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ORIGINAL ARTICLE

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Microcirculatory events in ischemia/reperfusion of the pancreas defined by continuous tissue oximetry

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Abstract In ischemia/reperfusion of the pancreas impairment of microcirculation after reperfusion is believed to be of critical importance. The 'no-reflow' phenomenon is thought to cause persisting tissue ischemia, while the 'reflow-paradox' is defined as secondary impairment of nutritive perfusion. These phenomena have been shown by intravital microscopy but their effect on tissue oxygenation as assessed by continuous tissue oximetry has not been identified. In landrace pigs tissue oxygenation was investigated in warm ischemia/reperfusion of the pancreas by the use of continuous tissue oximetry. After reperfusion rapid reoxygenation occurred which was followed by a period of secondary hypoxia. Thereafter, secondary reoxygenation was found, and finally tertiary hypoxia with a gradual decline of tissue pO_2 was noted. The data show a relevant impairment of tissue oxygenation after reperfusion. However, 'no-reflow' seems not to be a primary failure of capillary reperfusion but the consequence of a short reperfusion period followed by secondary ischemia. The 'reflow-paradox' most likely corresponds to tertiary ischemia.

Keywords Pancreas · Microcirculation · Oximetry · No-reflow phenomenon · Reflow-paradox · Shunt perfusion

Introduction

Graft pancreatitis as a consequence of ischemia/reperfusion (I/R) injury can cause considerable morbidity and graft loss after pancreas transplantation [6]. The pathophysiology is not fully understood, however animal studies have shown that impairment of microcirculation after reperfusion seems especially to be a crucial event in the development of severe tissue injury [9, 23]. Furthermore, not only in pancreas transplantation but also in acute pancreatitis, I/R with concomitant impairment of capillary perfusion seems to be relevant [14]. It is suspected that it is responsible for the transition of edematous into severe necrotizing pancreatitis.

The most important data about pancreatic microcirculation are derived from studies using intravital microscopy [9, 18, 23]. With this technique direct visualization of the capillary network and leukocyte-endothelial interaction is possible. However, the current technique of intravital microscopy does not allow continuous assessment of the same tissue volume over a long period of time. Also, for technical reasons it is very difficult to observe changes of capillary perfusion in the first few seconds and minutes after postischemic reperfusion. Furthermore, intravital microscopy is very diffi-

cult to perform in large animal models and currently impossible in the clinical setting in the investigation of intra-abdominal organs; this situation, however, may change with the advent of orthogonal polarization spectral (OPS) imaging [17]. Continuous tissue oximetry, on the other hand, is easy to perform and it has been used to show for the first time enormous relevance of an impaired microcirculation in the early reperfusion period in clinical pancreas transplantation [3]. However, phenomena such as 'no-reflow' and 'reflow-paradox' during postischemic reperfusion have not been defined using tissue oximetry. In particular, it is unknown whether these phenomena which have been defined on the microvascular level have any effects on tissue oxygenation of larger tissue areas and thus have a macroscopic correlation. We have, therefore, used this technique in conjunction with the assessment of total blood flow and oxygen consumption in a porcine model of pancreatic I/R injury [2] in order to determine whether continuous tissue oximetry yields a picture of microcirculation in I/R of the pancreas sufficiently detailed to identify the phenomena that correlate with those previously described by intravital microscopy. This, in turn, would be of major relevance for the clinical application of this technique.

Methods

Experiments were performed using ten female landrace pigs each weighing 50 kg. After induction of general anesthesia and endotracheal intubation a catheter was inserted in the external jugular vein to measure central venous pressure and to administer intravenous fluids. Another catheter was placed in the carotid artery for continuous blood pressure monitoring. This was followed by a midline incision and insertion of a catheter into the bladder. After splenectomy catheters were inserted in the distal parts of the splenic vein and artery, respectively. The pancreatic tail was mobilized together with the splenic vessels. The pancreas was then divided along the superior mesenteric vein. Peritoneal adhesions around the pancreatic head were not incised in order to leave the pancreatic head undisturbed. Thus, after dissection of the celiac axis and division of the left gastric vessels complete vascular isolation of the pancreatic tail was achieved. After the tail of the pancreas had been perfused with 10 ml of normal heparinized (1,000 I.E./100 ml) saline, it was then subjected to complete warm ischemia for 3 h. Intravenous fluids were replaced according to urine output and central venous and arterial pressure. Only crystalloid solutions were used.

Tissue oximetry of the pancreatic head and tail was performed by implantation of two pO_2-sensitive Clarke-type electrodes (LICOX, Fa. GMS, Germany) into the pancreatic tissue. The data were continuously registered on a personal computer. All electrodes were controlled for baseline shift over 1 h and calibrated by one point calibration as recommended by the manufacturer. Blood flow through the pancreatic tail was measured by the venous outflow method immediately before ischemia and at 0, 5, 10, 20, 30, 45, 60 min and then hourly after reperfusion. Oxygen consumption was calculated from blood gas analyses in the venous effluent of the pancreas and in the carotid artery. For the estimation of nutritional flow it was assumed that before ischemia 100% of the flow was nutritive. After reperfusion the nutritive flow was defined as the part of the total blood flow that was necessary for the oxygen consumption measured at that time in relation to the preischemic flow:

$$\mathrm{Flow_{nut}} = \mathrm{Flow_{preisch}} * \mathrm{O2-consumption_{pres}} / \mathrm{O2-consumption_{perisch}}$$

Shunt flow was estimated as follows:

$$\mathrm{Flow_{sh}} = \mathrm{Flow_{pres}} - \mathrm{Flow_{nut}}$$

Meaning of the indices: *sh* shunt, *pres* time point of interest, *preisch* preischemic, *nut* nutritive.

Biopsies were taken for immunohistochemistry before ischemia, at the end of the ischemia time, 10 min, 1 h and 6 h after reperfusion. Staining of granulocytes (PMN) by the APAAP method was performed using an anti-SWC-1 antibody (gift from Prof. Saalmueller, University of Tübingen, Germany) that detects a porcine granulocyte/monocyte antigen. For each time point in one section, positive cells were counted in five high-power fields (×160) and the mean value calculated.

The study protocol was approved by the Landwirtschaftsministerium Mecklenburg-Vorpommern as in accordance with the standards of care and use of laboratory animals.

Mean values were calculated and expressed ± standard deviations. Means were compared using the Mann-Whitney U-test for independent samples and the Wilcoxon rank test for grouped samples. *P* values smaller than 0.05 were considered significant.

Results

Hemodynamics

Mean arterial pressure (MAP) at the beginning of dissection was 94 ± 17 mmHg and gradually declined to 66 ± 8.9 mmHg at the end of the experiment. To maintain blood pressure after reperfusion, increasing amounts of crystalloid solution were required. Also, a gradual increase in heart rate was noted after reperfusion, from 95 ± 21/min to 133 ± 22/min at 3 h after reperfusion (Fig. 1).

Blood flow

Before ischemia, blood flow through the pancreatic tail (Fig. 2c) was 16.4 ± 6.7 ml/min. After reperfusion there was an increase to 43.7 ± 21.3 ml/min at 45 min after reperfusion. A decrease to 12.5 ± 9.5 ml/min at the end of the experiment was noted. The estimation of the shunt perfusion revealed that the increase of flow in the early reperfusion period was entirely due to shunt perfusion (39.9 ± 13.2 ml/min at 45 min after reperfusion). But also, at the end of the experiment, when total blood flow had decreased below preischemic levels, shunt flow accounted for approximately 50% of the total flow. In this estimation nutritive flow parallels oxygen consumption and therefore remains below preischemic control levels throughout the reperfusion period.

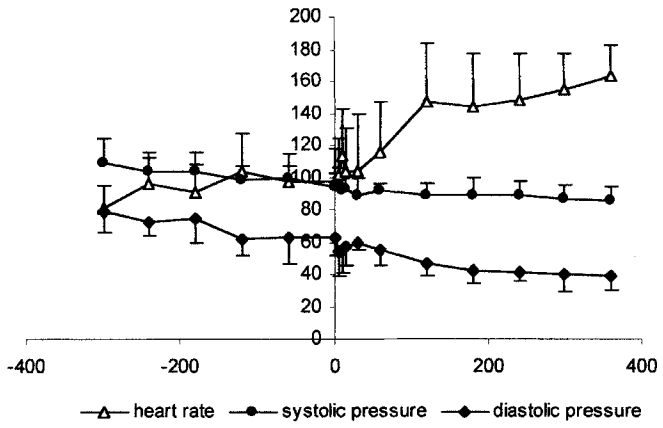

Fig. 1. Hemodynamic parameters in the course of the experiment. Blood pressure in mmHg, heart rate in beats/min

Tissue pO_2

The course of tissue pO_2 in the pancreatic tail (Fig. 2b) showed well-reproducible periods of increases and decreases of tissue oxygenation. Prior to ischemia, tissue pO_2 was 35 ± 9.9 mmHg (range: 50–22.7 mmHg). During ischemia a decrease to 0.1 mmHg was seen. This period was termed primary hypoxia. After reperfusion there was a steep increase to 25.0 ± 16.2 mmHg, called primary reoxygenation. Thereafter, a second highly significant ($P < 0.007$) decrease with a minimum of 9.2 ± 6.5 mmHg at 18 min after reperfusion occurred. This was called secondary hypoxia. In the further course a second peak was reached at 87 min after reperfusion, at 27.5 ± 16.3 mmHg ($P < 0.002$), which was called secondary reoxygenation. The last phase was a gradual but significant ($P < 0.04$) decrease, termed tertiary hypoxia.

This course, with primary reoxygenation and secondary hypoxia after reperfusion, was seen in all animals. A mere persistence of tissue hypoxia as equivalent of the 'no reflow' phenomenon has never been noted. In the pancreatic head, which served as control tissue pO_2 was 36.5 ± 14.0 mmHg after insertion of the electrode. It transiently increased to values around 60 mmHg and returned nearly to baseline at the end of the experiment (43.6 ± 8.7 mmHg). Compared with the pancreatic tail the values were significantly higher throughout the whole reperfusion period ($P < 0.001$).

Oxygen consumption

Hemoglobin oxygen saturation in the venous effluent of the pancreas before ischemia was $85.5 \pm 3.8\%$. This increased to $97.0 \pm 0.9\%$ at 3 h after reperfusion. At 6 h after reperfusion it decreased again to $90.6 \pm 2.4\%$ but

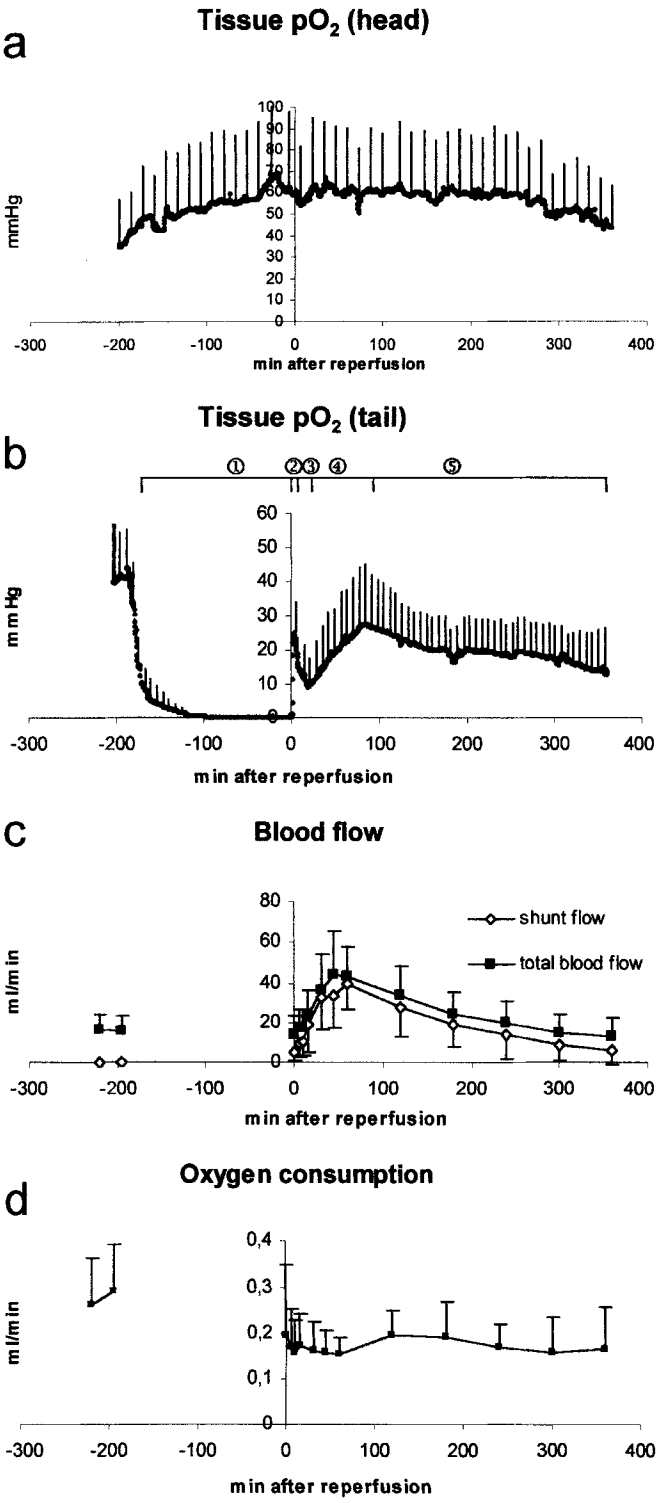

Fig. 2. Time course of tissue pO_2 in the pancreatic head (**a**) and tail (**b**). The five phases of tissue hypoxia and reoxygenation are represented by the encircled numbers: *1* primary hypoxia, *2* primary reoxygenation, *3* secondary hypoxia (no-reflow), *4* secondary reoxygenation, *5* tertiary hypoxia (see also Table 1). **c** Time course of total blood flow and estimated shunt flow and **d** oxygen consumption in the pancreatic tail ($n = 10$)

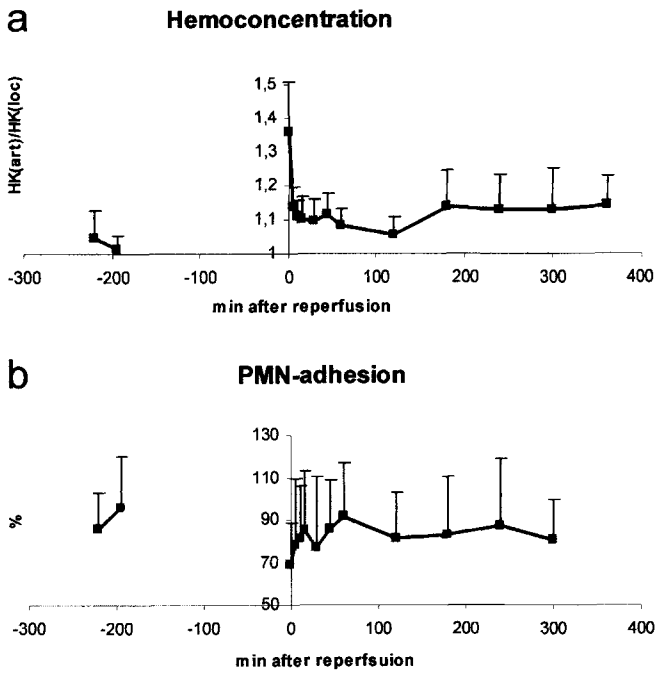

Fig. 3. **a** Ratio of hematocrit in the vena cava and the venous effluent of the pancreas as a measure for edema formation. The values on the Y-axis are equivalent with the proportion of perfusion volume that remains in the pancreatic tail during one passage. **b** Proportion of PMNs in the systemic circulation that appear in the venous effluent of the pancreatic tail ($n = 10$)

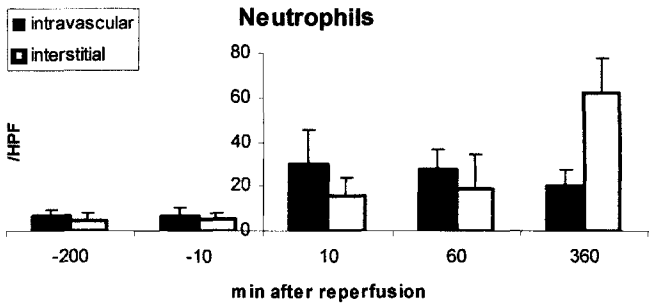

Fig. 4. Time course of neutrophil infiltration shown by immunohistochemistry (anti-SWC-1). Intravascular and interstitial PMNs were counted separately ($n = 10$)

was still elevated, compared with preischemic values. Oxygen consumption (Fig. 2d) before ischemia was 0.29 ± 0.13 ml/min. At 60 min after reperfusion it showed a minimum, at 0.15 ± 0.03 ml/min ($P < 0.04$). Until the end of the experiment it remained reduced between 34% and 48% below that of preischemic controls.

Hemoconcentration

Before reperfusion no significant difference in hematocrit was observed between the venous effluent of the pancreatic tail and the superior vena cava (Fig. 3a). Immediately after reperfusion, however, the hematocrit was elevated by $31 \pm 8\%$ in the venous effluent ($P < 0.001$). This elevation decreased until 15 min after reperfusion, although a slight but significant hemoconcentration (9%; $P < 0.04$) persisted throughout the whole reperfusion period.

Neutrophil adherence

In the first 5 min after reperfusion a reduction of neutrophils (PMN) in the venous effluent of the pancreatic tail was noted (Fig. 3b). This was interpreted as adherence of the PMNs in the pancreatic tail. The fraction of PMNs that became adherent during this time was $24.5 \pm 23.4\%$. Thereafter, only minor differences of $\pm 10\%$ were noted.

On immunohistochemistry with specific staining for PMNs 10 min after reperfusion a massive congestion of venules with nearly complete obliteration of the lumen was noted. At this time the highest number of intravascular PMNs was observed. (30.7 ± 15.3/hpf). In the further course intravascular PMNs gradually decreased to18.7 ± 6.4/hpf at 6 hours after reperfusion. During this time the number of PMNs in the tissue increased from 5.3 ± 3.4/hpf to 50.3 ± 24.5/hpf (Fig. 4).

Discussion

Reperfusion after long periods of ischemia causes an impairment of capillary perfusion [5, 7, 15, 20, 21, 24]. In this paper tissue oximetry, which had previously been shown to correlate highly significantly with tissue blood flow [30], was used to assess microcirculation. Since microcirculation is monitored continuously by this method, the time course was of particular interest in order to elucidate whether microcirculatory events such as 'no-reflow' and 'reflow paradox' cause correlating phenomena in tissue oxygenation that can be identified by this method.

In our experiments there was a typical pattern of changes in microcirculatory parameters which was present throughout nearly the whole reperfusion period. It included low tissue pO_2, and low oxygen consumption but high total blood flow. This clearly pinpoints an impairment of capillary blood flow with coexisting shunt perfusion. Thus, this finding verifies the occurrence of an impaired microcirculation after postischemic reperfusion.

This impairment of microcirculation has been classified by the time of occurrence into two phenomena. The first is the 'no reflow phenomenon' which by definition [20] is a primary failure of capillary reperfusion and

causes persisting tissue ischemia. The second phenomenon is the 'reflow paradox' which is defined as secondary failure of capillary perfusion after successful primary reperfusion [21, 22]. Tissue pO_2 in all our experiments showed a steep increase after reperfusion (primary reoxygenation). Thereafter, tissue pO_2 decreased again (secondary hypoxia). A mere persistence of tissue hypoxia or a slow gradual increase of tissue pO_2 has never been noted. This time course can hardly be explained by the strict definition of the 'no-reflow' phenomenon. In contrast, it must be hypothesized that a short, transient reperfusion of nutritive capillaries occurs immediately after unclamping of the supply vessels, which is rapidly followed by capillary failure. Similar observations confirming this notion were made by Kubes, in the intestine [16], and by Korthuis (personal communication), in the skeletal muscle. However, surprisingly little attention has been paid to the phenomenon of transient capillary perfusion, considering the abundance of studies dealing with the mechanism of the 'no reflow' in I/R. And indeed, there is no publication dealing explicitly with this problem. However, the difference between primary failure of capillary reperfusion on the one hand and transient reperfusion with rapidly following capillary failure on the other hand is of considerable relevance in at least three respects. The first is that reoxygenation after prolonged ischemia induces the whole cascade of reperfusion events such as formation of oxygen free radicals and release of proinflammatory mediators. Therefore, secondary ischemic insults are considerably less well tolerated than the simple prolongation of ischemia time [1, 12]. The second point is that only in the case of transient reperfusion is there a therapeutic window from the time of reperfusion until the onset of capillary perfusion failure (secondary hypoxia; Table 1) lasting less than 5 min which allows prophylactic treatment of microcirculation. Furthermore, it must be considered that this transient reperfusion, as it is described here, might not occur in partial or incomplete ischemia, because ischemia and reperfusion events can take place simultaneously, which makes the comparison of data between these different types of I/R -injury very difficult. The relevance of 'secondary hypoxia' is clearly supported by a clinical study by our group in which a highly significant correlation between tissue pO_2 and organ damage could be shown 1 h after reperfusion, but not within the first minutes after reperfusion [3].

A variety of mechanisms for the 'no-reflow' phenomenon have been proposed, including capillary obstruction by thrombi [27], leukocyte plugging of capillaries [28], swelling of capillary endothelium [4] and excessive increase of microvascular viscosity [29].

However, most likely more than one of these mechanisms are relevant in the development of capillary failure after reperfusion. In our experiment we see a marked extravasation of intravascular fluid leading to perivascular edema, capillary narrowing and increase of capillary viscosity. In addition, there is massive PMN adhesion in the first minutes after reperfusion. It is noteworthy, however, that all these mechanisms require transient reperfusion after complete ischemia.

In contrast to the abundance of data concerning the 'no-reflow' phenomenon, less is known about the further course. In our experiments the period of secondary hypoxia is followed by a phase of secondary reoxygenation, which implies an improvement in capillary perfusion. The level of preischemic control values was, however, not reached and secondary reoxygenation was also a transient phenomenon. A similar transient improvement was found on intravital microscopy in the skeletal muscle between 30 and 120 min after reperfusion, by Menger et al., which was, however, not discussed in this paper [20]. In a second paper a slight improvement in functional capillary density was seen during the same period [23]. A transient improvement in tissue perfusion at 120 min after reperfusion was also found by Hardy et al. who used the xenon-clearance technique [8]. From our data two findings might pinpoint a possible mechanism for the transient improvement. The first is, as already described, the only transient obstruction of venules by PMNs. The second relates to the extravasation of fluid. This is strongest immediately after reperfusion and shows a minimum at 120 min after reperfusion, nearly reaching the control level. It may cause decreasing formation of perivascular edema, decreasing interstitial pressure and a lower microvascular hematocrit, thus favoring better capillary perfusion.

Table 1. Definition of different phases in tissue oximetry with putative corresponding microvascular phenomenon

Finding (phase) in tissue oximetry	Definition	Corresponding microvascular phenomenon
Primary hypoxia	Decrease of tissue pO_2 during ischemia	Ischemia
Primary reoxygenation	Increase of tissue pO_2 within the first 5 min after reperfusion	Not defined
Secondary hypoxia	Decrease of tissue pO_2 within 20 min after reperfusion following primary reoxygenation	'No-reflow'
Secondary reoxygenation	Increase of tissue pO_2 after secondary hypoxia with a maximum around 90 min after reperfusion	Not defined
Tertiary hypoxia	Decrease of tissue pO_2 following secondary reoxygenation	'Reflow-paradox'

However, after secondary reoxygenation tissue pO_2 gradually decreases again until the end of the experiment at 6 h after reperfusion. This is most likely explained by the 'reflow-paradox'. It causes a progressive inflammatory reaction due to activation of the adherent granulocytes, with generation of oxygen free radicals and release of other proinflammatory mediators. This takes place in the vicinity of venules and perfused capillaries [20]. Consequently, microvascular permeability increases again leading to a reduction in tissue perfusion [19, 21, 25, 26].

Continuous tissue oximetry as described in this paper was used in our model for the first time in pancreatic I/R injury. The major advantage of this technique is the continuous monitoring of the tissue which allows the detection of rapid changes in nutritive perfusion during the reperfusion period. Therefore, it was possible to define distinct phases of tissue hypoxia and reoxygenation. On the basis of the data presented here and the discussion above we propose a correlation between these phases and the corresponding pathophysiological events shown in Table 1.

It is important to note that the term 'hypoxia' is used here only in a descriptive way, rather than a general pathophysiological way, meaning that tissue pO_2 during this period is low or declining, when compared with the physiological situation. Accordingly, the opposite is true for the term reoxygenation.

As was discussed above, early reperfusion failure is most likely preceded by a short primary reperfusion period. Therefore, the term no-reflow seems not really appropriate for this pathophysiological event. We would rather use 'early reperfusion failure' instead of 'no-reflow'. Consequently 'late reperfusion failure' could be used instead of 'reflow paradox'.

Our considerations so far have dealt only with impairment of capillary perfusion but have not explained shunt perfusion that was present at the same time. Shunt perfusion in experimental taurocholate pancreatitis was reported by Klar et al. using intravital microscopy. This shunt perfusion occurred due to perfusion failure of nutritive capillaries and resulted in exclusive perfusion of preferential pathway capillaries [14]. This study gave rise to the suggestion that in I/R of the pancreas also, shunt perfusion might contribute to the evolving tissue injury. However, it is important to note that there is another type of inadequate perfusion, which is reactive hyperemia. This already occurs after short ischemia times and is associated with an increase in capillary perfusion and total blood flow [10, 13]. Thus, there is no impairment of tissue oxygen supply.

In our experiments hyperemia seems to be dominant in the early period after reperfusion, with a marked hyperperfusion (total blood flow) of the pancreatic tail that exceeded the control value by nearly three times. However, in the further course tissue pO_2 falls to subnormal levels, despite the high total blood flow. This shows that hyperemia has turned into a state of high-volume shunt perfusion.

The crucial question is whether this shunt perfusion further disturbs tissue blood supply or is a harmless phenomenon coexisting with the much more important impairment of capillary perfusion discussed above. Although the experiments presented here are not sufficient to answer this question, observations from our group in human pancreas transplantation clearly show that high degrees of shunt perfusion (high hemoglobin oxygen saturation in the venous effluent of the pancreas graft) are significantly associated with little organ damage [3]. Similar data come from a model of experimental liver transplantation [11]. Therefore, shunt perfusion as it is described here seems not to be an additional harmful factor. For the most part it must be understood to be the result of the combination of the hyperemic response and the coexisting, (probably independent) impairment of capillary perfusion.

In conclusion, continuous tissue oximetry with its high temporal resolution gives a very detailed picture of microcirculation in I/R of the pancreas and detects the effects of phenomena previously defined by intravital microscopy. Clinical studies using this method in organ transplantation should, therefore, be intensified. This study, furthermore, shows that in the investigation of postischemic microcirculation more focus should be put on the first minutes after reperfusion, during which time primary reoxygenation and secondary hypoxia take place.

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