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CT hepatic perfusion measurement: Comparison of three analytic methods

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ABSTRACT

Objectives: To compare the efficacy of three analytic methods, maximum slope (MS), dual-input single-compartment model (CM) and deconvolution (DC), for CT measurements of hepatic perfusion and assess the effects of extra-hepatic systemic factors.

Materials and methods: Eighty-eight patients who were suspected of having metastatic liver tumors underwent hepatic CT perfusion. The scans were performed at the hepatic hilum 7–77 s after administration of contrast material. Hepatic arterial and portal perfusions (HAP and HPP, ml/min/100 ml) and arterial perfusion fraction (APF, %) were calculated with the three methods, followed by correlation assessment. Partial correlation analysis was used to assess the effects on hepatic perfusion values by various factors such as age, sex, risk of cardiovascular diseases, arrival time of contrast material at abdominal aorta, transit time from abdominal aorta to hepatic parenchyma, and liver dysfunction.

Results: Mean HAP of MS was significantly higher than DC. HPP of CM was significantly higher than MS and CM, and HPP of MS was significantly higher than DC. There was no significant difference in APF. HAP and APF showed significant and moderate correlations among the methods. HPP showed significant and moderate correlations between CM and DC, and poor correlation between MS and CM or DC. All methods showed weak correlations between HAP or APF and age or sex. Finally, MS showed weak correlations between HAP or HPP and arrival time or cardiovascular risks.

Conclusions: Hepatic perfusion values arrived at with the three methods are not interchangeable. CM and DC are less susceptible to extra-hepatic systemic factors.

1. Introduction

Because various liver diseases lead to significant changes in hepatic microcirculation, quantification of hepatic perfusion can improve the assessment and management of liver diseases. Various imaging techniques, such as xenon-enhanced computed tomography (CT), isotope scintigraphy, and Doppler ultrasound, as well as positron emission tomography using oxygen-15 labeled water, have been used for evaluation of hepatic perfusion. However, their acceptance and clinical application are limited due to high cost, low spatial resolution, or poor reproducibility [1,2].

CT perfusion with cine imaging and administration of contrast media is a relatively new method of hepatic perfusion analysis in which quantitative maps of tissue perfusion can be created from cine CT data and displayed by using a color scale, which allows for quantification of perfusion in absolute units at high spatial resolution [1–12]. This method is reportedly useful for evaluation of liver damage or severity of hepatic fibrosis associated with chronic liver disease [3–6], assessment of hepatic tumor perfusion [7,8], prediction of tumor response to therapies [9,10], and evaluation of hepatic perfusion changes after surgical or radiological interventions [11,12].

However, some problems remain with using this method, such as long breathholding for portal flow measurement, limited craniocaudal scan range, separation of arterial and portal blood flow, standardization of analytic methods, and unknown effects of extra-hepatic factors [1,2]. Our study dealt with the latter two problems.

The purpose of this study was thus to compare the efficacy of three analytic methods, maximum slope (MS), dual-input single-compartment model (CM), and deconvolution (DC), for CT measurements of hepatic perfusion and assess the effect of systemic and local factors on hepatic perfusion-related values estimated by CT perfusion. The three methods were the most widely used when this study was started.

2. Materials and methods

2.1. Patients

We considered 104 consecutive patients at high risk for malignant liver tumor as candidates in this study. Eight-five of these were suspected to have or had lung cancer, and abdomino-pelvic

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CT examinations were performed for preoperative systemic survey. CT hepatic perfusion was performed as the baseline study for early detection of liver metastasis in the post-operative period. The other 19 were suspected to have primary malignant liver tumor by ultrasonography or tumor markers done prior to the CT examinations. CT hepatic perfusion was performed for the pre-treatment evaluation of liver function. Before being enrolled, all subjects gave their informed consent after the nature of the procedure had been fully explained in accordance with the regulations of the institutional review board that approved our study. Eight patients were excluded from the study population because a 20-gauge catheter could not be placed properly in the peripheral vein of four patients, while two patients were found to have a history of active asthma and two of allergy to iodinated contrast medium. In addition, eight patients were excluded who showed malignant hepatic tumors on CT or other imaging modalities, including followed-up examinations, because previous reports have suggested significant changes occur in the perfusion of livers with overt malignant tumors [2,11].

Finally, 88 patients (50 men and 38 women, mean age: 67.5 years) were considered eligible for this study. Three patients had hepatic hemangiomas which were smaller than or equal to 2 cm in diameter. There were four patients with hepatic dysfunction due to ethanol-induced or non-alcoholic steatohepatitis, ten with type B and one with type C hepatitis virus infection and all 15 were classified as Child-Pugh A. One patient was diagnosed with chronic hepatitis and none with cirrhosis. Hepatitis and hepatic dysfunction were recorded as intra-hepatic factors. Risk of cardiovascular disease (including a history of myocardial infarction, angina pectoris, hypertension, diabetes mellitus, arteriosclerosis obliterans, or dialysis recorded on the patients' charts) was recorded as an extra-hepatic factor which could affect estimated hepatic perfusion values.

2.2. Perfusion CT

CT examinations were performed with multidetector-row scanners (Aquilion 16 or Aquilion 64; Toshiba Medical Systems, Ohtawara, Japan). Slices for CT perfusion were selected from pre-contrast abdomino-pelvic helical scans and included slices of the liver, abdominal aorta, and main portal vein. A 20-gauge catheter was placed in the antecubital vein and 40 ml of nonionic contrast material (Iopamiron 370; Bayer HealthCare, Osaka, Japan) was administered at a rate of 5 ml/s with a power injector. Dynamic scans at four slice levels were performed at the hepatic hilum 7–77 s after injection of contrast material under breathholding. Images were acquired with the following parameters for both scanners: 8 mm thickness, 4 slices, 512 × 512 matrices, 80 kV, 160 mA, 0.5 s/rot. First, 15 scans were performed every 2 s during one breathhold. Next, after a 9.6-s rest, three scans were performed every 7 s during one breathhold, and this procedure was repeated after another 9.6-s rest. A delayed-enhanced abdomino-pelvic scan was also acquired 70 s after additional injection of 60 ml of contrast material at a rate of 2 ml/s.

2.3. Image analysis

For the MS and CM methods, the CT images were then transferred to a personal computer (CF-Y5; Panasonic, Osaka, Japan). If necessary, respiratory misregistrations were compensated for manually by using the four slices. ROIs were placed on the abdominal aorta at the level of the celiac axis, the main portal vein, the liver and the spleen to generate time–density curves (TDC). Examples of ROI placements and TDCs are shown in Fig. 1. Subsequently, hepatic arterial and portal perfusions (HAP and HPP, ml/min/100 ml) and arterial perfusion fraction (APF, %) were calculated with the MS and CM methods using free software (basama Perfusion Ver. 3.1.0.4). For the DC method, the CT images were transferred to a workstation (Advantage Workstation; GE Healthcare Japan, Hino, Japan) and perfusion parameters were calculated by using commercially available software (CT perfusion 3; GE Healthcare Japan, Hino, Japan).

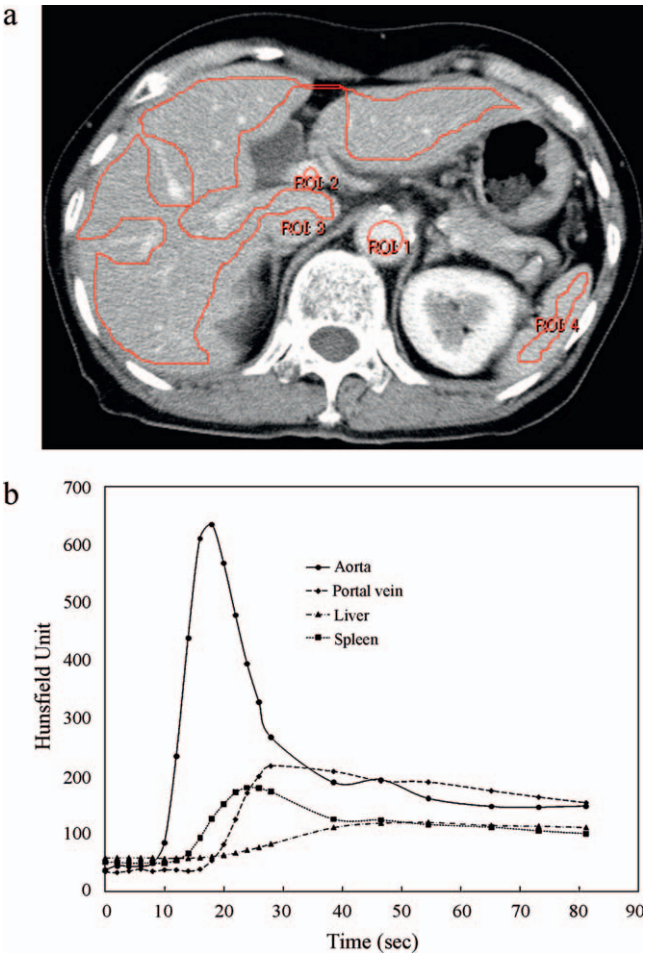

Fig. 1. Examples of region-of-interest (ROI) placements and time–density curves (TDCs). ROIs were placed on the abdominal aorta, main portal vein, liver, and spleen on the CT perfusion image of a 71-year-old woman with lung cancer (a). TDCs for the organ were also generated (b).

Based on these TDCs, in MS method, HAP was determined by dividing the peak gradient of the hepatic TDC before the peak splenic enhancement (arterial-dominant phase) by the peak aortic enhancement. Hepatic portal perfusion was calculated by dividing the peak gradient of the hepatic TDC after the peak splenic enhancement (portal-dominant phase) by the peak portal vein enhancement.

In CM method, HAP, PVP, and HPI were calculated pixel by pixel using the following equation:

$$\frac{dC_L(t)}{dt} = k_{1a}C_a(t - t_a) + k_{1p}C_p(t - t_p) - k_2C_L(t)$$

in which C_L, C_a, and C_p are the contrast agent concentrations measured over time respectively within the liver, hepatic artery, and portal vein derived from the ROIs and k_{1a}, k_{1p}, and k_2 are the arterial and portal venous inflow and liver outflow rate constants. By fitting measured $C_L(t)$, the constants k_{1a}, k_{1p}, and k_2 can be estimated, and can be used to calculate hepatic perfusion. Two delay parameters, t_a and t_p, are inserted to consider time differences between the beginnings of enhancement of the aorta or portal vein and liver

(transit time). In the software we used, t_a and t_p are assumed to be equal because of difficulty in measurement of t_p.

On the concept of convolution, if the impulse residue function (IRF, $R(t)$) is known, the tissue TDC can be obtained as a summation of scaled and time-shifted IRFs.

$$Q(t) = F \times C_a(t) \otimes R(t) = C_a(t) \otimes F \times R(t)$$

in which $Q(t)$, $C_a(t)$, and $\otimes$ are the tissue TDC, arterial input TDC, and convolution operator, respectively. The $F \times R(t)$ indicates blood flow. An estimate of $R(t)$ is firstly obtained by means of numerical deconvolution. Mean transit time (MTT, s) is calculated by dividing the area under $R(t)$ by the height of the $R(t)$ plateau. Blood flow is calculated by using the central volume equation (BF = BV/MTT).

In all methods, APF was calculated by dividing hepatic arterial perfusion by total hepatic perfusion (i.e., HAP/[HAP + HPP]). A detailed description of these methods is available elsewhere [1,2,12–16].

Liver ROIs on the perfusion maps for the perfusion measurements were made as large as possible to cover the entire hepatic normal parenchyma on the slice while avoiding large vessels and focal liver lesions if these were present. Arrival time of contrast material at the abdominal aorta (arrival time) and time difference between enhancement of aorta and liver (transit time) were recorded as extra-hepatic factors which could affect estimated hepatic perfusion values.

2.4. Statistical analysis

HAP, HPP, and APF obtained with the three methods were compared by means of one-way analysis of variance (ANOVA) and the Scheffé criterion, and correlations were assessed by means of correlation coefficient analysis. The effects of intra- and extra-hepatic factors on the estimated perfusion values were also assessed by using partial correlation analysis.

StatView version 5.0 (SAS, Cary, NC) was used for statistical analyses. Quantitative variables were expressed as mean ± SD, and statistical significance was established at a p value of <0.05.

2.5. Radiation exposure doses

Prior to scanning of the patients, the estimated volume computed tomographic dose indices ($CTDI_{VOL}$) for perfusion CT and helical CT examinations (120 kV, 400 mA, 0.5 s/rot, helical pitch of 15), which constitute our routine abdominal CT protocol, were measured by using the above-mentioned 16-row scanner, a 32cm-diameter cylindrical acryl phantom for CT, a 10 cm-long pencil type ion chamber and a dosimeter (Radcal's 20CT14 and 10X5-3CT, and multipurpose dosimeter Type 9150; Radcal Corp., Monrovia, CA, USA). These dose indices were then compared.

3. Results

Mean HAPs, HPPs, and APFs calculated using the three methods were shown in Table 1. Mean HAP of MS was significantly higher than that of DC ($p < 0.005$). Mean HPP of CM was significantly higher than that of MS ($p < 0.0001$) or CM ($p < 0.0001$), and mean HPP of MS was significantly higher than that of DC ($p < 0.001$). There was no significant difference in APF among the three methods.

Correlation coefficients for the three methods are shown in Table 2. The three methods showed significant and moderate correlations for HAP and APF, respectively. Correlations for HPP were significant and moderate between CM and DC, and poor between MS and CM or MS and DC.

All three analytic methods showed weak correlations between HAP or APF and age or sex (Tables 3–5). MS (Table 3) showed weak

Table 1
Hepatic perfusion values estimated with the three methods.

	HAP (ml/min/100 ml)	HPP (ml/min/100 ml)	APF (%)
MS	31.2 ± 18.4[a]	106.2 ± 57.9[b]	24.2 ± 9.1
CM	28.1 ± 16.9	148.5 ± 86.1[c]	22.1 ± 12.1
DC	20.9 ± 25.5	69.9 ± 34.3	21.4 ± 9.1

APF: arterial perfusion fraction; CM: compartment model; DC: deconvolution method; HAP: hepatic arterial perfusion; HPP: hepatic portal perfusion; and MS: maximum slope.
[a] Mean HAP of MS was significantly higher than that of DC ($p < 0.005$).
[b] Mean HPP of MS was significantly higher than that of DC ($p < 0.001$).
[c] Mean HPP of CM was significantly higher than that of MS ($p < 0.0001$) or CM ($p < 0.0001$).

Table 2
Correlation coefficients for hepatic perfusion values estimated with the three methods.

	CM and DC	MS and DC	CM and MS
HAP	0.558**	0.442**	0.455**
HPP	0.560**	0.233*	0.160
APF	0.526**	0.474**	0.548**

Numbers show correlation coefficients.
APF: arterial perfusion fraction; CM: compartment model; DC: deconvolution method; HAP: hepatic arterial perfusion; HPP: hepatic portal perfusion; and MS: maximum slope.
* $p < 0.05$.
** $p < 0.0001$.

Table 3
Effects of various factors on hepatic perfusion values estimated with the maximum slope method.

	HAP	HPP	APF
Sex	0.274*	−0.073	0.357**
Age	−0.276*	−0.025	−0.291*
Risk factors for cardiovascular disease[a]	−0.041	0.276*	−0.212
Arrival time[b]	−0.232*	−0.397***	0.012
Transit time[c]	−0.048	−0.179	0.096
Liver dysfunction or hepatitis virus infections	0.001	0.015	0.118

Numbers show partial correlation coefficients.
APF: arterial perfusion fraction; HAP: hepatic arterial perfusion; and HPP: hepatic portal perfusion.
[a] Risk factors for cardiovascular disease include history of myocardial infarction, angina pectoris, hypertension, diabetes mellitus, arteriosclerosis obliterans, or dialysis as recorded on the charts.
[b] Arrival time of contrast material at abdominal aorta.
[c] Time difference between the beginning of enhancement of the aorta or portal vein and that of the liver.
* $p < 0.05$.
** $p < 0.005$.
*** $p < 0.001$.

Table 4
Effects of various factors on hepatic perfusion values estimated with the dual-input single-compartment model.

	HAP	HPP	APF
Sex	0.121	0.015	0.257*
Age	−0.246*	−0.090	−0.154
Risk factors for cardiovascular disease[a]	−0.133	0.088	−0.210
Arrival time[b]	−0.060	0.046	0.076
Transit time[c]	−0.005	−0.018	0.238*
Liver dysfunction or hepatitis virus infections	−0.164	−0.154	0.099

Numbers show partial correlation coefficients and numbers in parentheses show p values.
APF: arterial perfusion fraction; HAP: hepatic arterial perfusion; and HPP: hepatic portal perfusion.
[a] Risk factors for cardiovascular disease include history of myocardial infarction, angina pectoris, hypertension, diabetes mellitus, arteriosclerosis obliterans, or dialysis as recorded on the charts.
[b] Arrival time of contrast material at abdominal aorta.
[c] Time difference between the beginning of enhancement of the aorta or portal vein and that of the liver.
* $p < 0.05$.

Table 5
Effects of various factors on hepatic perfusion values estimated with the deconvolution method.

	HAP	HPP	APF
Sex	0.161	−0.097	−0.388**
Age	−0.277*	−0.066	−0.365**
Risk factors for cardiovascular disease[a]	−0.184	0.010	−0.200
Arrival time[b]	−0.071	−0.047	0.014
Transit time[c]	−0.230	−0.405***	0.178
Liver dysfunction or hepatitis virus infections	−0.063	−0.066	−0.003

Numbers show partial correlation coefficients and numbers in parentheses show p values.
APF: arterial perfusion fraction; HAP: hepatic arterial perfusion; and HPP: hepatic portal perfusion.
[a] Risk factors for cardiovascular disease include history of myocardial infarction, angina pectoris, hypertension, diabetes mellitus, arteriosclerosis obliterans, or dialysis as recorded on the charts.
[b] Arrival time of contrast material at abdominal aorta.
[c] Time differences between the beginnings of enhancement of the aorta or portal vein and that of the liver.
* $p < 0.05$.
** $p < 0.005$.
*** $p < 0.001$.

correlations between HAP or PAP and arrival time or cardiovascular risks, while CM (Table 4) and DC (Table 5) showed weak correlation between APF or HAP and transit time.

In the phantom study, $CTDI_{VOL}$ was 95.0 mGy for perfusion CT and 30.3 mGy for routine helical CT.

4. Discussion

Hepatic CT perfusion is a minimally invasive method and has the advantage of providing highly reliable quantification of hepatic perfusion at low cost. Although many researchers have stressed the clinical usefulness of this technique, some problems remain. Two of these, standardization of analytic methods and evaluation of unknown effects of extra-hepatic factors, which we evaluated in this study, are essential for effective routine clinical use of this technique. The problems in standardization of analytic methods have already been raised by Goh et al. [17,18] and the detailed reports on effects of extra-hepatic factors have been addressed by Bae et al. [19,20].

The MS method was first introduced by Miles et al. [14] and because its underlying principle is relatively simple, it has come to dominate the field of hepatic perfusion measurement. However, this method can underestimate hepatic perfusion, especially portal perfusion, when the "no venous outflow" assumption is violated. This assumption states that washout of contrast medium should not occur prior to the peak time of the initial slope of the tissue TDC. Thus, a high injection rate of contrast medium is a prerequisite for accurate perfusion measurement. To overcome this drawback, a new method of perfusion analysis, the dual-input one-compartment model method, was proposed by Materne et al. [15]. In theory, hepatic perfusion can be estimated correctly with this method regardless of the injection rate. However, calculation is more complicated and time-consuming. Cuenod et al. [13] used a deconvolution technique to evaluate hepatic perfusion. This method provides more robust analysis without a high injection rate, and the estimated perfusion values are theoretically independent of cardiac output or possible bolus delay. However, the calculation is complicated and time-consuming and the results are affected by the hemodynamic model used. Since there is currently no consensus regarding the optimal analytic method for hepatic CT perfusion, we compared the three methods in this study.

Our results show a significant difference between mean HAP and HPP estimated with these methods, while the results were similar for APF. For HAP and APF, the methods showed significant and moderate correlations. Correlations between CM and DC were significant and moderate for HPP, and poor between MS and CM or MS and DC. To the best of our knowledge, no studies comparing the three methods have been published. As for the correlations between MS and CM, our findings were consistent with previously reported result [21,22]. However, the methods examined in our study showed moderate correlations for HAP and APF, and poor correlation for HPP, while previous studies reported significant correlations. One possible reason for this discrepancy is the relatively low injection rate used in our study (5 ml/s), which may have contravened the assumption of 'no venous outflow' for the MS method and thus could have affected our results. One study, for example, used a much higher rate of 8 ml/s [22]. In routine clinical use, such a high rate can produce severe hot flushes in the patient which then can cause motion artifacts and increase the failure rate of venous access. Another possible reason is that the previous studies were retrospective assessments of small populations.

The relationship between cardiac function and peak portal enhancement has not been fully investigated. No conclusions can be drawn from our results about the effects of cardiac function on HPP so that further studies are needed. Furthermore, portal peak enhancement may not have been scanned properly in some of our patients with cardiovascular diseases. Some researchers have suggested that CM is susceptible to image noise [2], and this may have affected our results. Overall, our results suggest that perfusion values estimated by the three methods are not interchangeable, especially when lower injection rates are used.

MS showed weak correlations for multiple extra-hepatic factors, indicating that MS is sensitive to these factors, especially cardiovascular factors, while CM and DC proved to be less sensitive to extra-hepatic factors. Possible reasons for these findings were differences in the theoretical underpinnings of the methods and delay of contrast material arrival in patients with cardiovascular diseases [20,21]. Moreover, CM and DC showed weak correlation between APF or HAP and transit time. Our results thus suggest that settings or estimation of transit time can affect perfusion values.

The effects of gender or age were observed in the results obtained with all three methods, and may reflect individual differences in body weight, surface area, or cardiac output. Male or younger patients in our study tended to show higher HAP and APF. Wintermark et al. reported that smaller doses of contrast material resulted in lower cerebral blood flow [23], and the dose of contrast material administered by us may have been insufficient for our male or younger patients. Further assessments are therefore needed regarding optimization of the contrast-enhancement technique and signal-to-noise ratio for each image.

CT perfusion correlated significantly with severity of liver damage and fibrosis [3–6], but our results did not indicate that hepatic dysfunction had an effect on hepatic perfusion values. A possible reason for this finding is that patients with moderate or severe hepatic dysfunction were not included in our population.

In our phantom study, the exposure dose of perfusion CT, measured as $CTDI_{VOL}$, was less than that of routine multi-phasic dynamic CT, indicating that perfusion CT is suitable for use in routine clinical examinations.

There are some limitations to this study. First, the perfusion values in our study were not compared to gold standard. PET is regarded as the gold standard in the fields of neuroradiology and cardiology. However, in the liver, arterial and portal perfusion values are estimated with the use of counts in the spleen and compartmental models. Manual blood samplings from the peripheral arteries are used for the estimation of arterial input. This is an invasive technique and the differences between peripheral and visceral arteries may lead to errors in perfusion estimation. These drawbacks can make it unreliable in this organ. Furthermore, the perfusion values estimated by PET have not been compared to those

obtained with microsphere study in the human liver. Currently, we do not have a non-invasive modality which can be used as a gold standard. Second, we did not assess the whole liver, but only one slice at the level of the hepatic hilum. Recently available newer multidetector CT systems or techniques such as the 320 detector-row CT or the volume shuttle scan can offer greater cranio-caudal coverage and may be able to overcome this limitation [16]. Third, we did not evaluate other perfusion parameters such as permeability or blood volume, which are commonly reported. Finally, we did not evaluate hepatic tumors because previous reports have suggested significant changes occur in the perfusion of livers with overt malignant tumors. It might affect our results. Most overt hepatic tumors are supplied by the hepatic artery only. Further studies are needed to standardize analysis method for routine clinical use of CT perfusion measurement.

5. Conclusion

Perfusion values estimated by means of MS, CM, and DC are not interchangeable. Differences between these analytic methods should be noted. CM and DC are less sensitive than MS to extra-hepatic factors.

Conflicts of interest

Takeshi Yoshikawa: Toshiba Corporation research grant and Koninklijke Philips Electronics NV research grant.

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