Visual Assessment of Regional Myocardial Perfusion Utilizing Radioactive Xenon and Scintillation Photography

By P. J. Cannon, M.D., J. I. Haft, M.D., and P. M. Johnson, M.D.

SUMMARY

A method was devised to visualize the areas of left ventricle supplied by various coronary arterial branches utilizing scintillation photography and an inert radioactive gas which distributes instantaneously between coronary blood and perfused myocardial cells. From 1 to 5 millicuries of $^{133}$Xe dissolved in saline solution was injected through a catheter into the anterior descending or posterior circumflex branch of the left coronary artery of 15 dogs. Scintillation images produced during arrival and washout of $^{133}$Xe in the various regions of the heart were recorded by an image intensifier scintillation camera and high speed television monitor and were reproduced on Polaroid film during replay of the videotape on an oscilloscope. The resulting scintiphotographs defined the region of the left ventricle supplied by the coronary arterial branch. In nine of the dogs acute myocardial infarctions were produced by occluding one or the other branch of the left coronary artery. When $^{133}$Xe was injected again into the coronary artery proximal to the occlusion, that area of the left ventricle that was deprived of nutrient blood flow was no longer visualized on the gamma-ray scintiphotograph. The results indicate that regional myocardial perfusion may be dynamically visualized in the intact animal.

Additional Indexing Words:
Coronary blood flow  Myocardial infarction  Inert gas
Radioisotope  Animal study

INVESTIGATION of the effectiveness of blood flow to various regions of the myocardium has acquired greater therapeutic significance since the demonstration that revascularization procedures may be of symptomatic value in the treatment of patients with coronary artery disease.1-4

Currently available technics to assess the regional myocardial circulation have intrinsic limitations, however. Coronary cineangiography affords precise visualization of major branches of the coronary arteries but does not provide information concerning the adequacy of perfusion of myocardial cells.5, 6 The limitations of angiography as a sole method of evaluating patients with coronary atherosclerosis have recently been emphasized in reports: (1) of patients without angina pectoris in whom significant narrowing or occlusion of coronary arteries was documented radiographically,5, 6 and (2) of patients with typical angina pectoris, electrocardiographic signs suggestive of ischemia, and evidence for increased myocardial lactate production in whom angiographically normal coronary arteries were found.7-10

Technics now employed clinically to measure the rate of myocardial blood flow in patients with coronary artery disease are also
of limited value because they provide a measurement of blood flow per unit volume or weight of a large mass of heart muscle and thus do not indicate regional variations of myocardial perfusion. It is probable that deficient perfusion of small areas of ventricular muscle in patients with angina pectoris\textsuperscript{11, 12} may remain undetected by these measurements.\textsuperscript{13–22}

The present experiments were undertaken with a twofold purpose: (1) to develop a technic by which the regions of left ventricle supplied by various branches of the left coronary artery of the dog could be dynamically visualized and (2) to ascertain whether, utilizing this technic, areas of myocardium where perfusion is inadequate could be localized in the intact animal. In the experiments, advantage was taken of the unique properties of radioactive xenon and of the recent development of the gamma-ray scintillation camera.

**Theoretical Considerations**

**Properties of \(^{133}\text{Xenon}\)**

\(^{133}\text{Xe}\) is a radioactive isotope of a gaseous element which is chemically inert and physiologically inactive.\textsuperscript{23, 24} Because of its small molecular size and lipid solubility, xenon is highly diffusible. After injection into an artery, its passage across capillary walls into the tissue supplied by the artery is rapid and is not limited by diffusion through pores.\textsuperscript{25, 26} The myocardium to blood partition coefficient (\(\gamma\)) is 0.72.\textsuperscript{27, 28} Due to its great diffusibility xenon also readily passes through pulmonary capillaries into alveoli and is largely eliminated into respired air in one passage through the lungs,\textsuperscript{29, 30} a feature which minimized recirculation after arterial injection into a regional vascular bed.\textsuperscript{26}

The isotope, \(^{133}\text{Xe}\), is produced in a nuclear reactor by fission of \(^{235}\text{Uranium}\). It decays to stable \(^{133}\text{Cesium}\) by emission of beta particles of a maximum energy of 347 kiloelectron volts (kev) followed by emission of gamma rays of 81 kev and characteristic x-rays of 31 kev; the physical half-life of \(^{133}\text{Xe}\) is 5.3 days. The beta emission of \(^{133}\text{Xe}\) is absorbed in 1-mm tissue and is unsuitable for external detection. The gamma radiation energy is detectable by external monitoring and is readily collimated owing to its relatively low energy; the short biologic half-life of the isotope also reduces radiation exposure.\textsuperscript{31} Because of the absence of significant recirculation, \(^{133}\text{Xe}\), as well as \(^{85}\text{Kr}\), has been widely utilized to measure nutrient blood flow in a variety of tissues by the Schmidt-Kety application of the Fick principle.\textsuperscript{32–38} The validity of blood flow measurements calculated from the externally monitored washout of these isotopes has been documented in heart muscle by several investigators.\textsuperscript{19–21}

**Scintillation Camera**

The principles of the Ter-Pogossian scintillation camera\textsuperscript{39, 40} used in the present studies are schematically illustrated in figure 1.\textsuperscript{*} The source of radioactivity (\(^{133}\text{Xe}\) deposited in dog myocardium by injection into the left coronary artery) emits gamma rays which pass through parallel holes in a 2-inch thick, fine collimator (2,611 channels, each 1/8 inch wide with septal thickness of 0.003 inch) and interact with a 9-inch diameter cesium iodide scintillation crystal where incident photons are converted


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to light flashes in proportion to their energy and abundance. The light flashes produced by the scintillator are detected by the light-sensitive photocathode of an image intensifier tube applied to the crystal which amplifies and focuses them to produce a small brighter image on an output phosphor screen. This screen is optically coupled to an Orthicon system which scans the image for additional amplification and display on a television monitor and videotape. Scintillation images produced in this fashion during arrival and washout of $^{133}$Xe in myocardium are thus dynamically recorded on videotape. During replay of the videotape on an oscilloscope, changes in isotope position and movement may be viewed and photographed on cine-film, or single or integrated photographs can be taken with a Polaroid camera at specific times after injection of the isotope. Since the position and energy of gamma-photon interactions in the large crystal determine the position and brightness of light flashes on the output phosphor of the image intensifier tube, the resulting scintiphotographs reflect the intensity and distribution of radioactivity in the tissue under study.

In preliminary studies the image intensifier scintillation camera employed in the present experiments was shown to be highly efficient for gamma-emitting isotopes with low energies, 35 to 150 keV$^4$; the detection efficiency of the instrument was poorer above 280 keV. Within the optimal energy range, higher energy events are more easily detected by the camera because they produce a brighter scintillation which is more easily distinguished from background. This particular system does not permit pulse height analysis, a disadvantageous feature at higher energies, but one which is less important at energies of 35 to 140 keV, where differences between the primary and scattered photons are often relatively small. Because the intrinsic tube resolution is about 2 mm, the effective resolving power of the system* is determined by the collimator.

By utilizing the fine collimator and phantom sources, the effective resolution was found to be slightly less than 1 cm over the energy range 35 to 280 keV.$^4$ The effective resolution did not decrease significantly when the collimator was separated from a $^{133}$Xe source by 1 to 4 cm of air or a tissue equivalent. Because collimation reduces efficiency, approximately a fourfold increase in source activity was required to produce an image with the fine collimator which was as bright as that obtained from the same source with a 700-hole, coarse collimator. Phantom studies also indicated good spatial linearity and minimal distortion of concentricity, or variation in field uniformity with the camera. The effective speed of the system was 30 videotape frames per second.$^4$

**Methods**

**Experimental Technic**

Myocardial perfusion patterns were studied in 15 mongrel dogs weighing 16 to 25 kg. Each dog was anesthetized with pentobarbital (30 mg/kg) and placed on his right side with the left anterior part of the chest directly beneath the multiholed collimator of the scintillation camera. Under fluoroscopic control a J-tipped, no. 7 cardiac catheter was passed down the right carotid artery and positioned in the anterior descending or in the posterior circumflex branch of the left coronary artery (fig. 2). A fine (0.1-mm outside diameter) radiopaque Teflon catheter was then rapidly threaded through the cardiac catheter into the branch of the coronary artery (fig. 2) and the no. 7 catheter was withdrawn into the aorta. Positioning of the fine catheter was done fluoroscopically, and coronary angiograms were made to verify the vascular anatomy. Femoral arterial blood pressure was recorded with a Sanborn 236 pressure transducer, and electrocardiograms were monitored with a Model 100 Sanborn ECG machine.

Four millicuries of $^{133}$Xe dissolved in 1 to 3 ml of sterile pyrogen-free saline solution was injected rapidly (2 to 6 sec) into the coronary artery, and the arrival and washout of isotope in the heart were viewed with the scintillation camera. The center of the fine collimator in each study was positioned 1 cm above the point of maximal impulse of the cardiac beat. Radioactive markers were attached to the dog to verify that

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*Effective resolution is defined as the minimum distance at which two line-sources of identical radioactivity can be distinguished clearly when separated by a gap containing no radioactivity.

+Obtained as "Xenisol-133" from Neisler Laboratories, Tuxedo Park, New York.
Illustration of the anatomy of the canine heart and of the experimental techniques employed to catheterize the coronary arteries and to produce experimental myocardial infarctions. For details see text.

there was no change in the relative positions of animal and collimator in sequential studies. Orthicon voltage and "beam" settings were optimized for each dog, the former usually ranged from 80 to 105, the latter from 145 to 155. The arrival and washout of $^{133}$Xe in dog myocardium was recorded on videotape at 30 frames/second. When the tape was replayed on the oscilloscope, Polaroid pictures integrated for 1-sec intervals were obtained at specific intervals after the isotope injection which had been recorded on the sound track of the videotape in each study. In 13 animals the washout of $^{133}$Xe from the myocardium was also monitored with a 2-inch NaI scintillation crystal coupled to a dual-rate computer and digital printout,* and myocardial nutrient blood flow was calculated according to the method described by Herd's$^{18}$ and Ross's$^{20}$ groups.

Experimental Myocardial Infarctions

In nine dogs acute myocardial infarctions were produced by a closed chest technic.$^{42}$ The fine Teflon catheter positioned in a branch of the left coronary artery in control studies was withdrawn and was replaced by another fine catheter with a Teflon plug on the tip (fig. 2). This plug was wedged into the anterior descending or posterior circumflex branch with the large J-shaped cardiac catheter and occluded the artery; following this the large positioning catheter was removed. Electrocardiographic changes of early myocardial infarctions were recorded in the nine dogs after positioning of the plug. Preliminary experiments had demonstrated that when ECG changes of infarction were not observed after positioning the plug, the coronary artery was not occluded, and neither the $^{133}$Xe perfusion patterns nor the $^{133}$Xe washout rates were altered significantly from control values. After myocardial infarctions had been demonstrated by ECG in the nine dogs, repeat studies of myocardial perfusion were performed by injecting $^{133}$Xe in saline proximal to the site of occlusion through a side-hole in the fine catheter (fig. 2).

Results

$^{133}$Xe dissolved in saline solution was injected into a branch of the left coronary artery of the 15 dogs; in each study the arrival and washout of isotope were recorded continuously on videotape which was subsequently replayed on an oscilloscope and photographed. Sequential scintiphotographs of 1-sec duration taken at various times after the injection into the posterior circumflex branch of dog J are depicted in figure 3. The maximal intensity of radioactivity was present in sec 4 after injection, and the washout of isotope from the left ventricle was sufficiently rapid that isotope was not visually detected after 45 sec. Myocardial nutrient blood flow during this study, calculated from the $^{133}$Xe washout curve, was 77 ml/100 g/min.

In figure 4 the scintiphotographs obtained during the 1 sec of peak radioactivity after injection of $^{133}$Xe into the anterior descending and posterior circumflex branches of dog N are depicted. Accompanying each photograph is a schematic representation of the cardiac silhouette, with the distribution of radioactivity in the myocardium indicated by diagonal lines. The different shapes and sizes of the areas of distribution of radioactivity in the left ventricular myocardium in the two studies are apparent. Similar radioisotope distribution patterns were observed in the other 14 dogs; characteristic and distinct perfusion patterns were visible after injection of isotope into either branch of the left coronary artery.

In nine dogs acute myocardial infarctions
were produced by plug occlusion of one of the coronary arterial branches after control studies had been completed. Injection of $^{133}$Xe in saline into the artery proximal to the occlusion was then repeated. The upper portion of figure 5 demonstrates the area of perfusion which was detected by the scintillation camera after injection of 4 millicuries of $^{133}$Xe into the left anterior descending coronary artery of dog P. Beneath the control study is the scintiphotograph obtained 20 min after experimental infarction had been produced.

The scintillation image was considerably smaller and altered in shape after the experimental infarction. The gray area on the accompanying schema indicates the region of left ventricular myocardium perfused in the control study no longer receiving adequate nutrient blood flow. Three days later this dog was sacrificed. The heart was photographed at postmortem examination (fig. 6); the area of infarction corresponds in size and shape to the area of deficient perfusion indicated by scintiphotographs in figure 5. The autopsy picture in figure 6 also shows the position of the occluding plug in the coronary artery. Scintiphotographs obtained in control studies and after occlusion of the...
left anterior descending branch of dog T are presented in figure 7.

In five dogs posterior myocardial infarctions were produced by plug occlusion of the posterior circumflex artery. Figure 8 demonstrates the characteristic electrocardiographic changes induced by this procedure. Figure 9 shows the typical control isotope perfusion pattern observed after the injection of $^{133}$Xe into the posterior circumflex artery and also depicts the loss of the distal perfusion area which occurred after plug occlusion of the artery. The gray stippled area on the schematic view represents that portion of myocardium no longer receiving adequate nutrient blood supply after the infarction.

Discussion

Because of its high diffusibility, short biologic half-life and low gamma energy, $^{133}$Xe was the isotope employed in the present studies of myocardial perfusion. Herd and associates$^{18}$ and Ross and co-workers$^{20}$ first used radioactive inert gases to study myocardial nutrient blood flow; these workers demonstrated that blood flow per gram of heart calculated from the unexponential washout curve of $^{133}$Xe or $^{85}$Kr when multiplied by cardiac weight equaled the total coronary flow measured by a flow meter.

The measure of blood flow per unit volume of heart muscle provided by these methods has not been of significant diagnostic value in the evaluation of patients with angina pectoris, possibly for two reasons: (1) It is likely that both heart muscle mass and blood flow can decline simultaneously in coronary heart disease,$^{42}$ a change which would be undetected by these methods. (2) The measure-
MYOCARDIAL PERFUSION BY SCINTIPHOTOGRAPHY

Figure 7
Control and experimental scintiphotographs of the heart of dog T in which an anterior myocardial infarction was produced.

Figure 8
Electrocardiographic changes in the standard leads in dog O 10 min after experimental occlusion of the posterior circumflex artery appears in the bottom of the figure. The characteristic pattern of an acute posterior infarction is visible.

Figure 9
Perfusion patterns produced by $^{133}$Xe in the myocardium of dog U before and after experimental posterior myocardial infarction.
ment obtained after injection of either isotope into the coronary arteries gives no information concerning myocardial perfusion in various areas of the ventricle perfused by the coronary artery studied. Two recent reports have suggested that significant differences in regional myocardial blood flow may exist in patients with coronary heart disease. Sullivan and associates\textsuperscript{12} found that the rate of washout of \textsuperscript{85}Kr (injected locally into the ventricular mass at time of thoracotomy) varied significantly in different areas of the hearts of such patients, and Klocke and associates\textsuperscript{22} showed that heterogeneous myocardial blood flow in animals or patients with varying degrees of coronary occlusion caused the slope of the cardiac washout curve of an inert gas to deviate significantly from a single exponential.

In the present experiments, \textsuperscript{133}Xe dissolved in saline solution was deposited in myocardial tissue through a fine catheter positioned in the left anterior descending or posterior circumflex coronary arteries, and the heart was photographed with a gamma scintillation camera to define the regions of left ventricle supplied by the various branches of the left coronary artery. Because of its high diffusibility, \textsuperscript{133}Xe, when injected into the branch of the coronary artery, did not remain within the blood vessel but rapidly diffused into the tissue supplied by that arterial segment. Since the radioactivity images recorded by the camera were generated by the presence of isotope within myocardial cells, the resulting scintiphotographs corresponded to the tissue bed which derives its nutrient blood supply from the vessel injected. Control \textsuperscript{133}Xe scintiphotographs thus delineated regions of left ventricle receiving adequate capillary perfusion and were therefore different from the coronary cineangiograms which defined the anatomy of large and medium-sized coronary blood vessels. The distinctive appearance and the absence of significant overlap of perfusion patterns suggest that few intercoronary anastomoses exist in the normal canine heart.

Use of a fine radiopaque indwelling catheter for injection of isotope was not necessary for successful visualization of myocardial perfusion by the present technic. Such a catheter was employed merely to facilitate serial measurements of coronary perfusion in the dog, a species in which it is technically difficult to maintain an arteriographic catheter in the main left coronary artery. Preliminary studies had demonstrated that placement of the coronary catheter did not alter myocardial blood flow. Other preliminary studies indicated that, if \textsuperscript{133}Xe was injected inadvertently into the left ventricle or aorta, the isotope was washed downstream rapidly in 2 to 10 sec; in the latter situations a radioisotope image of the cardiac chamber or aorta, or both, was visualized on the television monitor.

The fact that the maximal size of the image of \textsuperscript{133}Xe distribution in the normal myocardium coincided with the peak counts per second monitored externally provides evidence for an assumption concerning the inert gas technic for measuring coronary blood flow,\textsuperscript{20} namely, that blood-myocardial tissue equilibration of xenon is almost instantaneous. \textsuperscript{133}Xe was not visualized clearly on 1-sec scintiphotographs taken 45 to 90 sec after peak tissue activity in dogs with a normal washout of isotope from heart muscle (nutrient flow, 70 to 120 ml/100g/min). The chance observation in one dog who spontaneously developed ventricular fibrillation shortly after the isotope was injected, that scintiphotographs of \textsuperscript{133}Xe in myocardium persisted unchanged for over 3 min, supports another assumption concerning these methods, namely, that the inert gas leaves heart tissue almost entirely by way of the venous drainage.

The closed-chest technic utilized for producing acute myocardial infarctions in the animals\textsuperscript{43} was reproducible, and infarction was demonstrated at postmortem examination in all dogs who developed characteristic electrocardiographic changes. Scintiphotographs of \textsuperscript{133}Xe in myocardium after experimental infarctions showed that the radioisotope images were smaller and altered in shape in all studies, and the portion of the control isotope image no longer visible after the infarcts corresponded to the shape of the myocardial
infarction at autopsy when the heart was viewed from the left side of the animal. Thus, the technic was capable of demonstrating areas of myocardium which were no longer receiving nutrient blood flow in the intact animal.

Several other isotope technics for localizing myocardial infarctions have been developed in the past decade. Injections of macroaggregates of human serum albumin labeled with 131I have been employed to visualize the coronary vascular bed in dogs; however, the potential hazards of this procedure for patients with coronary insufficiency have precluded extensive use of this substance in man. Infarcted tissue takes up increased amounts of radioactive chlormerodrin and a derivative of mercurochrome labeled with 203Hg; hence external scans after injection of these isotopes have been reported to indicate areas of infarcted myocardium. The present technic is not dependent upon the presence of actual tissue necrosis since the distribution of 133Xe is a function of nutrient blood supply. Thus, it is likely that not only areas of tissue death, but also relatively avascular regions of myocardium which are not necrotic (for example, areas of fibrosis or ventricular aneurysms) can be detected with the new method.

Normal myocardial tissue is known to extract 86rubidium, 133cesium, and oleic acid labeled with 131I from coronary artery blood. Precordial scans obtained after injection of any one of these substances have indicated diminished uptake of tracer in areas of myocardial infarction. The present technic appears to afford several advantages over these methods, however: (1) The speed of the scintillation camera (30 frames/sec) far exceeds that of currently available rectilinear scanning equipment; hence dynamic studies of isotope arrival and washout can be obtained. (2) The resolving power of the detection system is slightly greater than that of such scanning procedures. (3) The shorter biologic half-life of 133Xe and the low energy of its gamma emission will reduce the possibility of radiation hazard to the patient if this technic, or a variation thereof, is used in man.

Two disadvantageous aspects of the technic employed in the present studies are related to the less-than-optimal effective resolution of the isotope imaging system and to the absence of quantitative regional blood flow data. Ideally one would desire the imaging system to have an effective resolution less than 0.5 cm. Although the resolving power of the system used in these experiments was sufficiently great to detect in vivo the myocardial infarctions produced in the dog hearts, nevertheless phantom studies indicated that the effective resolution with 133Xe was only slightly less than 1 cm. It is possible, however, that with improved collimators, this scintillation camera may be able to detect even smaller avascular areas in myocardium because its intrinsic tube resolution is 2 mm.

Quantitation of gamma intensity during 133Xe washout from different regions of the myocardium was not possible with the particular equipment employed in the present experiments, even though the design of the Ter-Pogossian image intensifier tube is such that the intensity of the photoemission recorded by the system is proportional to the amount of radioactivity in the tissue under study. If, in the future, quantitation of isotope activity in different areas of the scintillation detector becomes technically feasible, it is anticipated that it will then be possible to obtain quantitative measurements of the rate of myocardial blood flow in regions of the myocardium where vascular disease has reduced but not abolished blood flow. Currently, experiments are under way in this laboratory to develop methods for quantitative...
estimation of regional myocardial blood flow employing $^{133}$Xe, scintillation photography, and a variation of the procedures employed in the present preliminary studies.

Potential clinical applications of the approach to assessment of regional myocardial perfusion with radioactive inert gases and scintillation photography are several. They include the visualization and definition of functionally avascular regions of the myocardium, the assessment of adequacy of collateral circulation beyond coronary artery occlusions, study of diseases which affect the coronary microcirculation, and the critical evaluation of surgical procedures now employed to revascularize the myocardium. It is anticipated that such assessments would supplement but not replace the definition of coronary vascular anatomy obtained by cineangiography.

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Chains of Tradition in Scientific Journals

. . . The great defect of the scholastic philosophers in Bacon's view was that they placed too much emphasis on existing texts, neglecting their own powers of observation. The characteristic work of the pre-scientific period was the compilation and the commentary. In the era before printing this may have grown to some extent out of the fact that a manuscript is unique and that in the act of copying and transmitting a manuscript a scholar might not be able to resist yielding to the temptation of annotating and commenting on the omissions and deficiencies of the basic text. The scarcity of copies would lead to scholars compiling collections of notes from the sources they consulted much in the same way a scholar might today accumulate collections of notes. The availability of the original sources today would make the publication of such collections of little value, while in a period of scarcity they might have had an important function to perform. The change from manuscript to printing introduced new problems in the transmission of information but there was a considerable carry over from the manuscript, just as the printed character was an attempt to reproduce the hand drawn character. The practice of lengthy citation from original sources that persists in scholarship even today may perhaps be regarded as another example of the persistence of tradition. . . .

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