system plays a role in the early stages of Goldblatt hypertension.

In the dogs that received indomethacin, in contrast to those that did not, the systemic arterial pressure was elevated within 5 minutes after renal artery constriction and remained elevated throughout the experiment. Thus the earlier and more sustained hypertension in indomethacin-treated dogs was probably due at least in part to the inhibition of prostaglandin release. Apparently the opposite untouchable kidney attenuates Goldblatt hypertension, at least its early stages, not only by its excretory function but also by the release of vasodepressor prostaglandins.

Acknowledgments

We are deeply grateful to Dr. Francis J. Haddy for help and encouragement during the course of this study and preparation of this manuscript. During Dr. Overbeck's absence, Dr. J. B. Scott provided valuable guidance. We are greatly indebted to Dr. Michael D. Bailey for determinations of plasma renin concentrations. We thank Dr. Shirley Hoolker for supplying us with antirenalin serum and Dr. Erwin Haas, Beaumont Memorial Research Laboratories, for the renin. We also acknowledge the valuable technical assistance of Donald L. Anderson, Booker T. Swindall, and Josephine Johnston, and the excellent secretarial help of Lynn Dietrich.

References


Single-Passage Extraction and Permeability Estimation of Sodium in Normal Dog Lungs

TADA YIPINTSOI, M.D., Ph.D.

SUMMARY Bolus injections of 125NaCl, 125I-albumin, and indocyanine green dye were made into the right atria of anesthetized, ventilated dogs. Blood was sampled from the femoral artery, and from the dilution curves, instantaneous extractions, E(t), and area averaged extractions, E(A), were calculated for sodium at various plasma flows. (Fp). Flow reduction was produced by transient inferior vena cava obstruction. E(t) and E(A) within any dilution curve generally started off with a high value, then decreased with time. The Fp, that occurred at the peak of the albumin-dilution curve were about 0.11 for plasma flow of 0.75 liter/min and tended to decrease as flow increased. Parallel study of the sodium extravascular space at equilibrium gave values of 0.3-0.4 g of plasma sodium per g of tissue, suggesting that this volume is not infinitely small. Since the Fp was low it is unlikely that the high initial E(t) and the decreasing E(t) were due to early back flux. Calculation of capillary permeability surface area product (PS = Fp log, (1 - E)) showed an increasing PS with plasma flow. The injection of 9-um microspheres at low and high total blood flow gave evidence supporting a decrease of capillary surface area (S) with decreasing total blood flow. Regional pulmonary blood flow also showed marked heterogeneity. Because of the low average extraction of sodium in the lung, insensitivity of the method in normal lungs cannot be excluded.

PULMONARY capillary permeability is thought to be altered in several disease states, independent of whether the lung is the primary or secondary organ of involvement. However, quantification of pulmonary capillary permeability in intact animals and man is difficult because (1) there is an intrinsically high blood flow, (2) regional distribution of flow in the lung may change when total blood flow increases or decreases, (3) limitations exist in the techniques currently used for measurement of capillary permeability.

From the Department of Medicine and Physiology, Montefiore Hospital and Medical Center (Albert Einstein College of Medicine), Bronx, New York.

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Chinard and Yudilevich injected sodium and albumin in the same bolus into the right atrium and sampled blood from the arterial circulation. Because of the similarity between the dilution curves of the two isotopically labeled substances, i.e., low value of fractional extraction, it was thought that the lung capillary permeability is low or that the extravascular volume of sodium in the lung (calculated from the difference in the mean transit time volumes) is small, or both. Increased capillary permeability to sodium was implied when this mean transit time volume was increased or when sodium recovery was decreased. However, in these studies, it was not realized that lung blood flow per unit of weight is very high in comparison to that in other muscular organs like the heart. Such high flow would result in low tissue extraction of the probing molecules. Subsequently Effros, using the osmotic bolus technique, and Perl et al., summarizing their previous indicator-dilution results, reported that the capillary permeability of dog lungs probably is similar to that of heart or skeletal muscle.

Aside from the latest summary by Perl et al., other quantification of lung capillary permeability has been performed in isolated or exteriorized lungs or in situations in which pulmonary lymphatics could be sampled. Taylor and Gaar calculated the capillary pore radius to be 40–80 Å in isolated dog lung. Normand et al. calculated pore radius to be 150 Å in exteriorized lungs of fetal lambs.

The purpose of our present study was to use the indicator-dilution method and the single-passage extraction technique described by Crone to evaluate capillary permeability to sodium in intact canine lungs. The technique demands that the tissue extraction, E, result from a unidirectional flux from the intravascular plasma into the interstitium. The assumptions inherent in the technique are: (1) There is no back flux of the probing molecule from the interstitial space into the plasma stream during the period of measurement. This period of measurement is generally a fraction of a single transit time through the organ under study. The degree of back flux depends on the permeability of the membrane and the extravascular distribution space of the probing molecules. Greater back flux should occur with the more permeable substance or with the smaller volume of distribution or both. Hence the choice of probing molecule is important and so is the assurance that an adequate volume of distribution exists. (2) Interlaminar diffusion in the intravascular compartment is minimal. (3) There is an adequate extravascular volume of distribution for the hydrophilic probing molecule. (4) There is no marked heterogeneity of perfusion, volume of distribution, or of permeability in the lung. If marked heterogeneity of these parameters exist, then we should not allocate a single permeability surface area product (PS) to the lung (i.e., a lumped model), but rather a distribution of PS as functions of regional flow or of regional extravascular volume (i.e., a distributive model).

Since the assumptions listed require knowledge of the interstitial volume of distribution ($V_f$) and of heterogeneity of flow or the available capillary surface area (S), we also made measurements of the interstitial space and of the regional blood flow in the lungs.

Methods

Adult mongrel dogs weighing 18–36 kg were anesthetized with intravenous pentobarbital sodium (25 mg/kg). All studies were made with the dogs lying on their backs and ventilated with a constant volume Harvard respirator. The tidal volume was not altered during an experiment except for periodic hyperinflation. The inspiratory airway pressure was 10–15 mm Hg. An external jugular cutdown was performed and under fluoroscopic control catheters were positioned as follows: a no. 6 or 7 USCI (Bard) end-hole catheter was passed into the main pulmonary artery to monitor pressure; a multiple side-hole catheter (8 pigtail) with an internal volume of 1.2–1.6 ml was placed in the right atrium for the injection of indicators; and a catheter (7Fr.) with a terminal inflatable balloon (maximum inflated balloon diameter of 4 cm) was placed so that the inflated balloon was below the diaphragm in the inferior vena cava (IVC). An 18-gauge, 2-inch nylon needle was placed in the femoral artery to monitor pressure and to obtain sequential blood samples. In some experiments a separate needle was placed in the brachial artery to monitor systemic pressure during collection of blood from the femoral artery.

An indocyanine green dye (ICG) densitometer (Gilford 1031R) was connected to the femoral artery needle and blood was withdrawn through this by a rotating pump for sequential blood collection. The volume of the sampling system varied between 2 and 3.1 ml, and generally the pump flow was 60 ml/min when multiple indicators were used.

When only ICG was injected, arterial blood was withdrawn at 24 ml/min through a Harvard syringe. The calculated blood flow from ICG was similar with either the syringe or the rotating pump. When isoproterenol (0.001 mg/ml) was infused intravenously the rate was adjusted to produce a stable doubling of the cardiac output.

For the instantaneous extraction study, the bolus injection (about 0.8 ml) consisted of 3–5 uCi of $^{131}$I-albumin (RISA, Abbott) and 10–30 uCi of $^{22}$NaCl (New England Nuclear), both freshly diluted in normal saline, and about 1–2 mg of ICG, freshly diluted in distilled water. The bolus was flushed into the right atrium with 5–10 ml of normal saline. Blood was collected sequentially from the femoral artery into preweighed test tubes. The collection time for each sample was marked on the photographic record on which we also monitored the electrocardiogram, the pulmonary and the systemic arterial pressures, and the ICG-dilution curve.

The rate of blood sampling was as rapid as two samples per second during the upstroke of the dye curve and was slower, one sample per 1–2 seconds, prior to the appearance of the dye and after the peak of the dye curve. The samples then were covered with wax paper and subsequently were weighed. In three experiments the free iodide in the injectate obtained by 10% trichloroacetic acid precipitation represented less than 2% of the total iodide activity.

For each isotope-dilution curve, we analyzed samples of the injectate suitably diluted in blood. The $^{22}$Na gamma activity was counted first (Nuclear Chicago 1085 automatic gamma system); 4–6 days later (after 6–10 half-lives of $^{22}$Na), the remaining $^{22}$Na and $^{131}$I were counted. Aside
from the first few samples after the appearance time, the gross counts for $^{40}$Na and $^{131}$I alone were in excess of 10,000 counts. The concentration of each blood sample (counts/min per g of blood weight) then was expressed as a fraction of the injected dose. The flow was calculated from both the ICG and the $^{131}$I-albumin curve (corrected for density of blood) using a single exponential extrapolation to the descending portion of the dilution curve. Generally both indicators gave flow values within 10% of each other, but in instances of marked disparity, the albumin curve was assumed to be correct. The relative concentrations (f) of Na and albumin at any time were used to calculate the extraction, E(t).

$$E_d(t) = 1 - \frac{f_{Na}(t)}{f_{Alb}(t)}$$  
$$E_d(t) = 1 - \int f_{Na}(\lambda) d\lambda / \int f_{Alb}(\lambda) d\lambda$$

where $\lambda$ is the variable for integration up to time t.

The subscripts 2 and 3 refer to the two forms of extraction described previously, where $E_2$ is the instantaneous or instant-by-instant extraction derived from paired concentration at any time and $E_3$ is the area weighted extraction derived from paired areas of the dilution curves such that the extraction is influenced by the curve up to time $t$. This $E_3$ is 1 minus the ratio of the cumulative recovery. From the $E_3$, we calculated the permeability surface area (PS) for the whole lung as:

$$PS = - F_p \log_e (1 - E)$$

where $F_p$ is the plasma flow and E is an arbitrarily chosen extraction that occurs at the time of the peak $(t_p)$ of the albumin curve.

The present study does not include the calculation of recoveries or mean transit time volumes. Perl et al. have shown and we have found that the single exponential extrapolation of the descending slope of the sodium-dilution curve differs minimally from that of albumin, resulting in a very small difference in mean transit time volumes.

When we plotted E as a function of flow (see Results) the values used did not include those obtained after pharmacological interventions.

MEASUREMENT OF ALBUMIN AND SODIUM SPACES

We obtained heparinized arterial blood and tissue samples at least 30 minutes after the last bolus injection of $^{131}$I-albumin and $^{40}$NaCl. In most dogs this last bolus was the fourth or fifth, the first having been given several hours previously. In two dogs (7024A and B) only one bolus was given. A portion of the blood was centrifuged at 2,000-3,000 rpm for 20 minutes to obtain plasma and packed red cells. The tissue samples (lung, heart muscle, and skeletal muscle) were rinsed and blotted dry. No attempt was made to remove small bronchi from the lung. The tissues, plasma, and packed red cells were weighed and counted. The other tissues were weighed and dried at 80-90°C for 2-3 days and their water content was determined.

The relative isotope content, $v$, was the concentration of tissue or red cells divided by that of plasma. The extravascular sodium content, $v_{E-Na}$, was corrected for the albumin content and the equivalent red blood cell (RBC) content:

$$v_{E-Na} = v_{Na} - v_{Alb} - v_{RBC} \cdot Hct / (1 - Hct)$$

When the RBC sodium space ($v_{RBC}$) was measured, it varied from 0.2 to 0.4 g per g of packed red cells. We did not attempt to correct it to grams of pure red cells because this correction factor to obtain $v_{E-Na}$ was relatively small.

In two separate experiments, freshly drawn heparinized blood was kept stirred at 37°C, and labeled albumin and sodium were added. At varied intervals samples of blood were removed to estimate the isotopic concentrations of plasma, red cells, and blood. In these tests it was found that for constant hematocrit and plasma concentrations of sodium and albumin, the relative red cell sodium content was 0.08 g of plasma per g of RBC at 10 minutes and it increased to 0.3 at 60 or 120 minutes, suggesting that the time for equilibration of sodium between plasma and RBC is rather long. Because of this apparent plateau at 0.3 we used the same value in other dogs in which the $v_{RBC}$ was not measured.

We reported the lung sodium spaces in two ways. In one, the lung samples first were considered as a whole prior to evaluating the extravascular space. In the other, we evaluated $v_{E-Na}$ for each sample, then expressed these as mean (x) and standard deviation (SD) for n, number of pieces. In this report simultaneous volumes for heart and skeletal muscle were obtained so that their values could be compared with other normal values in the literature.

MEASUREMENT OF THE REGIONAL DISTRIBUTION OF LUNG BLOOD FLOW AT VARIED FLOWS

We injected labeled 9-μm microspheres (3M Co.) (5 million to 20 million particles) together with ICG solution into the right atrium. The microspheres were premixed with 2-3 drops of 5% polysorbate 80 (Tweeen 80) and agitated with an ultrasonic mixer for 10 minutes prior to injection. Total flow then was decreased by IVC occlusion or bleeding, or increased by isoproterenol infusion. When a stable state was achieved, we injected a differently labeled 9-μm microsphere. Arterial blood was withdrawn at 24 ml/min for the simultaneous ICG-dilution curve. The activity of microspheres from the collected arterial blood was never significantly above background. The dogs then were killed with excess pentobarbital, after which the chest was opened by sternal splitting. The lungs were kept inflated to facilitate recognition of their hydrostatic position in situ. In some dogs we analyzed the entire lung; in others, we sampled regions in which we expected the lowest and highest flows (e.g., anterior or nondependent and posterior or dependent portions with the dog lying on its back). The tissues that were not used for counting were minced and representative samples were taken to calculate total microsphere content in both lungs. The wet weight for pieces that were counted varied from 0.5 to 1.5 g. The relative concentration of microspheres in each piece was the count/min per g for the piece divided by the count/min per g for the whole lung. This regional distribution of the first microsphere injected at one total blood flow was plotted against the regional
distribution at another total blood flow. Total blood flow was calculated from the ICG-dilution curve.

Results

ISOTOPIC SPACES

Table 1 details the \(^{131}\)I-albumin and \(^{23}\)Na spaces in the heart, lung, and skeletal muscle in seven dogs. As shown in Table 1, some of the studies followed interventions such as isoproterenol or methoxamine infusion or repeated saline infusions, and one was after phlebotomy. The values following these interventions were included to show the variation of these volumes to the water content and the hematocrit. The present experiments were not designed specifically to study the isotopic spaces as a function of these other parameters.

In different lungs there was a wide range of values for \(v_{an}\) and \(v_{E,Na}\) but both generally were 2–3 times that of the heart. The wide range of \(v_{an}\) should not be used as a true measure of intravascular space, because no precautions were made to limit the intravascular volume during tissue sampling. We have no reasonable explanation for the high albumin space and relatively low sodium spaces in the lung in experiment 27024 (Table 1). This dog was given an isoproterenol infusion to increase total blood flow for regional perfusion study. Except for this dog, the \(v_{E,Na}\) generally was 0.33–0.47 g/g.

Since the study on \(v_{e}\) was made at an assumed steady state, we also evaluated sodium uptake at shorter intervals after injection. In two open-chest dogs (7024A and B), samples of arterial blood and lung pieces were taken at 2, 5, 10, 20, 30, and 40 minutes after injection of a bolus of sodium and albumin into the right atrium. The \(v_{HBc}\) was assumed to be zero. The values for \(v_{E,Na}\) for the lung in these quasi-steady state experiments were similar to the values obtained when the samples were taken an hour later (Table 1, experiments 7024A and B).

In experiment 24094 we evaluated \(v_{E,Na}\) following saline infusion. Here lung and blood samples were taken at three periods, each of which was 40–50 minutes after a bolus injection of the tracers into the right atrium; period a was the control, and periods b and c followed 500-ml infusions of Ringer’s lactate solution. The hematocrit (Table 1) decreased from 0.44 to 0.39; \(v_{an}\) decreased from 0.20 to 0.13 g/g; and \(v_{HBc}\) increased to 0.3 \(v_{E,Na}\) for lung and lung water remained unchanged.

SODIUM EXTRACTION

Figure 1A and B presents dilution curves and their extractions \([E_2(t)\) and \(E_8(t)\)\] for normal and low blood flows (produced by IVC balloon) in the same dog. The descending portions of the dilution curves were quite representative of our other curves in that there generally was no crossover between the sodium and albumin, and where the albumin showed recirculation the sodium concentration continued to decline, suggesting further extraction of sodium by other capillary beds.

The initial values of \(E_2(t)\) and \(E_8(t)\) were high; these decreased more gradually for \(E_8(t)\) than for \(E_2(t)\). The decrement of these extractions often does not allow recognition of a constant value around the peak of the albumin curve. Neither the initially high sodium extraction values nor the shape of its subsequent decay was altered by lengthening the sampling tubing from the femoral artery or by increasing or decreasing the pump flow rate.

Because of the often decreasing values of \(E_2(t)\) or \(E_8(t)\) and because of lack of distinct crossover between sodium and albumin, the extractions were evaluated arbitrarily at the time of peak of the albumin curves and \(E_8(t_c)\) (because of its area-weighting) was used as the \(E\) from which to calculate PS (Equation 3).

Table 2 gives the relevant hemodynamic data, the \(E_0\) and \(E_8\) (both at \(t_c\)), and the calculated PS in eight dogs. We specifically compared the \(E\) during the control period (C) to that after IVC obstruction (+IVC). Values for other interventions such as bleeding or saline infusion, or with or without assisted ventilation (on-and-off respirator) were also included to show the possible range of values for \(E_0\) and \(E_8\). The \(E_8(t_c)\) and PS obtained from these latter interventions.

### Table 1 Sodium and Albumin Space

<table>
<thead>
<tr>
<th>Exp no</th>
<th>Tissue wt (g)</th>
<th>% water</th>
<th>(v_{an}(g/g))</th>
<th>(v_{E,Na})</th>
<th>Intervention before sampling</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L</td>
<td>H</td>
<td>M</td>
<td>L</td>
<td>H</td>
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<tr>
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<td>8.5</td>
<td>4.1</td>
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<td>76</td>
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<tr>
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<tr>
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<td>73</td>
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<td>77</td>
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</tr>
<tr>
<td>23074</td>
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<td>—</td>
<td>—</td>
<td>79</td>
<td>—</td>
</tr>
<tr>
<td>24094*</td>
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<td>—</td>
<td>—</td>
<td>81</td>
<td>79</td>
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<tr>
<td>a</td>
<td>6.8</td>
<td>—</td>
<td>—</td>
<td>81</td>
<td>79</td>
</tr>
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<td>b</td>
<td>3.6</td>
<td>—</td>
<td>—</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>c</td>
<td>11.2</td>
<td>6.3</td>
<td>—</td>
<td>80</td>
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<td>19124†</td>
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<td>9.1</td>
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<td>78</td>
<td>78</td>
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</tbody>
</table>

Tissue wt = weight used for the analysis; L, H, M = lung, heart, and skeletal muscles; \(v\) = the isotopic distribution space; \(v_{E,Na}\) = the corrected extravascular sodium space where \(L\) refers to the value obtained from initially summed up the lung pieces, and \(x\) and \(SD\) are the mean and standard deviation for the \(n\) lung pieces evaluated individually; \(v_{HBc}\) = the relative sodium content in the red cells. Dash = no measurement made.

* In experiment 24094, a = the control period; b and c = the periods after 500-ml infusions of Ringer’s lactate solution.
† In experiment 19124, hypertension was induced by methoxamine (2 mg, iv) given in 20 minutes.
LUNG CAPILLARY PERMEABILITY/Yipintsoi

were not used for further illustrations. Figure 2A and B shows extraction and PS as a function of plasma flow where the plasma flow was obtained during control or during transient IVC obstruction. In five of the eight lungs, E decreased as plasma flow increased (Table 2 and Fig. 2A). Since the blood flows in these experiments were restricted to a narrow range by allowing only the estimations made of E with and without IVC occlusions, and since variations of E between dogs were large, linear correlation for significance of the slope between E and plasma flow was not done. The maximum E was 19% and the average E at flows of 0.5-1.0 liter/min was 10.5% (n = 16, SD = 3.2%) for an average plasma flow of 0.75 liter/min.

Figure 2B shows that the calculated PS (ml/min) increased nearly linearly with plasma flow, reaching a maximum PS value of around 150 ml/min. Other interventions did not produce marked alterations of E or PS except as they altered flow (Table 2).

REGIONAL DISTRIBUTION OF MICROSHERES IN THE LUNGS

The hemodynamic data during the injection of microspheres are given in Table 3. In five of the six dogs flow was altered by a single intervention (isoproterenol infusion, transient IVC occlusion, or bleeding). In one dog we first increased flow by isoproterenol infusion, then after return to control state we reduced flow by transient IVC occlusion. Figure 3 shows the regional concentration of microsphere at normal flow and when flow was increased by isoproterenol infusion. At initial blood flow of 1,540 ml/min, the pieces of lung with relative concentration of less than 1 (i.e., less than average) showed a disproportionate increase when total flow was elevated to 3,300 ml/min. The reverse was seen in lung pieces with initially high concentration. In another experiment, the decrease of total blood flow from 2,200 to 1,400 ml/min (by transient IVC occlusion) resulted in a disproportionately greater reduction in regions with a low microsphere content (presumably low flow) (Fig. 4). Of the six dogs studied, five showed this disproportionality in alteration of regional microsphere content when total flow was changed. The single exception was experiment 23074, in which total flow was decreased by bleeding. The phlebotomy resulted in an increase of arterial hematocrit as well as pulmonary artery pressure. In this study, when total flow was altered the relative microsphere concentration in each region changed proportionally.
**Discussion**

**LUNG EXTRAVASCULAR SPACE**

The steady state value for the extravascular space was 0.25–0.47 g/g of wet lung. Previous studies, also at a steady state, showed an extravascular space of 42–60% for sodium in human lung, 30% for sucrose in rabbit lung, and 57% for intra- plus extravascular sodium spaces in dog lung. Because our technique for estimating capillary permeability involves only a single transit of the probing molecules, the apparent extravascular space (sometimes called transient space) for the exchange may be different from the space evaluated at steady space.

The previous evidence that suggests a low extravascular volume for sodium in the lung is derived from indicator-dilution experiments following bolus injections. Mean transit times are evaluated by using single exponential extrapolation of the tail of the dilution curves. Minimal differences in the mean transit times of sodium and albumin resulted in calculated extravascular volumes which have a wide range as well as low values (from the data of Pearce; we calculated these volumes to be 0.001–0.044 ml/g of lung). The similarity of mean transit times and a consistently positive extraction of sodium imply (1) dilution curves whose shapes are similar throughout their major portions, and (2) inability to recover all the injected sodium. We suggest that extrapolation of the tail of the diffusible indicator-dilution curve introduces an error because it ignores the late return of sodium from the tissue, and thus the evidence for a small $v_{E_Na}$ is derived from an inadequate technique.

It is possible that the $v_{E_Na}$ is not solely interstitial; however, if it is, then the high albumin and the high sodium
volumes (2 times that of the heart) fit with the relative paucity of cellular elements in the structure of the lung.

**REGIONAL BLOOD FLOW IN THE LUNG**

There are no previous data on regional distribution of blood flow in discrete areas of the lungs at low and high total flow. Greenleaf et al. measured the distribution of flow in dogs in the left decubitus position and reported higher fractional flow per unit of volume in the dependent portion of the lung. Higher flows also were found at the diaphragmatic portion in comparison to the apex along an isogravitational axis of the thorax. However, in the reports of Greenleaf et al. and Edmunds et al. lobar or lobular sizes were evaluated rather than the 0.5- to 1.5-g pieces reported here.

The plots of Figures 3 and 4 support the contention that some lung pieces (e.g., the apex and the nondependent portion) have so low a flow that if total flow were further reduced there might be complete cessation of perfusion of

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**TABLE 3 Parameters Measured for the Regional Lung Blood Flow**

<table>
<thead>
<tr>
<th>Expt no.</th>
<th>Isotope</th>
<th>HR (beats/min)</th>
<th>A (mm Hg)</th>
<th>PA (mm Hg)</th>
<th>P\text{\textsubscript{o}} (mm Hg)</th>
<th>Hct</th>
<th>Blood flow (liters/min)</th>
<th>Intervention</th>
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<tr>
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<tr>
<td>20034</td>
<td>*\textsuperscript{111}Ce</td>
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<td>20</td>
<td>125</td>
<td>0.33</td>
<td>3.3</td>
<td>IV C balloon</td>
</tr>
</tbody>
</table>

Isotopes \*Sc, \*Sr, and 111Ce are the labels on the 9-\textmu m microspheres. Blood flow is calculated from indocyanine green dye-dilution curve. The other abbreviations are identified in Table 2. In experiment 26114, the right ventricular pressures are given instead of the pulmonary artery pressures. The interventions are given between the first and second introduction of microspheres into the right atrium.

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**FIGURE 3** Distribution of 9-\textmu m microspheres (experiment 12124) in lung samples at normal flow (Sc = \*Sc-labeled microspheres) and at high flow induced by intravenous infusion of isoproterenol (Sr = \*Sr-labeled microspheres). A relative concentration of unity implies samples that have microsphere concentrations (counts/min per g) equal to that of the average for the whole lung. The percentage distribution for each lung lobe (right upper, middle, lower, and accessory; left upper and lower) for the microspheres and for the wet weights are given in the inset. The samples with initially high microsphere concentration (Sc axis of greater than 1.5, where blood flow during Sr injection was 1,540 ml/min) show disproportionately less increment when total flow increases to 3,300 ml/min (during Sr injection). The anterior portions of the lungs are denoted by the open symbols and the posterior or dependent portions of the lung are denoted by the closed symbols. The asterisks refer to samples between anterior and posterior.

**FIGURE 4** Distribution of microspheres for experiment 29114. The \*Sr-labeled microspheres were injected at a normal flow of 2,200 ml/min and the \*Sc-labeled microspheres were injected at a flow of 1,400 ml/min produced by transient occlusion of the inferior vena cava. Since not every portion of the lung tissues was sampled, we do not have the fractional weight or fractional flows of each microsphere. Again, as flow decreases, the samples with initially low flow (Sr concentration around 0.5) show disproportionately more decrement. For identification of symbols, see inset.
SODIUM EXTRACTION

The early extractions, defined as $E(t)$ or $E_p(t)$, obtained within a few samples following the appearance time, were generally high and declined at various rates independent of the volume of the sampling system or the speed of sampling. This could be due to (1) analytical inaccuracy, (2) early back diffusion of sodium from the extravascular space, (3) inhomogeneity of flow and permeability, or (4) interlaminar diffusion in the convective stream.

If analytical inaccuracy affects early $E$ because it involves taking ratios of small numbers, this should result in $E$ with random values. Furthermore, the higher subsequent concentration values still result in decremental values for $E(t)$; therefore, analytical inaccuracy cannot cause high values of early $E$.

Rapid back diffusion of sodium has to be recognized because it implies a bidirectional and not unidirectional flux. For back diffusion of sodium to produce high values of early $E$, there should be low flow, low $v_{c-Na}$ or high capillary permeability, either alone or in combination. However, lung blood flow is high in comparison to the heart, and low $v_{c-Na}$ is not proven. High permeability is not compatible with peak extraction of less than 20%. For example, in the isolated heart, where flow is lower than in the lung, a high value of early $E$ for either sodium or potassium was not a common feature, yet the sodium and potassium extractions at the peak of the albumin curve were 40-60%. In the lung, tracer water probably shows limitation of flow and therefore permeability is infinite, but the earliest $E$ for water was 60-70%, decreasing to almost 30% at the time of albumin peak. These values of water extraction exceeded our present $E$ for Na, which has a lower free diffusion coefficient. Therefore, rapid back diffusion of sodium could not have produced high values of early $E$ in the lung.

To implicate heterogeneity of flow or permeability, or both, as a cause of high values of early $E$, there must exist areas in the lung with high PS/F, where $F$ is the plasma flow into the exchanging sites. However, because of their early appearance, the probing molecules that traverse the exchanging sites with high PS/F (or low $F$) also must exit rapidly from the area; therefore, they also must traverse nonexchanging vessels with small volumes. In the lung the anatomical areas that fulfill these implicit criteria would most likely be those around the large pulmonary vessels.

Interlaminar mixing in the flowing blood was shown by Lassen and Crone to produce apparent positive extractions in the brain, which is supposedly impermeable to sodium. This has been ascribed to large sampling volume or slow sampling rate, neither of which applies in our study. For interlaminar diffusion to be detectable, the convective flow should be relatively slow. It is unlikely that this occurs in the aorta, since the velocity of blood flow is quite high and, in the report of Perl et al., sampling at the carotid artery did not appear to alter the appearance of the high initial $E$. Hence by exclusion, if interlaminar diffusion is the dominant cause of high early $E$, we postulate that it occurs in the pulmonary venous system where the capacity is high and the pressure is low.

Because the cause for the high early $E$ is not known, the use of $E(t_p)$ to represent an average $E$ is arbitrary. $E_p$ may be more appropriate because it is less biased toward low concentration of tracers, although $E(t)$ often does not have a plateau value. $E_p$ at the mean transit time of the albumin curve cannot be used, because by then back diffusion will have assumed prominence. Since $E_p$ as a function of plasma flow showed a wide scatter and had values rarely exceeding 15%, we cannot exclude insensitivity of the method as applied to normal lung. This may negate correct evaluation of normal PS.

However, if the method is not insensitive, and the choice of $E$ is appropriate, then the highest value of PS is about 150 ml/min in three dogs. For a lung weight of 180 g, we calculate the PS to be 0.83 ml/min per g, which is not markedly different from the average sodium PS of 0.73 ml/min per g in the dog hearts. This similarity of PS between heart and lung is discussed by Perl et al. In Weibel's review, the pulmonary capillary surface area was taken to be 72 m² for a 20- to 24-kg dog, which should have lung weight of up to 240 g. This would result in capillary area of $72 \times 10^9/240 = 3,000 \text{ cm}^2$ per g, a value 6 times that of the heart. Hence, in spite of the possible similarity of PS.
between heart and lung, the capillary permeability in the lung is most likely less than that of the heart.

In conclusion, we have systematically studied the single-passage extraction technique for sodium in normal lung of dogs. We show that the sodium distributive volume outside the exchanging membrane is fairly large. In normal lungs we suggest that the calculated capillary PS, although giving results comparable to those of other investigators, may be incorrect either because of the insensitivity of the method or because of contamination of the appropriate E by high values of early E. In evaluating the distribution of regional lung blood flow with alteration of total flow, we think that as total flow is reduced, there are lung areas that will not be perfused from the pulmonary artery. We have also shown marked heterogeneity of flow such that it may not be appropriate to demand that the capillaries of the lung be represented by a single PS value.

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T Yipintsoi

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