INTRODUCTION

In spite of the development of medical intensive care, severe acute pancreatitis (SAP) is still a fatal disease with a high mortality rate. Severe acute pancreatitis is characterized by both systemic organ failure and pancreatic and/or peripancreatic necrosis with infection. Unfortunately, pharmacological therapy including anti-inflammatory drugs, antiproteases, and probiotics could not be clarified to having beneficial effects on the course of SAP as expected (1). Prophylactic antibiotics are also controversial in acute necrotizing pancreatitis (ANP) (2). A new strategy of treatment based on pathophysiology of the disease should be mandatory.

Niedokrwienie trzustki ze skurczem naczyń we wczesnej fazie ciężkiej postaci ostrego zapalenia trzustki oraz rola ciągłego dotętniczego wlewu inhibitora proteaz i antybiotyku

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Summary

Pancreatic ischemia with vasospasm precedes necrotic change of the pancreas in the early phase of acute necrotizing pancreatitis, and increase in coagulability accompanied by severe acute pancreatitis (SAP) may play a crucial role in the development of pancreatic necrosis. Adequate amounts of a protease inhibitor, which is also a potent anticoagulant, and an antibiotic delivered by continuous regional arterial infusion (CRAI) approach to the ischemic area of the pancreas may prevent necrotic changes in the pancreas and reduce pancreatic infection. Recently, a randomized controlled trial of CRAI therapy in patients with SAP was reported. CRAI therapy was effective in reducing the mortality rate and the frequency of urgent surgical intervention. CRAI therapy should be started as soon as possible after diagnosing pancreatic ischemia that leads to necrosis later. Pancreatic ischemia or necrosis is often underestimated or sometimes overestimated in the early stage on contrast-enhanced CT examination. Perfusion measurement using a MDCT has been developed as a useful tool for prediction of pancreatic necrosis and accurate detection of ischemic area in the early stage of SAP. New imaging technique such as perfusion CT might be applicable in CRAI approach in the management of SAP.

Key words: severe acute pancreatitis, ischemia, arterial infusion, protease inhibitor, antibiotic, perfusion

Streszczenie

Niedokrwienie trzustki ze skurczem naczyń poprzedza wystąpienie zmian martwicznych w trzustce we wczesnej fazie ostrego martwiczego zapalenia trzustki. Zjawisko to wraz ze wzrostem krzepliwości krwi, towarzyszącym ciężkiej postaci ostrego zapalenia trzustki (SAP), może odgrywać kluczową rolę w rozwinięciu martwicy trzustki. Odpowiednie ilości inhibitora proteaz, który jest także silnym antykoagulantem oraz antybiotyk, podawane ciągłym, regionalnym wlewu dotętniczym (CRAI) docierając do obszaru niedokrwienia trzustki mogą zapobiec rozwinięciu się martwicy i zmniejszyć zakażenie trzustki. Ostatnio, opublikowano wyniki badania klinicznego z zastosowaniem terapii CRAI w SAP. Terapia CRAI skutecznie zmniejszała śmiertelność i częstość piętnowej interwencji chirurgicznych. Terapia CRAI powinna być rozpoczęta najpierw jak to możliwe po rozpoznaniu niedokrwienia trzustki mogącego doprowadzić do martwicy. We wczesnej fazie SAP, niedokrwienie lub martwica trzustki są często niedoszacowane i czasami przeszacowane w badaniu CT z wzmocnieniem kontrastowym. Pomiar perfuzji przy pomocy MDCT jest użytecznym narzędziem do prognozowania martwicy trzustki i dokładnej oceny obszaru niedokrwienia we wczesnej fazie SAP. Nowa metoda obrazowania – perfuzyjne CT może być używana w czasie stosowania metody CRAI w leczeniu SAP.

Słowa kluczowe: ciężka postać ostrego zapalenia trzustki, niedokrwienie, infuzja dotętnicza, inhibitor proteaz, antybiotyk, perfuzyjne CT

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We have clarified pancreatic ischemia with vaso-
spasm precedes necrotic change of the pancreas in
the early phase of acute necrotizing pancreatitis (3).
Microcirculatory derangement due to ischemia and an
increase in intravascular coagulation associated with
SAP may easily cause microthrombi formation result-
ing occlusion of microvessels and necrosis. There-
fore, a therapeutic strategy to inhibit the intravascular
coagulant activity in the pancreas may be expected to
prevent evolution of pancreatic ischemia into necrosis.
Nafamostat mesilate is a potent serine-protease inhi-
bitor. In addition, it acts as an anticoagulant as well as
antiprotease (4, 5, 6). Regional arterial infusion techni-
que can provide enough amount of nafamostat to the
ischemic area of the pancreas. Early initiation of con-
tinuous regional arterial infusion (CRAI) of a protease
inhibitor and an antibiotic in ANP has been recommen-
ded in Japanese guidelines (7). Recently, Piascik et al
reported that CRAI of protease inhibitor nafamostat and
antibiotic imipenem was effective in preventing compli-
cations and reducing mortality rate in SAP based on a
randomized controlled trial (8).

Ischemic change of the pancreas associated with
vasospasm in the early phase of acute necrotizing
pancreatitis

Angiographic appearances of arterial irregularities in
acute pancreatitis have already been described since
1960’s (9, 10). However, main reason for angiography
was examination of the presence of complications,
such as a palpable mass, suspicion of abscess or pseudocyst. Nowadays contrast-enhanced computed
tomography (CE-CT) enabled us to detect pancreatic
abscess, pseudocyst and pancreatic necrosis easily.
In addition, pancreatic ischemia is also detected by
CE-CT in the early phase of ANP. Unfortunately, rela-
tionship between angiographic abnormalities and pan-
creatic ischemia and/or necrosis on CE-CT findings
has never been discussed in the literature.

Angiographic features in the early phase of acu-
tec necrotizing pancreatitis were investigated in a few
Japanese medical centers using digital subtraction
angiography with selective catheterization into the ce-
lic artery and superior mesenteric artery (3, 11, 12).
In the early phase of ANP, angiographic appearances
with irregularities in various grades were observed.
Angiographic abnormalities such as sudden tape-
ing, alternative narrowing and dilatation, angulations
and diffuse caliber irregularities of the intrapancreatic
branch arteries are characteristic of ANP. Severe ische-
ic change with diffuse vasospasm and/or obstruction
was observed not only in the intra- and peripancreatic
arteries, but also in the extrapancreatic arteries such
as the superior mesenteric artery and its branches (3).
Arterial irregularities with vasospasm were already visi-
ble on the initial angiography at 12 hours after the on-
set. Figure 1 shows a typical appearance of vasospasm
on angiography. CE-CT revealed a heterogeneous en-
hancement in the pancreatic head. Selective angiogra-
phy via the gastroduodenal artery showed alternative
narrowing and dilatation and sudden tapering of the in-
trapancreatic branch arteries consistent with the poorly
perfused area of the pancreas on CE-CT. Improvement
of ischemic change with angiographic irregularities of
the intrapancreatic branch arteries were also observed
on follow-up angiography (fig. 2). These findings stron-
gly suggested that the irregular narrowing of the arteries
was not caused by structural or irreversible change due
to postinflammatory fibrous adhesion but was caused
by vasospasm. The extent of ischemic changes with
vasospasm on angiographic appearance was correla-
ted with the extent of the poorly perfused area of the
pancreas on CE-CT findings and the severity of acute
pancreatitis (fig. 3, 4). Non-occlusive mesenteric ische-
emia (NOMI) associated with SAP was also investigated

Fig. 1. Vasospasm on angiographic appearance in a patient
with acute necrotizing pancreatitis 12 hours after the onset.
CE-CT revealed a heterogeneously perfused area of the
pancreatic head. Selective angiography via the gastroodu-
odenal artery demonstrated vasospasm such as sudden ta-
pering (short arrow) and alternative narrowing and dilatation
(long arrow) of the intrapancreatic branch arteries, consistent
with the poorly perfused area on CE-CT.
Pancreatic ischemia with vasospasm in the early phase of severe acute pancreatitis...

Based on the angiographic appearance by Hirota et al. (13) Severe vasospastic changes of both the celiac artery and the superior mesenteric artery were observed simultaneously in patients with NOMI accompanied by ANP. Severe ischemic changes in the intraabdominal vessels may aggravate microcirculation not only in the pancreas but also in the abdominal viscera leading to pancreatic necrosis and systemic organ failure.

**Hypothesis of the mechanism of vasospasm in severe acute pancreatitis**

The mechanism of vasospasm in SAP has not yet been elucidated. Hypovolemia and hypotension (14), and sympathetic stimulation (15) causes vasospasm. Local inflammation and activation of complement system (16) may be other possible causes of vasospasm. The activation of the complement system that is observed in SAP may be involved in vasospasm. The complement system-derived immune system is considered to contribute to the pathogenesis of cerebral vasospasm (17).

Recently, endothelin-1 (ET-1) has been noticed as a candidate for mediating the vascular changes of SAP. Infusion of endothelin changed edematous pancreatitis into hemorrhagic necrotizing pancreatitis in an animal model (18). Continuous infusion of ET-1 produced prolonged arterial narrowing (19). ET-1 receptor antagonist prevented pancreatic blood flow from decreasing in severe experimental acute pancreatitis (20). Thrombin has also been considered to play an important role in arterial vasospasm (21, 22). Thrombin suppresses endothelial NO synthase and upregulates endothelin-converting enzyme-1 (23). An imbalance between vasodilator NO and vasoconstrictor ET-1 may be involved in the regional vasospasm of the arteries in the inflamed pancreas. Production of ET-1 by HUVECs was significantly enhanced by stimulation of thrombin and that a close relationship may exist between ET-1 and vasospasm in acute pancreatitis (24).

Hypovolemia and/or hypovolemic shock, activation of thrombin, and coagulant system are commonly ob-

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**Fig. 2. Changes of the vasospasm in acute pancreatitis.** Initial angiography on admission (5 days after the onset) revealed sudden tapering of the dorsal pancreatic artery (short arrow) and impaired visualization of the intrapancreatic branch arteries (arrowhead) (A) and poor staining of the pancreatic parenchyma in the capillary phase (B). The patient was treated with CRAI therapy. Two weeks later, a follow-up angiography was carried out and it demonstrated improvement of the filling of the dorsal pancreatic artery (long arrow) and intrapancreatic branch arteries (C). Pancreatic gland was also stained homogenously in the capillary phase (D).
served in SAP, and they are concomitant with vaso-
spasm and pancreatic ischemia. Microcirculatory de-
rangements due to the formation of microthrombosis
in the pancreatic vessels may thus easily occur and
pancreatic ischemia may change to be necrotic.

Rationale of continuous regional arterial infusion
approach in severe acute pancreatitis

A synthetic protease inhibitor nafamostat mesilate
has a broad inhibitory action on pancreatic enzymes,
the coagulation system, the complement system and
the production of proinflammatory cytokines. Nafamo-
stat inhibits trypsin and phospholipase A2, and it also
inhibits the classical and alternative pathway of com-
plement system and the activation of thrombin, kalli-
klein, plasmin, factor VIIa and factor Xa. Nafamostat is
not only a protease inhibitor but also a potent antico-
agulant that is widely used for hemodialysis and the
treatment of disseminated intravascular coagulation.
Nafamostat suppresses activation of thrombin and the-
reby inhibits the production of ET-1, thus preventing
vasospasm. Nafamostat may also protect the pancreas
against necrotic change by inhibiting increase in co-
agulability and microthrombi formation.

However, protease inhibitors could not show bene-
ficial effects in human acute pancreatitis as expected.
Unfortunately, the protease inhibitors do not easily
reach the pancreas when administered intravenously
because of their pharmacokinetic characteristics (25)
and impaired microcirculation. On the other hand, ad-
ministration of a protease inhibitor through the cathe-
teter placed at one of the arteries supplying the inflamed
area of the pancreas dramatically increases the tissue
concentration of a protease inhibitor (26, 27). Mikami et
al. clarified the efficacy of continuous regional arterial
infusion of a protease inhibitor nafamostat mesilate on
severe acute pancreatitis in rats (27). The tip of needle was placed at the celiac artery in rats. CRAI rats had six times higher concentrations of nafamostat in the pancreas than those infused intravenously. CRAI significantly reduced the levels of serum IL-6. The mortality rate was significantly reduced after CRAI compared with the intravenous infusion of nafamostat.

The concentration of antibiotics was also markedly increased in the pancreatic tissue when administered intraarterially in a experimental acute pancreatitis models, and protective effect intraarterial infusion of an antibiotic against pancreatic infection was demonstrated (28, 29).

**Clinical impacts of CRAI therapy in SAP**

Takeda et al. reported a new trial of CRAI therapy for ANP in 1996 (30). CRAI of both a protease inhibitor and an antibiotic reduced not only the mortality rate but also the frequency of infected pancreatic necrosis. A nationwide survey of CRAI therapy in Japan also reported that CRAI of both the protease inhibitor and the antibiotic was superior to CRAI of the protease inhibitor alone (31). There was no significant difference in the mortality rate between patients who received the protease inhibitor via CRAI and the antibiotic intravenously, and patients who received both the protease inhibitor and antibiotic via CRAI. However, the frequency of infected pancreatic necrosis was significantly lower than in patients with involving both drugs that in patients with CRAI involving protease inhibitor alone. Imaizumi et al. reported efficacy of CRAI therapy in patients admitted to an intensive care unit (32). Cumulative survival rate at 1, 6 and 12 months were 77.9%, 48.9% and 48.9% in the non-CRAI group compared with 100%, 100% and 87.1% in the CRAI group. The rate of surgery was 32% in the non-CRAI group and 9% in CRAI group. Yasuda et al. also demonstrated that in the CRAI group, the incidence of infection, the frequency of surgery, and the mortality rate were lower than those in the non-CRAI group: 34% versus 51%, 27% versus 63%, and 37% versus 54% (33). Shirai et al. conducted a prospective randomized controlled trial in patients with SAP, comparing one group who were given meropenem and the another group who received imipenem using CRAI (34). There were no significant differences in the frequency of infected pancreatic necrosis, surgical treatment, and the mortality rate. CRAI of meropenem combined with nafamostat was effective as well as imipenem. Ino et al. evaluated the efficacy of CRAI of another protease inhibitor gabexate mesilate in patients with SAP (35). The duration of abdominal pain in the CRAI group was 1.9 + 0.29 d, whereas that in the non-CRAI group was 4.3 + 0.5. The duration of SIRS in the CRAI group was 2.2 + 0.22 d, whereas that in the non-CRAI group was 3.2 + 0.28. The average length of hospitalization was significantly shorter in the CRAI group than that in the non-CRAI group. As above-mentioned, many clinical trials on the efficacy of CRAI therapy have been reported, but unfortunately, there had been no published randomized clinical trials so far. However, recently, results of a randomized controlled study of CRAI therapy in patients with SAP were reported from Poland (8). 78 patients with SAP were included in that study. The CRAI patients were treated continuously with nafamostat mesilate 240 mg/d and imipenem 1 g/d for 5 days via one of the arteries perfusing the pancreas. The non-CRAI patients received imipenem 1 g/d intravenously. The additional antibiotics were applied in 8 of CRAI patients and in 18 of non-CRAI patients (p = 0.02). Urgent surgical intervention was necessary in 10.3% of CRAI patients and in 33.3% of non-CRAI patients (p = 0.01). The mortality rate was 5.1% in CRAI and 23.1% in non-CRAI group (p = 0.02). These results demonstrated that CRAI of a protease inhibitor and an antibiotic was effective in preventing complications and in reducing mortality rate in SAP.

Anai et al. evaluated the relationship between the therapeutic effect of CRAI therapy and drug distribution on CT-angiography (36). In patients having a good drug distribution on CT angiography, there was a rapid decrease of the APACHE II score and the CT severity index by Balthazar. The CT severity index was 5-10 (mean 7.9) before CRAI therapy, but it decreased to 0-3 (mean 0.6). Hirota et al. also reported a case with NOMI accompanied by SAP (13). In that case, severe vasospasm occurred in both the celiac artery, the superior mesenteric artery and their branches simultaneously. The patient received CRAI therapy with nafamostat solely via the celiac artery. The pancreas was spared from diffuse necrosis in contrast to the diffuse intestinal necrosis, which occurred due to mesenteric vasospasm.

**Timing of initiation of CRAI therapy in severe acute pancreatitis**

Theoretically, CRAI therapy should be initiated as soon as possible after diagnosing SAP and ischemic change of the pancreas on CE-CT, because pancreatic necrosis is established four to 10 days after the onset. The effect of the timing of the initiation of CRAI therapy on the outcome was evaluated in patients with ANP (37). The frequency of respiratory failure requiring mechanical ventilation was significantly low in patients with early initiation of CRAI (within 3 days after the onset) compared to that in patients with late initiation of CRAI (more than 4 days after the onset). The mortality rate was also significantly low in patients with early initiation of CRAI therapy. A nationwide survey also demonstrated that the mortality rate was significantly low in patients in whom CRAI therapy was initiated within 48 hours after the onset compared to that in patients in whom CRAI therapy was initiated more than 48 hours after the onset (31). Ishikawa et al. also reported that the mortality rate was significantly low in patients in whom treated with CRAI within 3 days after the onset (38). We investigated the timing of the initiation of CRAI therapy and the morphological changes examined on serial CE-CT (39). Morphological improvement was ob-
Fig. 5. Color map of perfusion CT imaging in a patient with acute necrotizing pancreatitis in the early stage of ANP. Contrast-enhanced CT (CE-CT) showed diffuse enlargement of the pancreas with slightly low enhancement (left). However, CE-CT could not clarify whether pancreas being necrotic or not. On the other hand, perfusion CT depicted necrotic area clearly as black color in the color map (right). Perfusion measurement demonstrated markedly low perfusion as 7.2 ml/ml/min in the ROI of T1.

Fig. 6. CE-CT and perfusion CT imaging in a patient with ANP. In upper panel, though CE-CT depicted poorly perfused area in pancreatic body, the extent of ischemic area was not clear. Perfusion CT showed ischemic changes of the pancreas and the extent of ischemic area clearly (black color in color map). Follow-up CE-CT demonstrated that ischemic area, which was detected in the initial perfusion CT, changed to be necrotic, but perfused area (blue color) was preserved (lower panel).
Pancreatic ischemia with vasospasm in the early phase of severe acute pancreatitis... served in 84%, 62.5%, and 53% in patients in whom CRI was initiated within 48 hours, 48-72 hours, and more than 72 hours, respectively.

How can we detect ischemic change of the pancreas or predict pancreatic necrosis accurately in the early phase (< 72 hours)?

Goal and aim of the CRI therapy is to prevent necrotic change of the pancreas and reduce the incidence of infection of the pancreas in SAP. CRI therapy should be indicated for patients with pancreatic ischemia before the necrotic change of the pancreas has been developed. CRI of nafamostat is expected to prevent vasospasm and the formation of microthrombi in the ischemic pancreas. CRI therapy is recommended to be started at least within 72 hours (within 48 hours, if possible) after the onset (31, 37). CE-CT has been a gold standard for the diagnosis of pancreatic necrosis so far. However, in the early phase of SAP, can CE-CT detect pancreatic ischemia or predict pancreatic necrosis accurately? The United Kingdom guidelines for the management of acute pancreatitis recommended late CE-CT examination to confirm pancreatic necrosis, because of low sensitivity of CE-CT to diagnose pancreatic necrosis in the early phase of SAP (40). Pancreatic ischemia or necrosis is often underestimated or sometimes overestimated in the early stage on contrast-enhanced CT examination. In CRI approach, it is important that the appropriate artery supplying the ischemic area of the pancreas should be selected as a route of administration. A new imaging method to detect pancreatic ischemia and ischemic region more accurately in the early stage should be necessary. If we can predict necrotic area of the pancreas accurately, super-selective angiographic approach is available to deliver adequate amounts of the drugs to ischemic area of the pancreas.

Recently, perfusion computed tomography (perfusion CT) has been proposed as a useful predictive tool of SAP or pancreatic necrosis. Bize et al. demonstrated that pancreatic perfusion measurement using multi-detector row CT (MDCT) with perfusion imaging could help in assessing the severity of acute pancreatitis (41). Tsuji et al. showed that perfusion CT is a useful tool for early detection of ischemic change in the pancreas that leads to pancreatic necrosis (42). The sensitivity and specificity of perfusion CT for predicting pancreatic necrosis was calculated to be 100% and 95.3%, respectively. We also clarified the usefulness of perfusion CT for diagnosis of necrotizing pancreatitis in the early phase of acute pancreatitis (43). Perfusion parameters such as pancreatic blood flow (perfusion), peak enhancement intensity and blood volume of the pancreas were significantly low in the ischemic area of the pancreas developing to necrosis later (fig. 5, 6). Perfusion CT should be a reliable tool for detection of pancreatic ischemia and ischemic region in the early stage of SAP.

CONCLUSION

Pancreatic ischemia with vasospasm precedes necrotic change of the pancreas in the early phase of acute necrotizing pancreatitis, and increase in coagulability accompanied by severe acute pancreatitis may play a crucial role in the development of pancreatic necrosis. Adequate amounts of a protease inhibitor, which is also a potent anticoagulant, and an antibiotic delivered by continuous regional arterial infusion approach to the ischemic region may prevent necrotic changes in the pancreas and reduce pancreatic infection.

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