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Advances in Brief

Interstitial Pressure of Subcutaneous Nodules in Melanoma and Lymphoma Patients: Changes during Treatment[1]

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Abstract

Interstitial pressure (IP) is a physiological variable that may have its greatest influence on the transport of high-molecular-weight therapeutic agents. IP in tumor nodules was measured in patients with metastatic melanoma or non-Hodgkin's lymphoma to determine the influence of this physiological variable on treatment outcome. The wick-in-needle technique was used to measure IP at time points before and after treatment with a variety of immunotherapy and chemotherapy regimens. Selected patients had IP measurements during chemotherapy or immunotherapy infusions. Ultrasound or computed tomography was used to evaluate the size of the studied lesions and their relationship to normal structures. The mean baseline IP in melanoma nodules (n = 22) and lymphoma nodules (n = 7) was 29.8 and 4.7 mm Hg, respectively (P = 0.013 for the difference between tumor types). In a subset of melanoma nodules for which IP had been measured before and after treatment, the IP increased significantly over time for nonresponding melanoma lesions from a baseline of 24.4 to 53.9 mm Hg after treatment (P = 0.005) and decreased in melanoma lesions that responded to treatment where the mean baseline and post-treatment IPs were 12.2 and 0 mm Hg, respectively (P = 0.001 for the difference in IP profiles between responding and nonresponding lesions). Six of seven lymphoma nodules responded completely to chemotherapy or radiation. The single nodule that did not respond had a baseline IP of 1 mm Hg that increased to 30 mm Hg after treatment. Tumor IP differs significantly between melanoma and non-Hodgkin's lymphoma. The changes in IP over time differ significantly between responding and nonresponding melanoma lesions. IP that increases during treatment appears to be associated with tumor progression in these tumor types.

Introduction

Interstitial pressure is the result of oncotic pressure in the interstitial space, oncotic and hydrostatic pressures in the microvascular space, the reflection coefficient, and the hydraulic conductivity of the vascular wall and interstitial space. It typically is expressed in mm Hg and can be measured by a variety of methods, including the wick-in-needle technique, micropuncture methods, and implantable capsules (1). Guyton measured IP[3] in normal tissues in the 1960s and reported values from −2 to −6 mm Hg (2, 3). Young *et al.* (4) were the first to measure IP in tumor-bearing rabbits in 1950 and found tumor IP to be elevated. Jain and his colleagues (5–8) have recently reported IP measurements in patients with melanoma; epidermoid carcinomas of the head and neck; cervical carcinomas; and breast, colorectal, and renal carcinomas. They found IP to be as high as 50 mm Hg in some melanomas. They also found a positive correlation between size and IP in epidermoid carcinomas and an inverse relation between response to radiation therapy and changes in IP in cervical carcinomas.

A number of the salient variables governing IP in tumors have been described in mathematical and animal models, and they show that the underlying mechanism for elevated IP is elevated microvascular pressure. However, the underlying mechanisms of elevated IP in animal and human tumors are not completely understood. Theories include an absence of functioning lymphatics, clot formation in tumor blood vessels, and abnormal permeability of tumor blood vessels (9–11). Although questions remain regarding the etiology of this phenomenon, a number of computer models have shown that IP dramatically influences transport processes, most notably convection and diffusion (12). These perturbations in transport can potentially cause uneven distribution of chemotherapy and immunotherapy agents and can remarkably decrease the residence time of drugs in tumor nodules. This effect is most pronounced for large molecules such as immunoglobulins and cytokines.

In cervical carcinomas, Roh *et al.* (7) found that IP measurements intercurrent with radiation treatments tended to decrease in clinically responding lesions. In another series of nonresponding melanoma patients treated with monoclonal antibody R-24 and interleukin 2, there was no change in IP with treatment (5). Data concerning responding and nonresponding melanoma and lymphoma lesions have not previously been defined. This study quantifies IP in metastatic melanomas, which are typically resistant to cytotoxic and immunotherapy agents, and lymphomas, which are often cured by intensive chemotherapy. The relationship between IP and response to treatment in these different cancers is compared, as well as the effect of immunotherapy on IP.

Patients and Methods

Wick-in-Needle Technique. Needles were prepared by placing four strands of 4-O silk suture material (Ethicon Corporation, Somerville, NJ) in the barrels of 19- or 21-gauge Huber needles (Davol Corporation, Cranston, RI). Huber needles have a curved and angulated bevel that does not produce a tissue core when inserted. Each wick-in-needle was then sterilized with ethylene oxide and packaged for individual use. At the time of an interstitial pressure measurement, the wick-in-needle was attached to polyethylene IV tubing (Abbott Laboratories, North Chicago, IL) while maintaining sterile technique and flushed with 0.9% normal saline containing heparin (2000 units/50 cc of 0.9% saline). The polyethylene tubing was connected to a pressure transducer (model P23XL; Viggo-Spectramed, Oxnard, CA). The transducer signal was processed by a signal conditioner and amplifier (model 11-G4113-01; Gould Electronics, Cleveland, OH). The output was recorded on a strip chart recorder (Omega Engineering, Stamford, CT). The system was periodically calibrated with a mercury manometer, and appropriate standard curves were generated in mm Hg.

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[3] The abbreviations used are: IP, interstitial pressure; IL, interleukin; BRMP, Biological Response Modifiers Program.

At the time of measurement, the subject was placed in either the seated or supine position, depending on the location of the designated lesion. The transducer was then positioned such that the transducer diaphragm was level with the lesion. The position was checked with a standard line level (Sears Craftsman, Chicago, IL). The skin over the lesion was cleansed with betadine, and a topical anesthetic was applied (cetacaine or ethyl chloride). The wick-in-needle was then placed into the lesion, and a tracing was obtained. The depth of needle insertion required to place the needle tip in the center of the tumor was determined by ultrasound or computed tomography before IP measurements. Fluid communication and system compliance were tested by clamping and unclamping the plastic tubing between the measurement needle and the transducer. This was done after the initial needle insertion and whenever the needle position was changed. The IP tracing had to return to its previous value within 1 min of the clamping procedure and had to remain stable (±2.0 mm Hg) for a minimum of 2 min before a result was reported. At the end of the IP measurement, the needle was removed in 2-mm increments with any changes in IP noted on the tracing. Ultrasound evaluation of the nodules was made for the first 10 patients immediately after IP determination. Since there was no change noted in the size or structure of the lesions, post-IP imaging studies were performed only if clinically apparent changes were observed during measurement. Systemic blood pressure was determined by automatic sphygmomanometer (Critikon Corp., Tampa, FL) at 10–15-min intervals during the study.

IP measurements were performed before starting protocol treatment and at the time the patient was scheduled for restaging of his or her tumor after treatment. A number of lesions were studied for up to 4 h during concurrent systemic chemotherapy, systemic immunotherapy, or intratumoral cytokine or antibody injections.

Patients. Tables 1 and 2 describe the patients who participated in multiple IP measurements during treatment. An additional seven melanoma patients had only one baseline IP measurement. Eligible patients were more than 18 years old, had metastatic melanoma or non-Hodgkin's lymphoma, and had received treatment on a protocol at the BRMP (Frederick, MD). All patients had easily palpable subcutaneous nodules or lymph nodes that were evaluated by ultrasound or computed tomography before measurement. The majority of the melanoma patients were treated either with a regimen combining IL-2 with monoclonal antibody R-24 (13) or IL-1α (14). The majority of lymphoma patients received chemotherapy with ProMACE-CytaBOM (15). A signed written informed consent was obtained from each patient before participation in this protocol. The institutional review boards of the National Cancer Institute-Frederick Cancer Research and Development Center and the Clinical Oncology Program, National Cancer Institute, reviewed and approved this protocol before patient accrual.

Statistics. Data in this study were evaluated using standard repeated measures analysis of variance, profile analysis, correlational analysis, *t* tests, and simple descriptive techniques. For some analyses, data were transformed to their common logarithms to satisfy homogeneity of variance and covariance requirements.

Table 2 *Characteristics of non-Hodgkin's lymphoma patients*

Patient	Size before[a] (cm)	Blood pressure (mm Hg)	IP (mm Hg)	Treatment
1	2.0 × 1.4	98/70	10	Observation
2	2.0 × 2.0	114/76	5	ProMACE-CytaBOM
3	4.0 × 5.0	120/80	1	ProMACE-CytaBOM
	1.0 × 1.5		2	
4	2.1 × 1.7	130/62	1	ProMACE-CytaBOM
5	6.0 × 4.0	134/67	12.5	Radiation
6	8.0 × 4.3	128/68	1 (30)[b]	EPOCH

[a] Lesions in patients 2–5 resolved completely with treatment.
[b] Nonresponder; IP was 30 mm Hg after treatment.

Results

Melanoma Patients. Sixteen patients had a baseline IP measurement performed in a total of 22 melanoma nodules before administration of protocol immunotherapy. The mean pretreatment IP for these patients was 29 mm Hg (range, 0–110 mm Hg). There was no correlation between lesion size or baseline blood pressure and IP (P = 0.616 and 0.247, respectively). There were five patients who had IP measured in two lesions. IP varied by as much as 100 mm Hg in different nodules on the same extremity. IP appeared uniform throughout the region of the nodule explored by the needle and generally would decrease to 0 mm Hg when the needle tip was in the normal surrounding subcutaneous tissue. In five of the tested melanoma nodules, IP remained elevated (*i.e.*, the same as intratumoral IP) for a distance of at least 1 cm from the outer edge of the tumor nodule. Repeated IP measurements were available on 11 nodules during immunotherapy from melanoma patients that did not respond. IP was measured before treatment and 2–4 weeks after completion of treatment. In four nodules, IP determinations were made while intratumoral injections of IL-1α or monoclonal antibody R-24 were being given. The volumes of the IL-1α and R-24 injections were approximately 1.0 and 3.5 ml, respectively. Patients who received intratumoral injections had at least one additional posttreatment time point to document the time course of IP elevations. For all of the studied nodules, respective baseline and posttreatment IP means of 24.4 and 53.9 mm Hg differed significantly (P = 0.005). The changes in IP did not correlate with increased nodule size at the time of measurement (P = 0.82); however, all of these lesions and the patients' other visceral metastases eventually progressed after treatment. In Table 1, patients 6 and 7 had simultaneous IP measurements during intratumoral injections of monoclonal antibody R-24 and IL-1α, respectively. IP increased acutely in both patients by more than 30 mm Hg. It is unknown whether this effect was secondary to local vascular effects of

Table 1 *Characteristics of melanoma nodules with IP measurements before and after treatment*

Patient	Size before (cm)	Size after (cm)	Blood Pressure (mm Hg)	IP before (mm Hg)	IP after (mm Hg)	Treatment regimen
1	3.6 × 3.4	4.0 × 3.6	110/80	30	60	IL-2/R-24[a]
2	2.3 × 2.4	3.1 × 2.8	107/74	60	65	IL-1[b]
3	5.9 × 5.6	7.0 × 6.0	100/53	20	35	IL-1
4	3.2 × 3.3	5.7 × 3.2	110/70	5	25	IL-1
	6.0 × 3.4	6.8 × 5.8		7	24	
5	2.3 × 2.2	2.4 × 2.3	132/78	8	30	IL-2/R-24
6[c]	2.5 × 2.2	2.6 × 2.2	120/90	5	92	IL-2/R-24
	2.5 × 2.1	2.4 × 2.1		30	60	
7[c]	1.0 × 0.8	1.4 × 0.9	146/85	38	107	IL-1
8	2.1 × 1.7	2.7 × 2.1	115/86	40	30	IL-2/R-24
	2.0 × 2.0	2.0 × 3.0		25	65	
9	11.0 × 5.4		121/58	12[d]	0	IL-2/R-24
	3.9 × 3.8			0[d]	0	
10	3.5 × 3.4	3.0 × 2.3	114/74	24[d]	0	IL-1

[a] IL-2 was given at 30 MU/m^2 i.v. (Roche units) twice weekly for 3 weeks, then 3 MU/m^2 twice weekly for 6 weeks. R-24 was given at doses from 20 to 60 mg/m^2 i.v. twice weekly on the fourth and fifth weeks of treatment.
[b] IL-1 was given at 0.1 μg/kg i.v. daily for 7 days or intratumorally for 5 days.
[c] Patients received intratumoral injections.
[d] Responding lesions. Patient 9 had a complete response in both nodules. The IP measurement posttreatment was taken in the remaining normal subcutaneous tissue.

the cytokines, the volume of the injection, or bleeding into these nodules (although there was no physical examination or ultrasound evidence of bleeding). At the time of follow-up, IP continued to increase after completion of intratumoral treatments.

Only three of the studied melanoma nodules responded to treatment (two complete and one partial response). These lesions had a mean IP of 12.2 mm Hg compared to 24.4 mm Hg for nonresponding lesions. Fig. 1 shows the changes in IP for responding and nonresponding nodules. Multivariate profile analysis and repeated-measures analysis of variance were performed on these patient groups. Analyses showed that while pretreatment IP means did not differ significantly (P = 0.287), there was a significant IP difference after treatment for responders and nonresponders (P = 0.001). A formal test for parallelism of the two IP profiles showed that the two groups are significantly divergent (P = 0.028). There was no significant difference in baseline size between the responding and nonresponding lesions (P = 0.083). The lesion that exhibited a partial response had a relatively high baseline IP (24 mm Hg), which decreased to 0 mm Hg at the time of best tumor response. For the two lesions that exhibited a complete response documented by computed tomography, the posttreatment IP value used was that of the normal tissues in the area previously occupied by the tumor. A number of lesions followed in this study had low pretreatment IP (*i.e.*, less than 15 mm Hg); all of these lesions had increased IP after immunotherapy and eventually increased in size.

In an effort to define any interactions between the high-pressure melanoma nodules and the surrounding normal tissues, four patients were put through a series of palpation maneuvers. These interventions consisted of the manual compression of surrounding tissues not involved with tumor at progressively greater distances from the measurement needle. Two patients had upper-extremity nodules; compression of biceps muscle proximal to the nodule at a distance of up to 15 cm from the measurement needle caused transient increases in IP, which returned to baseline almost immediately after compression was released. Compression distal to the nodule in one of these two patients caused a transient decrease in IP, which resolved after compression was relieved. The other two patients studied had neck lesions; one was located anteriorly at the base of the neck, and the other was in the postauricular area. The former lesion showed increases in IP from 80 mm Hg to more than 100 mm Hg whenever the patient turned his head laterally. This physiology was reproduced by compressing external jugular veins at the base of the neck. A portion of this tracing is shown in Fig. 2. The latter patient showed increases in IP when the paraspinal muscles at the base of the neck were palpated at a distance 10 cm from the mass. Similarly, palpation of external jugular veins caused transient increases in IP.

Lymphoma Patients. A total of seven nodules were studied in six patients with non-Hodgkin's lymphoma. Six nodules were assessable for response to treatment. The mean IP for these lesions was 4.7 mm Hg (P = 0.013 for the comparison of mean baseline IP between melanoma and lymphoma). No patient had a baseline IP greater than 12.0 mm Hg. Six of seven nodules responded completely to chemotherapy or radiotherapy. The nonresponding lesion had a baseline IP of 1 mm Hg and initially decreased in size with treatment; however, IP increased to 30 mm Hg concurrent with regrowth of the nodule. This lesion arose in a patient who had received multiple previous chemotherapies and radiotherapy for an indolent lymphoma.

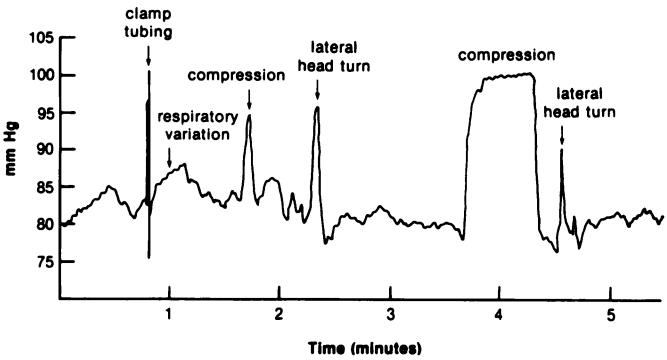

Fig. 2. IP tracing for a melanoma patient with a nodule located in the inferior portion of the neck. Note the sharp increases in IP during head turning and manual compression of the jugular veins.

Four lymphoma nodules had IP measured concurrently with i.v. chemotherapy infusions of cyclophosphamide. The infusions of cyclophosphamide were given over a period of 30 min, and the patients were followed for up to 4 h after their chemotherapy doses. IP increased transiently in these nodules by 4–12 mm Hg and returned to baseline after completion of the chemotherapy infusion.

Toxicities. All patients noted a mild amount of pain during needle insertion, and two patients had prolonged intralesional pain during the IP measurement period. There were no infections or clinically significant bleeding events from the procedure. One patient had rapidly progressive tumor growth in a measured lesion, but other sites of disease also progressed concurrently; thus it was not likely that IP measurement caused progression of the tumor.

Discussion

A review of the literature revealed only two other published studies of IP measurements in human melanoma nodules (5, 8) and no previous reports of IP in lymphomas. Our study reports a number of new observations that further our understanding of the physiology of the interstitial space of the tumor types examined. In addition, the interactions of the tumor interstitium with normal tissues and therapeutic agents are explored for the first time. Our data indicate that potentially useful prognostic information may be obtained by measuring the interstitial pressure of subcutaneous tumor nodules.

The maximum IP measured in any tumor nodule by Boucher and colleagues (5) was 41 mm Hg in a melanoma lesion. The maximum IP in the melanoma lesions presented here was 110 mm Hg. These enormous pressures provide a substantial gradient between the tumor and the surrounding normal tissues, which are thought to have IP values that are slightly negative (2). How can IP in tumors approach systemic blood pressure? A possible explanation can be deduced from the work of Boucher and Jain (10), who have recently published an elegant study showing the relationship between interstitial pressure and intravascular pressure in postcapillary venules. They concurrently measured IP and microvascular hydrostatic pressures in an animal model using R3230AC mammary adenocarcinoma. Their data showed that IP was dependent on the hydrostatic pressure in tumor venules. It

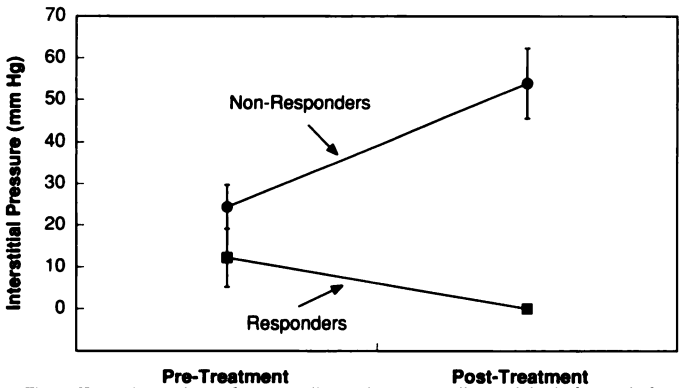

Fig. 1. IP trends are shown for responding and nonresponding nodules before and after cytokine treatment. There is a significant difference between the two groups (P = 0.001).

has also been shown that IP in tumors increases with vascular occlusion in a rat sarcoma model (16). The data presented here from the compression of external jugular veins in patients with neck metastases confirm that venous occlusion in human tumors directly influences interstitial pressure. If Boucher's findings can be generalized, the extremely high IP values shown here imply that very high venous pressures are extant in some human tumors. We have also measured high IP in other tumor histologies including subcutaneous metastases from renal cell carcinomas and lung carcinomas.[4] Elevated venous pressures in tumors could arise from intravascular thromboses, plugs from embolizing tumor cells, or abnormal regulation of vessel pressure by pre- and postcapillary sphincters in tumors. In an animal model using MCA-38 adenocarcinoma, we have shown that systemic anticoagulation with heparin (100 IU/day s.c.) or warfarin (1.0 mg/kg/day) can lower IP[5]; thus intravascular clotting may be the most important of these mechanisms. Alternatively, one could propose that arteries, in addition to venules, could contribute directly to IP. This would imply that both tumor arterioles and postcapillary venules are leaky and as such can affect the hydrostatic pressure of the interstitial space. This would be difficult to prove *in vivo* but would be consistent with IP values approaching systemic blood pressure. Previous investigations in head and neck malignancies and melanoma have shown a correlation between tumor size and IP (5, 6). The fact that IP did not correlate with tumor size in this study may be secondary to the larger tumor deposits measured here. The mean tumor volume in this study was approximately twice that of the nodules Boucher studied (5). The distribution of tumor volumes relative to other studies may also influence this result.

Increases in IP after cytokine administration are demonstrated by this study. Most of these patients received IL-1α or IL-2, both of which can cause increased vascular permeability in normal vessels (17, 18). This effect may be exaggerated in tumor blood vessels and result in increased IP. Increases in IP were not seen in normal subcutaneous tissue after i.v. administration of these cytokines (data not shown), supporting the notion that tumor blood vessels are differentially affected. Also, IL-1α stimulates endothelial cells to produce platelet-activating factor and plasminogen activator inhibitor (19, 20). These changes can lead to thrombosis and increased IP by the mechanisms discussed above. No responses (0 of 11) were seen in lesions that exhibited increased IP after cytokines. It is possible that these lesions were destined to have increasing IP by mechanisms other than those mediated by the cytokines given; however, it is far more plausible that the physiology of these nodules was altered by the treatment in a way that negatively influenced tumor response. IP also showed transient small elevations during chemotherapy infusions in lymphoma nodules. This suggests that at least some chemotherapy drugs dynamically alter the interstitial space and may influence the pressure or permeability of tumor vessels. Additional investigation is needed to understand this phenomenon.

The melanoma nodules that responded all had initial IP values of less than 25 mm Hg or attained low IP (0 mm Hg) during treatment. Melanomas that started with IP measurements greater than 25 mm Hg or that developed IP readings higher than baseline levels during treatment did not respond. Similarly, all of the responding lymphoma patients started with IPs of less than 12 mm Hg; the only nonresponder developed high IP (30 mm Hg) concurrent with regrowth of the involved lymph node. Although it is conceivable that the patients with increasing IP who failed treatment would have responded to an effective agent (if one were available), the evidence presented here favors the conclusion that elevated IP connotes a bad prognosis in these tumor histologies and may be part of the mechanism for the treatment failures.

The physiology described in these patients is not reproduced by any *in vitro* model and is reproduced by few animal models. These observations underscore the need for understanding how the peculiar physiology of the interstitial space of tumors influences interactions with normal tissues, the dynamics of drug delivery *in vivo*, and the processes of tumor metastasis and growth.

[4] B. D. Curti, unpublished data.

[5] B. D. Curti, manuscript in preparation.

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