

The Venous Thrombosis of the Pancreatic Graft

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Abstract

Background and aims. Venous thrombosis of the pancreatic graft is the main nonimmunological cause of the loss of transplants. It has a frequency between 0.8 to 20% according to literature. In this study our team tried to identify the risk factors related to the donor, the recipient and the surgical techniques involved. **Methods.** The study was conducted in the Department of Transplant Surgery, University Hospital Strasbourg-Hautepierre. 37 patients, with type I diabetes who had been submitted to 7 transplantations of segmentary pancreas and 30 of total pancreas and kidney during 09.07.1992 and 14.08.2006 were included in the study. The surgery comprised the retroperitoneal placement of the pancreas and kidney and the anastomosis with the urinary bladder. **Results.** In the immediate evolution we observed 4 thromboses (10.5%). All 4 thromboses were in the group of kidney and total pancreas transplantations. Two of these 4 patients were retransplanted and presented recurrence of thrombosis at 17 days and 1 year. **Conclusions.** To prevent thrombosis, it is necessary to perform surgery which avoids unnecessary handling and which ensures broad, tension free vascular anastomoses. The method of early monitoring by pulsed Doppler related to the biological data and the clinical state are suggestive to diagnose thrombosis. The venous thrombosis of the graft implies pancreatic explantation. Retransplantation in patients who have undergone thrombosis of the graft is possible only in well selected patients.

Key words

Transplantation - pancreas - venous thrombosis

Introduction

The discovery of Insulin by Banting and Best in 1922 changed the prognosis of type I diabetes - from a rapid

lethal disease to a chronic disease. Unfortunately, the exogenous administration of insulin does not allow perfect control of diabetes. Consequently, it has been clearly established that the degenerative complications induced by diabetes are directly related to the quality of glycemic control (1).

Pancreatic transplantation currently seems to be the only treatment of type I diabetes able to establish a physiological glycemic balance. However, the toxicity of the immunosuppressor treatment, the surgical complications which are sometimes serious and the rejection of the graft, limit its indications.

One of the most frequent surgical complications is the venous thrombosis of the pancreatic graft (from 0.8 to 20% according to series) which has a complex and not fully understood pathogenesis (2,3).

The purpose of this study, performed on 39 pancreatic grafts, isolated or coupled with one or more organs (kidney, liver, heart) in 37 patients with type I diabetes, all of them presenting degenerative complications of diabetes, is to analyze the occurrence and the therapeutic control of venous thrombosis of the pancreatic graft.

Patients and methods

The study was conducted between 09.07.1992 and 14.08.2006 in the Department of Transplant Surgery, University Hospital Strasbourg-Hautepierre and was performed on 39 pancreatic transplantations which were carried out in 37 patients insulin-dependent diabetics represented by 12 women and 25 men. The average age of the patients was 37.4 ± 7.4 years. The average duration of evolution of diabetes mellitus was 22.7 ± 6.6 years. Four patients had an early venous thrombosis of the graft (10.5 %).

All the patients in the study received the same immunosuppression. The treatment consisted of, immediately after transplantation, a quadruple sequential immunosuppression associating Solumedrol (2 mg/kg/day) in rapidly decreasing doses, Azathioprine (1 to 2 mg/kg/day) and Antilymphocytary Serum (60 mg/day) during 5 to 7 days, relayed by Cyclosporine (4 ng/kg/day), in order to

ensure a residual rate of cyclosporine ranging between 200 and 300 mg/ml.

All the grafts were taken and preserved with VIASPAN (the University of Wisconsin solution). All the grafts came from donors with ABO identity. The age of the donors was between 19 - 41 years. The cross - match was negative in all patients.

The pancreatic graft was considered functional when the *a jeun* glycemia was normal in the absence of exogenous insulin. The loss of the pancreatic graft has been defined by the need to resort to a final insulin treatment.

All the patients presented degenerative complications of the diabetes: 98 % peripheral neuropathy; 96 % retinopathy; 69 % severe macroangiopathy; 71 % of the patients had been dialysed for a period between 7 months and 15 years.

No anticoagulant medication was prescribed for the patients included in the study. Our series was arbitrarily divided into three groups: transplantation with segmentary pancreas; transplantation with total pancreas without vascular complications; transplantation with total pancreas followed by early venous thrombosis of the graft.

1. Transplantation with segmentary pancreas

This was carried out in 7 patients. They represented the first pancreatic grafts carried out in the Department. This group included 4 men and 3 women, average age of 39.6 ± 4.5 years, all in dialysis before transplantation. Six grafts were double (kidney-pancreas), and 1 was triple (kidney-pancreas-heart).

HLA compatibility was of 2 haplotypes in 2 cases, 1 haplotype in 4 cases and 0 in 1 case. In *ex vivo* for all the grafts, a splenic arteriovenous shunt was carried out. On the surgical level, the pancreatic and renal grafts were placed extraperitoneally in the iliac pits. The vascular anastomosis of the pancreatic graft was carried out on the iliac vessels. The immediate obliteration of the pancreatic duct with neoprene was carried out in 1 patient. Among 6 other patients, the Wirsung obliteration was performed later (approximately 5 weeks after transplantation). Pulsed Doppler monitoring was performed in all patients during postsurgical period (2nd and 5th day after surgery) and showed no particularities for this group of patients.

2. Isolated pancreas transplantation

This group consisted of 3 patients, all men, average age of 36.6 years. The duration of cold ischemia ranged between 8 and 14 hours, HLA compatibility less than 2 in all cases. The age of the donors ranged between 26 and 49 years. In *ex vivo*, arterial plasties using the junction of the internal and external iliac artery of the donor were performed in all the cases.

A venous prolongation plasty of donor's portal vein was not necessary. Among the patients of this group we did not perform a splenic arteriovenous shunt. The implantation of the duodeno-pancreatic block was extraperitoneal in all cases. The pancreatic exocrine secretion was drained in the urinary bladder using a duodeno-vesical anastomosis. The

vascular anastomosis of the pancreatic graft was carried out on the iliac vessels. All patients were submitted to postsurgery (2nd and 5th day) pulsed Doppler monitoring which showed no abnormality regarding the pancreatic graft.

3. Transplantation with total pancreas and kidney

This group consisted of 27 patients, 18 men and 9 women, average age of 36.5 ± 6.7 years. The age of the donors ranged between 16 and 52 years.

The duration of cold ischaemia ranged between 6 and 20 hours. HLA compatibility was 3 haplotypes in 2 cases, 2 haplotypes in 11 cases and less than 2 in the other cases. In *ex vivo*, arterial plasties using the junction of the internal and external iliac artery of the donor were performed in all subjects.

A venous prolongation plasty of donor's portal vein was performed in 15 cases. Among the patients of this group we did not perform a splenic arteriovenous shunt. The implantation of the duodeno-pancreatic block was extraperitoneal in all cases. The pancreatic exocrine secretion was drained in the urinary bladder using a duodeno-vesical anastomosis. The vascular anastomosis of the pancreatic graft was carried out on the iliac vessels. Pulsed Doppler was performed in all patients the 2nd and 5th day after surgery and showed in 3 of the cases venous thrombosis. In one case of venous thrombosis, pulsed Doppler showed no abnormality.

Thrombosis occurred in 4 male patients. In all of them, the anatomo-pathological study of the pancreatic graft confirmed pancreas necrosis with venous thrombosis. The presurgical general data of the receivers and grafts are presented in Table I. The surgical details related to the grafts and graft harvesting are presented individually.

Patient 1 - In *ex vivo*, interposition of a iliac venous graft extended to the portal vein; double arterial pedicle with splenic and superior mesenteric artery joined together on the internal-external iliac arterial fork of the donor; grafting the pancreas in termino-lateral on the vein and the external iliac artery in extraperitoneal right. We did not resort to the mobilization of the hypogastric vessels. Splenectomy was performed after vascular reconstruction without splenic arteriovenous shunt. The exocrine pancreatic drainage was done in the bladder; kidney grafted in the left iliac pit; peri-surgical period without complications.

Patient 2 - In *ex vivo*, arterial plasty using the internal and external iliac junction of the donor anastomosed with the splenic and superior mesenteric artery of the graft; the pancreas was grafted extraperitoneally in the right iliac pit; end-to-side venous anastomosis between the portal vein of the graft and the common iliac one after section of the hypogastric ones; arterial anastomosis was carried out end-to-side on the external iliac artery. The exocrine drainage of the pancreas was done by using duodeno-vesical anastomosis. Peri-surgical period without complications.

Patient 3 - In *ex vivo*, the splenic artery and the superior mesenteric artery of the graft were joined together by the fork of the internal and external iliac artery of the donor; pancreas grafting made extraperitoneally in the right iliac

Table I The presurgical general data of the receivers and grafts in patients who developed venous thrombosis

No.	Age	Duration of evolution of diabetes	Complications	Blood group/Rh	HLA	Cold ischemia
1	42	36 years (insulin pump)	- rethinopathy - peripheral neuropathy - terminal renal failure (6 years of dialysis) - high blood pressure - hipercholesterolemia	A+	No compatibility	16 hours
2	41	30 years	- terminal renal failure (insulin pump) - rethinopathy - high blood pressure - peripheral microangiopathy	B+	No compatibility	14 hours
3	41	30 years	- rethinopathy - neuropathy - recent terminal renal failure	A+	HLA compatibility	10 hours
4	32	10 years	- terminal renal failure - high blood pressure - neuropathy	A+	No compatibility	6 hours

pit; venous anastomosis was of end-to-side type, performed between the portal vein and the external iliac one; arterial anastomosis was end-to-side on the external iliac artery. After declamping, the central venous pressure rose to 8 cm of H₂O. We observed immediately thrombosis of the splenic artery in its distal part. We performed ligation of the splenic artery upstream of thrombosis and an excellent recoloration of the pancreatic graft was observed.

Patient 4 - *In vivo*, the celiac trunk was preserved with the pancreas. It was branched to the superior mesenteric artery by a "Y" patch of the donor's iliac graft. The pancreas grafting was done in extraperitoneal. Venous anastomosis was of end to side type between the portal vein and the inferior vena cava. Arterial anastomosis was end-to-side type on the aorta. The exocrine drainage of the pancreas was done by duodeno-jejunal anastomosis (in "Y" a la Roux). The renal graft was placed extraperitoneally in the right iliac pit. In peri-surgical, haemorrhage occurred at the level of the pancreatic graft at the time of declamping. The bleeding was controlled quickly.

Results

1. Transplantation with segmentary pancreas: no immediate or late vascular complications; 3 functional pancreatic grafts 8, 7, 5 and 6 years after transplant; 2 nonfunctional pancreatic grafts following chronic rejections. There were 2 deaths: one at the 8th postoperative day following severe pancreatitis - the patient with the obliteration of Wirsung during transplantation - complicated by MSOF; and one in the 16th month, ARDS during treatment with OKT 3 for corticoreistant rejection.

2. Isolated pancreas transplantation

No immediate or late vascular complications; all grafts were functional 18 to 48 months after transplant.

3. Transplantation with total pancreas and kidney

Fifteen functional pancreatic grafts 16 to 58 months after transplant; 4 nonfunctional pancreatic grafts following

chronic rejections. There were 4 deaths: 1 because of post-surgery MSOF following an early pancreatic leakage; 1 unexplained - death in residence (no necropsy carried out) 27 months after double transplantation whereas the pancreatic and renal functions were normal; 1 cerebral haemorrhage 38 months after transplantation in a patient turned back to hemodialysis but with a satisfactory pancreatic function not requiring insulin; 1 myocardial infarction in the 44th month in a hemodialysed insulin treated patient. Four patients presented venous thrombosis of pancreatic graft requiring explantation.

Clinical symptomatology, biological changes, and the radiological diagnosis of venous thrombosis are presented in Table II. The pancreatic retransplantation after a first thrombosis of the graft was performed on patients 1 and 2. The two attempts showed failures and the repetition of venous thrombosis, one 17 days and the other 1 year after explantation. Our results are similar with the results of the most published series (4-6).

Discussion

The venous thrombosis of the pancreatic graft is the main cause of the early loss of transplant. Most statistics found this complication at a frequency of 0.8 % to 20 %. Its pathogenesis is complex and not clearly explained. The pancreas has a reduced circulatory flow in comparison to other internal organs (roughly 1.3 % of the cardiac flow). This ratio remains identical in the graft, no matter what vascular technique is carried out. The changes of microcirculation on the level of the grafted pancreas play a paramount importance in the occurrence of venous thrombosis, and are represented by the following sequence: reperfusion - cellular death - edema - increase in local resistance to blood flow (2). In our study we tried to analyze the causes which led to the occurrence of venous thrombosis in our grafted patients. The factors which we

Table II Clinical symptomatology, biological changes and radiological diagnosis of venous thrombosis

Patients	Transplant	Date of diagnosis/ days post surgery	Clinical state	Biological state	Radiology
1	First transplant Kidney + total pancreas	Day 5 Day 7 explantation	Hematuria	Hyperglycemia	Doppler: absent venous pulsation
2	First transplant Kidney + total pancreas	Day 4 Day 5 explantation	Edema of the right lower limb		Phlebography : ilio - femoral thrombosis
3	Kidney + total pancreas	Day 5 Day 5 explantation	Deterioration of the clinical state	Hyperglycemia	Doppler day 2 – no particularity
4	Kidney + total pancreas	Day 2 Day 2 explantation	Oligoanuria Dark color blood on the intraperitoneal drains	Hyperglycemia Hyperamylasemia Amylase +++ in the intraperitoneal fluid	Doppler: no vascular signal

considered for the analysis as potential causes of these thromboses are dependent on the donor, the surgical technique, the hemodynamics during the surgery, the receiver and the peri-surgical period (anticoagulation, hemodynamic monitoring).

The age of the donor is a factor upon which the majority of the authors agree. The accepted higher limit is 45 years. Above this limit, age has a negative influence on the long-term function of the graft (7). In our series, all donors are located below this limit, except one (52 years). For the group of the patients presenting an early venous thrombosis, the age of the donors ranged between 15 and 40 years, with an average of 31.2 years.

ABO identity between receiver and donor is desirable (8). In our series, we performed 2 pancreatic retransplantations in compatible but nonidentical ABO group patients. In patients who presented an early venous thrombosis of the first graft, a repetition of venous thrombosis occurred up to 17 days and respectively 1 year after surgery. It is hazardous to suggest, on only 2 observations, that ABO nonidentity plays a part in the venous thrombosis pathogenesis. We can only acknowledge this coincidence and conclude that it is preferable to choose an identical ABO graft.

Regarding HLA identity, it does not have any influence in the occurrence of venous thrombosis in our patients.

During harvesting, it is necessary to avoid any unnecessary handling of the gland by using proper surgical techniques (9). There are authors who recommend administration of high amounts of steroids, which would have a role in preventing the edema of the gland which appears during perfusion with the cooling liquid and during mobilization of the internal organs (10). In our series, we never used steroids in the donors during the phase of explantation. The liquid of conservation was the solution of VIASPAN®, unanimously considered as the best, as it makes possible the preservation of the pancreas for 30 hours (11). The world's longest reported duration of cold ischemia was 34 hours with a functional pancreas immediately after revascularisation. Some studies do not find any correlation between the duration of cold ischemia and possible

complications if duration is lower than 24 hours (3,10). Considering these results, we can estimate that cold ischemia, if lower than 24 hours, does not influence the occurrence of venous thrombosis. The presurgical general data regarding the receivers and grafts (cold ischemia, ABO identity, HLA compatibility) are presented in Table I.

Two different processes are recommended for venous anastomosis and both have as purpose to decrease the risk of venous thrombosis. Certain authors suggest a venous anastomosis between a short portal segment and an iliac vein well mobilized, after the ligation of the hypogastric branches. This technique avoids portal angioplasty (12). Other authors will prefer a long portal segment (possibly extended in *ex vivo*), anastomosed with an external or primitive iliac vein without excessive mobilization and section of the hypogastric branches (13). We always carried out broad, tension free venous anastomoses. We are convinced that these conditions play a paramount importance in the prevention of venous thrombosis.

As the majority of the pancreatic grafts are coupled with renal grafts, many authors recommend a vascular filling with diluted albumin to increase the oncotic pressure and thus decrease the pancreatic edema. To ensure a more precise monitoring of the hemodynamic state of the patient, we usually used a Swan-Ganz catheter, in agreement with the majority of the authors (12).

It has been pointed out that the age of the receiver (<45 years) associated with a satisfactory cardiovascular state has a major importance for the immediate success of the grafts and the long-term functionality of the pancreatic graft (14). In our series, a cardiac and vascular careful assessment was carried out in all receivers. Four of them had undergone coronary bypass before transplantation and two of them developed an early venous thrombosis of the pancreatic graft. As already mentioned, all our receivers were younger than 45 years at the time of transplantation.

In most studies, venous thrombosis is more frequent in male patients, and this is also the case in our series. One of the established complications is the narrowness of the male pelvis compared with that of the female (10).

The problem of postoperative anticoagulant medication

remains uncertain. In all studies, the occurrence of venous thrombosis is fast, most frequently between 12 hours and 5 days. It has been shown that a hyperinsulinemia settles immediately after declamping. Insulin favors platelet aggregation and induces a state of hypercoagulability (15). We could assume that the massive insulin release in the systemic venous circulation of the graft can favor local venous thrombosis on the level of anastomosis. To confirm this, investigation studies must be carried out to compare venous anastomoses: pancreatic graft and portal system versus pancreatic graft and systemic circulation (16). Considering the fast developing nature of venous thrombosis, anticoagulant or antiaggregant medication must be carried out immediately after surgery. There are three approaches: systematic anticoagulation, antiaggregant medication and no anticoagulant or antiaggregant medication.

The great disadvantage of the anticoagulant treatment is the high risk of hemorrhagic complications, that is why many teams are reluctant to use it. In our series, we did not use anticoagulant treatment, except for one patient in whom we used a low molecular weight heparin. This patient presented a venous thrombosis of the first pancreatic graft (total), 7 days after transplantation. A retransplantation (segmentary pancreas) was decided upon and carried out 24 hours after explantation. In the 7th post-surgery day the patient presented acute kidney rejection with oligoanuria, the reason for which 4 hemodialysis sessions were necessary. During each hemodialysis session, 0.3 ml of low molecular weight heparin was used. The low molecular weight heparin administration did not prevent the occurrence of venous thrombosis after 10 days. Moreover, an accident due to its use (spontaneous haematoma of the abdominal wall requiring a surgical reintervention) occurred. This confirms the assertion that the anticoagulant treatment has hemorrhagic risk. Also it is interesting to assess the von Willebrand factor role, which was observed as being high in several cases of venous thrombosis of the graft (17). Platelet antiaggregant medication has many supporters. In a series which gathers 100 double consecutive kidney-pancreas grafts, only 2 venous thromboses occurred (18). Other teams that used anticoagulant or antiaggregant for disease prevention, published results of venous thromboses about 10 to 20%. Several series have exceptional results by using antiaggregant or anticoagulant medication (13, 18). Monitoring by thrombelastography may be useful in order to assess the efficacy of this medication (19). As for our series, we never used antiaggregant or anticoagulant treatment after the first transplantation. However, regarding the results, it seemed sensible to us to start antiaggregant medication in order to prevent the disease.

Immunosuppression was identical in all patients.

Regarding clinical, biological and radiological monitoring in peri-surgical period, in our series, pulsed Doppler color echography was used routinely and systematic examination was carried out in day 2nd 5 post-surgery. Pulsed Doppler echography does not always allow for a

cert diagnosis, and the vascular anomalies found during this examination must be confirmed by angiography (20). The importance of pulsed Doppler is also underlined by other studies (21). Taking into account the observations of our series, any deterioration of the clinical state with associated disturbances of the biological assessment (hyperglycemia or hyperamylasemia) must lead to a Doppler pulsed color echography and vascular thrombosis should be suspected. The angiography will be essential in case of uncertain diagnosis.

Regarding the surgical approach in the case of venous thrombosis of the pancreatic graft, the majority of teams prefer explantation to reperfusion (2, 22, 23). Reperfusion can be reduced to anticoagulant medication for 3 months in total venous thrombosis and only aspirin for partial thrombosis (24). This therapy is related to an early diagnosis of thrombosis (25). Other studies for reperfusion consider trombectomy associated with heparin followed by oral anticoagulation to be effective (26). Finally, this conduct is dictated by the serious deterioration of the clinical state (pancreatitis) associated with the malfunction of the renal graft (oligoanuria). After explantation, the clinical state as well as diuresis improves quickly. In the event of the association between venous thrombosis and partial graft necrosis (caudal area), thrombectomy and resection of the compromised tissue is an alternative with random results (27-29). Our solution was, in all cases, the explantation, as at the time of the intervention we regularly found ourselves confronted with a completely necrotised gland.

Conclusions

Venous thrombosis of the pancreatic graft is an early phenomenon (in 90% of the cases in the first 5 postsurgery days). The age of the donor and that of the receiver must be below 45 years. During harvesting, all unnecessary handling of the gland must be avoided. The duration of cold ischemia should be less than 24 h. Identical ABO grafts should be preferred. HLA identity does not play a part in the pathogenesis of venous thrombosis. Vascular anastomoses must be broad and tension free. In peri-surgery, the use of a Swan-Ganz catheter is necessary in order to adjust the vascular filling to the hemodynamic state of the patient as best as possible. Immunosuppression does not play a part in the occurrence of venous thrombosis of the pancreatic graft. Fast and early deterioration in the clinical and biological state are important signs of venous thrombosis of the pancreatic graft. Pulsed Doppler examination is very useful in the follow-up of the vascular state of the pancreatic graft. We recommend pancreatic explantation in the case of a venous thrombosis. After the first venous thrombosis of the pancreatic graft, retransplantation seems to us hazardous.

Conflicts of interests

None to declare.

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