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The Imaging of Myocardial Perfusion with ^{81m}Kr during Coronary Arteriography

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Abstract. The use of ^{81m}Kr was investigated for imaging myocardial perfusion during coronary arteriography using conventional catheters. When the significance of stenosis judged by arteriography is unclear, the effect on tissue perfusion can be established and the contribution to collateral flow by each artery separately evaluated. The distribution of ^{81m}Kr, due to its 13-s half-life, represents regional blood flow. In order to evaluate interventions, studies can be repeated at a low radiation risk to patients. A sterile pyrogen-free ^{81}Rb–^{81}Kr generator was developed. With slow infusion, inadequate mixing and streaming takes place due to laminar flow in coronary arteries. Fast intermittent 3-ml ^{81}Kr-dextrose bolus injections convincingly eliminated streaming artefacts. Imaging was performed in 13 patients with a mobile scintillation camera and digital imaging system. Blood flow was calculated using the inert gas washout technique. There was good correlation ($r=0.91$) between coronary blood flow determinations using ^{81m}Kr and ^{133}Xe respectively. The perfusion images correlated well with the coronary angiograms. Total coronary arterial occlusions as demonstrated by arteriography were all shown as perfusion defects during rest. During atrial pacing myocardial flow was increased two-fold in normal coronary arteries and to a lesser extent in arteries with significant disease. The most critical lesion in a branch of a left coronary artery leads to a redistribution of perfusion during pacing.

Introduction

Radionuclide imaging of the distribution of myocardial perfusion is complementary to coronary arteriography and provides a method of assessing the clinical significance of coronary stenosis in patients with ischaemic heart disease (Gould 1978; Selwyn et al. 1979a). This is important in some patients considered for coronary by-pass surgery when the effect of lesions on the perfusion is unclear. If regional perfusion is obtained by direct intra-coronary injection of the radio-tracer, the contribution to collateral flow by each artery can be separately evaluated.

The ultra-short half-life of the radio-nuclide ^{81m}Kr ($t\frac{1}{2}=13$ s) has favourable physical properties to image regional myocardial perfusion (Kaplan et al. 1976; Columbetti et al. 1974; Selwyn et al. 1979b and c). No recirculation or background activity is present and high count density images of excellent quality can be acquired. The 190-keV photon energy emitted by ^{81m}Kr is ideal for use with the scintillation camera. At equilibrium the distribution of the radio-nuclide is proportional to perfusion because ^{81m}Kr decays at a higher rate than the biological clearance (Selwyn et al. 1979b).

Images will represent relative perfusion. Defects will correlate with scarring with no perfusion or critical ischaemia when coronary artery obstruction is more than 85% (Gould 1978).

Repeated studies can be performed at low radiation risk to evaluate the influence of interventions. During pacing the coronary blood flow increases, except in critically stenosed arteries where flow cannot increase, resulting in ischaemia and relative under-perfusion. In this study pacing was investigated to induce new perfusion defects in images to indicate critically stenosed arteries.

When ^{81m}Kr solution is infused into coronary ostia inadequate mixing occurs as a result of the laminar flow in the coronary arteries. This results in streaming with the radio-nuclide solution distributed into preferential arteries. Methods to eliminate streaming were investigated.

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Methods

A sterile pyrogen-free ^{81m}Kr generator was developed for perfusion studies (Kaplan et al. 1976; Van Zyl et al. 1979). The generator consists of a column 80 mm in height and 15 mm in diameter, filled with sterilized Dowex 50-X8 cation exchange resin. A millipore filter was connected to the generator output. To overcome the resistance of the millipore filter a plastic bag containing sterile 5% dextrose solution was enclosed in an airtight pressure chamber connected to a cylinder containing compressed medical air. The solution was forced through the generator and millipore filter and directly connected to the angiographic catheter.

The study was performed after informed consent was obtained from the 13 patients who underwent coronary angiography for chest pain. A pacemaker electrode was inserted in the right atrium prior to coronary angiography. Coronary angiography was performed by the Judkins technique using Urographin R 76 as contrast medium. The X-ray equipment used was a Siemens Cardioscope U. Radionuclide imaging was performed using a mobile Ohio Nuclear scintillation camera fitted with a converging collimator. The camera was interfaced to a MDS Mugacart imaging

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system that was used for data collection. The scintillation camera was positioned in a 45° LAO projection for the radio-nuclide investigations. The data was acquired in frame mode as 2-s images consecutively for 120 s. Two methods were investigated to eliminate streaming. Firstly ^{81m}Kr was infused into the right coronary ostium at 40 ml/min for 40 s. This was subsequently followed for another 40 s by repeated bolus injections of 3 ml ^{81m}Kr into the coronary ostium. Each injection was given as fast as possible to fill the proximal coronary artery and ideally to cause an overflow spilling from the ostium. Following the last injection the washout data was acquired for 40 s. The right Judkins coronary catheter was then removed and a left catheter was inserted.

Basal radio-nuclide studies were performed for the left coronary artery (LCA), using the same protocol as for the right coronary artery (RCA). After the angiogram the heart rate was increased by pacing. Pacing rate was increased stepwise to 140 beats/min or to a rate where either A-V block or angina developed and then decreased by 5 beats/min. When the maximal heart rate was reached, the radionuclide studies were repeated, using the same protocol. In four patients, 74 MBq (2mCi) ^{133}Xe was injected as a bolus into the LCA after the ^{81m}Kr data acquisition was completed while still pacing at the same heart rate. The ^{133}Xe washout data was collected for 5 min. Time-activity curves were generated from areas of interest in the region perfused by the RCA, the circumflex artery (Cx) and the left anterior descending artery (LAD) respectively. A ratio-curve was calculated from the Cx and the LAD time-activity curves. If these ratio-curves remained constant during infusion or injections, no streaming was assumed. For visual interpretation the 2- s images acquired during equilibrium were integrated, generating images for the RCA and LCA. Care was taken not to move the patient or the scintillation camera until all the radionuclide investigations were completed so that the geometric relation was the same for RCA and LCA images.

The global myocardial perfusion image was generated by digital summation of the LCA and RCA images. The images were normalized before summation so that the maximum pixel counts in each image were equal (Ritchie et al. 1975; Maseri et al. 1977; Gould 1978).

Myocardial flow was calculated from the washout curves following correction for the decay of ^{81m}Kr. A least squares Newton iteration method to fit a single exponential curve was used (De Valois et al. 1970). The ^{133}Xe washout curves were similarly analyzed.

Results

In none of the present series of 13 cases, or in a previous study of 23 cases were there any deleterious effects during the infusion of ^{81m}Kr. All the haemodynamic parameters, i.e. blood pressure, pulse rate, left ventricular end-diastolic pressure and left ventricular maximum pressure change, remained constant or improved during infusion or bolus injections of ^{81m}Kr. High quality images with negligible background were obtained. This is demonstrated by the perfusion images (Fig. 1) obtained from a patient with a normal coronary arteriogram. The images (Fig. 1 A and B) were obtained by repeated bolus injections. When ^{81m}Kr solution was administered by continuous infusion, streaming occurred, even when the flow rate was increased to 40 ml/min creating serious artefacts. This is demonstrated by the infusion image (Fig. 1 D) in the same patient. Repeated bolus injections eliminated streaming in 69 studies performed in 13 patients. The ratio of the time-activity curves generated from the Cx and LAD regions when images were obtained by bolus injection was constant indicating that streaming did not occur. A typical ratio time-activity curve is demonstrated in Fig. 2. The total myocardial perfusion image (Fig. 1 C) was obtained by digital summation of the RCA (Fig. 1 A) and the LCA (Fig. 1 B) images.

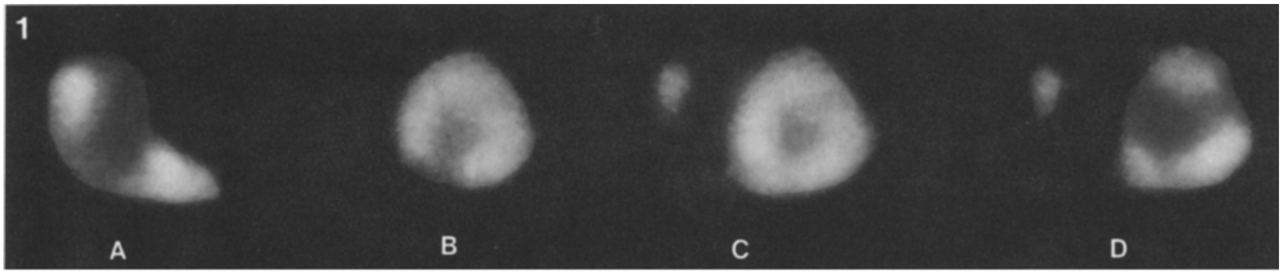
Table 1. Comparison of ^{81m}Kr-Perfusion and contrast angiography

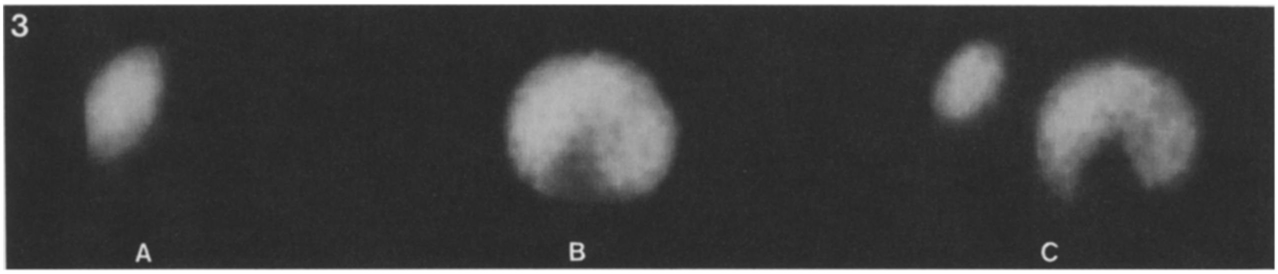
Patient identity	Angiography[a]			^{81m}Kr-Perfusion				
				Rest			Pacing	
	RCA	LAD	Cx	RCA	LAD	Cx	LAD	Cx
1	100	85	85	+	–	–	–	–
2	–	–	–	–	–	–	–	–
3	100	–	–	+	–	–	–	–
4	–	–	–	–	–	–	–	–
5	–	–	–	–	–	–	–	–
6	75	85	60	–	+	–	++	–
7	80	100	–	–	+	–	+	–
8	50	100	50	–	+	–	+	–
9	–	–	–	–	–	–	–	–
10	100	60	75	+	–	–	–	+
11	–	–	–	–	–	–	–	–
12	100	80	40	+	–	–	–	–
13	–	100	–	–	+	–	+	–

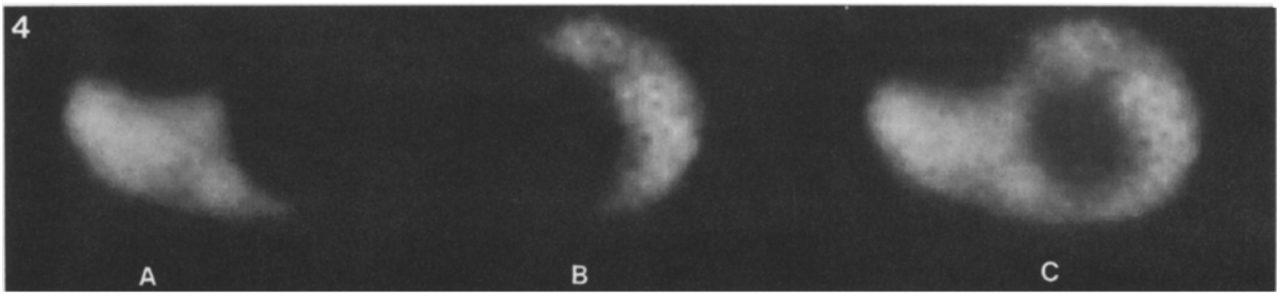
[a] Angiographic values express percentage coronary artery occlusion
\+ = perfusion defect detected
– = no perfusion defect detected
++ = increased perfusion defect during pacing

Table 1 summarises the results obtained from perfusion imaging and corresponding arteriography. Patients are identified by number. Coronary occlusions with scars from previous myocardial infarctions confirmed by arteriography were all demonstrated by resting ^{81m}Kr perfusion defects (patients 1, 3, 7, 8, 10, 12 and 13). Perfusion images obtained during rest in patient 12 with three-vessel disease and totally occluded RCA is demonstrated in Fig. 3; the perfusion defect corresponds to the previous inferior myocardial infarction. No perfusion defects were found in patients (2, 4, 5, 9 and 11) whith normal coronary angiograms. In patient 6 with 85% obstruction of the LAD and 60% obstruction in the Cx, a defect in the LAD region indicates hypoperfusion during rest. With pacing this defect increased in size. In patient 1 no defect was demonstrated in spite of 85% lesion in the LAD and an 85% lesion in the Cx. Pacing did not change the perfusion pattern. In patients 7 and 13 the LAD was totally occluded and collateral vessels from the RCA were present at angiography. The images of patient 13 are demonstrated in Fig. 4. The LCA image shows no detectable perfusion in the region of the occluded LAD, while the RCA image reveals unusual perfusion in this region best appreciated on the summation image. The extent of the perfusion by collateral vessels is well demonstrated.

Specific myocardial blood flow determinations on ^{81m}Kr studies were compared with ^{133}Xe studies in the same patients. Correlation coefficients of 0.99 for the LAD,







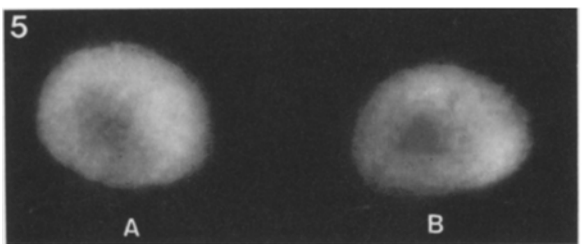


Fig. 1 A–D. Perfusion images obtained in a patient with normal coronary arteries. (**A**) represents RCA perfusion, (**B**) LCA perfusion with repeated bolus injection and (**C**) was obtained by digital summation of the right and the left coronary artery images. (**D**) Artefacts resulting from streaming were observed in this patient when continuous infusion of 40 ml/min was used. **Fig. 3 A–C.** Resting perfusion images of a patient with three-vessel disease and a totally occluded RCA. The RCA resting defect of a previous inferior myocardial infarction is illustrated by (**A**) and the LCA perfusion by (**B**). The global image (**C**) is obtained by summation of images (**A**) and (**B**). **Fig. 4 A–C.** Presence of collateral flow is demonstrated. (**A**) The RCA demonstrates unusual perfusion in the LAD region (**B**) The lack of perfusion represents a totally occluded LAD. The summed image (**C**) confirms the collateral flow from the RCA. **Fig. 5 A–B.** Redistribution during pacing is demonstrated. (**A**) demonstrates the resting image and (**B**) the perfusion image during pacing when a lower septal defect is induced

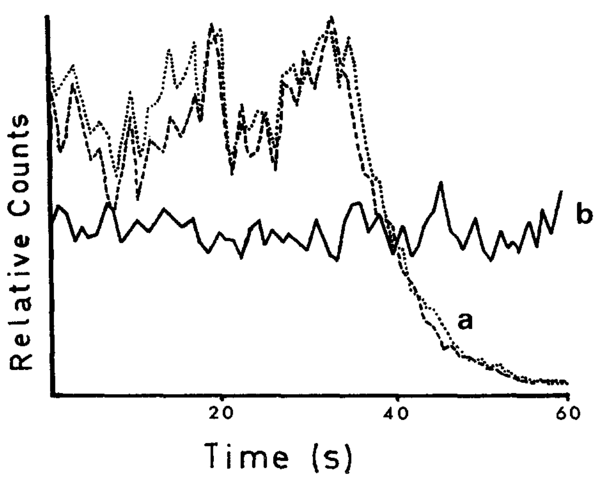


Fig. 2. The time-activity curves (*a*) from LAD and Cx regions obtained during repeated bolus injections. The ratio curve (*b*) calculated from these time-activity curves is constant, indicating absence of streaming

Table 2. Correlation of myocardial flow measured with ^{81m}Kr and ^{133}Xe

Patient		LAD ml/100 g/min	Cx ml/100 g/min	Total LCA ml/100 g/min
9	^{81m}Kr	90	92	89
	^{133}Xe	86	88	88
10	^{81m}Kr	114	100	94
	^{133}Xe	98	88	94
12	^{81m}Kr	146	122	134
	^{133}Xe	137	130	139
13	^{81m}Kr	45	107	87
	^{133}Xe	40	90	65
r		0.99	0.89	0.95

LAD = Left anterior descending coronary artery
Cx = Circumflex left coronary artery
LCA = Left coronary artery
r = Linear correlation coefficient

Table 3. Pacing/rest ^{81m}Kr blood flow ratio

Patient	LAD	Cx	LCA Total
6	1.22	1.98[a]	1.77
10	2.59[a]	1.58	1.95
11	1.96[a]	2.03[a]	1.91
12	1.48	1.27	1.49
13	1.01	1.16	1.01

The unmarked ratios refer to diseased arteries

[a] Normal coronary arteries by angiography

0.89 for the Cx and 0.95 for the total LCA were found (Table 2).

Specific myocardial blood flow was calculated following washout in five patients during both rest and pacing (Table 3). In normal coronary arteries ratios of flow during pacing and rest were between 1.96 and 2.59. Pacing did not increase the flow in regions supplied by severely diseased coronary arteries. A redistribution of myocardial blood flow was shown in patients 6 and 10 (Table 3). This is demonstrated by the perfusion images at rest and during pacing when a lower septal defect was induced (Fig. 5).

Discussion

The ultra-short half-life of ^{81m}Kr makes it ideal for intervention studies that can be performed within 2 min following the first control study. The activity dose can be much higher than that of ^{133}Xe, resulting in high quality images with negligible background and better counting statistics. No recirculation occurs. Separate investigation of the RCA and LCA allows appraisal of the collateral circulation. Unfortunately the image of global heart perfusion can only be computed by digital summation of the RCA and LCA images. As the absolute flow in the RCA and LCA is unknown, the exact proportion of the RCA/LCA counts must be arbitrary. The best method proved to be normalization so that the maximum pixel counts in the two images were equal.

When ^{81m}Kr was infused, streaming occurred in the LCA creating perfusion image artefacts. Streaming was eliminated by repeated bolus injections into the coronary arteries. This was confirmed by the constant value of the ratio time-activity curves. No artefacts seen with infusion could be detected on the images with bolus injections. Bolus injection might momentarily disturb the pressure and flow when the proximal artery is filled, but a plug of radioactivity is left in the artery and this is cleared by physiological flow during the period before the next bolus injection (Maseri 1976; Wolf et al. 1978).

All the specific flow calculations were done on the washout data when any possible disturbance of flow during injection would no longer have an effect. Only the initial portion of the washout is reflected by the clearance curves due to the fast decay of ^{81m}Kr. The agreement of ^{81m}Kr and ^{133}Xe washout blood flow calculations in this small number of patients support the feasibility of global blood flow evaluation with ^{81m}Kr.

Our results on the detection of perfusion defects during rest are in agreement with the present literature (Kaplan et al. 1976; Maseri et al. 1977; Gould 1978; Wolf et al. 1978; Selwyn et al. 1979a–c) where radio-nuclide microspheres, ^{133}Xe and ^{81m}Kr have been used. Previous myocardial infarction with scar tissue was observed as a defect during rest. Perfusion images of the LCA will indicate relative hypoperfusion of the LAD and Cx. This is demonstrated in patient 6 where the LAD was critically (85%) obstructed with normal perfusion in the Cx. In patient 1 no defect was detected with lesions of 85% in both LAD and Cx. The perfusion image represents the relative perfusion. When both branches are equally affected there will be no difference in the perfusion of the two systems so that the lesions will not be detected.

During pacing the coronary blood flow was increased two-fold in normal coronary arteries while there was no significant increase in the arteries with a high degree obstruction (Table 3). A marked difference in the degree of obstruction between LAD and Cx arteries leads to a redistribution during pacing. The coronary artery branch with the most significant obstruction was indicated by perfusion image defects developing after pacing (patient 6, Table 1) and by the specific myocardial flow calculations (Table 3, patient 6 and 10) and by the perfusion image (Fig. 5). The results obtained in this small series of 13 cases are in agreement with the current literature on the detection of coronary artery disease by measurement of perfusion during increased blood flow induced by pacing (Kaplan et al. 1976; Gould 1978; Selwyn et al. 1979a–c).

The perfusion studies prolonged coronary angiography by approximately 15 min and was uneventful. Repeated bolus injections eliminated the main objection to direct intra-coronary injection, namely false positive studies as a result of streaming.

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