

1982

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Charles F. Babbs

*Purdue University*, [babbs@purdue.edu](mailto:babbs@purdue.edu)

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# Biology of local heat therapy for cancer

Charles F. Babbs, M.D., Ph.D.

Biomedical Engineering Center, Purdue University, West Lafayette, Indiana, USA.

## Abstract

Successful cancer therapy must selectively destroy tumor tissue while sparing the host's normal tissues. Local heat treatment can have such a selective effect because abnormalities in tumor blood vessels supply less oxygen to heat-stressed tumor cells and are less efficient in cooling tumor tissue by blood perfusion.

**Key words:** cancer, treatment of; heat therapy; hydralazine; hyperthermia; vasodilators; tumors

[MEDICAL INSTRUMENTATION 1982; 16(1):23-26]

Heat therapy for cancer dates back to ancient times, when physicians as notable as Hippocrates and Galen used hot irons to destroy fungating cancers (Stonn et al. 1980). In the past decade numerous reports of the antitumor effects of heat in a variety of animal models, and in man, have kindled a renaissance of interest in hyperthermia therapy. Clinical studies from several institutions suggest that a significant number of tumors unresponsive to conventional radiation or chemotherapy have shown dramatic responses to heat, either alone (Crile 1962; LeVeen et al. 1976; Storm et al. 1979; LeVeen et al. 1980) or in combination with radiation (Hornback et al. 1977; Hahn and Kim 1980; U et al., in press).

Crile, for example, provided anecdotal reports of regressions of squamous cell carcinomas, neuroblastomas, and metastatic melanomas after the tumor-bearing member was immersed in a 46-47 °C water bath. LeVeen and coworkers reported substantial regressions in 21 patients with a variety of carcinomas after local heating with radiofrequency current. Hornback and associates pursued the combination of microwave-induced hyperthermia and ionizing radiation in 21 patients with far-advanced, histologically proven malignancies that were considered to be refractory to further medical treatment. Complete regression occurred in 16 of the patients, and 9 of the 16 were free of disease at 9 months. Although not strictly controlled clinical trials, these studies seem to indicate that hyperthermic therapy is quite effective in many patients whose cancers most certainly would have continued to spread without treatment and who, in the opinion of their physicians, would have had a poor response to further conventional therapy.

There are probably several reasons for the delayed rediscovery of heat therapy. Technically, there have been and still are practical difficulties with apparatus for heating. Hot wax baths, hyperthermic arterial perfusion, radiofrequency waves, microwaves, high-intensity ultrasound, and whole-body hyperthermia (fever therapy) have been tried. None has been developed to an

entirely satisfactory state, although gradual progress is being made. There are also difficulties with clinical thermometry--i.e., the process of recording the temperature distribution in and around the treated tumor (Cetas and Connor 1978). At present, most heat therapy centers rely on needle-like probes (thermistors or thermocouples mounted on needles) to measure temperatures at a few selected points in the treatment field, which must be assumed to be representative. These technical limitations have made it difficult to perform local heat therapy well. However, the most important reason why heat therapy has not been accepted until recently has been the lack of a physiologic rationale for its selective action against tumor cells and tissues.

Ideally, heat therapy must destroy cancer cells without affecting nearby normal cells, in much the same way that modern antibiotics destroy bacteria without damaging the host. Bacteria can be selectively destroyed by antibiotics because their cell walls, protein synthesizing apparatus, or chromosomes are chemically different from mammalian cells. The corresponding chemical differences between cancer cells and normal cells are much more subtle, and have proved elusive targets for selective therapeutic action without toxicity. However, several lines of evidence are beginning to develop that explain why tumor tissue may be especially vulnerable to local heat treatment. These include evidence of the metabolic deficiencies of cancer cells, which seem to produce selective heat sensitivity, coupled with an abnormal pattern of blood vessels in many tumors, which tends to limit blood flow. The abnormally reduced perfusion of tumor tissues delivers less oxygen than the tumor cells require when their metabolism is raised at higher temperatures. Moreover, the reduced blood flow in the tumor tends to carry away heat less rapidly from the tumor tissue than from adjacent normal tissues. As a result, the tumor tissue reaches higher steady-state temperature; thus multiplying the selective effects of heat on individual tumor cells. This double-edged sword, in principle, provides a significant therapeutic lever for the selective destruction of tumor tissue.

### **Normal vs. Neoplastic Cells In Vitro**

Cell culture studies suggest that malignant cells may be slightly more heat sensitive than their (normal) tissues of origin (Mondovi et al. 1969; Giovanella et al. 1973; Cavaliere et al. 1967; Muckle and Dickson 1971). For example, Mondovi and coworkers found that exposure of hepatoma cells to an aerobic environment at 43 °C caused inhibition of oxygen uptake, while normal regenerating liver cells were not affected. Muckle and Dickson found that 42 °C hyperthermia decreased oxygen uptake and viability of rabbit VX2 carcinoma cells while normal rabbit kidney, liver, and red blood cells were unaffected by the elevated temperature.

There are several possible explanations for such results. A relative lack of membrane repair enzymes or DNA repair enzymes, or both, in the abnormal tumor cells might mean thermal damage accumulates faster. A relative lack of ATP-generating enzymes might mean the cells are unable to meet the metabolic demands of higher temperatures. Whatever may be the critical cellular differences, they seem to account for the occasional success of whole-body hyperthermia (fever therapy) in producing remissions of cancer. Recently, investigators at the Universities of Edinburgh, New Mexico, and Mississippi have reported favorable responses, including tumor necrosis or regression, in patients maintained at 41-42 °C for several hours (Storm et al. 1981). Even greater anatomic and physiologic differences seem to exist between normal and neoplastic tissues than between isolated normal and neoplastic cells. These differences provide a specific

rationale for local heat therapy--i.e., application of energy only to the tumor-bearing region in such a way that core body temperature remains close to normal.

### **Normal vs. Neoplastic Tissues In Vivo**

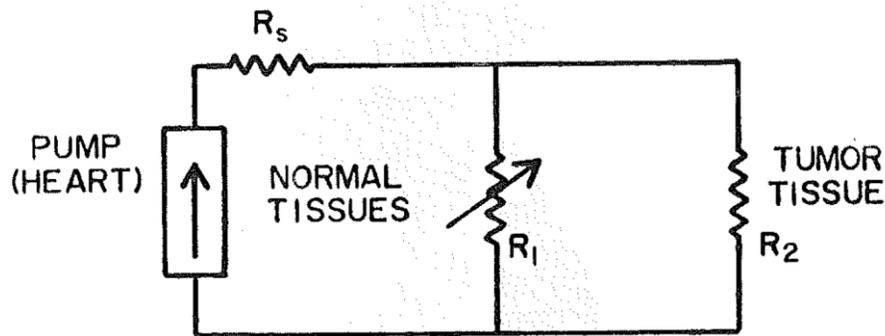
Solid tumor masses in vivo seem even more heat sensitive than cells from the same tumor line grown in vitro (Song, in press; Kang et al., in press; Song et al. 1981). When grown in tissue culture, normal and neoplastic cells look much the same under the microscope. However, in vivo tumor tissues are recognizably different from their normal tissues of origin. The tumor cells are typically packed together in disorganized clusters, and perhaps more important, the blood vessels nourishing them are subtly abnormal in character. Instead of the usual distribution of small arteries, capillaries, and small veins, there seems to be a predominance of sinusoidal capillary beds in most solid tumors. These capillary sinusoids are broader and longer, and are separated by larger intercapillary distances than are normal capillaries (Folkman 1976; Ide et al. 1939; Vaupel 1977; Intaglietta et al. 1977). Because blood flow in tumor capillaries is more sluggish than that in normal capillaries (Intaglietta), oxygen delivery to tumor tissues is far from optimal.

Recent work by Folkman (1976) has shown that tumor blood vessels are formed in response to a chemical tumor angiogenesis factor (TAF) liberated by tumor cells. TAF seems to stimulate the growth of capillaries, but not to stimulate the development of these capillary sprouts into well-differentiated, larger caliber arterioles. Consequently, the density of arteries and arterioles in many tumor tissues is abnormally small in relation to the venous vasculature (Intaglietta; Endrich et al. 1979; Gross 1979). The arterial vessels, found near the tumor surface, seem to be pre-existent and do not proliferate as the tumor grows (Peterson 1979). These arterioles tend to be pushed aside as the tumor expands, and their capacity to supply blood to the tumor capillaries becomes limited. They exhibit little vasomotion (Goodall et al. 1965) and seem to be already maximally dilated during tumor growth (Song; Gross). This general pattern of tumor vascularity has been observed in a variety of systems, including rat myeliosarcoma (Habighorst 1977), transplanted Brown-Pearce rabbit epithelioma (Ide et al.), hamster malignant neurilemoma (Eddy and Casarett 1973), and rat BA 1112 sarcoma implants (Gross).

The abnormal vascular pattern of tumors tends more often than not to produce relatively poor blood flow, as measured in milliliters per minute per gram of tissue (Peterson). Moreover, the abnormal tumor vessels seem unable to increase perfusion in response to the metabolic stress imposed by heat. For example, Storm and coworkers (1979) and Song have shown that blood flow to larger tumor masses does not increase when the tumor tissues are heated, although blood flow in heated normal tissues does increase. This physiologic vasodilation of normal tissues, in response to heat, increases blood cooling to prevent excessive temperature rise. Tumor tissues, on the other hand, may be quite limited in their ability to increase heat dissipation by augmenting blood flow, simply because the tumor vessels are relatively lacking in smooth muscle capable of dilating in response to local needs.

It is easy to summarize the abnormal character of tumor blood vessels by means of the electrical analogy in Fig. 1. Distribution of blood flow between normal tissues and tumor tissue depends upon regional vascular resistance. Vascular resistance in normal tissues is variable and subject to manipulation by drugs and metabolites that act upon vascular smooth muscle. Vascular

resistance in tumor tissue tends to remain constant. The heart feeds the parallel normal and tumor tissue beds. During local heat therapy dilation of the normal vessels will create an effective arteriovenous shunt around the tumor. Such changes in the distribution of blood flow would enhance cooling of normal tissues and simultaneously reduce cooling of the tumor to produce actual selective heating. As described previously (Babbs and DeWitt 1981), larger tumors are especially vulnerable to such selective heating effects because of limits imposed by the physical processes of heat transfer.



*Fig. 1. Electrical analogy of blood flow in normal and neoplastic tissues. Variable resistor  $R_1$  = normally reactive arterioles; fixed resistor  $R_2$  = tumor vessels. Series resistance  $R_3$  = resistance of arterioles that branch to feed both tumors and normal vessels.*

Furthermore, reduced blood flow in tumors during that therapy has important biochemical effects. Hypoxia and the resultant anerobic metabolism and lactic acidosis make the tumor tissue in the heated region even more vulnerable to thermal injury. Such potentiating of thermal injury by hypoxia and acidosis has been shown quite clearly both in vitro and in vivo (Gerweck and Rollinger 1976; Dewey and Freeman 1980; Song). Thus, because of the vascular abnormalities of tumor tissue, larger tumor masses can be raised to higher temperatures than surrounding normal tissues, and they are biochemically more heat sensitive.

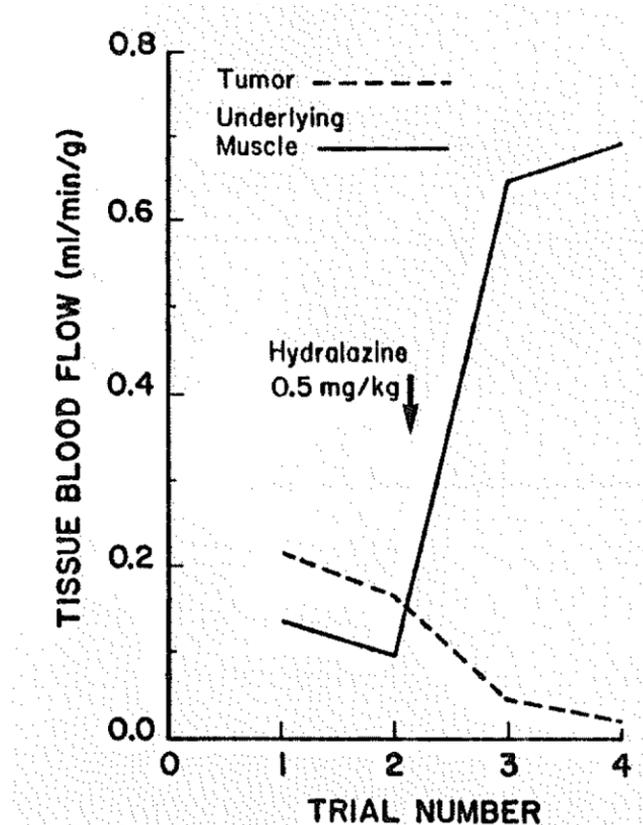
### **Exploitation of Vascular Abnormalities**

Our own group is actively pursuing the enhancement of local heat therapy with vasodilators, which are drugs that act directly or indirectly to relax vascular smooth muscle. They enhance regional blood flow when given in moderate doses by causing dilation of normal resistance vessels (arterioles). Since tumor vessels tend to be lacking in smooth muscle, such drugs should have a selective effect on normal tissues that would significantly improve local heat therapy for cancer. Indeed, the selective ineffectiveness of vasodilators on tumor vessels is becoming an established fact.

In the experimental literature, Kruuv and coworkers (1967) have reported that the vasodilators chlorpromazine, isoproterenol, or inhaled amyl nitrite, which are known to increase blood flow in normal tissues, actually decreased blood flow in mammary tumors--a finding consistent with

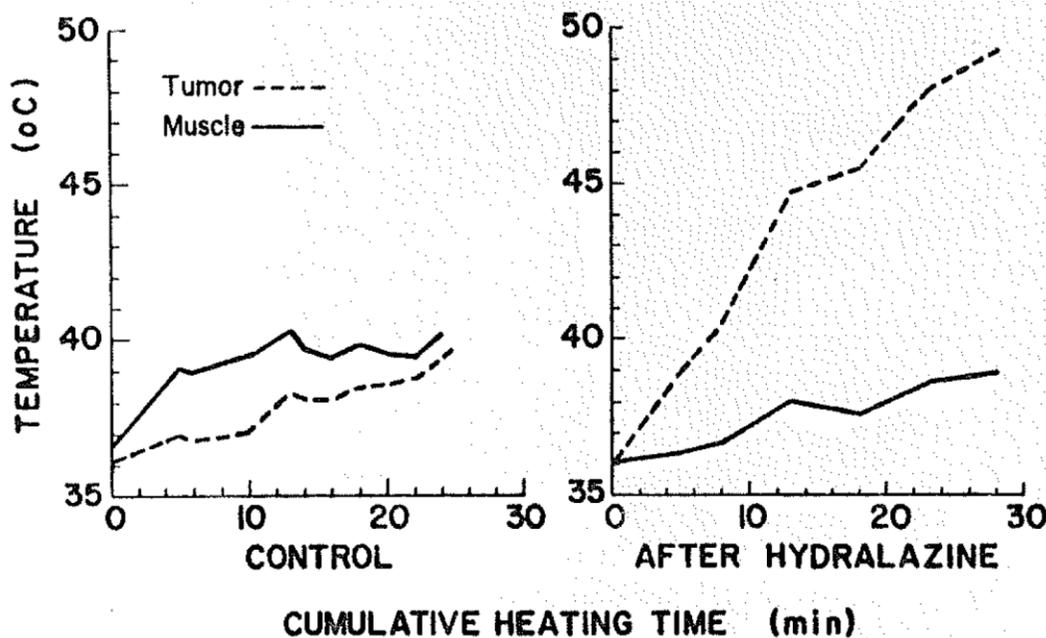
the conceptual model of Fig. 1 and with previous observations that smooth muscle is relatively lacking in the microvasculature of tumors. In human patients, Jonsson and associates (1978) studied the effects of intra-arterial prostaglandin E1, a potent vasodilator, as an adjuvant to angiography of tumors of the extremities in 10 cases. Except in one case, involving an hemangioma, the visualization of tumor vessels and delineation of the extent of disease were worse after the use of prostaglandin E1, whereas visualization of small normal muscular arteries improved. Evidently, prostaglandin increased blood flow in normal tissues relative to the tumor in a manner that would be quite helpful in improving the selectivity of local heat therapy.

In our own laboratories we have been investigating the use of the vasodilator, hydralazine, for improving the selective heating of transplantable venereal tumors in dogs. Fig. 2 shows the results of a typical experiment in which blood flow to the tumor and underlying normal tissue samples was measured with radioactive microspheres at roughly 10-min intervals. Before hydralazine was injected intravenously (0.5 mg/kg), the tumor had a slightly greater level of perfusion than the surrounding normal tissue. Hydralazine increased tissue perfusion in the normal tissue samples fivefold. At the same time, perfusion of the tumor tissue dropped nearly fivefold. Indeed, the vasodilator actually caused a reversal in the ratio of tumor to normal tissue perfusion. We have now performed more than six experiments of this type with similar results.



**Fig. 2. Regional blood flow in a dog with transmissible venereal tumor before (trials 1 and 2) and after (trials 3 and 4) administration of hydralazine (arrow). Dashed line indicates tumor flow. Solid line indicates flow in normal muscle underlying the tumor.**

Fig. 3 shows the temperatures measured during vasodilator-enhanced tumor heating in one of these dogs. The tumor-bearing region of one hindlimb was heated by passing 13.56 MHz radiofrequency current, generated by a diathermy unit (Birtcher Corp., El Monte CA), through a Helmholtz coil that encompassed the limb. The plots show center tumor temperature and subjacent normal tissue temperature as a function of time. The normal tissue (muscle) was exposed to essentially the same field strength as the tumor. Records demonstrate a dramatic increase in the tumor temperature during inductive heating with minimal increase in normal tissue temperature following hydralazine pretreatment. The position of the heating coils remained the same, but we were able to increase the intensity and duration of heating after the hydralazine injection, while keeping the normal tissue temperature  $\leq 40^{\circ}\text{C}$ . Note that prior to drug treatment, normal tissue temperature was slightly greater than tumor temperature. Hydralazine reversed this state of affairs; tumor temperature reached 48-50  $^{\circ}\text{C}$ , at which level a treatment time of less than 15 min can be expected to cause irreversible cellular injury (Babbs and DeWitt; Dickson and Calderwood 1980; Henle and Dethlefsen 1980). Encouraged, we are now beginning trials of vasodilator-enhanced selective heat therapy in dogs with spontaneous tumors of the extremities.



**Fig. 3.** Temperature time curves for transmissible venereal tumor and underlying normal muscle in a dog during local inductive heat therapy. Left: temperature records for heating trial before hydralazine injection. Right: temperature records after the hydralazine injection.

## **Biologic Limitations of Local Heat Therapy**

For the reasons just discussed, local heat therapy has significant potential for selectively destroying tumor tissue in a particular location. However, like radiation, local heating will never be a cure for widespread metastatic disease. Moreover, it remains to be seen whether heat therapy can be made consistently effective in destroying all the tumor tissue at a given site. In theory, spherical tumors may be heated effectively, if one is willing to accept damage to a thin shell of surrounding normal tissue (Babbs and DeWitt). Irregularly shaped tumor masses, however, may be much more difficult to heat uniformly.

Viable cells remaining near the tumor edge may require follow-up radiation or chemotherapy. In addition, certain areas may be off-limits to heat therapy. The eyes, for example, contain vitreous humor, which is devoid of blood flow and so would be heated as efficiently as the most poorly perfused tumor. Moreover, there may be certain tumor types, such as hemangiomas, that have blood flow much greater than most normal tissues; thus they might never be treated effectively by local heat.

Nonetheless, as more is learned about the biologic rationale for heat treatment of cancer and as instrumentation for heating and thermometry improve, it is likely that heat will become a standard therapeutic modality in selected patients with certain types of tumors. At present, all forms of hyperthermia are experimental, and this modality should not be used in lieu of standard forms of effective cancer therapy. The challenge for the biomedical engineer in the future will be to design selective heat therapy of cancer, so that someday it will become routine, safe, and effective treatment for well-defined groups of patients.

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Charles F. Babbs received his B.A. from Yale University in 1968 and his M.D. with honor from Baylor College of Medicine, Houston, in 1974; his M.S. in anatomy from Baylor in 1975; and his Ph.D. in pharmacology from Purdue University in 1977. He is currently associate research scholar at the Purdue Biomedical Engineering Center and clinical instructor in family medicine at Indiana University School of Medicine.

Work supported by Research Career Development Award HL-00587 from the National Heart, Lung, and Blood Institute, U.S. Public Health Service.