SAFETY OF THE DIRECT CORONARY INJECTION
OF RADIOLabeled PARTICLES

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Myocardial perfusion scintigraphy with labeled particles injected directly into the coronary arteries has been performed in relatively small numbers of humans, and thus the safety of this procedure has not been established. We have studied 800 patients with this technique. Macroaggregates of albumin (MAA) labeled with $^{131}$I and $^{99m}$Tc were injected into the right and left coronary arteries, respectively, at the time of coronary angiography. Microspheres of albumin (HAM) labeled with $^{99m}$Tc were substituted for macroaggregates in the last 400 patients and injected into the left coronary artery. The radiopharmaceutical was carefully prepared with strict limitation of the number and size of particles and total amount of carrier protein. The electrocardiogram and aortic blood pressure were monitored following the injection of labeled particles. No significant electrocardiographic or aortic pressure changes occurred secondary to the radioactive microemboli. There was no mortality and no demonstrable morbidity. It is concluded that the intracoronary injection of labeled particles is safe in humans when performed under carefully controlled conditions.

The development of coronary angiography has provided access to the coronary arterial system for the injection of substances other than contrast material. Diffusible and nondiffusible tracers have been injected directly into the coronary arteries without detrimental effects (1,2). However, the injection of labeled particles directly into the coronary arteries has potential, serious hazards. Quinn, et al (3) first described the coronary injection of radioactive macroaggregates in dogs. He warned of the potential hazards of this procedure in humans. Schelbert, et al (4) performed toxicity studies in dogs and concluded that there was a wide margin of safety when the number and size of the particles injected were carefully controlled. Endo, et al (5) first reported the use of labeled macroaggregates (MAA) in humans in the evaluation of myocardial ischemia. Ashburn, et al (6) also reported their preliminary studies with radioactive particles injected directly into the coronary arteries of patients with coronary artery disease. We have recently reported our experience in myocardial color scintigraphy (7,8) with MAA in 400 patients and have now extended this study to a total of 800 cases.

RADIOPHARMACEUTICAL PREPARATION

Macroaggregates are labeled with $^{99m}$Tc by a modification of the method of Cragin (9,10). After labeling and preparing the macroaggregates, particle size is reduced by forceful passage through a 22-gage needle. Stringy and oversized particles are removed by passage through a special filter (thin film of glass wool over a stainless steel disk with 75-micron holes) into a sterile, rubber-stopped test tube. The filtrate is centrifuged for 12 sec in an international clinical centrifuge Model CL. The supernatant is discarded, and the particles are resuspended in 0.9% NaCl. By this technique 20–30% of the original activity is recovered in the form of usable particles of 10–80 microns with an average of 35 microns. The dose range for the left coronary injection is 1.0–1.5 mCi of $^{99m}$Tc-MAA consisting of 300,000–800,000 particles and 0.1–0.3 mg of albumin.

In the last 400 cases microspheres (HAM) have been labeled with $^{99m}$Tc using a 3M commercial kit. The particle size ranges from 10 to 40 microns with

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an average of 30 microns. The number of particles per dose ranges from 10,000 to 30,000 with 0.1–0.3 mg of albumin.

A commercial preparation of $^{131}$I-MAA is used for the right coronary injection. It may be used as received, but often there is an excess of small particles that must be removed by the centrifuge technique. We have found that the remaining large particles are most stable when resuspended in the original fluid; thus the supernatant is filtered through a 0.45-micron Millipore filter and reconstituted with the macroaggregates. By this technique the dose of $^{131}$I is maintained at approximately 100 $\mu$Ci without exceeding 800,000 particles and 0.5 mg albumin.

**METHOD**

The macroaggregates are injected into the coronary arteries following the completion of the contrast study of each coronary artery. The particles are first injected into a 10-cc syringe containing 8 cc of normal saline; after gentle agitation to insure adequate suspension, manual injection is made through the coronary catheter at the rate of 3 cc/sec. Continuous electrocardiographic and coronary pressure monitoring is maintained throughout the procedure and following removal of the catheter. The patient is then transferred to the nuclear medicine section for myocardial imaging.

The absorbed radiation dose to the heart with particles labeled with $^{99m}$Tc and $^{131}$I is based on an estimated absorbed fraction of 0.1 and heart volume according to MIRD (11). The dose to the heart with MAA labeled with $^{99m}$Tc based on an effective half-life of 2.7 hr is approximately 420 mrad/m Ci. The dose of $^{131}$I-MAA based on an effective half-life of 4.9 hr is approximately 580 mrad/100 $\mu$Ci. The dose of $^{99m}$Tc microspheres based on an effective half-life of 3.6 hr is approximately 570 mrad/m Ci.

**RESULTS**

From April 1970 through October 1972 800 patients undergoing coronary angiography at this institution have been studied with direct coronary injection of labeled particles without apparent sequelae. Initially only macroaggregates of albumin were used for labeling with $^{99m}$Tc and $^{131}$I. However, in the last 400 cases both macroaggregates and microspheres were used. Ideally microspheres would be used for both radionuclides. Because of the difficulty in tagging iodine to microspheres, macroaggregates have continued as the carrier for $^{131}$I. Hence, technetium-labeled microspheres were injected into the left coronary artery and iodine-labeled macroaggregates were injected into the right coronary artery.

The monitoring records of the first 226 cases were

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<th>TABLE 1. ELECTROCARDIOGRAPHIC CHANGES ASSOCIATED WITH CORONARY INJECTION OF TAGGED PARTICLES</th>
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<td>Finding</td>
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<tr>
<td>Normal</td>
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<td>P, QRS, or ST-T abnormalities</td>
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<td>without rhythm disturbances*</td>
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<td>Sinus tachycardia</td>
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<td>EVC†</td>
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<td>PAC†</td>
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<td>Nodal rhythm</td>
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<td>Atrial fibrillation</td>
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<td>Sinus brachycardia</td>
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<td>Misc. rhythm disturbances</td>
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* 21 patients had similar abnormalities with superimposed rhythm disturbances (9% of total) and are listed under the latter.
† EVC = ectopic ventricular contraction.
‡ PAC = premature atrial contraction.
** Coronary injection of contrast in normal patients uniformly produced transient ST-T wave changes and slowing of the heart rate.
studied (Table 1). The pre-examination electrocardiogram (ECG) was normal in 60% of cases. The baseline ECG was abnormal in 20% because of ST-T-wave, QRS, or P-wave abnormalities without associated rhythm disturbances. Nine percent of the total had similar abnormalities associated with minor rhythm disturbances. The remaining 11% had minor rhythm disturbances alone. These patients (20%) with baseline rhythm disturbances were largely represented by sinus tachycardia 8%, ectopic ventricular contractions (EVC) 6%, and premature atrial contractions (PAC) 3%. The sinus tachycardia was considered related to the routine premedication with atropine.

The coronary injection of radiographic contrast in normal patients was uniformly associated with transient ST-T-wave changes and transient slowing of the heart rate. Inasmuch as standard lead II was commonly used for monitoring, the most striking ST-T-wave abnormalities were seen with the right coronary injection (Fig. 1). Following the injection of radiographic contrast into the left coronary artery, reciprocal ST-T-wave changes in lead II were invariably observed. In patients with heart disease and baseline ST-T-wave abnormalities, the coronary injection of contrast resulted in similar changes although frequently not as marked (Fig. 2). During ventriculography catheter-induced EVCs including short runs of coupled beats were common. However, following injection of contrast into the coronary arteries the incidence of PACs was 2.0% and that of EVCs was also 2.0%, both being somewhat less than the prestudy incidence. No other rhythm disturbances were observed following contrast injection in this group of patients.

Electrocardiographic abnormalities could not be attributed to the coronary injection of MAA. There were minimal or no ST-T-wave changes in 55%. In 35% of cases the ST-T-wave changes following contrast injection remained unchanged after coronary injection of MAA. In 5.5% of cases the contrast-induced abnormalities were in the process of returning to baseline during the period following the injection of tagged particles into the coronary arteries. The incidence of PACs (2%) and EVCs (2%) was similar to that following contrast injection.

One patient developed transient ventricular tachycardia (VT) shortly after the coronary injection of MAA into the right coronary artery. However, he had had no similar rhythm disturbance following injection of tagged particles into the left coronary but he did have short runs of VT during the contrast study.

Although transient decreases in the blood pressure recordings were observed following coronary injection of contrast, no apparent decrease in pressure was noted in any patient in this group following the injection of tagged particles into the coronary arteries.

**DISCUSSION**

The theoretical objection to producing microemboli in a vital organ such as the heart cannot be lightly dismissed. This is particularly true when the clearance of the particulate matter requires several hours, the biologic half-life of MAA and HAM being approximately 5 hr and 9 hr, respectively.

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**FIG. 1.** Electrocardiographic (lead II) and blood pressure tracings in normal patient. (A) Recordings following contrast injection into left coronary artery. Note reciprocal T-wave change. (B) Recordings following HAM injection into left coronary artery. (C) Recordings following contrast injection into right coronary artery. Note T-wave inversion. (D) Recording following MAA injection into right coronary artery.
Schelbert, et al (4) injected MAA directly into the left coronary circulation of dogs in doses of 0.02 mg/kg body weight (a tenfold excess for satisfactory imaging) without evidence of significant left ventricular dysfunction. The similar administration of MAA 0.002 mg/kg body weight (dose suitable for satisfactory imaging) resulted in no measurable alteration in heart rate, epicardial electrocardiogram, or left ventricular end-diastolic pressure. Microscopic examination of the myocardium showed no inflammatory reaction within the vessel walls or adjacent myocardium in the location of the particles.

Weller, et al (12) injected HAM directly into the left coronary circulation of dogs without measurable changes in heart rate, blood pressure, or ventricular end-diastolic pressure until a level of 10 mg was reached (200 times the diagnostic dose). Microscopic examination of the myocardium 1 week post-injection in dogs that received 0.5–2.0 mg (10–40-fold excess) showed no abnormalities that could be attributed to the microspheres.

Poe (13) studied the effects of intracoronary injection of MAA in dogs. He monitored not only the ECG, heart rate, and arterial pressure, but also the myocardial contractile force and coronary blood flow. He found that slow injection of MAA (60–70 microns) containing less than 0.05 mg albumin (approximately 500,000 particles) could be administered without significant changes in coronary blood flow or myocardial contractile force. However, as the mass of albumin or particle size was progressively increased, coronary flow and contractile force were reduced. Only after marked flow and contractile changes had occurred did abnormalities in pressure and ECG develop.

The myocardium has been noted to contain an estimated 3,300 capillaries/mm² (14). Assuming a left coronary cardiac mass of 200 gm and uniform distribution of particles, the density of MAA with a 600,000 particle dose would be approximately 3,000 particles/gm whereas that of a 20,000 particle dose of HAM would be 100 particles/gm. Therefore the ratio of obstructed capillaries to total capillary bed is extremely low even in myocardium severely compromised by coronary artery disease. This was illustrated by one patient who had marked coronary disease and was studied with the standard procedure. He had striking occlusive disease of all three major coronary arterial systems and experienced severe angina at rest. On myocardial scintigraphy his residual capillary bed was quite minimal compared with the normal. Nonetheless he developed no aggravation of angina or additional symptomatology following the injection of labeled particles. Furthermore, he developed no associated electrocardiographic abnormalities or decrease in aortic blood pressure.

No ECG changes could be related to the coronary injection of labeled particles. Although minimal transient T-wave changes were observed in a few patients, the catheter was not always flushed of contrast before injection of the particles. Premature atrial and ventricular contractions which were present following contrast injection persisted through the period following particle injection. This relationship was also present in the patient who developed transient ventricular tachycardia following the second
injection of particles inasmuch as a similar arrhythmia occurred during the contrast study.

One patient not included in the first 226 cases had severe coronary artery disease and developed ventricular fibrillation (VF) within 1 min after the injection of HAM into the left coronary artery. He was electrically defibrillated, and the study of the right coronary artery was subsequently completed with contrast and MAA without recurrence of VF. This was the only patient who developed VF after the injection of labeled particles (0.12%). Of 1,077 previous cases undergoing coronary angiography, including 291 cases before myocardial scintigraphy, eight patients (0.74%) developed VF during or shortly after the contrast study. None of these patients received labeled particles following this rhythm disturbance. It is therefore considered improbable that the episode of VF was precipitated by the injection of the microspheres.

In the total group of 800 cases there has been no mortality and no demonstrable morbidity. However, it must be stressed that careful quality control of the radiopharmaceutical was constantly maintained with strict limitation of the size and number of particles and the total amount of carrier protein.

ACKNOWLEDGMENT

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REFERENCES


