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Assessment of pancreatic blood flow with positron emission tomography and oxygen-15 water

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Dynamic positron emission tomography (PET) was performed following an intravenous bolus injection of ^{15}O-water for the assessment of regional pancreatic blood flow in 4 normal volunteers and 11 patients with pancreatic cancer. The regional pancreatic blood flow index (PFI) was calculated by the autoradiographic method assuming the time-activity curves of the aorta as an input function. The mean PFI value was 0.514±0.098 in the normal pancreas but it was decreased in pancreatic cancer (0.249±0.076) ($p<0.01$), with a concomitant decrease in the pancreatic region distal to the tumor. On the other hand, in cases with body or tail cancer, the part proximal to the tumor (nontumorous head region) had a similar PFI value (0.554±0.211) to that of normal cases. Thus, a PET study with ^{15}O-water permits quantitative assessment of pancreatic blood flow which decreased in both pancreatic cancer and concomitant obstructive pancreatitis distal to the tumor.

Key words: blood flow, pancreatic cancer, positron emission tomography, ^{15}O-water

INTRODUCTION

THE BLOOD FLOW in the pancreas plays an important role in its excretory and endocrine functions. Although pancreatic cancer is thought to have a relatively low blood flow compared to the normal pancreatic tissue according to the findings of selective celiac angiography,[1-6] it has not been possible to measure pancreatic blood flow non-invasively. Recent developments in positron emission tomography (PET) have made it possible to measure regional blood flow in the brain and the heart non-invasively.[7,8] In this report, we applied the same technique to measuring pancreatic blood flow by PET with intravenous injection of ^{15}O-water in normal pancreas and pancreatic cancer.

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MATERIALS AND METHODS

1) Synthesis of ^{15}O-water

Sterile and pyrogen free ^{15}O labeled water was prepared by chemical reaction of $^{15}O_2$ with H_2 with a palladium catalyst according to a method previously reported.[9] $^{15}O_2$ was produced via ^{14}N(d,n)^{15}O nuclear reaction with a 7.5 MeV proton beam on a target of N_2 gas including 2% of O_2 in an ultra compact cyclotron (Sumitomo CYPRIS Model 325). This labeled water was passed through a 0.22 μm millipore filter before administration to the patients.

2) Subjects

Four normal volunteers and 11 patients with pancreatic cancer were studied. Five of the 11 patients had their cancer located in the head, 4 in the body and 2 in the tail of the pancreas. Histological examination proved that all cases had ductal cell carcinoma. In the patients with pancreatic cancer, 6 had secondary diabetes mellitus and 7 showed excretory dysfunction (Table 2). Informed consent was obtained from all the patients before the examination.

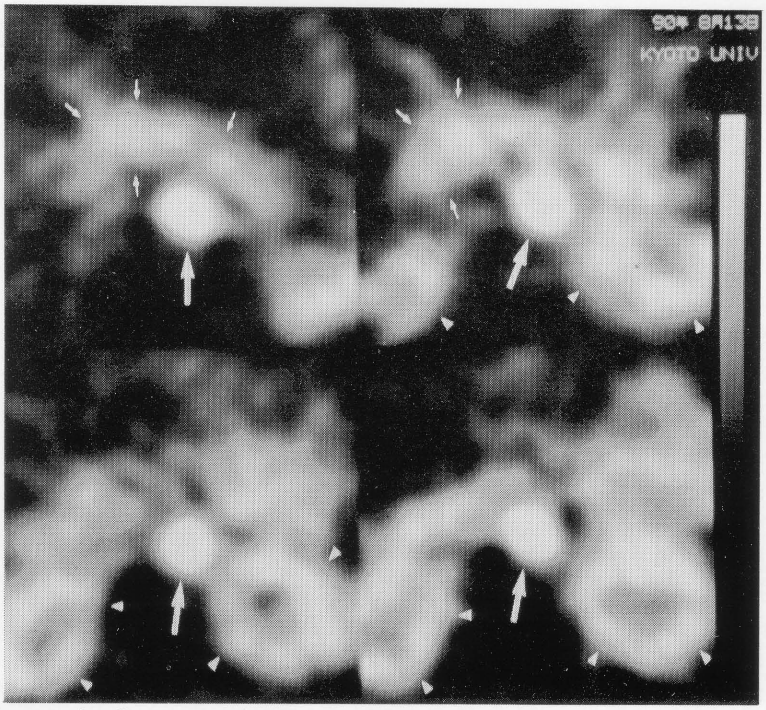

Fig. 1 Consecutive four transaxial images of functional mapping of blood flow in a normal subject. Pancreas is identified as high blood flow area (small arrows) anterior to the abdominal aorta (large arrows) as much as bilateral kidneys (arrow heads).

3) PET study procedure

Positologica III (Hitachi Medical Corporation, Japan) was used for all PET studies.[10] It has 4 rings with 192 BGO detectors in each ring, providing 7 tomographic images at 16 mm intervals. The intrinsic spatial resolution in the tomographic plane is 7.6 mm FWHM at the center, and the axial resolution is 12 mm FWHM. In this study, however, all PET images were reconstructed with a Shepp and Logan filter convoluted with Gausian function ($\sigma=2$ mm), and the spatial resolution fell to 9 mm FWHM in the clinical images.

The patient was positioned in the gantry to include the pancreas among 7 tomographic slices and the position of the pancreas was determined by ultrasonography prior to the study. After the transmission scan with a ^{68}Ga standard plate source, 200 to 400 MBq of ^{15}O-water was injected from the peripheral vein as a bolus, and a serial PET scan was performed every 4.5 seconds for 90 seconds. A total of 140 transaxial images were reconstructed from these data (7 slices $\times$ 20 frames). In addition to these serial dynamic images, PET images of the total 90 sec data were obtained by summation of 20 frames.

4) Calculation of pancreatic blood flow index (PFI)

The kinetics of ^{15}O-water in the pancreas was assumed to follow the single compartment model by Kety-Schmidt[11] and the differential equation (1) will hold.

$$dCi(t)/dt=f\cdot Ca(t)-(f/p+\lambda)Ci(t) \quad (1)$$

f: regional blood flow (ml/g/min)
p: distribution coefficient (ml/g)
$Ci(t)$: tissue tracer concentration (μCi/g)
$Ca(t)$: arterial tracer concentration (μCi/ml)
λ: decay constant

This equation can be solved on the assumption that p=1 to the equality (2) with convolution integration as:

$$Ci(t)=f\cdot Ca(t)* \exp\{-(f+\lambda)t\} \quad (2)$$

$*$: convolution

Therefore, PET data acquired for a certain period (t) can be expressed as follows:

$$\int_0^t Ci(t)dt=f\cdot\int_0^t Ca(t)* \exp\{-(f+\lambda)t\}dt \quad (3)$$

Regional blood flow (f) can be calculated by a look-up table method using equation (3) if $Ca(t)$ and $\int_0^t Ci(t)dt$ are obtained.[8] In this examination, however, $A(t)$ was used as an input function. $A(t)$ reveals activity in the region of interest (ROI) set on the abdominal aorta from the serial transaxial PET images instead of serial arterial blood sampling. Since the diameter of the abdominal aorta is not large enough for accurate determination of a tracer concentration, we calculated an index of regional blood flow (FI) in each pixel of the transaxial PET images acquired for 90 sec to do functional mapping

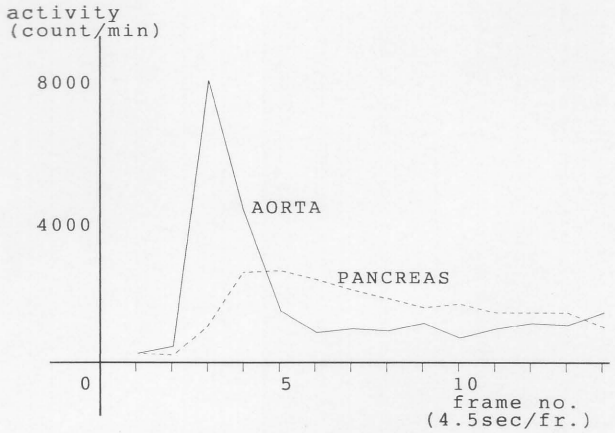

Fig. 2 Time-activity curve of the ROI set in the abdominal aorta obtained from serial PET measurement.

Table 1 Regional pancreatic blood flow index (PFI) of normal pancreas

Case No.	Age (year)	PFI
1	67	0.677
2	56	0.506
3	43	0.440
4	46	0.434
Mean	53.0	0.514
SD	9.4	0.098

of the blood flow index according to the following equation (4).

$$\int_0^t Ci(t)dt = FI \cdot \int_0^t A(t) * \exp\{-(FI+\lambda)t\}dt \quad (4)$$

The pancreatic regional blood flow index (PFI) was then determined by setting ROIs over the pancreatic regions in the obtained blood flow index images. To avoid a partial volume effect, ROIs were set on the central part of the pancreatic and tumor regions. PFI values obtained for each region were compared with each other by means of the paired t-test.

RESULTS

Normal pancreas was identified as a relatively higher blood flow region on the transaxial blood flow images obtained (Fig. 1). On dynamic images, the abdominal aorta was clearly identified from the 2nd to the 4th frame (4.5 to 18 seconds after injection). Figure 2 shows a time-activity curve for the ROI placed over the aorta. The mean PFI value for the normal pancreas was 0.514 ± 0.098 (Table 1).

In the patients with pancreatic cancer, not only the tumor but also the distal part of the pancreas (pancreatic tail in the patient with body cancer, for example) was not identified on the blood flow image (Fig. 3). The mean PFI value for the pancreatic cancer was 0.249 ± 0.076 (Table 2) with the ROI placed supposedly over the tumor whose site was determined from the X-ray CT image. The PFI of the distal part of the pancreas could not be determined precisely because of atrophic changes, but it was estimated to be not so high as that of the normal pancreas from its image. On the other hand, in the evaluation of the nontumorous proximal part from the tumor (pancreatic head in the patient with body cancer, for example), two patients had high PFI (>0.8) and 3 of the remaining 4 had a similar PFI (0.416–0.471) to that of the normal pancreas. Thus, the PFI revealed about the same level of blood flow (0.554 ± 0.211) as in the normal pancreas (Table 2).

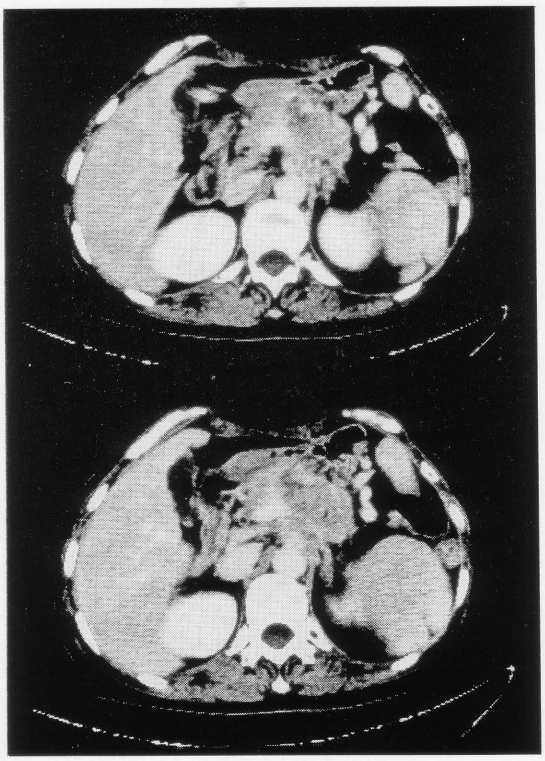

Fig. 3–1 X-ray CT images of the advanced pancreatic body cancer. An invasive large mass is identified in the pancreatic body and tail region.

Although a significant difference was observed between the normal pancreas and the pancreatic cancer ($p<0.01$) in the PFI, there was no significant difference between the normal pancreas and the nontumorous part proximal to the pancreatic cancer (Fig. 4).

DISCUSSION

Blood flow in the normal pancreas has been considered to be relatively high according to selective

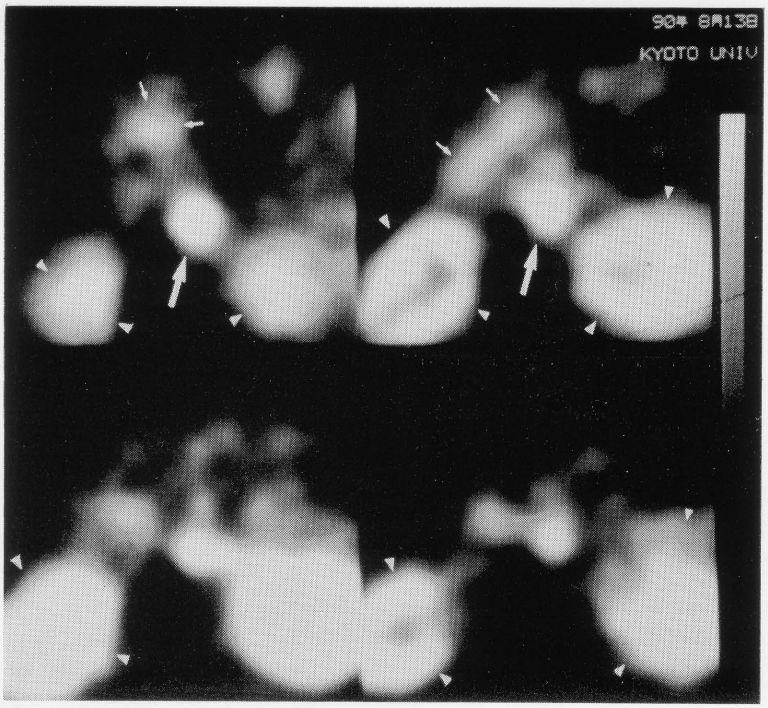

Fig. 3–2 Consecutive four transaxial blood flow images with the same patient as Fig. 3-1. Remained pancreatic head revealed high blood flow (small arrows), whereas the body and tail of the pancreas cannot be identified. Large arrows: aorta, Arrow heads: bilateral kidneys.

Table 2 PFI of pancreatic cancer

Case No.		Age (year)	PFI tumor	Remaining tissue	
5	head ca	57	0.372	<0.295	
6	head ca	43	0.296	<0.258	
7	head ca	75	0.286	<0.220	
8	head ca	77	0.236	<0.247	
9	head ca	69	0.198	<0.231	
10	body ca	51	0.267	0.876	
11	body ca	60	0.330	0.805	
12	body ca	49	0.280	0.471	
13	body ca	66	0.081	0.302	
14	tail ca	71	0.177	0.416	
15	tail ca	39	0.215	0.454	
Mean		59.7	0.249	0.250	0.554
SD		12.4	0.076	0.029	0.211
(Case No.)				(5–9)	(10–15)

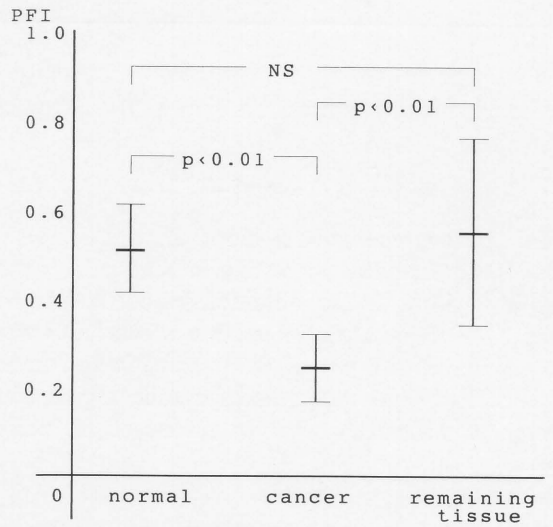

Fig. 4 RPBF of normal pancreas, pancreatic cancer, and nontumorous pancreatic head in body or tail cancer.

contrast angiographic findings but angiography has limitations in quantitative assessment of tissue blood flow. Pancreatic blood flow has been measured in dogs by several methods, including the electromagnetic flow meter,[12,13] radiolabeled gas clearance method[14,15] and radiolabeled microsphare method.[16] However, these methods require direct surgical manipulations, therefore, they cannot be applied to human studies. Moreover, the determination of pancreatic blood flow by direct measurement of the blood flow in pancreatic vessels is not possible because the pancreas is supplied by a number of arteries which also supply blood to other abdominal organs. The pancreatic head is supplied by the arcade arteries (superior pancreaticoduodenal and inferior pancreaticoduodenal artery) between the gastroduodenal and superior mesenteric artery which also supply the duodenum and small intestine. The

pancreatic body and tail are supplied by the splenic artery and its branches which also supply the spleen.

On the other hand, PET measurement of blood flow by means of the Kety-Schmidt model, which was originally applied to the brain,[11] can be applied to the pancreas also. The advantages of PET measurement are; (1) tissue perfusion of the interest region can be measured; (2) only venous injection of ^{15}O-water is needed with this method. Serial arterial blood sampling is usually required to determine the arterial input function ($Ca(t)$) in a conventional method.[8] We tried to estimate the arterial concentration of radioactivity from the serial dynamic PET images to simplify the examination. The reasonable shape of the time-activity curve was obtained by this method (Fig. 2). To avoid background influence on the input function, the first several frames (about for 15 to 20 seconds) are used as an input function. The problem with this method, however, is that the diameter of the abdominal aorta is not large enough to neglect a partial volume effect. This may cause underestimation of the input function and overestimation of the calculated blood flow. Therefore, we used the term pancreatic blood flow 'index' (PFI) in this study instead of absolute blood flow. Nevertheless, because the diameter of the abdominal aorta does not differ greatly among subjects, the possible error would not create serious problems in a comparison between patients. No subject in this study was seen to have an enlarged or small abdominal aorta in the X-ray CT images.

Pancreatic blood flow in dogs varied greatly according to the method, ranging from 30 to 120 ml/min/100 g-tissue.[12–16] Our results in normal subjects (0.514 ± 0.098) correspond to about 50 ml/min/100 g-tissue if the partial volume effects, both on the arterial input function (abdominal aorta) and on the pancreatic tissue activity, are ignored.

There was a significant difference between the blood flow in the normal pancreas (0.514 ± 0.098) and that in pancreatic cancer (0.249 ± 0.076), and there was no difference between the normal pancreas and the nontumorous part proximal to the pancreatic tumor (Fig. 4). The mean PFI value in the nontumorous pancreatic head of the patients with pancreatic body or tail cancer was 0.554 ± 0.211. However, the part of the pancreas more distal than the tumor revealed a severe decrease in PFI probably due to obstructive pancreatitis.

^{15}O-water is a widely used tracer for the mapping of brain function by PET. The major advantages with this method are that it is a non-invasive technique and the data acquisition time is relatively short. In addition, the short half life of ^{15}O (2 min) permits repeated measurements of regional blood flow, which may be suitable for assessment under various interventions. However, the accuracy of the measurement of tissue blood flow by this technique is limited, mainly owing to the partial volume effect, which may underestimate the radioactivity both for the input function and for the tissue activity. In addition, the tissue perfusion may be overestimated due to the underestimstion of the input function, so the flow index values in the pancreatic tissue were calculated instead of the true value for tissue perfusion. The atrophy of the pancreatic tissue associated with pancreatic cancer may be responsible for decreased PFI. Further studies with compartment analysis may clarify this point.

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