Temperature Influences on Arteriovenous Anastomoses[1] (37646)

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Arteriovenous anastomoses (AVAs) are precapillary channels between arteries and veins, which allow little or no metabolic interchange between the intravascular and extravascular compartments (1). Blood passing through AVAs does not reach the capillaries, and therefore, represents nonnutritive blood flow which serves no function with regard to tissue metabolism. The role of these blood vessels in the normal circulation has been the subject of much speculation. One widely held view is that AVAs are concerned with local and systemic temperature regulation (1). The present study was designed to determine in a quantitative fashion the influence of body and local temperatures on arteriovenous anastomotic blood flow in the dog hind limb. Although the major emphasis of the study was on AV shunting, distribution of blood flow among the tissue was also measured.

Methods. The technique employed takes advantage of the fact that AVAs have diameters larger than capillaries. Anatomic reports describe these channels as ranging from 20 to well over 100 μm in diameter (1). Microspheres injected into an artery lodge in arterioles of their own diameter or, alternatively, reach arteriovenous channels with larger bores, pass through into the veins, and are carried to the next microcirculatory bed in series, the lung. For this study the femoral artery was the site for injection of these radioactive particles. Radioactivity recovered in the lung represented the fraction of femoral artery blood flow which traversed arteriovenous channels larger than the sphere diameter. The kidney, an organ with high blood flow, was employed as a monitor for the possibility that spheres reached the systemic circulation. If the pulmonary microcirculation failed to retain some of the spheres, radioactivity would be found in the kidney.

The microspheres employed for this study were made of polystyrene and had a density of approximately 1.3. Sizing with a microscope and eyepiece micrometer, the mean diameter was 28 μm with a range of 18-34 μm and a SD of 3.3 μm. ^{169}Ytterbium, a γ-emitting isotope, was incorporated during manufacture.[2] Approximately 100,000 spheres per ml were suspended in 10% low mol wt dextran. The microspheres were delivered through a No. 23 needle inserted percutaneously into the femoral artery. A 1 ml bolus was injected rapidly against the flowing blood stream to enhance mixing. Previous data from our laboratory indicate that this mode of injection does provide good mixing (2). Percutaneous arterial puncture and the use of lungs as a "sieve" for sphere collection served to eliminate dissection of either artery or vein. Avoidance of trauma to perivascular nerves is important in that sympathetic denervation greatly enhances AVA flow (3).

Twenty-five healthy adult mongrel dogs, weighing between 12–19 kg were anesthetized with iv sodium pentobarbital, 30 mg per kg of body wt. Mechanical ventilation was accomplished with a piston-type respirator through a cuffed endotracheal tube. Respiratory rate and tidal volume were adjusted to maintain arterial pH with the range 7.40–7.44. This is a significant technical detail in that acidosis, by itself, leads to marked en-

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[2] Supplied by the 3M Company, St. Paul, Minnesota.

hancement of arteriovenous anastomotic blood flow (3). A polyvinyl catheter was passed to the aortic arch via the right carotid artery and connected to a strain gauge for continuous monitoring of blood pressure and pulse rate. The same catheter was used to withdraw blood for arterial dye dilution curves. These and all other recordings were made on a Gilson Polygraph Recorder. Cardiac output was estimated periodically during the experiment using the cardiogreen dye dilution technique. Dye injections were made into the right atrium via a jugular vein catheter and blood withdrawn from the aorta by a Harvard constant speed pump through a Gilson cuvette densitometer. pH, pCO_2, and pO_2 were periodically determined on samples from femoral vein, right atrium, and aorta using an Instrumentation Laboratories Model 127 blood gas analyzer. Room temperatures ranged from 23–25°.

Central or whole body heating was carried out with electric pads applied to the surface of the trunk, carefully avoiding contact with the hind extremities. To accomplish local limb heating, a blanket was wrapped around the hind limbs and shortwave diathermy coils wrapped about the blanket. For cooling studies ice packs were applied to the hind legs or to the trunk. Temperatures were monitored by thin copper-costantan wire thermocouples threaded into the tissues, the paw pad, skin of the paw, skin of the leg, and leg muscle. Right atrial temperature, measured by means of an iv thermocouple, was taken as body or core temperature. Temperatures were recorded to the nearest one-half degree.

When the desired tissue or core temperature had been achieved the microspheres were injected. Blood gases, cardiac output, and vital signs were again recorded and the animal then sacrificed by a rapid iv injection of hypertonic potassium chloride. The lungs, the injected lower extremity, and one kidney were removed. The leg was dissected into skin, muscle and bone. Each tissue sample was counted in its entirety in a lead chamber by means of a collimated crystal scintillation detector with a 1.5 in. sodium iodide crystal set at a distance of 50 cm from the surface of the sample.

Results. In no instance was any radioactivity detected in the kidney, thus demonstrating the adequacy of the lungs as a trap for all spheres passing through AVAs into the venous circulation. Mean arterial pCO_2 and pO_2 did not differ appreciably between the groups. Arterial pH was maintained constant at 7.40–7.44 by altering minute ventilation. Mean blood pressure, pulse rate, and cardiac index were surprisingly comparable from one group to another. One might anticipate significant differences in these circulatory parameters with more prolonged and/or profound systemic heating or cooling.

Table I summarizes the results. In the control group of 5 normothermic dogs, average arteriovenous anastomotic blood flow was 4% of femoral artery flow with a range of 2–5%. The paw received a mean of 21% of the spheres or of the femoral artery blood flow. Of those spheres retained in the leg proper, an average of 67% was recovered in the muscle, 27% in bone, and 6% in skin.

The dogs subjected to systemic heating had central venous temperatures ranging from 39–41°. With these core temperatures a mean of 25% of the injected radioactivity was found in the lungs. Stated differently, the blood flow through AVA channels exceeding 28 μm in diameter amounted to 25% of the total femoral artery flow. Mean tissue distribution of flow with systemic hyperthermia was nearly identical to that found in the control group.

During limb heating, mean tissue temperatures, particularly in the paw pad, exceeded central temperatures and were considerably higher than the tissue temperatures recorded in animals subjected to systemic hyperthermia. Mean distribution of blood flow within the limb, paw vs leg, and skin vs muscle vs bone, was practically identical with distribution in the control group and in the animals subjected to core heating. One dog in this group demonstrated an AVA flow of 35%. The other 4 were in the control range. Careful assessment of all measured parameters did not provide an explanation for the one animal that deviated substantially from the rest of the group.

Essentially no arteriovenous anastomotic

TABLE I. Distribution of Injected Radioactive Microspheres.

			Temperature (°)					Distribution among leg tissues (%)		
	% to lungs	% to paw	Core	Paw pad	Foot skin	Leg skin	Leg muscle	Muscle	Bone	Skin
Control	2	23	37.5	32.5	33	34.5	35.5	57	33	10
	4	25	38	36	35.5	35.5	37	68	25	7
	5	20	37	33	34	34	35.5	68	26	6
	5	21	38.5	35.5	36	36	37	71	26	3
	2	16	38	31	34	34	36.5	69	27	4
	4	21	37.5	33.6	34.5	34.8	36.3	67	27	6
Core heating	14	29	39.5	36	33	34.5	37.5	61	30	9
	12	22	40	37	38.5	38.5	39	59	28	12
	41	25	41	38	36.5	37.5	39.5	72	16	12
	33	21	40	33	38	37	38	78	15	7
	25[a]	24	40	36	36.5	36.9	38.5	68	22	10
Peripheral heating	3	19	36	48	39	42	40	72	19	9
	35	37	36	46	41.5	41	42	59	27	15
	2	25	38	41	40	41	40	52	37	11
	4	20	37.5	41	40	40	38	64	20	16
	8	15	35.5	47	42	46	39	82	14	4
	10	23	36.6	44.6	40.5	42	39.8	66	23	11
Core cooling	<1	8	28	27	27	29	30	77	19	4
	<1	3	32	24	23	32	32	86	9	4
	<1	6	29	28	28.5	29	29	77	21	2
	<1	6[a]	29.6	26.3	26.2	30	30.3	80	16	3
Peripheral cooling	1	4	37.5	29	31	30	36	86	11	2
	<1	1	37	21	22	29	34	67	29	3
	3	6	34.5	27.5	26	26.5	29.5	87	12	3
	2	4[a]	36.3	25.8	26.3	28.5	33.2	80	17	3

[a] Significantly different from the control mean, $p < 0.01$ (Student t test).

blood flow was detected when the dogs were cooled, either centrally or peripherally. Cooling the limbs, which took 30–40 min, did not appreciably alter body temperature. The mean temperature of the paw pad and of the foot and leg skin were 25.8°, 26.3°, and 28.5°, respectively, while the leg muscle was 33.2°. With central cooling, mean tissue temperature in the parts of the limb were quite comparable one to the other and approximated the core temperature.

Because very little limb AVA shunting is found in the normothermic dog, it is possible to state only tentatively that cooling actually constricts AVAs. It seems probable, however, in that 1% or less of the spheres were recovered from the lung in 5 of 6 animals, while control normothermic dogs showed AVA shunting in the 2–5% range.

Discussion. Validity of the technique. Microspheres injected into an artery do distribute among the tissues in the same pattern as does the blood flow. Delaney and Grim (4) first demonstrated this point using both radiopotassium and radioactive microspheres to measure distribution of blood flow in the stomach wall. The calculated partition of flow among the mucosa, submucosa, and muscalaris was nearly identical with the two methods. This agreement between two techniques, which depend on totally different assumptions, provided persuasive evidence that both are valid. Kane and Grim (5), Neutze *et al.* (6, 7), Meyer and colleagues (8), and Edlich (9, 10) have also demonstrated good correlations between the micro-

sphere technique and other methods for estimating blood flow distribution (11, 12).

For purposes of this study AVAs are arbitrarily defined as channels which exceed 28 μm in diameter. Smaller arteriovenous communications with thick walls also might function as precapillary nonnutritive shunts but would not be detected. At present, perfectly uniform-sized spheres are not available. In this particular batch a few were as small as 18 μm. To use a smaller mean size would introduce the possibility of microsphere passage from artery to vein through capillary type vessels.

Rapid injection of spheres as a bolus, even though only 1 cc vol, might acutely or transiently alter pressure and flow. However, the control and other groups would be subjected to the same experimental circumstances.

Temperature and AVA flow. The relationships between body temperature, environmental temperature, local temperature, and limb circulation are complex. Lewis (13) studied the response to cold of the human digital circulation. With the subject comfortably warm and the fingers exposed to temperatures of 0–60°, vasodilation occurred, judged by sudden rises in skin surface temperatures as cold was applied. When the local temperatures were 15–20°, the vessels were constricted and there was diminished digital blood flow. Lewis and Pickering (14) noted a blunting of such skin temperature changes when superficial venous return from the finger was occluded with a rubber band. Their explanation was that the effects of dilation of AVAs were negated by occluding flow in the superficial veins.

Kunkel and Stead (15) found that between 25–45° the foot blood flow increased directly as temperature of a surrounding water bath was raised. One proposal to rationalize these observations is that AVAs open and allow large quantities of blood to flow through superficial veins where heat loss to the environment might occur more efficiently.

Grant (16, 17) observed AVAs in the rabbit ear to dilate with elevations of local temperature but more so with heating of the entire body. He concluded that the AVAs served to help regulate body temperature by abetting heat dispersal, presumably by diverting blood flow through the superficial ear veins. He found a critical temperature in the vicinity of 40° above which the AVAs dilated widely. Conversely, local cooling was associated with AVA closure until 15° was reached at which point sudden dilation occurred. Grant postulated that the increased AVA flow with low temperatures helped protect the ear from cold injury. In the present study control central venous temperatures up to 38° were associated with insignificant AVA flow while body heating over 39° lead to marked enhancement of such blood flow; this is in excellent agreement with Grant's observation in the rabbit ear.

After reviewing available experimental data, Folkow (18) concluded that cutaneous AVAs are controlled chiefly by the central nervous system, specifically the hypothalamic heat loss center. Results found in the present experiment tend to support Folkow's view. We would propose that increased temperature of the blood reaching the central nervous system leads to a relaxation of "sympathetic tone" and consequent AVA opening. This interpretation would be consistent with our observations of enhanced AVA flow following sympathectomy (3) and during alpha adrenergic blockade (19).

Most students of the subject have assigned thermoregulation as a major potential function of AVAs. Theoretically two distinct purposes might be served by shunting blood through AVAs from deeper arteries to more superficial veins. The first is an increase in heat loss to the environment by enhanced superficial blood flow. The second is that the skin itself might be protected by increased blood flow when threatened by cold injury.

Data from the studies reported here favor the concept that the AVAs are more sensitive to systemic temperature elevations than to local alterations. Body heating to 39° or higher led to marked increases in the fraction of limb blood flow passing through arteriovenous channels exceeding 28 μm in diam. Local heating did not cause significant increases in precapillary arteriovenous shunting through such channels. Both systemic and

local cooling were marked by nearly total absence of blood flow through AVAs. While most previous investigators have measured skin temperature or noted the temperature of the surrounding enviroment, the present study was based upon actual tissue temperatures. In this preparation the tissue temperatures never approached the low levels shown by Grant (7) and Lewis (13) to cause opening of AVAs.

With respect to tissue distribution of blood flow, the animals subjected to cooling, either local or systemic, had a far smaller fraction of the total femoral artery flow reaching the paw and the skin than did control or heated animals. This is presumably due to greater vasoconstriction in paw and in skin than in bone or muscle vessels. Possibly, more peripheral or superficial small arteries are particularly sensitive to cold. A likely alternative explanation with limb cooling is that the temperature in the immediate vicinity of skin and paw arterioles is lower than muscle or bone arterioles. Clark's (20) observations in the rabbit ear indicate that AVAs are more sensitive to cold than are arterioles.

Piiper and Schoedel (21) found that amputation of the paw virtually eliminated arteriovenous anastomotic blood flow. We have similarly observed that absence of the paw greatly reduced such flow but that the skin of the entire limb must be removed to eliminate all AVAs.

Femoral vein pO_2 did not show any consistent correlation with AVA flow. A probable explanation is that in addition to AVA shunting other factors help determine the tension of oxygen in the venous effluent.

Arterial blood oxygen content, the total blood flow rate, and the limb oxygen consumption all are important. These three variables were not controlled and the latter two not even measured.

Because the techniques used here for cooling and heating precluded accurate measurement of total femoral artery blood flow, nothing can be concluded about temperature effects on nutritional or capillary perfusion.

Summary. A technique is described which employs radioactive microspheres injected into the femoral artery of the dog to quantitate the fraction of blood flow passing through precapillary arteriovenous shunts. The lung serves to retain all the spheres reaching the venous circulation through arteriovenous anastomoses. In the control state very little shunting is detectable. With rises in body temperature, there is an increase in flow through arteriovenous anastomoses. Local limb heating does not consistently enhance arteriovenous anastomotic blood flow. With cooling, either systemic or local, shunt flow diminishes to nearly zero. Cooling is associated with a significant redistribution of tissue blood flow in the limb away from the paw and away from the skin.

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