Interstitial Hypertension in Human Breast and Colorectal Tumors

Joanne R. Less, Mitchell C. Posner, Yves Boucher, Dennis Borochovitz, Norman Wolmark, and Rakesh K. Jain

ABSTRACT

The efficacy of present day antineoplastic regimens depends upon the delivery and penetration of therapeutic agents through the tumor vascular and interstitial spaces to the tumor cell target. The distribution of relevant molecules or cells in a solid tumor is often poor and heterogeneous and is believed to be due to a number of pathophysiological factors, including elevated interstitial fluid pressure (IFP). Using the wick-in-needle technique, IFP was measured in primary breast and colorectal carcinomas as well as their respective metastases to the lymph nodes and liver in a total of 17 patients. IFP was also measured in one recurrent renal cell carcinoma, one melanoma metastasis to the lung, and another melanoma metastasis to the lymph nodes and liver in a total of 17 patients. IFP varied from 4 to 50 mm Hg with a mean ± SD of 20 ± 13 mm Hg in the neoplasms (n = 41 measurements; n = 21 tumors), while IFP in normal tissues had a mean of 2 ± 4 mm Hg (n = 11). The mean IFPs for metastatic melanoma, primary breast carcinoma, and liver metastases from a colorectal primary were found to be 33 ± 14, 15 ± 9, and 21 ± 12 mm Hg, respectively. In the renal cell carcinoma, the pressure was 38 mm Hg. These results agree with the findings of our 3 previous studies examining IFP in human superficial melanomas (14.3 ± 12.5 mm Hg, n = 12), cervical carcinomas (15.7 ± 5.7 mm Hg, n = 12), and head and neck tumors (13.2 ± 8.8 mm Hg, n = 19), and indicate that in all types of human tumors studied to date, IFP was significantly elevated above that of normal tissue. This observation may be useful in localizing tumors during needle biopsy.

INTRODUCTION

The delivery of blood-borne therapeutic and diagnostic agents to the tumor cell entails the transport of relevant molecules or cells through the tumor microcirculation, across the microvascular wall, and through the interstitial space (1, 2). Transmural and interstitial transport in tumors are passive processes, occurring predominantly by convection and diffusion. Interstitial hypertension, well documented in experimental tumors during needle biopsy.

MATERIALS AND METHODS

Patient Selection. The protocol to measure interstitial fluid pressure intraoperatively in human tumors was approved by the Biomedical Institutional Review Board of the University of Pittsburgh, and written informed consent was obtained for all patients who participated in the study. Interstitial fluid pressure was measured in primary breast carcinoma and colorectal carcinoma, liver metastases from colorectal primaries, and nodal metastases from breast cancer. In addition, IFP was measured in one recurrent renal cell carcinoma, and in lymph node and lung metastases from primary melanoma. For each patient, the type of treatment administered (radiation-, chemo-, or immunotherapy), if any, and the time between therapy and the IFP measurement were recorded. The time between the completion of therapy and IFP measurement was quite variable and in almost all cases greater than 2 months. Therefore, an in-depth examination of the possible effect of the anticancer agent on tumor IFP was not attempted. The type of treatment administered, however, is presented for reference. The age of the patients who participated in the study ranged from 22 to 83 years.

Experimental Setup. Interstitial fluid pressure was measured using the wick-in-needle technique originally developed by Fadnes et al. (9). Briefly, a 2–3-mm sidehole was drilled 5 mm from the tip of a 23-gauge hypodermic needle. Five–6–0 ethilon, surgical sutures were threaded through the needle. Following sterilization, the needle was connected to a pressure transducer (model P23XL; Gould, Inc., Cleveland, OH) via cancer macromolecules from the tumor periphery to the surrounding normal tissue, where the interstitial pressure is essentially zero (4).

Although interstitial hypertension could have significant implications with regard to the delivery and penetration of anticancer agents in tumors, there is a paucity of data in human tumors. Much of the work in this area has concentrated on theoretical (4) and experimental (5) examinations of interstitial fluid pressure in rodent tumors. Recently, Boucher et al. (6) examined IFP in human superficial malignant melanomas using the wick-in-needle method and found that IFP is indeed elevated above that of normal tissue and increases with the size of the lesion. A positive correlation between IFP and tissue oxygenation. Finally, IFP decreased in tumors that showed complete response, suggesting that IFP may have potential as a prognostic indicator for radiation therapy.

A thorough understanding of tumor interstitial milieu would enable a realistic prediction of the efficacy of present day anticancer regimes. Therefore, the objective of this study was to measure the interstitial fluid pressure in a variety of human tumors and also to examine the relationship between IFP and clinicopathological variables such as tumor type, tumor size, TNM stage, histological grade, the degree of vascular invasion, lymph node involvement, and necrosis. Elucidation of the relationship between IFP and these readily available clinicopathological parameters may help define a role for IFP measurements in individualizing therapeutic protocols.
INTERSTITIAL HYPERTENSION IN HUMAN TUMORS

Table 1  IFF measurements for the 19 patients who participated in this study

<table>
<thead>
<tr>
<th>Patient</th>
<th>Patient sex/age (yr)</th>
<th>Tumor type</th>
<th>Vol. (cm³)</th>
<th>IFF (mm Hg)</th>
<th>BPb (mm Hg)</th>
<th>Treatment (if any)</th>
<th>Primary tumor stage</th>
<th>Primary tumor grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>F33</td>
<td>Renal Cell CA</td>
<td>800</td>
<td>38</td>
<td>90/60</td>
<td>Chemo., immu.</td>
<td>IV</td>
<td>WD</td>
</tr>
<tr>
<td>B</td>
<td>F22</td>
<td>Melanoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>M63</td>
<td>Nodal met.</td>
<td>133</td>
<td>20, 45, 50</td>
<td>110/60</td>
<td></td>
<td>IV</td>
<td>MD</td>
</tr>
<tr>
<td>D</td>
<td>F61</td>
<td>Lung met.</td>
<td>14</td>
<td>22, 27</td>
<td>130/75</td>
<td>Rad., chemo.</td>
<td>IV</td>
<td>MD</td>
</tr>
<tr>
<td>E</td>
<td>F43</td>
<td>Breast</td>
<td>14</td>
<td>5, 8</td>
<td>106/71</td>
<td></td>
<td>IIA, T2NOMX</td>
<td>PD</td>
</tr>
<tr>
<td>F</td>
<td>F45</td>
<td>Breast</td>
<td>19</td>
<td>4, 6</td>
<td>120/70</td>
<td></td>
<td>IIB, T2N1M</td>
<td>PD</td>
</tr>
<tr>
<td>G</td>
<td>F60</td>
<td>Breast</td>
<td>118</td>
<td>8, 10</td>
<td>95/61</td>
<td>Chemo.</td>
<td>IIIA, T3N2MX</td>
<td>PD</td>
</tr>
<tr>
<td>H</td>
<td>F71</td>
<td>Breast</td>
<td>45</td>
<td>30</td>
<td></td>
<td></td>
<td>IIIB, T4N1M</td>
<td>PD</td>
</tr>
<tr>
<td>I</td>
<td>F83</td>
<td>Breast</td>
<td>23</td>
<td>18, 20</td>
<td>90/60</td>
<td></td>
<td>IIIB, T4N2MX</td>
<td>MD</td>
</tr>
<tr>
<td>J</td>
<td>F34</td>
<td>Breast</td>
<td>14</td>
<td>9, 21, 33</td>
<td></td>
<td></td>
<td>IIIB, T4N1M</td>
<td>PD</td>
</tr>
<tr>
<td>K</td>
<td>F34</td>
<td>Breast</td>
<td>38</td>
<td>11, 29</td>
<td></td>
<td>Rad., chemo.</td>
<td>IV, T4NOMI</td>
<td>PD</td>
</tr>
<tr>
<td>L</td>
<td>F76</td>
<td>Colorectal</td>
<td>31</td>
<td>25</td>
<td>110/50</td>
<td></td>
<td>T3N2MX, Duke's C</td>
<td>PD</td>
</tr>
<tr>
<td>M</td>
<td>M74</td>
<td>Liver met.</td>
<td>4</td>
<td>25</td>
<td>95/55</td>
<td></td>
<td>T3N2MX, Duke's C</td>
<td>MD</td>
</tr>
<tr>
<td>N</td>
<td>F55</td>
<td>Liver met.</td>
<td>14</td>
<td>4, 6, 7</td>
<td>140/60</td>
<td></td>
<td>T3NXM1, Duke's C</td>
<td>MD</td>
</tr>
<tr>
<td>O</td>
<td>F59</td>
<td>Liver met.</td>
<td>3</td>
<td>28, 30</td>
<td>130/70</td>
<td></td>
<td>T3NXM1, Duke's D</td>
<td>MD</td>
</tr>
<tr>
<td>P</td>
<td>F63</td>
<td>Liver met.</td>
<td>34</td>
<td>5, 5, 10, 29</td>
<td>135/65</td>
<td>Rad., chemo.</td>
<td>T3N1M1, Duke's C</td>
<td>MD</td>
</tr>
<tr>
<td>Q</td>
<td>F60</td>
<td>Liver met.</td>
<td>34</td>
<td>37, 5, 45</td>
<td>90/50</td>
<td>Chemo.</td>
<td>T3NXM1, Duke's C</td>
<td>WD</td>
</tr>
<tr>
<td>R</td>
<td>M62</td>
<td>Liver met.</td>
<td>15</td>
<td>23</td>
<td>110/72</td>
<td></td>
<td>T3N1M1, Duke's C</td>
<td>MD</td>
</tr>
<tr>
<td>S</td>
<td>M63</td>
<td>Liver met.</td>
<td>23</td>
<td>14, 18, 32</td>
<td></td>
<td>Chemo.</td>
<td>T2N0M1, Duke's B</td>
<td>MD</td>
</tr>
</tbody>
</table>

* BP, blood pressure; Met, metastasis; Chemo., chemotherapy; Rad., radiation; Immun., immunotherapy.
* Data not available.

polystyrene tube (P50) filled with sterile, heparinized (70 units/ml) saline. The pressure signal was amplified by a preamplifier (model 134615–50; Gould, Inc.) and recorded on a dual channel chart recorder (model 35-V7202–10; Gould, Inc.).

IFF Measurement. All interstitial fluid pressure measurements were made under general anesthesia with the patient in a supine position. With the patient in this position, the tumor was at approximately heart level, and thus, the contribution of hydrostatic pressure to the interstitial pressure was minimized. The pressure transducer was calibrated, and under sterile conditions the needle was introduced approximately 2 cm into the tumor and left in place without external fixation. In most cases, the interstitial fluid pressure stabilized within a few minutes, after which the fluid communication was checked by slightly compressing and decompressing the polystyrene tubing (6). If the pressures before compression, after compression, and after decompression did not differ by more than 15%, the measurement was considered valid, and a mean pressure was calculated from these three values. In the cases when the interstitial fluid pressure did not stabilize within a few minutes of the needle's introduction into the tumor, the needle was removed, flushed with saline, and reinserted in a new location. Whenever possible, 2–3 measurements were made for each tumor, and for each measurement a new needle was used. If time permitted, a control measurement was made in normal host tissue at the end of the experiment. The systolic and diastolic blood pressures and tumor dimensions were also recorded.

Statistical Analysis. The relationship between parameters was examined using a simple linear regression model. The null hypothesis was rejected if the β1-coefficient differed from zero at the 0.05 level of significance.

Determination of Clinicopathological Variables. The clinicopathological variables studied were tumor volume, TNM stage, histological grade, and the degree of vascular invasion, lymph node involvement, and necrosis. Tumor volume was determined from the relationship: V = L1L2L3/6, where L1, L2, and L3 were measurements of the 3 perpendicular axes of the tumor. For each tumor, at least 3 slides were examined with reference to the histopathological parameters (tumor stage, cellular differentiation, vascular invasion, lymph node involvement, and necrosis). For consistency, all of these evaluations were performed by the same pathologist. Determination of tumor stage was based upon the rules established in TNM classification of malignant tumors (10), while histologically, the tumors were classified as poorly, moderately, or well differentiated. The degree of vascular invasion and necrosis were evaluated on a scale of 0 to 3. Lymph node involvement was assessed as either present or absent. For breast lesions, estrogen and progesterone receptor levels, DNA ploidy and S-phase fractions were also evaluated.

RESULTS

Interstitial fluid pressure was measured in a variety of primary tumors, including breast, renal cell, and colorectal carcinoma as well as in metastatic lesions in a total of 19 patients as shown in Table 1. For all patients, several measurements were made at different locations in the tumor. In some cases, however, individual measurements were discarded due to poor fluid communication. If possible, a control measurement of interstitial fluid pressure was also made in the tumor's host tissue. In normal breast, IFF varied between –0.5 and 3 mm Hg and had a mean value of 0 mm Hg, while IFF in normal liver was found to vary between 7 and 10 mm Hg (n = 3). When more than one IFF measurement was made for a particular tumor, variations in IFF could be as great as 2–3-fold. For the smaller tumors (volume <15 cm³), however, there was less variation in the IFF measurements, suggesting a single nodule consistency.

In the carcinomas and melanomas examined, interstitial fluid pressure ranged from 4 to 50 mm Hg. The mean interstitial fluid pressures for metastatic melanoma, primary breast carcinoma, and liver metastases from a colorectal primary were 33 ± 14 (SD), 15 ± 9, and 21 ± 12 mm Hg, respectively. It is interesting to note that 2 liver lesions (patients N and P) had IFPs comparable to that observed in normal liver.

Table 1 lists the tumor stage for the primary breast lesions and the stage at initial presentation of the primary colorectal tumors associated with the liver metastases studied. For both the mammary and colorectal lesions, the tumor stage was determined using the TNM classification system, which incorporates the anatomic extent of the disease (T), nodal involvement (N), and distant metastases (M) in its assignment of a tumor stage (10). The relationship between IFF and the extent of the disease (T) was examined using the regression model described above. The relationship between IFF and the extent of the disease (T) was examined using the regression model described above. The relationship between IFF and the extent of the disease (T) was examined using the regression model described above.

In Table 2, a more complete histological description of various tumors is given. Included in the table is the degree of vascular invasion, lymph node involvement, and tumor...
The poorly differentiated mammary carcinomas tended to exhibit higher interstitial fluid pressures than the moderately differentiated tumors, although this relationship could not be proven statistically significant. The IFP in mammary carcinoma also did not correlate with hormone receptor levels or cytometric data. Similarly, because all of the liver metastases studied were found to be moderately differentiated, no relationship could be determined between the IFP of the liver metastases and the cellular differentiation of the lesion.

**DISCUSSION**

The present study demonstrates that interstitial fluid pressure in human tumors, both primary and metastatic, is significantly elevated above that of normal tissue. IFP in the neoplastic lesions ranged from 4 to 50 mm Hg and exhibited much variation not only within tumor types but also between tumor types. Nodal metastases from a melanoma primary exhibited the highest interstitial pressure in the present group of patients. This lack of significant correlation could be due to a limited number of tumors and/or limited range of tumor size. Differences in the interstitial fluid pressure among various tumors could also be due to biological factors, e.g., different degrees of invasion of the host tissues (Fig. 1). Previously, interstitial hypertension in tumors has been attributed to 3 mechanisms: (a) the absence of functioning lymphatics; (b) the high vascular permeability and filtration coefficient of neoplastic blood vessels; and (c) the collapse of blood vessels, especially in the relatively low pressure return vessels, due to the proliferation of cells in a confined space (for review, see Refs. 2 and 5). If each of these factors were operating to the same degree in all tumor types for a given stage of development, one might expect to see little variation in IFP among tumor types. Another important factor involved in the maintenance of the interstitial fluid pressure in a given tumor is the hydraulic resistance encountered by the fluid as it moves through the interstitial spaces and across the tumor normal tissue boundary. Finally, Boucher and Jain (11) have recently shown that in conjunction with the above factors the principal driving force for the interstitial hypertension is the pressure in the tumor exchange microvessels. Therefore, it is quite likely that the microvascular pressures differ from one tumor to another depending upon the vascular architecture and viscous resistance offered to blood flow (12-14).

Several studies have suggested that interstitial fluid pressure may have important clinical implications with regard to cancer therapy. Roh et al. (8) presented evidence of a possible inverse relationship between tumor IFP and tissue oxygenation and hypothesized that IFP may aid in predicting the efficacy of radiation therapy. In the present study, we examined the correlation between IFP and other prognostic indicators such as in IFP measurements, lending support to the hypothesis that random central IFP measurements may characterize an entire single nodule tumor. For other tumors in this study, however, large variations in IFP for an individual lesion were observed. These large variations may consist of multiple nodules (6), each nodule having its own biological characteristics. As discussed next, these regional differences may contribute to the observed variations in IFP within a lesion.
tumor stage and tumor grade. For mammary tumors, IFP tended to increase with the extent of invasion at the primary site and was highest in the less differentiated tumors. However, these trends need to be confirmed with data from a large number of patients. The value of IFP as a predictor of response to radiation therapy, photodynamic therapy, hyperthermia, and chemotherapy should be assessed prospectively. Finally, the knowledge that IFP in tumors is elevated may be used to facilitate tumor localization during needle biopsy.6

ACKNOWLEDGMENTS

We wish to thank Dr. Robert Zlotecki and Dr. Thomas Skalak for their insightful comments, Dr. James Efird for the statistical analysis, and Carol Lyons for typing this manuscript.

REFERENCES


6 D. Kopans, Y. Boucher, A. Stacey-Clear, R. Moore, and R. K. Jain, unpublished observations.
Interstitial Hypertension in Human Breast and Colorectal Tumors


Updated version

Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/52/22/6371

E-mail alerts

Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions

To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.