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Perfusion imaging of pancreas allografts using technetium-99m hexamethyl propylene amine oxime

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Abstract. The vascular integrity and major changes in perfusion can be determined by visual interpretation of radionuclide flow studies. We studied the potential of a new radiopharmaceutical technetium-99m hexamethyl propylene amine oxime (^{99m}Tc-HMPAO) in the particular setting of pancreas transplantation. Perfusion was measured by perfusion indices (PI). Changes in graft perfusion were estimated by three independent observers. A predefined scale from 0 to 4 was used, with 0 representing no visualisation of the graft and 4 denoting sharp countour delineation and distinct demarcation from the background. In order to investigate the relation between perfusion of the pancreas graft and its exocrine function, we measured the amylase excretion rate (AER) in the urine, expressed in units per hour. It is concluded that ^{99m}Tc-HMPAO is a suitable radiopharmaceutical for pancreas allograft imaging. For the assessment of the vascular integrity in the direct postoperative period, the scintigram is very reliable. Although a correlation between exocrine function of the graft and the perfusion score was not established, it is possible to make a clear sorting of AER measurements into different groups.

Key words: Pancreas transplantation – Perfusion – Scintigraphy – HMPAO

The early diagnosis and treatment of graft rejection and graft thrombosis are of major importance in pancreas transplantation since these grafts have little potential for recovery. The vascular integrity and major changes in perfusion can be determined by visual interpretation of radionuclide flow studies. Many different radiopharmaceuticals have been proposed, but each one has certain drawbacks. Background activity, bolus variations and changes in systemic flow often make it impossible to interpret the results. The potential of a new agent, technetium-99m hexamethyl propylene amine oxime (^{99m}Tc-HMPAO), was demonstrated in cerebral perfusion studies. This highly lipophilic complex passively penetrates biological membranes, as shown by a high brain uptake after IV injection. After passing the cell membrane, an intracellular reaction with glutathione takes place, converting the agent into a hydrophilic compound. Due to this intracellular metabolism, the compound remains in the cell and is not cleared from the tissue as easily as, for instance, the widely used perfusion marker in kidney transplantation, diethylene triamine penta-acetic acid (^{99m}Tc-DTPA). It is therefore possible to make static scintigraphic images in which the extraction of HMPAO is proportional to the regional perfusion of the graft. We studied the potential of ^{99m}Tc-HMPAO in the particular setting of pancreas transplantation.

Patients and methods

Pancreas transplantation was carried out in 20 diabetic type 1 patients (13 men, 7 women). Mean age at the moment of transplantation was 36 years. Of these 20 patients, 10 underwent a combined pancreas/kidney transplantation, 7 a pancreas-alone transplantation and 3 a pancreas subsequent to a kidney transplantation. The pancreas graft included a donor duodenal segment, and exocrine drainage was established via an anastomosis between the duodenal segment and the bladder. In case of pancreas-alone grafting, the donor spleen was always included to maintain the normal anatomical vascular interrelation. In those cases, the spleen was ex vivo irradiated with 1200 rad in order to prevent graft-versus-host disease.

The patients were studied in the supine position. After IV administration of 185–370 MBq ^{99m}Tc-HMPAO, images were taken with a large field-of-view gamma-camera (Gemini 700). Thirty frames of 2 s each were immediately followed by 50 frames of 30 s. Perfusion studies were carried out on the first day after transplantation, subsequently within the next 2 weeks and thereafter dependent on the clinical course.

Perfusion was measured by perfusion indices (PI). Changes in graft perfusion were estimated by three independent observers. A predefined scale from 0 to 4 was used, with 0 representing no visualisation of the graft and 4 denoting sharp contour delineation and dis-

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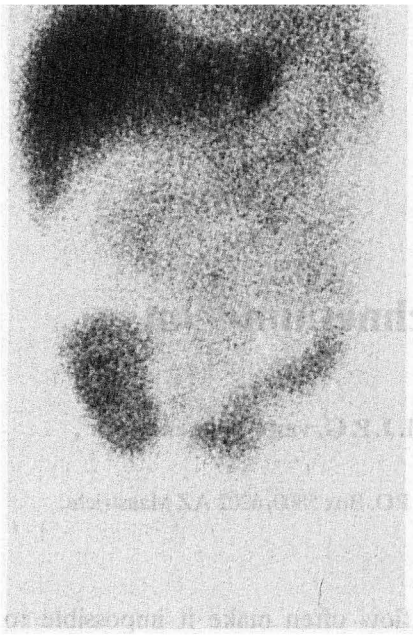

Fig. 1. Technetium-99m hexamethyl propylene amine oxime (^{99m}Tc-HMPAO) perfusion image obtained 20 min after injection. This patient received a combined pancreas/kidney transplantation. Both organs are visualised very well, and there is a high target-to-background ratio. Perfusion indices (PI) score was 4

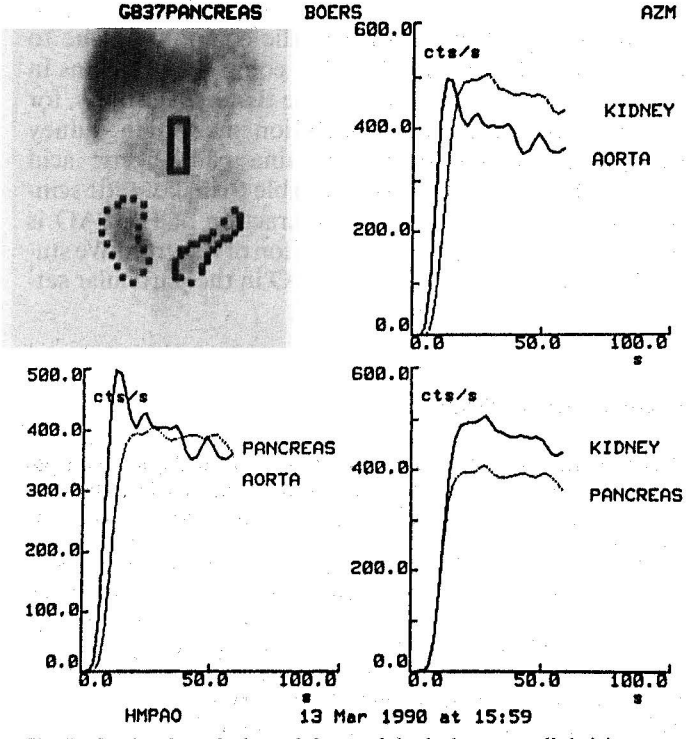

Fig. 2. Optimal perfusion of the graft includes a parallel rising configuration of the graft and aorta time-activity curves

tinct demarcation from the background. Furthermore, a semiquantitative analysis of aorta versus graft time-activity curves was performed.

In order to investigate the relation between perfusion of the pancreas graft and its exocrine function, we measured the amylase excretion rate (AER) in the urine, expressed in units per hour.

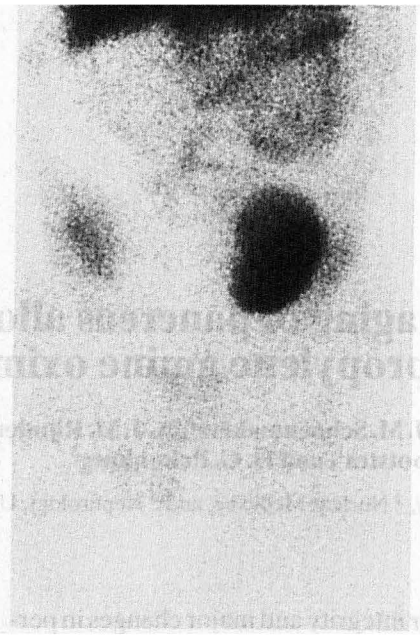

Fig. 3. Typical scintigraphic image of pancreas graft thrombosis. This patient received a combined pancreas/kidney transplantation. However, no activity is seen in the lower right abdomen and in the area of the aortal bifurcation, where the pancreas was transplanted. The simultaneously transplanted kidney has a good perfusion

Results

Quality of the scintigraphic images

The ^{99m}Tc-HMPAO scintigraphic images had a high target-to-background ratio. Static images with clear definition of the inserted grafts were obtained up to 20 min after administration of the tracer (Fig. 1). Optimally perfused grafts (PI = 4) showed parallel rising configurations of the graft and aorta time-activity curves (Fig. 2). The results were not affected by variation in the bolus injection, systemic flow or organ depth. Uptake of the tracer reflected the regional perfusion of the graft.

Vascular integrity assessment

In the direct postoperative period (within 24 h after transplantation) HMPAO scintigraphic studies invariably indicated in 4 patients a non-perfused allograft with a PI score of 0 (Fig. 3). The AER was minimal in these patients (less than 400 U/h). Exploration of the grafts showed thrombosis in 3 and accelerated acute rejection in 1 patient. In-

Table 1. Relationship between relative amylase excretion rate (AER%) and PI score 3 months after transplantation

	n	Mean AER%	Interval
PI = 0	9	3%	0.5–14.5
PI = 1	8	9%	1 –30.5
PI = 2	8	74%	1.3–97.8
PI = 3	8	82%	52.3–95.8
PI = 4	1		

itial PI scores from 2 to 4 were found in 16 patients. All these patients had AER above 4000 U/h.

In patients who had received a combined pancreas/spleen transplant, variable persistent reductions in perfusion of the spleen with time were observed up to the point at which there was almost no splenic uptake at all. This reduction in splenic perfusion did not affect the pancreas perfusion. Histological studies of spleens removed 7 months after transplantation revealed extensive fibrosis.

Relation between PI score and AER

There was no relation between the magnitude of the PI score and that of the AER. In order to be able to compare results between recipients, the AER had to be expressed as a percentage of the maximum observed rate (AER %) in each recipient.

In the first 3 months after transplantation, no statistical correlation between AER % and PI score could be established. HMPAO scintigraphic studies failed to detect acute rejection in 6 out of 10 cases.

In 10 of the 20 patients, the follow-up was long enough to evaluate the relationship between AER % and PI score after 3 months (Table 1).

The overall effect of differences in AER % between PI scores was significant ($P < 0.008$; Kruskas-Wallis 1-way ANOVA test). This effect was mainly caused by the significant difference between groups PI = 1 and PI = 3 ($P < 0.011$; Wilcoxon rank sum test). During long-term follow-up, both AER % and PI score exhibited gradually decreasing values. Histological examination of the pancreas graft at 9 months' follow-up in 2 patients with a PI score of 0 revealed chronic rejection with extensive fibrosis.

Discussion

With HMPAO scintigraphic studies it is possible to assess perfusion in pancreas allograft recipients. The quality of the scintigraphic images is high, and extraction of the lipophilic compound is proportional to the regional perfusion of the graft.

Non-perfused allografts were invariably discriminated with a PI score of 0 in our study. This makes ^{99m}Tc-HMPAO scintigraphy a very reliable method for detecting early graft thrombosis.

Acute rejection was not detected in all cases. This is probably due to the fact that the macrovascular changes caused by acute rejection do not appear as rapidly as, for instance, clinical and laboratory findings. If HMPAO is employed as a promising tool for pancreas allograft rejection, the value of monitoring becomes questionable.

Although a clear correlation between PI scores and the AER was not found, PI scores stratified AER measurements 3 months after transplantation. Furthermore, a gradual persistant decline of values was observed in the PI scores as well as in the AER, indicating the relationship between chronic rejection and deteriorating graft perfusion.

In summary, ^{99m}Tc-HMPAO is a suitable radiopharmaceutical for pancreas allograft imaging. For assessment of the vascular integrity in the direct postoperative period, the scintigram is very reliable. Although a correlation between exocrine function of the graft and the PI score was not established, it is possible with the PI score to make a clear sorting of AER measurements into different groups.

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Prospective analysis of pancreatic grafts with duplex-Doppler ultrasound: value of resistive index in the diagnosis of rejection

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The diagnosis of rejection and its differentiation from other causes of pancreatic graft dysfunction remain the basic problem in pancreas transplantation. A previous study with pulsed Doppler (PD) done at our institution demonstrated an increase of the resistive index (RI) during pancreatic graft rejection episodes [1]. The aim of the study was to determine prospectively the utility of duplex-Doppler (DD) ultrasound (US) in identifying the cause of pancreatic graft dysfunction. The major clinical categories were graft rejection and graft pancreatitis.

Key words: Duplex-Doppler ultrasound, pancreatic rejection – Pancreatic rejection diagnosis

Patients and methods

The study group included 23 whole pancreas grafts transplanted in to 22 patients (16 male, 6 female; mean age 36 years). Eighteen patients had combined kidney/pancreatic grafts from the same donor, 3 patients had sequential (not simultaneous) kidney and pancreatic grafts, and 2 patients had pancreas-alone grafts. The surgical technique consisted of whole pancreas transplantation with anastomosis of the graft's portal vein and celiac trunk to the recipient vena cava and iliac artery, respectively. The exocrine graft secretions were drained into the urinary bladder. DD examinations were performed with a 3.75-MHz transducer. Pancreatic size, echostructure, perigraft and intra-abdominal fluid were evaluated by US. The PD study was done to assess the permeability of the vascular pedicle at the hilar level. A venous and arterial Doppler spectrum (DS) were also obtained at the graft parenchyma (head, body, tail). The arterial DS was quantified by the RI [RI = (peak systolic velocity – end diastolic velocity)/peak systolic velocity], and the final RI was derived from the average of the 3 parenchymal levels sampled in the study. All patients underwent a baseline study 48–72 h after grafting, during graft dysfunction episodes and in the follow-up investigation.

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The diagnosis of graft pancreatitis was based on clinical data (abdominal pain), increase of serum amylase and lipase levels (> 800 U/l or > 400 U/l, respectively), improvement after urinary drainage, rise of cytomegalovirus immunoglobulin (IgG)/IgM antibody or pancreatic biopsy (+) revealing inclusion bodies. The rejection status of the graft was based on clinical data (pain, temperature > 38 °C), reduction of urinary amylase levels (> 50% of normal pre-rejection value), fluctuations of serum amylase level and improvement after rejection treatment.

Results

Normal grafts have a homogenous structure, and the graft size did not exceed the expected dimensions of a normal pancreas. Peripancreatic fluid was found in 22.7% of these grafts after surgery, but it did not persist more than 6 weeks in uncomplicated cases. On PD examination, the venous spectrum consisted in a continuous flow. The arterial waveform was characterized by a systolic peak followed by a continuous flow throughout diastole. No significant differences were observed between RI on baseline exploration (0.63 ± 0.01) and those obtained in stable grafts (0.62 ± 0.01). Nineteen episodes of graft pancreatitis were diagnosed, being documented at a mean time after transplantation of 246 ± 58 days ($r = 11$–850). The aetiology of these episodes was bladder dysfunction or urethral stenosis in 13 and infection in 5 (cytomegalovirus infection in 4, urinary tract infection due to *Pseudomonas aeruginosa* in 1). The cause of the remaining episode could not be determined. US results were pathological in 10 of 19 episodes of graft pancreatitis, disclosing perigraft fluid ($n = 10$), hypoechogenicity ($n = 2$) and heterogenous echostructure ($n = 1$). No increase of RI was observed during the episodes of graft pancreatitis: mean RI was 0.61 ± 0.001, which is not significant when compared with RI prior to the episode of graft pancreatitis (0.63 ± 0.006) and with RI in stable grafts.

Some 24 episodes of pancreatic graft rejection were diagnosed; simultaneous kidney/pancreas rejection in 13 and pancreas-alone rejection in 11. Rejection episodes occurred at a mean time after transplantation of

54 + 11 days (r = 7–235). Kidney graft rejection preceded the pancreas rejection in 6 episodes. US results were pathological in 14 episodes of graft rejection, disclosing perigraft fluid (n = 9), increase of graft size (n = 8), heterogenous echostructure (n = 8), hypoechogenicity (n = 3) and duodenal wall oedema (n = 1). PD showed an increase of RI in 18 episodes of pancreatic graft rejection: mean RI was 0.75 + 0.03 in simultaneous kidney/pancreas rejection. These values were statistically significantly higher, $P < 0.001$, when compared with basal pre-rejection values; the mean increase of RI was also significantly higher in isolated pancreas rejection (38 %) than in cases of simultaneous kidney/pancreas rejection (22 %). Reversal of the rejection was seen in 18 episodes (75 %). Loss of pancreatic function occurred in 6 episodes, with progressive worsening on PD study in spite of rejection therapy.

In conclusion, real-time US abnormalities were more prominent in pancreatic graft rejection than in graft pancreatitis. The RI in graft pancreatitis was not significantly different than that in stable grafts. Rejection was associated with a significant drop of the urinary amylase activity and a marked increase of RI. The mean increase of RI over basal values was 22 % in pancreas grafts with simultaneous kidney rejection and 38 % in isolated pancreas graft rejection.

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