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The influence of age on N-isopropyl-p-[^{123}I]iodoamphetamine accumulation in the human heart

Masayuki NAKAJO, Yoshiaki NAKABEPPU, Shinji IWASHITA and Shinji SHINOHARA

Department of Radiology, Faculty of Medicine, Kagoshima University, Kagoshima, Japan

Variations in heart intensity in the 30 min and 4 hr chest images of the radiolabelled lipophilic amine, N-isopropyl-p-[^{123}I]iodoamphetamine (^{123}I-IMP) were observed in 130 patients with lung diseases, aged 23 to 85 yrs. The heart intensity had a significant positive linear correlation with age (r=0.43 at 30 min, 0.66 at 4 hr). The ratio of 4 hr heart intensity to 30 min heart intensity also had a positive linear correlation (r=0.59), suggesting slower clearance of the radioactivity from the heart in older than in younger patients during this interval. Other parameters including sex, EKG findings, liver function, blood pressure, the presence of diabetes mellitus and smoking history had no relationship to heart intensity. A significant difference between heart intensities in bronchogenic carcinoma and pneumonia patient groups might be probably due to the age difference between the two groups. Therefore heart intensity in the 4 hr ^{123}I-IMP image may reflect certain metabolic and/or myocardial change(s) with aging.

Key words: ^{123}I-IMP, heart, aging

INTRODUCTION

N-isopropyl-p-[^{123}I]iodoamphetamine (^{123}I-IMP) is a lipophilic radiolabelled amine which was developed as a cereberal perfusion imaging agent.[1] Biodistribution studies in humans revealed that high uptake of ^{123}I-IMP was present in the lung, liver and brain.[2] Although this radiolabelled amine has been clinically used in the assessment of brain diseases related to abnormalities of cerebral perfusion and function,[3,4] it would also be a potential imaging agent for the assessment of metabolism or function of organs other than the brain. In fact, basic studies on the application of this agent to the *in vivo* measurement of pulmonary metabolism have been reported by several investigators.[5,6] We have also applied this agent to the assessment of pulmonary diseases. This tracer accumulated gradually in the pulmonary inflammatory lesion and atelectasis but was not taken up by bronchogenic carcinoma, tuberculoma or pleural effusion.[7,8] In the course of these studies, we observed that the heart image varied in intensity among patients. In this paper, we examine the factors related to the myocardial accumulation of ^{123}I-IMP and found that it had a significant positive linear correlation with aging.

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For reprints contact: M. Nakajo, Department of Radiology, Faculty of Medicine, Kagoshima University, 1208–1 Usuki-cho, Kagoshima-shi, Kagoshima 890, JAPAN.

MATERIALS AND METHODS

Subjects

^{123}I-IMP lung imaging was performed in a total of 130 patients with a variety of lung diseases; 102 male and 28 female patients, aged 23 to 85 yrs. The patient population consisted of 78 with bronchogenic carcinoma, 6 with metastatic cancer (3 from colon cancer, one from hepatocellular carcinoma, one from malignant fibrous histiocytosis and one from malignant lymphoma), 18 with pneumonia (12; bacterial, 2; viral, 2; radiation, 1; obstructive and 1; hypersensitivity pneumonia), 14 with tuberculosis, 4 with pneumoconiosis, 5 with lung abscess and

5 with other benign lung disease (2; bronchiectasis, one each of lung fluke disease, cystic lung and pulmonary pseudotumor).

Imaging methods

Thyroidal uptake of free ^{123}I was blocked by oral administration of potassium iodide 100 mg TID, beginning on the day before i.v. injection of 111 MBq (3 mCi) of ^{123}I-IMP in a volume of 3 m*l* (Nihon Mediphysics, Japan). The specific activity of the ^{123}I-IMP was 248 MBq (6.7 mCi)/mg. After dynamic anterior or posterior imaging at one frame/min for 25 mins, additional 30 min and 4 hr lung static images from six projections: anterior, posterior, bilateral, and both anterior or posterior 45° oblique views were obtained. Imaging was performed with a gamma camera with a medium energy multiparallel hole collimator. A 20% window was centered on the 159 KeV photopeak and 500,000 counts were acquired for each view.

Grading of heart intensity

Heart uptake intensities in the 30 min and 4 hr anterior lung images were rated independantly by two nuclear medicine radiologists (M.N., Y.N.) by means of a semiquantitative grading system using the following scales: Grade 0 (no visible uptake), Grade 1 (faint uptake above mediastinal background), Grade 2 (moderate uptake less than that of left lung activity), Grade 3 (same uptake as that of left lung activity) and Grade 4 (prominent uptake greater than that of left lung activity) (Fig. 1). When the left lung activity was not appropriate as a reference due to a left lung lesion, the right lung activity was used instead. The agreement between the gradings by the two observers was good. In the case of disagreement (25%), they reexamined the anterior lung image together, discussed the findings and reached a consensus grading.

Stratification of age

The age of patients was divided into 9 ranges based on the decade: 1 (0–9-year-old), 2 (10–19-year-old), 3 (20–29-year-old), 4 (30–39-year-old), 5 (40–49-year-old), 6 (50–59-year-old), 7 (60–69-year-old), 8 (70–79-year-old) and 9 (80–89-year-old).

Analysis of data

Heart intensity and age were compared. The number of cases in each grade corresponding to each age range was obtained at 30 min and 4 hr and the mean grade$\pm$S.D. of heart intensity was calculated for each age range. The linear correlation coefficient for heart intensity and age range was calculated and its significance was determined.

In order to semiquantitatively assess the change in heart activity between 30 min and 4 hr, the ratio of 4 hr heart intensity to 30 min heart intensity (4 hr/30 min heart intensity ratio) was calculated. The mean ratio$\pm$S.D. was calculated for each age

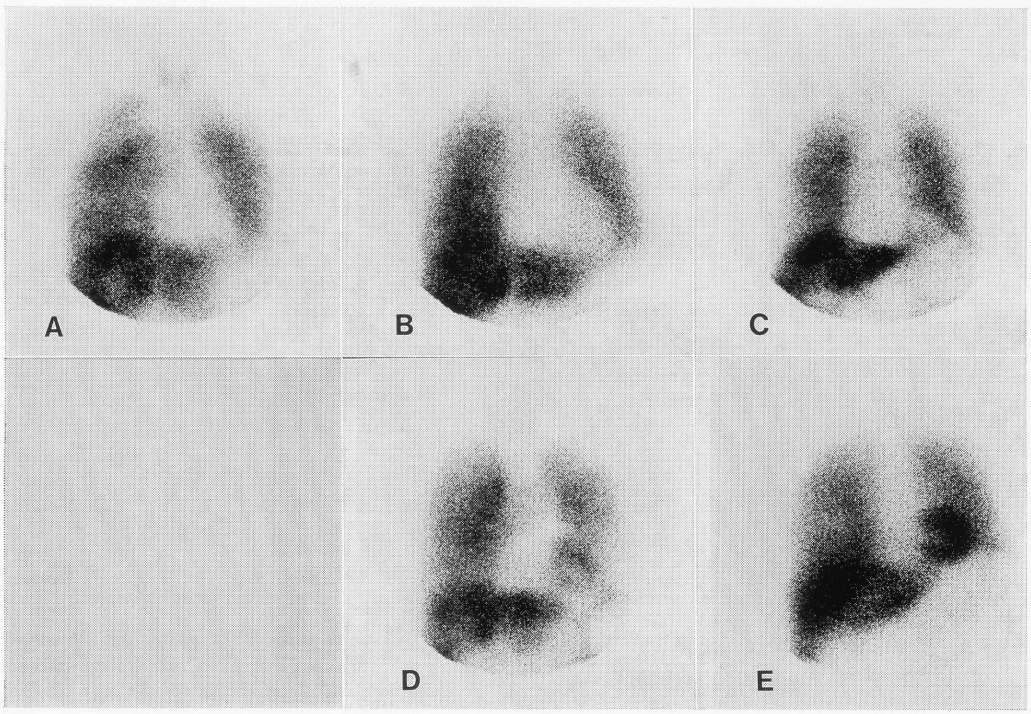

Fig. 1 Grades of heart intensity. Anterior lung images 4 hr after injection of ^{123}I-IMP. A=Grade 0, B=Grade 1, C=Grade 2, D=Grade 3, E=Grade 4.

range. The linear correlation coefficient for the ratio and age range was also obtained and its significance was calculated.

The relationships of 30 min and 4 hr heart intensities to other parameters including sex, EKG findings, liver function, blood pressure, diabetes mellitus and smoking were examined. The patients were divided into two groups for each parameter: sex: male v. female; EKG findings: normal v. abnormal; liver function: normal v. abnormal; blood pressure: normotension v. hypertension; diabetes mellitus: absence v. presence and smoking: nonsmoker v. smoker. Abnormal EKG findings included LVH, flat, depressed or elevated ST, inverted T, atrial or ventricular premature beat, complete or incomplete RBBB, atrial fibrillation, Q waves, giant negative T and sinus bradycardia. Hypertension was defined as a systolic pressure more than 150 mmHg and a diasystolic pressure more than 90 mmHg. The presence or absence of diabetes mellitus was determined from the fasting blood sugar concentration and 75 g GTT. Routine liver function tests (measurements of serum total bilirubin, GOT, GPT, ALP, LDH, ZTT, TTT, CHE and LAP) were performed in all patients. Of these, 18 patients including one with liver cirrhosis showed more than one abnormal result and were put into the abnormal group. The mean heart intensity $\pm$S.D. was calculated for the two groups of each parameter. As to smokers, the linear correlation coefficient between heart intensity and smoking index (average no. of cigarettes smoked per day$\times$ smoking years; 180–3420) was also obtained and its significance was calculated.

In addition, mean heart intensity$\pm$S.D. was calculated for each type of lung disease to examine whether any difference between the heart intensities of the different lung disease groups existed.

Statistical analyses were performed by means of the unpaired t-test.

RESULTS

Comparison of heart intensity with age.

Table 1 shows relationships of age range to ^{123}I-IMP heart intensity at 30 min and 4 hr, and to the 4 hr/30 min heart intensity ratio. In general, mean heart intensity at 30 min and 4 hr increased with age. Mean heart intensity was greater at 30 min than at 4 hr except for age range, 9. The mean 4 hr/30 min heart intensity ratio also increased with age. A statistically significant ($p<0.001$) positive linear correlation existed between age and 30 min and 4 hr heart intensity (Fig. 2) and the 4 hr/30 min heart intensity ratio (Fig. 3). The correlation coefficient was greater at 4 hr (0.66) than at 30 min (0.43). When the correlation coefficient was obtained separately for the 102 male patients and 28 female patients, it was 0.42 ($p<0.001$) for male patients and 0.51 ($p<0.01$) for female patients at 30 min, and 0.62 ($p<0.001$) in the former and 0.75 ($p<0.001$) in the latter at 4 hr. There was however no statistical difference between the correlation coefficients in male and female patients at either imaging time.

Relationships of the heart intensity with other parameters and lung disease groups.

Table 2 shows the relationships of heart intensity to sex, EKG, liver function, blood pressure, diabetes mellitus and smoking. None showed a statistically significant difference between the intensities of heart uptake in the two groups. Of 24 patients with abnormal EKG findings, 5 had ischemic heart diseases. Their heart intensities were 2.20$\pm$0.447 at 30 min and 1.60$\pm$0.548 at 4 hr, respectively. These values also were not significantly different from those of the normal group. In smokers, no statistically significant linear correlation existed between heart intensity and smoking index (30 min: $r=-0.047$, $p>0.05$; 4 hr: $r=0.16$, $p>0.05$) ($n=44$). Table 3 shows the relationships between heart in-

Table 1 Relationships of age range to ^{123}I-IMP heart intensity at 30 min and 4 hr, and ratio of 4-hr heart intensity to 30-min heart intensity (4-hr/30-min heart intensity ratio)

Age range	No. of patients	Imaging time: 30-min Grade of heart intensity						4-hr Grade of heart intensity						Mean$\pm$S.D. of 4-hr/30-min heart intensity ratio
		0	1	2	3	4	mean$\pm$S.D.	0	1	2	3	4	mean$\pm$S.D.	
3 (20–29)	4	0	2	2	0	0	1.50$\pm$0.58	3	1	0	0	0	0.25$\pm$0.50	0.13$\pm$0.25
4 (30–39)	5	0	1	4(1)*	0	0	1.80$\pm$0.45	1(1)	4	0	0	0	0.80$\pm$0.45	0.50$\pm$0.35
5 (40–49)	12	0	0	12(3)	0	0	2.00$\pm$0.00	1(1)	9(1)	2(1)	0	0	1.08$\pm$0.51	0.54$\pm$0.26
6 (50–59)	21	0	1	18(5)	2(2)	0	2.05$\pm$0.38	1	14(6)	6(1)	0	0	1.24$\pm$0.54	0.60$\pm$0.26
7 (60–69)	36	0	1	26(5)	8(1)	1(1)	2.25$\pm$0.55	0	11(3)	19(4)	4	2	1.92$\pm$0.81	0.86$\pm$0.35
8 (70–79)	41	0	0	23(4)	13(1)	5(2)	2.56$\pm$0.71	0	7(1)	17(3)	13(2)	4(1)	2.34$\pm$0.88	0.94$\pm$0.29
9 (80–89)	11	0	0	6	4(2)	1(1)	2.55$\pm$0.69	0	0	2	8(3)	1	2.91$\pm$0.54	1.23$\pm$0.36

* ( )=Number of female patients

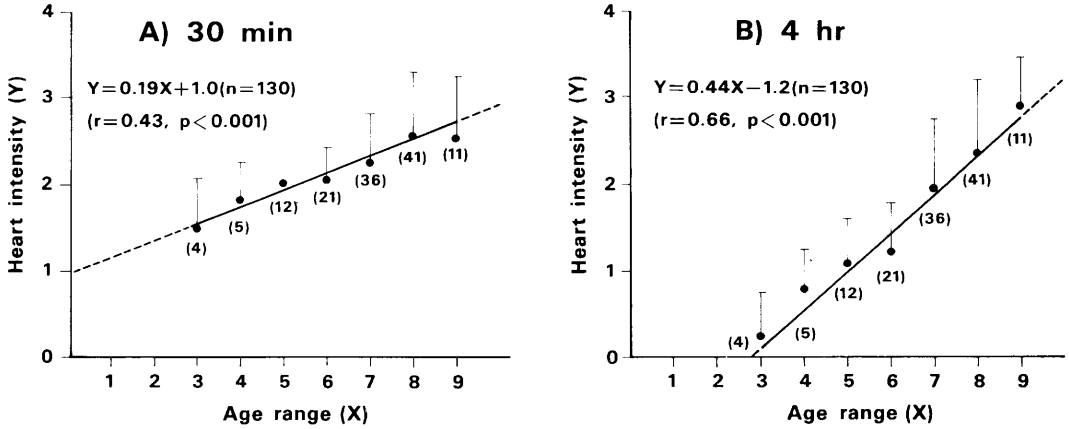

Fig. 2 Positive linear correlation of heart intensity with age range at 30 min (A) and 4 hr (B) after injection of ^{123}I-IMP. Solid circles and bars show mean heart intensities and S.D.s respectively.

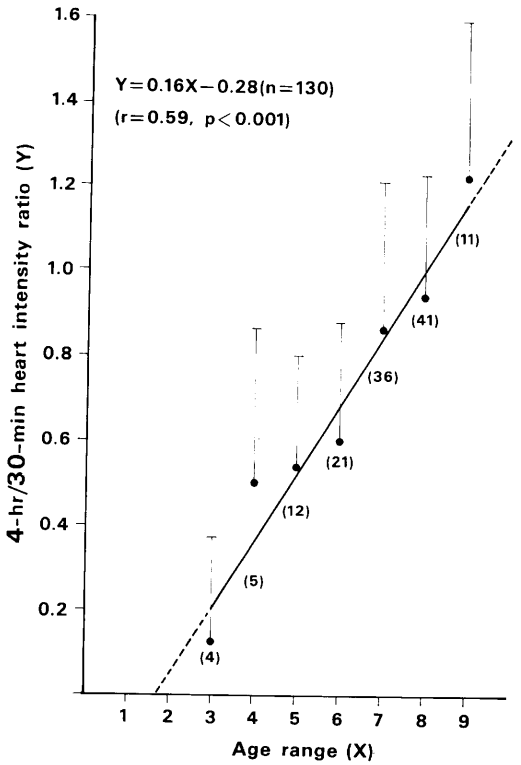

Fig. 3 Positive linear correlation of 4-hr/30-min heart intensity ratio with age range. Solid circles and bars show the mean ratios and S.D.s respectively.

tensity and age in lung disease groups. The mean heart intensity value at 30 min was almost identical in the different disease groups. At 4 hr, it was greater in the bronchogenic carcinoma group (2.09) than the other groups (1.39–1.64). It was however only between the bronchogenic carcinoma and pneumonia patient groups that there was a statistically significant difference ($p<0.01$). There was also a statistically significant difference ($p<0.01$) between these two groups in age and this may be an underlying factor.

DISCUSSION

The present study revealed that the intensity of ^{123}I-IMP heart uptake correlated positively with aging but not with other parameters including sex, normality or abnormality of EKG findings and liver function tests, normotension or hypertension, presence or absence of diabetes mellitus and smoking history. Although there was a statistically significant difference between the 4 hr heart intensities in the bronchogenic carcinoma and pneumonia patient groups, this was probably due to the statistically significant age difference between the two groups and thus lung pathology may not be an independent variable.

The significant positive linear correlation of the 4 hr/30 min heart intensity ratio with the age range suggests that clearance of ^{123}I-IMP from the heart becomes slower with aging. The mechanism of ^{123}I-IMP accumulation in the heart has not been directly studied to date, probably because this agent was developed as a brain perfusion imaging agent. It is hypothesized that initial uptake of ^{123}I-IMP in the brain is a consequence of its lipophilicity and its progressive brain accumulation is probably a combined consequence of intravascular/extravascular intracerebral pH gradients, favorable brain lipid/aqueous partition coefficients, and the affinity of ^{123}I-IMP for high-capacity, relatively nonspecific binding sites for amines located in the brain and/or brain capillary endothelium.[1,9] Pulmonary uptake may be due to endothelial amine receptor binding of ^{123}I-IMP.[5,6]

Although the mechanism(s) of ^{123}I-IMP accumulation in the heart remains to be elucidated, there is

Table 2 Relationships of ^{123}I-IMP heart intensity with other parameters

Parameter	Group	30-min			4-hr		
		Heart intensity	(n)	P	Heart intensity	(n)	P
Sex	Male	2.22±0.574	(102)	>0.05	1.86±0.965	(102)	>0.05
	Female	2.46±0.745	(28)		1.79±0.957	(28)	
EKG	Normal	2.33±0.661	(30)	>0.05	2.00±1.08	(30)	>0.05
	Abnormal	2.21±0.588	(24)		1.92±0.881	(24)	
Liver function	Normal	2.29±0.653	(112)	>0.05	1.86±0.985	(112)	>0.05
	Abnormal	2.17±0.383	(18)		1.72±0.752	(18)	
Blood pressure	Normotension	2.28±0.670	(58)	>0.05	1.83±0.994	(58)	>0.05
	Hypertension	2.10±0.316	(10)		1.70±0.675	(10)	
Diabetes mellitus	Absence	2.23±0.643	(61)	>0.05	1.82±0.922	(61)	>0.05
	Presence	2.24±0.626	(7)		2.14±1.22	(7)	
Smoking	Nonsmoker	2.36±0.700	(25)	>0.05	1.80±0.913	(25)	>0.05
	Smoker	2.16±0.526	(44)		1.84±0.834	(44)	

Table 3 Relationships between ^{123}I-IMP heart intensity and age in different lung disease groups

Lung disease	No. of patients	^{123}I-IMP heart intensity		Age (yrs)
		30-min	4-hr	
Bronchogenic carcinoma	78	2.35±0.62	2.09±0.90	68.8±10.5
Metastatic lung tumor	6	2.33±0.82	1.50±1.05	50.0±17.9
Pneumonia	18	2.28±0.46	1.39±0.92*	56.0±12.8*
Tuberculosis	14	2.07±0.73	1.64±1.01	57.6±17.8†
Pneumoconiosis	4	2.25±0.50	1.50±0.58	54.8±8.0†
Lung abscess	5	2.00±0.00	1.40±0.55	55.6±7.1*
Other benign lung disease	5	2.00±1.00	1.40±1.52	58.0±22.5

*$p<0.01$; †$p<0.05$, when the value is compared to that of the bronchogenic carcinoma

evidence that, in the rat heart, a greater amount of amphetamine was located extraneuronally and this nonspecific binding of amphetamine may be related to its highly lipophilic properties.[10,11]

The positive linear correlation of the intensity of ^{123}I-IMP uptake and the slower clearance of the activity from the heart with aging may be related to metabolic enzymatic decline and/or myocardial changes with aging.

The proposed metabolic pathway of IMP is as follows:[12] IMP is dealkylated to p-iodoamphetamine. Dealkylation occurs in brain, lungs and liver. The next step is deamination or scission of the C-N bond, leading to formation of p-iodophenylacetone. This intermediate does not accumulate in tissues, but is rapidly further degraded to p-iodobenzoic acid by reactions that appear to occur mainly in the liver. P-iodobenzoic acid in turn is conjugated with glycin to p-iodohippuric acid, the end product of metabolism excreted in the urine. The metabolism of IMP is thought to be related to the mixed function oxidase (MFO) system.[13] As it has been suggested that the enzymatic activity of the MFO system declines with aging,[14] the percentage of nonmetabolized IMP and p-iodoamphetamine in circulation may increase with age. IMP and p-iodoamphetamine are the only amines found in the brain, and a similar pattern was seen in the lung.[12] Assuming that as with brain and lung, only IMP and p-iodoamphetamine accumulate in the heart, this metabolic enzymatic decline with age may be the cause of age-related accumulation of ^{123}I-IMP in the human heart.

Another possible explanation for the age-related accumulation of ^{123}I-IMP in the human heart is myocardial changes with aging. It is well known that in the human heart there is a linear increase in the amount of lipofuscin with age.[15] The age related myocardial accumulation of ^{123}I-IMP may be analogous to that of lipofuscin in that both of them accumulate linearly with age and that neither seems to be significantly altered by functional abnormalities of the heart or to be dependent on sex or disease. Lipofuscin appears to be composed of polymers of lipid and phospholipids complexed with protein.[16] Assuming that the age related accumulation of ^{123}I-IMP in the heart is related to lipofuscin, IMP and its metabolite, p-iodoamphetamine may be bound to certain lipophilic components of lipofuscin.

Lipofuscin also contains melanin and the quantity of melanin extracted from human heart and liver tissue is directly proportional to lipofuscin granule counts.[17] ^{123}I-IMP has been reported to concentrate in the pigmented tissues of the eyes of dogs, rodents, and monkeys where melanin is produced.[9,18] Holman et al[19] showed that ^{123}I-IMP is avidly incorporated into melanocytes actively producing melanin, incorporation is substantially less in melanocytes where production of melanin has ceased. They suggest that the high concentration of ^{123}I-IMP in the eyes of most animal species studied is due to a marked affinity and slow release of this tracer for melanin, in pigmented tissues. Therefore, the age related accumulation of ^{123}I-IMP in the human heart may be related to the amount of lipofuscin with a proportional amount of melanin.

Further studies will be required to clarify whether the age related accumulation of ^{123}I-IMP in the heart is related to metabolic enzymatic decline, myocardial changes or both.

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