Title: Perfusion CT is superior to angiography in predicting pancreatic necrosis in patients with severe acute pancreatitis

Short Title: Pancreatic perfusion CT and angiography

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Abbreviations used in this paper: CT, computed tomography; P-CT, perfusion CT; CECT, contrast-enhanced CT; SAP, severe acute pancreatitis; H.U, Hounsfield unit

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Abstract

Background: We performed perfusion CT (P-CT) and angiography of the pancreas in patients with severe acute pancreatitis (SAP) and compared the usefulness of these two methods in predicting the development of pancreatic necrosis.

Methods: We compared P-CT and angiography results taken within three days after symptoms onset in 21 SAP patients. We divided the pancreas into three areas, the head, body and tail, and examined each area for perfusion defects (via P-CT) and the arterial vasospasms (by angiography). Three weeks later, all patients underwent contrast-enhanced CT to confirm the development of pancreatic necrosis.

Results: Of the 21 SAP patients, 16 exhibited perfusion defects, while 17 proved positive for vasospasms in at least one area. Fourteen patients developed pancreatic necrosis. Of the 63 pancreatic areas from 21 SAP patients, perfusion defects appeared in 25 areas (39.7%), 24 of which showed vasospasms (96.0%). Angiography showed 33 areas with vasospasms (52.4%), of which 24 showed perfusion defects (72.7%). Of the 25 areas with perfusion defects, 21 developed pancreatic necrosis (84.0%). Of the 33 areas with vasospasms, 21 developed

necrosis (63.6%). Pancreatic necrosis developed only in the areas positive both for perfusion defects and for vasospasms. No areas without perfusion defect or vasospasms developed pancreatic necrosis. P-CT predicted the development of pancreatic necrosis with significantly higher accuracy than angiography.

Conclusion: While both P-CT and angiography are useful in predicting the development of pancreatic necrosis, P-CT appears to be superior in it prediction in patients with SAP.

Key words: pancreatic necrosis; perfusion CT; angiography

Introduction

Despite recent improvements in the treatment of severe acute pancreatitis (SAP), mortality rates remain high[1], reaching as high as 20% in Japan.[2] SAP often leads to necrotizing pancreatitis,[2] the most severe form of pancreatitis, that results from pancreatic ischemia caused by vasospasms of the intra-pancreatic arteries.[3] Accordingly, early detection of vasospasms in the intra-pancreatic arteries is critical in successfully treating SAP and improving prognosis.[4, 5] At present, vasospasms of the intra-pancreatic arteries can only be diagnosed accurately by angiography. However, neither unstable nor emergent cases lend themselves to examination by angiography: thus, an alternative non-invasive method for diagnosing pancreatic ischemia is required.

We recently reported that perfusion CT is capable of detecting pancreatic perfusion defects non-invasively, and accurately predict the development of pancreatic necrosis at the early stages of SAP.[6, 7] Since vasospasms of the intra-pancreatic arteries are likely to cause perfusion defects in the pancreas, it might appear reasonable to assume that perfusion defects detected by perfusion CT reflect vasospasms of the intra-pancreatic arteries. However, no reports to date have examined the relationship between pancreatic perfusion defects

detected by perfusion CT[6, 8-11] and vasospasms of the intra-pancreatic arteries as diagnosed by angiography.[3-5]

In this study, we examined the relationship between the results of pancreatic perfusion defects detected by perfusion CT and those of vasospasms of the intra-pancreatic arteries diagnosed by angiography in patients with SAP. We then compared the usefulness of the two methods in predicting the development of pancreatic necrosis.

Methods

Patients

The study population consisted of 21 consecutive adult patients with SAP admitted to the department of gastroenterology at Kurashiki Central Hospital, Kurasiki, or Kyoto University Hospital, Kyoto, Japan, within three days of the onset of symptoms during the period from 2003 through 2008. A diagnosis of acute pancreatitis was based on physical findings of acute abdominal pain, laboratory findings of abnormal elevated serum amylase and serum lipase levels (more than three times above normal), and radiographic (CT) findings of pancreatitis[12, 13] (Figures 1A and 2A). SAP was diagnosed by Atlanta classification. [14, 15] After patients were diagnosed with SAP in the emergency room, perfusion CT was performed. Angiography was performed following perfusion CT. The study excluded patients in whom acute pancreatitis was related to cancer or a side effect of endoscopic retrograde cholangiopancreatography.

All patients were treated with fluid resuscitation in the intensive care unit to maintain central venous pressures above 8 mmHg. The patients were also administered a continuous regional arterial infusion therapy of prophylactic

antibiotics (TIENAM®; Imipenem/cilastatin, BANYU PHARMACEUTICAL CO., LTD, Tokyo, Japan) with anticoagulation factors (FUTHAN®; nafamostat mesilate, TORII PHARMACEUTICAL CO., LTD, Tokyo, Japan) for 5 days. [16-18] To perform regional arterial infusion therapy, the tips of the catheters were placed at both celiac trunk and superior mesenteric artery. Patients who were free of severe ileus were administered enteral feedings through a nasojejunal tube.[19]

Study protocol

We evaluated sequentially-performed perfusion CT and angiographies of 21 patients with SAP, dividing the pancreas into three areas (the head, body, and tail) and examining each area for perfusion defects by perfusion CT and arterial vasospasms by angiography (Figures 1 and 2). The development of pancreatic necrosis was confirmed by conventional contrast-enhanced CT (CECT) at three weeks following onset. The study protocol was approved by the Ethics Committee of each institution.

Perfusion CT protocol

A 16-slice or 64-slice helical CT scanner (Toshiba Aquillion 16® or Toshiba Aquillion 64®, Toshiba Medical Systems Co., Ltd., Tochigi, Japan) was used. After obtaining transaxial images of the upper abdomen, we selected four sections (slice thickness of 5.0 mm), covering as much of the pancreas as possible. As previously described,[7] perfusion CT was performed after a bolus injection of 600 mgI/kg of contrast matter (Iomeron®; iomeprol, Eisai Co., Ltd., Tokyo, Japan) of 10 seconds duration into a cubital vein [80 kVp, 40 mA, 1.5 s/rot, 60 sec, radiological exposure; 63.8±4.7 mGy (CT dose index)].[20]

For each pixel, changes in CT value were observed and a time-density curve obtained.[6, 7,21] Commercially-available software (box-MTF, Ziosoft, Inc., Tokyo, Japan) was then used to analyze the time-density curve. We calculated the pancreatic blood flow at each pixel by perfusion CT, as previously described.[6, 7,22, 23] The deconvolution method was adjusted to enable analysis of pancreatic blood flow, which was then displayed as color maps.[6, 7,24-26] The deconvolution method required placement of regions of interest on one artery and one vein to generate arterial input functions and venous outflow functions, respectively.[24, 27-29] In this study, the splenic artery was regarded as input and the splenic vein as outflow.[6, 7, 30]

In perfusion CT, the color scale appears as a bar on the left edge of the perfusion images (Figures 1B and 2B). The red areas in the perfusion images indicate faster blood flow (>150 ml/100 g/min), while purple areas indicate slower blood flow (<5 ml/100 g/min).[6, 7]

Diagnosis of pancreatic perfusion defect by perfusion CT

We made a diagnosis of pancreatic perfusion defect by perfusion CT as previously described.[6, 7] In brief, if the color map on perfusion CT demonstrated homogeneously high pancreatic blood flow within the entire pancreatic area, the area was determined to be negative for pancreatic perfusion defects (Figure 1B). If the color map on perfusion CT demonstrated partial pancreatic perfusion defect with pancreatic blood flow slower than hepatic blood flow (Figure 2B, red arrow), the area was defined to be positive for a pancreatic perfusion defect.

Diagnosing vasospasms of the intra-pancreatic arteries

We applied angiography to examine the celiac artery, supra mesenteric artery, and branches for arterial vasospasms.[3, 4] Vasospasms of the arteries were defined as luminal narrowing of <50% (Figure 2C).

Diagnosing pancreatic necrosis

The final diagnosis of pancreatic necrosis was made by performing conventional CECT at three weeks following symptom onset (Figures 1D and 1E).[28]

Statistical analysis

The unadjusted relationship between areas with perfusion defects and areas with vasospastic arteries was assessed by chi-square analysis. The unadjusted relationship between the results of prediction for development of pancreatic necrosis by perfusion CT and by angiography was also assessed by chi-square analysis. *P* values below 0.05 were regarded as statistically significant. All statistical analysis was performed using SPSS 11 (SPSS Inc., Chicago, IL, USA).

Results

Twenty-one SAP patients underwent both perfusion CT and angiography in a sequential manner within three days following the onset of symptoms. The average age and APACHE II score of the SAP patients were 53.2±13.2 and 12.0±6.8 (mean ± standard deviation), respectively (Table 1). Of the 21 patients, 14 patients developed pancreatic necrosis, as diagnosed by conventional CECT performed three weeks following onset. Four of these SAP patients died (Table 1). Causes of death included infectious endocarditis, multiple organ failure due to infected pancreatic necrosis, multiple organ failure with systemic infection, and non-occlusive mesenteric ischemia (Table 1).

Of the 21 SAP patients, 16 were diagnosed as positive for pancreatic perfusion defects by perfusion CT in at least one area, while five were diagnosed as negative in all areas. On the other hand, of the 21 patients, 17 were diagnosed as positive in at least one area for vasospasms of the intra-pancreatic arteries by angiography, while four were negative in all areas (Table 1).

Of the 63 pancreatic areas (head, body, and tail) analyzed in the 21 SAP patients, seven occurred in the head areas, 12 in the body areas, and six in the tail areas, for a total of 25 areas (39.7%) with perfusion defects. Eight head

areas, 16 body areas, and nine tail areas for a total of 33 areas (52.4%) were diagnosed with vasospastic arteries by angiography (Table 1).

Of the 25 areas with perfusion defects detected by perfusion CT, 24 areas were positive for vasospastic arteries (96.0%) and only one negative. Of the remaining 38 areas without perfusion defects, nine areas were positive and 29 areas negative for vasospastic arteries (Table 2). Of the 33 areas with vasospastic arteries, 24 were positive (72.7%) and nine negative for perfusion defects by perfusion CT. Of the remaining 30 areas without vasospastic arteries, only one area was positive for perfusion defects. Thus, a diagnosis of the presence or absence of perfusion defects by perfusion CT and the presence or absence of vasospastic arteries by angiography was concordant for 53 (84.1%) of the 63 areas (Table 2).

Of the 25 areas with perfusion defects as determined by perfusion CT, 21 finally developed pancreatic necrosis (84.0%). Of the 33 areas with vasospastic arteries as determined by angiography, 21 developed pancreatic necrosis (63.6%). Notably, pancreatic necrosis developed only in areas positive for both perfusion defects and vasospasms of the intra-pancreatic arteries. None of the areas free of either perfusion defects or vasospasms developed pancreatic

necrosis (Table 2). Thus, both perfusion CT and angiography successfully predicted the development of pancreatic necrosis at statistically significant levels ($P < 0.01$ and $P < 0.05$, respectively) (Tables 2 and 3).

While perfusion CT and angiography showed the same sensitivity (100% vs. 100%) and negative predictive values (NPV; 100% vs. 100%) in predicting the development of pancreatic necrosis, perfusion CT showed higher specificity (90.4% vs. 71.4%) and a higher positive predictive value (PPV; 84.0% vs. 63.6%), with a positive finding under perfusion CT associated with a higher likelihood for developing pancreatic necrosis than areas identified by angiography (10.5 vs. 3.5) (Table 3). The accuracy of perfusion CT in predicting the development of pancreatic necrosis was significantly greater than for angiography (93.7% vs. 81.0%, $p < 0.05$) (Table 3).

Discussion

Pancreatic necrosis is a serious complication of SAP that determines patient prognosis.[31, 32] To improve the prognosis for SAP, it is crucial to predict the development of necrosis early and to initiate treatment as early as possible. Pancreatic necrosis results from pancreatic ischemia caused by vasospasms of the intra-pancreatic arteries.[3-5] While angiography is currently the only established method for detecting vasospasms of the intra-pancreatic arteries,[3, 4] angiography is often difficult to perform in cases of unstable or emergent patients. In response to these drawbacks, we recently applied perfusion CT for patients with SAP. We found perfusion CT useful in the early detection of ischemic change in the pancreas. Here, we compared usefulness of angiography and perfusion CT in predicting the development of pancreatic necrosis in 21 patients with SAP, and found that both perfusion CT and angiography are useful for predicting development of pancreatic necrosis, but perfusion CT is superior to angiography for prediction.

Our study divided the whole pancreas into three areas, the head, body, and tail, and evaluated the results of perfusion CT and angiography for each area. Our examination showed 24 areas positive for both perfusion defects by

perfusion CT and vasospasms by angiography and 29 areas negative by either method. Thus, the results of perfusion CT and angiography were concordant in 84.1% of all pancreatic areas from the 21 patients. The data indicates a high correlation between perfusion defects detected by perfusion CT and vasospasms of the intra-pancreatic arteries detected by angiography. However, it is worth noting that areas with vasospastic arteries clearly outnumber areas with perfusion defects (33 vs. 25); Moreover, although not all areas positive for vasospastic arteries of the intra-pancreatic arteries by angiography were positive for perfusion defects, most areas with perfusion defects by perfusion CT were positive for vasospasms of the intra-pancreatic arteries, potentially suggesting that perfusion defects detected by perfusion CT in most cases result from vasospasms of the intra-pancreatic arteries. In a finding that supports this idea, Inoue et al. reported that endothelin-1, which can produce spastic change in the arteries, is an important mediator in the development of pancreatic ischemia in cases of severe acute pancreatitis.[33]

Our study found both perfusion CT and angiography useful in predicting the development of pancreatic necrosis. Indeed, sensitivity and NPV were 100% for both methods, and specificities were 90.4% and 71.4%, respectively, for

perfusion CT and angiography. The angiography data in this study was comparable to data from previous studies,[3,4] while the perfusion CT data was comparable to data from our previous study.[7] An important finding of the present study is that 84.0% of the areas with perfusion defects developed pancreatic necrosis; this was true of only 63.6% of the areas with vasospastic arteries. Moreover, none of the areas negative for both perfusion defects or vasospastic arteries developed pancreatic necrosis. In short, perfusion CT proved more accurate in predicting the development of pancreatic necrosis than angiography.

The reasons why the discrepancy exists between angiography and perfusion CT and why perfusion CT is superior to angiography for predicting pancreatic necrosis in patients with SAP are unknown at present. It has been shown that perfusion CT can diagnose microcirculation failure[24,29,34,35]. In contrast, angiography can diagnose spastic lesions of large arteries, which might not always result in impairment of microcirculation. Thus, our data might suggest that vasospasm of large arteries does not always result in impairment of microcirculation. In any event, our present data may suggest that disturbance of microcirculation detected by perfusion CT is a critical event for development of pancreatic necrosis, and thus, perfusion CT is superior to angiography for

predicting development of pancreatic necrosis.

We should emphasize that pancreatic necrosis developed only in areas positive for both perfusion CT and angiography, and none of the areas negative by either method developed necrosis in this study. Therefore, patients positive under both perfusion CT and angiography would appear to be at very high risk for pancreatic necrosis. In contrast, a negative result for either perfusion CT or angiography alone might rule out the future development of necrosis. This data is consistent with our previous study,[7] which showed that 9 of 10 patients in whom perfusion defects were detected by perfusion CT developed pancreatic necrosis, whereas necrosis did not develop in any patient in whom no perfusion defects were detected. The data is also in agreement with the report by Takeda et al. showing that by analyzing 147 patients with acute necrotizing pancreatitis no pancreatic tissue with the absence of vasospasms in the intra-pancreatic arteries developed pancreatic necrosis.[3]

As previously reported, prognosis of acute necrotizing pancreatitis[1-3] and that of ischemic acute pancreatitis[4-9] are generally poor. However, the prognosis of our SAP patients with vasospasm or ischemia was not so poor in this study. Although the reason for such different outcomes between our patients and those

There has been vigorous recent debate on treatment methods for SAP. For

instance, the effectiveness of prophylactic antibiotics[36-41] in cases of SAP

remains an open question. Some reports argue for the efficacy of prophylactic

antibiotics,[41] while others reach the opposite finding.[39,40]   If the goal of a study is

to determine whether administering prophylactic antibiotics prevents pancreatic

necrosis, the most severe manifestation of SAP, antibiotics must, of course, be

administered before pancreatic necrosis actually develops. Indeed, Besselink et

al. reported that in their cohort study infection occurred early in acute pancreatitis and had a significant impact on mortality, suggesting that prophylactic strategies should be examined as early intervention.[41] In this regard, all previous studies have involved the administration of antibiotics to patients in whom pancreatic necrosis had already been diagnosed.[39-41] As we demonstrate in this paper, perfusion CT offers a safe and accurate route to diagnosing pancreatic ischemia, a precondition of pancreatic necrosis. Thus, by enabling the diagnosis of pancreatic ischemia, perfusion CT should prove useful in studies investigating effectiveness of the administration of antibiotics as a prophylactic measure.

In conclusion, this study found both perfusion CT and angiography useful in predicting the development of pancreatic necrosis, although perfusion CT proved more accurate. Perfusion CT, moreover, is less invasive and more readily available than angiography. Further study is needed to ascertain whether perfusion CT can substitute for angiography as a primary screening method when evaluating the severity of acute pancreatitis.

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Figure 1   Severe acute pancreatitis without vasospasms of the

intra-pancreatic arteries or pancreatic perfusion defects

Shown here are images from patient 2 in Table 2. The pancreas is homogeneously enhanced in contrast-enhanced CT (A). In perfusion CT (B), pancreatic blood flow is homogeneously high, and the pancreas is free of any areas with perfusion defects (red arrow). Angiography showed no vasospastic arteries in the pancreas. Mild diffuse staining of the pancreas was observed (White arrows) (C). Contrast-enhanced CT three weeks later showed no signs of pancreatic necrosis (D).

Figure 2   Severe acute pancreatitis with vasospasms of the

intra-pancreatic arteries and pancreatic perfusion defects

Shown here are images from patient 6 in Table 2. The pancreas is homogeneously enhanced in contrast-enhanced CT (A). Perfusion CT shows markedly slower blood flow (red arrows) in the pancreas body (B). Thus, this case was diagnosed as positive for perfusion defect. Angiography (C) shows the splenic artery (white arrow) and its branches (Blue arrows) were found to be positive for vasospasms in the pancreas head, body and tail. Contrast-enhanced CT three weeks later detected pancreatic necrosis in the body (D, yellow arrow), and viable tissue in the tail (the image was not included in this slice).

Figure1

Figure2