Feasibility of Measuring Human Pancreatic Perfusion In Vivo Using Imaging Techniques

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Objective: The objective of this study was to demonstrate the feasibility of pancreatic perfusion computed tomography (CT) and review pancreatic perfusion measurements by various imaging modalities.

Methods: Dynamic CT data from 8 patients (4 men; mean age, 64.8 [SD, 12.1] years; range, 40–80 years) with normal pancreas were analyzed using 2 analytical models: the maximum-slope and compartment-model methods. Literature search was also performed.

Results: Although the perfusion value estimated by the maximum-slope method (88.1 [SD, 42.1] mL/min per 100 mL) was significantly smaller than that of the compartment-model method (127.0 [SD, 70.5]; $P < 0.001$), there was a linear correlation between them ($r = 0.97$, $P < 0.001$). In the literature review, 15 studies that reported the absolute values of normal pancreatic perfusion, by using perfusion CT, dynamic magnetic resonance imaging, hydrogen gas clearance method, and ^{15}O-H_2O–positron emission tomography were found. The reported mean values of normal pancreatic perfusion ranged from 38.4 to 356 mL/min per 100 mL, and there was a great deal of individual variation.

Conclusions: Perfusion CT may provide reliable perfusion measurements of the pancreas, and the normal value was estimated at around 100 mL/min per 100 mL with a great deal of individual variation. The maximum-slope method may provide a lower perfusion value compared with the compartment-model method.

Key Words: pancreas, perfusion, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET)

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The noninvasive quantification of blood flow of abdominal organs has been challenging. To the best of our knowledge, human pancreatic perfusion measurement in vivo was first archived by Ishida et al[1] using the hydrogen gas clearance method under laparoscopy. The recent technical development of computed tomography (CT) equipment and perfusion calculation software enables us to obtain pancreatic parenchymal blood flow noninvasively, not only for research purposes but also in the clinical setting.

The determination of tissue perfusion using CT is based on examining the relationship between the arterial, tissue, and, in some methods, venous enhancement after the introduction of a bolus of iodinated contrast media.[2] Repeated rapid CT scans are acquired at the same location to allow determination of time-attenuation curves (TACs). Several methods have been proposed for analyzing these curves to obtain a perfusion value, such as the indicator dilution theory (moment method), the compartment-model method, the maximum-slope method, and a linear systems approach (deconvolution method).[2] For abdominal organs and tumors, the maximum-slope method was first reported by Miles et al.[3] Although the principle of the maximum-slope method is quite simple, making it attractive, this method may underestimate perfusion when the "no venous outflow" assumption cannot be made: theoretically, there should be no contrast material washout before the time of the maximum slope of the tissue TAC, but in reality, some washout may occur in human organs.[2–4] Materne et al[5] proposed the dual-input 1-compartment-model method for hepatic arterial and portal perfusion measurements, in which one does not need to assume "no venous outflow." Miyazaki et al[4] compared the results of maximum-slope and dual-input 1-compartment-model methods in human hepatic perfusion CT and concluded that both arterial and portal perfusion obtained with the maximum-slope method were lower than those obtained with the dual-input 1-compartment-model method, suggesting possible underestimation by the maximum-slope method. Originally, this method was proposed for a dual-input organ, but can be applied to a single-input organ such as the pancreas.

Some other modalities have been also proposed for quantitative evaluation of pancreatic perfusion in humans, including magnetic resonance imaging (MRI),[6] hydrogen gas clearance method under laparoscopy[1] and endoscopy,[7] and ^{15}O-labeled water positron emission tomography (PET).[8] However, because there is no practical method to evaluate human pancreatic perfusion in vivo as a criterion standard, it is quite difficult to conclude which method is best for this purpose.

In the first part of this study, we demonstrated the difference between the maximum-slope and compartment-model methods in pancreatic perfusion CT using the same dynamic CT data from the same patients. Next, we reviewed pancreatic perfusion analyses by various imaging modalities.

MATERIALS AND METHODS

Patients

We reviewed the dynamic CT data obtained in our previous study[4] and selected the patients in whom the pancreas was included in the dynamic CT sequence. Institutional review board approval was obtained, and all patients gave their written informed consent to participate in this study.

Ten studies of 9 patients were found, and their dynamic CT data were reanalyzed. One patient (1 study) revealed pancreatic head cancer and was excluded from further analysis. The remaining 8 patients (4 men and 4 women; mean age, 64.8 [SD, 12.1] years; range, 40–80 years) did not show any radiological evidence of pancreatic disease, but 3 patients have diabetes. Two of 6 patients with chronic hepatitis C virus infection had hepatocellular carcinomas, 1 patient (2 studies) was shown to have multiple metastatic liver tumors from melanoma, and 1 patient had breast cancer with normal liver.

Perfusion CT

After an overnight fast, a single-location dynamic CT sequence was obtained with a 64-detector CT scanner (Aquilion

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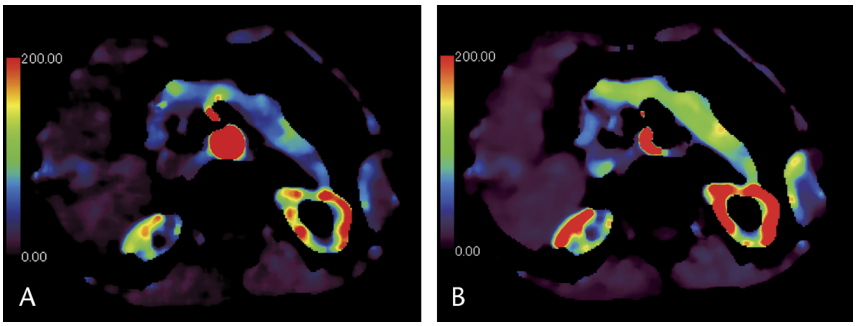

FIGURE 1. Perfusion CT of the pancreas created by the maximum-slope method (A) and compartment-model method (B). Both techniques provide similar images, but the obtained pancreatic parenchymal perfusion was slightly lower in the maximum-slope method compared with the compartment-model method.

64; Toshiba Medical Systems, Tochigi, Japan). An initial nonenhanced helical CT scan was obtained to select the slice for single-location dynamic CT including the liver, spleen, and portal vein. Image data were obtained dynamically (0.5 second/rotation, 8 × 4- mm slice collimation, 512 × 512 matrices, 120 kV, 50–165 mAs) every 2 seconds from the initiation of contrast material administration to 40 seconds.

For the bolus injection of contrast media, an 18-gauge cannula was placed in an antecubital vein, and 40 mL of nonionic contrast media (iopamidol 370 mL I/mL [Iopamiron370]; Bayer Yakuhin, Osaka, Japan) was given at a rate of 8 mL/s using a power injector. The patients were instructed to hold their breath during the scan time under oxygen inhalation, followed by quiet breathing.

The dynamic CT data were transferred to the workstation (Body Perfusion; Toshiba Medical Systems) by DICOM protocol. The data were compressed to 256 × 256 matrices, and color-scaled perfusion maps were constructed, using the 2 analytical models, that is, the maximum-slope and compartment-model methods. The detailed principles of these methods have been discussed elsewhere.[2,4]

Perfusion is calculated as the concentration of contrast media in the tissue divided by the difference between total amount of contrast media that has flowed into the tissue and the amount of contrast media that has flowed out of the tissue:

$$\frac{F}{V} = \frac{c(t')}{\int_0^{t'} a(t)\ \mathrm{dt} - \int_0^{t'} v(t)\ \mathrm{dt}} \qquad (1)$$

where F/V is flow per volume of the tissue, and $c(t')$, $a(t)$, and $v(t)$ are the concentration of contrast media in the tissue, artery, and vein, respectively. By restricting the time of measurement to before the time the contrast media starts to flow out of the tissue [$v(t) = 0$], the tissue perfusion can be calculated by dividing the peak gradient of the pancreatic TAC by the maximum arterial enhancement,

$$\frac{F}{V} = \frac{\frac{d}{\mathrm{dt}}\, c(t)\max}{a(t)\max} \qquad (2)$$

This simple method is called the "maximum-slope method." It should be noted that this method may underestimate perfusion when the "no venous outflow" assumption cannot be made. Because of this, a high-bolus injection is an absolute requirement for acquisition of accurate data.

A 1-compartment-model method was proposed by Materne et al[5] and summarized by the following formula:

$$\mathrm{dc}(t) = k_a a(t)\cdot(t - T_t) - k_v c(t) \qquad (3)$$

in which k_a and k_v reflect arterial inflow and hepatic outflow constants, respectively. The delayed parameter (T_t) represents the transit time from the aorta to the tissue evaluated. The values of k_a and k_v are calculated using the Levenberg-Marquardt method, and the tissue perfusion is calculated as k_a/E, where E is the extraction fraction of the contrast media in the tissue, which is assumed to be 1 in the normal pancreatic tissue because the contrast media has free access to the extravascular space. In this method, perfusion is calculated using all TAC points, and one does not need to assume "no venous outflow."

Parenchymal regions of interest (ROIs) were drawn as large as possible to allow for regional variations in the pancreatic head, body, or tail. Vessels and pancreatic margins were carefully excluded from ROIs with reference to conventional enhanced CT images. Regions of interest were also drawn in the aorta as an input

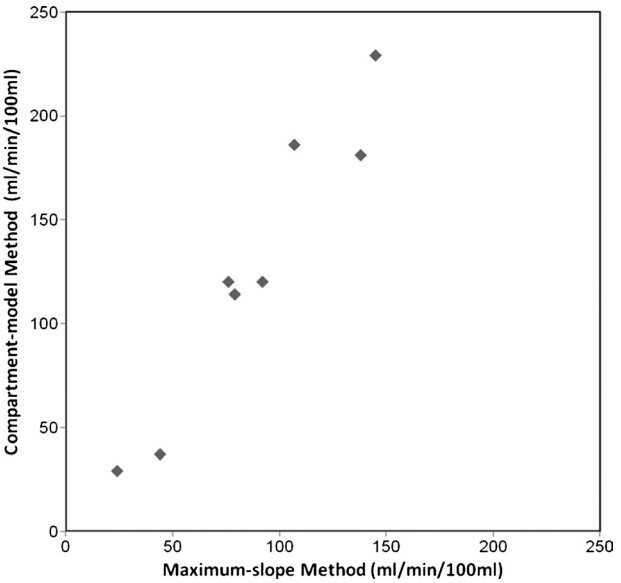

FIGURE 2. Correlation between the perfusion values of pancreas obtained by the maximum-slope and compartment-model methods. The values obtained by the maximum-slope method were lower than those obtained by the compartment-model method ($P < 0.001$), although there was a linear correlation between them ($r = 0.97$, $P < 0.001$).

TABLE 1. Reported Perfusion Values of the Human Pancreas In Vivo by Various Techniques

Algorithm	Author	Year	Modality	Contrast Media: Total Amount	Contrast Media: Injection, mL/s	Normal Perfusion, mL/min per 100 mL: Range	Normal Perfusion, mL/min per 100 mL: Mean (SD)	Normal Subjects Examined: n	Normal Subjects Examined: Age Distribution, Mean (SD), y	Diseases	Perfusion Value, Mean (SD), mL/min per 100 mL
Maximum-slope method											
	Bize et al[9]	2006	CT	40 mL of iopromide300	5	9.4–228.1	61.2	21	32–92	AP	47.2
	Takeda et al[10]	2007	CT	NR	5	NR	64.1 (9.2)*	10	26–54	AP	37.5 (6.1) (e), 6.5 (3.1) (n)
	Current study	2010	CT	40 mL of iopamidol370	8	24–145	88.1 (42.1)	8	40–80, 64.8 (12.1)	—	—
	Kandel et al[11]	2009	CT	60 mL of 350 mg I/mL	8	20–187 (body)	94 (59)	30	48–88	Cancer	32 (28)
	Tsushima and Kusano[12]	1998	CT	40 mL ioversol 320	5	55.4–169.8	96.3 (25.0)	23	25–71	—	—
	Miles et al[3]	1995	CT	50 mL of iopamidol 300	Rapid	125–166	152 (16)	8	NR	—	—
Deconvolution method											
	Tsuji et al[13]	2007	CT	40 mL of iodixanol	4	NR	38.4 (12.0)	5	28.2	AP	57.3 (55.9) (e), 10.9 (2.0) (n)
	Xu et al[14]	2009	CT	50 mL of iopromide 300	5	NR	135.24 (48.36)*	36	56.97 (11.59)	Cancer	29.50 (21.44)
	d'Assignies et al[15]	2009	CT	40 mL of iobitridol 350	4	NR	130.4	28	18–78, 53	Endocrine tumors	239.8
	Wang et al[16]	2005	CT	50 mL of 300 mL I/mL	4	NR	176.54 (76.18)	31	27–74, 53.57	Cancer	74.89 (91.50)
Compartment-model method											
	Current study	2010	CT		8	29–229	127 (70.5)	8	40–80, 64.8 (12.1)	—	—
	Sheiman and Sitek[17]	2008	CT	40 mL of ioversol 320	4	96.1–640.5	356 (190)		35–57 (median, 40)	—	—
Patlak analysis											
	Huang et al[18]	2009	CT	50 mL of 300 mg I/mL	5–8	NR	90.6 (29.2)	42	25–74, 52.5	Cancer	22.9 (10.64)
Compartment-model method on MRI											
	Bali et al[6]	2008	MRI	Gadodiamide 0.05 mmol/kg	3.5	NR	207 (77)*	10	22–29, 24.7 (1.9)	—	—
Hydrogen gas clearance method											
	Ishida et al[1]	1983	Laparoscopy	—	—	NR	87.8 (20.6)	9	NR	CP	58.0 (33.3)
	Lewis et al[7]	2000	Endoscopy	—	—	NR	91.7 (16.5)	11	29–65 (median, 45)	CP	51.5 (6.3)
^{19}O-H_2O–PET											
	Komar et al[8]	2009	PET	—	—	NR	113.8 (48.2)	7	NR	Tumors	45.7 (18.2)

*In these reports, perfusion at the pancreatic body was expressed.

NR indicates not reported; AP, acute pancreatitis; CP, chronic pancreatitis; e, edematous acute pancreatitis; n, necrotizing acute pancreatitis.

function. The same ROIs were drawn on the images constructed by both methods to accurately compare the results from 2 methods.

Dynamic CT data acquisition was performed by one of the authors (M.M.), and ROI settings and the perfusion map construction were performed by Y.T.

Literature Review

Japana Centra Revuo Medicina (Japanese medical literature data base) and MEDLINE were searched using the key words "perfusion" and "pancreas" and their corresponding Japanese terms. Only full articles reporting absolute values of normal pancreatic perfusion (per volume or per weight) were selected. The perfusion was expressed as milliliters per minute per 100 milliliters. When perfusion was expressed as milliliters per minute per 100 grams, the unit was converted by using a specific gravity of 1.0. Case reports, meeting abstracts, and the articles reporting only relative values were excluded. Data search was performed by one of the authors (Y.T.), and all these articles were reviewed entirely.

Statistical Analyses

Numerical variables were expressed as mean (SD). The paired Student t test and linear regression analysis were used, and $P < 0.05$ was considered significant.

RESULTS

Comparison Between the Maximum-Slope and Compartment Model Methods

In 1 patient, the whole pancreas was included in the dynamic CT data; thus, the perfusion was calculated by both methods at the head (92 and 127 mL/min per 100 mL, respectively), body (83 and 117 mL/min per 100 mL), and tail (94 and 115 mL/min per 100 mL) (Fig. 1). In 2 patients, perfusion data were obtained at the pancreatic head, in 4 patients at the body, and in 1 patient at the tail.

The perfusion value of the normal pancreas by the maximum-slope method (88.1 [SD, 42.1] mL/min per 100 mL; range, 24–145 mL/min per 100 mL) was significantly smaller than that estimated by the compartment-model method (127.0 [SD, 70.5] mL/min per 100 mL; range, 29–229 mL/min per 100 mL; $P < 0.001$) (in the patient in whom perfusion values were obtained at the head, body, and tail, the perfusion value at the body was used for this analysis). There was a significant linear correlation between them ($r = 0.97$, $P < 0.001$; Fig. 2).

In 1 patient, perfusion CT was performed twice within a 1-month interval, and the obtained perfusion values at the body were 138 and 156 mL/min per 100 mL by the maximum-slope method and 181 and 209 mL/min per 100 mL by the compartment-model method, respectively.

Literature Review

We found 15 studies that were consistent with our criteria (Table 1, Fig. 3), and 11 studies reported perfusion values of various pancreatic diseases. Eleven studies used perfusion CT technique: in 5 studies, the perfusion values were calculated by the maximum-slope method, in 4 studies by the deconvolution method, in 1 study by the compartment-model method, and in 1 study by Patlak analysis. There was also 1 study using MRI with the compartment-model method, 1 study using ^{15}O-H_2O–PET, and 2 using hydrogen gas clearance methods.

The reported mean perfusion values of the normal pancreas had a wide range: the minimum mean value (38.4 mL/min per

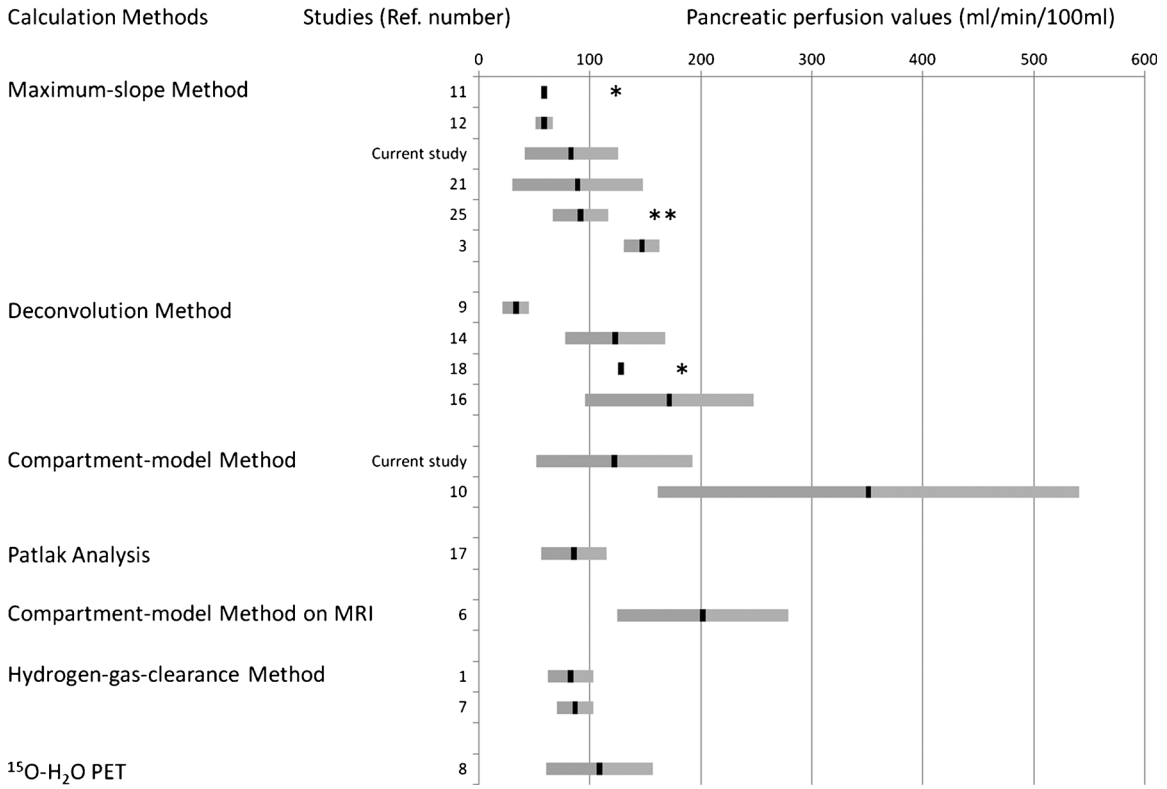

FIGURE 3. Reported perfusion values of the normal human pancreas in vivo by various techniques. Bars indicate the mean (SD). The reported mean perfusion values of normal pancreatic parenchyma had a wide range. *SD was not reported. **SD was recalculated from the original data.

100 mL) was obtained by perfusion CT using the deconvolution method,[13] and the maximum mean value (356 mL/min per 100 mL) was by the compartment-model analysis.[17] There was also a great deal of individual variation in the reported perfusion values of the pancreas. For instance, Bize et al[9] reported the normal pancreatic perfusion values between 9.4 and 228.1 mL/min per 100 mL.

In 3 studies,[9,10,13] the perfusion values in acute pancreatitis were reported: Bize et al[9] reported decreased perfusion in acute pancreatitis (47.2 mL/min per 100 mL) compared with the normal control (61.2 mL/min per 100 mL), and Takeda et al[10] and Tsuji et al[13] reported significantly decreased perfusion in acute necrotizing pancreatitis (6.5 and 10.9 mL/min per 100 mL, respectively) compared with acute edematous pancreatitis (37.5 and 57.3 mL/min per 100 mL, respectively). In chronic pancreatitis, the perfusion values were also significantly decreased.[1,7] Pancreatic carcinomas showed a decreased perfusion compared with the normal parenchyma,[14–16,18–20] but the perfusion of islet cell carcinomas was reported to be increased.[15]

DISCUSSION

The usefulness and importance of measuring pancreatic parenchymal perfusion in various diseases has been reported by many investigators. In acute pancreatitis, early and accurate detection of pancreatic ischemia and prediction of pancreatic necrosis caused by vasospasm are quite important in improving the mortality rate in severe cases.[13,21,22] Tsuji et al[13] reported that perfusion CT was very useful in detecting ischemia in the early stage of severe acute pancreatitis and recommended its routine use. In chronic pancreatitis, a significantly decreased pancreatic perfusion compared with that in normal control patients has also been reported by using hydrogen gas clearance methods.[1,7] This finding is compatible with pathological changes in chronic pancreatitis, such as poor vascularity with severe periductal and arterial fibrosis, decreased numbers of arterioles, and sparseness of capillary networks.[7,23] It has been reported that pancreatic cancer may reveal a decreased perfusion compared with normal parenchyma.[11,14,16,18] and that there was a high correlation between tumor blood flow and intratumoral microvascular density.[15] Perfusion evaluation may also be useful in predicting tumor response to concurrent chemotherapy and radiation therapy.[19]

However, because of the inaccessibility of the organ and the lack of an established noninvasive method, quantification of pancreatic perfusion still presents a challenge in routine clinical practice. Although several imaging techniques have been proposed for perfusion measurement of the pancreas, perfusion CT may be the best choice not only because of easy access to a CT unit, but also because of a linear correlation between iodinated contrast media concentration and density (CT number). The linearity between the tracer and signal obtained by an imaging technique is essential for quantitative measurement using a calculation model. On MRI, the linearity between concentration of gadolinium contrast media and signal intensity is not guaranteed.

A problem common to all these methods, when used in humans, is the lack of an accepted reference standard. This also partly explains why the reported perfusion values of normal pancreatic tissue measured in previous studies has varied substantially. We cannot conclude which method is most accurate. However, as previously shown,[24,25] ^{15}O-H_2O–PET may be the most reproducible and reliable method for the quantification of blood flow in tumor and other tissues such as the brain and heart. ^{15}O-H_2O–PET demonstrated the perfusion value of the pancreatic parenchyma as 113.8 (SD, 48.2) mL/min per 100 mL. Excluding the exceptional data,[13,17] the mean perfusion values of normal pancreatic parenchyma that were evaluated by perfusion CT technique were in almost the same range, despite the different models used. Although these results came from different subjects, making case-by-case comparison impossible, these results partially support the reliability of perfusion CT for the purpose of pancreatic perfusion measurement. In the current study, there was a significant linear correlation between the perfusion values calculated by the maximum-slope and compartment-model methods, but the former was significantly lower than the latter. These results were not surprising, because it has been speculated that the broken assumption of no venous outflow in the maximum-slope methods may result in underestimation.[2,4] Similar results were also reported in perfusion CT of the liver.[4] We suspected that the compartment-model method would provide reliable results in pancreatic perfusion measurement. We did not evaluate the reproducibility of pancreatic perfusion CT. However, in 1 patient in whom perfusion CT was performed twice, the obtained perfusion values were similar.

At the same time, it should be noted that the perfusion value of normal pancreatic parenchyma showed a wide range among individuals. For instance, in our current study, the perfusion value was distributed from 29 to 229 mL/min per 100 mL. It is unclear to us what factors contributed to such a wide range of normal perfusion values. Some previous studies[6,10,14] reported that the pancreatic perfusion value did not depend on the anatomical location. In fact, in 1 patient in whom the entire pancreas was included in the perfusion map (Fig. 1), the perfusion value was almost homogenous. Tsushima and Kusano[12] demonstrated an age-dependent decline in parenchymal perfusion in the normal human pancreas by using perfusion CT technique. In our current study, such a tendency was not observed, possibly because of the small number of the patients examined, but age-related atrophy, particularly affecting the exocrine portion of the pancreas, may be responsible for the decline in parenchymal perfusion.[12,26,27] In our study, the patients without known pancreatic disease, and in whom the pancreas was radiologically normal, were selected as the subjects, but some pathological changes may be present (such as an early stage of chronic pancreatitis), which may reduce pancreatic perfusion. Further research is necessary to clarify possible factors affecting pancreatic parenchymal perfusion.

In conclusion, perfusion CT may provide reliable perfusion measurement in the pancreas, and the normal value was estimated around 100 mL/min per 100 mL despite a wide range of normal values. The maximum-slope method may provide lower perfusion value compared with the compartment-model method.

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