Cesium-129 Myocardial Scintigraphy to Detect Myocardial Infarction

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SUMMARY
Cesium-129 is concentrated in the myocardium after intravenous administration permitting myocardial imaging. The dosage used was 2-2.5 mCi in dogs and 3-4 mCi in patients. Four or more views with 200,000 counts per view were obtained 30 to 90 minutes after administration. Control images were obtained in 30 dogs. In two dogs anatomic landmarks were obtained using technetium-99m markers. In 24 dogs, either the anterior descending or circumflex coronary artery was ligated. An area of absent uptake of $^{129}$Cs was seen involving the anterior wall and apex or the inferior-posterior wall, respectively. At postmortem this represented a myocardial infarction (MI) averaging 4 x 5 cm. Smaller MI (2 x 3 cm) at postmortem were seen as defects of the anterior wall. Evolution of an acute MI was followed in four dogs. The defect appeared at one hour and gradually increased on serial images. Fifty patients were studied. Each of 20 patients without evidence of MI had the normal horseshoe or doughnut appearance of the left ventricle surrounding the interventricular cavity. Each of 15 patients with acute MI and 10 of the 13 patients with an old MI had a defect on the myocardial image. The three patients without defects had infarction of the inferior wall. One of two patients with coronary insufficiency had a defect. These studies show that good quality myocardial images were obtained with $^{129}$Cs and strongly suggest its potential usefulness in quantification of an acute MI.

Additional Indexing Words: Radionuclides Myocardial scanning Coronary artery disease

There is a need for an intravenously administered radioisotope which produces high quality myocardial images permitting detection and quantification of infarcted myocardium. In 1964 Carr and co-workers described the use of Cesium-131 for the visualization of myocardial infarction. The disadvantage of Cesium-131 for deep tissue imaging was its low energy emissions, which were difficult to detect above the electron noise of the photon spectrometer system, and the attenuation of the low energy emissions by the structures of the chest wall. Many other intravenously administered radionuclides including rubidium-86, potassium-42 and $^{133}$I, nitrogen-13 labelled ammonia, $^{14}$C, $^{15}$N, $^{19}$F, $^{203}$Hg, $^{15}$NH$_4$Cl and $^{125}$I labelled fatty acids, $^{18}$F and gallium-67 have been evaluated for efficacy in detection of myocardial infarction by myocardial imaging. None of these radionuclides have proved entirely satisfactory to delineate the myocardium clearly.

We have recently described a method for the extraction of Cesium-129, a radioisotope with certain advantages for myocardial imaging. Cesium-129 is suitable for deep tissue imaging being a pure gamma emitter with major energy peaks at 372 KeV and 412 KeV. It has a desirable 33-hour half-life, which allows sufficient time for shipment from a cyclotron to the clinician without inordinate loss of radioactivity. This report describes our initial experience with the development of good quality Cesium-129 myocardial images and the application of this technique to recognition of myocardial infarction in animals and patients.
CELSIUM-129 MYOCARDIAL SCINTIGRAPHY

Methods

Cesium-129 was produced at the Cyclotron Facility of the Naval Research Laboratory in Washington, D. C. by the bombardment of sodium iodide targets via the $^{151}$T (s, 2n) reaction. The $^{129}$Cs was separated from the dissolved target using 4-sec-butyl-2-(s-methylbenzyl) phenol or BAMBP as described by Sodd, Blue and Scholz, resulting in carrier free Cesium-129. The yield of $^{129}$Cs has been increased from an initial rate of 0.2 mCi/mA-h to a rate of 0.4 mCi/mA-h. Final yields of 25 to 55 mCi have been produced routinely following 10 to 12 hr of target irradiation.

Following intravenous administration of $^{129}$Cs, optimal images were obtained at 30 to 90 min and adequate images were still possible 18 to 21 hr following a single injection. Images were obtained using a gamma scintillation camera with a coarse pinhole collimator, with an energy setting of 360 KeV and a 35 percent window. Initially 100,000 counts were collected per view. To improve resolution, counts were increased to 200,000 per view, each view requiring from five to eight min. Recognition of a myocardial infarction as an area of decreased to absent uptake of $^{129}$Cs was enhanced by obtaining multiple views so that the infarction was a border-forming structure in one or preferably several views. Cesium-129 also was concentrated in the liver, skeletal muscle and spleen. The radiation dose with $^{129}$Cs to the whole body was approximately .24 rad/mCi.18

Animal Studies

Initial studies designed to develop myocardial imaging techniques were performed using six mongrel dogs. The dosage of $^{129}$Cs in 15 to 20 kg dogs was 2 to 2.5 mCi. Four views of the heart were obtained routinely: right anterior oblique, anterior, left anterior oblique and left lateral.

The following studies were done in 30 mongrel dogs, each of whom had a control image. The control image was performed one week prior to any intervention except in the four dogs in whom we followed the course of the acute infarction with serial images. Anatomic orientation was obtained in two of these dogs by sewing small plastic capsules filled with technetium-99m to various regions of the heart and then taking sequential images utilizing the different energy levels of $^{129}$Cs and the technetium-99m markers. The corresponding images for each view were then superimposed to determine which regions of the heart were border-forming structures in each of the views taken. At postmortem the exact location of the capsules was documented in each view.

Myocardial infarctions were reproduced by two stage ligation of the anterior descending coronary artery. The anterior descending coronary artery was ligated at the level of the inferior border of the left atrial appendage in 16 dogs and distal to the level of the left atrial appendage in four dogs. The circumflex artery was ligated in four dogs. The images were taken 24 to 72 hr after ligation of the coronary artery in these 24 dogs.

Cesium-129 was used to follow the course of an acute myocardial infarction in four additional dogs. The $^{129}$Cs was given and the control image taken. The anterior descending coronary artery was then immediately ligated and serial images were obtained during the next 21 hr after the infarction using the same initial dose of $^{129}$Cs given prior to the ligation of the coronary artery. Additional images were then taken at one week following another dose of $^{129}$Cs.

Patient Studies

Fifty patients were studied with $^{129}$Cs in accordance with a protocol approved by the Committee on Human Research of the University of Cincinnati College of Medicine. Informed consent was obtained from all patients. The dose of $^{129}$Cs varied from 3.0 mCi in small women to 4.0 mCi in muscular large men. Five views were taken routinely: right anterior oblique, anterior, left anterior oblique, left lateral, and left posterior oblique. The images were interpreted by three investigators independent of the clinical and electrocardiographic data. The three investigators who interpreted the images in this study were also responsible for selecting subjects for myocardial imaging; however, at the time of interpretation the images were not identified by patient name.

There were 20 patients without clinical or electrocardiographic evidence of myocardial infarction. Eighteen of these 20 patients had diagnostic coronary arteriograms performed for chest pain. Nine of these arteriograms were normal. In the other nine patients coronary arteries showed narrowing greater than 50 percent, but none had clinical or electrocardiographic evidence of myocardial infarction. Two patients who did not have coronary arteriography were in the third decade; in one patient the diagnosis was atrial septal defect, and in the other aortic stenosis and insufficiency.

We studied 28 patients with clinical or electrocardiographic evidence of myocardial infarction. Fifteen of the 28 patients were studied within two weeks following an acute myocardial infarction which was diagnosed by serial changes in the electrocardiogram and serum enzymes. The median time the scan was performed after the onset of chest pain was six days; five patients were studied within 72 hours of the onset of chest pain. One patient, studied three hours after the onset of severe substernal chest pain and before the development of diagnostic electrocardiographic and serum enzyme changes, had ST elevation in leads II, III and aVF on the electrocardiogram. He subsequently developed diagnostic changes. Patients were moved from the coronary care unit to the Radionuclide Laboratory in their own bed by the investigators. Portable monitoring and resuscitative equipment accompanied the patient.

Thirteen patients who were undergoing coronary arteriography were selected because they had clinical and/or electrocardiographic evidence of an old myocardial infarction. In addition, two patients diagnosed as having acute coronary insufficiency or unstable angina were studied. One had Prinzmetal variant angina with a 90 percent obstruction of the circumflex branch of the left coronary artery and was without electrocardiographic evidence of myocardial infarction. The other patient with acute coronary insufficiency had electro-
Cardiographic changes suggestive but not diagnostic of an anterior wall myocardial infarction.

In addition, in two patients $^{125}$I Cs myocardial images were obtained after direct intracoronary injection at the time of coronary angiography. Repeat myocardial images were obtained after intravenous administration of the same total dose of $^{125}$I Cs two months later.

**Results**

**Animal Studies**

The 36 mongrel dogs each had a normal image prior to any intervention. In each view the myocardium of the left ventricle appeared as a smooth walled structure surrounding the interventricular cavity resulting in either a horseshoe or doughnut configuration (fig. 1). The right ventricle was usually seen as a thin wall or structure extending from the superior aspect of the interventricular septum.

Anatomic orientations and landmarks were determined using the sequential imaging with $^{125}$I Cs and technetium markers followed by superimposition of corresponding images (fig. 1). Scintillations from the apex were less intense in the oblique and lateral views giving some difficulty in interpretation.

Ligation of the anterior descending coronary artery at the level of the left atrium resulted in a large defect involving the anterior wall and apex in all 16 dogs (fig. 2, upper panel). At postmortem this defect represented an infarction of the anterior wall and apex which averaged four by five centimeters. In four dogs the anterior descending coronary artery was ligated distal to the left atrium. In two of these dogs this resulted in a defect on the anterior wall (fig. 2, middle panel) which represented a two by three centimeter infarction at

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**Figure 1**

*Myocardial image of a normal dog with orientations. Abbreviations: S = septum, AW = anterior wall, AP = apex, LW = lateral wall; PW = inferior posterior wall, L = liver; RV = right ventricle; IC = interventricular cavity; APW = edge of anterior or posterior wall depending on rotation of the heart.*
postmortem. In the other two dogs the defect was larger, involving both the anterior wall and the apex, and the infarction measured three by four centimeters at postmortem. In the four dogs with ligation of the circumflex artery, there was a large defect of the inferior posterior wall (fig. 2, lower panel) corresponding to a posterior wall myocardial infarction which averaged five by five centimeters at postmortem.

Evolution of an acute myocardial infarction was studied in four dogs by serial imaging. A control image was obtained following administration of $^{124}$Cs and one hour prior to complete ligation of the anterior descending coronary artery. In two of these dogs a small defect appeared at the apex one hour after ligation, which gradually increased in size on the three and 18 hour images and involved the anterior wall and apex (fig. 3). The background was increased on the 18 hour image reflecting an increase of $^{124}$Cs in skeletal muscle and a decrease in the myocardial content; thus, the ratio of overall target organ activity to non-target organ activity was decreased. A repeat image was obtained one week following the ligation and one hour after a second dose of $^{124}$Cs demonstrating a large defect of the anterior wall and apex. At postmortem one week later, the infarction measured four by five centimeters. In the other two dogs the defect

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**Figure 2**

(Upper panel) Myocardial image of a dog with a large myocardial infarction of the septum, anterior wall and apex at postmortem. (Middle panel) Myocardial image of a dog with a small myocardial infarction of the anterior wall at postmortem. (Lower panel) Myocardial image of a dog with a large myocardial infarction of the inferior posterior wall at postmortem.
appeared on the one hour image as decreased scintillations of the anterior wall and apex. Although the defect did not enlarge, there was a gradual and progressive loss of counts in the involved area on the serial images. The infarcts measured about four by five centimeters at postmortem one week later.

**Patient Studies**

Each of the 20 patients without clinical or electrocardiographic evidence of myocardial infarction had images which were regarded as normal (table 1). As was seen in the dog there was a doughnut or horseshoe appearance of the heart with the myocardium of the left ventricle surrounding the interventricular cavity. In three patients the right ventricle was seen as a thin linear structure extending anteriorly from the upper aspect of the interventricular septum.

Each of the 15 patients with clinical and electrocardiographic evidence of acute myocardial infarction had a defect on the image (table 1). A 69-year-old man with an acute anterolateral wall myocardial infarction on the electrocardiogram had a large defect involving the apex, septum and entire anterior wall on the image (fig. 4, upper panel). A 37-year-old man with an acute inferior wall myocardial infarction on the electrocardiogram had a defect of the posterior wall on an image obtained three hours after the onset of chest pain (fig. 5, upper panel). He had an uncomplicated clinical course. A repeat image was performed two weeks following the myocardial infarction and the size of the defect was unchanged.

Of the 13 patients with clinical and electrocardiographic evidence of an old myocardial infarction, ten had a defect on the image (table 1). A 73-year-old man with an old myocardial infarction involving the anterior, lateral and inferior walls on the electrocardiogram had a large defect of the septum, apex, anterior and lateral walls (fig. 4, middle panel). A 49-year-old man with an old inferior wall myocardial infarction on the electrocardiogram and complete obstruction of the right coronary artery on a coronary arteriogram had a defect involving the entire posterior wall on the image (fig. 5, middle panel).

The three patients without defects on the myocardial image had electrocardiographic and angiographic evidence of involvement of the inferior wall, an area somewhat more difficult to visualize by the imaging technique. Two of these three patients had episodes of chest pain lasting one to two hours with T wave inversion in leads II, III and aVF; one had left axis deviation without Q waves and the other had nondiagnostic Q waves; however, both had complete obstruction of the right coronary artery on subsequent coronary arteriograms. The third patient with a normal image had an episode of chest pain lasting two

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**Table 1**

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<th>Number of patients studied</th>
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hours, significant Q waves in leads II, III, and aVF, and a 90 percent obstruction in the right coronary artery on a subsequent coronary arteriogram.

The patient with Prinzmetal variant angina, in whom a 90 percent obstruction of the circumflex branch of the left coronary artery was seen at angiography, had a normal image about one hour after an episode of chest pain associated with ST elevation in leads II, III, and aVF. The patient with unstable angina and an electrocardiogram with poor R wave progression in the precordial leads and T wave inversion in the right precordial leads had an abnormal image with decreased uptake of $^{129}$Cs in the septum.

The images of a normal patient who received both intracoronary and intravenous $^{129}$Cs two months apart are presented (fig. 6) for comparison of the two modes of administration. The intracoronary administration increased the clarity of the myocardial image; in particular the right ventricle was seen clearly. The improvement in clarity of the myocardial image with the intracoronary injection is related to the increased uptake of the $^{129}$Cs by the myocardium which is 22 percent on the first passage following intracoronary administration compared to about 5 percent after intravenous administration.

**Discussion**

Our initial efforts with Cesium-129 were concentrated on the development of good quality myocardial images which would define the normal myocardial image and would permit identification of small myocardial infarctions. After intravenous injection of $^{129}$Cs the myocardium of the left ventricle appeared as a horseshoe or doughnut,
depending on the view taken and the rotation of the heart within the chest. Myocardial infarction resulted in an area of decreased uptake interrupting the normal doughnut or horseshoe appearance of the myocardium of the left ventricle. The right ventricular free wall could be seen as a thin linear structure extending from the superior aspect of the interventricular septum in most dogs. It was seen only occasionally in patients. Intracoronary injection of $^{120}$Cs improved the clarity of the myocardial image; right ventricle and septum were defined easily. This technique could be applied routinely and safely at the time of diagnostic coronary arteriography. However, the real advantage of myocardial scanning with $^{120}$Cs is its noninvasive, intravenous application.

The quality of the myocardial images obtained with $^{120}$Cs and the gamma camera appeared significantly better than published images using rubidium-86,$^5,6$ mercury-203 fluorescein and mercury-203 chloromerodrin,$^{12-14}$ radioiodinated fatty acids,$^15$ gallium-67,$^{16}$ and nitrogen-13 labelled ammonia,$^{8-11}$ and probably better than those using potassium-42 and -43.$^5,7$ Additional disadvantages of nitrogen-13 labelled ammonia are its ten minute half life, which requires that the accelerator be located very close to the hospital, and the possible need for a positron camera for imaging.$^{16}$ The short

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**Figure 5**

(Upper panel) 37-year-old man with an acute inferior myocardial infarction on the electrocardiogram and a defect of part of the posterior wall on the myocardial image. (Middle panel) 49-year-old man with an old inferior myocardial infarction on the electrocardiogram and a defect of the posterior wall on the myocardial image. (Lower panel) Normal myocardial image from a 52-year-old man without clinical or electrocardiographic evidence of myocardial infarction.
Comparison of the intravenous and intracoronary routes of administration of the same total dose of \(^{129}\)Cs for myocardial imaging in a 34-year-old man with a normal electrocardiogram and coronary arteriogram. The upper panel is the intracoronary injection and the lower panel is the intravenous injection. The right ventricle is defined better and the background is less on the intracoronary injection.

The half-life of nitrogen-13 labelled ammonia is, however, advantageous for repeat images in acute myocardial infarction. Potassium-43 is removed more efficiently from the blood by the myocardium in a single passage (71 percent) than is \(^{129}\)Cs (22 percent) after intracoronary injection.\(^{20}\) Thus, \(^{43}\)K imaging can be started five to ten minutes after intravenous administration whereas with \(^{129}\)Cs we have waited about 30 minutes. A possible advantage of \(^{129}\)Cs is that it remains longer in the myocardium after a single dose, thus permitting serial imaging. The lower gamma energies of \(^{129}\)Cs may allow better resolution of gamma camera images since there is less collimator septum penetration than by the higher gamma energies of \(^{43}\)K.

The specificity of imaging defects for myocardial infarction may be questioned. Zaret and co-workers\(^{7}\) have described myocardial defects in patients exercised on a treadmill to angina pectoris at which time \(^{43}\)K was administered. These defects were not present on scans performed at rest, presumably reflecting an area of ischemia. We have also found that experimentally induced hypoxic regions of myocardium in the dog appeared as defects on the image and disappeared when hypoxia was reversed. Presumably these radioisotopes are actively taken up by the myocardial cells and thus are dependent on an intact enzymatic system at the cellular level. Therefore, it was not surprising that ischemia also produced defects on the image. It is not known to what extent ischemia contributes to the defect seen on the images in patients with acute myocardial infarction. One patient (fig. 5, upper panel), however, was studied three hours after the onset of his chest pain and again two weeks following the infarction. There was no difference in the size of the defect on the two images suggesting that the initial defect represented infarction and not ischemia. Also, it is
reasonable to assume that diseases that infiltrate the myocardium such as sarcoid, amyloidosis or tumor could produce defects on myocardial images. The precise sensitivity and specificity of this method will require postmortem correlative studies, particularly in patients with equivocal clinical and laboratory findings.

One potentially important area for Cesium-129 myocardial imaging is the quantification of infarcted myocardium in patients with acute myocardial infarction. Page and associates reported a correlation between the percentage of infarcted myocardium and the development of cardiogenic shock; patients who died with cardiogenic shock had 40 percent or more of their myocardium infarcted. With \(^{129}\)Cs there should be no difficulty in identifying these large infarctions. Cesium-129 has the potential of being a noninvasive technique that could quantify and locate infarcted myocardium in an effort to predict those patients most likely to develop cardiogenic shock, so that medical and surgical interventions could be instituted early before the condition became irreversible.

Two other potentially useful areas for \(^{129}\)Cs are the screening of high risk populations for the prevalence of silent myocardial infarctions and in large clinical trials evaluating drug or diet efficacy in decreasing the incidence of myocardial infarction. In addition, \(^{129}\)Cs may be of value in detecting myocardial infarction when the electrocardiographic diagnosis is obscured by bundle branch block. Use of \(^{129}\)Cs images in these settings will depend on further evaluation of factors such as sensitivity for detecting small defects confirmed at postmortem, and the availability and cost of \(^{129}\)Cs.

We are currently producing 25 to 35 mCi of \(^{129}\)Cs per 10 to 12 hour bombardment. If myocardial imaging with \(^{129}\)Cs is to be available for routine clinical application, inexpensive, high yield production methods will be needed. Initial feasibility studies of cesium production by the spallation method have been reported by Scholz and associates. Yields of \(^{129}\)Cs by the spallation method are approximately one curie per hour. At the same time large quantities of Cesium-127 are produced. This isotope has the same imaging characteristics as Cesium-129 but only a six hour half life. The spallation production of \(^{127}\)Cs and \(^{129}\)Cs at high energy proton facilities would result in sufficient cesium after separation and transportation for widespread clinical use.

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