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Introduction

Many researchers proved tumor cells are radioresistant when irradiated under hypoxic condition and tumor tissue has hypoxic fraction. Hypoxic fraction is thought to be one of the reasons for difficulties in cure all cancer patients by conventional radiotherapy.

New anti-tumor agents are recently developed which selectively kill hypoxic fraction of tumors. Antihypertensive agents, such as hydralazine, reduce the tumor blood flow which subsequently increase the hypoxic fraction in the tumors. Concomitant use of antihypertensive agents may increase the chance for such anti-cancer agents to kill tumor cells.¹

We have found heterogeneous distribution of blood flow in an experimental tumor, rat transplantable hepatoma - AH109A². Tumor blood flow has been estimated either as a whole tumor or small parts of tumor. It is difficult to estimate regional tumor blood flow because of heterogeneity.

However, with the help from positron emission tomography (PET) and positron labeled water (H₂¹⁵O), we can observe both whole and partial tumor blood flow. It is also easy to observe the change of the blood flow induced by vasoactive agents, such as antihypertensive or hypertensive agents. We studied the effect of antihypertensive agents, i.e. hydralazine and nifedipine, on blood flow of rabbit tumor VX2.

Materials and Methods

Tumor (VX2) was implanted into the left thigh of the rabbits. Tumor grew up to, at least, 4 - 6 cm in diameter, the experiment was performed. They were anesthetized by intravenous administration of sodium pentobarbital (50 - 100 mg/kg) and were catheterized through right external iliac artery. Arterial blood pressure were monitored and arterial blood radioactivities were detected by β-detector through this arterial line which was, at the end, connected to an infuse/withdrawal pump.
Hydralazine and nifedipine were chosen for antihypertensive agents. Hydralazine is a vasodilator and nifedipine is a calcium-channel blocker which cause vasodilatation. Hydralazine (0.4 mg/kg) was administered i.v. and nifedipine (5 mg/kg) was administered buccally.

PET-931 was used for a scanner. After transmission scan of the pelvis region including tumor, twenty times 6 seconds emission scans were performed immediately after bolus injection of $\text{H}_2^{15}\text{O}$. Arterial blood was withdrawn by the pump and, simultaneously, the arterial blood $\beta$-ray activity was continuously recorded throughout the $\beta$-detector.

A set of emission scans were performed: first scan for control and second scan for response to the antihypertensive agents. During interval of each scan, rabbit was fixed to the scanner. After administration of antihypertensive agents, blood pressure was monitored. When blood pressure decreased and flattened, second scan was conducted.

Several regions of interest (ROI) were set on a tumor having high accumulation of radioactivities. Also ROI was set on contralateral normal tissues - muscles. Radioactivities of the ROI were summed from 1 to 20 planes. Arterial blood counts were integrated for 120 seconds as an arterial input. Comparison between the 2 scans was done as follows; ROI counts divided by the arterial input. They were expressed as percentage relative blood flow change.

Results

Figure 1 shows PET images of rabbit pelvis region including tumor using $\text{H}_2^{15}\text{O}$. Markedly heterogeneous distribution of the tumor blood flow was noted. The low accumulation in the tumor showed necrosis tumor which was confirmed by autopsy. It is difficult to say which represents tumor blood flow; whole tumor or highly accumulated part of the tumor?

Results after comparison were summarized in Table 1. Blood pressures were down to 70 to 85% at the time of the second scan. Blood flow of the muscles were down to 69 to 89 %.

On the contrary, tumors showed different response. Some tumor increased to 107% and some were constant and some decreased to 70%. It is obvious that the changes in both blood pressure and muscle blood flow were due to the vasoactive agents. It is also obvious that the changes in tumor blood flow were independent to the different kind of vasoactive agents.

Discussion

There are lots of methods to assay the tumor blood flow. For clinical feasible study, we chose this method; PET and $\text{H}_2^{15}\text{O}$. There is another assay method for this purpose using PET; continuous inhalation of $\text{C}^{15}\text{O}_2$. We did not adopt this method because inhalation of radioactive gas, causing accumulation of high radioactivities in the airway system, such as nasal cavity, oral cavity, trachea and lungs, may hide tumors located in head, neck and lungs.
The advantage of our method are such as, 1) repeated measurement of tumor blood flow, 2) comparison the results between the changes in tumor and that in the normal tissues before and after administration of vasoactive agents, 3) measurement of both absolute and relative changes in the tumor blood flow and 4) assessment of both regional and a whole tumor blood flow.

Regardless of the vasoactive agents, varied responses in the tumor to decreased blood pressure were observed. Precise mechanism is obscure. But we think such heterogeneous response might be due to the structures and immaturities of the tumor vessels. Some tumor vessels were immature structurally and functionally and some were not. Some tumor vessels responded like normal tissues and some did not. It is likely that tumor is heterogeneous not only distribution of blood flow but response to vasoactive agents.

In human tumors, it might be the same story. But we can check the tumor response to such vasoactive agents using PET. When tumor responds well, we will have a good result with concomitant use of vasoactive agents. When tumor does not, we will select another treatment planning. We emphasize that PET study is the must for anti-cancer therapy to know whether tumor respond to vasoactive agents.

References


Table 1. Changes in mean blood pressure and relative blood flow.

<table>
<thead>
<tr>
<th>Experimental Number</th>
<th>Antihypertensive Agents</th>
<th>Changes in Mean Blood Pressure (%)</th>
<th>Region of Interest</th>
<th>Changes in Relative Blood Flow (%)</th>
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<td>muscle</td>
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Fig. 1. Rabbit VX2 tumor image with PET and H$_2^{15}$O.