Transpl Int (1999) 12: 50–55

ORIGINAL ARTICLE

B. Vollmar
J. Janata
J. Yamauchi
B. Wolf
M. Heuser
M.D. Menger

Exocrine, but not endocrine, tissue is susceptible to microvascular ischemia/reperfusion injury following pancreas transplantation in the rat

Received: 4 June 1998
Received after revision: 17 September 1998
Accepted: 25 September 1998

B. Vollmar (✉) · J. Janata
J. Yamauchi · B. Wolf
M. Heuser · M.D. Menger
Institute for Clinical &
Experimental Surgery,
University of Saarland,
D-66421 Homburg/Saar, Germany
Fax: + 49 6841 166553
e-mail:exbvol@med-rz.uni-sb.de

Abstract While post-transplant pancreatitis is still a frequently occurring complication of whole pancreas transplantation, dysfunction of the endocrine tissue is rarely observed. Given that microcirculatory disorders play a major role in the pathogenesis of pancreatitis, we hypothesized a dissociation of endocrine and exocrine microvascular control in pancreas transplantation (cold ischemia-reperfusion) and studied this dissociation quantitatively, analyzing the pancreatic microcirculation after heterotopic isogeneic pancreaticoduodenal transplantation in rats by means of fluorescence microscopy. Functional capillary density (FCD) of both exocrine and endocrine tissue of pancreatic grafts after 1 h of cold storage in HTK solution did not differ when compared to sham-operated, time-matched controls. Intermittent capillary perfusion, which is absent under sham control conditions and which is proposed to be operative as a compensatory mechanism to counteract malperfusion, was observed in 52% of the exocrine, but in only 8% of the endocrine, tissue studied ($p < 0.05$). In contrast, cold storage of pancreatic grafts for 6 h in HTK resulted in a complete loss of intermittent capillary perfusion in exocrine tissue and, consequently, marked exocrine perfusion failure (decrease in FCD), while FCD of pancreatic endocrine tissue was preserved without any significant change in the incidence of intermittent capillary perfusion. Thus, our results indicate a higher susceptibility of the exocrine pancreas to cold ischemia/reperfusion events that is associated with significant alterations in nutritive perfusion and, thus, with limitations of the oxygen supply to the tissue. This may lead to inflammatory tissue reactions in the clinical setting of pancreas transplantation.

Key words pancreas transplantation, rat · exocrine tissue, reperfusion · Endocrine tissue, reperfusion · Microcirculation

Introduction

Pancreas transplantation is presently the only established method to achieve long-term normoglycemia in patients with diabetes mellitus. In the last decade, the technical success rate of pancreatic grafting has markedly improved and now approaches the results of other solid organ transplants [27, 29, 30]. This is due to improved surgical techniques (2, 24), progress in organ procurement and preservation [4], and new types of immunosuppression [18, 25]. However, vessel thrombosis and graft pancreatitis with the risk of acute graft failure are still major problems in pancreas transplantation. While graft thrombosis occurs in 10%–30% of reported cases, requiring removal of the gland, the incidence of post-transplant graft pancreatitis can range anywhere

from 17% [5, 6] to 22% [8] to 35% [26] to 87.5% [3], and it can lead to the loss of an otherwise viable organ in 20%–100% of cases [20], depending on the severity of the disease. The clinical picture of post-transplant pancreatitis is ascribed to microvascular damage caused by ischemia and/or preservation of the organ, followed by reperfusion [3]. In contrast to inflammatory complications of the exocrine gland, ischemia/reperfusion-induced dysfunction of the endocrine tissue is rarely observed [31]. To elucidate this dissociation in the postischemic response, we studied the exocrine and endocrine tissue microcirculation using a rat model of pancreas transplantation and intravital fluorescence microscopy.

Materials and methods

The experimental protocol met the criteria established by German legislation on the protection of laboratory animals and set forth in the "Principles of laboratory animal care" (NIH publication No. 86–23, revised 1985).

Surgical procedure

Inbred male Sprague Dawley rats weighing 200–250 g were used throughout the study as either donors or recipients. After overnight fasting, but with free access to tap water, the animals were anesthetized with chloralhydrate (36 mg/100 g body weight i.p.). Spontaneous respiration was facilitated by tracheotomy, and body temperature was maintained between 36 °C and 37 °C by placing the animals in the supine position on a heating pad. PE 50 catheters were inserted into the left carotid artery and left jugular vein for sampling of arterial blood and continuous monitoring of arterial blood pressure and heart rate, as well as for intravenous injection of fluorescent dyes. Transplantation of the pancreas was performed according to the technique described in detail by Benetti et al. [1], anastomosing the graft's arterial supply and venous outflow to the left renal vessels of the recipient. After simultaneous release of the clamps, the pancreatic graft was gently exteriorized on a specially designed stage for microscopic analysis. To keep the exteriorized pancreas moist and to exclude the effect of ambient oxygen, the pancreatic surface was covered with oxygen-impermeable Saran wrap. Reperfusion of the pancreas was allowed for a period of 2 h.

Experimental protocol

A total of 17 recipient animals were divided into three groups. Animals in group 1 received grafts stored for 1 h in histidine-tryptophane-ketoglutarate (HTK) solution at 4 °C ($n = 7$). Grafts from group 2 were similarly stored in HTK, but for a period of 6 h ($n = 5$). Nontransplanted animals with exteriorization of the pancreas served as controls ($n = 5$).

Intravital fluorescence microscopy

At 15, 60, and 120 min after the onset of reperfusion, in vivo microscopy of pancreatic exocrine and endocrine tissue was performed using a modified Leitz-Orthoplan microscope (Leitz, Wetzlar, Germany) with a 100-watt mercury lamp attached to a Ploemopak illuminator with an $I_{2/3}$ blue filter block (excitation wavelength 450–490 nm, emission wavelength 515 nm, Leitz). For contrast enhancement, fluorescein-isothiocyanate (FITC)-labeled dextran (MW 150000; 50 µg/kg body weight) was injected intravenously. The observations were recorded by means of a charge-coupled device video camera (COHU FK 6990; Prospective Measurements, San Diego, Calif., USA) and transferred to an S-VHS video recorder (AG-7350-E, Panasonic, Tokyo, Japan) for off-line evaluation. Using a water immersion objective (W 25 x/0.60, Leitz), a final magnification of x820 was achieved on the video screen (PVM 2042 QM, diagonal 500 mm, Sony, Munich, Germany). The time of recording was 60 s per observation field.

Microcirculatory analysis

Quantitative analysis of the microcirculation of pancreatic exocrine and endocrine tissue included the determination of functional capillary density and intermittency of capillary perfusion, as well as measurement of capillary red blood cell velocity and capillary diameters.

As previously described [19, 35], functional capillary density (FCD), which is defined as the length of all blood cell-perfused nutritive capillaries per observation area (400 µm × 350 µm) and expressed in cm/cm^2 (cm^{-1}), was assessed in three endocrine and five to seven exocrine observation areas per time point in accordance with the method described by Schmid-Schoenbein et al. [23]. A grid system with a grid width of 41 mm, representing 50 µm, was superimposed on the video screen. By counting the number of intersections between the grid and the capillaries (N_c), FCD for each observation area was calculated in accordance with the equation $FCD = \pi/2 \cdot N_c/L$ [cm^{-1}], where L represents the total length of the grid system. Red blood cell velocity in capillaries was measured by frame-to-frame analysis. Intermittent capillary perfusion was defined as the alternate cessation of capillary blood flow (red blood cell velocity = 0 mm/s) and onset of capillary perfusion (red blood cell velocity > 0 mm/s), and its frequency is given in cycles per minute (cpm).

Statistical analysis

In accordance with the statistical procedure recommended by Looney and Stanley [16], data were first proven to fit the assumption of normality. After a multivariate analysis of interaction between time and group, differences between groups were tested by an analysis of variance, followed by an appropriate multiple post hoc comparison. To test for time effects separately for each group, a multivariate ANOVA for repeated measures was carried out, followed by the paired Student's *t*-test, including the correction of the α-error according to the Bonferroni probabilities for repeated measurements. All values are given as means ± SEM, and statistical significance was set at $P < 0.05$.

Results

Reperfusion was successful in all animals, with the pancreata returning to their normal pink color and the anastomosed vessels pulsating.

Quantitative analysis of the endocrine tissue in pancreatic grafts stored for 1 h revealed values of functional capillary density in the range of 450–500 cm^{-1} without

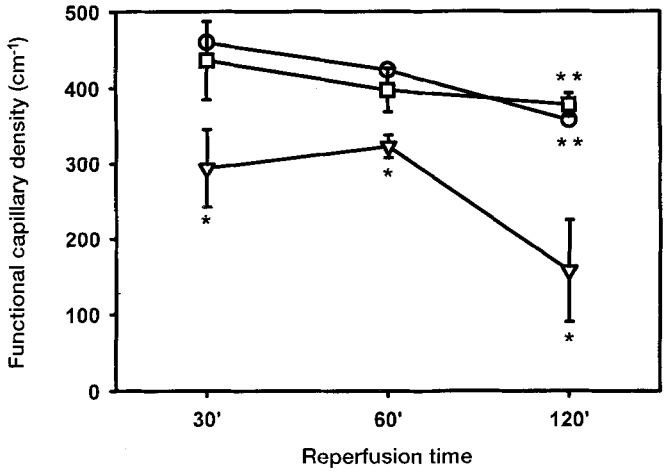

Fig. 1 Functional capillary density of rat exocrine tissue after whole pancreas transplantation, assessed by means of intravital fluorescence microscopy after either 1 h (*square*; $n = 7$) or 6 h (*triangle*, $n = 5$) of cold storage in 4 °C HTK solution and 30, 60, and 120 min of reperfusion. Nontransplanted animals with exteriorization of the pancreas served as controls (*circle*; $n = 5$). Values represent means ± SEM. * $P < 0.05$ vs controls; ** $P < 0.05$ vs 30 min of reperfusion by ANOVA, multiple post hoc comparison

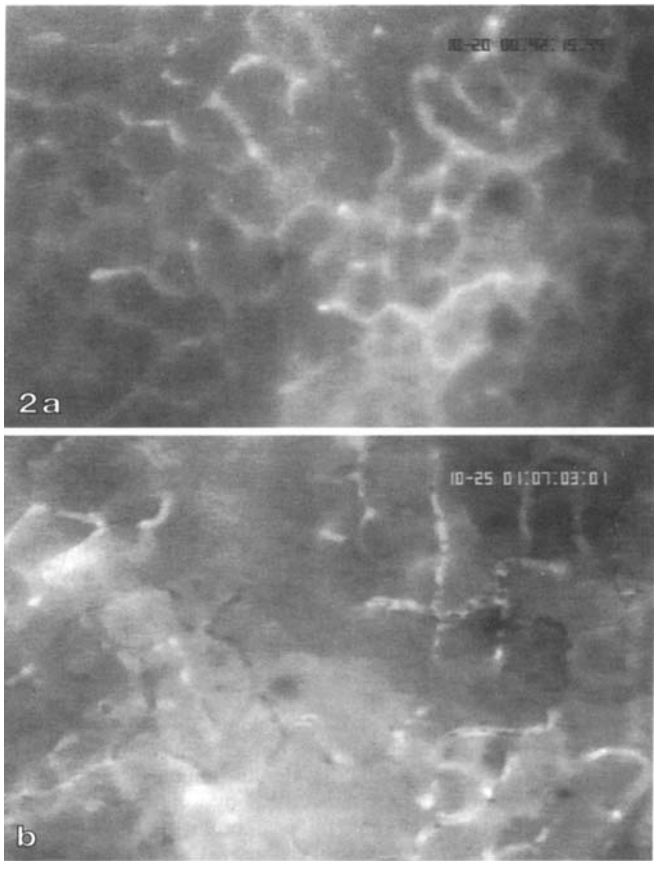

Fig. 2 A, B Intravital fluorescence microscopic images of rat exocrine tissue after **A** 1 h and **B** 6 h of cold storage in 4 °C HTK solution and 120 min of reperfusion in a model of whole pancreas transplantation. Note the remarkable perfusion deficits after the prolonged storage time of 6 h in contrast to the homogeneous perfusion pattern of the exocrine tissue after 1 h cold storage (magnification × 170)

significant changes during the 120 min of reperfusion (Table 1). Intermittent capillary perfusion was observed in only 7.9 % of the islets studied during the 120 min of reperfusion (Table 2), presenting a frequency of 2.0 ± 0.3 cycles/min (mean cessation time 6.7 ± 2.3 s; mean perfusion time 24.0 ± 1.7 s). Prolongation of graft storage to 6 h did not cause impairment of nutritive perfusion within the insular tissue (Table 1). In addition, the incidence of intermittent capillary perfusion remained low (6.6 %; Table 2) and did not change in terms of frequency. Overall, the capillary network density of islets in pancreatic grafts was found to be slightly, but not significantly, lower than that of sham-operated control animals (Table 1). Intermittent capillary perfusion was not apparent in islet tissue of sham-operated controls (Table 2).

Quantitative microvascular analysis of the exocrine tissue in pancreatic grafts stored for 1 h revealed a mean functional capillary density of 459 ± 3.7cm^{-1} at 30 min of reperfusion, that only slightly decreased during the 2-h observation period (Figs. 1, 2A). These absolute values of functional capillary density were not different from those of sham-operated controls (Fig. 1). However, cold-stored and reperfused exocrine tissue frequently displayed intermittency of capillary perfusion (52.0 %) which, in contrast, was not detectable in any exocrine observation areas of control animals (Table 2). Intermittent capillary perfusion in the exocrine tissue was characterized by a mean cessation time of 4.4 ± 0.7 s and a mean perfusion time of 14.6 ± 2.1 s, resulting in an average frequency of 3.3 ± 0.3 cycles/min. After 6 h of cold storage, intermittency of capillary perfusion was apparent in only 6.2 % of all exocrine observation areas studied during the 120 min of reperfusion (Table 2). As a consequence, pancreatic exocrine tissue revealed marked perfusion deficits, as reflected in a functional capillary density of only ~ 290–320 cm^{-1} during the first 60 min of reperfusion and a further decrease to 158 ± 68 cm^{-1} after 120 min of reperfusion (Figs. 1, 2B). In endocrine and exocrine tissue, capillary diameters and red blood cell velocities were found in a range of 5.5–9.0 μm and 5.0–7.5 μm, and 550–880 μm/s and 340–780 μm/s, respectively, and they did not differ between the groups.

Table 1 Functional capillary density (cm^{-1}) of rat pancreatic endocrine tissue after whole pancreas transplantation. Values given represent mean ± SEM

	30 min of reperfusion	60 min of reperfusion	120 min of reperfusion
1 h of cold storage	456 ± 29	478 ± 29	463 ± 31
6 h of cold storage	463 ± 71	448 ± 55	454 ± 51
Controls	609 ± 79	662 ± 84	621 ± 78

Table 2 Incidence of intermittent capillary perfusion (%) in rat endocrine and exocrine pancreatic tissue after whole pancreas transplantation. Values given represent mean ± SEM

	Endocrine tissue	Exocrine tissue
1 h of cold storage	7.9 ± 4.6	52.0 ± 10.6*, **
6 h of cold storage	6.6 ± 6.6	6.2 ± 6.2
Controls	0.0 ± 0.0	0.0 ± 0.0

* $P < 0.05$ vs 6 h of cold storage and controls; ** $P < 0.05$ vs 1 h of cold storage (endocrine tissue) (ANOVA, Student-Newman-Keuls test)

Discussion

In the present study we demonstrated that 1 h of cold ischemia followed by 120 min of reperfusion affected neither exocrine nor endocrine tissue in terms of nutritive capillary perfusion. However, for maintenance of capillary blood flow, exocrine and endocrine tissue differed significantly. More than 50% of acinar tissue displayed intermittent capillary perfusion while only ~ 8% of the insular tissue did. After a 6-h period of cold storage and reperfusion, exocrine tissue failed to exhibit intermittent capillary perfusion; consequently, there was a significantly reduced nutritive blood flow, as indicated by a decreased functional capillary density. In contrast, endocrine tissue maintained continuous capillary perfusion after 6 h of cold storage and reperfusion. These results strongly imply that, in terms of manifestations of microvascular injury, the graft's endocrine tissue is less susceptible to prolonged periods of cold ischemia and reperfusion.

Vascular mechanisms, defined as any impairment of pancreatic inflow and outflow or as disturbances of the pancreatic microcirculation, have been advocated as key elements in the initiation and progression of acute pancreatitis [10, 11, 14, 21, 36]. In a previous study [19], we demonstrated that warm ischemia of the pancreas, followed by reperfusion, is associated with microcirculatory derangements, i.e., capillary perfusion failure as well as activation and microvascular adherence of leukocytes, that are similar in nature to those observed in other organs like the liver [33, 34] and intestine [7]. Cold ischemia of the pancreas, followed by reperfusion and reoxygenation, is classically akin to the situation encountered with pancreas transplantation. However, unlike the results after 1 h of warm ischemia and 120 min of reperfusion [19], cold storage of the pancreas for 1 h in the present study did not lead to a reduction in functional capillary density during reperfusion, which is probably due to the onset of intermittent capillary perfusion. As previously shown for exocrine pancreatic tissue under hemorrhagic hypotension [35], the alternate cessation and onset of capillary perfusion is caused by arterial vasomotion and must be interpreted as a local regulatory component aimed at counteracting potential perfusion failure-associated curtailment of the oxygen supply to the tissue. It is common knowledge that preservation of organs under cold conditions reduces tissue metabolic oxygen demand and, thus, allows longer periods of ischemic storage. It is, therefore, not surprising that a 1-h period of cold ischemia (present study) but not of warm ischemia [19] appeared to be tolerated by the exocrine pancreas without any significant manifestation of microvascular damage during the following 2 h of reperfusion. After prolongation of cold ischemia up to 6 h, however, the exocrine tissue failed to compensate further for limited reperfusion via intermittency of capillary perfusion. The ultimate result of this significant reduction in functional capillary perfusion is permanently unperfused tissue areas instead of intermittently perfused/oxygenated areas of exocrine tissue.

Persistent perfusion failure of individual capillaries, the so-called "no-reflow", results in prolongation of tissue hypoxia around those capillaries with increased susceptibility of the gland to pancreatitis. Indeed, analysis of sequential biopsies of human pancreatic allografts confirmed both clinical and morphological signs of acute pancreatitis, making post-transplant pancreatitis a manifestation of ischemia-reperfusion injury [2, 3]. Besides the disturbed integrity of structures within the acinar cells, which can clearly be attributed to the ischemic insult, reperfusion-associated events are thought to account for other distinct cellular and metabolic responses, including autophagocytosis, acceleration of cellular metabolism, and leukocyte activation/reaction. These, in turn, may lead to acinar cell necrosis [2, 3]. Accordingly, reperfusion of pancreatic transplants after 6 h, but not after 1 h, of cold storage revealed classical pancreatitis-associated microvascular injury, i.e., the deterioration of nutritive blood supply (no-reflow), lending support to the role of ischemia/reperfusion-associated mechanisms in the manifestation of acute post-transplant pancreatitis. The significance of preservation time, in terms of the nature and magnitude of postischemic reperfusion injury, has further been demonstrated in studies by Pi et al. [22]. They demonstrated that nitric oxide is produced during reperfusion as a function of preservation time, so that inhibition of nitric oxide synthase during pancreatic reperfusion protects exocrine tissue from becoming damaged, but only after quite short ischemic times. At the same time, cold ischemia

time was found to be a significant factor for inadequate perioperative release of pancreatic polypeptide and C-peptide, which reflect endocrine tissue damage [31].

Not only storage time, but also storage solution has been shown to significantly influence graft function. For the pancreas, HTK resulted in better postischemic organ function than Euro-Collins solution [12], however, it was neither superior nor inferior to preservation with University of Wisconsin (UW) solution [13]. During reperfusion, amylase levels, which are a prognostic factor for pancreatic graft function and survival [17, 32], were significantly higher after 24-h preservation in EC solution than they were in UW or HTK solution, indicating poor organ protection by EC, but adequate preservation by both HKT and UW. Specific modifications of the UW solution have produced superior results, not only in comparison to standard UW, but also to HTK [28], and have allowed the successful extension of cold storage preservation times [9]. Further studies are needed to evaluate the role of extended preservation times on microcirculatory disorders and the potential effectiveness of different preservation solutions in counteracting this microcirculatory dysfunction.

The significantly lower incidence of intermittent capillary perfusion in endocrine versus exocrine tissue after only 1 h of cold storage implies that endocrine tissue is far less challenged by the ischemia-reperfusion event. This discrepancy in microvascular vulnerability became most obvious after the 6-h cold storage period, when exocrine tissue failed to counteract malperfusion conditions by intermittent capillary perfusion and, thus, exhibited marked microvascular perfusion deficits. In contrast, perfusion of endocrine tissue was maintained without any change in either the incidence or frequency of intermittent capillary blood flow. To what extent the individual exocrine and endocrine arterial supplies and/or the insulo-acinar portal system [15] are responsible for the dissociation of the tissues' microvascular response to cold ischemia and reperfusion remains to be determined.

It is clear from the present results that intermittent capillary perfusion is an intriguing mechanism that allows the maintenance of nutritive perfusion in transplanted exocrine pancreatic tissue under distinct conditions. Our results also indicate a higher susceptibility of the exocrine pancreas to cold ischemia-reperfusion events that is associated with significant alterations in nutritive perfusion and, thus, with limitations of the oxygen supply. This fact might explain the relatively high incidence of inflammatory reactions of exocrine tissue in the clinical setting of pancreas transplantation.

Acknowledgements This research was supported by grants from the European Community (BMH 4-CT95-0875) and from the Deutsche Forschungsgemeinschaft (Me 900/1-3). B. V. is supported by a Heisenberg-Stipendium of the Deutsche Forschungsgemeinschaft (Vo 450/6-1).

References

1. Benetti L, Bassi C, Zamboni G, Radin S, Falconi M, Girelli R, Elio A, Briani GF, Cavallini G, Pederzoli P (1989) Pancreaticoduodenal graft in the rat: an original microsurgical technique. Eur Surg Res 21: 162–167
2. Büsing M, Hopt UT, Schareck WD, Becker HD (1992) Pancreatic transplantation: success and problems. Z Gastroenterol 30: 431–435
3. Büsing M, Hopt UT, Quacken M, Becker HD, Morgenroth K (1993) Morphological studies of graft pancreatitis following pancreas transplantation. Br J Surg 80: 1170–1173
4. D'Allesandro AM, Stratta RJ, Sollinger HW, Kalayoglu M, Pirsch JD, Belzer FO (1989) Use of UW solution in pancreas transplantation. Diabetes 38: 7–9
5. Douzdjian V, Abecassis MM, Cooper JL, Smith JL, Corry RJ (1993) Incidence, management and significance of surgical complications after pancreas transplantation. Surg Gynecol Obstet 177: 451–456
6. Fernandez-Cruz L, Sabater L, Gilabert R, Ricart MJ, Saenz A, Astudillo E (1993) Native and graft pancreatitis following combined pancreas-renal transplantation. Br J Surg 80: 1429–1432
7. Gonzalez AP, Sepulveda S, Maßberg S, Baumeister R, Menger MD (1994) In vivo fluorescence microscopy for the assessment of microvascular reperfusion injury in small bowel transplants in rats. Transplantation 58: 403–408
8. Grewal HP, Garland L, Novak K, Gaber L, Tolley EA, Gaber AO (1993) Risk factors for postimplantation pancreatitis and pancreatic thrombosis in pancreas transplant recipients. Transplantation 56: 609–612
9. Kin S, Stephanian E, Gores P, Shirabe K, Tanaka T, Salazar A, Brayman K, Gruessner R, Sutherland DER (1992) Successful 96-hr cold-storage preservation of canine pancreas with UW solution containing the thromboxane A2 synthesis inhibitor OKY046. J Surg Res 52: 577–582
10. Klar E, Messmer K, Warshaw AL, Herfarth C (1990) Pancreatic ischaemia in experimental acute pancreatitis: mechanism, significance and therapy. Br J Surg 77: 1205–1210
11. Kusterer K, Poschmann T, Friedmann A, Enghofer M, Zendler S, Usadel KH (1993) Arterial constriction, ischemia-reperfusion, and leukocyte adherence in acute pancreatitis. Am J Physiol 265: G165–G171
12. Leonhardt U, Barthel M, Tytko A, Dröge M, Siegel EG, Nebendahl K, Köhler H, Creutzfeldt W (1990) Preservation of the porcine pancreas with HTK and Euro-Collins solution: studies in a reperfusion system. Eur J Clin Invest 20: 536–539
13. Leonhardt U, Tytko A, Exner B, Barthel M, Stöckmann F, Köhler H, Siegel EG, Nebendahl K, Creutzfeldt W (1993) The effect of different solutions for organ preservation on immediate postischemic pancreatic function in vitro. Transplantation 55: 11–14

14. Lewis MP, Reber HA, Ashley SW (1998) Pancreatic blood flow and its role in the pathophysiology of pancreatitis. J Surg Res 75: 81–89
15. Lifson N, Kramlinger KG, Mayrand RR, Lender EJ (1980) Blood flow to the rabbit pancreas with special reference to the islets of Langerhans. Gastroenterology 79: 466–473
16. Looney SW, Stanley WB (1989) Exploratory repeated measures analysis for two or more groups. Am Stat 43: 220–225
17. Lundgren G, Wilczek H, Klintmalm G, Tydén G, Groth CG (1984) Procurement and preservation of human pancreatic grafts. Transplant Proc 16: 681–683
18. Mellert J, Hopt UT, Büsing M, Holzer H (1990) Differential immunosuppressive strategies after combined pancreaticoduodenal and isolated kidney transplantation. Transplant Proc 22: 1584
19. Menger MD, Bonkhoff H, Vollmar B (1996) Ischemia-reperfusion-induced pancreatic microvascular injury. An intravital fluorescence microscopic study in rats. Dig Dis Sci 41: 823–830
20. Mittal VK, Toledo-Pereyra HL, Prough D, Frantzis P (1989) Effect of graft pancreatitis on the outcome of whole pancreatic transplants. Transplant Proc 21: 2856–2857
21. Panum P (1886) Experimentelle Beiträge zur Lehre von der Embolie. Virchows Arch 25: 308–321
22. Pi F, Hotter G, Closa D, Prats N, Fernández-Cruz L, Badosa F, Gelpi E, Roselló-Catafau J (1997) Differential effect of nitric oxide inhibition as a function of preservation period in pancreas transplantation. Dig Dis Sci 42: 962–971
23. Schmid-Schoenbein GW, Zweifach BW, Kovalcheck S (1977) The application of stereological principles to morphometry of the microcirculation in different tissues. Microvasc Res 14: 303–317
24. Sollinger HW, Geffner SR (1994) Pancreas transplantation. Surg Clin North Am 74: 1183–1195
25. Sollinger HW, Stratta RJ, Kalayoglu M, Pirsch JD, Belzer FO (1987) Pancreas transplantation with pancreaticocystostomy and quadruple immunosuppression. Surgery 102: 674–679
26. Stratta RJ, Taylor RJ, Lowell JA, Byon JS, Cattral M, Langnas AN, Shaw BW (1993) Selective use of sandostatin in vascularized pancreas transplantation. Am J Surg 166: 598–605
27. Stratta RJ, Larsen JL, Cushing K (1995) Pancreas transplantation for diabetes mellitus. Annu Rev Med 46: 281–298
28. Sumimoto R, Dohi K, Urushihara T, Jamieson NV, Ito H, Sumimoto K, Fukuda Y (1992) An examination of the effects of solutions containing histidine and lactobionate for heart, pancreas, and liver preservation in the rat. Transplantation 53: 1206–1210
29. Sutherland DE (1992) Pancreatic transplantation: state of the art. Transplant Proc 24: 762–766
30. Sutherland DE, Dunn DL, Goetz DL, Kennedy W, Ramsay RC, Steffes MW, Mauer SM, Gruessner R, Moudry Munns KC, Morel P (1989) A 10-year experience with 290 pancreas transplants at a single institution. Ann Surg 210: 274–285
31. Tamsma JT, Schaapherder AFM, Bronswijk H van, Frölich M, Gooszen HG, Woude FJ van der, Lamers CBHW, Hermann J, Lemkes HHPJ (1993) Islet cell hormone release immediately after human pancreatic transplantation. Transplantation 56: 1119–1123
32. Tydén G, Wilczek H, Lundgren G, Östman J, Gunnarsson R, Jaremko G, Groth CG (1985) Experience with 21 intraperitoneal segmental pancreatic transplants with enteric or gastric exocrine diversion in humans. Transplant Proc 17: 331–335
33. Vollmar B, Glasz J, Post S, Leiderer R, Menger MD (1994) Hepatic microcirculatory perfusion failure is a determinant for liver dysfunction in warm ischemia-reperfusion. Am J Pathol 145: 1421–1431
34. Vollmar B, Menger MD, Glasz J, Messmer K (1994) Impact of leukocyte-endothelial cell interaction in hepatic ischemia/reperfusion injury. Am J Physiol 267: G786–G793
35. Vollmar B, Preissler G, Menger MD (1994) Hemorrhagic hypotension induces arteriolar vasomotion and intermittent capillary perfusion in rat pancreas. Am J Physiol 267: H1936–H1940
36. Warshaw AL, O'Hara PJ (1978) Susceptibility of the pancreas to ischemic injury in shock. Ann Surg 188: 197–201