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ORIGINAL ARTICLE

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Oxygen-15 positron-emission tomography for predicting selective delivery of a chemotherapeutic agent to hepatic cancers during angiotensin II-induced hypertension

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Abstract *Purpose*: Selective drug delivery is important for successful chemotherapy. In patients with hepatic cancer, we used ^{15}O-carbon dioxide (steady-state) and ^{15}O-water (dynamic) positron emission tomography (PET) to evaluate changes in blood flow induced by angiotensin (AT) II in the liver parenchyma, hepatic tumors, and spleen. *Methods*: The study group comprised 13 patients, 6 with hepatic metastasis and 7 with hepatocellular carcinoma. PET was performed before and during AT II administration to induce hypertension. *Results*: Steady-state PET images showed a preferential increase in blood flow to hepatic tumor compared with liver parenchyma during hypertension. In dynamic PET, tumor blood flow was maintained during induced hypertension while hepatic arterial blood flow, portal blood flow, total hepatic blood flow, and splenic blood flow decreased to 71.4% (not significant), 65% ($P < 0.01$), 67.2% ($P < 0.001$), and 72.3% ($P < 0.01$) of the respective baseline values. *Conclusion*: AT II-induced hypertension produced a relative increase in tumor blood flow. Oxygen-15 PET should be useful for predicting preferential drug delivery to hepatic cancers.

Keywords Angiotensin II · Hypertension chemotherapy · Metastatic liver cancer · Hepatocellular carcinoma · Positron emission tomography

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Introduction

Although the most important factor for successful chemotherapy is activity of the drug against the cancer, effective delivery of sufficient drug to the tumor also is important. Selective drug targeting to a tumor is highly desirable for the effective treatment of solid tumors with minimal drug toxicity to normal tissues. Hypertension induced by angiotensin (AT) II can selectively increase blood flow in tumor tissue without increasing blood flow in normal tissue [4, 13]. Improved antitumor drug activity has been achieved in the clinical setting by this method [22], and AT II has been used as a biologic response modifier in the treatment of malignant hepatoma and colon cancer metastatic to the liver [2, 9]. AT II-induced changes in the distribution of hepatic blood flow in patients with hepatic cancer have been investigated in several studies [3, 10]. These have demonstrated that AT II can decrease hepatic arterial blood flow to that of normal liver tissue, resulting in relatively increased delivery of chemotherapeutic drug given via the hepatic artery to the tumor. However, similar AT II-induced selectivity of delivery for systemically administered drugs has not yet been demonstrated. For accurate investigation of distribution of drugs during systemic chemotherapy, arterial and portal blood flows must be measured simultaneously and separately. The liver has a dual blood supply from both the hepatic artery and portal vein, while hepatic tumors most often are supplied solely by the hepatic artery. However, simultaneous measurement of arterial and portal blood flow in the liver has proven technically difficult. We have reported success in making such simultaneous measurements using positron emission tomography (PET) with oxygen-15 in patients not treated with AT II [14, 17, 18, 20].

To examine the possibility of enhancing treatment of hepatic tumors by inducing hypertension with AT II during systemic chemotherapy, we used PET with oxygen-15 to quantify the changes in blood flow in the

liver, spleen, and hepatic tumor during hypertension induced by systemic infusion of AT II.

Subjects and methods

We investigated 13 patients with hepatic cancer (11 men and 2 women, age range 43 to 65 years), who underwent hepatic resection after PET study. Two patients who participated in the same study with PET and have previously been reported [16] were included in the 13 patients. Six patients had metastatic cancer (MET), and seven had hepatocellular carcinoma (HCC). The nonneoplastic liver the of the seven patients with HCC was affected by cirrhosis or chronic hepatitis, while patients with MET had healthy hepatic parenchyma with neither cirrhosis nor hepatitis. No patient studied was being treated for hypertension, cerebral infarction or heart disease. Informed consent was obtained from all subjects.

Blood flow measurement

We performed both steady-state and dynamic methods in this study. The steady-state method is superior to the dynamic method in demonstrating images visually, while the dynamic method is superior in quantifying blood flow [15].

Steady-state method

After fasting, PET measurements were taken with the patient lying supine on the bed of a whole-body PET scanner [17]. The scan position for each patient was determined with reference to CT images to obtain PET images of the same slices. Oxygen-15-carbon dioxide gas was produced by a medical cyclotron. After a transmission scan, patients continuously inhaled air containing 2 mCi/min (74 MBq/min) of [^{15}O]carbon dioxide. After reaching a steady state, PET data were acquired for 5 min. Regions of interest (ROI) for the liver, spleen and hepatic tumors were defined in PET images by referring to the corresponding CT images. Ratios of radioactivity concentrations in tissue and arterial blood (i.e. the blood flow ratio, BFR) were calculated.

Dynamic method

After the steady-state PET scan, a dynamic PET scan was obtained. Intravenous bolus injection of 20 mCi (740 MBq) of [^{15}O]water was followed by 12 PET measurements at 5-s intervals and then another eight measurements every 30 s. Blood samples were obtained from the left brachial artery at 10, 15, 20, 25, 30, 35, 60, 120, 180, and 240 s after the beginning of the emission scan. Radioactivity concentrations in blood samples were measured immediately in a precalibrated well counter. Radioactivity in the liver parenchyma and the tumor were measured from these PET images using the same ROIs employed as in the steady-state method.

The mathematical model and theory used for calculating hepatic arterial blood flow (HBFa), hepatic portal blood flow (HBFp), and total hepatic blood flow (HBFt) were as reported previously [14, 17, 18, 20]. In the current study, assuming that Kety's single-compartment model can be applied and that a given hepatic neoplasm is supplied by only the hepatic artery, tumor blood flow (TBF) was expressed as follows:

$$Ct(t) = TBF \cdot \int_0^t Ca(t) \cdot e^{-\frac{TBF}{\rho}(t-x)} dx,$$

where Ct(t) and Ca(t) are radioactivity concentrations in the hepatic tumor and the blood, respectively, and ρ is the tumor-blood partition coefficient for water. The specific gravity of the tumor was assumed to be 1. The physical decay of ^{15}O was corrected every 2.5 s. TBF was determined by the Simplex method [8], a nonlinear multiple regression analysis, using a personal computer. Splenic blood flow (SBF) and the spleen-blood partition coefficient for water (ρs) were quantified by the dynamic method as previously described [18].

Repeat examination during induced hypertension

After completion of the initial PET scans during the normotensive (N) state, a hypertensive (H) state was induced using recombinant AT II. Intravenous administration of AT II was initiated at a rate of 5 ng/kg per min. The infusion rate was then increased until the mean blood pressure (MBP) was increased by 50% above the baseline level. The blood pressure was measured at 1-min intervals and the infusion rate of AT II was controlled according to the estimated MBP level (half the value of the systolic blood pressure, SBP, and diastolic blood pressure, DBP). During the H state, steady-state and dynamic PET were repeated, using the same ROIs employed in the initial PET scans during the N state. The procedure is briefly illustrated in Fig. 1, which shows an example record.

To evaluate the relative change in TBF compared to HBFt after AT-II infusion, which would reflect the relative change in chemotherapeutic drug delivery to the tumor in comparison with delivery to the liver parenchyma during AT II-enhanced chemotherapy, we defined a hepatic delivery index (HDI) as follows:

$$\text{Hepatic delivery index (HDI)} = \frac{\text{TBF (H state)}/\text{HBFt (H state)}}{\text{TBF (N state)}/\text{HBFt (N state)}}$$

A splenic delivery index (SDI) was defined similarly to evaluate the likely relative change in chemotherapeutic drug delivery to the tumor in comparison with delivery to the spleen during AT II-enhanced chemotherapy. The formula for SDI is analogous to that for HDI.

The indocyanine green retention rate at 15 min (ICG-R15) was determined and the hepaplastin test was performed during the N and the H states to detect changes in liver function. ICG-R15 measurement and the hepaplastin test during the N state were performed on the day before PET examination.

Data processing was carried out using a specially developed program on a personal computer (PC-LT23/4; NEC, Tokyo, Japan). Statistical evaluation was performed with correlation testing using Microsoft Excel 2000 for Windows (Japan Microsoft, Tokyo, Japan), one-way analysis of variance, *H* testing, or Wilcoxon nonparametric testing. *P* values < 0.05 were considered to indicate statistical significance. Each value represents the mean $\pm$ 95% confidence interval.

Results

Steady-state method

Imaging

Figure 2 shows steady-state PET images and the ROIs in a patient with MET during the N and the H states, and the corresponding CT image. Radioactivity in the metastatic liver tumor was slightly higher than in the normal liver parenchyma. During the N state, the BFRs in the metastatic liver tumor and in the liver were 0.56 and 0.49, respectively. During the H state, PET images demonstrated preferentially increased tracer activity in the hepatic metastasis relative to activity in the liver parenchyma. The BFR in the metastatic liver tumor did

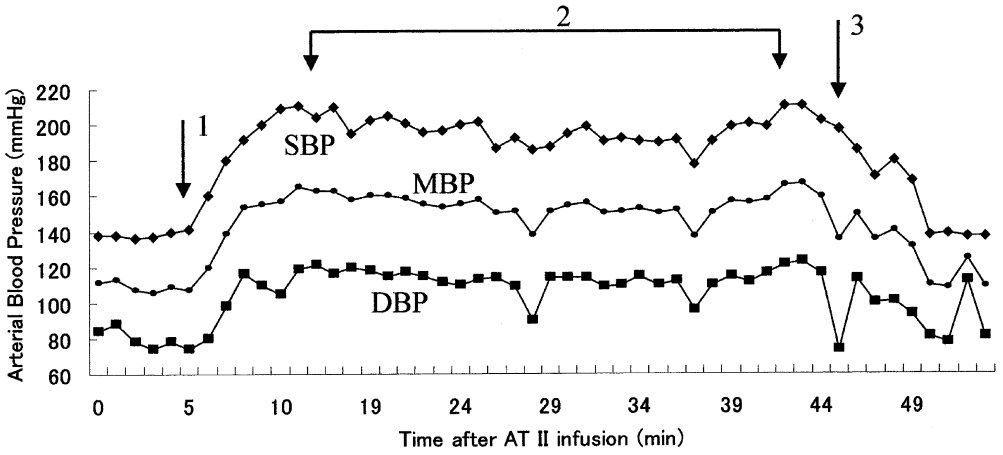

Fig. 1 Procedure for repeat PET examination during induced hypertension. After intravenous infusion of AT II was started (1), systolic blood pressure (*SBP*) and diastolic blood pressure (*DBP*) were measured every minute. The infusion rate of AT II was controlled according to the estimated mean blood pressure (*MBP*) level (half the value of SBP and DBP). As the MBP increased to 50% above the baseline level, steady-state and dynamic PET was repeated (2), After the repeat examination, infusion of AT II was stopped (3), and blood pressure returned to the previous level

not change (0.55), but the BFR in the liver decreased to 0.39. Figure 3 shows steady-state PET images and the ROIs in a patient with HCC during the N and the H states, and the corresponding CT image. PET images in the N state indicated a higher radioactivity concentration in the HCC than in noncancerous areas of the liver. The BFRs in the HCC and the liver were 0.53 and 0.4, respectively. During the H state, PET images demonstrated increased tracer activity in the HCC relative to that in the liver parenchyma. The BFR in the HCC did not change (0.50), but the BFR in the liver parenchyma decreased to 0.29.

Blood flow ratio

During the H state, the mean BFR in the liver and spleen decreased significantly ($P = 3.41\times10^{-3}$, $P = 1.7\times10^{-2}$, respectively), while the mean BFR in the hepatic cancers did not change (Fig. 4A).

Blood flow ratio in the liver In the six patients with MET, the BFR in the liver was 0.522 ± 0.024 (mean ± 95% confidence interval) during the N state, and decreased significantly to 0.404 ± 0.041 during the H state ($p = 6.5\times10^{-4}$). In the seven patients with HCC, the BFR in the liver was 0.527 ± 0.066 during the N state, and decreased to 0.441 ± 0.086 during the H state; this decrease was not statistically significant. Considering all 13 patients together, the BFR in the liver was 0.525 ± 0.036 during the N state, and decreased significantly to 0.424 ± 0.049 during the H state ($P = 3.41\times10^{-3}$).

Blood flow ratio in the spleen In the six patients with MET, the BFR in the spleen was 0.713 ± 0.059 (mean ± 95% confidence interval) during the N state, and decreased significantly to 0.615 ± 0.044 during the H state ($P = 2.7\times10^{-2}$). In the seven patients with HCC, the BFR in the spleen was 0.73 ± 0.065 during the N state, and decreased to 0.674 ± 0.057 during the H state (not significant). Considering all 13 patients, the BFR in the spleen was 0.722 ± 0.043 during the N state, and decreased significantly to 0.646 ± 0.039 during the H state ($P = 1.7\times10^{-2}$).

Blood flow ratio in the tumor (Fig. 4B) No significant change in mean BFR in the tumor was seen between the N and the H states in any patient group.

Dynamic method

Hepatic blood flow

Hepatic arterial blood flow The HBFa results for the H and N states are shown in Fig. 5A. HBFa for the six patients with MET was 34.9 ± 9.46 ml/100 g per min (mean ± 95% confidence interval) during the N state, and decreased significantly to 19.8 ± 5.63 ml/100 g per min (56.7% of baseline) during the H state ($P = 2.3\times10^{-2}$). HBFa for the seven patients with HCC was 30.8 ± 11.0 ml/100 g per min during the N state, and decreased to 26.4 ± 12.4 ml/100 g per min (85.7% of baseline) during the H state (not significant). Considering all 13 patients, HBFa was 32.7 ± 7.13 ml/100 g per min during the N state, and decreased to 23.4 ± 7.12 ml/100 g per min (71.4% of baseline) during the H state (not significant).

Hepatic portal blood flow The HBFp results for the H and N states are shown in Fig. 5B. HBFp in the six patients with MET was 66.5 ± 20.6 ml/100 g per min during the N state, and decreased to 38.7 ± 17.5 ml/100 g per min (58.1% of baseline) during the H state. HBFp in the seven patients with HCC was 59.6 ± 9.47 ml/100 g per min during the N state, and decreased to 42.7 ± 13.2 ml/100 g per min (71.7% of baseline) during the H state. The change in HBFp between the N and the H states did not reach

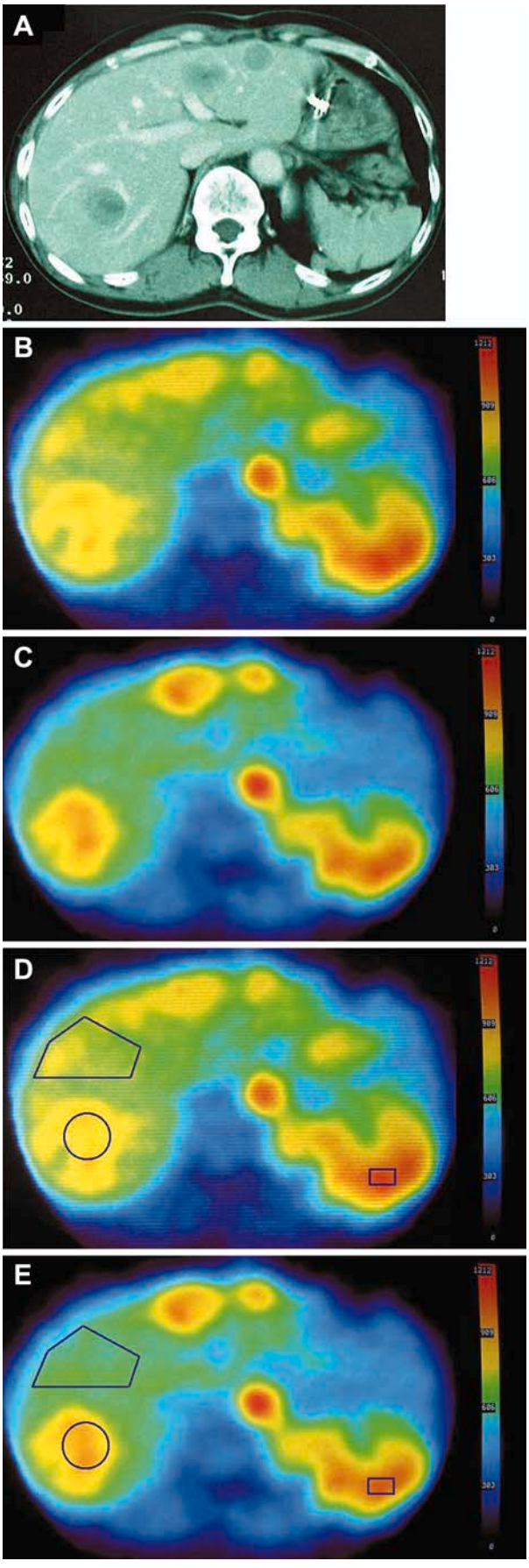

Fig. 2A–E A metastatic liver tumor. **A** Computed tomography. **B**, **C** PET images of the same slice during normotensive (N) and hypertensive (H) states, respectively. **D**, **E** ROIs indicated on the PET images during the N and the H states, respectively. Compared to the N state, blood flow in the metastatic lesion was enhanced relative to the liver parenchyma in the H state

significance in either of these small groups. However, considering all 13 patients, HBFp was 62.8 ± 10.5 ml/100 g/min during the N state, and decreased significantly to 40.9 ± 10.3 ml/100 g per min (65% of baseline) during the H state ($P = 7.5 \times 10^{-3}$).

Total hepatic blood flow The HBFt results for the H and N states are shown in Fig. 5C. HBFt in patients with MET was 101.5 ± 18.5 ml/100 g per min during the N state, and decreased significantly to 58.5 ± 18.9 ml/100 g per min (57.6% of baseline) during the H state ($P = 9.7 \times 10^{-3}$). HBFt in patients with HCC was 90.3 ± 9.61 ml/100 g per min during the N state, and decreased to 69.1 ± 16.8 ml/100 g per min (76.5% of baseline) during the H state (not significant). HBFt considering all patients was 95.5 ± 10.0 ml/100 g per min during the N state, and decreased significantly to 64.2 ± 12.4 ml/100 g/min (67.2% of baseline) during the H state ($P = 7.8 \times 10^{-4}$).

Splenic blood flow

The SBF results for the H and N states are shown in Fig. 6. SBF in patients with MET was 114.7 ± 22.0 ml/100 g per min during the N state, and decreased significantly to 72.1 ± 23.6 ml/100 g per min (62.9% of baseline) during the H state ($P = 2.7 \times 10^{-2}$). SBF in patients with HCC was 105.6 ± 15.5 ml/100 g per min during the N state, and decreased to 85.7 ± 13.7 ml/100 g per min (81.2% of baseline) during the H state (not significant). Considering all patients, SBF was 109.8 ± 12.8 ml/100 g per min during the N state, and decreased significantly to 79.4 ± 13.1 ml/100 g per min (72.3% of baseline) during the H state ($P = 3.4 \times 10^{-3}$).

Tumor blood flow

The TBF results for the H and N states are shown in Fig. 7. During the N state, TBFs for patients with MET, for patients with HCC, and for patients overall were 34.0 ± 9.81, 63.5 ± 11.0, and 48.7 ± 11.2 ml/100 g per min, respectively. During the H state, TBFs were 33.9 ± 16.5, 75.1 ± 20.2, and 54.5 ± 17.4 ml/100 g per min, respectively. None of the changes in TBF between the N and the H states were significant in any group of patients.

In this study, no significant change in partition coefficient was seen between the N and the H states.

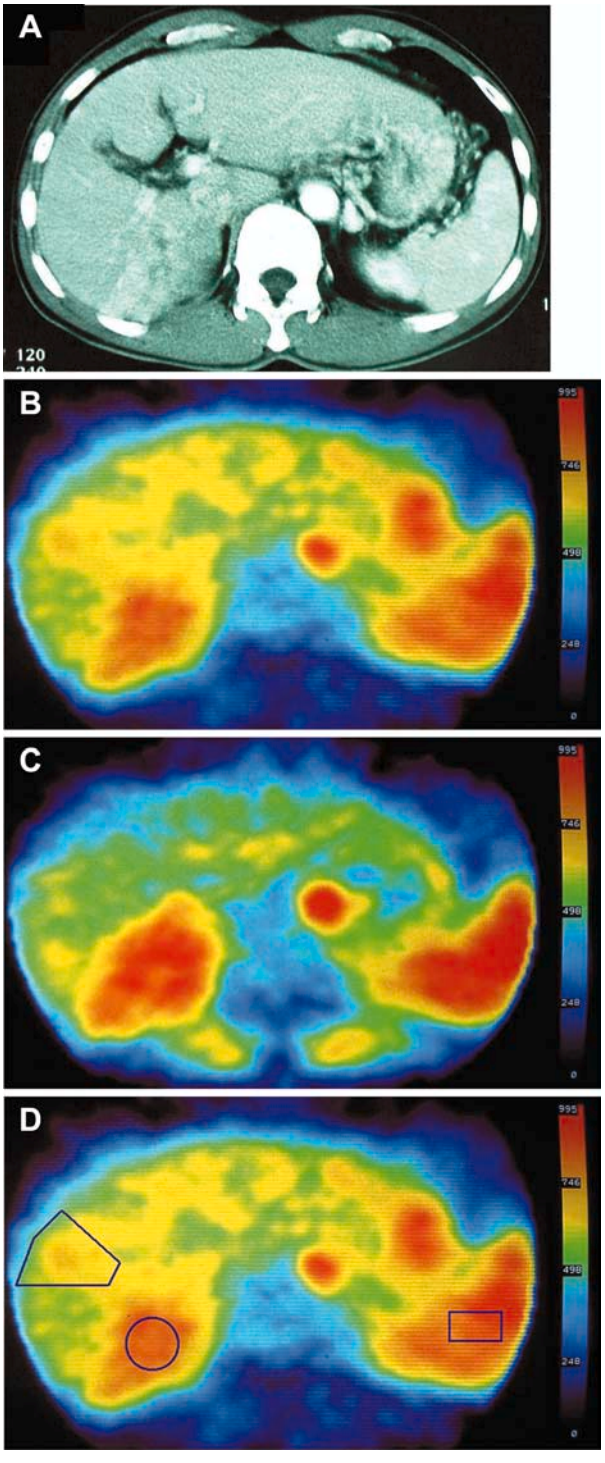

Fig. 3A–D A hepatocellular carcinoma. **A** Computed tomography. **B**, **C** PET images of the same slice during normotensive (N) and hypertensive (H) states, respectively. **D** ROIs indicated on the PET images during the N state. Compared to the N state, images show a preferential increase in blood flow to the tumor compared with the liver parenchyma in the H state

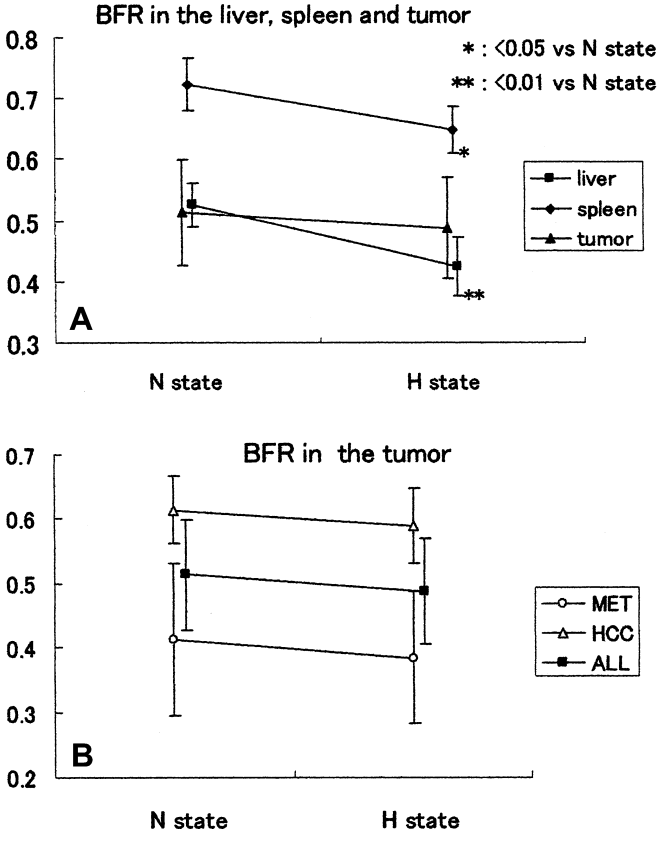

Fig. 4A, B Differences in blood flow ratio (BFR) between the N and the H states in the liver, spleen, and tumor (mean BFR). **A** During the H state, the BFR in the liver and spleen decreased significantly, while the BFR in the hepatic cancers did not change. **B** No significant change in BFR in the tumor between the N and the H states was noted in any group of patients. *Vertical lines* indicate 95% confidence intervals. BFR denotes the ratio of radioactivity concentrations in tissue to that in arterial blood (*MET* 6 patients with metastatic cancer, *HCC* 7 patients with hepatocellular carcinoma, *ALL* all 13 patients)

Delivery indices

Delivery indices are shown in Table 1. Median HDI values for patients with MET, patients with HCC, and patients overall were 1.54, 1.62, and 1.54, respectively. Median SDI values for patients with MET, patients with HCC, and patients overall were 1.56, 1.47, and 1.49, respectively.

Large variations between individual values were observed. In all but two cases, the HDI and SDI both exceeded 1.00, reflecting increased blood flow in the hepatic tumor during AT II-induced H state relative to hepatic parenchyma or spleen. However, the HDI was 0.99 in one patient with HCC, and the SDI was 1.00 in one patient with MET. These two patients showed no distinctive characteristics in blood pressure, liver function, or any of the other parameters measured.

Indocyanine green retention rate and hepaplastin test

The ICG-R15 in patients with MET was $4.25 \pm 1.99\%$ during the N state, and increased significantly to $13.9 \pm 2.36\%$ (327.1% of baseline) during the H state ($P = 1.1 \times 10^{-4}$). The ICG-R15 of the patients with HCC

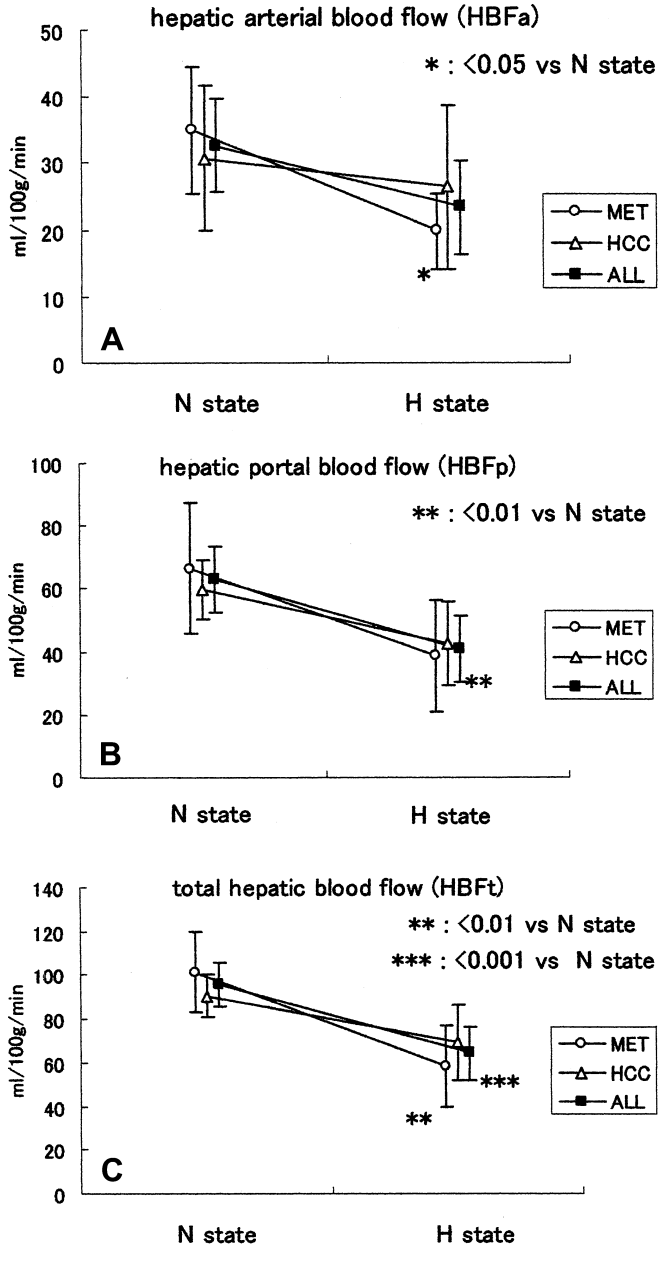

Fig. 5A–C Differences in HBF between the N and the H states (mean HBF, milliliters per 100 g per minute). **A** HBFa for MET decreased significantly during the H state, while HBFa for HCC and ALL did not decrease significantly. **B** HBFp for ALL decreased significantly during the H state, while HBFp for MET and HCC did not decrease significantly. **C** HBFt for MET and ALL decreased significantly during the H state, while HBFt for HCC did not decrease significantly. *Vertical lines* indicate 95% confidence intervals (*MET* 6 patients with metastatic cancer, *HCC* 7 patients with hepatocellular carcinoma, *ALL* all 13 patients)

was 18.5±5.30% during the N state, and increased to 28.5±8.68% (154.1% of baseline) during the H state (not significant). Considering all patients, ICG-R15 was 11.9±4.9% during the N state, and increased significantly to 21.8±6.19% (182.6% of baseline) during the H state ($P=2.3\times10^{-2}$).

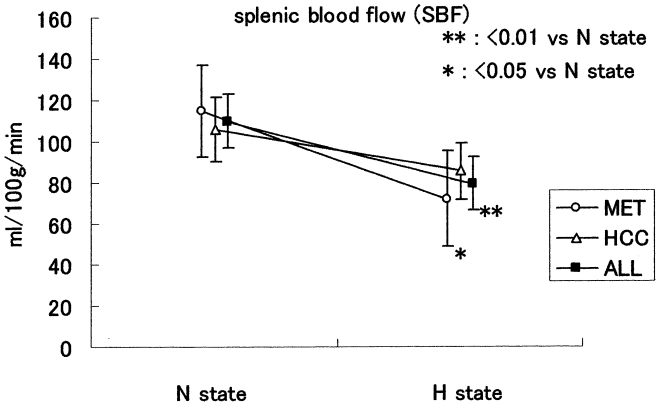

Fig. 6 Differences in SBF between the N and the H states (mean SBF, milliliters per 100 g per minute). SBF for MET and ALL decreased significantly during the H state, while SBF for HCC did not decrease significantly. *Vertical lines* indicate 95% confidence intervals (*MET* 6 patients with metastatic cancer, *HCC* 7 patients with hepatocellular carcinoma, *ALL* all 13 patients)

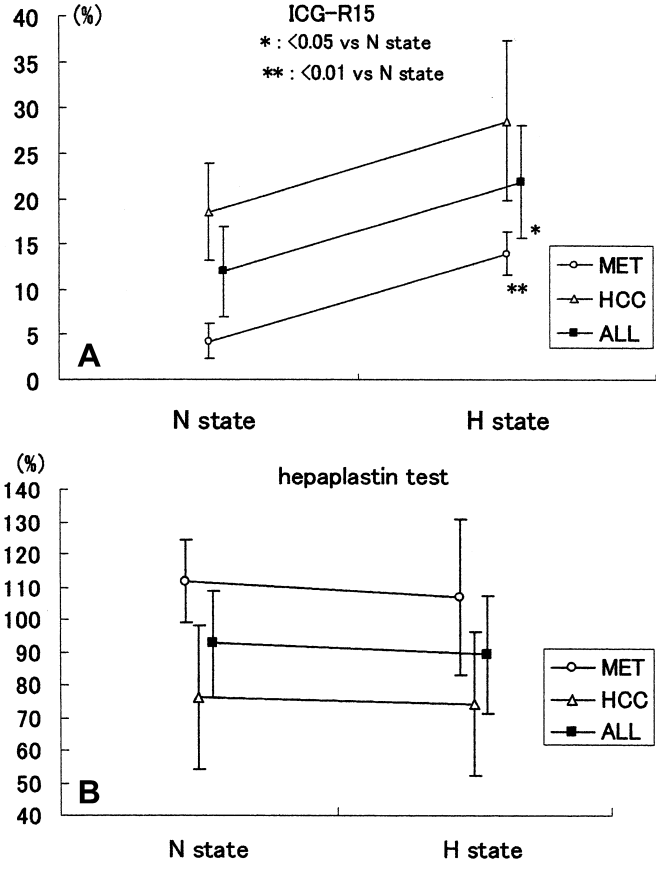

Fig. 7 Differences in TBF between the N and the H states (mean TBF, milliliters per 100 g per minute). No significant change in TBF between the N and the H states was seen in any group of patients. *Vertical lines* indicate 95% confidence intervals (*MET* 6 patients with metastatic cancer, *HCC* 7 patients with hepatocellular carcinoma, *ALL* all 13 patients)

Table 1 Drug delivery indices observed withAT II infusion. The values shown are median (range). The delivery indices are the TBF/HBFt ratio (hepatic delivery index, *HDI*) and the TBF/SBFratio (splenic delivery index, *SDI*) after AT II infusion (*MET* 6 patients with metastatic cancer, *HCC* 7 patients with hepatocellular carcinoma, *ALL* all 13 patients)

	HDI	SDI
MET	1.54 (1.13–2.84)	1.56 (1.00–2.57)
HCC	1.62 (0.99–3.05)	1.47 (1.08–1.96)
ALL	1.54 (0.99–3.05)	1.49 (1.00–2.57)

During the N state, the hepaplastin test for patients with MET, patients with HCC, and patients overall yielded values of 111.8 ± 12.8, 76.0 ± 22.0, and $92.5 \pm 16.3\%$, respectively. During the H state, equivalent values were 106.7 ± 23.8, 74.1 ± 22.0, and $89.2 \pm 18.0\%$, respectively. No significant changes in results of the hepaplastin test were noted between the N and the H states in any group of patients.

Discussion

Liver metastases and HCC are both common worldwide. Most patients present at a stage when surgical resection is no longer possible, and face a dismal prognosis. Local/regional and intraarterial treatments are feasible and effective only in selected patients whose disease is confined to the liver. Systemic chemotherapy, the only option available for patients with extrahepatic disease, has not been successful in the past and has been associated with significant, sometimes fatal adverse effects [6, 7]. More successful chemotherapy will require methods that ensure maximum delivery of chemotherapeutic agents to the tumor with minimal distribution to nontumor tissues. Among such possibilities, hypertension-enhanced cancer chemotherapy using AT II is being developed with the intention of increasing the proportion of blood flow directed to the tumor and decreasing the proportion of blood flow to nontumor tissues. Hypertension-enhanced cancer chemotherapy is based on the observation that tumor-induced vessels show less vasoconstriction than normal vessels during the hypertensive state induced by AT II [13]. The resulting selective blood flow and drug distribution may reduce adverse side effects to normal tissue while enhancing effects of systemically administered anticancer drugs on neoplastic tissue [16].

This approach has been applied to various types of advanced cancer since 1978 [5]. With respect to the liver, AT II has been used as a biologic response modifier in the treatment of hepatoma (HCC) and of colon cancer metastatic to the liver [2, 9]. In previous studies in which changes in hepatic arterial blood flow induced by AT II infusion in patients with these hepatic cancers were examined in [3, 10], hepatic artery infusion chemotherapy has been demonstrated to provide more selective delivery of chemotherapeutic drugs to liver tumors when AT II is administrated. However, only in a few studies concerning patients with hepatic cancer have AT II-induced changes in delivery of systemically administered antineoplastic drugs, which reach the liver via both the hepatic artery and the portal vein, been considered. Therefore, accurate investigation of blood flow changes induced by systemic infusion of AT II in the liver tumors (and corresponding changes in delivery of chemotherapeutic drugs) depends on simultaneous and separate measurement of arterial and portal blood flow [16]. Although several methods exist for measuring hepatic blood flow, study has been impeded by technical difficulties in simultaneous quantitation of arterial and portal blood flow.

We have previously described several evolving models for quantitation of hepatic blood flow by means of PET with oxygen-15, and have succeeded in simultaneously quantifying arterial and portal blood flow in the liver [14, 17, 18, 20]. In addition, PET using a biologic radiotracer such as oxygen-15 provides measurement of blood flow under physiologic conditions, and repeated measurements are possible because the radioisotope used has a very short half-life. Thus, PET with oxygen-15 should be an ideal method for quantifying hepatic blood flow and performing repeated measurements [20]. Flower et al. [1] have reported the usefulness of PET with copper-62 (II) pyruvaldehyde bis-(^{4}N-methyl)thiosemicarbazone, [^{62}Cu]-PTSM, for investigating changes in hepatic blood-flow distribution in the liver induced by intraarterial infusion of AT II in patients with liver metastasis who underwent local/regional chemotherapy. However, physiologic measurement with PET using [^{62}Cu]-PTSM is not possible, since [^{62}Cu]-PTSM is not a biologic radiotracer. Furthermore, simultaneous, separate measurement of arterial and portal blood flows with PET is not possible using this tracer.

Oxygen-15 PET, which provides an accurate quantitative estimate of organ blood flow, was used in the present study to noninvasively measure blood flow in 13 hepatic tumors, hepatic parenchyma and spleen before and after systemic AT II administration.

Blood flow in the hepatic parenchyma

In previous studies [11, 20], in which the reproducibility of repeated blood flow measurement was evaluated, it was found that the repeated measurement of cerebral blood flow is lower than the first measurement because of habituation, while the repeated measurement of hepatic and splenic blood flow is higher than the first measurement. According to our previous study [20], the repeated measurement of HBFa is higher than the first measurement, and a drug is considered to have decreased HBFa if the blood flow measurement after drug administration is less than 101% of the measurement before drug administration. On the other hand, a drug is considered to have decreased HBFp and HBFt when repeated measurement of each blood flow is less than

95% and 98% of the first measurement, respectively. These criteria also would apply for detecting changes in response to AT II administration. All three categories of hepatic blood flow in all of our patients decreased after AT II administration, by these criteria. Therefore, when the decrease was found to be significant in this study, AT-II was judged to have an effect in decreasing the blood flow.

Hepatic arterial blood flow

HBFa decreased during the H state, and corresponding changes would be expected for chemotherapeutic drug delivery to nonneoplastic hepatic parenchyma during AT II-induced hypertension. In the present study, the decrease in HBFa in patients with cirrhosis (HCC group) was not significant, while the HBFa in the patients with healthy hepatic parenchyma (MET group) decreased to a significant extent. The limited decrease in the HCC group probably reflects a limited response to AT II infusion by the splanchnic vasculature, including the hepatic artery, in portal hypertension [12, 23].

Portal blood flow

HBFp also decreased during the H state, and this result suggests that in intraportal chemotherapy for hepatic cancer, AT II administration might decrease delivery of chemotherapeutic drug to the nonneoplastic hepatic parenchyma. In the present study, however, neither the decreases in HBFp in patients with MET nor those in patients with HCC were significant, while the decrease for all patients considered together was significant. In addition to the small numbers of patients in the MET and HCC groups, this result may have been related to the occurrence of a somewhat greater measurement error in the determination of HBFp than in the determination of HBFa.

Total hepatic blood flow

Sasaki et al. [10] infused krypton-81m into the hepatic artery of patients with liver tumors to separately estimate arterial flow to the liver and the tumor based on detected radioactivity. They demonstrated that the ratio of tumor to liver blood flow increases after intraarterial infusion of AT II. However, for accurate evaluation of changes in distribution of the blood flow in the liver following systemic infusion of AT II, portal blood flow as well as hepatic artery blood flow must be measured. After measuring both hepatic artery and portal blood flow simultaneously and separately by dynamic PET scanning using ^{15}O-water, we calculated the overall total of the arterial and portal blood flow as total hepatic blood flow (HBFt). In this study, HBFt decreased significantly after AT II infusion both in the MET group and in patients overall, but HBFt did not change significantly in the HCC group. These results are compatible with the observed decrease in BFR in the liver after AT II infusion. These findings also suggest that systemic infusion of AT II would decrease delivery of a systemically administered antineoplastic drug to the hepatic parenchyma, especially in patients with a healthy liver.

Despite such advantage, there are limitations in the clinical use of AT II for the treatment of liver tumor: (1) systemic infusion of AT II did not increase delivery to the tumor, but merely decreased delivery to the liver; (2) decreasing delivery to the normal liver will only be of benefit if the dose-limiting toxicity is seen in the liver; (3) the magnitude of the decrease in drug delivery to normal liver is about 30–50%, while direct delivery to the tumor by hepatic artery delivery will lead to a higher tumor/normal liver uptake ratio.

Indocyanine green retention rate and hepaplastin test

Both ICG-R15 measurement and the hepaplastin test were performed for evaluation of liver function. As ICG-R15 reflects hepatic blood flow, the significant increase in ICG-R15 after AT-II infusion in this study corresponded to a decrease in HBF after AT II infusion. On the other hand, since the hepaplastin test does not reflect HBF but rather assesses the coagulation function of the liver, the test revealed no significant AT II-related changes.

Splenic blood flow

A second advantage demonstrated in this study was reduction in SBF following systemic AT II infusion. Such infusion significantly decreased SBF considering all patients and also in patients with healthy hepatic parenchyma (MET group), while the SBF decrease in patients with cirrhosis (HCC group) was not significant. This result is also attributable to attenuation of the response of the splanchnic vasculature including the splenic artery to AT II infusion in patients with portal hypertension.

According to our previous study [19] in which we evaluated the reproducibility of repeated splenic blood flow measurements using a dynamic PET scan with ^{15}O-water, repeated measurement of SBF can be judged to show a decrease if the result is less than 97% of the first measurement. In the present study, repeated measurement of SBF after AT II administration yielded values less than 97% of baseline, and the decrease was significant. Therefore, AT II can be judged to have decreased SBF, which suggests that systemic chemotherapy enhanced by AT II-induced hypertension would result in decreased delivery of chemotherapeutic drug to the spleen. Furthermore, these findings suggest that hypertension-enhanced chemotherapy may decrease delivery of chemotherapeutic drugs to

nonhepatic organs other than the spleen, such as the stomach, intestines, kidneys and/or bone marrow; such organs are supplied solely by the aorta, where chemotherapeutic drug toxicity is more common than in the liver.

Tumor blood flow

Blood flow in brain tumors during hypertension induced by AT II has been measured by Tomura et al. [21]. Blood flow to hepatic tumors is most often similarly systemic, supplied solely by the hepatic artery. Accordingly, we based our calculation of TBF on the assumption of a single arterial supply, resembling the situation in the previous study of brain tumors. Tomura et al. reported that blood flow in brain tumor is increased by hypertension, while flow in surrounding tissues is not. In contrast, in our study, blood flow in noncancerous liver tissue decreased after administration of AT II but did not change significantly in hepatic tumors. This difference may be explained by the fact that blood flow to the brain is maintained even during the hypertensive state by autoregulation, while blood flow to the liver is decreased by vasoconstriction under hypertensive conditions induced by AT II as mentioned above.

Delivery indices

In our present study of AT II administration, blood flow in normal hepatic parenchyma decreased in the H state while being maintained in the hepatic tumors. Consequently, the TBF/HBFt ratio increased after AT II infusion. The HDI expresses the rate of increase of the TBF/HBFt ratio after AT II infusion, thereby indicating the relative rate of blood flow increase in the H state in the tumor compared to flow changes in the liver parenchyma. Therefore, as HDI would indicate the relative rate of increase in delivery of a chemotherapeutic drug to the tumor compared to the liver parenchyma with AT II-induced hypertension-enhanced chemotherapy, a high HDI predicts improved selectivity of drug delivery to the tumor in contrast to normal liver.

Splenic blood flow decreased in the H state in this study, and the TBF/SBF ratio increased after AT II infusion. SDI expresses the rate of increase of the TBF/SBF ratio after AT II infusion. A high SDI predicts improved selectivity of drug delivery to the tumor in contrast to the spleen. Further, a high SDI suggests that adverse effects in multiple organs from chemotherapeutic drugs should be decreased by systemic AT II infusion.

Large variations between individual values for HDI and SDI were seen in the present study. In two patients the delivery index was not above 1.00 (the HDI was 0.99 in a patient with HCC, and the SDI was 1.00 in a patient with MET). As no distinctive characteristics of blood pressure, liver function, or other measured parameters were evident in these two patients, individual low sensitivities to AT II might have been responsible. The wide range of individual patient responses to AT II infusion suggests that the delivery index should be calculated before initiating AT II-induced hypertension to enhance chemotherapy in a given patient. Thus, increased selective delivery of a chemotherapeutic drug to the hepatic cancer can be ensured by using oxygen-15 PET to identify patients likely to benefit.

Conclusion

In conclusion, oxygen-15 PET is an elegant method for quantifying changes induced by systemic infusion of AT II in blood flow distribution in the liver. Blood flow in hepatic tumors was maintained in the H state while blood flow to the normal hepatic parenchyma and spleen was decreased, especially in patients with healthy hepatic parenchyma. Consequently, a relative increase was observed in TBF in the H state, which would result in more selective drug delivery. Furthermore, oxygen-15 PET could be used to predict enhanced delivery of a chemotherapeutic drug to hepatic cancers during AT II-induced hypertension in a given patient.

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