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Tumor Blood Flow and Systemic Shunting in Patients Receiving Intraarterial Chemotherapy for Head and Neck Cancer[1]

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ABSTRACT

Radionuclide techniques have been used to estimate the systemic shunt and to quantitate blood flow to the tumor and a reference normal tissue in nine patients undergoing intraarterial chemotherapy for head and neck cancer. The systemic shunt was calculated as the percentage of pulmonary trapping of intraarterially injected ^{99m}Tc-labeled macroaggregated albumin. The mean systemic shunt in the 12 separate arteries studied was 23 ± 13% (SE) (range 8–43%). Quantitative blood flow was determined from the slope of the washout curve of intraarterially injected ^{133}Xe. The mean tumor blood flow was 13.6 ± 6.7 ml/100 g/min, while the mean blood flow to the scalp was 4.2 ± 2.1 ml/100 g/min providing a mean tumor/normal tissue ratio of 3.9 ± 2.7. An estimate of blood flow distribution was obtained by calculating the ratio of counts/pixel in the tumor mass *versus* the remainder of the head as determined by single photon emission computed tomography following an intraarterial injection of ^{99m}Tc-labeled macroaggregated albumin. The mean ratio of tumor to normal tissue perfusion by this technique was 5.6 ± 3.7. These techniques have allowed noninvasive determination of the blood flow parameters associated with intraarterial chemotherapy. At least part of the therapeutic advantage of regional chemotherapy in patients with head and neck cancer is due to a tumor/normal tissue blood flow ratio that favors drug delivery to the tumor contained within the infused volume.

INTRODUCTION

i.a.[3] chemotherapy has the potential advantages of increased drug concentration at the tumor site and decreased systemic drug levels and toxicity. The rationale for regional delivery is based on the steep dose/response curve exhibited by most antineoplastic agents (1). The therapeutic advantage of i.a. therapy is defined as the incease in tumor drug exposure compared to that achieved by systemic therapy with both treatments given at the maximum tolerated dose (2).

Following i.a. drug administration, the major factors determining drug concentration at the tumor site are the dose rate, the quantitative regional blood flow, and the tumor tissue flow rates within the infused volume. The higher the dose rate (quantity per unit time) and the lower the regional blood flow (volume per unit time) the greater the drug concentration in the local tumor blood supply (3). Tumor drug exposure will then be determined by the rate of diffusion or transport of drug across capillary endothelium into the extracellular fluid (4). Tumor drug exposure would be maximized by increasing the dose rate, by infusing into low blood flow regions (or decreasing the blood flow), and by using rapidly diffusing antineoplastic agents (5). Selectivity could be improved by decreasing normal tissue perfusion relative to tumor perfusion.

Under ideal circumstances an agent infused i.a. would be entirely removed from the blood during initial transit through the tumor capillary bed thereby preventing systemic drug exposure. The first pass extraction actually attained depends upon vascular considerations (the capillary surface area and endothelial integrity), the rate of diffusion of the drug across the endothelium into the extracellular space (partition coefficient), drug uptake from the extracellular space into the tumor cell (to maintain the diffusion gradient between the blood and the extracellular space), and cell retention of the drug (determined by drug binding to the intracellular target and/or intracellular metabolism, and the presence or absence of an active transport system extruding the drug) (4, 5). Even with a high first pass extraction in the capillary bed, substantial systemic toxicity may occur if a high percentage of the dose is shunted from the arterial to the venous circulation via precapillary shunts.

Although systemic toxicity can occur with i.a. therapy, in the majority of instances the dose-limiting side effects are local (6). The major determinant of local toxicity is the drug sensitivity of the normal tissue within the regional area. Since toxicity follows a steep dose/response curve similar to that of tumor cytotoxicity, physiological conditions that would increase drug delivery to the tumor relative to normal tissue could be advantageous. A low total regional blood flow improves the regional advantage of i.a. therapy by increasing the drug concentration at a given dose rate; however, once drug/blood mixing has occurred, drug delivery becomes proportional to the blood flow rate with greater blood flow providing higher drug delivery (5).

The purpose of this study was to evaluate the physiological conditions of blood flow and systemic shunting associated with i.a. chemotherapy in patients with head and neck cancer. Determination of these conditions would allow rational assessment of the validity of a regional approach for these neoplasms and could provide a basis for subsequent interventions designed to improve the therapeutic advantage.

MATERIALS AND METHODS

Patient Population. The clinical characteristics of the patients who participated in this study are shown in Table 1. All patients were receiving i.a. chemotherapy using a surgically implanted infusion pump (Infusaid Corp., Norwood, MA) and radionuclide injections were given either through the auxilliary side port of the Model 400 pump or through s.c. injection ports (Infuse-a-port; Infusaid Corp.) attached to the surgically placed infusion catheters. The surgical implantation procedures have been previously described (7, 8). This investigation was reviewed and approved by the Committee to Review Grants for Clinical Research and Investigation Involving Human Beings of the University of Michigan in accord with an assurance filed with and approved by the Department of Health, Education, and Welfare.

Quantitation of Blood Flow. Imaging was performed on a large field-of-view gamma camera with a low energy all purpose parallel hole collimator interfaced to a nuclear medicine computer system (MDS, A[2]; Medical Data Systems, Ann Arbor, MI).

Ten mCi ^{133}Xe were injected as a bolus into the side port of the infusion pump. Computer acquisition was started immediately prior to injection. Dynamic images were acquired at 3 s/frame for 100 frames. TACS[3] were generated from representative regions of interest drawn

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[3] The abbreviations used are: i.a., intraarterial(ly); Tc-MAA, ^{99m}Tc-labeled macroaggregated albumin; SPECT, single photon emission computed tomography; TACS, time activity curves.

Table 1 *Patient characteristics*

Patient	Age	Sex	Primary	Tumor location	Cell type	Prior therapy		
						Surgery	Radio-therapy	Chemo-therapy
1	46	F	Parotid	Left face	Adenocarcinoma	Yes	Yes	Yes
2	62	F	Tonsil	None	Squamous	No	Yes	Yes
3	70	M	Palate	Left palate	Adenocarcinoma	No	No	No
4	54	F	Tonsil	Left tonsil; left soft palate	Squamous	No	Yes	Yes
5	45	M	Tongue	Midline tongue	Squamous	No	Yes	Yes
6	56	M	Oropharynx	Midline oropharynx	Squamous	No	Yes	Yes
7	61	F	Floor of mouth	Bilateral jaw; floor of mouth	Squamous	Yes	Yes	Yes
8	57	M	Floor of mouth	Bilateral floor of mouth	Squamous	No	Yes	Yes
9	31	M	Parotid	Left face	Undifferentiated	Yes	Yes	Yes

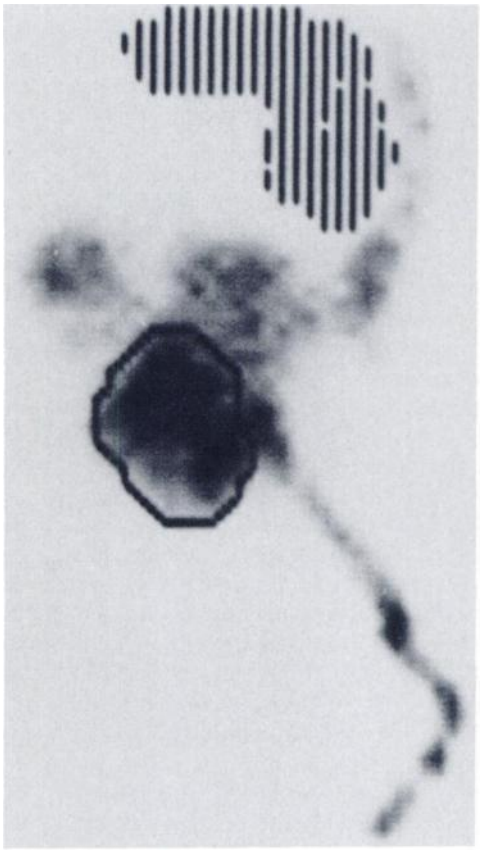

Fig. 1. Computer acquired image of lateral view of ^{133}Xe blood flow study with regions of interest drawn for the dominant tumor mass and the scalp. The i.a. catheter, placed in the external carotid artery, is also seen.

on computer for the dominant tumor mass and the scalp (see Fig. 1). The tumor TACS were corrected for radioactivity in overlying skin by subtracting the scalp TACS (normalized for the number of pixels) from the tumor TACS. The scalp was chosen as the normal tissue of reference since it is vascular in the same blood flow distribution as the tumor, and it was not possible to ensure that tissue immediately adjacent to the tumor mass was completely free of tumor. ^{133}Xe blood flow values have previously been determined for skin (9). The half-time of ^{133}Xe clearance was determined by a semiautomated computer generated exponential fit of the second portion of the TACS (10, 11). Blood flow was then calculated using the formula

$$BF = \lambda \times \left(\frac{\ln 2}{t_{1/2}}\right) \times 100$$

where the partition coefficient (λ) used was 0.7 for scalp and 1.0 for tumor (9–12). The area of tumor involvement was determined by correlation with physical examination and roentgenographic studies.

Quantitation of Systemic Shunting. Quantitation of sytemic shunting was performed using Tc-MAA. Quality control was performed on each dose to ensure that over 90% of the particles were between 15 and 90 μm diameter and that at least 97% of the ^{99m}Tc was bound to the MAA particles. Mixing and dispersion of the particles was ensured by agitating the syringe prior to injection.

To determine the detection efficiency of a known activity (mCi) of Tc-MAA injected into the venous system (100% shunting to the lung), 0.5 mCi was injected i.v. and a lung field image was acquired on computer for 5 min. Two mCi were then slowly injected (over 30–60 seconds) i.a. via the pump side port, the pump side port was flushed with saline, and the same lung image was acquired for equal time. The exact activity of radiotracer injected i.v., A(i.v.), and i.a., A(i.a.), was determined by counting the pre- and postinjection of the syringe and correcting for decay. A region of interest was drawn on computer for the lung, and total counts within that region were determined for the i.v., C(i.v.), and i.a., C(i.a.), injections, with the C(i.a.) corrected for residual activity remaining in the lung from the i.v. injection. The shunt index (SI) was calculated by dividing the calculated activity in the lung as a result of the i.a. injection by the total activity that would result from 100% shunting (*i.e.*, the i.v. injection).

$$SI = \frac{\frac{A(i.v.)}{C(i.v.)} \times C(i.a.)}{A(i.a.)} \times 100$$

SPECT Analysis of Blood Flow Distribution. Tomographic data was acquired by rotating the gamma camera about the patient's head in a 360° arch with 64 equally space projection images of 15 s duration each. Transaxial tomographic images were reconstructed using filtered back projection algorithms. Attenuation correction was not performed because the perfusion bed of the external carotid artery is relatively superficial and deep structures do not receive significant perfusion and therefore do not contribute to the counts collected. The analogue images, rotating cinematic display, and selected transaxial slices were reviewed. Regions of interest were chosen in each transaxial slice for the tumor and the whole head. Total counts for tumor and non-tumor areas were determined for each slice. The results of all slices were summed and a total tumor/non-tumor ratio was calculated.

RESULTS

Systemic Shunting. The percentage of systemic shunting of i.a. injected Tc-MAA in the nine patients studied is shown in Table 2. Four patients had dual catheter pumps implanted to allow infusion of both external carotid arteries and each artery was evaluated separately. The mean shunt during the 12 studies performed was 23%. There was wide variation from patient to patient and between one artery and the opposite side in the

Table 2 *Systemic shunting of i.a. Tc-MAA*

Tc-MAA (0.5 mCi) was injected i.v. [A(i.v.)] and the lung field was acquired on computer for 5 min [C(i.v.)]. Tc-MAA (2.0 mCi) was then injected i.a. [A(i.a.)] and the lung field was again acquired [C(i.a.)]. The syringes were then assayed for residual counts, corrected for decay, and the dose was injected. The shunt index (SI) was calculated as

$$SI = \frac{\frac{A(i.v.)}{C(i.v.)} \times C(i.a.)}{A(i.a.)} \times 100$$

Patient	Artery	% shunt
1	Left external carotid artery	11
2	Right external carotid artery	43
3	Left external carotid artery	29 (35)[a]
4	Left external carotid artery	8
5	Left external carotid artery	25
	Right external carotid artery	41
6	Left external carotid artery	11
	Right external carotid artery	38
7	Left external carotid artery	19 (9)
	Right external carotid artery	15
8	Left external carotid artery	10
	Right external carotid artery	28 (24)
9	Left external carotid artery	20
Mean ± SD		23 ± 11

[a] Numbers in parenthesis, separate determinations.

same patient. Studies were repeated in three patients 1 month following the initial evaluation. The results were quite consistent. In patient 7 the shunt with the left external carotid injection decreased from 19–9%. In patients 3 and 8 the shunt calculation increased by 5–6%.

Tumor and Normal Tissue Blood Flow. Table 3 details the quantitative tumor blood flow determined by ^{133}Xe washout in seven patients and nine separate arteries. Patient 2 had no detectable tumor at the time these studies were performed and patient 8 was not studied. Tumor blood flow ranged from 5.9–22.3 ml/100 g/min. The mean scalp blood flow was 4.2 ± 2.1 (SE) ml/100 g/min. The mean ratio of tumor to normal tissue blood flow was 3.9 with a range of 1.9–10.6.

The relative perfusion of tumor *versus* normal tissue was also assessed by SPECT. The quantitative distribution of i.a. injected Tc-MAA to the tumor and the remainder of the infused volume were determined and the tumor/non-tumor ratio was calculated. These ratios are shown in Table 3. In general the blood flow ratios determined by xenon washout and the relative perfusion ratios calculated from the SPECT analysis were similar.

DISCUSSION

Despite almost three decades of experience, the use of i.a. chemotherapy for the treatment of head and neck is not universally accepted (13). The overall reported response rates are not substantially different from the therapeutic results obtained with systemic therapy. The additional complications associated with establishing and maintaining arterial access have further dampened enthusiasm for this approach. It is clear that considerable improvement in regional therapy technique and efficacy will be necessary before widespread clinical acceptance of i.a. infusion is attained. This improvement must be based on the anatomic and pharmacological factors that determine the success of regional therapy.

Regional therapy is not applicable to all malignancies or patients. The factors that are necessary for a successful regional approach include (*a*) a tumor natural history that demonstrates primarily local aggressiveness rather than widespread metastatic dissemination, (*b*) a definable and accessible arterial supply that provides selective access to tumor blood supply with minimal normal tissue distribution, (*c*) antineoplastic agents with favorable pharmacokinetic properties and demonstrable antitumor activity, and (*d*) a delivery system that permits safe continuous long-term infusion with minimal inconvenience.

The principle objective of regional chemotherapy, as for cancer chemotherapy in general, is tumor cell kill. The rationale for regional delivery is based on the steep dose/response curve exhibited by most antineoplastic agents (1). The drug concentration at the tumor site is determined by the dose rate, the regional arterial blood flow, the differential tumor blood flow within the infused volume, and the first pass extraction. A low regional blood flow with a high tumor distribution should increase drug delivery. The systemic drug level is determined by the dose rate, the first pass extraction, and the total body drug clearance. The first pass extraction will be limited by the amount of precapillary arteriovenous shunting within the infused volume. The vascular conditions that favor i.a. drug delivery are a low systemic shunt and a high tumor/normal tissue blood flow ratio.

The availability of direct access to the arterial blood supply

Table 3 *Quantitative and qualitative tumor and normal tissue blood flow*

^{133}Xe (10 mCi) was rapidly injected i.a. Three s/frame dynamic images were acquired for 100 frames in 64 × 64 byte mode starting just prior to the injection. TACS were generated for the two outlined regions of interest drawn for the tumor and the scalp. The $t_{½}$ for the ^{133}Xe clearance was determined by semiautomated computer generated exponential fit of the second portion of the downslope of the time activity curve. Blood flow is calculated as

$$\frac{\ln 2}{t_{½}} \times \lambda \times 100$$

The partition coefficient (λ) was 0.7 for the scalp and 1.0 for the tumor. The perfusion ratio was determined by summation of tumor and non-tumor counts obtained by SPECT following injection of 2 mCi Tc-MAA.

Patient	Artery	Blood flow (ml/100 g of tissue/min)			Perfusion ratio (tumor/total head)
		Tumor	Scalp	Ratio	
1	Left external carotid artery	12.3	3.1	4.0	4.6
3	Left external carotid artery	22.3	3.4	6.6	6.2
4	Left external carotid artery	11.5	6.2	1.9	1.9
5	Left external carotid artery	10.9	5.2	2.1	6.6
6	Left external carotid artery	6	3.1	1.9	1.5
	Right external carotid artery	10.5	4.6	2.3	2.9
7	Left external carotid artery	15.6	1.5	10.6	
	Right external carotid artery	5.9	1.8	3.2	8.6
9	Left external carotid artery	27	8.6	2.8	
Mean ± SD		13.6 ± 6.7	4.2 ± 2.1	3.9 ± 2.7	5.6 ± 3.7

of patients with head and neck tumors has given us the opportunity to directly study and quantitate tumor blood flow. ^{133}Xe is an inert gas which is freely diffusible across cell membranes. Kety (10) first proposed that blood flow could be quantitated by observing the rate of xenon washout from tissue (10). Kety (14), Zierler (15), Lassen (16), and Bassingthwaigthe and Yipintsoi (17) have studied the theory and application of this method. The washout rate is dependent upon tumor blood flow and the relative affinity of xenon for the tissue *versus* blood (partition coefficient). Partition coefficients have been determined for some tumors and considerable variation exists (12, 18). O'Brien and Veal (12) found a range of 0.72–1.37 with a mean of 0.968 ± 0.002. We have chosen a partition coefficient of 1.0 for calculation of tumor blood flow based on this mean.

In experimental animal studies, the local injection technique of xenon clearance has been generally used (18–20). Blood flow has been found to vary between 1–22 ml/100 g/min with the measured blood flow usually decreased with increasing tumor size (18). Blood flow in tumors was typically found to be nonhomogeneous (19, 20).

In studies of superficial human tumors (lymphomas, anaplastic carcinomas, and various differentiated malignant tumors), ^{133}Xe was injected into central parts of tumor nodules (21). Different blood flow rates were determined in the various types of tumors, *i.e.*, lymphoma (38 ± 14 ml/100 g/min), anaplastic carcinomas (11 ± 5 ml/100 g/min), and differentiated malignant tumors (14 ± 9 ml/100 g/min). The results showed good reproducibility within the specific tumor type; however, variations in the calculated blood flow could occur if the isotope was injected into necrotic parts of a tumor.

The ^{133}Xe washout technique has been used after i.a. injection into the femoral artery to study the blood flow to Walker 256 tumors transplanted into the rat tail (22). Sasaki *et al.* used the bolus i.a. xenon washout technique to study tumor blood flow in 9 patients with hepatic cancer and hepatic arterial catheters (23). The radioactivity ratio of tumor to non-tumor was greater than 1.0 in these patients. Tumor blood flow also exceeded normal tissue perfusion in all patients reported in this study. The observed relative increase in tumor perfusion is in agreement with other reports that have used the xenon washout technique in human subjects (21, 23).

The major aim of this investigation was to examine the blood flow factors within the infused volume which affect regional drug delivery, particularly perfusion distribution and tissue blood flow. Antitumor activity depends upon achieving a high tumor concentration of the chemotherapeutic agent, and within the infused volume, drug delivery will be influenced by the tumor tissue blood flow (5). Selectivity, particularly for agents that produce injury to normal tissue within the region, would be favored by the higher rate of tumor tissue blood flow than normal tissue blood flow demonstrated in this study. In addition, the blood flow distribution demonstrated by SPECT analysis clearly shows that the majority of blood entering the region goes to the tumor. The ratio of flow distribution between tumor and non-tumor will depend on the blood flow rate and the size of the neoplasm. The similarity between the distribution ratio and flow ratio shown in Table 2 is probably due in part to large tumors present in this patient population.

The tumor to normal tissue blood flow ratios shown in Table 2 actually compare the rate of ^{133}Xe clearance from the tumor and the scalp as a reference normal tissue. Conversion to blood flow depends upon the mathematical incorporation of the partition coefficient. The partition coefficient has not been determined for the head and neck cancers studied; therefore, the mean tumor partition coefficient published by O'Brien and Veal (12) has been used. In view of the range of values reported, the actual tumor flow rates could vary by ±30%. While different partition coefficients would result in different absolute flow rates, the consistently high tumor to normal tissue ratios would still be of comparable magnitude as reported.

The systemic shunt has been calculated by determining the quantity of Tc-MAA trapped in the lung following an i.a. injection. Tc-MAA particles average 30–40 μm diameter (range, 10–90 μm). Particles of 15 μm size or greater will be trapped in the capillary bed, whereas arteriovenously shunted particles will be trapped in the pulmonary vasculature (24, 25). The mean systemic shunt in the 13 arterial infusions evaluated was 23%. In 8 of the 13 infusions the shunt was ≤25%. In 3 infusions the shunt varied from 38–43%. Arteriovenous communications have been demonstrated within tumors (26, 27); however, the highest shunt was observed in a patient who had been rendered clinically free of tumor for over 1 year prior to this evaluation. A second patient had bilateral external carotid catheters. The shunt with the left catheter was 11% whereas the shunt on the right was 38%. The majority of the tumor mass was perfused by the left catheter. It is therefore possible that a considerable proportion of the arteriovenous shunting was occurring within normal tissues rather than within the tumor.

The development of regional chemotherapy as a therapeutic strategy must be firmly based on knowledge of the pharmacological and physiological conditions that affect i.a. drug delivery. This study demonstrates that the relative and quantitative blood flow within the infused volume provides a selective advantage for drug delivery to the tumor for rationally selected antineoplastic agents with a high total body clearance.

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