Myocardial Perfusion Scintigraphy after Intracoronary Injection of $^{99m}$Tc-Labeled Human Albumin Microspheres

Toxicity and Efficacy for Detecting Myocardial Infarction in Dogs; Preliminary Results in Man

By Daniel A. Weller, M.D., Robert J. Adolph, M.D., Henry N. Wellman, M.D., Robert G. Carroll, M.D., and Onja Kim, M.D.

SUMMARY
Myocardial perfusion scintigraphy was performed in 30 intact anesthetized dogs following intracoronary injection of $^{99m}$Tc-labeled human albumin microspheres (HAM). The normal dog myocardial image pattern was established. This technic detected myocardial infarcts resulting from small vessel occlusions and flush coronary branch occlusions when the coronary angiogram appeared normal. Myocardial infarcts as small as 1½ cm were seen. Toxicologic studies in 47 dogs failed to demonstrate significant changes in blood pressure, heart rate, electrocardiogram, or serum CPK activity following intracoronary injections of HAM in doses up to 200 times that required for adequate myocardial scintigraphy. Gross and microscopic examination of hearts 1–6 weeks after HAM injection showed minor abnormalities also seen in matched controls receiving coronary arteriography alone. Preliminary results in 33 patients substantiate the safety of this technic. Human myocardial scintigrams reported here reveal anatomic detail not previously demonstrated by other external imaging methods.

Additional Indexing Words:
Radioisotope Scintiscan Myocardial infarction CPK
Toxicity Coronary arteriography

A TECHNIC capable of detecting abnormalities in the coronary microcirculation would greatly improve our understanding of coronary heart disease. In this study we tested the hypothesis that intracoronary injection of radioactive-labeled human albumin microspheres at the time of coronary angiography is safe and provides useful information regarding the presence, location, and size of areas of myocardial infarction and ischemia. We attempted to answer the following questions: What are hemodynamic, enzymatic, and histologic changes after intracoronary HAM injection?
injection in dogs? What is a safe yet effective dose? Can the technic detect myocardial infarction when the coronary angiogram is normal? What is its sensitivity for detecting small infarcts?

It is now recognized that there are patients who have normal coronary angiograms despite clinical or electrocardiographic evidence of myocardial ischemia or infarction. Among the possible explanations for this apparent paradox are: (1) recanalization of a coronary thrombus following myocardial infarction; (2) disease in vessels too small to be seen on angiography; and (3) occlusion of a major coronary artery branch at its origin, flush with the parent vessel, so that absence of the branch is not appreciated on coronary angiography. A technic capable of detecting diminished myocardial vascularity at the arteriolar and capillary level should detect myocardial infarction or fibrosis even when the coronary arteriogram appears normal. If such a technic could accurately define the location and size of areas of diminished myocardial vascularity, it would help determine the functional significance of coronary lesions seen with coronary angiography. It would also be valuable for assessing the results of myocardial "revascularization" procedures.

Endo and Ashburn used intracoronary MAA labeled with $^{131}$I or $^{99m}$Tc for myocardial imaging in man. The images were superior to earlier ones utilizing diffusible isotopes and impressed the authors with their great potential for diagnosis in coronary artery disease. The history of myocardial scintigraphic technics was well reviewed by Ashburn.

We chose human albumin microspheres for our study because this product, developed by the 3M Company and extensively tested by Rhodes, Burdine, and others, seemed to have several advantages over MAA: (1) the particle size is uniform and consistent from batch to batch; (2) labeling with $^{99m}$Tc is rapid and easy; (3) higher specific activities can be obtained, thereby reducing the number of particles needed for each image; and (4) an ultrasonic mixer can be used to assure complete dispersion of particles prior to injection.

Published experimental data on the effects of intracoronary albumin particles is limited. Available reports do not include detailed or controlled studies of histologic and serum myocardial enzyme changes and none includes studies on the effects of selective coronary HAM injection.

### Materials and Methods

#### Animal Studies

We studied 47 mongrel dogs weighing from 16 kg to 26 kg. Intravenous pentobarbital anesthesia (25 mg/kg) was used in all dogs. A preformed coaxial polyethylene catheter was introduced into a coronary artery through the left carotid artery under fluoroscopic control. The small nonobstructing inner catheter (4.1 F) was advanced approximately 2 cm into the left anterior descending or circumflex branch of the left coronary artery or the right coronary artery for injection of radiographic contrast medium or human albumin microspheres. Coronary angiograms were obtained using a rapid-sequence cut-film technic. Electrocardiograms and aortic or left ventricular pressures were recorded using an Electronics for Medicine or a four-channel direct-writing Sanborn recorder and Statham P23dB pressure gauges. Myocardial scintigraphy was performed using a gamma scintillation camera with a 16,000 parallel-hole, low-energy, high-resolution collimator. Gating of the image to selected portions of the cardiac cycle was done in selected cases using an adjustable electronic gating device previously described. Gamma-camera images were recorded simultaneously on Polaroid paper and 35-mm film. Human albumin microspheres with a mean diameter of 22 micra, 95% falling between 16 and 30 micra, were used. They were supplied in dry form, sealed in sterile pyrogen-free labeling vials which contained all the reagents necessary for labeling. Each milliliter of prepared product contained 0.5 mg (75,000) microspheres. Details of the methods of preparation have been described elsewhere. The microspheres were labeled with $^{99m}$Tc pertechnetate from a technetium generator. For diagnostic studies we used a specific activity of 10–20 mCi.

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*Elema-Schonander Corporation, Stockholm, Sweden.*


*3M-brand serum albumin microspheres (human).*

*Squibb Technetone, New Brunswick, New Jersey.*
per mg of HAM, injecting 0.05 mg into each coronary artery. The microspheres were washed twice with saline after labeling, and the suspending solution normally contained less than 5% of the total activity. The physical half-life of $^{99m}$Tc is 6 hours, and the biologic half-life of albumin microspheres in tissue is less than 24 hours.\footnote{6}

Toxicologic studies were performed in 47 dogs. In 10 dogs the anterior descending or circumflex branch of the left coronary artery was injected with 0.5–2.0 mg HAM (10–40 times the diagnostic dose). Aortic pressure and the electrocardiogram were continuously recorded. In three other dogs massive doses of HAM (25–30 mg, or approximately 500 times the diagnostic dose) were injected into the left anterior descending coronary artery in small increments while we recorded the electrocardiogram and aortic or left ventricular pressure. Six dogs received left anterior descending and circumflex artery injections of 76% meglumine diatrizoate\footnote{Renografin-76, E. R. Squibb and Sons.} plus 1.0–3.0 mg HAM, whereas six control dogs of similar size were injected with intracoronary contrast medium alone. Each of the 12 dogs was sacrificed 1 week after coronary artery injection for gross and histologic examination of heart tissues. Tissue samples were taken from the apex, septum, right ventricular free wall, anterolateral aspect of the left ventricle, and posterobasal aspect of the left ventricle of each heart, stored in formalin and later sectioned, mounted, and stained with hematoxylin and eosin, saffron, and periodic acid Schiff. Twelve additional dogs were studied in a similar manner after 6 weeks in order to detect any delayed histologic effects. In 10 dogs serum CPK activity was measured by the Sigma UV method\footnote{Sigma Chemical Company, St. Louis, Missouri.} on blood samples drawn before and at 4 hours, 24 hours, and 48 hours following coronary angiography plus anterior descending and circumflex injection of 0.5 mg HAM. Samples were obtained from 10 dogs which received intracoronary radiographic contrast medium alone and served as controls.

Myocardial scintigrams were obtained in 30 normal dogs. HAM was injected selectivity into the right coronary artery, left anterior descending branch of the left coronary artery, circumflex branch of the left coronary artery, or combinations of these vessels in an attempt to define the normal myocardial scintigraphic pattern. Coronary artery ligation was performed in seven dogs, and all survived. In two, the left anterior descending coronary artery was ligated midway between its origin and the apex of the left ventricle. In three dogs the first large diagonal branch of the left anterior descending coronary artery was ligated flush with its origin from the left anterior descending artery, and infarction occurred in one. In two dogs a large branch of the circumflex artery was ligated at its origin and infarction occurred in one. Seven to thirteen days later coronary angiography and myocardial scintigraphy were performed on all seven dogs. The dogs were then sacrificed and their hearts examined to determine the extent of myocardial infarction. In six additional dogs the left anterior descending coronary artery was injected with carbonized microspheres in an attempt to produce myocardial infarction by small vessel occlusion. Carbonized spheres 250 micra in diameter were used in three dogs of which two died. The surviving dog exhibited an extensive anteroseptal infarct at autopsy. Carbonized spheres 20 micra in diameter were used in three dogs and all survived. All surviving dogs were subjected to coronary angiography and myocardial scintigraphy 7–14 days after injection of carbonized microspheres, followed by postmortem examination for evidence of myocardial infarction.

**Human Studies**

Patients were studied according to a protocol approved by the Committee on Human Research of the University of Cincinnati College of Medicine.\footnote{Investigational New Drug Approval no. 484, Division of Biological Standards, Department of Health, Education and Welfare.} Thirty-three patients, 28 men and five women, who were already scheduled for diagnostic coronary angiography at the University of Cincinnati Medical Center agreed to participate after having been fully informed of the investigative nature of the study. Selective coronary catheterization was performed in each patient. After completion of the angiographic study of each coronary artery and before the catheter was removed, 0.05 mg HAM (7,500 particles) labeled with 0.5–1.0 mCi of $^{99m}$Tc was injected into the catheter and slowly flushed into the coronary artery with 5 ml of saline. An ultrasonic mixer was used to disperse the microspheres immediately prior to injection. Coronary artery pressure and an electrocardiographic lead showing a large QRS deflection were continuously monitored in all patients and recordings made before and after coronary artery injection in most patients. If a left ventriculogram was obtained, left ventricular end-diastolic pressure was measured after HAM injection. Aliquots from each vial of HAM were tested for sterility, and pyrogen testing was done on each batch. Scintigraphy was performed from...
½ hour to 2 hours after HAM injection. One hundred thousand counts were collected for each scintigram, and a minimum of five views obtained in each patient: anterior, left lateral, right and left anterior oblique, and left posterior oblique. The time required for each scintigram varied from 2 to 10 min. If the scintigraphy time was short we obtained additional oblique views. For gated views we selected a 0.08-sec period just before the P wave for diastole and the apex of the T wave for systole, collecting 20,000 to 40,000 counts per scintigram.

Results

Dog Studies

Toxicity

Figure 1 summarizes the serum CPK activity and hemodynamic changes following intracoronary HAM injection as compared to the effects of intracoronary radiographic contrast injection alone. The mean CPK activity following intracoronary HAM is actually lower at each sampling period, but these data do not provide evidence for a significant difference when Student's t test is used (P values are shown). Arterial blood pressure and heart rate changed very little after HAM injection, the difference between group means being so small that it failed to provide evidence for a significant difference (P values are shown). Figure 2 demonstrates graphically the change in blood pressure and heart rate in one dog following incremental doses of intracoronary HAM into the anterior descending coronary artery. Only after injecting 10 mg HAM (200 times the diagnostic dose) did we record an increase in left ventricular end-diastolic pressure, followed by a rise in heart

![Figure 1](http://circ.ahajournals.org/)

Mean serum CPK activity, arterial blood pressure, and heart rate following intracoronary HAM injection as compared to intracoronary injection of radiographic contrast medium alone. The brackets include 95% confidence limits for the mean. The number of observations in each group is indicated at the base of each bar. Students t-test was used to obtain P values (unpaired for CPK data, paired for pressure and heart rate data).

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rate, and eventually a precipitous drop in systolic blood pressure in this 20-kg dog.

Pathology Studies

Of sixty myocardial tissue sections obtained from the first group of 12 dogs (six received 10–40 times the diagnostic dose of HAM, and six controls received radiographic contrast only) one tissue section from each of two control dogs and a total of seven sections from three HAM-injected dogs showed abnormalities thought to be significant (myocytolysis). Except for one control dog with an organizing thrombus in a 200 micra-diameter artery, myocytolysis was restricted to minute patches, averaging approximately 1% of the cross-sectional area of the positive slides from the control dogs and 0.75% of positive sections from HAM-injected dogs. Other findings such as focal chronic granuloma and epicardial calcification seen in two HAM-injected dogs were thought unlikely to have resulted from HAM injection 1 week before. One control dog exhibited a focus of granulomatous vasculitis. These data do not exclude the possibility that high doses of HAM (20–40 times the human diagnostic dose) produce minute areas of myocytolysis when myocardial tissue is examined within 1 week after injection, but we consider this unlikely for two reasons. First, myocytolysis was seen in two dogs receiving 1 and 2 mg HAM, respectively, whereas a dog receiving 3 mg HAM did not exhibit myocytolysis. Second, myocytolysis was also seen in two control dogs.

In the second group of experiments concluded at 6 weeks in which three to five times the diagnostic human dose was given, no myocytolysis was seen in sections from either control or HAM-injected dogs. The following abnormalities were noted only in dogs from the control group: focal granuloma, mild interstitial fibrosis, one minute focus of recent hemorrhage, and one focus of chronic active subendocardial interstitial inflammation without evidence of fiber damage.

Myocardial Scintigrams

Figure 3 demonstrates, for purposes of orientation, the normal myocardial image patterns which result from injecting different coronary arteries in the dog. The dog's left coronary artery is so short as to be virtually nonexistent, and selective catheterization of the anterior descending and circumflex coronary arteries was necessary to insure a predictable distribution of microspheres in the left ventricle.

Figure 4 displays myocardial scintigrams and coronary angiograms recorded before and 14 days after ligation of a large branch of the anterior descending coronary artery flush with its origin from the parent vessel at a point indicated by the arrow in panels A and B. Without the control angiogram it would be difficult to detect the absence of this large branch following ligation. Figure 5 demonstrates that the myocardial scintigram can detect myocardial infarction produced by arteriolar occlusion (20 micra-diameter carbonized microspheres) when the coronary angiogram appears normal.

Four additional dogs exhibited myocardial infarction at autopsy, and in each case the myocardial scintigram showed a defect corresponding to the anatomic site of infarction. Two additional dogs did not develop myocardial...
Normal myocardial scintigraphic patterns in the dog. (A, B, and C) Scintigraphic pattern resulting from injection of three coronary vessels: the right coronary artery, left anterior descending coronary artery (LAD CA), and the circumflex coronary artery (CIR CA). The left ventricular cavity is indicated by a central area of diminished radioactivity, seen in C. (D, E, and F) Scintigrams resulting from injection of the LAD CA only. (G, H, and I) Scintigrams resulting from injection of the CIR CA only. Combining corresponding scintigraphic views from the middle and lower panels would create a pattern similar to that seen in the corresponding upper panels, except for the radioactivity indicated by arrows in A and B which resulted from injection of the right coronary artery.

Figure 3
A myocardial infarct, 1.5 cm in diameter, produced by ligating a branch of the left anterior descending coronary artery at its origin, flush with the parent vessel (arrows, A and B). Upper panels: (A) Coronary angiogram before ligation; (B) coronary angiogram after ligation; (C) autopsy specimen showing an apical infarct (arrows). Middle panels: (D) Anterior scintigram; (E) left anterior oblique scintigram; (F) left lateral scintigram before ligation. Lower panels: A small area of diminished radioactivity can be seen in the scintigram following infarction (arrows, G and H) which corresponded to the anatomic site of infarction shown in C. Only the LAD CA was injected.

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Detection of a myocardial infarct by myocardial scintigraphy when the coronary angiogram was normal. The infarct (C) was produced by small vessel occlusion following injection of carbonized microspheres into the left anterior descending coronary artery (LAD CA). Upper panels: (A and B) Normal LAD CA and circumflex (CIR CA) coronary arteries. The autopsy specimen (C) revealed a high anterolateral myocardial infarct (arrows). Middle panels: Normal control scintigrams before small vessel occlusion. Lower panels: Scintigraphic defects (arrows) corresponded to the anatomic site of infarction.

Electronic gating of the scintigram by means of electrocardiogram signal did not improve the resolution of the system and greatly prolonged the time required to obtain each image. It was therefore abandoned.

Clinical Studies
Toxicity
Table 1 summarizes the hemodynamic data from 33 patients. In some instances recordings were not made or were technically inadequate
Table 1

Summary of Blood Pressure Changes in Patients following Intracoronary HAM Injection

<table>
<thead>
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<th>Pt</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>HAM dose (mg)</th>
<th>Left CA pressure Before</th>
<th>Left CA pressure After</th>
<th>Right CA pressure Before</th>
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<td>-</td>
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<tr>
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<td>M</td>
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Average systolic BP before HAM injection = 98 ± 20 mm Hg.
Average systolic BP after HAM injection = 102 ± 22 mm Hg.
Average diastolic BP before HAM injection = 66 ± 12 mm Hg.
Average diastolic BP after HAM injection = 69 ± 12 mm Hg.

(asterisks). However, arterial pressures and the ECG were continuously monitored by a physician during each procedure, and no change in these variables was observed at the time of HAM injection. Although the differences between means are small, analysis of the recorded change in blood pressure following HAM injection (Student t test for paired differences) provided evidence for a significant increase in both systolic and diastolic blood pressure. This was probably due to the commonly observed upward drift in blood pressure following the drop caused by intracoronary contrast injection. HAM was injected during this recovery period. Intracoronary HAM injection did not produce electrocardiographic changes in any patient. Left ventricular end-diastolic pressure was measured following intracoronary HAM and radiographic contrast injection in 19 patients. It was elevated (greater than 11 mm Hg) in two patients, each of whom had an extensive
anterior wall infarct, cardiomegaly, and myocardial aneurysm. LVEDP was measured both before and after radiographic contrast and HAM injection in one patient, and it did not change.

Myocardial Scintigrams

Figure 6 shows the angiographic and scintigraphic abnormalities found in patient E.M., a 45-year-old man with Fredrickson type II hyperlipoproteinemia and clinical and electrocardiographic evidence of an acute anteroseptal myocardial infarction 4 months prior to this study. Figure 7 shows the angiographic and myocardial image findings in F. W., a 51-year-old man who developed clinical and electrocardiographic evidence of acute inferior myocardial infarction 7 months prior to this study. Included for comparison are the scintigrams from R. L., a 41-year-old man without clinical evidence of myocardial infarction whose myocardial image was thought to be normal.

Figure 6

Apical anterior infarct in patient E.M. The coronary angiogram (A) demonstrated 75% narrowing of the proximal left anterior descending coronary artery (arrow). The left ventriculogram (B, diastole; C, systole) showed akinesis of all but the inferior wall. Middle panels: The scintigrams showed diminished radioactivity in the region of the cardiac apex, septum, and the anterior wall (arrows). Lower panels: Corresponding views of a normal scintigraphic pattern from another patient, C.C., whose electrocardiogram and coronary angiogram were normal. Note in the LAO views that these high-resolution scintigrams show right and left ventricular walls, septum, and right and left ventricular cavities.
Figure 7

Inferior infarct in patient F.W. The coronary angiogram (A) demonstrated complete occlusion of the right coronary artery (arrow). The left ventriculogram (B, diastole; C, systole) showed moderate hypokinesia of the inferior wall. The arrows in C indicate the excursion of ventricular walls during systole (broken line represents the diastolic dimensions). Middle panels show diminished radioactivity in the inferoposterior wall of the left ventricle, septum, and inferior wall of the right ventricle (arrows). Lower panels: Corresponding views of a normal pattern from another patient, R.L., who had no clinical evidence of myocardial infarction and whose myocardial scintigram was considered normal. Hyperconcentration of radioactivity in the distribution of the proximal right coronary artery (note scintillations in area of the atrium in D) indicates a smaller vascular bed on the right, in this case presumed to be due to obstruction of the right coronary artery.

Discussion

It is reasonable to assume that radioactive microsphere distribution accurately reflects blood flow distribution, based on experience with carbonized microspheres and MAA particles. The theoretic considerations and validation of the method are summarized by Wagner in a recent review. Domenech and his associates demonstrated that certain anatomic features of the coronary circulation caused nonhomogeneous myocardial distribution of microspheres 50 micra in diameter or larger, whereas smaller microspheres such as those used in this study were more uniformly distributed.

The largest experience with human albumin microspheres has been reported by Rhodes and his associates. They have performed
liver scans using HAM since 1968 and report only five adverse reactions in more than 1,500 intravenous injections. These reactions were brief and self-limited. Only two possible adverse reactions, both self-limited, occurred in 5,700 patients who received 3M-brand HAM for lung scanning, according to investigator reports submitted to the 3M Company during clinical trials (Hoogland DR: Personal communication). Rhodes demonstrated that the LD-50 for intravenous HAM injection in mice was greater than 200 mg per kg or 5,000 times the normalized human dose and that HAM was less toxic than MAA or ferric hydroxide particles. Burdine performed histologic studies in dogs following intravenous, carotid artery, renal artery, and celiac artery injections of HAM and observed no ischemic, hemorrhagic, or necrotic changes. Fortuin and co-workers recently measured coronary blood flow, peak reactive hyperemic coronary blood flow, cardiac output, mean aortic pressure, and heart rate following injection of 15-micra carbonized microspheres into the dog's left atrium. Assuming that 5% of the cardiac output went to the coronary circulation, they found no significant change in these variables following intracoronary doses as large as 200,000 particles. Peak reactive hyperemic coronary blood flow was unaltered with intracoronary doses as large as 600,000 particles.

The normal myocardium is an extremely vascular tissue containing about 4,000 capillaries/mm² cross-sectional area, one for each muscle fiber. The ability of the heart to tolerate embolization with small particles when the dose is carefully controlled probably reflects the small proportion of the total capillary and arteriolar bed occluded. If we assume homogeneous distribution in a 300-g heart, the final microsphere density would be only 50 particles/cc when a 0.1-mg HAM dose is used. It has been feared that albumin microspheres may be more hazardous than MAA because the spherical nature of the particles produces a "... propensity for total plugging of the vessel in which they lodge and probably resultant slower clearance." This fear is not borne out by the results of our toxicity studies.

Ashburn modified his method of MAA production and labeling, enabling him to reduce the number of particles required for a heart scan from approximately 400,000 to 200,000. With HAM, very high specific labeling activities can be obtained, allowing us to further reduce the number of particles required for heart imaging to approximately 15,000.

The use of radioactive-labeled HAM for myocardial scintigraphy is investigational. We have observed no adverse reactions during our limited experience with patients, but there may be unforeseen hazards, evident only after more patients are studied and longer follow-up is obtained. Further, the diagnostic usefulness of the procedure for patients has not yet been established. Interpretation of myocardial images is a deductive process at present, and it remains to be shown that myocardial scintigraphy provides information not obtainable using existing technics such as contrast ventriculography, cardiac fluoroscopy, and electrocardiography. The future usefulness of the technic can be judged only after correlation with clinical, surgical, and autopsy findings. However, our animal data indicate that recent infarcts as small as 1½ cm in diameter may be detected, and myocardial infarcts resulting from small vessel occlusion and "flush occlusions" may be detected by myocardial scintigraphy even when the coronary arteriogram appears normal.

To be interpretable, myocardial scintigrams must demonstrate myocardial anatomy and be able to distinguish small defects in the coronary circulation. Our method employs clinical scintigraphy equipment designed for high-resolution scintigraphy when using 99mTc, an isotope having a nearly ideal energy peak for this purpose. This may explain why the scintigrams reported here show anatomic detail not demonstrated in previous reports dealing with myocardial perfusion scintigraphy.

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