally anticipated that the small MAA would yield results comparable to the microspheres because of size similarity. Unfortunately, consistent production of particles of the desired size range was not achieved. The very large amount of activity frequently found in the liver in most of the animals studied indicated that

the majority of the administered particles passed through the capillary bed and were extracted by the reticuloendothelial system. The conclusion is that too few aggregates were retained in the myocardium for satisfactory counting statistics. Nevertheless, the technical aspects of small particle production can be overcome and this type of particle would be preferred for clinical studies because relatively large numbers can be given with only temporary blockade of the vascular bed.

As noted above, extraction of potassium, and presumably its cesium analog, is a function of both flow and cell viability. Severely damaged or dead cells lose the capacity to selectively incorporate and retain these ions (12). Under certain circumstances, for example following temporary arterial occlusion, cellular injury could be extensive enough to interfere with the transmembrane transport mechanism but actual blood flow could be substantial or even normal. In this situation blood flow presumably would be more accurately measured by the particle method than by ionic transfer. Further experiments will have to be performed to clarify this point and determine if this would be a significant problem clinically.

Based on observations in dogs, potassium would be preferable to cesium for intracoronary injection because of more efficient potassium extraction by the myocardium (10). In anesthetized animals approximately 70% of injection potassium is removed on a single course through the coronary vessels. This value is three times the value obtainable for cesium. Presumably a similar relationship holds true in humans. The higher potassium extraction would reduce the amount of activity available for recirculation to the heart and overlying tissue which in turn would lower tissue

background and enhance the quality of myocardial scans

—Several conclusions regarding the use of particulate and soluble tracers for regional coronary flow measurements following intracoronary arterial injection can be drawn from this investigation and the related studies referred to in the foregoing discussion. 1) Potassium analogs can be substituted for radioactive particles for localization of myocardial ischemia in most clinical situations. 2) The high myocardial extraction of potassium may make it preferable to cesium. 3) Because of negligible recirculation and independence of cellular function, small radioactive particles are theoretically better indicators of regional coronary blood flow than the soluble substances particularly in acutely damaged myocardium. 4) Particles have an additional advantage in that they can be labeled with several radionuclides of different gamma energies making possible a variety of simultaneous or sequential studies. The only suitable soluble radiopharmaceuticals, potassium-43 and cesium-129, have similar energies which preclude simultaneous use. 5) To avoid perfusion alterations or production of distribution and sampling errors, particles should be of uniform size and unit density with diameters just sufficient for vascular retention.

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LEGENDS

1. Comparison of cesium distribution with three different technetium labeled particles following left atrial injection in animals with coronary arterial occlusion. A) small MAA, B) large sulfide MAA, C) large resin microspheres. The symbols represent individual animals. Note the greater variations in the particle values and the tendency for relatively lower particle to cesium ratios as blood flow diminishes, i.e. as flow approaches 0. The circled symbols are the reference values representing normal blood flow.
2. Anterior in vitro scans showing cesium (A) and technetium microsphere (B) distribution following simultaneous left atrial injection. Previously the anterior descending coronary artery had been ligated. A more discrete ischemic pattern is found with the particles.
3. In vivo radionuclide distribution scans of cesium (A) and small technetium MAA (B) after intracoronary injection. The technetium pattern is slightly more restricted and irregular than the cesium pattern.
4. In vitro high resolution scans after cesium (A) and large technetium sulfide MAA (B) injection into the anterior descending coronary artery. The "hot spot" in B is caused by MAA attraction to the damaged endothelium at the injection site. Note the highly irregular particle distribution pattern compared to the homogeneous cesium pattern.

TABLE 1 Comparative Left Ventricular Distribution Patterns of Technetium Particles and Cesium after Intra-atrial Injection in Normal Dogs: Mean + SD

Particle	Dog	Technetium	Cesium	Tc/Cs
Albumin MAA	1	1.07±.13	.98±.01	1.08
	2	.93±.08	.98±.03	0.95
	3	1.35±.35	.98±.02	1.38
	Mean	1.12±.19	.98±.02	1.14
Sulfide MAA	4	1.22±.26	.97±.04	1.27
	5	.98±.20	.95±.03	1.03
	6	.69±.22	.90±.09	0.77
	Mean	.92±.22	.94±.05	1.03
Resin Spheres	7	1.10±.18	.98±.02	1.12
	8	.84±.11	.91±.06	0.93
	9	1.21±.20	.98±.02	1.24
	Mean	1.05±.16	.96±.03	1.10
Microfine Resin Spheres	10	.94±.04	.98±.02	0.96
	11	1.00±.03	.97±.03	1.03
	12	.96±.08	.97±.02	0.98
	Mean	.96±.05	.97±.02	0.99

A

B

A

B

A

B