Regional Blood Flow in Human Tumors

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Abstract

Blood flow in 97 human tumor nodules, of which 31 were lymphomas, 31 were anaplastic carcinomas, and 35 were differentiated cancers, was measured using the $^{133}$Xe clearance method. The lymphomas showed statistically higher blood flow ($36.4 \pm 21$ (S.D.) ml/min/100 g) than did the anaplastic carcinomas ($15.4 \pm 11.4$ ml/min/100 g; $p < 0.001$) and the differentiated cancers ($22.8 \pm 14.9$ ml/min/100 g; $p < 0.05$). The size of the tumors did not correlate with the blood flow. In the group of differentiated cancers, the blood flow in nodules in areas of earlier irradiation was lower ($9.0 \pm 6.3$ ml/min/100 g) than in nodules in intact regions ($25.0 \pm 14.5$ ml/min/100 g; $p < 0.05$). Nodules in cicatrival areas after surgical operation had lower blood flow than did nodules in the intact areas, but the difference is not statistically significant. It is obvious that most human tumors have a considerably lower blood flow than what one would expect to find in the surrounding normal tissue.

Introduction

Data on tumor blood flow are of importance both for a proper evaluation of tumor growth, metabolism, and radiosensitivity and for obtaining maximal benefit from chemotherapy. In 1904, Ribbert (24) postulated that tumors have a better blood flow than do other tissues, which became a dominating concept for the following 50 years. With the increase in papers on microscopy and angiography, the concept of abundant pathological vascularity in the majority of tumors was established, although, on the other hand, avascular tumors were also known. In 1927, Lewis (16) described extensive afferent and efferent vascularity in tumors. Furthermore, according to Lewis, "each type of tumor has its own particular type of vascular pattern." New capillaries are formed in neoplasms (1). It is vital for neoplasia that the formation of capillaries and the proliferation of cells and capillaries take place approximately at the same time. Tumors release a diffusible material, the tumor angiogenesis factor, which induces vascular proliferation in the host and is essential for tumor growth (6, 7, 23). Several workers have made angiographic and histological studies on tumor blood flow in animals (5, 10, 14, 15, 18, 19, 25, 27). Only a few authors have quantitatively examined the blood flow in human tumors (2, 3, 11, 17, 21, 28). The $^{133}$Xe clearance method is useful for a quantitative measurement of perfusion in superficial tumors in particular. The purpose of this work was to investigate the blood flow in different types of human superficial tumors, using the $^{133}$Xe clearance method.

Materials and Methods

Ninety-seven superficial tumor nodules from 80 patients were measured. The tumors studied are listed in Table 1 according to types. The size of the tumors varied from 0.3 to 440 ml.

Xenon Measurements $^{133}$Xe dissolved in 0.9% NaCl solution was used as a tracer. A volume of 0.1 ml (100 to 200 $\mu$Ci) was slowly injected into the middle of the nodule studied. The disappearance rate of the tracer was followed with a collimated NaI scintillation detector for 15 to 20 min. The counts were fed on line into a minicomputer (NOVA 1220). A 2-exponential curve was fitted with the measuring points. A typical curve is presented in Chart 1. The local blood flow was calculated from the equation

$$F = \lambda \cdot \frac{(A/B \cdot k_1 + k_2)}{(A/B + 1)^{-1}}; \quad k_1, 2 = 0.69/T_1, 2$$

where $k_1$ and $k_2$ are the disappearance rate constants and $A$ and $B$ are the corresponding scale constants for the exponential terms. The factor $\lambda$ is the partition coefficient (100 ml/100 g) between the nodule tissue and blood. The reproducibility of the method is adequate (about $\pm 2$ ml/min/100 g). In the statistical analysis the $t$ test was used.

Results

Chart 2 shows the individual values in the different tumor types. Blood flow in the lymphomas was greater than that in the differentiated tumors and the anaplastic carcinomas. The mean blood flow was $34.6 \pm 21$ (S.D.) ml/min/100 g in the lymphomas, $15.4 \pm 11.4$ ml/min/100 g in the anaplastic carcinomas, and $22.8 \pm 14.9$ ml/min/100 g in the differentiated tumors. The blood flow was highly significantly ($p < 0.001$) greater in the lymphomas than in the anaplastic carcinomas, but the difference between the lymphomas and the differentiated tumors was only nearly significant ($p < 0.05$). In the anaplastic group, 8 nodules were in areas of earlier surgical operation; and in the differentiated group, 11 nodules were in areas of earlier surgical operation. The blood flow in the nodules in the anaplastic group was $10.5 \pm 8.2$ ml/min/100 g, and the blood flow in the differentiated group was $21.6 \pm 14.3$ ml/min/100 g. The difference in the blood flow between the tumor nodules in areas of earlier surgical operation and the nodules in intact regions was not statistically significant.

In the differentiated group, 5 nodules were in areas of earlier irradiation. The blood flow in these 5 nodules ($9.0 \pm 6.3$ ml/min/100 g) was lower than in nodules in intact regions ($25.0 \pm 14.5$ ml/min/100 g), and the difference was statistically nearly significant ($p < 0.05$). In the lymphoma group, 2 nodules were in areas of earlier irradiation; and in these nodules, the blood flow was 32.3 and 19.8 ml/min/100 g (mean, 26.1 ml/min/100 g), respectively.

There was no significant correlation between the size of the tumor and the local blood flow.

Discussion

Studies on tumor vasculature have been reported by many investigators. Most of the studies concerning the blood flow in...
tumors have been performed in animals, and several workers have done microangiographic and histological studies on the tumor blood flow and vascularization. Different types of vascular patterns have been described in different tumors (5, 16, 18, 19, 25). All aspects of the vascularity or vascular transport cannot be explained by the anatomic arrangement of the fine vasculature. An increased number of capillaries per unit volume does not necessarily mean that the blood flow is greater in normal host tissue (4, 8, 14, 22). Gullino and Grantham (8) have shown tumor blood flow in different mouse and rat tumors to be 7 to 8 ml/min/100 g. They have also shown the distribution of 42K to be 1:20 in hepatoma versus normal liver tissue.

In experimental tumors, the blood flow has been shown to be from 1 to 50 ml/min/100 g (8, 9, 12, 22, 27—29). Several anesthetics and circadian variations have greater or lesser effects on the tumor blood flow, which may be one cause of the great variations observed in the tumor blood flow (20, 29).

During the last 20 years, several quantitative methods for the determination of tumor blood flow have been developed. In 1961, Gullino and Grantham (8) reported a venous outflow method for experimental tumors in an organ for which the blood supply had been isolated from a single artery and vein. Cataland et al. (4) measured the total blood flow in transplantable tumors by the tissue uptake of diffusible ions as a fraction of cardiac output. In 1968, Gump and White (9) reported tumor blood flow values of a transplantable rabbit carcinoma by the tissue clearance of the radioactive inert gas 86Kr. The methods using diffusible ions will give tumor blood flow in relation to the cardiac output, while the methods using radioactive inert gas clearance will give the flow per g tissue if the tissue blood distribution coefficient of, λ, is known and a flow-limited transport of the gas might be assumed. Gump and White (9) determined the λ value to average 1.07 for certain types of malignant tumors in rabbits. Song et al. (27) determined the tumor-blood partition coefficients of xenon to be 0.959 ± 0.044 and 0.966 ± 0.042 for Walker carcinoma of rats. In the present study, a value of 1.00 ml/g (100 ml/100 g) has been used. The partition coefficient depends strongly on the fat content of the tissue and slightly on the hematocrit (13). The fat content can cause an error in the results. This is important in s.c. tumors since the greater part of the subcutis is adipose tissue. The loss of xenon through the intact epidermis was demonstrated to be quite negligible, but considerable loss of xenon is possible by sweating (26). The injection of 0.1 ml of tracer solution into a small tumor may cause a change in tumor circulation.

In humans, tumor blood flow has been investigated to some extent.
extent, and most of the methods described above are not suitable for studies on humans (2, 3, 11, 17, 21, 28). By the clearance technique using the radioactive inert gas, $^{133}$Xe, it is possible to measure blood flow in human tumors. In the present study, blood flow was greater in the lymphomas than in the other tumors. This result agrees with some single observations of Tanaka (28) and Bru et al. (3). This may partly explain the radiosensitivity of lymphomas, which generally is higher than those of the other tumors. Great variations have been observed in human tumor blood flow. These variations may be due to methodological factors and, among other things, the degree of necrosis.

Johnson (11), using a thermodynamic method, reported somewhat higher tumor blood flow values in 5 patients than does this paper. Tumor blood flow values of other human measurements using the xenon clearance method agree with the values of this paper (2, 3, 21, 28). These values show considerably lower blood flow than what one would expect to find in the surrounding normal tissue.

The size of the nodules did not correlate with the blood flow values in the present study, which contradicts the results of experimental tumors. A reduction of tumor blood flow has been found during tumor growth in many experimental tumors (4, 28). However, the experimental tumors measured have been clearly smaller than the human tumors studied in the present work. The present results show that tumors in cicatrical areas of earlier surgical operation and especially in areas of earlier irradiation have a lower blood flow than tumors in intact regions. Obviously, the scar formation in the tumor bed causes a decrease in tumor circulation. Regional blood flow in human tumors seems to correlate to the radiosensitivity of the tumor (17, 28). The quantitative measurement of the regional blood flow seems to be a useful indicator of radiosensitivity of a tumor before irradiation.

References

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