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THE EFFECTS OF INCREASED CARDIAC OUTPUT, SURGICAL ISOLATION AND COUNTERCURRENT EXCHANGE AT THE FEMORAL ARTERY ON THE RESIDENCE TIME OF XENON IN MUSCLE

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The experiments reported herein were conducted according to the principles set forth in the current edition of the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

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This report describes a series of pilot experiments performed to guide the planning of NMRI's inert gas exchange research work unit after 1990. We conducted 5 experiments to examine the relationship of xenon residence time in tissue to cardiac output. In these experiments xenon mean residence time was not reduced when we increased the cardiac output using intravenous infusions of drugs. We found mean residence times to be generally longer in intact versus isolated muscle preparations, possibly due to differences in lipid content. In a 6th experiment, we recorded the profile of xenon radioactivity in the femoral artery and found that any countercurrent exchange above this level could account for a maximum of 4% of the mean residence time observed in the muscle. We modified the fitting routine to include the switching times as parameters to be estimated by the data. The mean transit times estimated using this model were more consistent with the time course of xenon observed on visual inspection of the curves. The results of these experiments produced a modification of the gas exchange project work unit and 5-year plan for Fiscal Year 1990.

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TABLE OF CONTENTS

page

ACKNOWLEDGEMENTS ii

INTRODUCTION 1

METHODS 2

Anesthesia, instrumentation, and xenon administration 2
Analysis of xenon data 4

RESULTS 6

Estimating xenon switching times 6
Effects of increased cardiac output and muscle preparation 8
Countercurrent exchange of xenon at the femoral artery 9

DISCUSSION 13

The effect of increased cardiac output 13
Intact versus isolated muscles 13
Countercurrent exchange above the femoral artery 14
Estimating xenon switching times 14

CONCLUSION 15

REFERENCES 17

LIST OF TABLES

TABLE 1 Mean Residence Times 7

TABLE 2 Cardiac Output 8

LIST OF FIGURES

FIGURE 1 Cardiac Ouptput, 18JY9 10

FIGURE 2 Muscle Xenon and Asymmetric Curve Fit, 18JY9L 11

FIGURE 3 Xe at Femoral Artery vs. Muscle and Inspired Air 12

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The experimental protocol for this project was reviewed by the institutional Animal Care and Use Committee and certified as conforming to the guidelines in the Institute for Laboratory Resources, National Research Council, "Guide for the Care and Use of Laboratory Animals" (DHHS Publ. 86-23).

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INTRODUCTION

In a study conducted in this laboratory (8), the observed mean residence time of xenon in muscle was, on average, more than 5 times longer than that predicted by a perfusion-limited model of xenon exchange. Further, the observed and predicted mean residence times were not correlated to any convincing degree ($r=0.59$; $p=0.13$). This general failure of the perfusion-based model led us to consider three factors not considered in the previous study, which may better account for the observed residence times. First, the observed means were strongly correlated with the inverse of the cardiac outputs, which were in the resting state, during each experiment ($r=0.93$; $p=0.0009$). This led us to hypothesize that the mean residence time of xenon in tissue can be shortened by increasing the cardiac output. Second, the high lipid content of the cutaneous tissues overlying the muscles might have accounted for the observed residence times, because the solubility of xenon in lipid is more than ten times that in lean tissues. We hypothesized that the mean residence time of xenon is significantly shorter in muscles without the overlying cutaneous tissues than in intact muscles. Third, the exchange of gas between arterial and venous vessels has been shown to influence the residence time of inert gas in tissue (5). The locations of this process in the vascular system have not been determined, mainly because of the technical difficulties involved in resolving the details of gas exchange in small (1 cm or less) anatomic features. However, the techniques for examining countercurrent exchange at the level of the femoral artery are available. Here we report the results of a pilot experiment to quantify the countercurrent exchange at this level.

METHODS

Anesthesia, instrumentation, and xenon administration

To examine the effects of both muscle preparation and cardiac output, we studied five male mongrel dogs. The anesthetic procedure was as done earlier in this laboratory (8). The animals were ventilated using a mechanical closed-circuit ventilator (Harvard). A #5F pediatric Swan-Ganz catheter (American Edwards) was inserted into the pulmonary artery via the external jugular vein. Correct positioning was confirmed by a continuous pressure recording (Gould). We removed the skin and subcutaneous tissues of the left gastrocnemius muscle by blunt dissection. We covered the muscle with a sheet of plastic (Saran) and moistened it by a continuous flow of normal saline at room temperature. The right calf muscle was studied intact, as done previously (8).

Xenon-133 gas was administered as before (8). Lead-collimated cadmium-telluride probes were placed over the calf muscles of the hind legs, with the same orientation for both legs. The non-muscle tissue of the isolated side was shielded from the field of view of the detector by a 3-mm-thick sheet of lead. The radioactivity of xenon was recorded in 1.3-min cycles for 150 min of xenon uptake followed by 150 min of xenon elimination.

Cardiac output was stimulated pharmacologically to produce an increase during xenon elimination. The following drugs were used: Dobutamine (50 mg/ℓ D5W, 25 μ/min IV), nitroprusside (100 μ/ml D5W, 30 μ/min IV), and hydralazine (20 mg IV). Dobutamine was selected as the primary agent for stimulating cardiac output because of its rapid pharmacologic half-life ($t\frac{1}{2}$=2 min), which enables precise control by continuous intravenous infusion. In addition to any effects due to increased cardiac output, the muscle blood flow

may also be increased by a mild direct effect on muscle β_2 receptors (4). Dobutamine was selected over isoproterenol because the latter is primarily chronotropic (versus inotropic) and may not reliably increase the cardiac output (4). The rate of infusion was increased at 10-minute intervals according to the response observed in measured cardiac output.

Nitroprusside and hydralazine were also used for their potential synergistic effect on cardiac output through reductions in systemic vascular resistance. Nitroprusside was selected because of its rapid half-life (t½=2 min) and because, like dobutamine, it is administered by continuous intravenous infusion. Hydralazine was evaluated only secondarily, because its elimination half-life (2-4 h) is considerably longer than the other agents (4). However, because unexpected reductions in cardiac output were observed on infusion of nitroprusside in both the first and second experiments (05JY9, 06JY9), this agent was discontinued. Hydralazine was then utilized in the last experiment (20JY9).

We measured cardiac output by the thermodilution technique at 10-min intervals during the experiments. We did not measure tissue blood flow using radioactive microspheres in these experiments, because microspheres may exert confounding influences on the cardiac output, the tissue blood flow, and the xenon exchange process.

To examine countercurrent exchange at the femoral artery, we studied a sixth animal, and recorded the profile of xenon radioactivity in the femoral artery throughout xenon uptake and elimination. The anesthetic preparation and methods of xenon administration were as described above. We cannulated the proximal end of the left femoral artery using 240-gauge polyethylene (PE) tubing, bypassed the blood through a 5-ml glass tube, and then recannulated the distal femoral artery again with PE tubing. Heparin (130 U/kg bolus, 26

U/kg/h infusion) was administered intravenously to reduce clotting. The calf muscle was surgically isolated as described above. We placed lead-collimated CdTe probes over the glass tube and the muscle. Particular effort was made to ensure that the arterial probe detected xenon activity only from the arterial blood and not from the adjacent leg tissue. The collimator around the arterial xenon detector attenuated the ambient radioactivity by a factor of 1/10,000.

<u>Analysis of xenon data</u>

An exponential function was fitted to the xenon data using a nonlinear least-squares fitting routine (8). The model used is capable of symmetric or asymmetric fitting of the uptake and elimination halves of the experiment. The asymmetric form of the model estimates separate mean residence times for the uptake and the elimination halves of the xenon data. In this way, the mean residence time during pharmacologic stimulation of the cardiac output can be compared to the unstimulated mean residence time.

The equation for fitting the tissue xenon data is

$$F(t) = (Q\infty/M1)\ [U(t)P(t) - U(t-d)P(t-d)] \quad [1]$$

where $Q\infty$ is the asymptotic xenon radioactivity and M1 is the mean residence time; $U(t) = 0$ for $t<O$, $U(t) = 1$ for $t>0$; d is the xenon gas switching time when the radioactivity in the inspired air drops to background levels upon changing to open-circuit ventilation.

The function P(t) is expressed as

$$P(t) = (B_i\beta_i)\beta i\ (1 - \exp(-t/\beta_i) \quad [2]$$

where $(B_i\beta_i)$ is the weighing factor and β_i is the time constant for the ith exponential term.

The parameters $Q\infty$, B_i, and β_i are estimated from the experimental data. The

asymmetric analysis, which fits the uptake and elimination periods separately, estimates a separate set of parameters (time constants and weighing factors) for each period of the data. The symmetric analysis, which fits the uptake and elimination periods together as one data set, estimates one set of parameters for the entire experiment. The background radioactivity level, the average of a 5-minute background measurement before the xenon administration begins, is entered as a fixed parameter.

The switching times at the beginning and the end of xenon uptake can be treated either as fixed values or as parameters estimated by the data. The time of xenon injection into the ventilator circuit is known to a precision of approximately ± 5 s. We usually enter these times as fixed values (8,9). However, the transition from a background of 4-6 counts per minute (CPM) to the first data point, which may be 100 times the background level, takes 1 min of live-time counting and another 20 s to reset the collection cycle. This then limits the resolution of any of the events in the data to some multiple of 1 min and 20 s. Thus, the on-time (at the first data point) is resolvable in the data with substantially less precision than is the time of xenon injection. Our initial attempts at analyzing the data using fixed switching times were not successful, particularly with the asymmetric model used here. We have not encountered this problem in previous experiments of this type. Our solution was to analyze all the data sets using a model that estimated the switching times instead of including them as fixed values. This is further discussed in the results below.

Each experiment produced four mean residence times for analysis: unstimulated and stimulated states for the effect of cardiac output, and right and left sides for the effect of muscle preparation. We analyzed the data using a repeated measures analysis of variance.

RESULTS

Estimating xenon switching times

We encountered an unexpected problem in the analysis of the xenon data from one of the experiments (18JY9): The asymmetric model estimated unusually short time constants, therefore yielding short mean residence times, for the uptake phase in both the right (R) and left (L) sides. The time constants of 0.22 (R) and 0.04 (L) min estimated in this case are markedly shorter than the sampling interval (1.33 min) of the data from which they are estimated. The uptake mean residence times of 3.7 (R) and 0.5 (L) min were also markedly shorter than the other observed means (Table 1). These inconsistencies caused us to re-examine the data from 18JY9.

The estimation of the mean residence times in the 18JY9 data was unusually sensitive to the values of the switching times. Therefore, we analyzed the data again with the two-exponent asymmetric model, this time with the xenon switching times estimated by the data. The resulting mean residence times, 31.2 (R) and 42.0 (L), were similar to the mean residence times estimated from the other eight curves. The effect of allowing the data to estimate the switching times was most pronounced in the estimations of the xenon on-times. Both of these were estimated to be earlier than the real time of xenon injection by 1.27 min (R) and 1.91 min (L). These changes are close to the resolution of the 1.33-minute cycle reset time of the data collection routine. The xenon off-times were changed less: -0.89 (R) and +0.01 min (L).

TABLE 1

Mean Residence Times

Expt	U	(SD)	S	(SD)
05JY9L	34.1	(2.2)	39.4	(3.5)
R	35.6	(0.1)	37.2	(1.7)
06JY9L	19.1	(0.5)	32.8	(1.0)
R	40.3	(1.5)	58.2	(2.1)
10JY9L	38.9	(2.7)	26.8	(0.8)
R	61.7	(4.3)	67.5	(3.0)
18JY9L	42.0	(5.2)	59.6	(5.0)
R	31.2	(11.0)	68.4	(2.9)
20JY9L	12.6	(4.9)	27.8	(1.4)
R	53.6	(9.0)	39.3	(4.8)

Mean residence time in min during pharmacologic stimulation (S) and unstimulated conditions (U). The right (R) side was studied intact, the left muscle (L) was isolated from the overlying non-muscle tissue. (SD = standard deviation).

To evaluate any potential bias introduced by the model's estimation of switching times in the 18JY9 data, we analyzed the other four data sets with this model. In these data sets, the estimated switching times were close to the actual times of xenon switching. The on-times estimated using this model were all earlier than the actual times, an average of 0.20 min earlier (range 0 to 0.61 min, ± 0.22 SD). The uptake mean residence times estimated using this model were slightly longer than those estimated using the model with fixed switching times, with an average increase of 15.8% for the right side and 4.8% for the left side. These differences are considerably smaller than the 7-fold (R) and 73-fold (L) differences observed for the 18JY9 data set. The estimated elimination mean residence times were 1.6% longer for the right side and 3.1% shorter for the left side than those estimated using the model with fixed switching times.

Effects of increased cardiac output and muscle preparation

The cardiac outputs are shown in Table 2. The unstimulated cardiac outputs were within the expected range of normal in four of the experiments (2), but were slightly higher than the expected range of 1.63 - 4.25 ℓ/min in the fifth (20JY9). This may have been caused in part by an episode of hypoxemia during the surgery/instrumentation portion of the experiment. The hypoxemia persisted and was resistant to efforts to correct it (recessing the endotracheal tube, increasing airway pressures) for the duration of the experiment. An inspired oxygen fraction of 35% was required to maintain adequate blood oxygenation.

The profile of the cardiac output values for a typical experiment (18JY9) is displayed in Fig. 1. The cardiac output during unstimulated conditions was on average 2.1 ℓ/min, which increased to an average 2.5 ℓ/min during stimulated conditions ($p=0.13$).

TABLE 2
Cardiac Output

Expt	U	S
05JY9	2.9 (0.19)	4.1 (0.61)
06JY9	2.7 (0.23)	2.7 (0.54)
10JY9	3.4 (0.50)	3.4 (0.24)
18JY9	2.1 (0.17)	2.5 (0.46)
20JY9	4.6 (0.58)	6.5 (1.00)

Averages of cardiac output (ℓ/min) during pharmacologic stimulation (S) and unstimulated conditions (U) with their standard deviations (SD).

The mean residence times shown in Table 1 were all estimated using an asymmetric model containing two exponential terms, which included the xenon switching times as an estimated parameter. This model fits the data well, as shown in Fig. 2. The mean residence

times under unstimulated conditions had an average of 36.9 min compared with an average of 45.7 min under stimulated conditions ($p=.19$). There was no evidence of interaction between the effect of stimulation and the effect of intact versus isolated preparation ($p=.86$). The intact side had an average mean residence time of 41.7 min compared with an average of 33.3 min for the isolated side ($p=.08$).

Countercurrent exchange of xenon at the femoral artery

Figure 3 displays the arterial xenon profile and the concurrent profiles of xenon in the ventilator circuit and in the muscle distal to the artery. The arterial xenon data required a two-exponent model to obtain a satisfactory fit. The mean residence time of xenon in the artery was 1 min and 20 sec for both uptake and elimination. The corresponding mean residence times in the muscle were 37.4 min and 38.1 min, respectively.

At the termination of the experiment, flushing the arterial tubing with 100 cc of normal saline reduced the counts from 65 to 34 CPM. Additional flushing with 50 cc did not further reduce the counts. Inspection revealed no clot in the tubing or the glass. The glass was slightly clouded with a tan film, possibly fibrin and platelet material. Re-analyzing the data with 34 CPM residual radioactivity as a fixed background parameter did not appreciably alter the results.

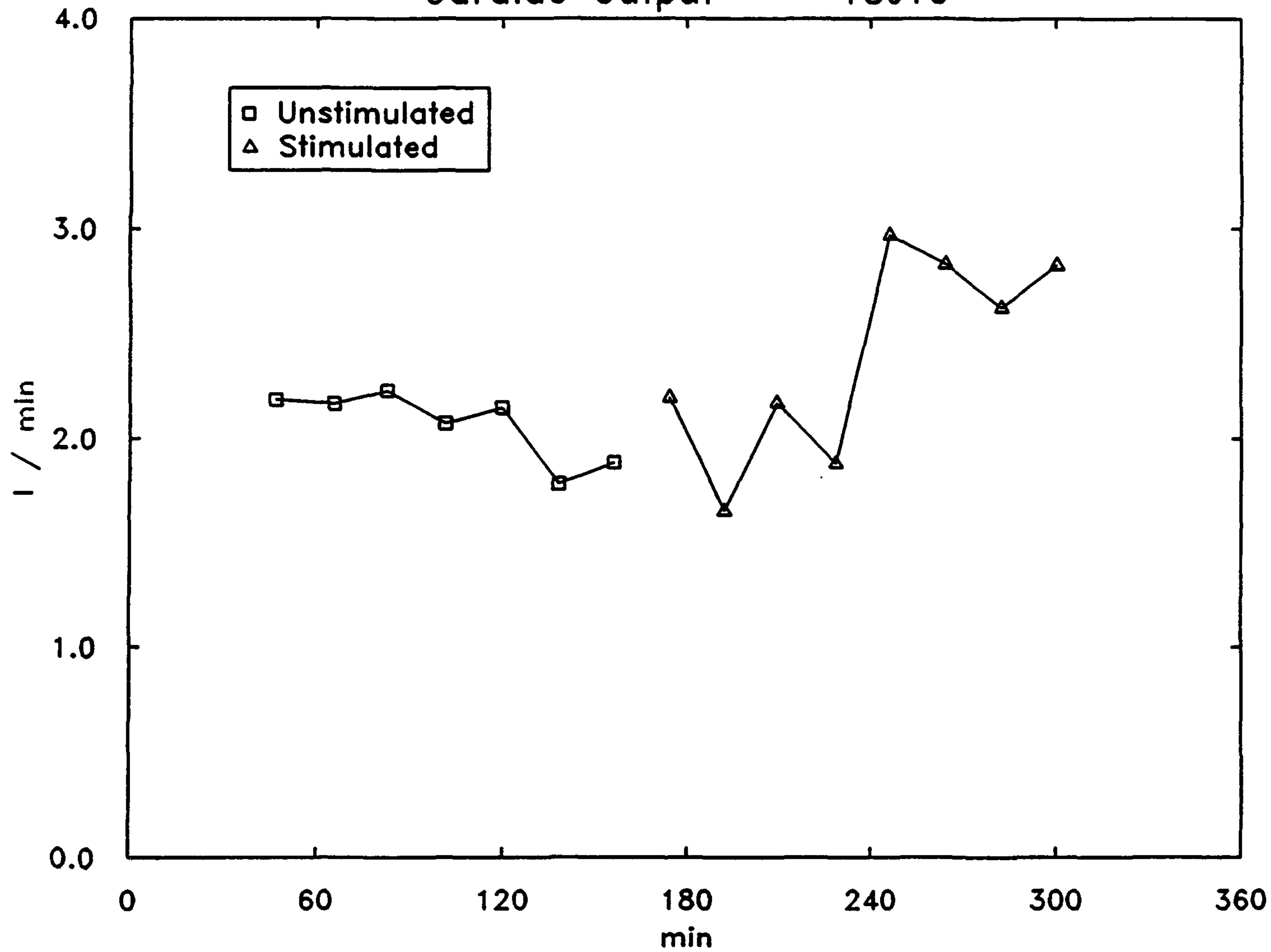

Figure 1. Profile of cardiac output measurements over time in experiment 18JY9.

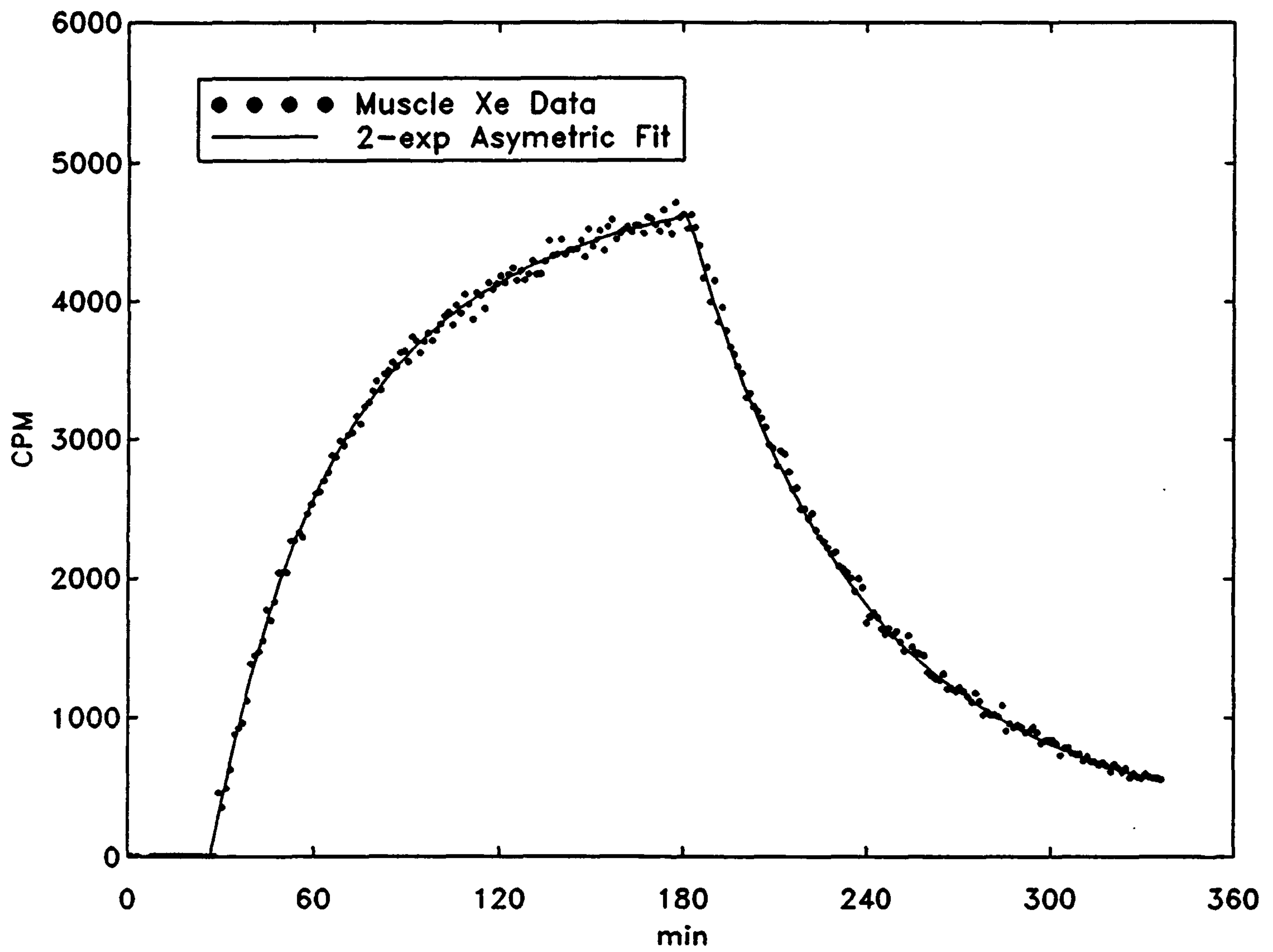

Figure 2. Xenon data and 2-exponential, asymmetric curve fit for experiment 18JY9.

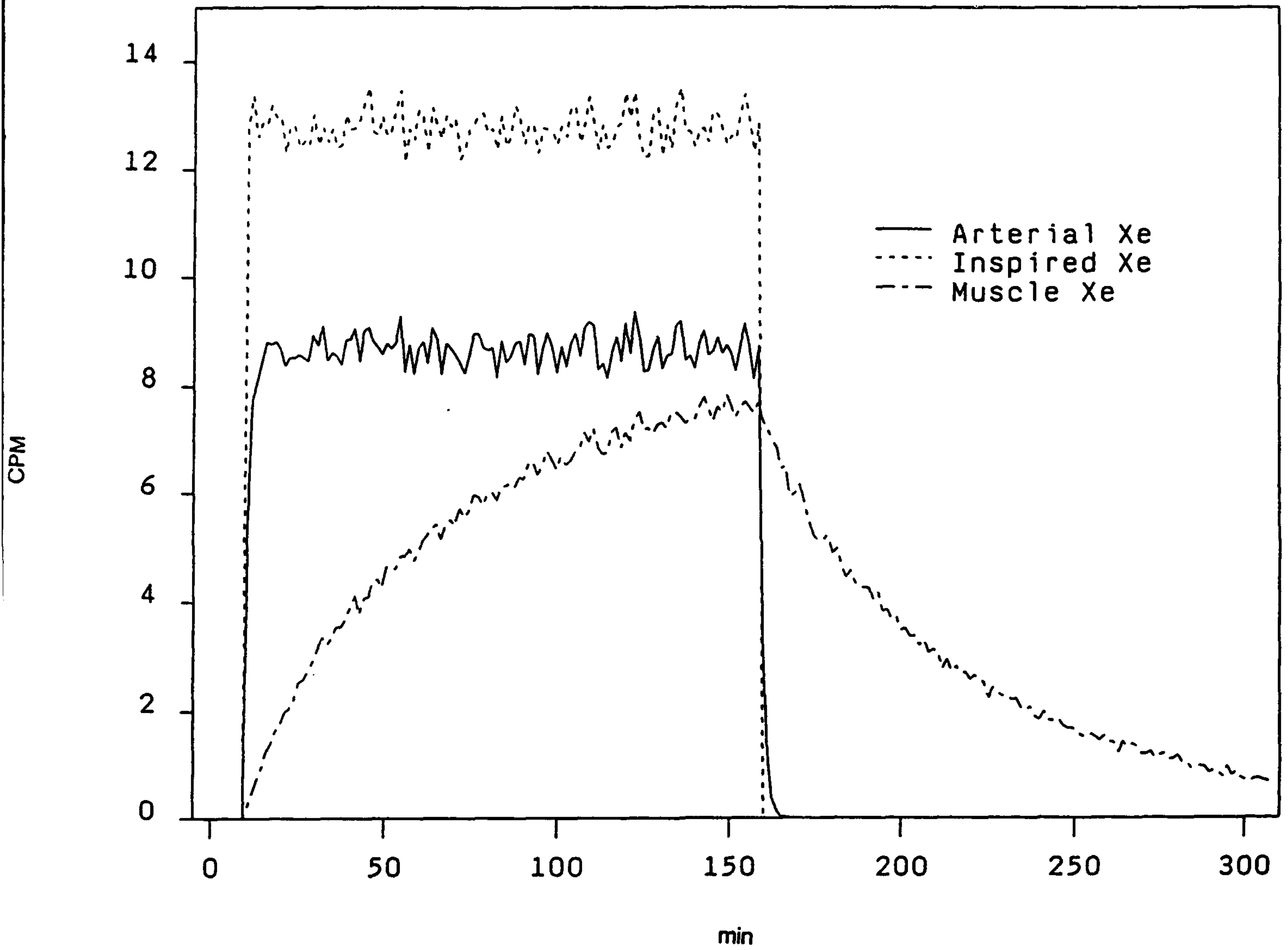

Figure 3. Profile of femoral arterial xenon radioactivity and the corresponding profiles in the ventilator and the muscle.

DISCUSSION

The effect of increased cardiac output

The data gathered in these trial experiments suggests that increasing the cardiac output by pharmacologic stimulation does not shorten the mean residence time of xenon in muscle. This finding is contrary to our expectations based on earlier data in which higher resting cardiac outputs were associated with shorter mean residence times. An examination of Table 2 reveals that, although the cardiac output response to pharmacologic stimulation was not strong in all experiments, there were two cases (05JY9, 20JY9) where the cardiac output increased by 41%. However, even in these strongest cases the mean residence times during stimulation were longer than those during the unstimulated portion in three of the four data sets. Our design involved pharmacologic stimulation only on xenon elimination, so the effect of stimulation is confounded with the effect of time. A randomized design of stimulation on either uptake or on elimination might yield different results.

Intact versus isolated muscles

The mean residence times of xenon are generally longer in an intact than an isolated muscle preparation. One explanation, assuming similar blood flows on both sides, might be that the intact side, because of its subcutaneous tissue, contains a higher fraction of lipid. Another possibility is that the blood flows of the isolated muscle were higher than those of the intact side. How much lipid would be required to account for the observed xenon mean residence times? This question has been examined theoretically (8), but not experimentally. An experiment measuring the lipid contents of both the muscle and the overlying tissues could address this question.

Countercurrent exchange at the femoral artery

The profiles of xenon in the inspired air and at the femoral artery closely match. The small lag observed in arterial xenon at both of the switching times (Fig. 3) was estimated to be 1 min and 20 s. The time course of xenon in the artery may be influenced by several factors. First, the residence time estimated from the arterial xenon data reflects, in part, the time of convective and diffusive transport from the inspired air to the femoral artery. This would account for only about 5 s (7). Second, the experimental apparatus - the solubility of the polyethylene tubing and debris accumulated on the glass - also contributes some to the lag, but probably only a small fraction, as the residual radioactivity after flushing with saline was less than 0.01% of the peak arterial radioactivity. From this data we would conclude that countercurrent exchange of xenon at the level of the femoral artery accounts for no more than a few percent of the mean residence time observed in the tissue. Most of the countercurrent exchange of gas must occur distal to this level.

Estimating xenon switching times

The estimation of the mean residence times was sensitive to the values of the xenon switching times. This problem has not been encountered previously in our experience with the symmetric models, nor was it encountered in a re-analysis of the 1987 xenon data (8) using an asymmetric model. In the present experiments, the curves of the 18JY9 data are, on visual inspection, no different from those of the other data sets. However, using a model that estimates the switching times markedly changes the estimated mean residence times. The reason for the switching-time problem is not apparent. No methodological differences between the experiments were noted. However, two potential technical problems with the

experimental setup are apparent. First, the differences between the estimated and the actual switching times are similar in size to the 1.33-min cycle/reset time, which may simply reflect the imprecision of this system. Second, the large changes in the ambient radioactivity from the movement of radioactive gas into and out of the ventilator circuit could appear in the data as an apparent shift in the time of xenon switching.

CONCLUSION

Considering the results of these trial studies, we make the following recommendations concerning the planning of the inert gas exchange project.

1. A quantitative evaluation of the effect of lipid in tissue on the exchange of xenon should be performed.

2. The effect of countercurrent exchange of xenon should be further evaluated in a study that examines the xenon kinetics in both the venous and the arterial vessels of a tissue. Also, the ongoing computer simulations of gas exchange should be expanded to include architectural details on vessels 100 μ and larger. Methods of obtaining such data, such as casting of the microvasculature, should be explored.

3. Methods for studying xenon exchange in other tissues, for example the central nervous system, should be explored to provide a comparison with the results obtained using muscle tissue. The use of quantitative magnetic resonance imaging is one possibility.

4. The role of local blood flow in xenon exchange should be further evaluated using laser-doppler flowmetry in addition to radioactive microspheres.

5. The gas exchange work unit and five-year plan should be modified according to

the above conclusions. Studies of tissue gas kinetics in hyperoxic and hyperbaric conditions will be delayed.

REFERENCES

1. Anderson, A.M. and J. Ladefoged. Partition coefficient of 133-xenon between various tissues and blood in vivo. Scandinavian Journal of Clinical and Laboratory Investigation, Vol. 19, pp. 72-72, 1967.
2. Cissik, J.H., W.H. Ehler, G.D. Hankins, J.C. Hauth, and W.A. Pierson. Determination of cardiac output and other reference physiology parameters in lightly anesthetized dogs. Comparative Biochemistry and Physiology, 88A(1), pp. 89-93, 1987.
3. Froberg, S.O. Determination of muscle lipids. Biochimica Et Biophysica Acta, Vol. 144, pp. 83-93, 1967.
4. Gilman, A.G., L.S. Goodman, and A. Gilman. The pharmacologic basis of therapeutics. Sixth Edition, MacMillian, 1980.
5. Homer, L.D. and P.K. Weathersby. How well mixed is inert gas at the lungs and tissue? Journal of Applied Physiology, Vol. 60, No. 6, pp. 2079-2088, 1986.
6. Kety, S.S. The theory and applications of the exchange of inert gas at the lungs and tissues. Pharmacological Reviews, Vol. 3, pp. 1, 1951.
7. Mountcastle, V.B. Medical Physiology, 14th Edition, Vol. 2, Chapter 37, 1980.
8. Novotny, J.A., D.L. Mayers, Y.J. Parsons, S.S. Survanshi, P.K. Weathersby, and L.D. Homer. Xenon gas kinetics in skeletal muscle are not explained by a model of multiple parallel, perfusion-limited compartments. Journal of Applied Physiology, Vol. 68, No. 3, pp. 876-890, 1990.

9. Weathersby, P.K., E.E.P. Banvard, L.D. Homer, and K.G. Mendenhall. Stochastic description of inert gas exchange. Journal of Applied Physiology, Vol. 47, pp. 1263-1269, 1979.

10. Weathersby, P.K. and L.D. Homer. Solubility of inert gases in biological fluids and tissues: a review. Undersea Biomedical Research, Vol. 7, No. 4, pp. 277-296, 1980.