Angiotensin-II-Induced Hypertension Chemotherapy: Evaluation of Hepatic Blood Flow with Oxygen-15 PET

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We quantitatively measured blood flow in liver parenchyma and hepatic tumors in two patients using ^{15}O-carbon dioxide (steady state) and ^{15}O-water (dynamic) PET imaging. Images were acquired before and during administration of angiotensin-II to achieve a hypertensive state. Blood flow in the hepatocellular carcinoma was greater than that of the parenchyma. Blood flow in the colon metastasis was similar to that in the parenchyma and lower in the center than in the periphery. During a hypertensive state induced by angiotensin II, blood flow in both the primary and secondary liver tumors did not change, while blood flow in the liver parenchyma decreased. As a result, there was a relative increase in tumor blood flow during the hypertensive state on PET images. Furthermore, blood flow to the spleen decreased to 55% of baseline during the hypertensive state. These findings suggest that hypertensive cancer chemotherapy may protect normal tissue. Furthermore, PET imaging may be able to predict the efficacy of hypertensive cancer chemotherapy in the patients with liver tumors.

Key Words: angiotensin-II; hepatocellular carcinoma; metastatic liver cancer; blood flow; PET

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Hypertension cancer chemotherapy is based on the phenomenon that tumor-induced vessels show less vasoconstriction than normal vessels during the hypertensive state induced by angiotensin-II (AT-II) (*1*). This therapy may reduce adverse side effects to normal tissue while enhancing the effects of systemically administered anticancer drugs on neoplastic tissue. However, this benefit would be dependent on the preferential perfusion of particular hepatic tumors with AT-II.

PET provides an accurate quantitative estimate of organ blood flow, and we have applied PET imaging to noninvasively measure blood flow of hepatic tumors (*2*). We report on two patients with hepatic tumors who underwent PET imaging before and after AT-II administration to evaluate blood flow in hepatic parenchyma and tumors. We discuss the potential for PET imaging to predict sensitivity of hepatic tumor to hypertension chemotherapy.

CASE REPORTS

Methods

Two patients were studied after informed consent was obtained. The first patient was a 49-yr-old man with hepatocellular carcinoma (HCC) secondary to liver cirrhosis. The other was a 46-yr-old woman with hepatic metastases from carcinoma of the transverse colon.

PET measurements were performed after fasting by placing the patients in a recumbent position on the bed of a whole-body PET scanner (*3*). Oxygen-15-carbon dioxide gas was produced continuously by a medical cyclotron. After a transmission scan, patients inhaled air containing 2 mCi (74 MBq)/min of ^{15}O-carbon dioxide. After reaching a steady-state, PET data were acquired for 5 min. Attenuation correction was performed every 2.5 sec. Regions of interest (ROIs) for the liver, spleen and hepatic tumors were defined in PET images by referring to CT images at corresponding levels. The ratio of radioactive concentrations in tissue and in the abdominal aorta (T/B ratio; hepatic blood flow index) was calculated. After the steady-state PET scan, a dynamic PET scan was obtained. After intravenous bolus injection of 20 mCi (740 MBq) ^{15}O-water, 12 PET measurements were made every 5 sec followed by another 8 measurements every 30 sec. Blood samples were obtained from the left brachial artery at 10, 15, 20, 25, 30, 35, 60, 120, 180 and 240 sec after the beginning of the emission scan. Radioactivity concentrations in the blood samples were measured immediately in a precalibrated well counter. From these PET images, the radioactivity in the liver parenchyma and the tumors was calculated. In the current study, assuming that Kety's single-compartment model can be applied and that a given hepatic neoplasm is supplied only from the hepatic artery, liver tumor blood flow (TBF) was expressed as the follows:

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

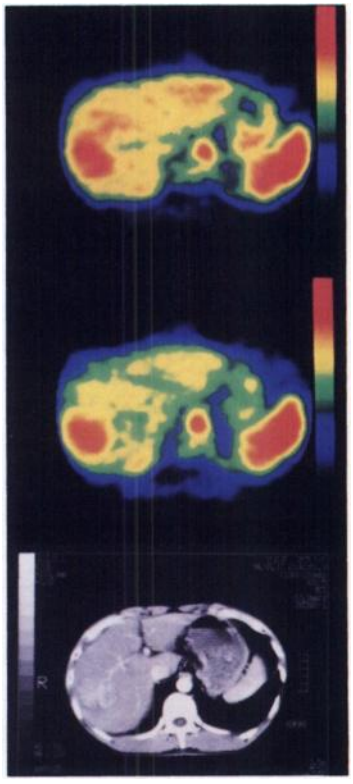

FIGURE 1. A 49-yr-old man with hepatocellular carcinoma (HCC). Top, middle and bottom images are PET images of normotensive and hypertensive states and a CT scan, respectively. Compared to the normotensive state, PET images show a preferential increase in blood flow to the tumor compared with liver parenchyma, in the hypertensive state.

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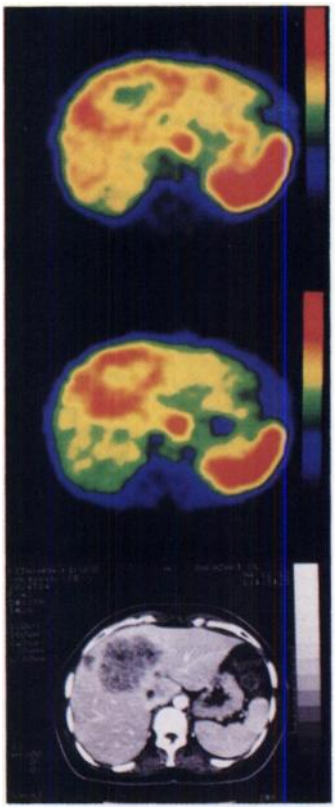

FIGURE 2. A 46-yr-old woman with hepatic metastasis from colon cancer. Top, middle and bottom images are PET images during normotensive and hypertensive states and a CT scan, respectively. Compared to the normotensive state, the metastatic lesion shows increased flow relative to liver parenchyma in the hypertensive state.

where Ct(t) and Ca(t) are the radioactive concentrations in the hepatic tumor and the blood, respectively, and ρ is the tumor-blood partition coefficient for water. In the current study, the specific gravity of the tumor was assumed to be 1. TBF was determined by the Simplex method (*4*), which is 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 (*5*).

After completion of the initial PET scans, a hypertensive state was induced using recombinant AT-II. Initially, this drug was administered intravenously at a rate of 5 ng/kg/min, and the infusion rate was increased until the mean blood pressure was increased by 50% above the baseline level. During the hypertensive state, the blood pressure was measured every minute, and steady-state and dynamic PET scans were repeated.

Results

Figure 1 shows the steady-state PET images of the first patient before and during the AT-II-induced hypertensive state, and the corresponding CT image. The PET images revealed that the radioactivity concentration in the HCC was higher than in noncancerous parts of the liver in the normotensive state. The HCC and liver T/B ratios were 0.88 and 0.73, respectively. During the hypertensive state, PET images demonstrated increased tracer activity in the HCC relative to liver parenchyma. The HCC T/B ratio did not change (0.91), but the liver parenchyma T/B ratio decreased to 0.65. TBF and ρ of the HCC determined by the dynamic method were 66.4 ml/100 g/min and 0.83, respectively. During the hypertensive state, TBF and ρ changed to 68.4 ml/100 g/min and 0.79, respectively; SBF decreased from 122.0 to 65.0 ml/100 g/min, and ρs did not change (0.94 to 0.95).

The radioactivity of metastatic liver tumors in the second patient was similar to normal liver parenchyma (Fig. 2). The T/B ratios of the hepatic metastases and the liver were 0.75 and 0.73, respectively. During the hypertensive state, the PET image demonstrated preferential increase in tracer activity of the hepatic metastases. The T/B ratio of hepatic metastases did not change (0.76), but the T/B ratio of the liver decreased to 0.61. TBF and ρ of the hepatic metastases determined by the dynamic method were 41.0 ml/100 g/min and 0.77, respectively. During the hypertensive state, these values changed to 32.9 ml/100 g/min and 0.82, respectively; SBF decreased from 125.2 to 72.8 ml/100 g/min and ρs did not change (0.80 to 0.80).

DISCUSSION

The blood flow in an organ can be measured quantitatively using PET, which also allows repeat measurements to be performed noninvasively and under physiologic conditions because of the use of very short-lived positrons. Blood flow to hepatic tumors most often is supplied solely from the hepatic artery (*7*). Accordingly, we based our calculation of TBF on the assumption of a single arterial supply, similar to a previous study of brain tumors (*6*). The hepatic blood flow index was calculated and estimated using the tissue-to-blood ratio because hepatic parenchyma is also supplied through the portal vein.

Quantification of tumor blood flow in a hypertensive state induced by AT-II has been previously performed by Tomura et al. (*6*). They reported that blood flow in the tumor increased while that of surrounding tissues did not change. In contrast, in our two patients, blood flow in noncancerous liver tissue (T/B) decreased after administration of AT-II but did not change in HCC and was only slightly decreased in hepatic metastases. This difference may be explained by the fact that blood flow to the brain is maintained even during the hypertensive state (i.e., autoregulation), while blood flow to the liver is decreased by vasoconstriction under the hypertensive conditions induced by AT-II.

If an anticancer drug is administered systemically, most of the drug is delivered to normal tissues. However, in our patients, blood flow in the hepatic tumors was maintained in the hypertensive state while it decreased in normal hepatic parenchyma by approximately 10%–15%. This effect may result in improved drug selectivity. Furthermore, adverse effects in other organs may be decreased: For example, blood flow in the spleen decreased to 55% of baseline in the hypertensive state. Further clinical studies of AT-II induced hypertension chemotherapy may establish it as a useful means of increasing drug selectivity.

CONCLUSION

PET imaging may be useful in determining whether a patient with a liver tumor is a candidate for hypertension chemotherapy.

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