*Kazunori Takeda

Pancreatic ischemia with vasospasm in the early phase of severe acute pancreatitis and the role of continuous regional arterial infusion of a protease inhibitor and an antibiotic

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

Department of Surgery, National Hospital Organization Sendai Medical Center
Head of Department: prof. Kazunori Takeda

S u m m a r y

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

S t r e s z c z e n i e

Niedokrwienie trzustki ze skurczem naczyń poprzedza wystąpienie zmian martwiczych 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 rozwoju martwicy trzustki. Odpowiednie ilości inhibitora proteaz, który jest także silnym antykoagulantem oraz antybiotyk, podawane ciągłym, regionalnym wlewem 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 pilnych interwencji chirurgicznych. Terapia CRAI powinna być rozpoczęta najszybciej 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, perfuzja

INTRODUCTION

In spite of 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.

We have clarified pancreatic ischemia with vasospasm 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 resulting occlusion of microvessels and necrosis. Therefore, 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 inhibitor. In addition, it acts as an anticoagulant as well as antiprotease (4, 5, 6). Regional arterial infusion technique can provide enough amount of nafamostat to the ischemic area of the pancreas. Early initiation of continuous regional arterial infusion (CRAI) of a protease inhibitor and an antibiotic in ANP has been recommended in Japanese guidelines (7). Recently, Piascik et al reported that CRAI of protease inhibitor nafamostat and antibiotic imipenem was effective in preventing complications 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, relationship between angiographic abnormalities and pancreatic ischemia and/or necrosis on CE-CT findings has never been discussed in the literature.

Angiographic features in the early phase of acute necrotizing pancreatitis were investigated in a few Japanese medical centers using digital subtraction angiography with selective catheterization into the celiac 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 tapering, alternative narrowing and dilatation, angulations and diffuse caliber irregularities of the intrapancreatic branch arteries are characteristic of ANP. Severe ischemic 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 visible on the initial angiography at 12 hours after the onset. Figure 1 shows a typical appearance of vasospasm on angiography. CE-CT revealed a heterogeneous enhancement in the pancreatic head. Selective angiography via the gastroduodenal artery showed alternative narrowing and dilatation and sudden tapering of the intrapancreatic 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 strongly 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 correlated 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 ischemia (NOMI) associated with SAP was also investigated

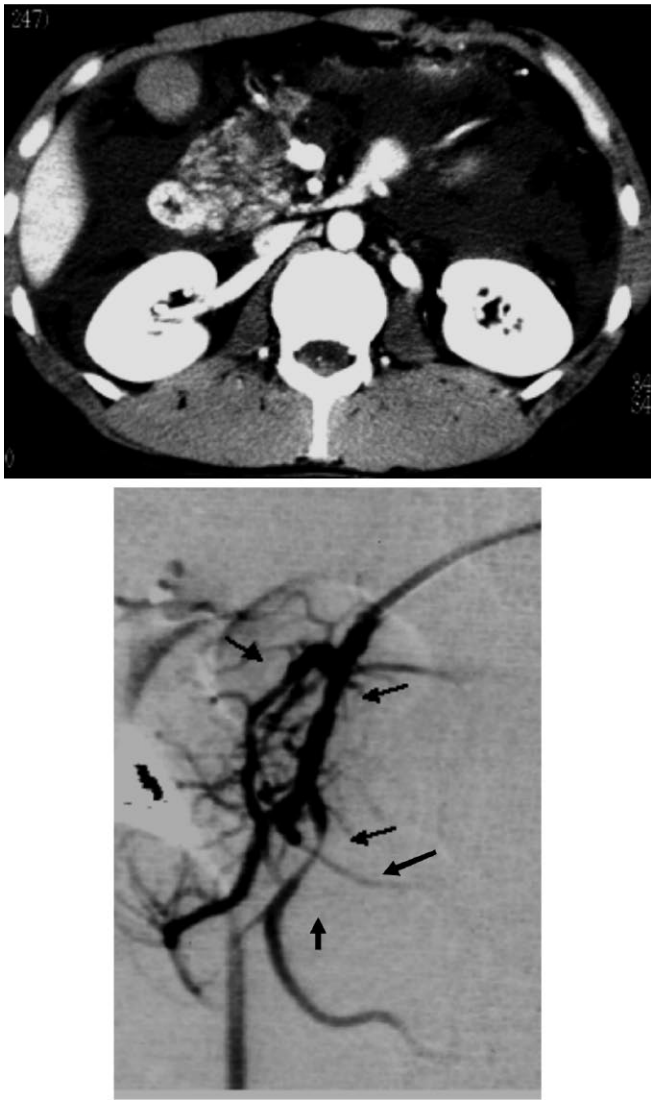

Fig. 1. Vasospasm on angiographic appearance in a patient with acute necrotizing pancreatitis 12 hours after the onset. CE-CT revealed a heterogeneously perfused area of the pancreatic head. Selective angiography via the gastroduodenal artery demonstrated vasospasm such as sudden tapering (short arrow)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

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-

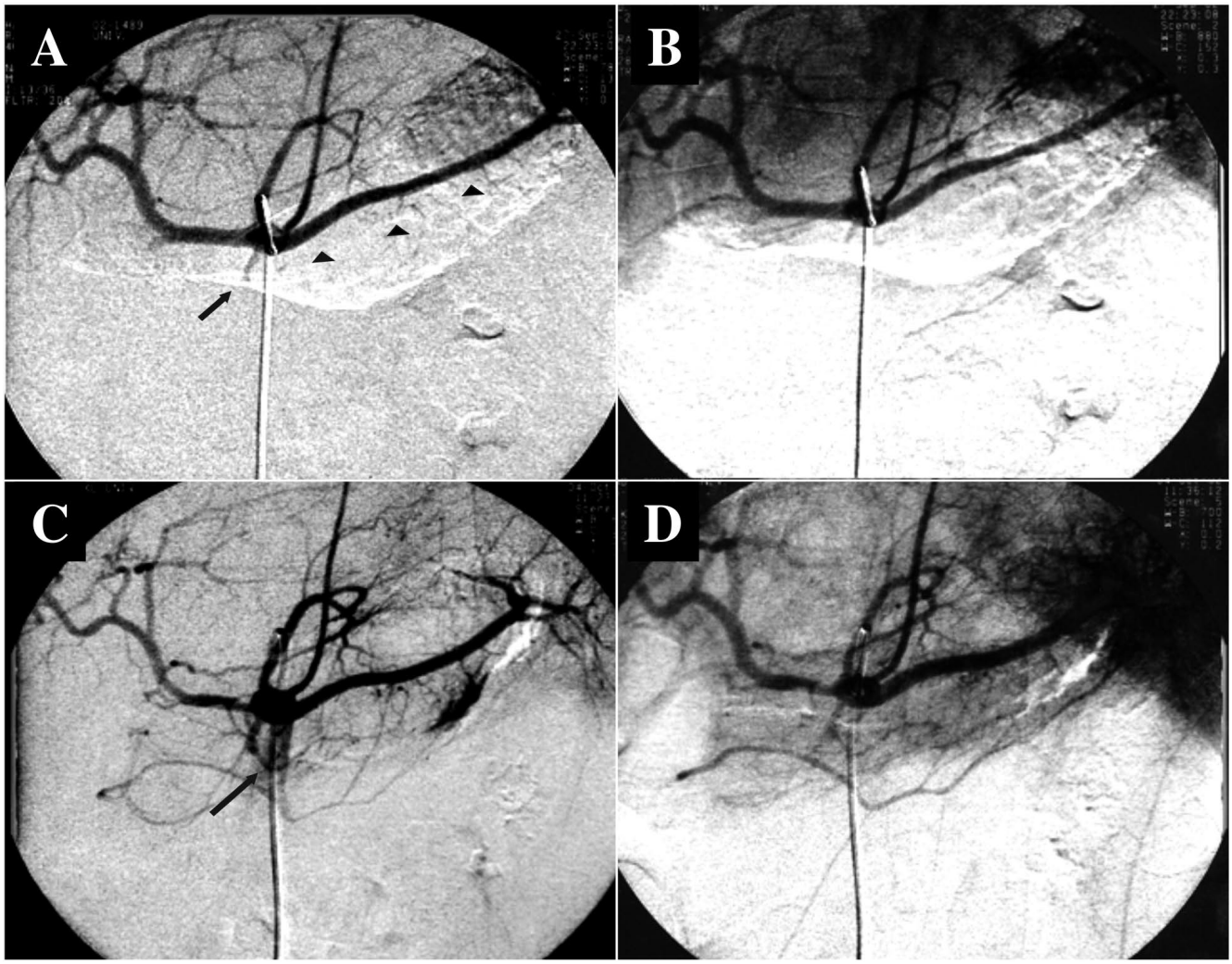

Fig. 2. Changes of the vasospasm in acute pancreatitis. Initial angiography on admission (5 days after the onset) revealed sudden tapering of the dorsal pancreatic artery (short arrow) and impaired visualization of the intrapancreatic branch arteries (arrowhead) (A) and poor staining of the pancreatic 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).

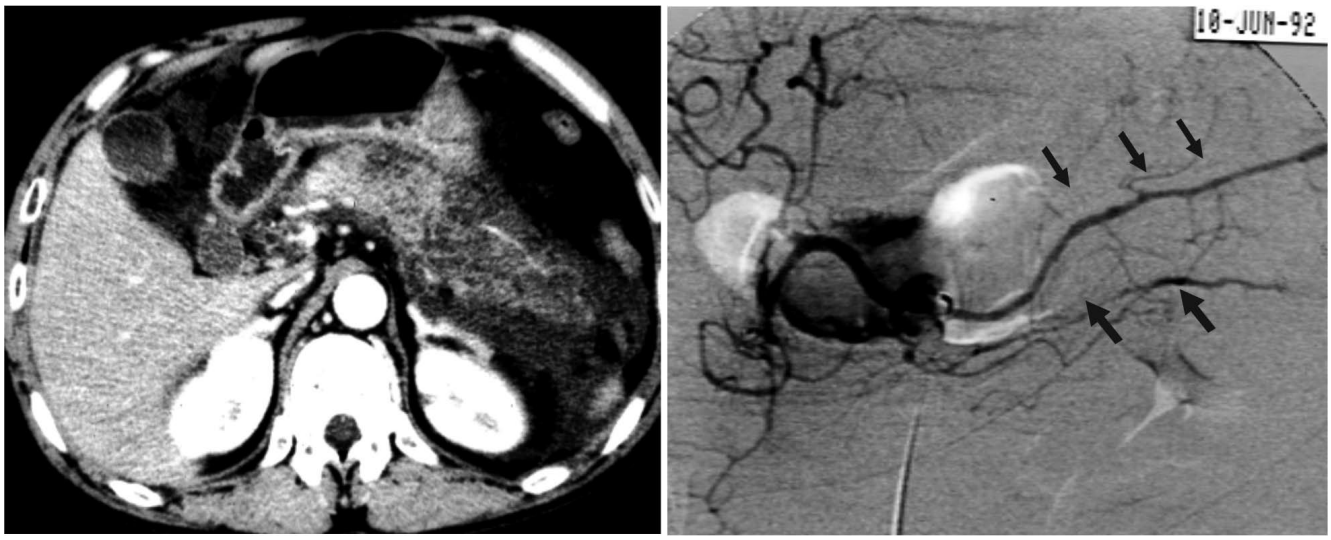

Fig. 3. A typical appearance of vasospasm on angiography. CE-CT showed a poorly perfused area in the pancreatic body and tail. Angiography showed diffuse caliber irregularities with narrowing in the intrtapancreatic branch arteries (long arrow). Focal ischemic change with diffuse narrowing of the splenic artery was also observed (46 hours after the onset).

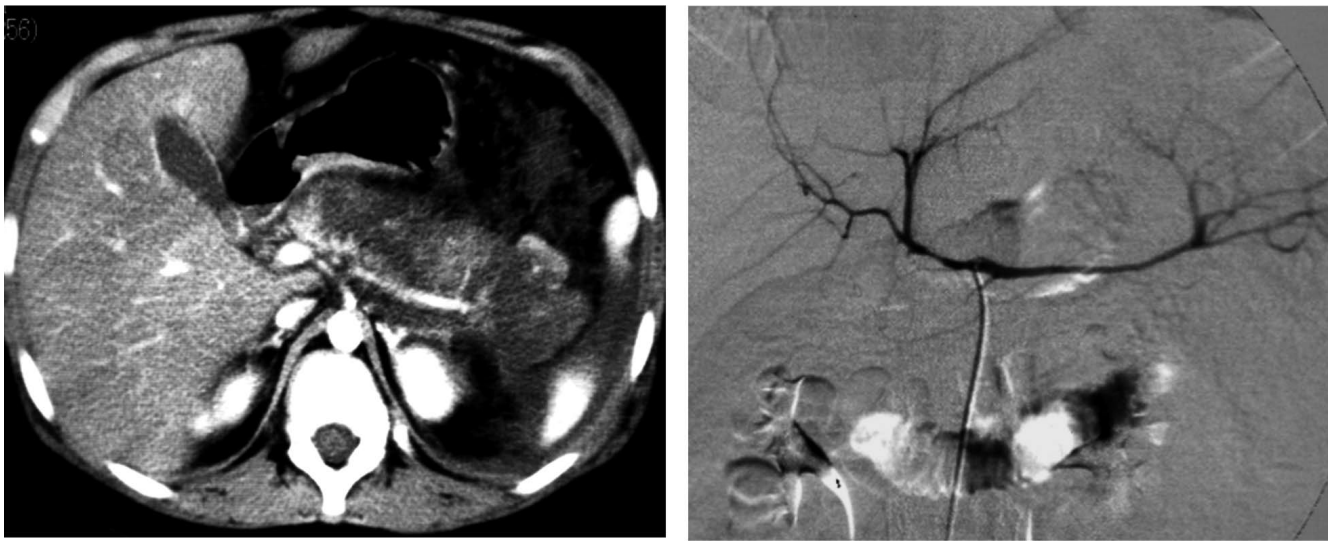

Fig. 4. Severe ischemic change with diffuse narrowing of the extrapancreatic arteries. Angiography demonstrated diffuse narrowing of the splenic artery and common hepatic artery and impaired visualization of the ramifications (arrowhead), consistent with the poorly perfused area on CE-CT (56 hours after the onset).

served in SAP, and they are concomitant with vasospasm and pancreatic ischemia. Microcirculatory derangement 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. Nafamostat inhibits trypsin and phospholipase A2, and it also inhibits the classical and alternative pathway of complement system and the activation of thrombin, kallikrein, plasmin, factor VIIa and factor Xa. Nafamostat is not only a protease inhibitor but also a potent anticoagulant that is widely used for hemodialysis and the treatment of disseminated intravascular coagulation. Nafamostat suppresses activation of thrombin and thereby inhibits the production of ET-1, thus preventing vasospasm. Nafamostat may also protect the pancreas against necrotic change by inhibiting increase in coagulability and microthrombi formation.

However, protease inhibitors could not show beneficial 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, administration of a protease inhibitor through the catheter 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 5days 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-

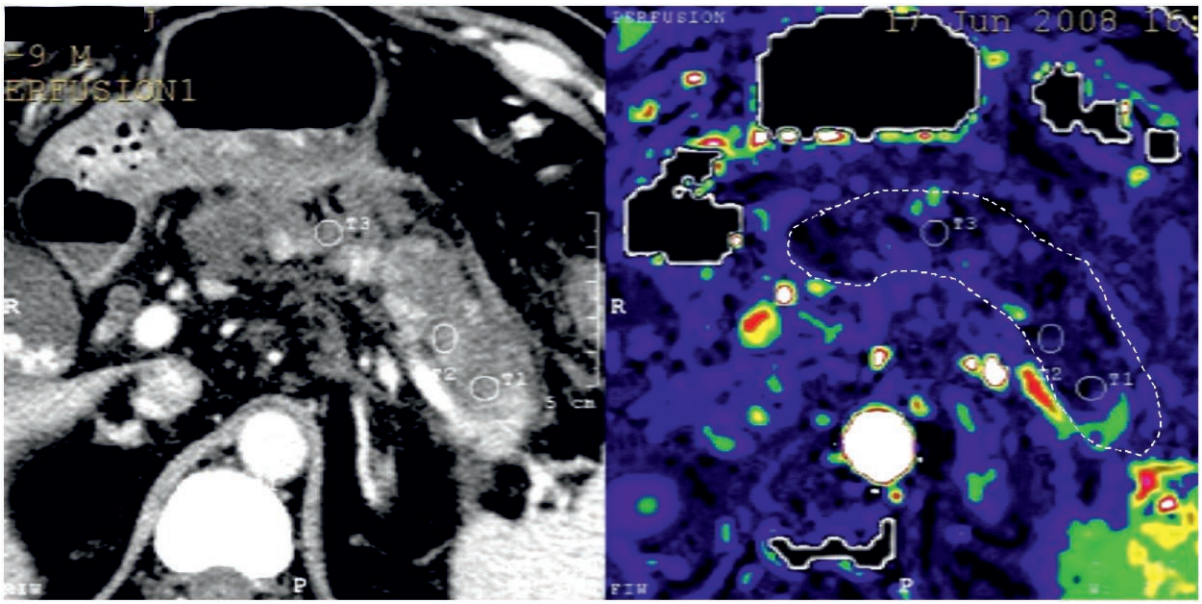

Fig. 5. Color map of perfusion CT imaging in a patient with acute necrotizing pancreatitis in the early stage of ANP. Contrast-enhanced CT (CE-CT) showed diffuse enlargement of the pancreas with slightly low enhancement (left). However, CE-CT could not clarify whether pancreas being necrotic or not. 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.

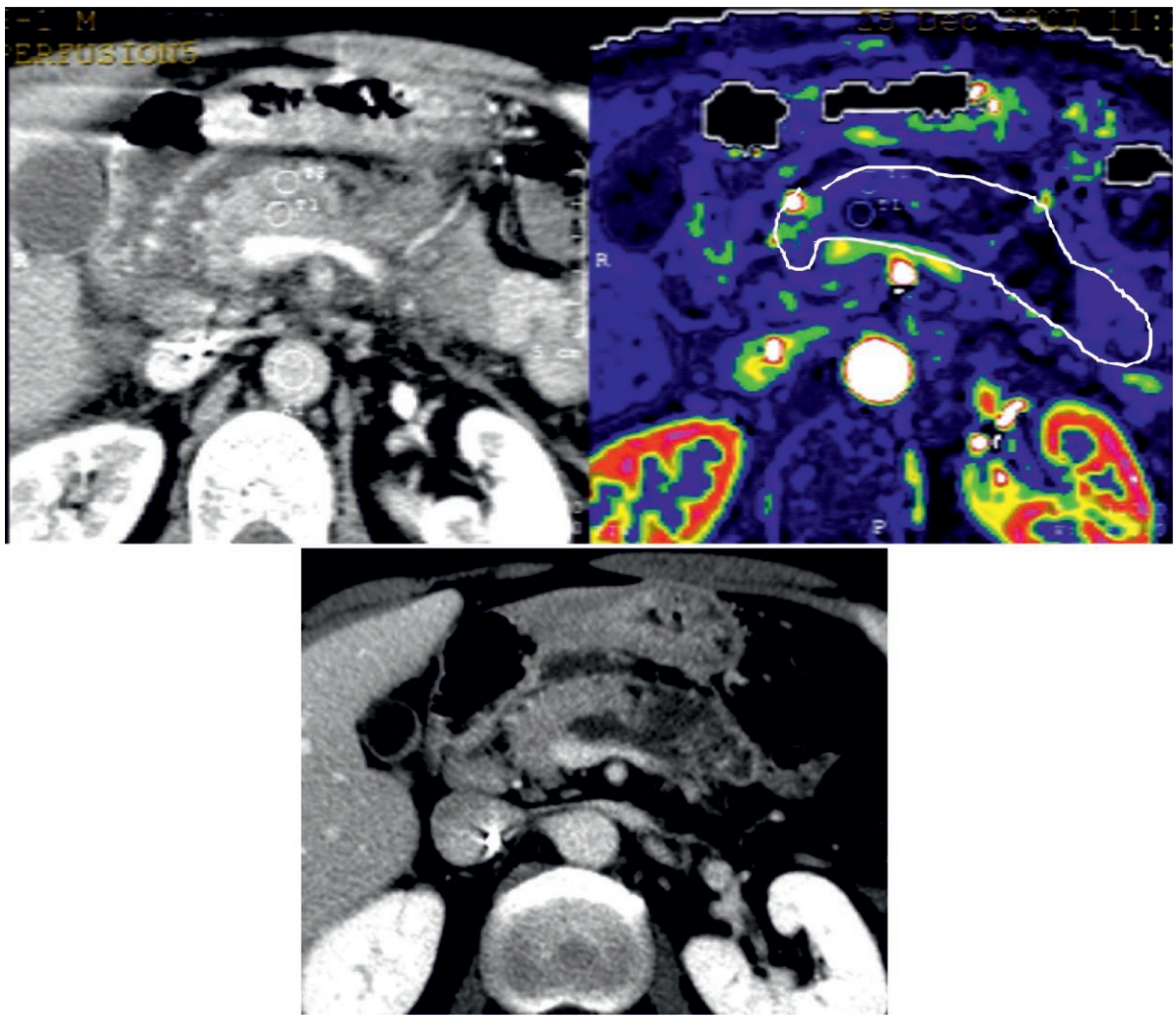

Fig. 6. CE-CT and perfusion CT imaging in a patient with ANP. In upper panel, though CE-CT depicted poorly perfused area in pancreatic body, the extent of ischemic area was not clear. Perfusion CT showed ischemic changes of the pancreas and the extent of ischemic area clearly (black color in color map). 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).

served in 84%, 62.5%, and 53% in patients in whom CRAI 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 CRAI therapy is to prevent necrotic change of the pancreas and reduce the incidence of infection of the pancreas in SAP. CRAI therapy should be indicated for patients with pancreatic ischemia before the necrotic change of the pancreas has been developed. CRAI of namafmostat is expected to prevent vasospasm and the formation of microthrombi in the ischemic pancreas. CRAI 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 CRAI 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.

BIBLIOGRAPHY

1. Bang UC, Semb S, Nojgaard C et al.: Pharmacological approach to acute pancreatitis. World J Gastroenterology 2008; 21: 2968-2976.
2. Banks PA, Freeman ML: Practice guidelines in acute pancreatitis. Am J Gastroenterol 2006; 101: 2379-2400.
3. Takeda k, Mikami Y, Fukuyama S et al.: Pancreatic ischemia associated with vasospasm in the early phase of human acute necrotizing pancreatitis. Pancreas 2005; 30: 40-49.
4. Fujii S, Hitomi Y: New synthetic inhibitors of C1r, C1 esterase, thrombin, plasmin, kalikrein and trypsin. Biochim Biophys Acta 1981; 661: 342-345.
5. Aoyama T, Ino Y, Ozeki M et al.: Pharmacological studies of FUT-175, nafamostat mesialte. I Inhibition of protease activity in vitro and in vivo experiments. Jpn J Pharmacol 1984; 35: 203-227.
6. Iwaki M, Ino Y, Motoyoshi A et al.: Pharmacological studies of FUT-175, nafamostat mesialte. V. Effects on the pancreatic enzymes and experimental acute pancreatitis in rats. Jpn J Pharmacol 1986; 41: 155-162.
7. Hirota M, Takada T, Kitamura N et al.: Fundamental and intensive care of acute pancreatitis. J Hepatobiliary Pnacreatic Sci 2010; 17: 45-52.
8. Piascik M, Rydzewska G, Milewski J et al.: The results of severe acute pancreatitis treatment with continuous regional arterial infusion of protease inhibitor and antibiotic: A randomized controlled study. Pancreas 2010 (in press).
9. Reuter SE, Redman HC, Joseph RR: Angiographic findings in pancreatitis. Am J Roentgenol Radium Ther Nucl Med 1969; 107: 56-64.
10. Rosch J, Bret J: Arteriography of the pancreas. Am J Roentogenol Radium Ther Nucl Med 1965; 94: 182-193.
11. Inoue K, Hirota M, Beppu T et al.: Angiographic features in acute pancreatitis: The severity of abdominal vessel ischemic change reflects the severity of acute pancreatitis. JOP J Pancreas (Online) 2003; 4: 207-213.
12. Yasuda T, Takeyama Y, Ueda T et al.: Nonocclusive visceral ischemia associated with severe acute pancreatitis. Pancreas 2003; 26: 95-97.
13. Hirota M, Inoue K, Kimura Y et al.: Non-occlusive mesenteric ischemia and its associated intestinal gangrene in acute pancreatitis. Pancreatology 2003; 3: 316-322.
14. Toung T, Reilly PM, Fuh KC et al.: Mesenteric vasoconstriction in response to hemorrhagic shock. Shock 2000; 13: 267-273.
15. Gilsdorf RB, Long D, Moderg A: Central nervous system influence on experimentally induced pancreatitis. JAMA 1965; 192: 394-397.
16. Dumont AS, Dumont RJ, Chow MM et al.: Cerebral vasospasm after subarachnoid hemorrhage: putative role of inflammation. Neurosurgery 2003; 53: 123-133.
17. Yanamoto H, Kikuchi H, Okamoto S: Effects of protease inhibitor and immunosuppressant on cerebral vasospasm after sub-

arachnoid hemorrhage in rabbits. Surg Neurol 1994; 41: 382-387.
18. Liu XH, Kimura T, Ishikawa H et al.: Effect of endothelin-1 on the development of hemorrhagic pancreatitis in rats. Scand J Gastroenterol 1995; 30: 276-282.
19. Ahn YM, Gajdusek C, London S et al.: Sustained arterial narrowing after prolonged exposure to perivascular endothelin. Neurosurgery 2002; 50: 843-848.
20. Foitzik T, Faulhaber J, Hubert G et al.: Endothelin receptor blockade improves fluid sequestration, pancreatic capillary blood flow, and survival in severe experimental acute pancreatitis. Ann Surg 1998; 228: 670-675.
21. Jenius H, Beall A, Woodrum D et al.: Thrombin-induced vasospasm: cellular signaling mechanism. Surgery 1998; 123: 46-50.
22. Knoepp L, Bagwell CD, Carlich P et al.: Thrombin contraction of vascular smooth muscle: implications for vasospasm. Int J Surg Investig 1999; 1: 285-290.
23. Eto M, Barandier C, Rathgeb L et al.: Thrombin suppresses endothelial nitric oxide synthase and upregulates endothelin-converting enzyme-1 expression by distinct pathways: role of Rho-Rock and mitogen-activated protein kinase. Circ Res 2001; 89: 583-590.
24. Inoue K, Hirota M, Kimura Y et al.: Further evidence for endothelin as an important mediator of pancreatic and intestinal gangrene in acute pancreatitis. Pancreatology 2003; 3: 316-322.
25. Kaller H, Patzschke K, Wegner LA et al.: Pharmacokinetic observations following intravenous administration of radioactively labeled aprotinin in volunteers. Eur J Drug Metab Pharmacokinet 1965; 3: 79-85.
26. Yamauchi J, Takeda K, Shibuya K et al.: Continuous regional applications of protease inhibitor in the treatment of acute pancreatitis. An experimental study using closed duodenal obstruction model in dogs. Pancreatology 2001; 1: 662-667.
27. Mikami Y, Takeda K, Matsuda K et al.: Rat experimental model of continuous regional arterial infusion of protease inhibitor and its effects on severe acute pancreatitis. Pancreas 2005; 30: 248-253.
28. Hayashi J, Kawarada Y, Isaji S et al.: Therapeutic effects of continuous intraarterial antibiotic infusion in preventing pancreatic infection in experimental acute necrotizing pancreatitis. Pancreas 1996; 13: 184-192.
29. Takagi K, Isaji S: Therapeutic efficacy of continuous arterial infusion of an antibiotic and a protease inhibitor via the superior mesenteric artery for acute pancreatitis in an animal model. Pancreas 2000; 21: 279-289.
30. Takeda K, Matsuno S, Sunamura M et al.: Continuous regional arterial infusion of protease inhibitor and antibiotics in acute necrotizing pancreatitis. Am J Surg 1996; 171: 394-398.
31. Takeda K, Matsuno S, Ogawa M et al.: Continuous regional arterial infusion (CRAI) therapy reduces the mortality rate of acute necrotizing pancreatitis: results of a cooperative survey in Japan. J Hepatobiliary Pancreat Surg 2001; 8: 216-220.
32. Imaizumi H, Kida M, Nishimaki H et al.: Efficacy of continuous regional arterial infusion of a protease inhibitor and antibiotic for severe acute pancreatitis in patients admitted to an intensive care unit. Pancreas 2004; 28: 369-373.
33. Yasuda T, Ueda T, Takeyama Y et al.: Treatment strategy against infection: clinical outcome of continuous regional arterial infusion, enteral nutrition, and surgery in severe acute pancreatitis. J Gastroenterol 2007; 42: 681-689.
34. Shirai K, Tanjou K, Shinohara K et al.: The effectiveness of continuous regional arterial infusion therapy with meropenem in severe acute pancreatitis compared with imipenem: A prospective, randomized study. Jpn J Gstroeneterol Surg 2008; 41: 1-11.
35. Ino Y, Arita Y, Akashi T et al.: Continuous regional arterial infusion therapy with gabexate mesilate for severe acute pancreatitis. World J Gastroenterol 2008; 14: 6382-6387.
36. Anai H, Sakaguchi H, Uchida H et al.: Continuous arterial infusion therapy for severe acute pancreatitis: correlation between CT arteriography and therapeutic effect. J Vasc Interv Radiol 1999; 10: 1335-1342.
37. Takeda K, Yamauchi J, Shibuya K et al.: Benefit of continuous regional arterial infusion of protease inhibitor and antibiotic in the management of acute necrotizing pancreatitis. Pancreatology 2001; 1: 668-673.
38. Ishikawa T, Imai M, Kamimura H et al.: Therapeutic efficacy of continuous arterial infusion of the protease inhibitor and the antibiotics and via celiac and superior mesenteric artery for severe acute pancreatitis – pilot study. Hepatogastroenterology 2009; 56: 524-528.
39. Fukuyama S, Takeda K, Matsuda K et al.: Does intra-arterial infusion therapy ameliorate pancreatic perfusion? J Abdom Emerg Med 2005; 25: 633-636.
40. British Society of Gastroenterology: United Kingdome guidelines for the management of acute pancreatitis. Gut 1998; 42: (suppl. 2): s1-s13.
41. Bize PE, Platon A, Becker CD et al.: Perfusion measurement in acute pancreatitis using dynamic perfusion MDCT. AJR Am J Roentgenol 2006; 186: 114-118.
42. Tsuji Y, Yamamoto H, Yazumi S et al.: Perfusion computerized tomography can predict pancreatic necrosis in early stages of severe acute pancreatitis. Clin Gastroenterol Hepatolo 2007; 5: 1484-1492.
43. Takeda K, Kimura K, Sato A: Dignosis of acute necrotizing pancreatitis by perfusion CT. J Jpn Panc Soc 2007; 22: 547-555.

otrzymano/received: 10.01.2011
zaakceptowano/accepted: 22.02.2011

Adres/address:
*Kazunori Takeda
Department of Surgery,
National Hospital Organization Sendai Medical Center
2-8-8, Miyagino, Miyagino-ku, Sendai, Japan, 983-8520
fax: +81 (22) 291-81-14
e-mail: kktakeda@snh.go.jp