CHAPTER 7

Vascular Effects of Localized Hyperthermia

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Abstract
When hyperthermia is applied in vitro, no fundamental differences can be seen between the response to normal and tumor cells. In vivo however, selective damage of tumor cells can be achieved and this phenomenon can be largely attributed to a number of characteristic properties of the blood vessels within solid tumors. Changes in blood flow induced by hyperthermia can influence the response of a tumor to heat either by affecting the delivery of heat through changes in heat dissipation or by a modulation of the tumor microenvironment which may in turn affect the thermosensitivity of tumor cells. Studies in experimental and human tumors suggest however that an accurate prediction of changes in blood flow during heating is not possible so that such changes cannot be used as a basis for the combination of hyperthermia with other therapy modalities. Even so, when the underlying mechanisms responsible for the antitumor effects of a combination of hyperthermia with either radiotherapy or chemotherapy are considered, it becomes evident that either an increase or a decrease in blood flow could potentially contribute to the cytotoxic effect. A further interesting approach is in the use of antivascular drugs or vascular-targeted photodynamic therapy in order to specifically reduce tumor blood flow prior to or during hyperthermia treatment. Experimental data suggest that a considerable enhancement of the antitumor effect can be achieved with this approach. By reducing heat dissipation, such an approach may in future also be of use in overcoming problems related to insufficient temperature increases frequently seen in the clinical setting.

Introduction
The impact of tumor blood flow on the success of different forms of cancer therapy is already well established. When hyperthermia is considered, blood flow changes induced by this therapy form can influence the tumor response to heat in two ways. Firstly, changes in tumor blood flow will affect the delivery of heat to the tumor mass by causing changes in heat dissipation away from the tumor. Secondly, changes in blood flow will affect the metabolic microenvironment and are thus capable of modulating the thermosensitivity of tumor cells. With this in mind, numerous investigations have been undertaken to assess changes in blood flow in tumor and normal tissues during hyperthermia. These are summarized below. At the same time, blood flow changes occurring when hyperthermia is combined with other therapy modalities are examined.

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When the effects of hyperthermia on normal and tumor cells are assessed under in vitro conditions, no fundamental differences are found with respect to thermosensitivity. The therapeutic benefits of hyperthermia cannot therefore be attributed to a greater susceptibility of tumor cells to heat. In vivo however, a quasi-selective damage of tumor cells can be achieved when the tissue is heated to temperatures between 40 and 44°C. A number of characteristic properties of blood vessels in solid tumors appear to be responsible for this "selectivity". Microscopic examination reveals a number of structural and functional features of tumor blood vessels including tortuosity, excessive branching, blind endings, lack of smooth muscle in the vessel walls together with a lack of pericytes, interrupted endothelial linings and basement membranes. Additionally, a hierarchical organization is missing and significant arterio-venous shunt perfusion and temporal variations in blood flow (including temporary stasis) have been shown to occur. The competence of the vasculature to regulate flow in response to changes in a tissue's demands is limited in tumor tissue compared to normal tissue. Subsequently, an insufficient nutrient and oxygen supply in tumor tissue results in the development of hypoxic tissue areas, acidosis and energy depletion. When cells in vitro are artificially exposed to hypoxic conditions, low pH or low intracellular ATP levels, they are found to be more susceptible to hyperthermia, so that the development of such conditions within tumors as found in vivo can at least partially explain the enhanced sensitivity of tumors to hyperthermia. The relative importance and the individual role of hypoxia, low pH and depleted energy levels is difficult to decipher since they are closely interrelated, so that alterations in any one of these parameters may affect the others.

When the physiological response of normal tissue to being heated up to temperatures between 41°C and 45°C is investigated, an increase in perfusion is typically seen since this is the major route by which heat is normally dissipated away from tissues such that a deleterious heat load can be avoided. Numerous investigators have attempted to quantify this response in terms of the increase in blood flow seen, and these investigations have been summarized in reviews by Vaupel and Song et al., where increases in skin perfusion and skeletal muscle perfusion of up to a factor of 15 and 10 respectively were found, although the magnitude of flow increase appears to vary considerably depending on the species and tissue investigated, the technique used for heating and the heating protocol. Comparable measurements in tumor tissue (both in experimental and human tumors) have revealed pronounced tumor-to-tumor variation, with increases, decreases and lack of change in tumor perfusion having been reported. While some of this variability may again be explained by factors such as different heating-up rates, heating duration, thermal doses, temperature monitoring and heating systems, the use of tumors with different histology, implantation or growth sites and different tumor volumes together with the variability in the response to hyperthermia of different areas within the same tumor need to additionally be considered. When the available data are taken together, it appears that the change in blood flow upon heating is generally much greater in normal tissue than in tumors. Where increases in tumor perfusion occur, these are usually no greater than 1.5-2.0 fold. Within a single tumor entity, the changes seen depend upon the degree of heating applied, as exemplified by Song and colleagues who carried out investigations in SCK tumors in mice. This study showed a significant increase in blood flow following heating to 42.5°C for 1 h followed by a decline thereafter with recovery to the control level within 5 h. Heating to 43.5°C induced an initial increase in perfusion over the first 30 min followed by a pronounced reduction from which the tumor had not completely recovered even 24 h after heating. Upon 44.5°C hyperthermia, only a decrease in blood flow occurred, which became even more pronounced after completion of heating. Similar temperature-related effects were also seen in the R3230 adenocarcinoma growing in rats. The variability in the response to heating within a single tumor model has also been assessed in a study of the microregional physiology of rat DS-sarcomas during hyperthermia. Here, tumors of different sizes were heated to 44°C for 60 min and microregional perfusion was assessed...