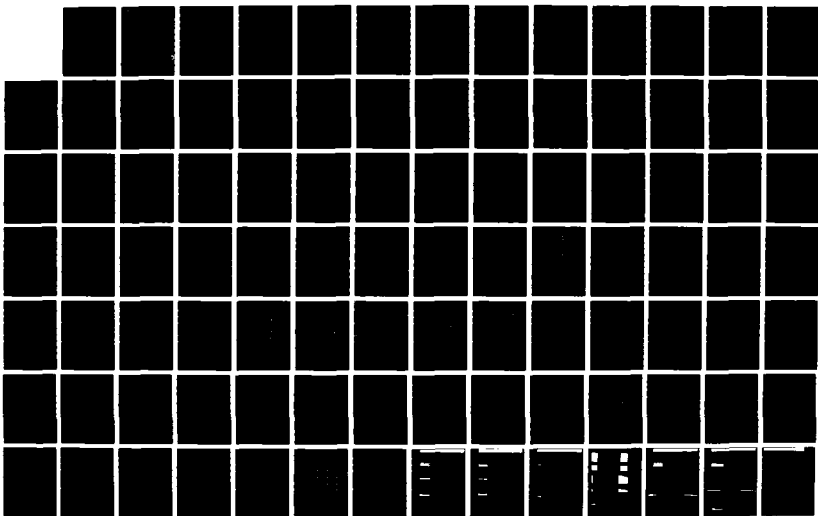
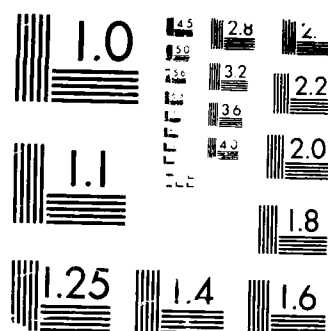


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STUDY OF THE EFFECTS OF DRUGS UPON THE
CARDIOVASCULAR AND RESPIRATORY SYSTEMS

ANNUAL PROGRESS REPORT

by

Robert W. Caldwell

Clinton B. Nash

February 1, 1985

(January 1, 1984 - December 31, 1984)

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

Fort Detrick, Frederick, Maryland 21701-5012

Contract No: DAMD17-83-C-3011

University of Tennessee Center for the Health Sciences
Memphis, Tennessee 38163

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19. ABSTRACT (Continue on reverse if necessary and identify by block number) During this past year we have: 1. Completed study of <u>Cardiovascular and Pulmonary Effects of WR-6026-2HCl vs Primaquine Diphosphate</u> . A copy of this report is attached (Section I). 2. Written a protocol to determine the <u>Involvement of Histamine in the Blood Pressure Responses to Liposome Carriers</u> (Section II). 3. Performed preliminary experiments on the <u>Effects of Carrier Liposomes on the Canine Cardiovascular System</u> . A copy of results is attached (Section III).					
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Summary

During this past year we have:

1. Completed study of Cardiovascular and Pulmonary Effects of WR-6026-2HCl vs Primaquine Diphosphate. A copy of this report is attached (Section I).
2. Written a protocol to determine the Involvement of Histamine in the Blood Pressure Responses to Liposome Carriers (Section II).
3. Performed preliminary experiments on the Effects of Carrier Liposomes on the Canine Cardiovascular System. A copy of results is attached (Section III).

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FOREWARD

In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

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SECTION I.

COMPARISON OF CARDIOVASCULAR AND PULMONARY EFFECTS
OF
WR-6026-2HCl and PRIMAQUINE DIPHOSPHATE

by
Robert W. Caldwell and Clinton B. Nash

with:
Terrye Thomas
and
Mary Rose Loftus

Department of Pharmacology
University of Tennessee
Center for the Health Sciences

Interim Report No. 8

2 March, 1984

Contract No. DAMD 17-82-C-3011

for
Headquarters, U.S. Army Medical
Research and Development
Command Office of Surgeon General
Washington, D. C. 20314

Summary:

A comparison was made of a variety of cardiovascular and pulmonary effects of WR-6026·2HCl and primaquine diphosphate in anesthetized dogs utilizing dose rates which were either only minimally effective in producing changes (1.0 μ moles/kg/min for WR-6026 and 0.5 μ moles/kg/min for primaquine) or those producing marked effects just short of death (4.0 μ moles/kg/min for WR-6026 and 1.75 μ moles/kg/min for primaquine). Cardiopulmonary actions of these two drugs differed. Note that the molar dose range for WR 6026 amounted to approximately twice that for primaquine.

In the cardiovascular system, the predominant effect of primaquine was an increase in pulmonary vascular resistance. A modest depression of cardiac contractility was noted for all dose-rates, but this was evident only at the end of the experimental period. The EKG changes indicated some transient slowing of A-V transmission and ventricular conduction. Although these changes were not prominent, one animal did develop ventricular arrhythmias at the high dose, reverting about 25 minutes later. A 2 μ mole/kg/min dose-rate of primaquine caused ventricular arrhythmias and death in one of two dogs tested.

The major effects of WR-6026·2HCl were a weakening of ventricular contractility and a constriction of the pulmonary vasculature. These effects were significant at the middle and high doses, but either did not occur or were unimportant at the low dose. There was some short-lived increase in P-R interval and Q-T interval by the high dose, but no cardiac arrhythmias.

Respiratory rate was transiently raised during high dose-rate infusion of primaquine. Compliance appeared variably affected by the different dose-rates of primaquine.

On the respiratory system, WR-6026 produced immediate elevations of respiratory rate and minute volume at all dose-rates tested. WR-6026 also produced a prominent depression in airways resistance at the higher doses.

The most dangerous effect of WR-6026 is progressive depression of cardiac contractility to the point of ineffective cardiac pumping. In contrast, the potentially lethal action of primaquine is upon cardiac rhythm.

**Cardiovascular and Pulmonary Effects of
WR-6026•2HCl vs Primaquine•2H₃PO₄**

BACKGROUND

During World War II there was a great interest in developing new anti-malarial drugs. A very fruitful source of active compounds was found to be the 8-aminoquinolines. Early in the experimental studies of these agents it was noted that they had a wide variety of cardiovascular effects.

WR-6026 is an 8-aminoquinoline originally synthesized in the malarial research program during World War II. However, more recently this substance has been noted to be the most active antileishmanial compound tested in the WRAIR screening program from more than 3000 compounds. Because of structural similarities of WR-6026 to primaquine (see below), one would expect similar cardiopulmonary actions from these two agents. This protocol describes experiments to make such a comparison.

The purpose of these experiments is to compare the effects of intravenous infusions of WR-6026 with those of primaquine upon the rhythm, electrical activity and the function of the heart, the pulmonary blood pressure and circulation, the systemic blood pressure and circulation and the pulmonary ventilation, including blood O₂, CO₂ and pH.

Previous Studies with WR-6026•2HCl (hereafter referred to as WR-6026) --

According to Korte and Basmania (1981), the cardiopulmonary profile of WR-6026, determined following intravenous administration, was unique in that it produced urticaria and angioneurotic edema in the anesthetized dog. This

response was hypothesized to be due to a non-hypersensitive release of endogenous autocooids, such as histamine. The hypotensive effect of bolus injections of WR-6026 and the increase in hematocrit observed during a 45-minute infusion of WR-6026 were consistent with a hypothesis of histamine release. Infusion of WR-6026, 17.8 mg/kg over a 45-minute period, also produced a decrease in heart rate and prolongation of the PR, QTc and QRS intervals of the electrocardiogram similar to that observed with primaquine. WR-6026, like primaquine, may affect reflex sympathetic activity as it blunted the expected increase in pulse pressure and heart rate following carotid occlusion. However, unlike primaquine, WR-6026 did not attenuate the cardiopulmonary responses of isoproterenol.

PRELIMINARY DOSE-RANGING EXPERIMENTS -- In our initial studies with WR-6026 we determined the range of dose-rates of the candidate drug that, in our preparation, produce either: (1) minor but perceptable changes in the cardiopulmonary variables, or (2) the most severe alterations in cardiovascular and pulmonary function short of death. Dogs were anesthetized and prepared as described in the Methods Section outlined later in this report. Following surgical preparation, application of monitoring instruments, and a period for stabilization of cardiopulmonary function, control values were recorded over a 30-minute period followed by intravenous infusion of drug or phosphate buffer vehicle at selected dose rates over a 20-minute period in a total volume of 80 ml.

Dose-rates initially selected for investigation were those, on a molar basis, which in our previous studies of candidate antimalarials produced definite but non-lethal cardiopulmonary effects. We were also guided by

information provided by Dr. Howard Lowensohn of WRAIR. Our results indicated a dose-response curve of similar slope to that previously noted for primaquine (Interim Report No. 6, University of Tennessee, 10 November, 1980).

A. Determination of Maximum Tolerated Dose-rate of WR-6026 -- Successive increases in dose-rate of WR-6026 in anesthetized dogs have demonstrated that 4 μ moles/kg/min is the maximum tolerated dose-rate. An infusion of 6 μ moles/kg/min produced death of both dogs so treated during the 20-minute drug infusion. An example of one of these range-finding experiments is given in TRACINGS 1A,B,C&D. An infusion rate of 5 μ mole/kg/min caused death in 3 out of 5 animals. There were progressive decreases in systemic arterial pressure, heart rate, left ventricular dP/dt max. and airway resistance with loss of effective cardiac function and arterial perfusion pressure by the end of the 20-minute period. Respiratory rate, tidal volume, pulmonary wedge and pulmonary arterial pressure increased before death. Respiration ceased when arterial blood pressure was about 35/8 mm Hg.

The 4 μ mole/kg/min dose-rate of WR-6026 produced the same pattern of actions; however, the 2 dogs given this dose survived the 120 minute experimental period. Alterations in ECG patterns were prominent. Marked increases in P-R and Q-T intervals have been noted.

B. Minimum Effective Dose-rate of WR-6026 -- A dose-rate of 0.5 μ moles/kg/min has been noted in two dogs to produce only minor cardiopulmonary changes. Slight rises in systolic blood pressure and LV dP/dt have been noted during the drug infusion period. Respiratory rate and minute volume have also been modestly raised during this period.

Three pilot experiments employing 1.0 μ mole/kg/min have demonstrated much more definite effects, some similar and others dissimilar. Left ventricular

dP/dt is elevated (5-12%) early in the infusion period (+5 min) and then falls to values slightly below baseline by the end of the infusion. Pulmonary artery pressure and pulmonary vascular resistance are modestly elevated during the infusions. The P-R and Q-T intervals are modestly increased by the 1.0 μ mole/kg/min dose.

A dose-rate of 2.5 μ mole/kg/min of WR-6026 produced effects intermediate to the other doses tested.

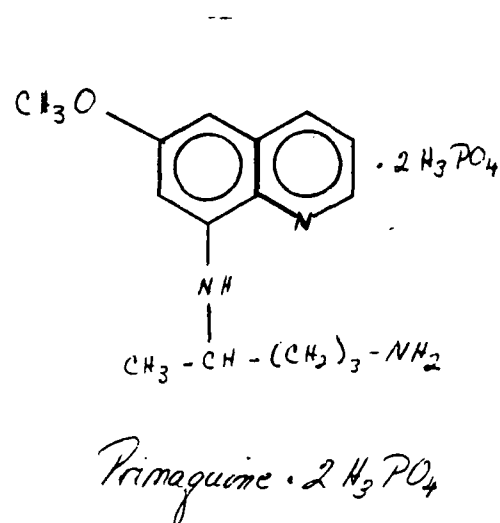
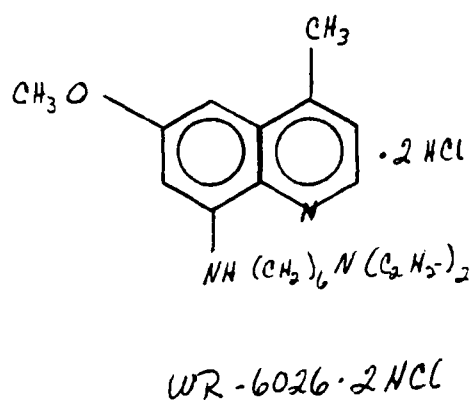
C. Previous Studies with Primaquine Diphosphate (hereafter referred to as primaquine) -- Primaquine, when infused i.v. at dose-rates of 0.5, 1.0, and 1.5 μ mole/kg/min for 20 minutes in anesthetized dogs, produced changes in several pulmonary and cardiovascular variables. These changes occurred at a 4-fold lower dose-rate than those employed in the previous studies of mefloquine, quinine, and WR-184,806. The major effects of primaquine at dose-rates of 1.0 to 1.5 μ moles/kg/min were: 1) increases (30-50%) in pulmonary artery pressure and vascular resistance, 2) an approximately 30% prolongation of P-R interval and P wave and QRS complex duration which waned after cessation of infusion, 3) a transient depression of airway compliance, and 4) a modest production of methemoglobin (see Caldwell, R.W. and Nash, C.B. Interim Report No. 6, University of Tennessee, to WRAIR, 10 November 1980).

In this previous study, preliminary range-finding experiments demonstrated that a 2 μ mole/kg/min dose-rate produced severe ventricular arrhythmias, including ventricular flutter, and caused death in 1 of the 2 dogs tested. One experiment is summarized in TRACINGS 2A,B,C&D. We conclude that high doses of primaquine have significant effects upon the pulmonary vasculature and cardiac electrical conduction.

D. Present Studies with Primaquine -- We performed experiments during the winter of 1983 to determine if our previous range of primaquine dose-rates were appropriate. A 0.5 $\mu\text{mole/kg/min}$ dose-rate of primaquine, again, proved to be the lowest which would consistently produce some noticeable cardiopulmonary effect. The dose-cardiopulmonary response relationships for primaquine were considerably steeper than observed for the antimalarials we had studied previously (Caldwell and Nash, 1980).

In experiments to determine the maximum tolerated dose, we noted in 2 dogs that a dose-rate of 1.75 $\mu\text{mole/kg/min}$ caused severe cardiopulmonary changes but did not result in death. Therefore, we tested primaquine at dose rates of 0.5, 1.0 and 1.75 $\mu\text{moles/kg/min}$ for 20 minutes in anesthetized dogs as a reference compound to compare the above stipulated doses of WR-6026.

Formulae for WR-6026 $\cdot 2\text{HCl}$ and Primaquine Diphosphate:



OUTLINE OF STUDIES

We used the following protocol and experimental scheme: Approximately 60 minutes were required following induction of anesthesia to perform the necessary surgery, cannulation procedures, and to establish calibrations. This was followed by a stabilization period of 20 to 30 minutes to insure that all recordings were steady, and this, in turn, was followed by a control period of 30 minutes during which data was recorded at 10-minute intervals. The drug infusion was then begun and continued for 20 minutes. There was a post-infusion period of 100 minutes for observation of recovery.

I. OBSERVATIONS -- 30-minute control period (-30,-20,-10, and 0 minutes)

A. Cardiovascular Measures

1. arterial blood pressure -- continuous
2. left ventricular pressure -- continuous
 - a. dP/dt -- continuous
 - b. left ventricular end diastolic pressure -- continuous
3. electrocardiogram -- at 10-minute intervals: all six limb leads are recorded at 25 mm/sec and strips at 100 mm/sec for analysis
4. heart rate -- continuous: by cardi tachometer
5. pulmonary vascular --
 - a. pulmonary artery pressure -- continuous
 - b. pulmonary wedge pressure -- at 10-minute intervals
 - c. cardiac output -- at 10-minute intervals
 - d. pulmonary vascular resistance -- calculated at 10-minute intervals

B. Pulmonary Ventilatory Measures

1. Airways differential pressures
 - a. air flow -- signal integrated by preprogrammed computer
 - b. transpulmonary pressure (bronchial vs esophageal) -- signals utilized by preprogrammed computer
2. Airways integrated measure -- tidal volume, continuous
3. Airways computer measures
 - a. compliance -- continuous = $\Delta V/\Delta P$
 - b. resistance -- continuous = $\Delta P/\Delta F$
4. Respiratory rate -- continuous

C. Hematological Measures - (-30 and 0 minutes only)

1. Blood P_{CO_2} -- arterial and venous
2. Blood P_{O_2} -- arterial and venous
3. Blood pH -- arterial and venous
4. Hematocrit -- central venous

II. DRUG INFUSION FOR 20 MINUTES -- Observations as described in I: A, B, and C. (Drug infusion time = 0 - +20 minutes)

- A. Measures A and B from I., plotted at +10, and +20 minutes -- expanded record (25 and 100 mm/sec)
- B. Measure C from I., plotted at +20 minutes

III. OBSERVATION PERIOD -- 100 minutes post-drug

- A. Measures A and B from I., plotted at 10 minute intervals beginning at +30 minutes (beginning of drug = 0 time) -- expanded records
- B. Measure C from I. taken at +40, +60, +80, +100, and +120 minutes

Experimental Groups

<u>Group/Drug</u>	<u>Dose-Rate</u>	<u>Number of Dogs</u>
1) WR-6026•2HCl	1.0 $\mu\text{mol/kg/min}$ = .42 mg/kg/min	6
2) WR-6026•2HCl	2.5 $\mu\text{mol/kg/min}$ = 1.0 mg/kg/min	6
3) WR-6026•2HCl	4.0 $\mu\text{mol/kg/min}$ = 1.67 mg/kg/min	6
4) vehicle (control)	80 ml phosphate buffer (pH 7.4)	6
5) Primaquine•2H ₃ PO ₄	0.5 $\mu\text{mol/kg/min}$ = .27 mg/kg/min	6
6) Primaquine•2H ₃ PO ₄	1.0 $\mu\text{mol/kg/min}$ = .45 mg/kg/min	6
7) Primaquine•2H ₃ PO ₄	1.75 $\mu\text{mol/kg/min}$ = .80 mg/kg/min	6

METHODS

I. Drug Preparation and Delivery

WR-6026•2HCL (MW=416.44) (BN# BK01845) 6-Methoxy-8-(6-diethylamino hexyl-amino) lepidine dihydrochloride, supplied by WRAIR, was dissolved in phosphate buffer*, (pH 7.4) prepared fresh daily for each experiment. The WR-6026•2HCl

*Stock solutions A and B of:

A=27.8 g monobasic sodium phosphate in 1000 ml double distilled H₂O and
B=53.65 Na₂HPO₄•7H₂O in 1000 ml of double distilled H₂O; 19.0 ml A and 81.0 ml B were mixed and brought to a total volume of 200 ml

is readily soluble in the desired concentrations. Primaquine•2H₃PO₄ (MW=455.35, AldrichChem Co., lot #2429BE, 99+% by certificate of purity, -see Appendix H) was purchased. The concentration of the solution was adjusted to the weight of each dog such that a fixed intravenous volume infusion rate of 4.0 ml/min contained the appropriate amount of drug, as the salt, in moles. The total volume infused over 20 minutes was, thus, 80 ml.

II. Animals

Mongrel dogs of either sex, weighing between 8.0 and 15.0 kg were supplied by the University of Tennessee Vivarium for these studies. The dogs were physically examined for disease symptoms and only animals that appeared healthy and had a normal ECG were accepted for the study. One ml of blood was taken and checked for presence of microfilaria using the Knott's test (Knott, 1939) before the experiment. Dogs were anesthetized with pentobarbital Na, 30 mg/kg intravenously, and maintained with intravenous injections of 1.0 mg/kg as necessary to maintain a stable anesthesia. The absence of corneal and plantar reflexes, response to pain, and a respiratory rate of 16-20 breaths/min were used in "titrating" the dog to the desired level of anesthesia.

III. Cardiovascular Measurements

- N. B. 1. See Appendix of protocol for WR-228,258, Dec. 1981, for details of instrument calibration procedures.
2. See Cardiovascular Measurements Section of protocol for WR-228,258, Dec. 1981, for details; procedures were the same except the blood sampling procedures that follow:

IV. Blood Sampling Procedures

A period of about 30 minutes was allowed following surgical and recording instrument preparation for the dog to assume stable cardiorespiratory function.

At this point, the first arterial and venous blood samples (6 ml each) were withdrawn following evacuation of the void volume in the arterial and venous cannulas. The glass syringes used were lubricated with mineral oil and rinsed prior with heparinized saline (500 units/ml). Syringes containing blood were immediately capped with tight-fitting rubber nipples and put in ice until analysis. The first samples drawn were designated as -30 minutes. At time 0, the beginning of the 20 minute i.v. infusion of pH 7.4 phosphate buffer or drug solution at 4 ml/min, another set of blood samples were taken. Additional sets of blood samples were taken at +20, +40, +60, +80, +100, and +120 minutes. Withdrawal of blood was performed by a person other than the operator of the blood gas analyzer. All samples were immediately capped, placed in ice and analyzed by using the Corning, Model 165/2, Blood Gas Analyzer in accordance with the manufacturer's instructions, within the intervening 20 minute period or as rapidly as possible. In addition, she ran three microhematocrits on all blood samples. We established the sensitivity for the Corning Blood Gas Analyzer, Model 165/2 and our precision for analyzing pO_2 , pCO_2 and pH using the test format established by Corning (See Appendix G). We used Curtin Mathison Gas Trak control standard samples for testing the normal, alkalotic and acidotic states for the above indicated variables. Each 6 ml sample was analyzed in triplicate. We identified and eliminated outliers using the technique of Dixon, 1953. A critical alpha

value of 0.10 represents a reasonable, critical value for exclusion of outliers in this study. We entered mean values for blood chemistry variables in the accompanying tables. Raw data entries for the blood chemistry variables remain on file at the investigators' laboratory and in the Archives at the Division of Experimental Therapeutics, WRAIR.

V. Pulmonary Ventilatory Measurements

For the measurement of pulmonary function, while breathing room air unassisted, an endotracheal tube with a side arm was connected directly to a mesh screen Fleish pneumotachograph and the pressure difference across the screen measured by a differential pressure transducer (Validyne transducer, Model MP45-24). This signal, when calibrated against a known air flow, corresponds to tidal airflow rate and, in turn, when integrated, yields tidal volume. An esophageal tube (Porter ID6-5) was inserted into the esophagus for the assessment of intrapleural pressure. The pressure difference between the airway and esophagus, or transpulmonary pressure, was measured by a second differential pressure transducer (Validyne transducer Model MP45-14). Dynamic airway resistance and dynamic airway compliance were derived using a Buxco Electronics Pulmonary Mechanics Computer, Model 6, and were recorded along with tidal volume on a Grass, Model 7b, polygraph.

N.B. 1. See the Pulmonary Ventilatory Measurements Section of the Appendix of protocol of WR 228,258, Dec. 1981, for details of theory for structural program for the derivation of dynamic resistance and dynamic compliance and the appropriate calibration procedures for each variable using the Buxco computer.

VI. Data Presentation

Samples of analog tracings for cardiovascular and respiratory indices illustrate changes that take place due to primaquine and WR-6026, with respect to baseline and vehicle control. All measurements called for in this study are presented in tabular form using percent change of baseline where baseline equals 100 percent (unless otherwise indicated). Summary graphs have been constructed to show percentage change from baseline (or control) which we established as 100 percent. Variability for each measurement is entered as ± 1 S.E.M. for the mean percent of baseline (unless otherwise indicated). We established baseline at 100% for the variable levels at 0 time. A graphic representation of each variable defines the comparative responses to all dose levels of a test substance with respect to vehicle control (PO₄ buffer). A composite of the related single variables, one for the cardiovascular system and one for the respiratory system for each test substance, facilitates an understanding of response mechanisms for these organ systems to the intravenous infusion of the test substance.

RESULTS

Pulmonary Function

A summary of all baseline (time zero) data as absolute values appears in Table 1 (appendix B). The raw experimental data for each dog is given in tables of Appendix F.

Baseline values for respiratory rate in the seven experimental groups ranged from 5.2 ± 1.0 to 8.6 ± 1.8 cycles/min (Table 1). Phosphate buffer vehicle infusion appeared to cause an increase in respiratory rate, perhaps due to an

effect of volume or to constituents of the buffer. Infusion of 1.0 μ moles/kg/min of WR-6026 increased the respiratory rate prominently over the first 10 minutes of infusion, but the rate was about that of the control group from +20 min on (Fig 1a). Both the higher dose-rates of WR-6026 increased respiratory rate as much as 180% above control values at +20 mins.; this tachypnea was maintained. Primaquine at the two lower dose-rates did not alter respiratory rate (Fig 1b). The 1.75 μ moles/kg/min dose-rate produced a transient elevation of rate of about 100% during the infusion. This tachypnea waned quickly with the cessation of infusion.

Baseline tidal volume values for these groups at time zero ranged from 249 ± 13 ml/breath to 370 ± 71 ml/breath and, in general, correlated with weights of the dogs. Tidal volume dropped by about 20% during infusion of PO_4 buffer. The 1.0 μ moles/kg/min dose-rate of WR-6026 had no effect on tidal volume but the middle dose-rate infusion was associated with about a 15% depression of this variable (Fig 2A). Tidal volume tended to be depressed by the high dose-rate but responses were quite variable. Primaquine at the high dose-rate also depressed tidal volume; but the other dose-rates did not produce any significant change (Fig 2B).

Minute volume, which is the product of the average tidal volume and respiratory rate, was increased by WR-6026. At zero time the baseline values for the experimental groups ranged from 1.54 ± 0.25 to 2.68 ± 0.46 l/min (Table 1). All dose-rates of WR-6026 produced a similar peak rise in minute volume at +10 min. (Fig 3A). Minute volume for the upper dose-rate groups remained elevated throughout the rest of the observation period; minute volume for the low dose group returned towards control values by the end of the infusion. Primaquine had no significant effect upon minute volume (Fig 3B).

Airways compliance remained fairly stable in the control group given phosphate buffer (Fig 4A&B); baseline values for the experimental groups ranged from 18.8 ± 3.1 to 35.3 ± 8.0 cu (Table 1). WR-6026 had no apparent effect upon airways compliance at any dose-rate (Fig 4A). Primaquine appeared to increase airways compliance at the lower dose-rate (from +30 to +50 mins.), but depressed airways compliance at the middle dose. The high dose-rate of primaquine had no effect (Fig 4B).

Airways resistance for the seven experimental groups at baseline time point (time 0) ranged from 5.6 ± 2.8 to 12.5 ± 3.7 ru (Table 1); phosphate buffer infusion (control) tended to depress resistance, but values were quite variable. The two higher dose-rates of WR-6026 depressed airways resistance over the entire experimental period; the low dose-rate of WR-6026 had no effect (Fig 5A). Primaquine had no obvious action on airways resistance (Fig 5B).

Blood oxygen tension in arterial samples was not affected by either WR-6026 or primaquine (Figs 6A&B). Venous blood oxygen was also not affected by these drugs (Figs 7A&B).

Blood carbon dioxide tension tended to drop in all groups during the infusion period (Figs 8A&B and 9A&B). There were, however, no apparent drug-related effects.

Blood pH values remained essentially the same throughout the experimental period for each of the groups (Figs 10A&B and 11A&B). There was some variability in values among the groups. Venous blood hematocrit was not affected by any of the drug treatments (Figs 12A&B).

Cardiovascular Function

Baseline heart rate ranged from 138 ± 10 to 165 ± 23 beats/min (Table 1). Phosphate buffer infusion tended to depress heart rate. WR-6026 had no effect on heart rate except, perhaps, causing a small rise after +10 min of the high dose-rate (Fig 13A). Primaquine given at both the high and low dose-rates had no action upon heart rate; the middle dose, however, appeared to elevate heart rate by about 20% (Fig.13B).

Diastolic blood pressure at zero time ranged from 106 ± 9 to 119 ± 11 mmHg (Table 1). This variable dropped by about 10 - 15% in the control group over the course of the experimental period (Fig. 14A and 14B). The middle and high dose infusion of WR-6026 transiently depressed diastolic blood pressure by about 20 - 25%. The low dose group demonstrated a stable diastolic pressure over time (Fig 14A). Primaquine did not affect diastolic blood pressure at the dose-rates tested (Fig 14B).

Systolic blood pressure values at time zero range from 162 ± 12 to 186 ± 17 mmHg (Table 1). Neither WR-6026 nor primaquine altered systolic blood pressure at the dose-rates tested (Figs 15A&B). --

Cardiac contractile force, as indicated by left ventricular (LV) dP/dt (Figs 16A&B), waned slightly in the controls during the infusion of phosphate buffer but stabilized after +30 min. Baseline (Time 0) values for LV dP/dt ranged from 1710 ± 450 to 3020 ± 380 mmHg/sec in the seven groups (Table 1). LV dP/dt was severely depressed by the upper two dose-rates of WR-6026 (Fig 16A). Contractility was maximally depressed at the end of the infusion to 50% and 42% of baseline. Recovery from the effects of these dose-rates was slow and only partial to 60% of baseline. The low dose-rate of WR-6026 did not

depress cardiac contractility. In contrast, primaquine at all doses tested did not acutely affect LV dP/dt (Fig 16B). LV dP/dt, however, gradually fell from +80 to +120 min in the primaquine-treated groups.

Cardiac Output values at zero time ranged from 1.54 ± 0.17 to 1.95 ± 0.21 l/min (Table 1). Cardiac output in the control group was maintained until about +90 min when it began to fall (Figs 17A&B). The high dose-rate of WR-6026 appeared to depress cardiac output by about 20% at the end of the infusion; the middle dose-rate depressed cardiac output markedly, also, during infusion. In general, cardiac output was depressed during the middle of the infusion period in the 2 elevated doses (Fig 17A). The low dose-rate of WR-6026 was without effect. Primaquine had no effect on cardiac output (Fig 17B).

Pulmonary artery pressure (PAP) was prominently elevated during the infusion of the high dose-rate of WR-6026 (Fig 18A); PAP, in this group, returned to baseline levels by about +50 mins. The low and middle dose also elevated PAP by +20 mins but the magnitude of the response was considerably less. Primaquine modestly elevated PAP at the middle and high dose-rate; the low dose had no action on PAP (Fig 18B). Baseline PAP values ranged from 9.4 ± 1.5 to 16.5 ± 3.0 mmHg (Table 1). Phosphate buffer infusion appeared to depressed PAP.

Pulmonary Vascular Resistance (PVR) changes were, in general, similar to those of pulmonary artery pressure. Baseline values ranged from 5.5 ± 0.8 to 9.2 ± 1.6 mmHg/l/min (Table 1). The low dose-rate of WR-6026 did not significantly alter PVR (Fig 19A). The higher doses, however, caused prominent elevations of PVR during the infusion; PVR in these groups rapidly

returned to baseline values after the WR-6026 infusion, but tended to remain slightly above values in the control group. Primaquine at the upper two dose-rates produced only a modest elevation of PVR (Fig 19B). The low dose group for primaquine displayed a response similar to that observed for control vehicle infusion, a slow gradual fall.

Pulmonary wedge pressure (PWP) values at time zero ranged from 1.4 ± 0.8 to 3.5 ± 1.2 mmHg among the groups (Table 1). Phosphate buffer infusion did not alter PWP. The high and middle dose-rates of WR-6026 caused marked rises in PWP; PWP returned toward baseline values over 40 min after the infusion (Fig 20A). The low dose of WR-6026 produced only a modest rise in PAP. Primaquine infusion produced rises in PWP, but the magnitude of the effect was considerably less than that observed with WR-6026 (Fig 20B). The rise in PWP due to the high dose infusion was the most prominent (3.5 mmHg).

Electrocardiographic Effects

WR-6026, 4 $\mu\text{mole/kg/min}$, did not cause any abnormal beats in any animals; there was no change in rhythm or QRS configuration; and no significant alteration in P-wave, T-wave, or electrical axis of the ventricle (Table 2). There was a 75% increase in QRS width, a 42% increase in P-R interval, and a 43% increase in Q-T interval by the end of drug administration. These effects waned following the infusion. Even with the maximum change in duration of the P-R, Q-T intervals, & QRS, these values are within the normal range of values for dogs (Crawley and Swenson, 1966).

Primaquine, 1.75 $\mu\text{mole/kg/min}$ caused similar but somewhat lesser changes in P-R interval (increased 30%), in QRS width (increased 33%), and Q-T

interval (increased 10%) at + 20 min. These changes also diminished soon after the infusion. Primaquine did not alter the QRS configuration, P-wave, T-wave, or electrical axis of the ventricle. One dog in the high dose group developed a sustained run of ventricular flutter and tachycardia during the drug infusion which reverted after 25 minutes. Pilot experiments indicated that a 2.0 μ mole/kg/min dose of primaquine produces this arrhythmia. The vehicle infusion caused no consistent or significant changes, with the possible exception of a 14% decrease in heart rate.

The overall effects of WR-6026 on the EKG were rather modest at the high dose. The increase in P-R interval indicates some interference with A-V transmission and the prolongation of the QRS width and Q-T interval suggests a depression of ventricular conduction and repolarization. However, none of these changes resulted in development of ectopic beats or a change in rhythm. Primaquine, on the other hand, did cause ventricular flutter and tachycardia in one animal, even though conduction changes were smaller than those from WR-6026.

Representative tracings of EKG leads I, II and III for each of the experimental groups is given in Figure 21.

SUMMARY OF CARDIOVASCULAR COMPOSITE DATA

WR-6026 (Composite Figures 1 and 2)

Heart rate changes with the three dose levels did not follow a dose-response pattern and were of minor importance. Systolic blood pressure gradually declined by some 10 - 15% and a similar decline was seen in the vehicle control group. Again, a strict dose-response pattern was not seen.

However, diastolic blood pressure did decrease more than the control group during drug infusion at the high dose, and possibly at the middle dose also. No fall in diastolic blood pressure was seen at the low dose; on the contrary, it tended to remain slightly above the controls. Cardiac outputs drifted downwards some 20 to 30% over the experimental period, including the control group. The low dose group was quite similar to the control group, while the upper two dose groups were below control most of the experimental period, with the middle group being the lowest. The one measurement that was clearly affected the most was contractile force. Control dP/dt decreased about 15-20% over 2 hours and the lower dose group closely paralleled the control. The middle and high doses caused a maximum fall in contractile force during the infusion of about 50%, and these two groups were only different from each other for a short period near the end of the first hour. Even after two hours, the dP/dt was still down to 60% of control, indicating a long lasting weakening of contractile force.

In the pulmonary vascular bed, arterial pressure was above control values at all three dose levels for the first hour, and this was especially prominent with the high dose. The middle and high doses also caused a sharp rise in wedge pressure, lasting at least an hour. Pulmonary vascular resistance was significantly elevated by the two higher doses. Resistance quickly recovered to a plateau near the zero time value but was still above the control group. The decrease in contractile force, causing an overfilling of the left atrium, is reflected in the sudden increase in wedge pressure. A considerable vasoconstriction of the pulmonary bed is indicated by the prominent increase in resistance to the two higher doses.

Primaquine (Composite Figures 3 and 4)

The middle dose of primaquine produced a modest increase of some 15% in heart rate, bordering on significance. However, the high and low doses were not different from, and closely parallel to, the control group. No important changes in either systolic blood pressure or diastolic blood pressure occurred during the infusion, although during the last 20 minutes or so of the experiment both pressures were somewhat above controls at the 1 μ M low dose. Contractile force declined steadily at all dose levels but was only prominently depressed during the last 30 minutes. Since the greatest effect was caused by the lowest dose, no dose-effect relationship was seen. Cardiac output progressively declined with all groups, including the controls. Thus, no significant homodynamic effects were seen.

Pulmonary artery pressure fell about 30% during infusion of the vehicle. The low dose of primaquine produced similar changes, but the middle and high dose resulted in an elevation of pulmonary artery pressure during the infusion with the high dose causing the greatest effect. The middle dose response recovered in about 40 to 50 minutes while the pressor response to the high dose was still evident at the conclusion of the experiment. Wedge pressure was elevated by all three doses. Responses to the low and middle doses waned within 60 minutes. The high dose produced the greatest rise but pressure had quickly recovered by 40 minutes and fell below control during the last hour.

Primaquine exhibited dose-effect responses in the pulmonary vascular bed, in contrast to the systemic vascular system. Pulmonary resistance was unaffected by the low dose; modestly increased by the middle dose; and

significantly increased by the high dose. The changes in pulmonary resistance seemed to be persistent, and above control at the end of the experiment.

SUMMARY OF RESPIRATORY COMPOSITE DATA

WR-6026 (Composite Figure 5)

A prompt and marked increase in respiratory rate was produced by all dose-rates of WR-6026 tested; the minute volume was elevated with the profile of changes for these dose-rates against time being quite similar to the pattern for respiratory rate. The upper two dose-rates produced elevations in these variables which endured for the entire experimental period. Tidal volume was only transiently diminished during drug infusion.

Airway resistance dropped during the infusion of the upper two dose-rates; the same groups which exhibited the marked rises in respiration rate and tidal volume. As was noted for these latter variables, the depression in resistance was maintained for the entire experimental period. Airways compliance was not affected by this drug.

Primaquine (Composite Figure 6)

Only the high dose-rate of primaquine elevated respiratory rate and only during the drug infusion. Because tidal volume fell during this period, minute volume was not affected.

Airways resistance was not altered by primaquine. This drug, however, may have varied actions on airways compliance, elevating compliance at a low dose and depressing it at a higher dose.

DISCUSSION

It is clear from our data that both WR-6026 and primaquine produce steep dose-response curves for cardiopulmonary actions; both possess a maximum tolerated dose/minimum effective toxic dose ratio of about 4. On a molar basis, two times more of WR-6026 is required to produce cardiopulmonary toxic responses than primaquine. The most dangerous effect of WR-6026 is progressive depression of cardiac contractility to the point of ineffective cardiac pumping. In contrast, the potentially lethal action of primaquine is upon cardiac rhythm.

Pulmonary: WR-6026 possesses a greater ability to raise respiratory rate than does primaquine. The mechanism for the maintained tachypnea produced by the upper doses of WR-6026 is unknown. However, no other aminoquinoline studied so far has such potential [see studies of Caldwell and Nash on WR-228,258 (1982) and WR-184, 806 (1978)].

The tachypnea produced by both drugs was, in general, associated only with a modest fall in tidal volume. Thus minute volume, the product of tidal volume and rate, was prominently elevated by administration of WR-6026. This increase in pulmonary air movement was not associated with a drug-related fall in blood carbon dioxide tension.

Neither drug had remarkable actions on airways compliance. Primaquine may have exerted a biphasic action, which depended on dose. The lower dose-rate slightly raised compliance while the middle dose depressed it. The mechanism for such actions is not apparent; primaquine did not exert prominent effects upon the pulmonary vasculature which might be involved in altering airways compliance.

Airways resistance was decreased throughout the observation period by the middle and upper dose-rate of WR-6026. This effect might be considered beneficial. Such an action is unusual for the quinolines with which we have experience. Mefloquine causes a prominent and dose-related elevation of airways resistance (Caldwell and Nash, 1976). WR-228,258 did not produce changes in airway resistance (Caldwell and Nash, 1982). Whatever the mechanism for reduced airways resistance, it does not appear to involve β -adrenergic receptors as changes in cardiovascular functions expected in response to β -adrenergic agonists and sympathetic nerve stimulation were not observed.

Blood gas tension was not affected remarkably by either drug. The only possible exception was an apparent rise in venous P_{O_2} at the end of the high dose-rate infusion of primaquine. The change was not striking in graphic data of averages, but was apparent with inspection of data from individual experiments. These observations suggest primaquine may depress peripheral O_2 utilization.

Cardiovascular: None of the heart rate changes in this study were impressive. WR-6026 produced a small decrease at the end of the perfusion, as did the vehicle. With primaquine, there were only minor fluctuations with the high dose, although the $1.0 \mu\text{mole/kg/min}$ dose caused a small increase of borderline significance. There is little to indicate any important effects of WR-6026 on the automaticity of the heart, either directly or indirectly via the autonomic nervous system.

Over the period of the experiment systolic and diastolic blood pressures tended to drift downward with the vehicle group. The initial vasodepression

by WR-6026 was transient as blood pressure recovered rather promptly after the end of the infusion and neither WR-6026 nor primaquine produced any lasting effect on blood pressure. It seems that neither drug has any prominent or persistent vasodilating action.

WR-6026 produced a clear-cut depression of contractile force which began with the initiation of the middle and high dose infusions, and reached maximum depression at the end of the infusion. This indicates a direct cardiac depressant action by WR-6026 which is persistent since there was only a partial recovery of contractility during the 20 minutes after the infusion, and a stable lower level was maintained from about 40 minutes to 120 minutes. Primaquine was distinctly different since it did not cause any changes in dP/dt during the infusion, although a slow, steady decrease in contractile force had just reached a significant difference at the end of the experimental period. Primaquine, thus, may have a degree of cardiac depression of slow onset; however, WR-6026 definitely causes cardiac weakening with an immediate onset.

It is well documented that the anesthetized dog under barbiturates will experience a gradual fall in cardiac output over a period of a few hours (Nash, 1956). In this study the vehicle group confirmed previous findings in this regard. Primaquine infusions resulted in decreases in cardiac output which closely paralleled the vehicle group; indicating that primaquine had no significant effect on cardiac output. WR-6026 tended to reduce cardiac output at the two higher doses. It is probable that the reductions in cardiac output are related to the depression of myocardial contractile force and changes in total vascular resistance produced by WR-6026.

In the pulmonary vascular bed, WR-6026 raised the pulmonary artery pressure in a dose-related manner during the drug infusion. The pressor effect declined rather promptly with cessation of infusion and was not different from the vehicle group from about +60 minutes to the end of the experiment. Primaquine had a similar effect and the PAP elevation at the high dose was definitely longer lasting. Both drugs appear capable of causing pulmonary vasoconstriction in a dose-related manner. They differ in that WR-6026 has a strong acute effect of short duration while primaquine has an initial effect of lesser intensity but is more prolonged and even tends to increase with time as indicated by the data on pulmonary vascular resistance.

Pulmonary wedge pressure is an indirect indicator of left atrial pressure. Primaquine infusion initially raised PWP as the drug was increased. WR-6026 in the two higher doses resulted in a considerable increase in PWP which recovered within 40 to 50 minutes. These data indicate that blood was backing up in the left atria due to the depression of contractile force, and WR-6026 was more active in these doses than primaquine.

The electrocardiograms indicated that WR-6026, and to a lesser degree primaquine, produced a slowing in A-V transmission and a slowing in ventricular conduction. However, it is doubtful if the changes seen at these doses are of great significance in themselves, since the values were still within the range of normal measurements (Crawley and Swenson, 1966). On the other hand, it does indicate that both drugs have the potential for interfering with transmission and conduction. The outstanding finding was the development of serious ventricular arrhythmias by primaquine. One animal in the primaquine group had an episode of ventricular flutter/tachycardia lasting

for 25 minutes. In two other dogs in the range-finding experiments, primaquine caused fatal and near fatal ventricular arrhythmias. In contrast, no such events were seen with WR-6026.

Conclusions: WR-6026 may produce prominent depression of cardiac contractility, elevate respiratory rate and depress airways resistance. Primaquine has far less prominent actions on cardiovascular, hemodynamic, and pulmonary variables. Both agents slow A-V nodal and ventricular conduction velocity; primaquine, however, may produce dangerous ventricular arrhythmias.

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COMPARISON OF CARDIOVASCULAR AND PULMONARY EFFECTS
OF

WR-6026-2HCl and PRIMAQUINE DIPHOSPHATE

March 2, 1984

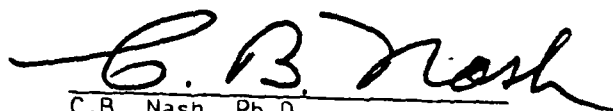
These studies were conducted in accordance with current Good Laboratory Practice Regulations of the Food and Drug Administration, dated December 22, 1978, with subsequent amendments.



R.W. Caldwell, Ph.D.
Study Director



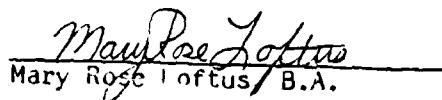
K.U. Malik, Ph.D., D.Sc.
Quality Assurance Officer



C.B. Nash, Ph.D.



Terry R. Thomas, B.S.



Mary Rose Loftus, B.A.

APPENDIX A
LEGEND OF TERMS USED

<u>Abbreviation</u>	<u>Definition</u>
TV-ml/breath	Tidal Volume-ml/breath
Resp-breaths/min	Respiration Rate-breaths/min
MV-l/min	Minute Volume-liters/min
C-cu	Respiratory Dynamic Compliance-compliance units
R-ru	Respiratory Dynamic Resistance-respiratory units
SBP-mmHg	Aortic Systolic Blood Pressure-mmHg
DBP-mmHg	Aortic Diastolic Blood Pressure-mmHg
ABP-mmHg	Aortic Blood Pressure
HR-beats/min	Heart Rate-beats/min
C.O.-l/min or CO	Cardiac Output-liters/min
dP/dt-mmHg/sec	Acceleration of pressure, a quantitative expression for defining contractility of the heart
PWP-mmHg	Pulmonary Wedge Pressure - an estimate of left atrial pressure
PAP-mmHg	Pulmonary Artery Pressure
PVR-mmHg/1/min	Pulmonary Vascular Resistance
A-Po ₂ -mmHg	Arterial Blood Oxygen Tension
A-Pco ₂ -mmHg	Arterial Blood Carbon Dioxide Tension
A-pH	Arterial Blood pH
V-Po ₂ -mmHg	Venous Blood Oxygen Tension
V-Pco ₂ -mmHg	Venous Blood Carbon Dioxide Tension
V-pH	Venous Blood pH
Hct-% cells	Hematocrit-% Red Blood Cells

Appendix B
Tables 1 and 2

Table 1
baseline values $\pm$ 1 S.E.M.

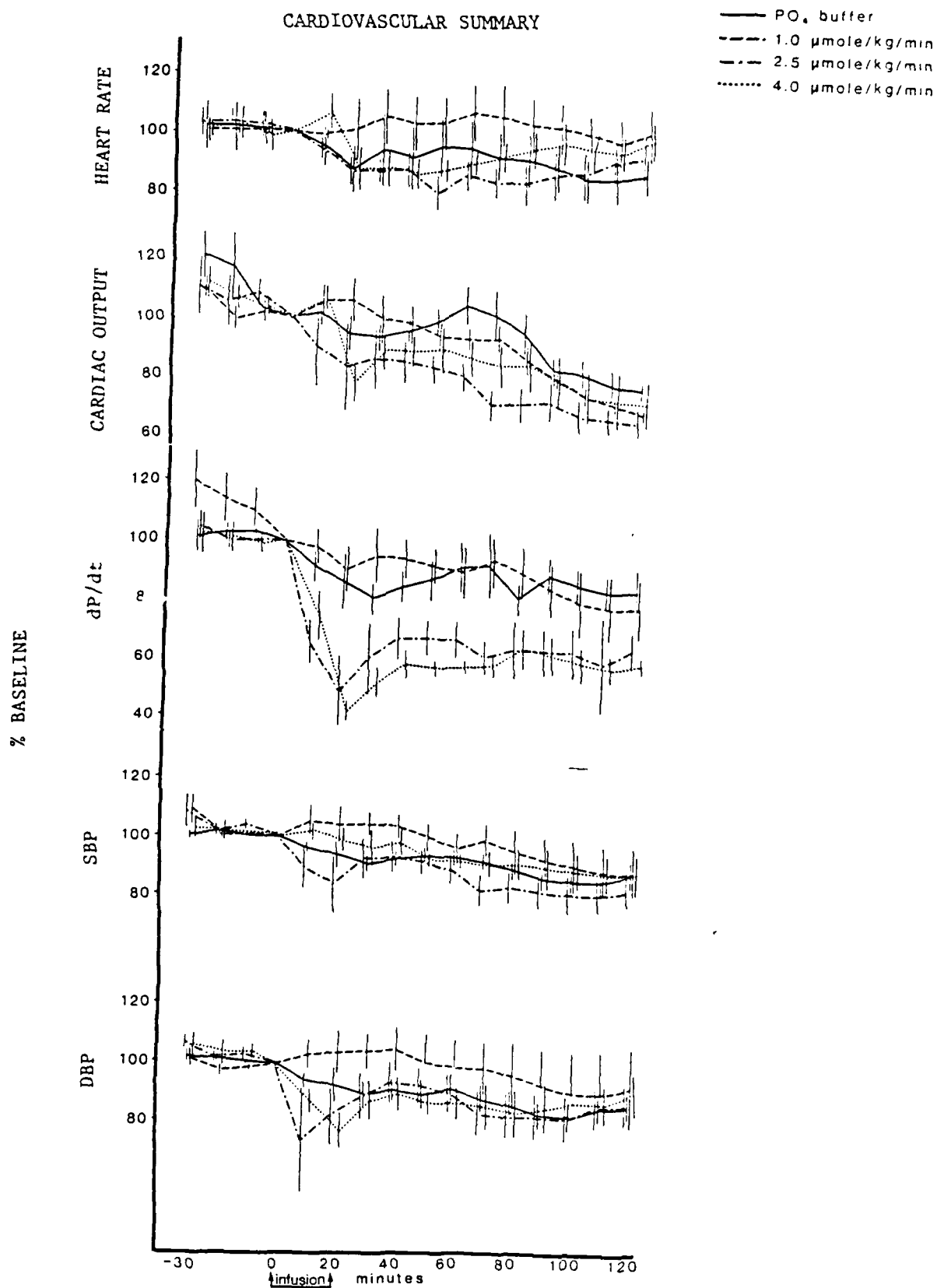
	PO ₄ -buffer	WR-6026 1.0 μ mole/kg/min	WR-6026 2.0 μ mole/kg/min	WR-6026 4.0 μ mole/kg/min	Primaquine 0.5 μ mole/kg/min	Primaquine 1.00 μ mole/kg/min	Primaquine 1.75 μ mole/kg/min
TV-ml/breath	333 $\pm$ 60	306 $\pm$ 34	356 $\pm$ 36	342 $\pm$ 52	269 $\pm$ 34	370 $\pm$ 71.4	249 $\pm$ 13
Resp-breaths/min	8.0 $\pm$ 2.8	6.2 $\pm$ 1.3	5.6 $\pm$ 0.9	8.6 $\pm$ 1.8	8.5 $\pm$ 2.2	5.2 $\pm$ 1.0	6.1 $\pm$ 0.8
MV-l/min	2.09 $\pm$ 0.30	1.79 $\pm$ 0.30	2.00 $\pm$ 0.41	2.68 $\pm$ 0.46	2.11 $\pm$ 0.59	1.70 $\pm$ 0.17	1.54 $\pm$ 0.25
C-cu	31.3 $\pm$ 8.0	35.3 $\pm$ 8.0	18.8 $\pm$ 3.1	24.0 $\pm$ 6.0	22.9 $\pm$ 7.5	21.5 $\pm$ 4.4	26.3 $\pm$ 5.1
R-ru	11.2 $\pm$ 7.6	9.0 $\pm$ 7.0	5.9 $\pm$ 1.0	12.5 $\pm$ 3.7	6.4 $\pm$ 3.3	11.2 $\pm$ 3.8	5.6 $\pm$ 2.8
SBP-mmHg	162 $\pm$ 12	171 $\pm$ 14	173 $\pm$ 11	178 $\pm$ 11	186 $\pm$ 17	183 $\pm$ 20	165 $\pm$ 8
DBP-mmHg	109 $\pm$ 8	106 $\pm$ 9	116 $\pm$ 3	110 $\pm$ 10	113 $\pm$ 10	119 $\pm$ 11	115 $\pm$ 6
HR-beats/min	165 $\pm$ 23	152 $\pm$ 13	159 $\pm$ 11	156 $\pm$ 15	160 $\pm$ 15	138 $\pm$ 10	155 $\pm$ 14
C.O.-l/min	1.54 $\pm$ 0.17	1.71 $\pm$ 0.18	1.62 $\pm$ 0.10	1.64 $\pm$ 0.07	1.75 $\pm$ 0.13	1.95 $\pm$ 0.21	1.58 $\pm$ 0.15
dP/dt-mmHg/sec	1710 $\pm$ 450	2560 $\pm$ 330	2400 $\pm$ 530	2580 $\pm$ 360	3020 $\pm$ 380	2330 $\pm$ 400	2470 $\pm$ 390
PWP-mmHg	2.4 $\pm$ 0.9	2.5 $\pm$ 0.8	3.5 $\pm$ 1.2	1.4 $\pm$ 0.8	2.2 $\pm$ 1.1	3.2 $\pm$ 1.2	1.7 $\pm$ 1.0
PAP-mmHg	13.8 $\pm$ 2.2	9.4 $\pm$ 1.5	12.5 $\pm$ 2.4	12.7 $\pm$ 2.2	14.5 $\pm$ 2.2	16.5 $\pm$ 3.0	10.2 $\pm$ 1.4
PVR-mmHg/l/min	9.2 $\pm$ 1.6	5.5 $\pm$ 0.8	7.9 $\pm$ 1.5	7.7 $\pm$ 1.3	8.4 $\pm$ 1.4	8.4 $\pm$ 1.3	6.6 $\pm$ 0.9
A-Po ₂ -mmHg	70.5 $\pm$ 6.3	66.3 $\pm$ 9.6	74.8 $\pm$ 7.2	72.0 $\pm$ 4.3	74.0 $\pm$ 4.6	68.8 $\pm$ 7.0	70.4 $\pm$ 6.9
A-Pco ₂ -mmHg	43.2 $\pm$ 3.2	47.1 $\pm$ 6.0	45.2 $\pm$ 3.3	40.2 $\pm$ 2.7	43.7 $\pm$ 2.7	46.6 $\pm$ 3.0	47.2 $\pm$ 3.5
A-pH	7.306 $\pm$ 0.034	7.251 $\pm$ 0.045	7.298 $\pm$ 0.020	7.296 $\pm$ 0.031	7.312 $\pm$ 0.020	7.250 $\pm$ 0.030	7.276 $\pm$ 0.030
v-Po ₂ -mmHg	45.4 $\pm$ 2.2	41.2 $\pm$ 5.7	44.7 $\pm$ 2.3	38.9 $\pm$ 1.7	45.1 $\pm$ 2.5	40.8 $\pm$ 2.7	43.2 $\pm$ 3.8
v-Pco ₂ -mmHg	47.9 $\pm$ 3.8	53.6 $\pm$ 5.3	52.6 $\pm$ 2.8	48.4 $\pm$ 2.8	48.6 $\pm$ 2.6	54.9 $\pm$ 3.5	52.8 $\pm$ 3.3
v-pH-	7.284 $\pm$ 0.034	7.222 $\pm$ 0.039	7.259 $\pm$ 0.020	7.248 $\pm$ 0.034	7.268 $\pm$ 0.020	7.216 $\pm$ 0.030	7.261 $\pm$ 0.030
Hct-% cells	36.2 $\pm$ 3.1	39.4 $\pm$ 2.6	41.1 $\pm$ 3.2	32.9 $\pm$ 2.5	39.0 $\pm$ 2.67	39.2 $\pm$ 3.34	39.1 $\pm$ 4.1

Appendix C
Composite Summaries

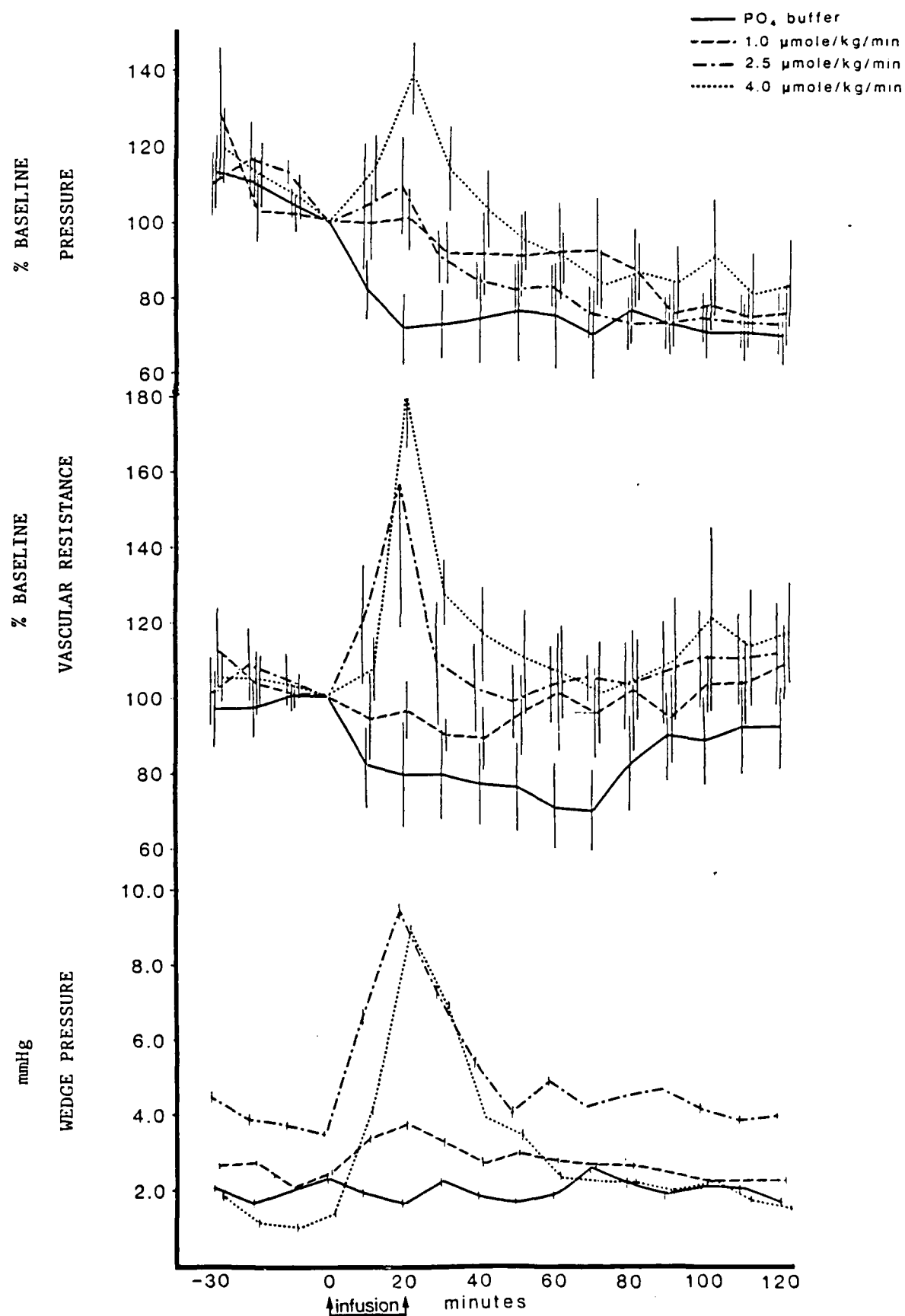
Note: All variation bars represent S.E.M.

WR-6026

CARDIOVASCULAR SUMMARY

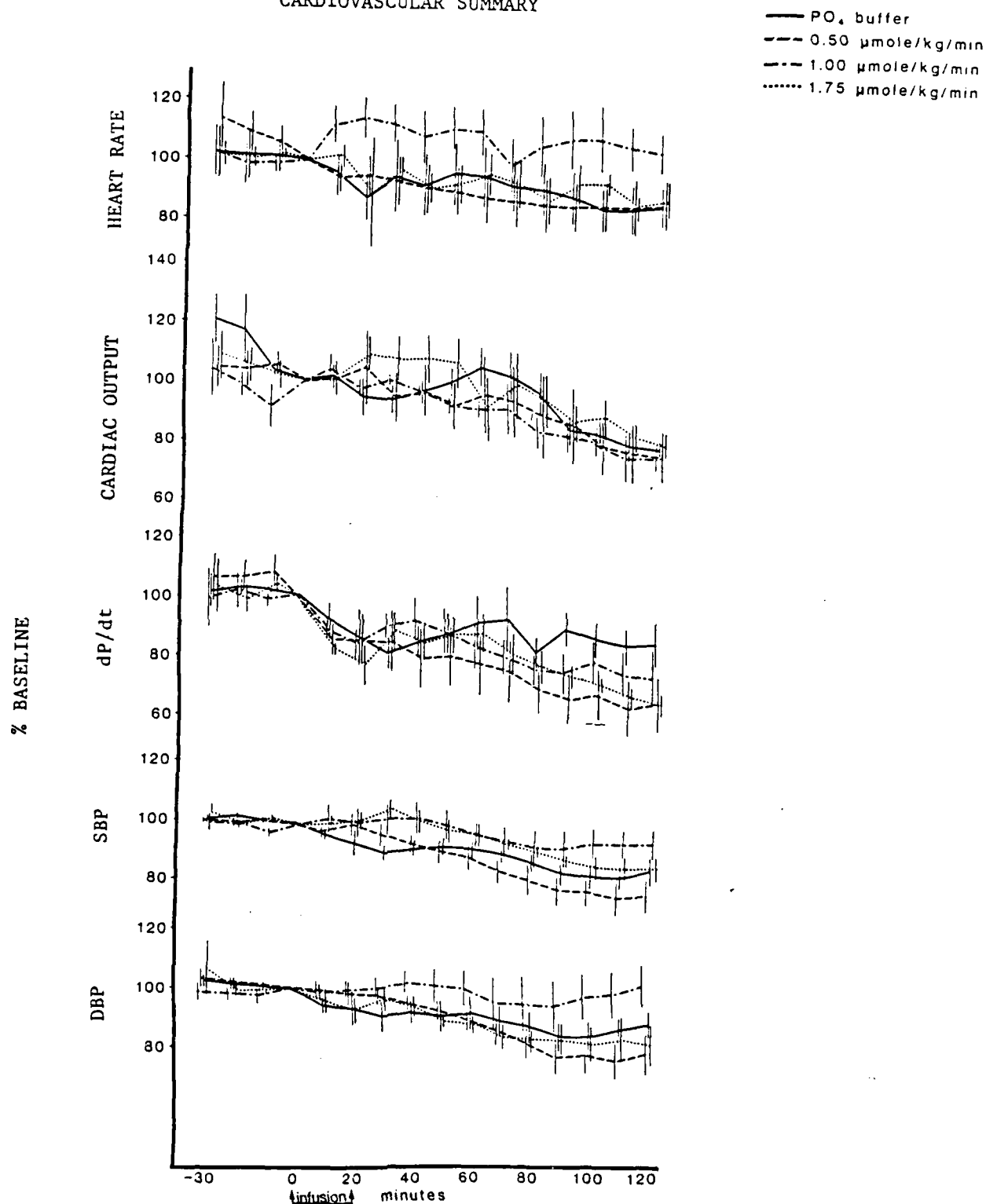


PULMONARY ARTERY SUMMARY



PRIMAQUINE

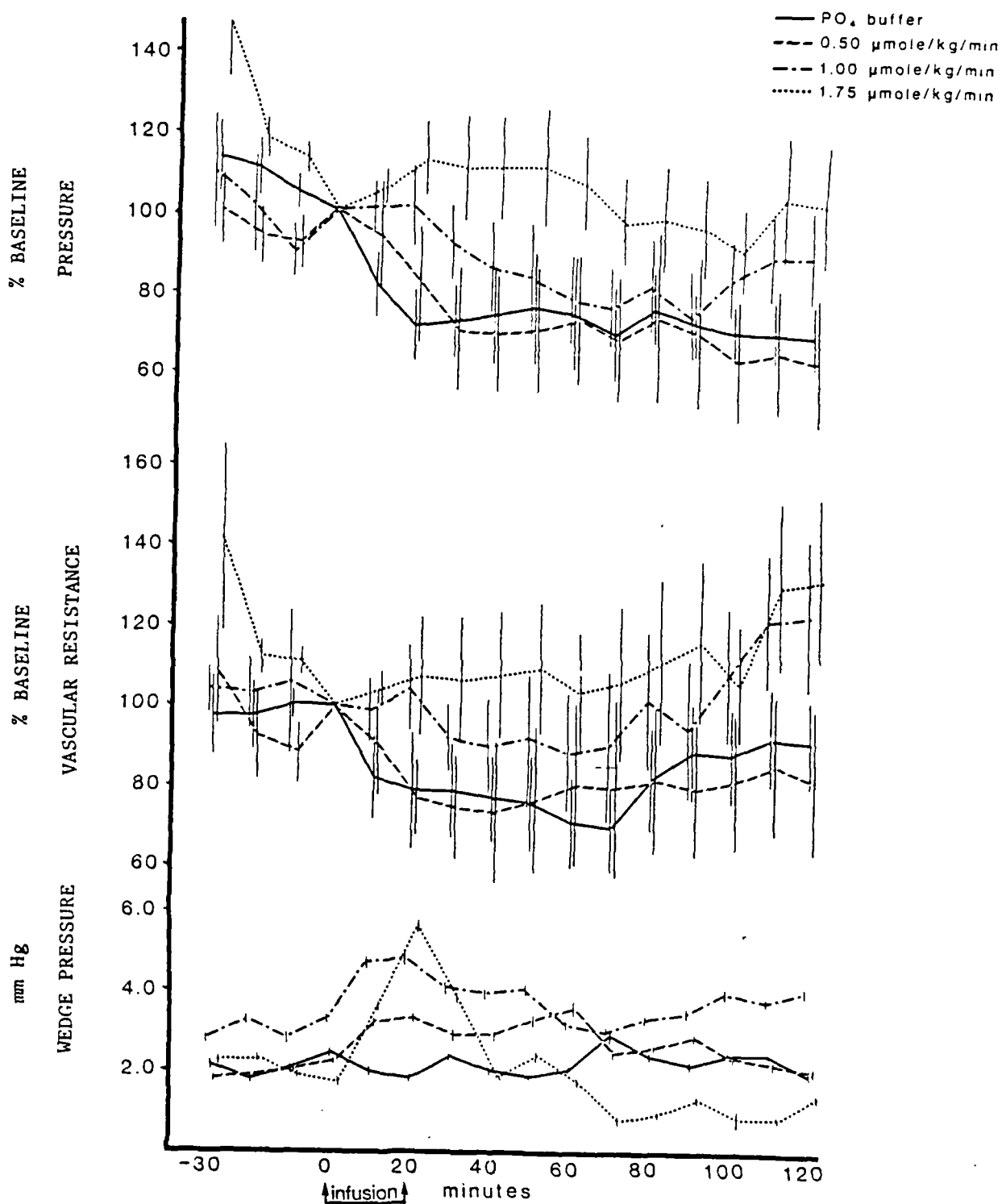
CARDIOVASCULAR SUMMARY



PRIMAQUINE

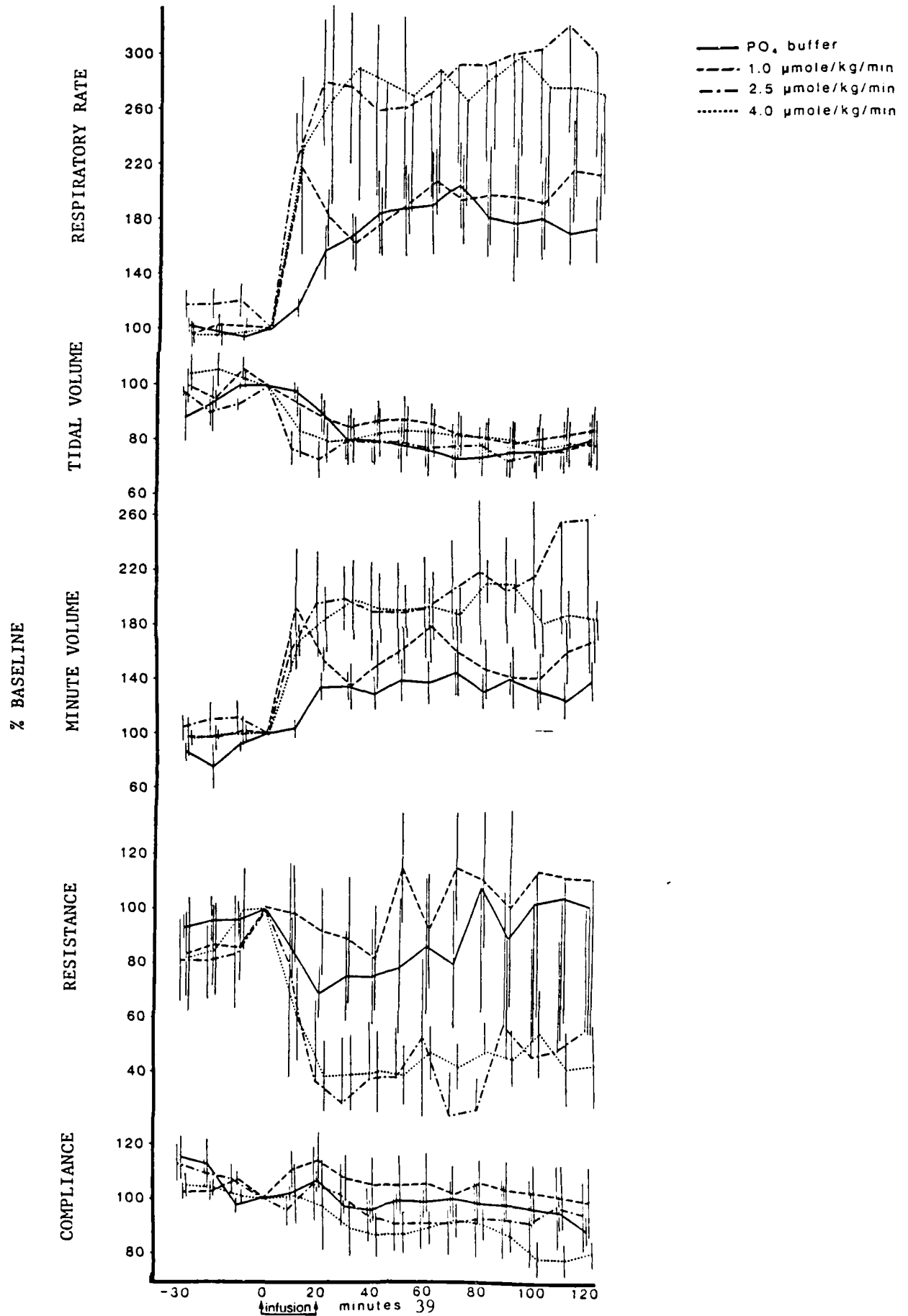
composite fig. 4

PULMONARY ARTERY SUMMARY



RESPIRATORY SUMMARY

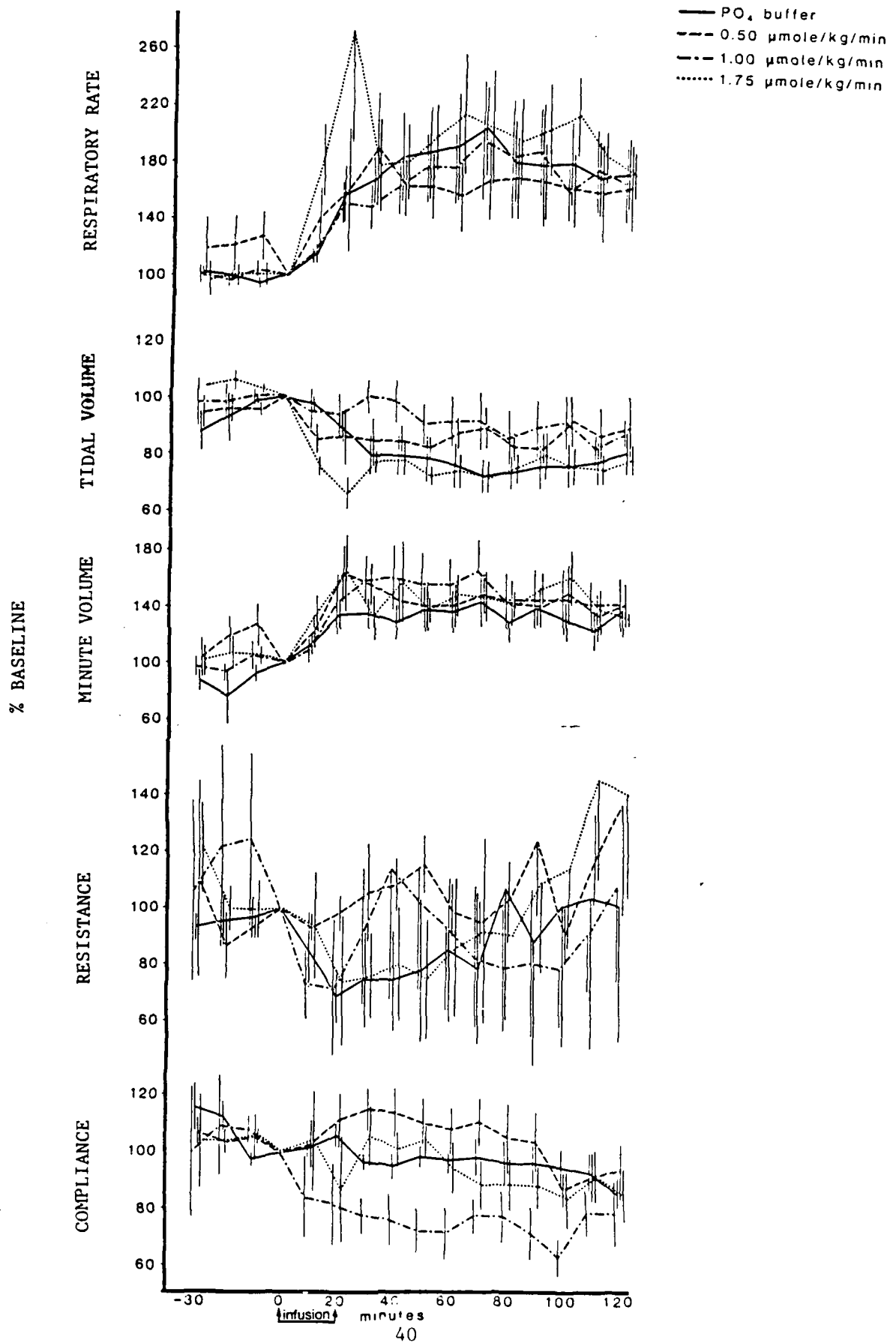
composite fig. 5



PRIMAQUINE

RESPIRATORY SUMMARY

composite fig. 6



APPENDIX D
Variable Plots

Note: All variation bars represent S.E.M.

RESPIRATORY RATE

WR-6026

figure 1A

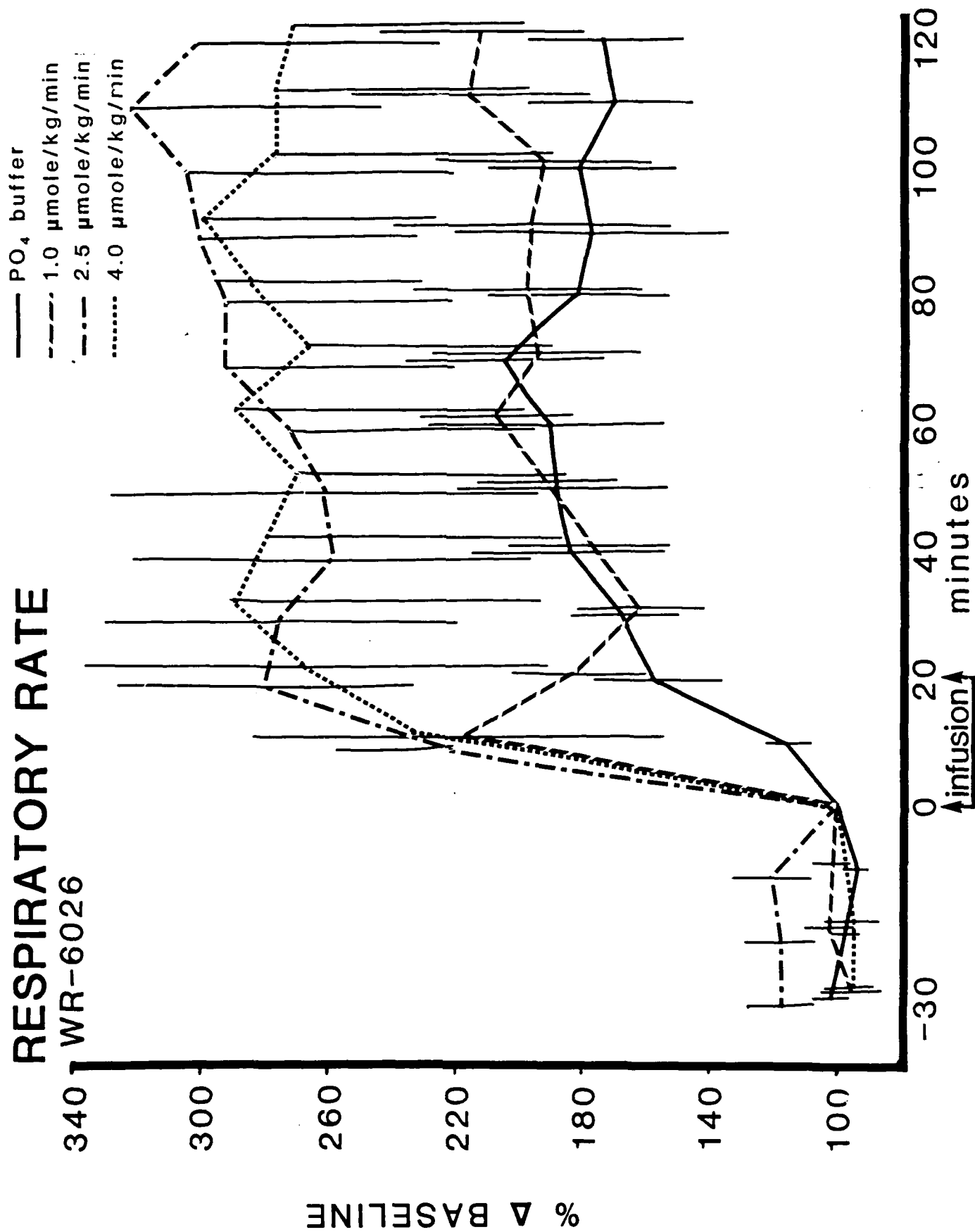
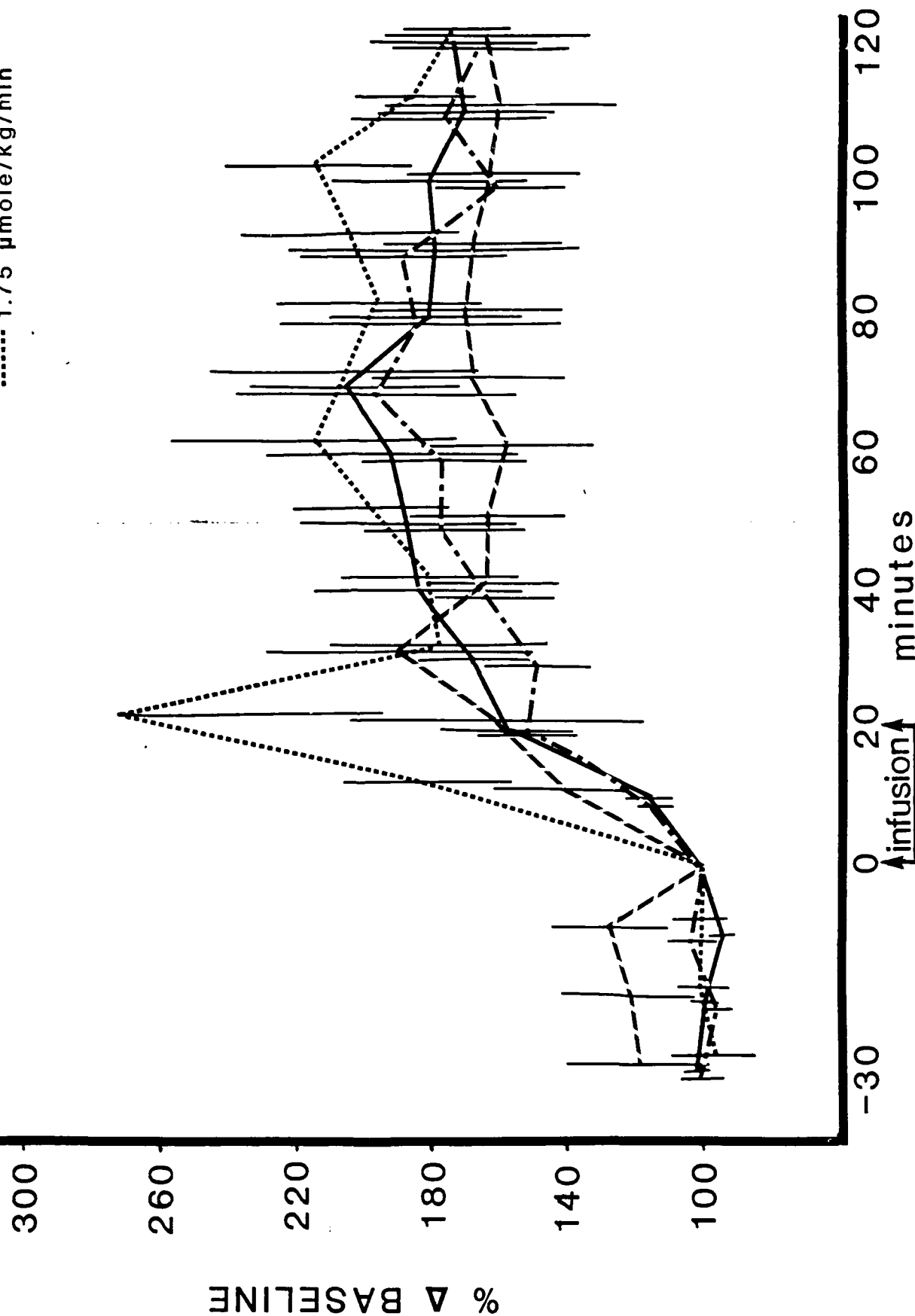


figure 1B

RESPIRATORY RATE

Primaquine

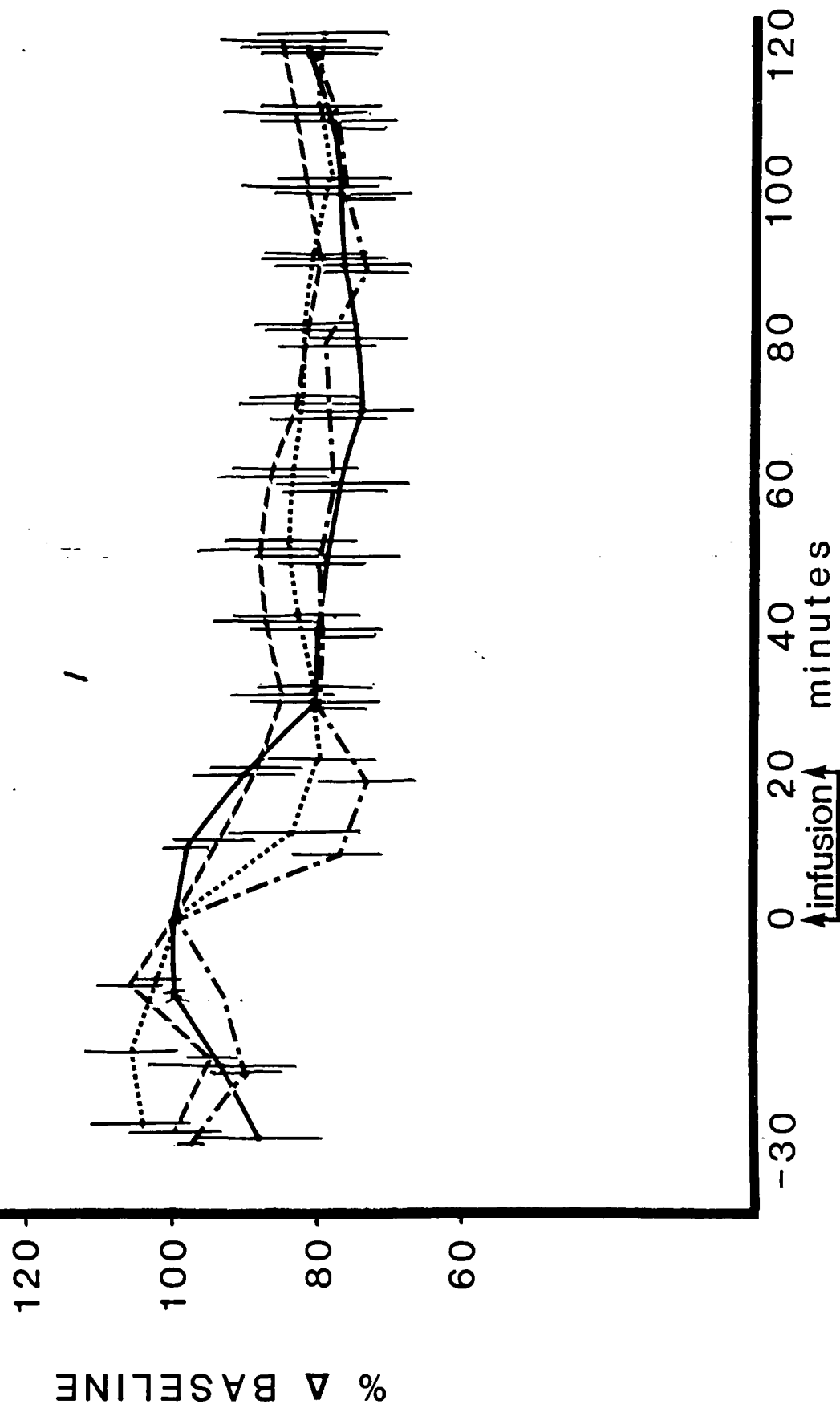
- PO_4 buffer
- - - 0.50 μ mole/kg/min
- · - 1.00 μ mole/kg/min
- · · 1.75 μ mole/kg/min



TIDAL VOLUME WR-6026

figure 2A

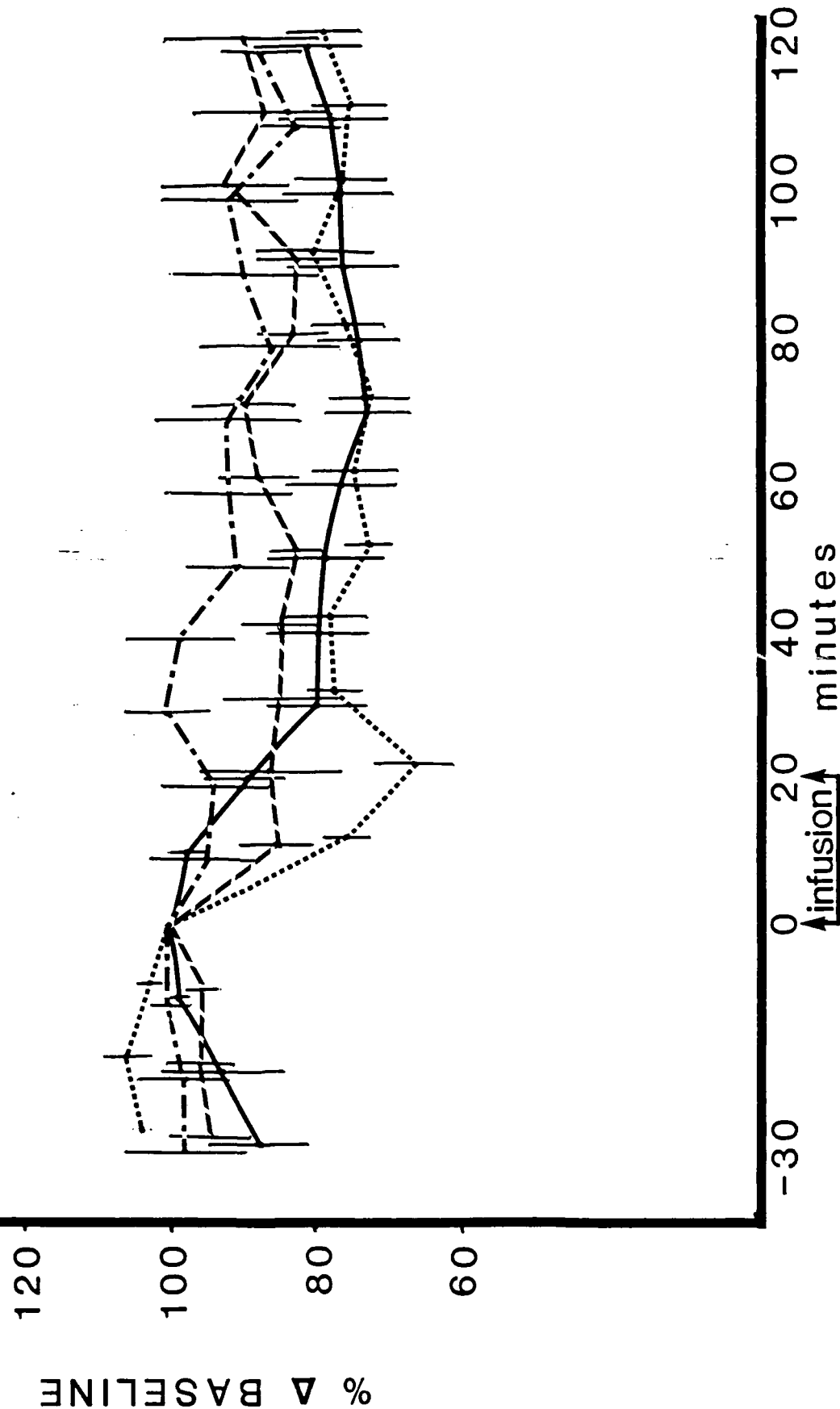
- PO_4 buffer
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- . - 2.5 $\mu\text{mole/kg/min}$
- 4.0 $\mu\text{mole/kg/min}$



TIDAL VOLUME Primaquine

figure 2B

- PO_4 buffer
- - - 0.50 $\mu\text{mole/kg/min}$
- · - · 1.00 $\mu\text{mole/kg/min}$
- · · · 1.75 $\mu\text{mole/kg/min}$

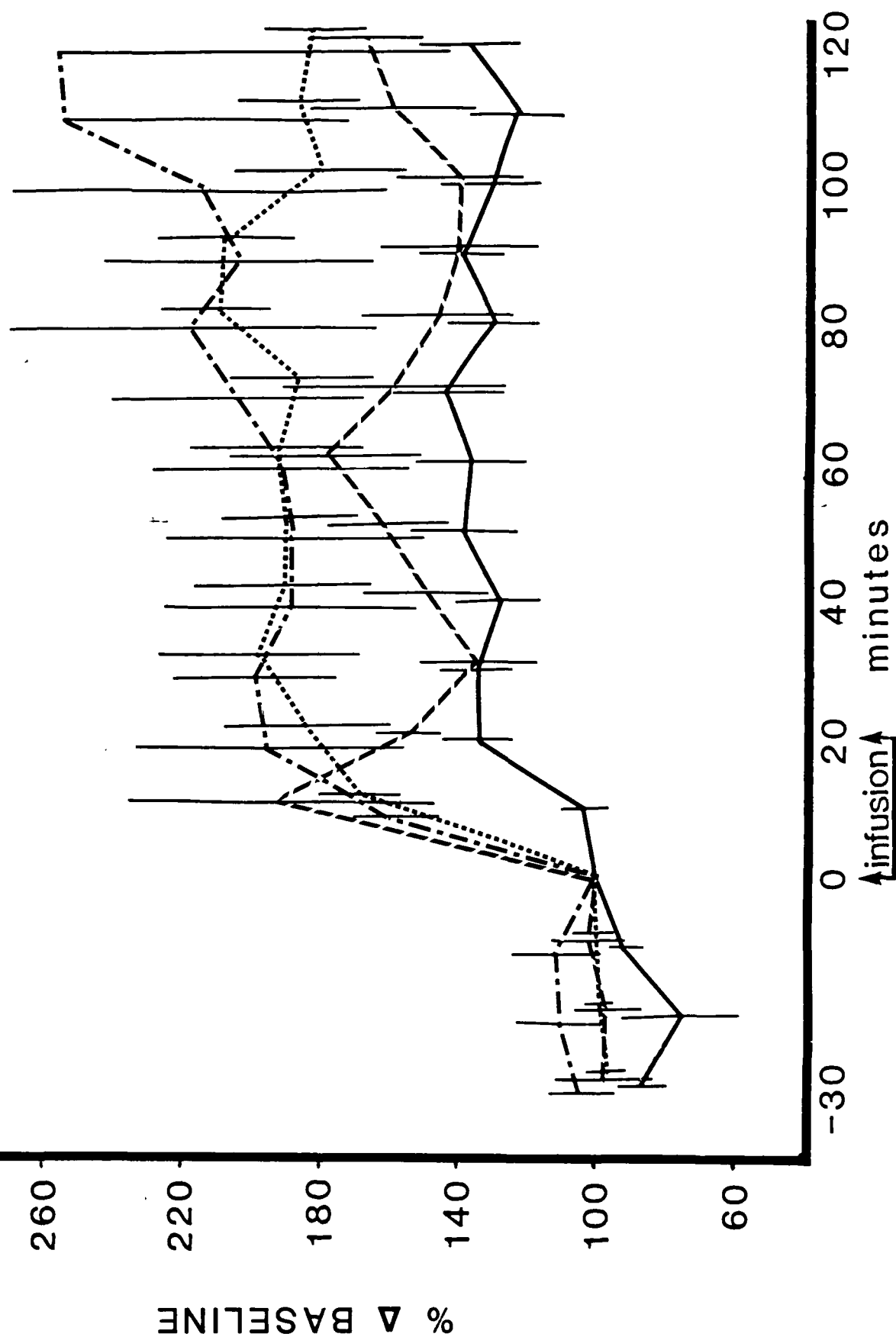


MINUTE VOLUME

WR-6026

figure 3A

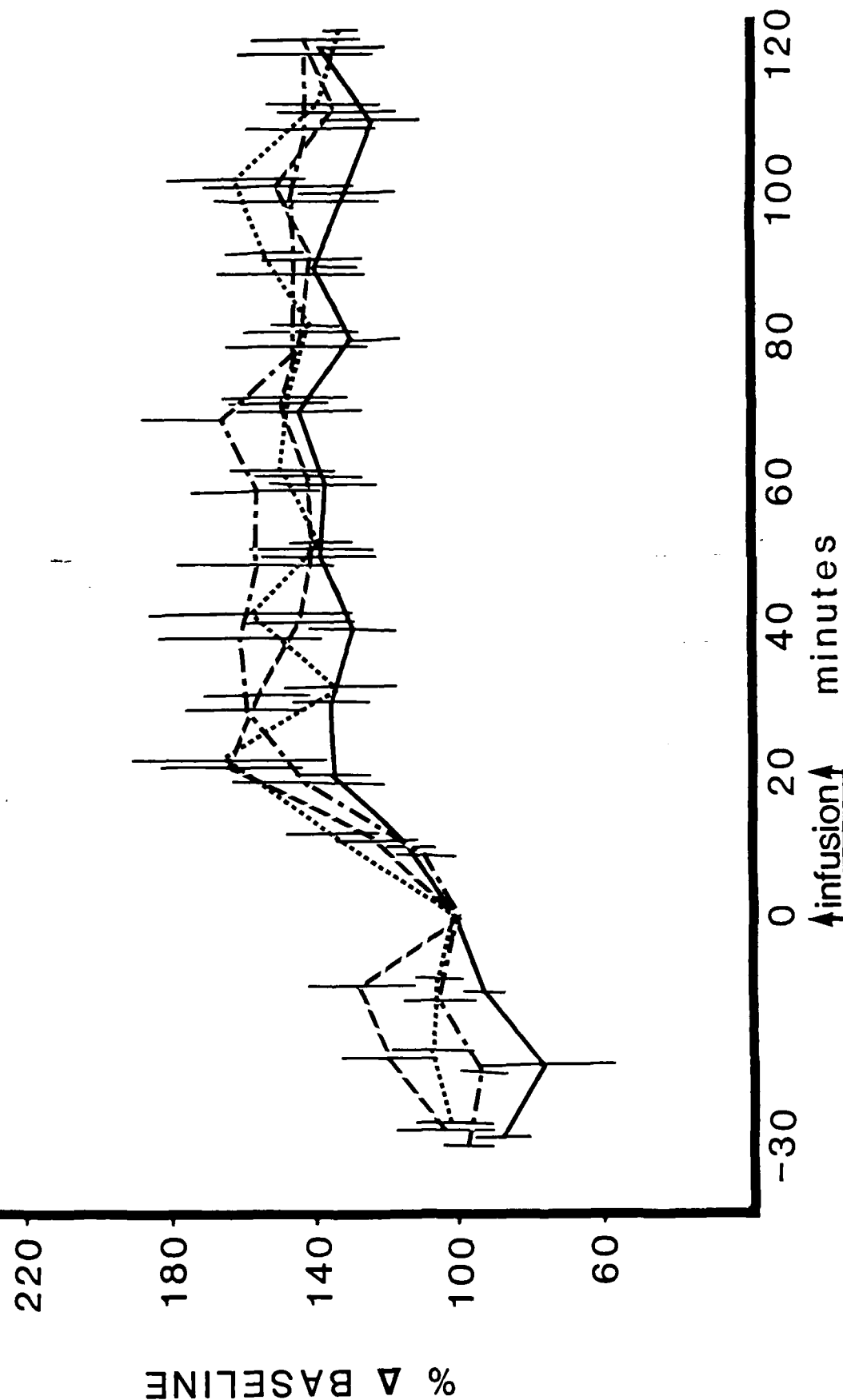
- PO_4 buffer
- - - 1.0 $\mu\text{mole/kg/min}$
- · - 2.5 $\mu\text{mole/kg/min}$
- · · · 4.0 $\mu\text{mole/kg/min}$



MINUTE VOLUME Primaquine

figure 3B

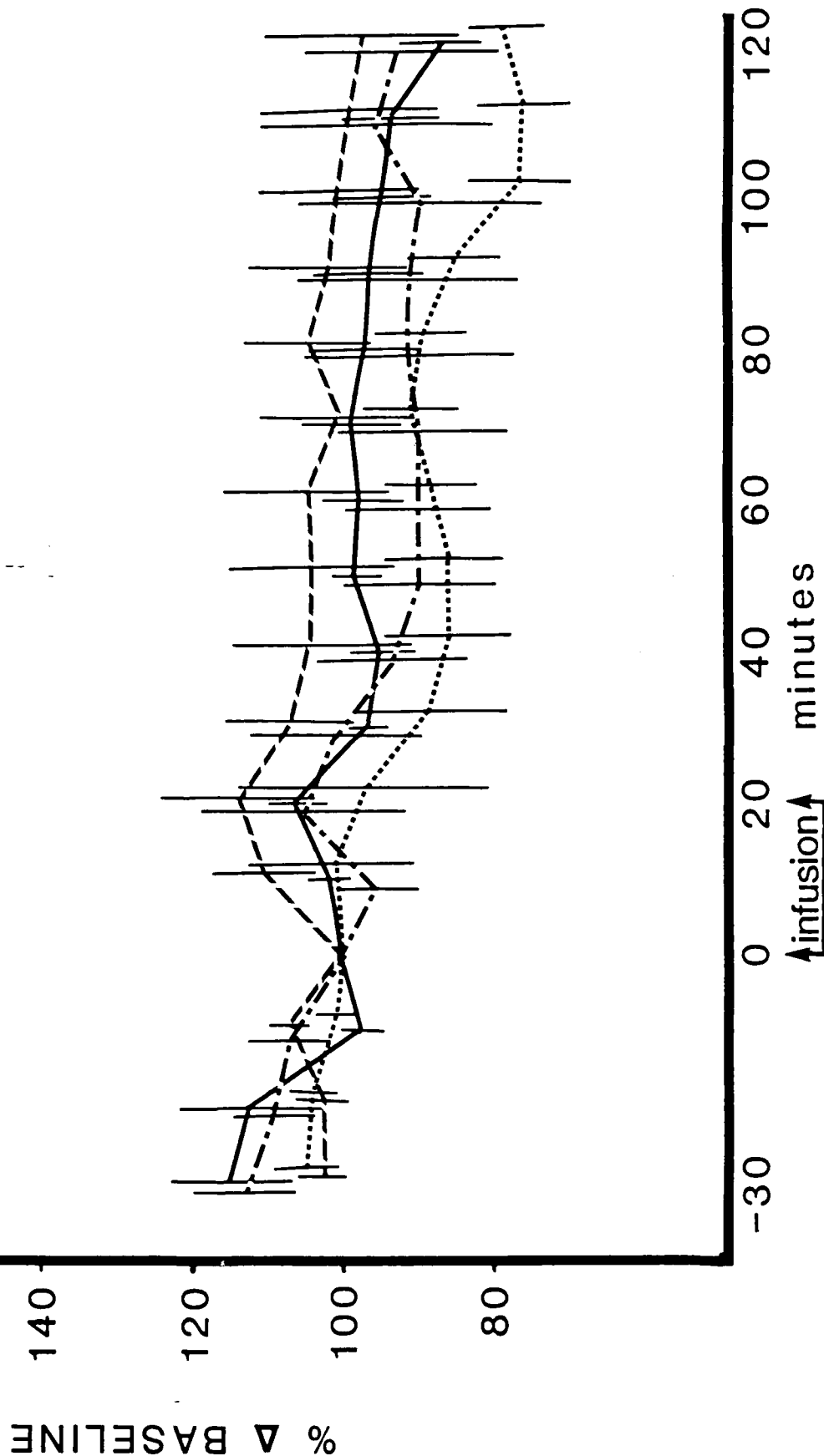
- PO_4 buffer
- - - 0.50 $\mu\text{mole/kg/min}$
- · - 1.00 $\mu\text{mole/kg/min}$
- · · · 1.75 $\mu\text{mole/kg/min}$



COMPLIANCE WR-6026

figure 4A

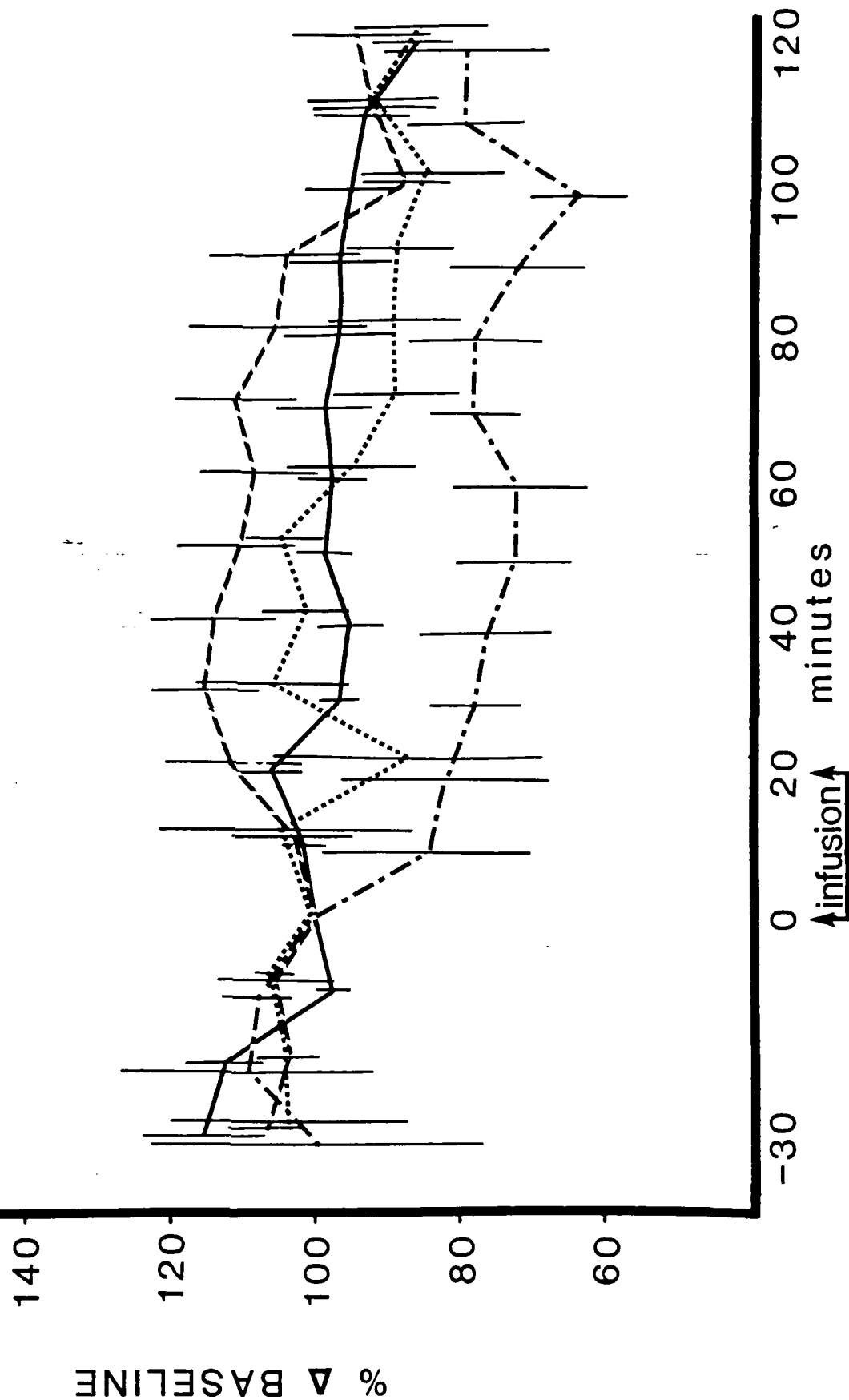
- PO_4 buffer
- - - 1.0 $\mu\text{mole/kg/min}$
- . - . 2.5 $\mu\text{mole/kg/min}$
- 4.0 $\mu\text{mole/kg/min}$



COMPLIANCE Primaquine

figure 4B

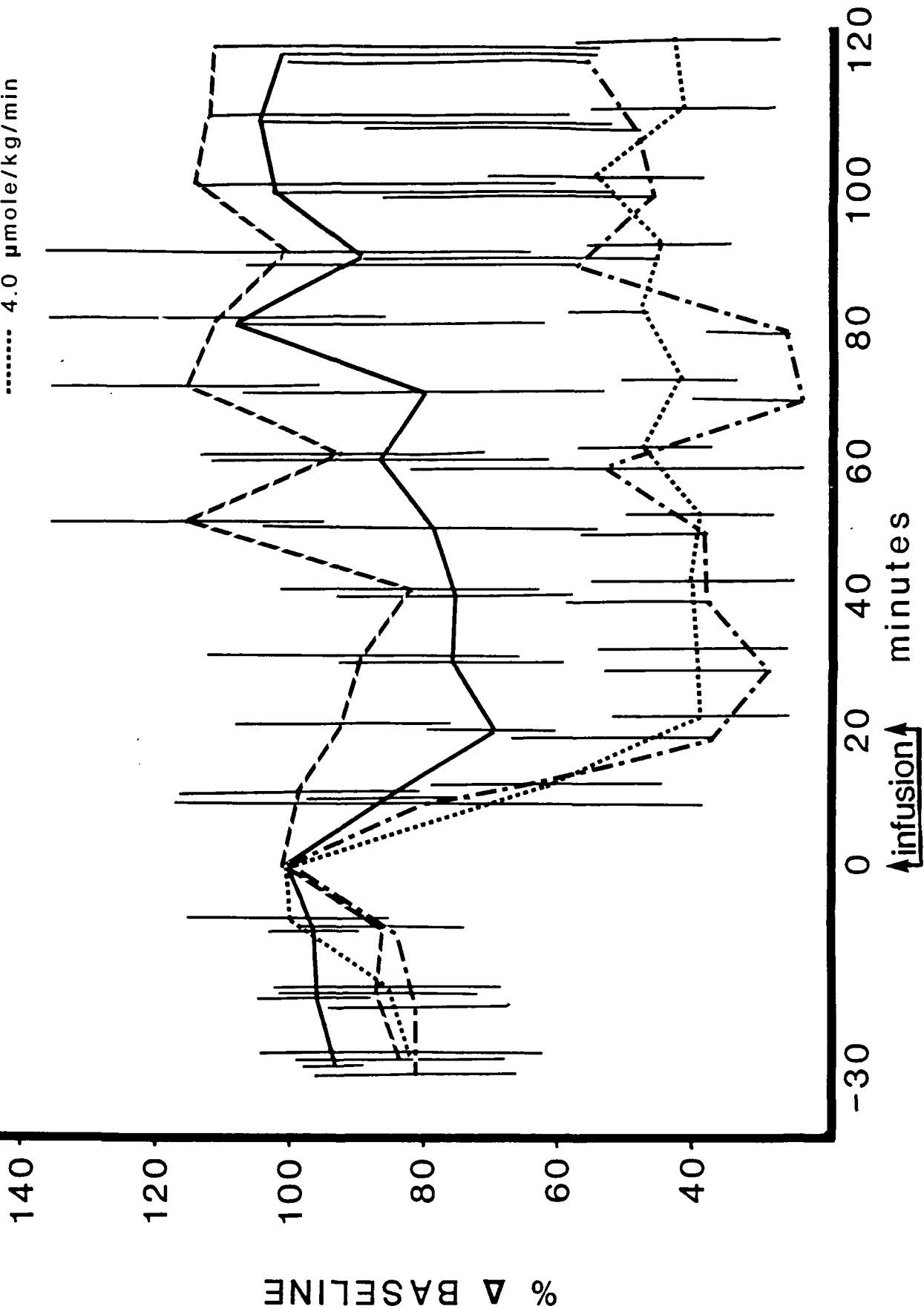
- PO_4 buffer
- - - 0.50 $\mu\text{mole/kg/min}$
- · - · 1.00 $\mu\text{mole/kg/min}$
- · · · 1.75 $\mu\text{mole/kg/min}$



RESISTANCE WR-6026

figure 5A

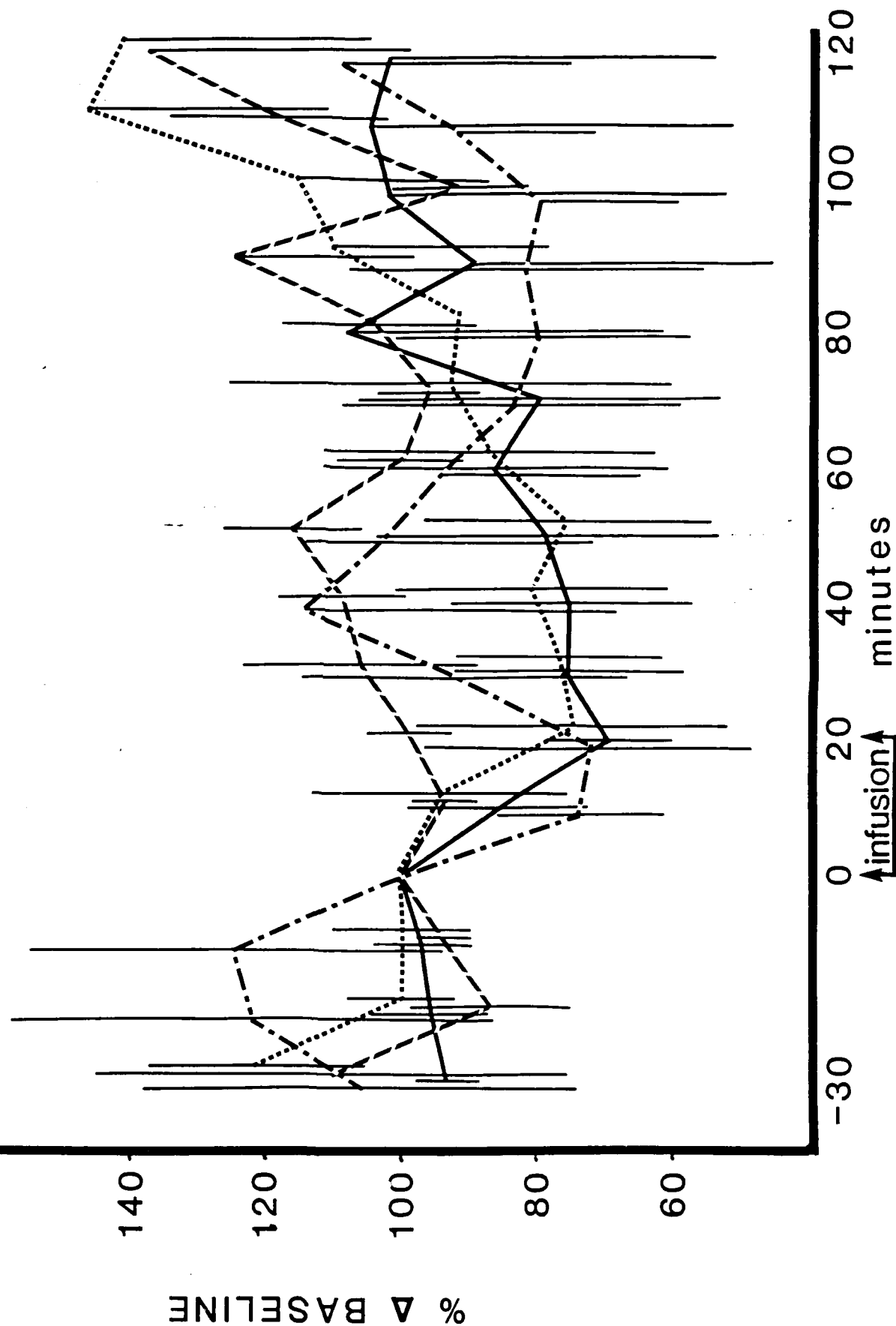
- PO_4 buffer
- - - 1.0 $\mu\text{mole/kg/min}$
- - - 2.5 $\mu\text{mole/kg/min}$
- 4.0 $\mu\text{mole/kg/min}$



RESISTANCE Primaquine

figure 5B

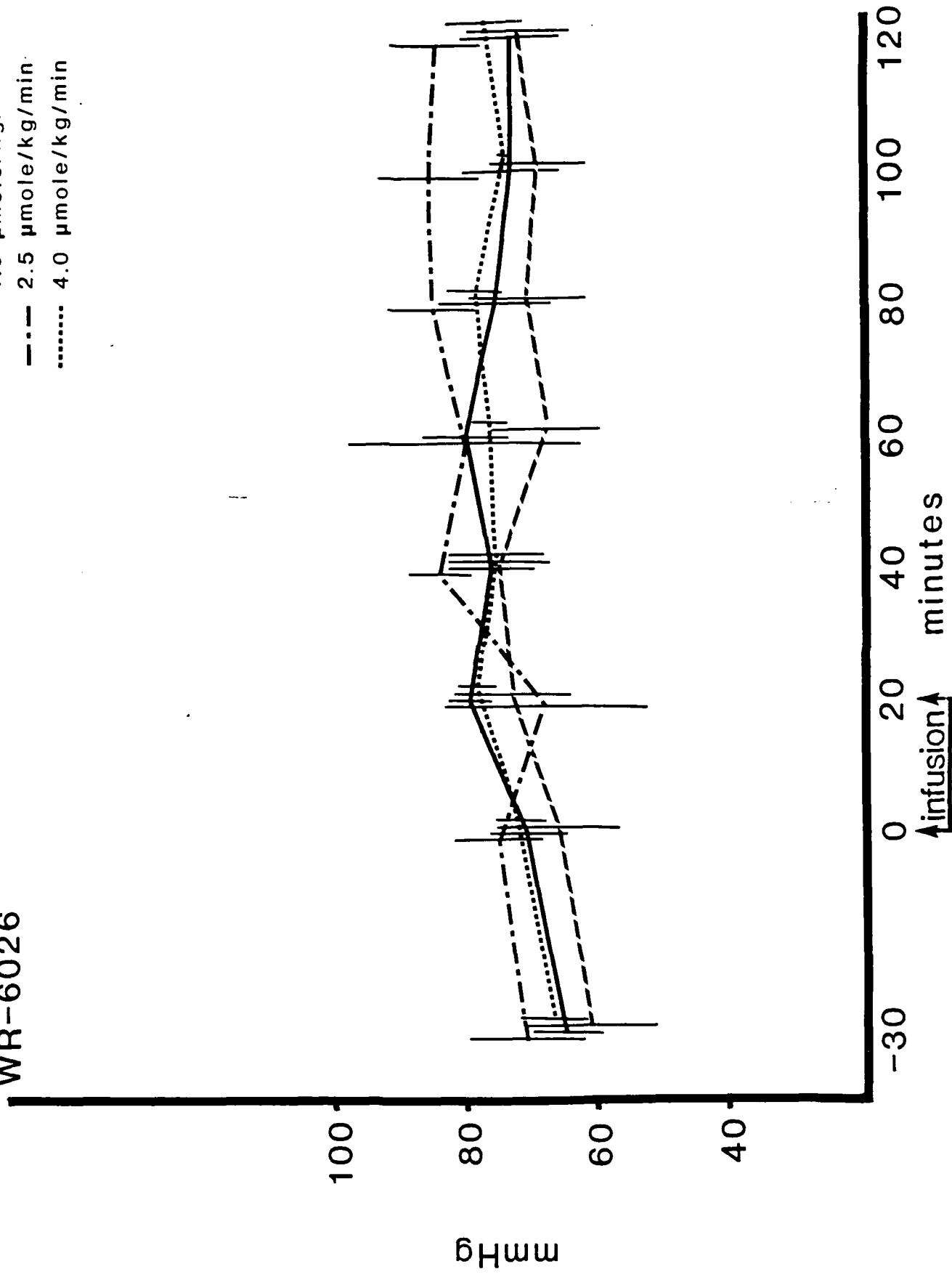
- PO_4 buffer
- - - 0.50 $\mu\text{mole/kg/min}$
- · - 1.00 $\mu\text{mole/kg/min}$
- · · 1.75 $\mu\text{mole/kg/min}$



arterial PO_2
WR-6026

figure 6A

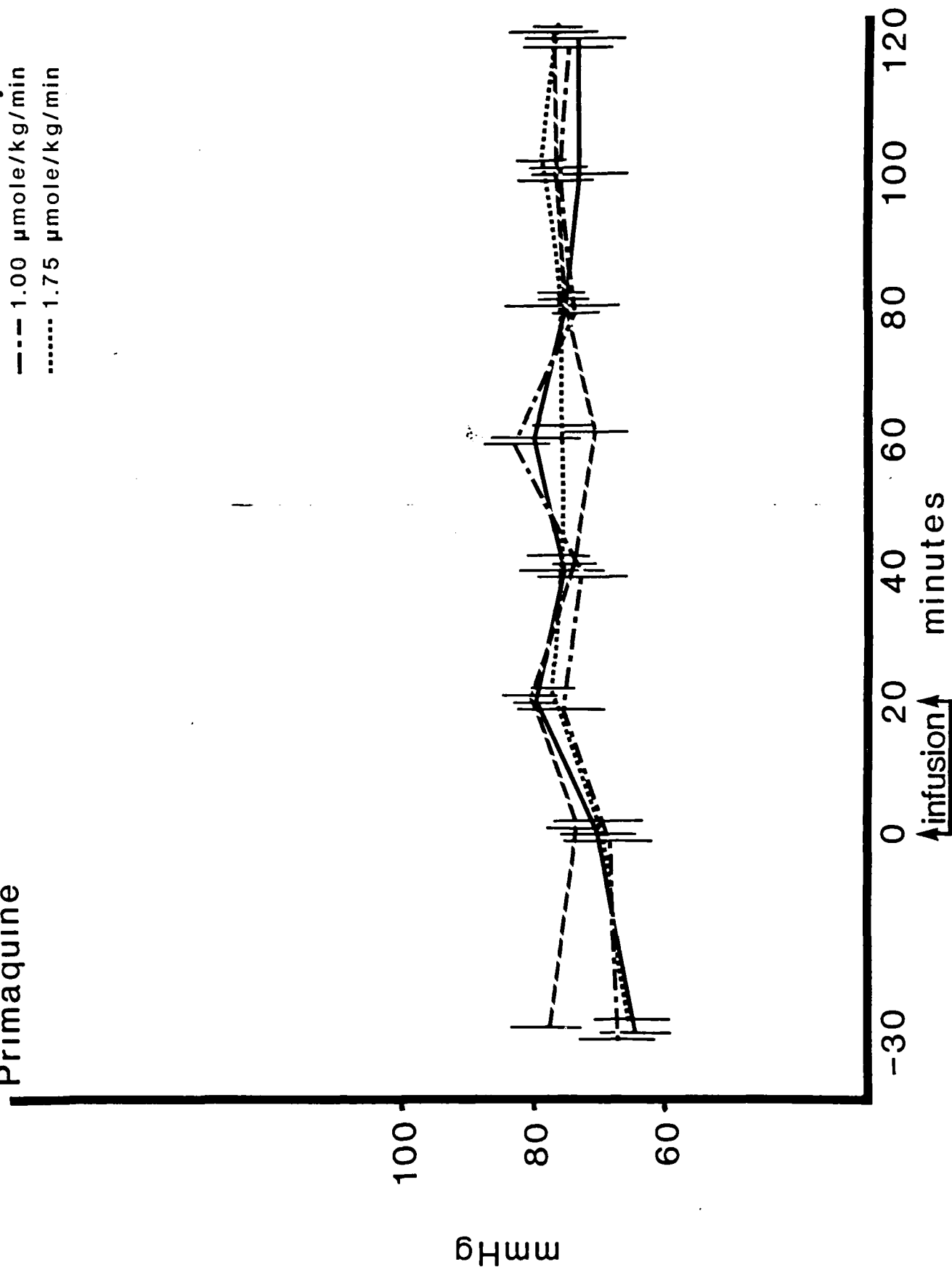
- PO_4 buffer
- - - 1.0 $\mu\text{mole/kg/min}$
- . - 2.5 $\mu\text{mole/kg/min}$
- 4.0 $\mu\text{mole/kg/min}$



arterial PO_2
Primaquine

— PO_4 buffer
 - - - 0.50 $\mu\text{mole/kg/min}$
 - - - 1.00 $\mu\text{mole/kg/min}$
 1.75 $\mu\text{mole/kg/min}$

figure 6B



venous PO_2
WR-6026

figure 7A

- PO_4 buffer
- - - 1.0 $\mu\text{mole/kg/min}$
- · - 2.5 $\mu\text{mole/kg/min}$
- · · · 4.0 $\mu\text{mole/kg/min}$

mmHg

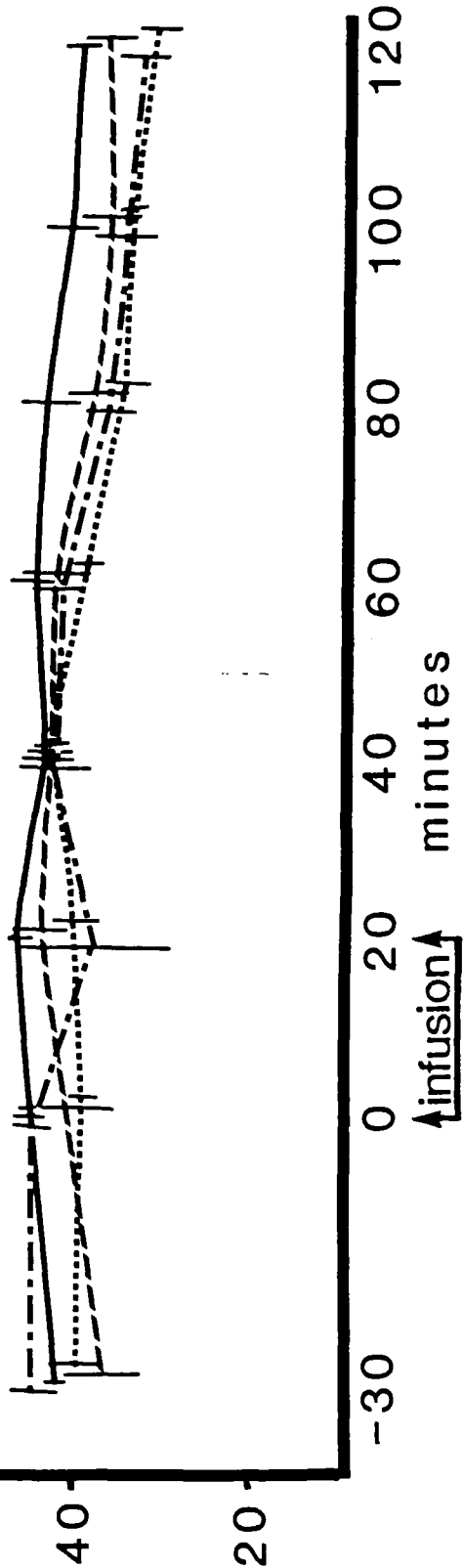


figure 7B

venous PO_2
Primaquine

— PO_4 buffer
 - - - 0.50 μ mole/kg/min
 - - - 1.00 μ mole/kg/min
 1.75 μ mole/kg/min

mmHg

60

40

-30

0 20 40 60 80 100 120

infusion ↑ minutes

arterial P_{CO_2}
WR-6026

figure 8A

— PO_4 buffer
- - - 1.0 $\mu\text{mole/kg/min}$
- . - 2.5 $\mu\text{mole/kg/min}$
..... 4.0 $\mu\text{mole/kg/min}$

mmHg

60
40
20

-30

0

20

40

60

80

100

120

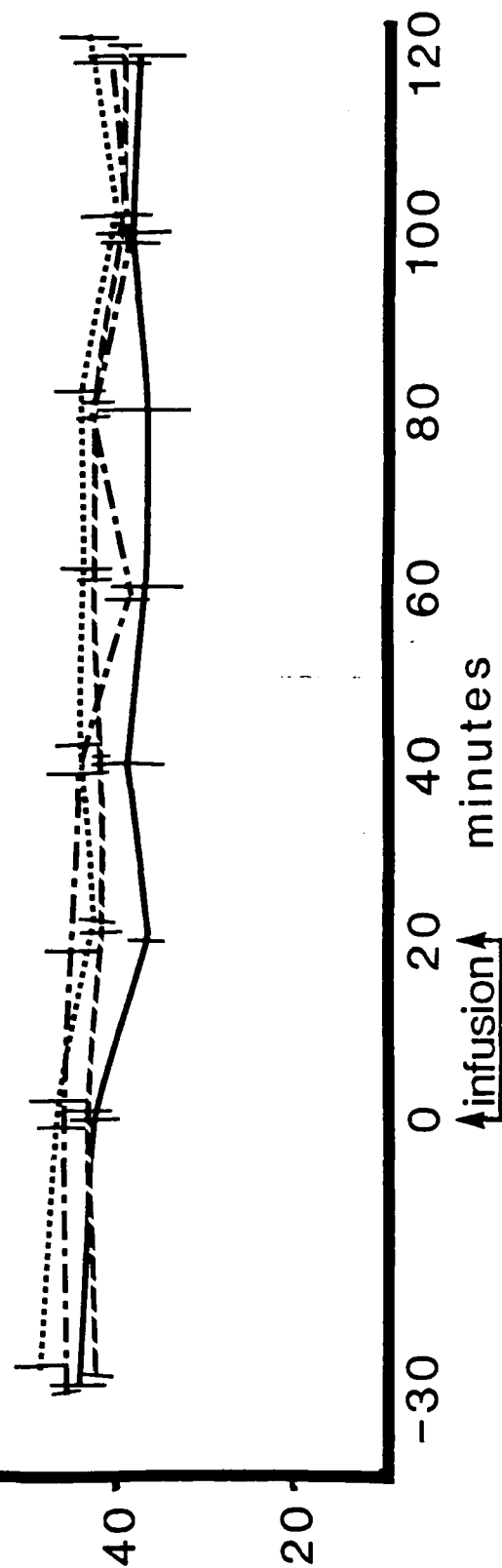
infusion ↑
minutes

arterial P_{CO_2}
Primaquine

figure 8B

— PO_4 buffer
- - - 0.50 $\mu\text{mole/kg/min}$
- · - 1.00 $\mu\text{mole/kg/min}$
· · · · 1.75 $\mu\text{mole/kg/min}$

mmHg



venous P_{CO_2}
WR-6026

figure 9A

— PO_4 buffer
- - - 1.0 $\mu\text{mole/kg/min}$
- . - 2.5 $\mu\text{mole/kg/min}$
..... 4.0 $\mu\text{mole/kg/min}$

mmHg

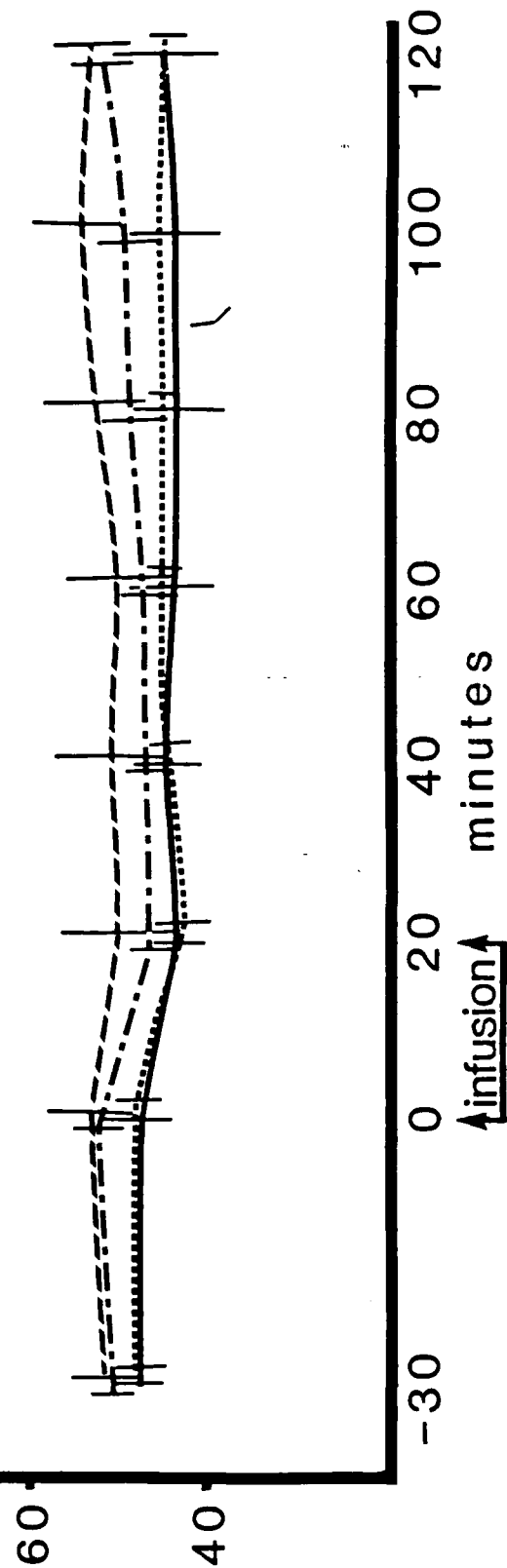


figure 9B

venous P_{CO_2}
Primaquine

- PO_4 buffer
- - - 0.50 $\mu\text{mole/kg/min}$
- . - 1.00 $\mu\text{mole/kg/min}$
- 1.75 $\mu\text{mole/kg/min}$

mmHg

60
40

-30

0 20 40 60 80 100 120
↑infusion minutes

arterial pH
WR-6026

figure 10A

— PO_4 buffer
- - - 1.0 $\mu\text{mole/kg/min}$
- · - 2.5 $\mu\text{mole/kg/min}$
· · · · · 4.0 $\mu\text{mole/kg/min}$

H^+

7.400

7.200

-30

0

20

40

60

80

100

120

infusion Δ minutes

arterial pH
Primaquine

figure 10B

— PO_4 buffer
- - - 0.50 $\mu\text{mole/kg/min}$
- - - 1.00 $\mu\text{mole/kg/min}$
..... 1.75 $\mu\text{mole/kg/min}$

pH

7.400

7.200

-30

0

20

40

60

80

100

120

infusion ↑ minutes

venous pH
WR-6026

figure 11A

— PO_4 buffer
- - - 1.0 $\mu\text{mole/kg/min}$
- . - . 2.5 $\mu\text{mole/kg/min}$
..... 4.0 $\mu\text{mole/kg/min}$

Hd
62

7.400

7.200

-30

0

20

40

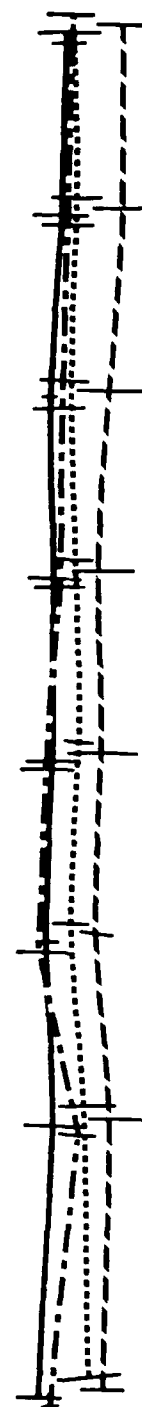
60

80

100

120

↑infusion↑
minutes



venous pH
Primaquine

figure 11B

- PO_4 buffer
- - - 0.50 $\mu\text{mole/kg/min}$
- · - · 1.00 $\mu\text{mole/kg/min}$
- · · · 1.75 $\mu\text{mole/kg/min}$

Id

7.400

7.200

-30

0

20

40

60

80

100

120

↑infusion↑ minutes



figure 12A

HEMATOCRIT
WR-6026

— PO_4 buffer
 - - - 1.0 $\mu\text{mole/kg/min}$
 - - - 2.5 $\mu\text{mole/kg/min}$
 4.0 $\mu\text{mole/kg/min}$

% cells

60

40

20

-30

infusion ↑

minutes

80

100

120

figure 12B

— PO_4 buffer
 - - - 0.50 $\mu\text{mole/kg/min}$
 - · - · 1.00 $\mu\text{mole/kg/min}$
 · · · · 1.75 $\mu\text{mole/kg/min}$

% cells

60

40

20

-30

0

20

40

60

80

100

120

infusion ↑ minutes

HEART RATE WR-6026

figure 13A

- PO_4 buffer
- - - 1.0 $\mu\text{mole/kg/min}$
- . - . 2.5 $\mu\text{mole/kg/min}$
- 4.0 $\mu\text{mole/kg/min}$

% Δ BASELINE

120

100

80

-30

0

20

40

60

80

100

120

minutes

infusion

HEART RATE Primaquine

figure 13B

- PO_4 buffer
- - - 0.50 $\mu\text{mole/kg/min}$
- · - · 1.00 $\mu\text{mole/kg/min}$
- · · · 1.75 $\mu\text{mole/kg/min}$

% Δ BASELINE

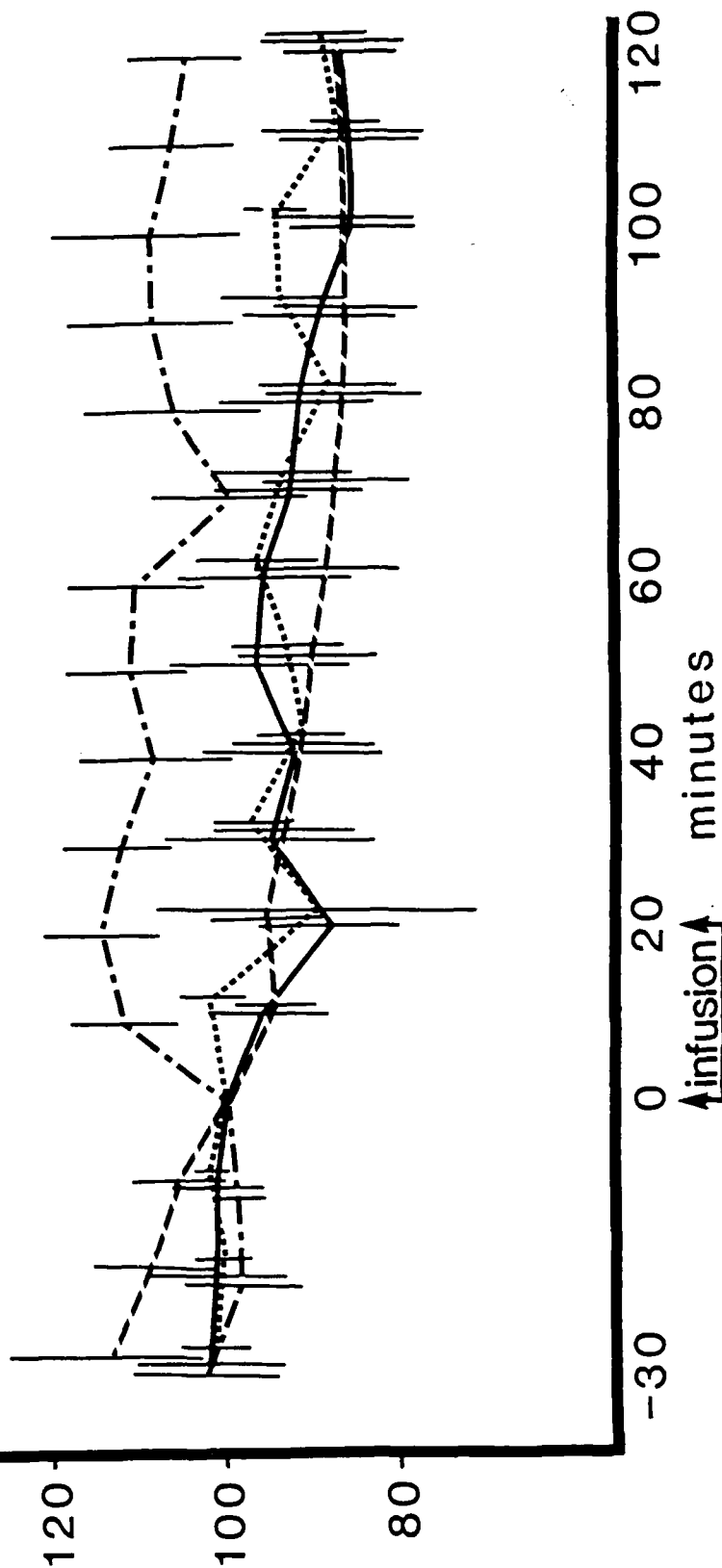


figure 14A DIASTOLIC BLOOD PRESSURE WR-6026

— PO_4 buffer
 - - - 1.0 $\mu\text{mole/kg/min}$
 - · - · 2.5 $\mu\text{mole/kg/min}$
 · · · · · 4.0 $\mu\text{mole/kg/min}$

% Δ BASELINE

120

100

80

-30

0

20

40

60

80

100

120

infusion $\uparrow$ minutes

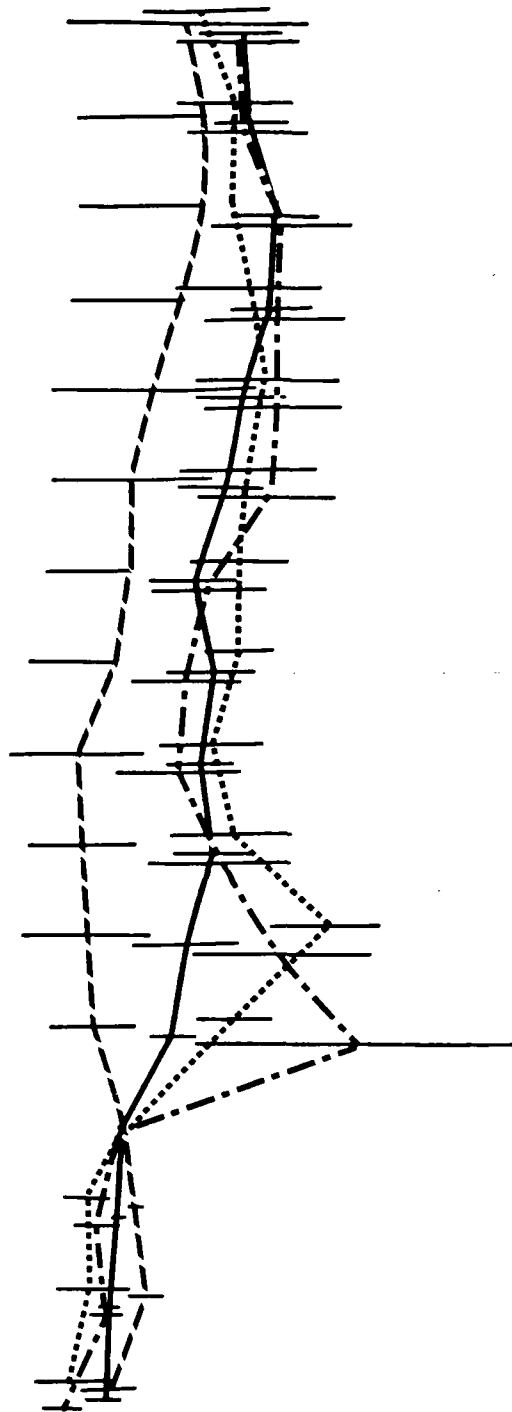


figure 14B DIASTOLIC BLOOD PRESSURE Primaquine

— PO_4 buffer
 - - - 0.50 $\mu\text{mole/kg/min}$
 - - - 1.00 $\mu\text{mole/kg/min}$
 1.75 $\mu\text{mole/kg/min}$

% Δ BASELINE

120

100

80

-30

0

20

40

60

80

100

120

infusion ↑ minutes

figure 15A SYSTOLIC BLOOD PRESSURE

WR-6026

— PO_4 buffer
 - - - 1.0 $\mu\text{mole/kg/min}$
 - · - 2.5 $\mu\text{mole/kg/min}$
 · · · · 4.0 $\mu\text{mole/kg/min}$

% Δ BASELINE

120

100

80

-30

0

20

40

60

80

100

120

infusion ↑ minutes

figure 15B Primaquine SYSTOLIC BLOOD PRESSURE

— PO_4 buffer
 --- 0.50 $\mu\text{mole/kg/min}$
 - - - 1.00 $\mu\text{mole/kg/min}$
 1.75 $\mu\text{mole/kg/min}$

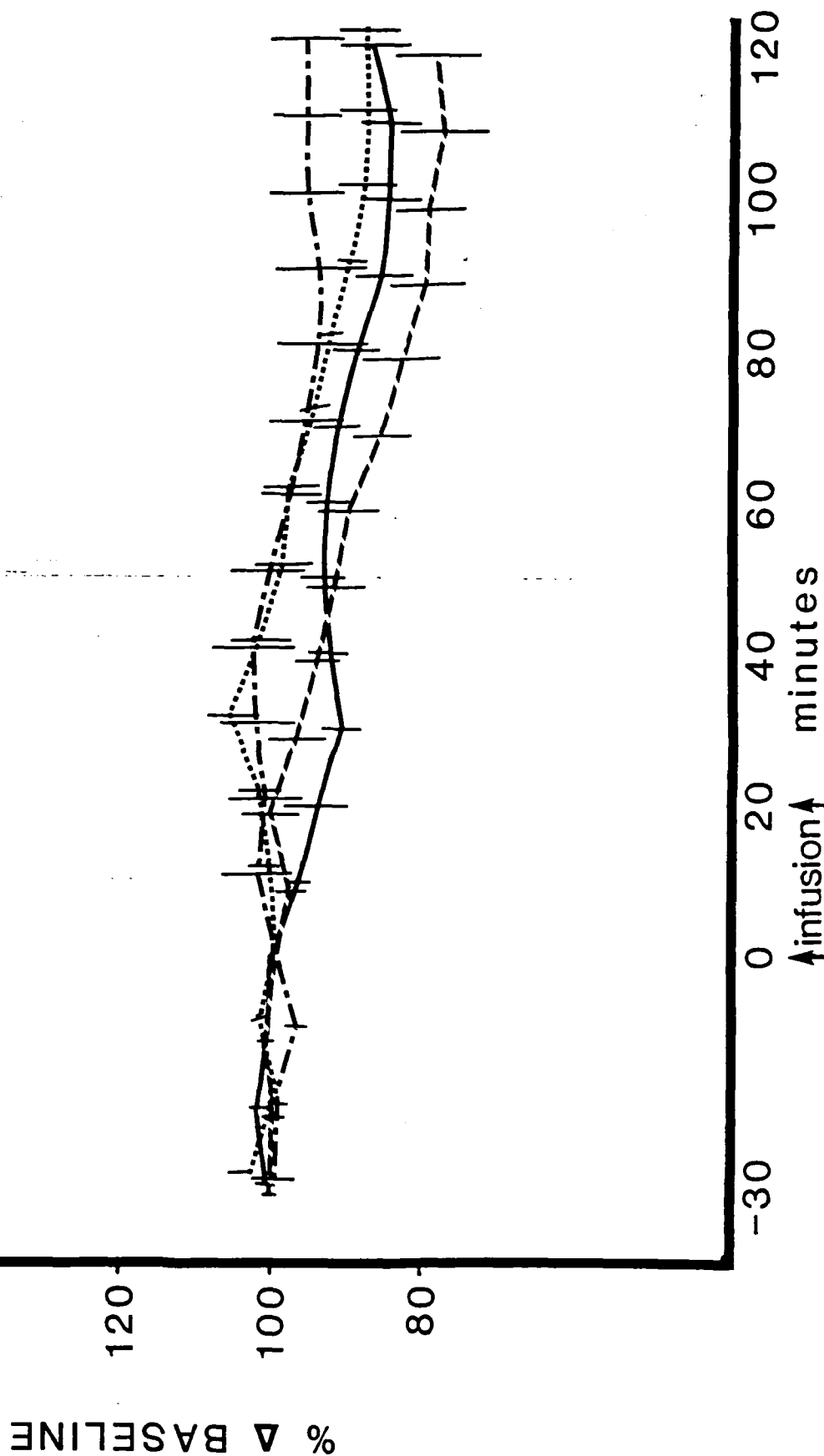


figure 16A

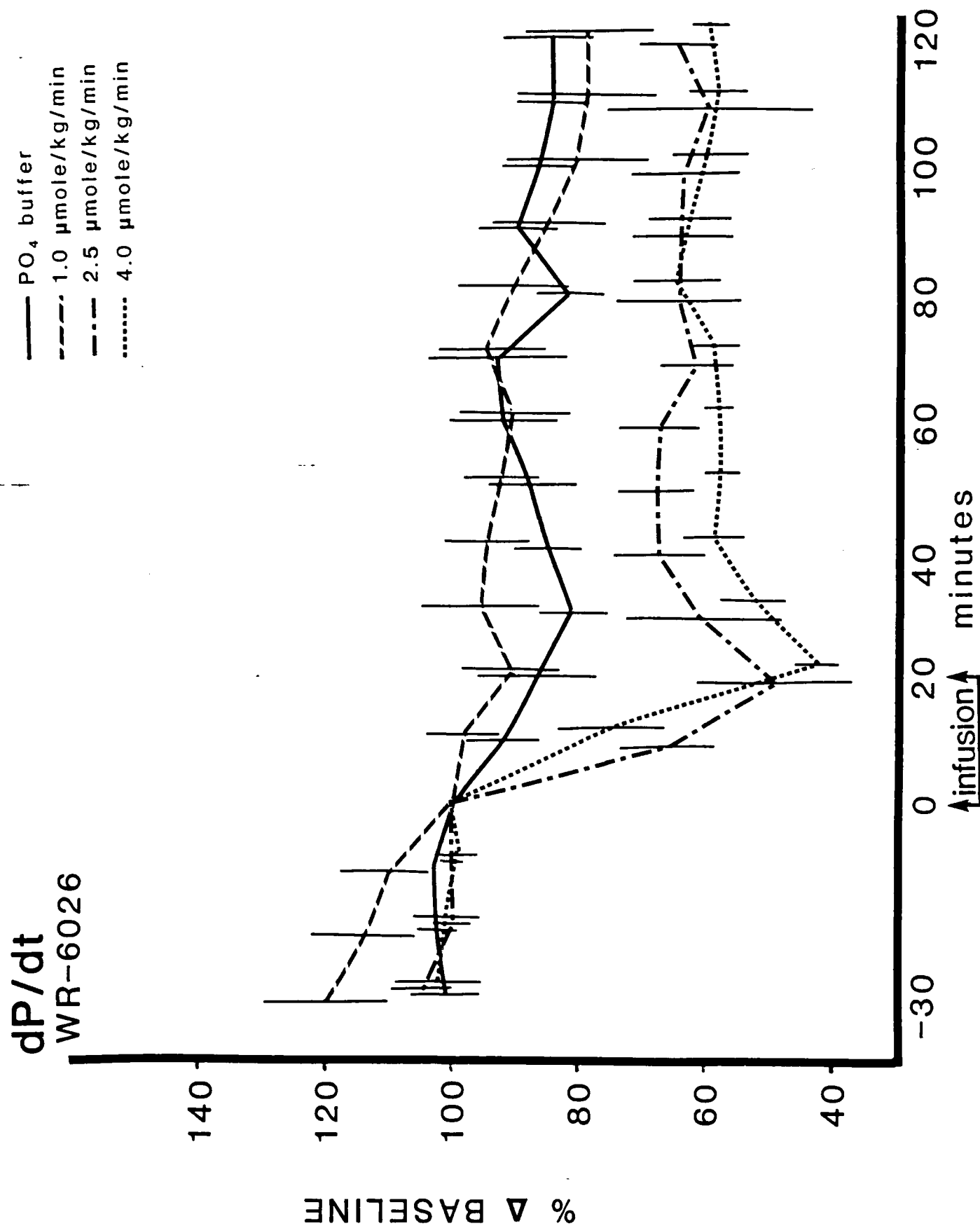
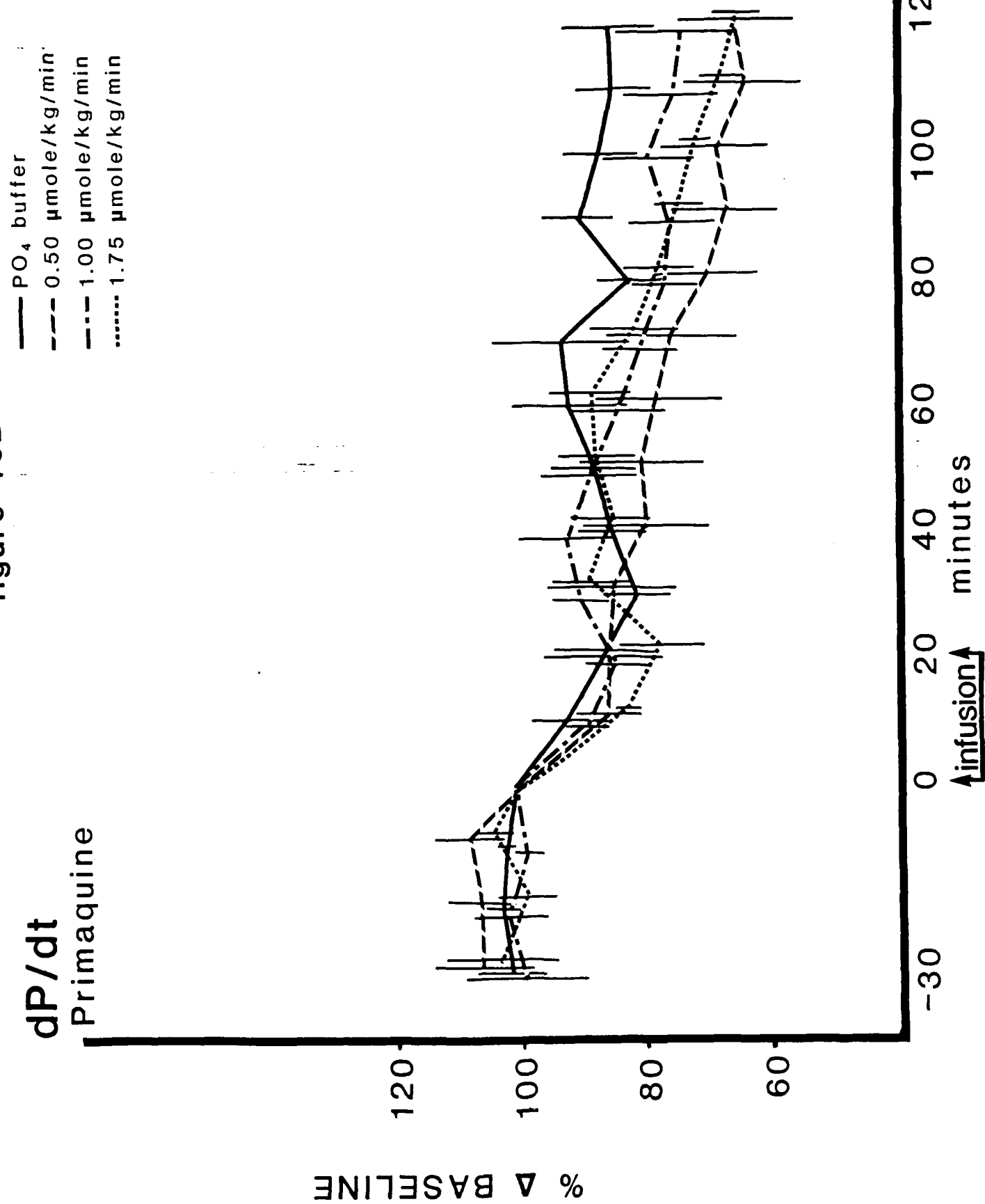


figure 16B

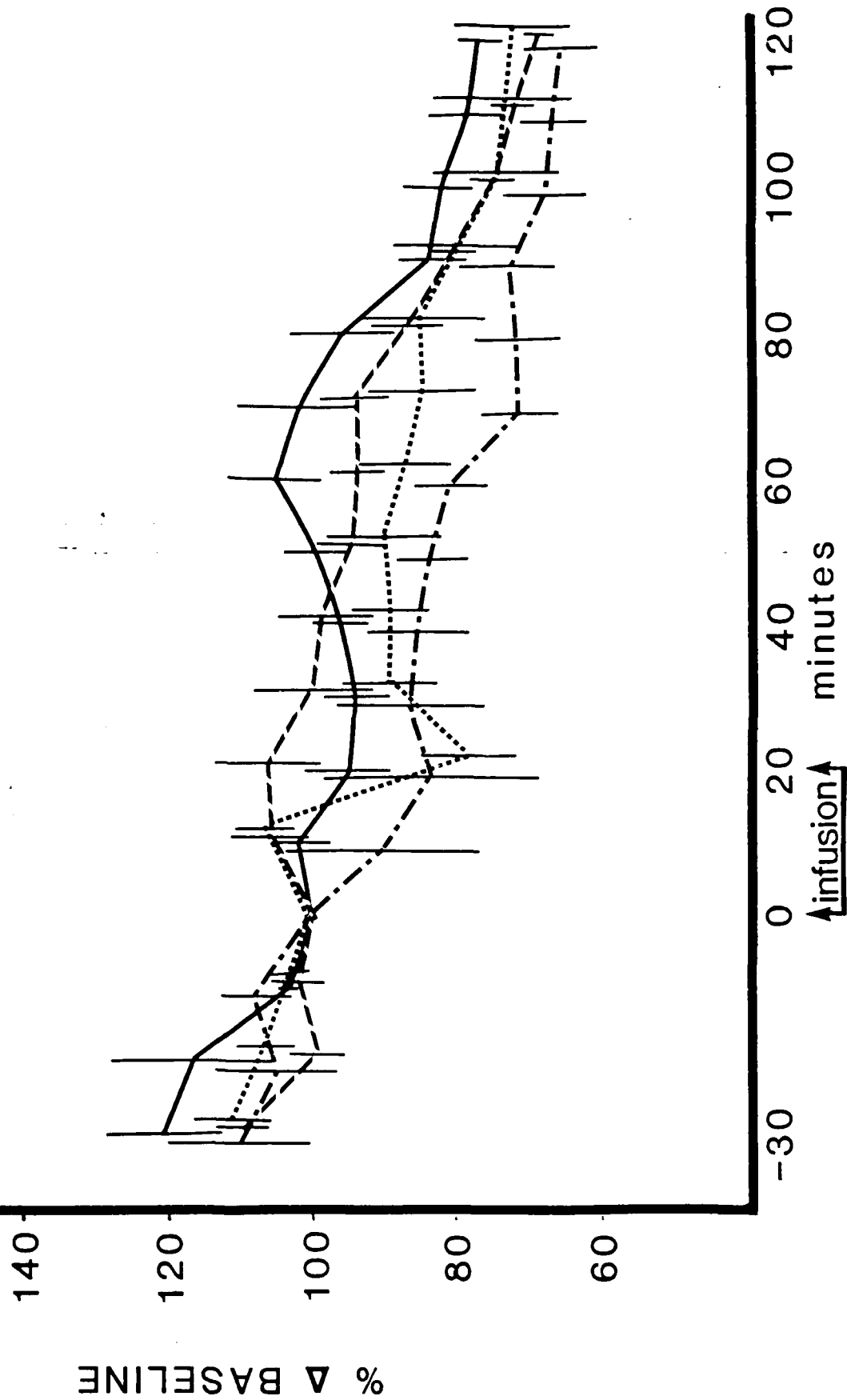


CARDIAC OUTPUT

WR-6026

figure 17A

- PO_4 buffer
- - - 1.0 $\mu\text{mole/kg/min}$
- · - 2.5 $\mu\text{mole/kg/min}$
- 4.0 $\mu\text{mole/kg/min}$



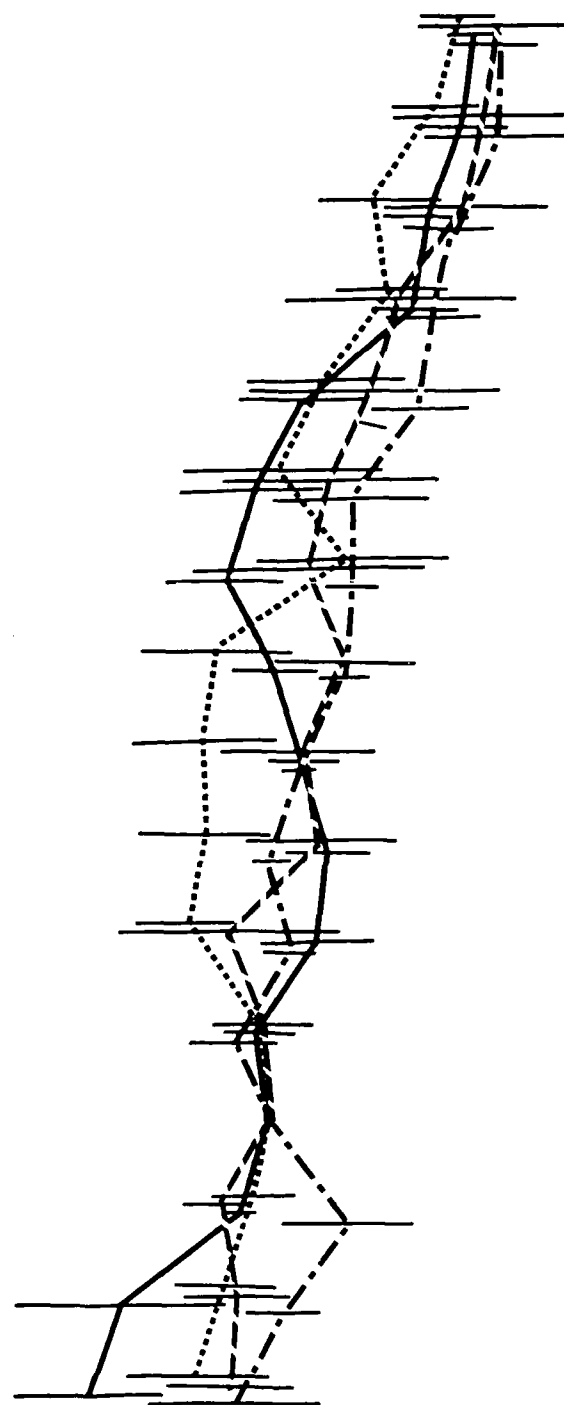
CARDIAC OUTPUT Primaquine

figure 17B

- PO_4 buffer
- - - 0.50 $\mu\text{mole/kg/min}$
- . - 1.00 $\mu\text{mole/kg/min}$
- 1.75 $\mu\text{mole/kg/min}$

% Δ BASELINE

140
120
100
80
60



infusion ↑ minutes

-30 0 20 40 60 80 100 120

figure 18A

mean PULMONARY ARTERY PRESSURE

WR-6026

- PO_4 buffer
- - - 1.0 $\mu\text{mole/kg/min}$
- . - 2.5 $\mu\text{mole/kg/min}$
- 4.0 $\mu\text{mole/kg/min}$

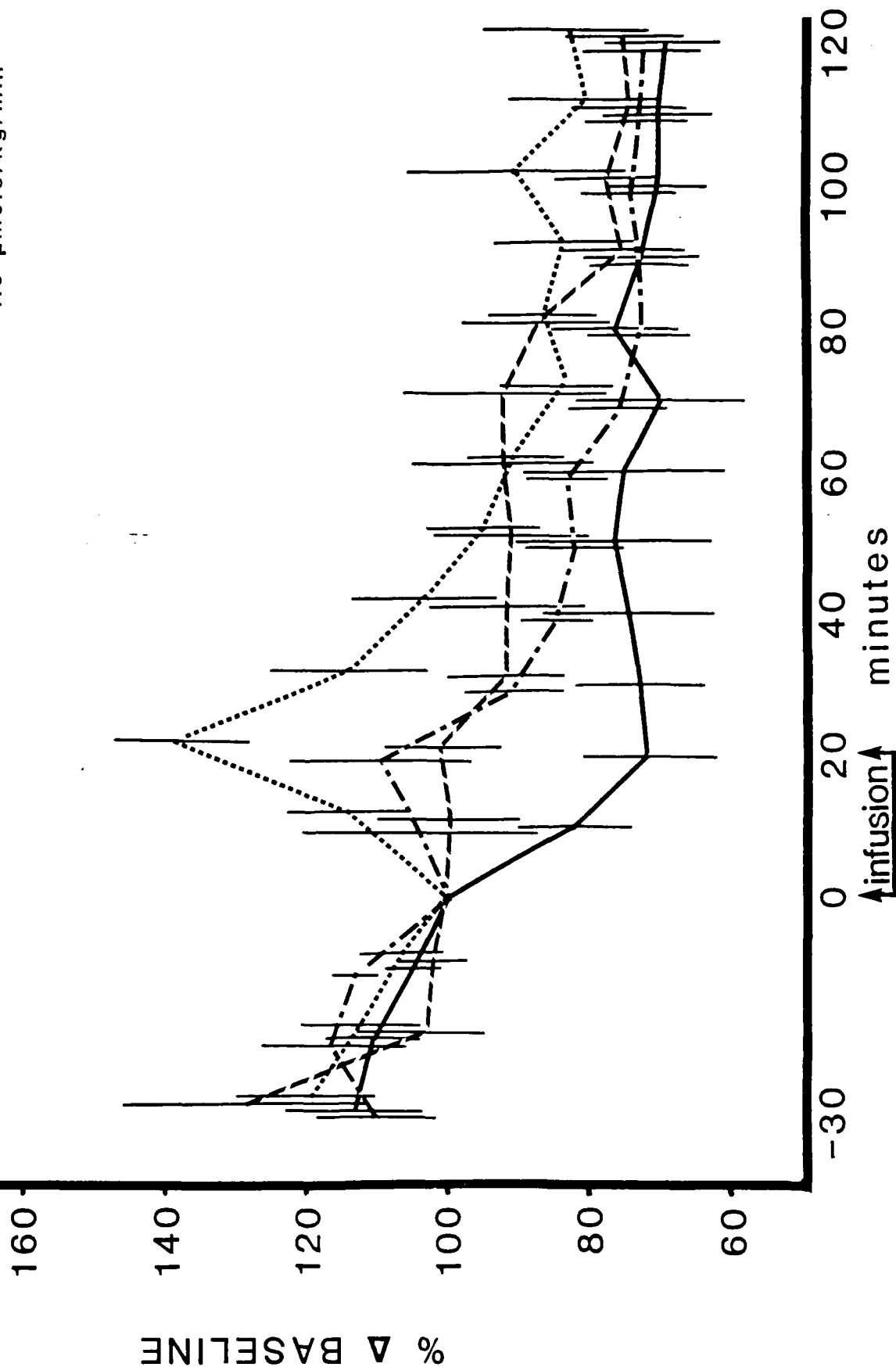


figure 18B

mean PULMONARY ARTERY PRESSURE

Primaquine

- PO_4 buffer
- - - 0.50 $\mu\text{mole/kg/min}$
- · - · 1.00 $\mu\text{mole/kg/min}$
- · · · 1.75 $\mu\text{mole/kg/min}$

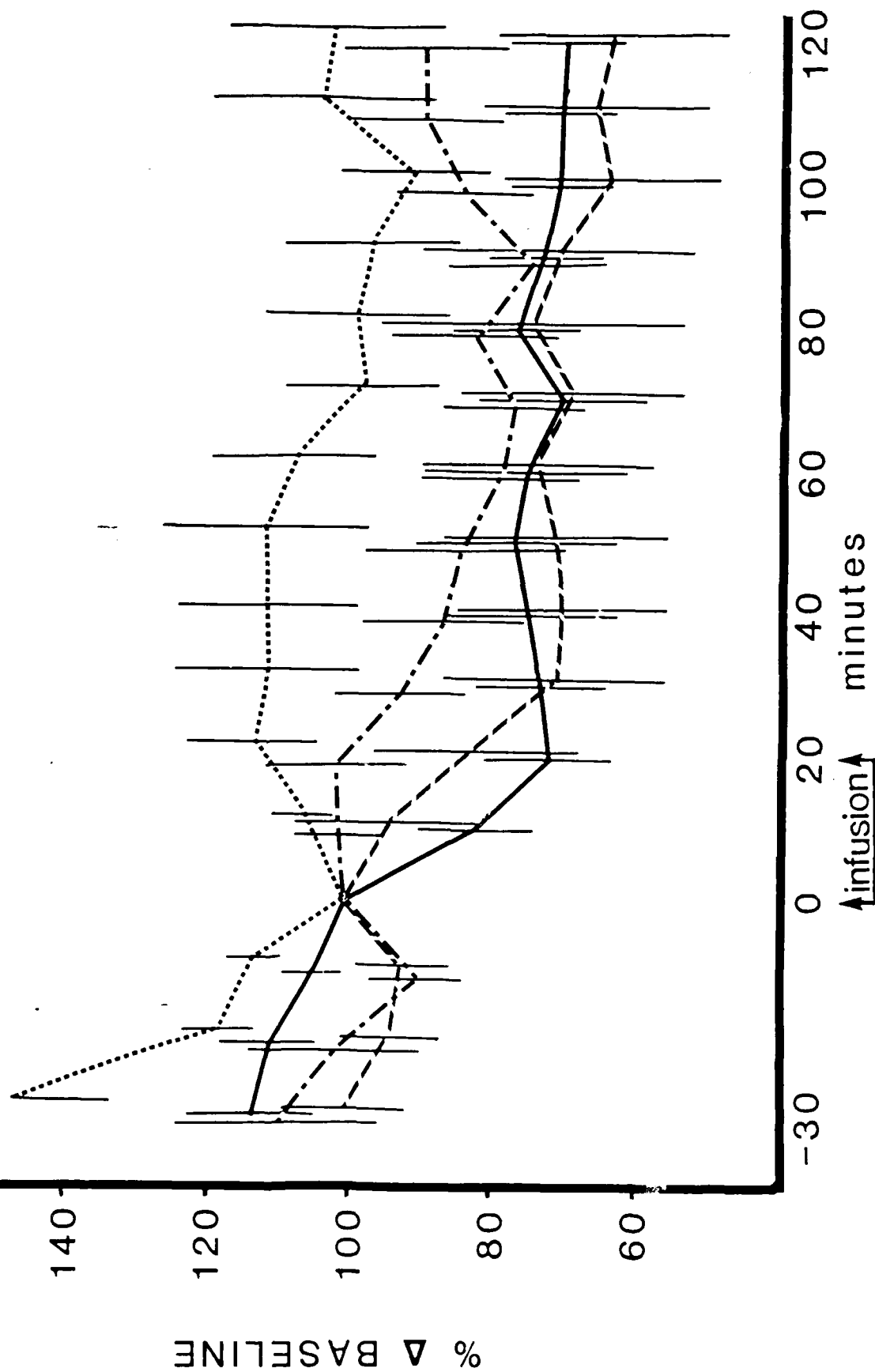


figure 19A

PULMONARY VASCULAR RESISTANCE

WR-6026

— PO_4 buffer
 - - - 1.0 $\mu\text{mole/kg/min}$
 - - - 2.5 $\mu\text{mole/kg/min}$
 4.0 $\mu\text{mole/kg/min}$

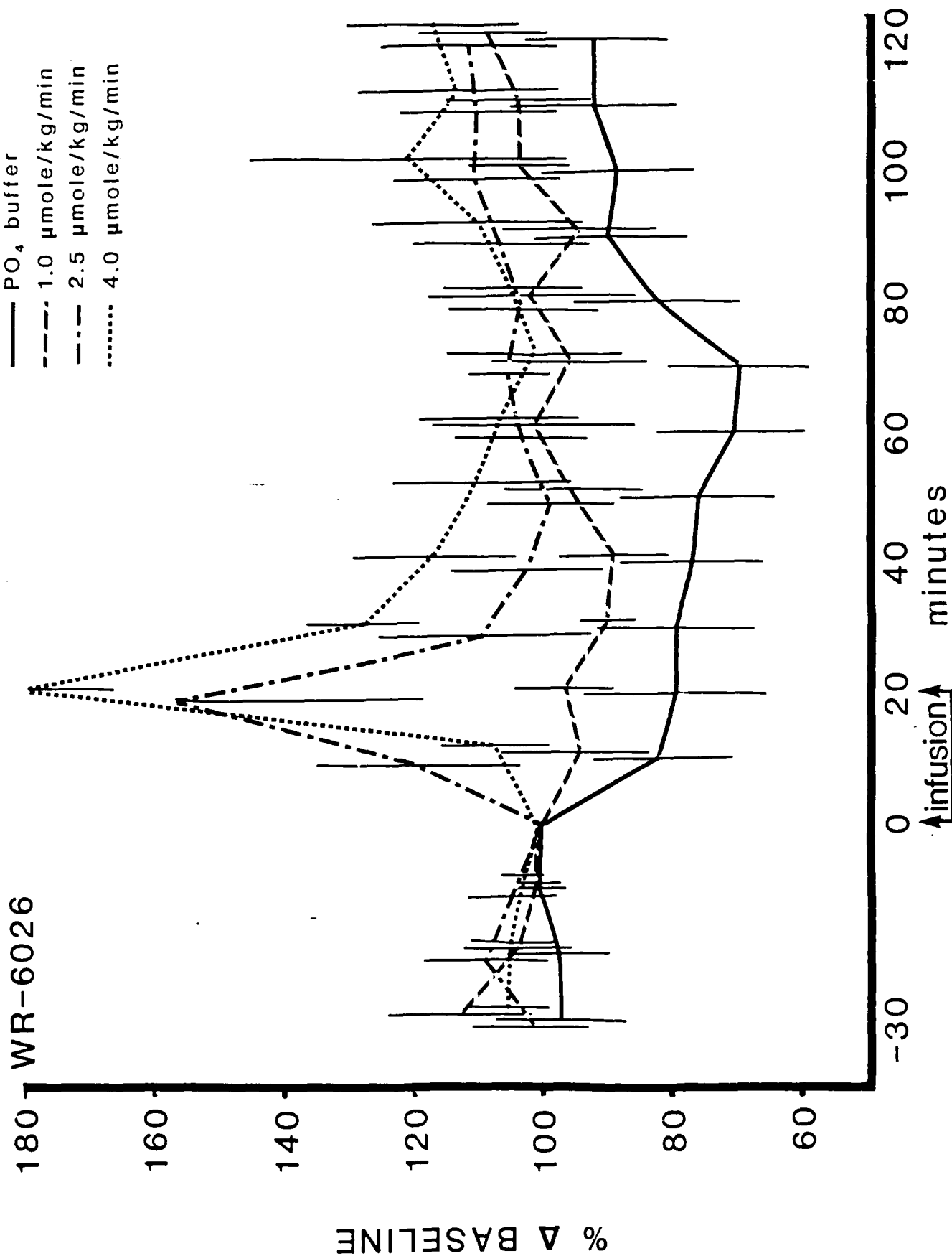


figure 19B

PULMONARY VASCULAR RESISTANCE

Primaquine

- PO_4 buffer
- - - 0.50 $\mu\text{mole/kg/min}$
- . - . 1.00 $\mu\text{mole/kg/min}$
- 1.75 $\mu\text{mole/kg/min}$

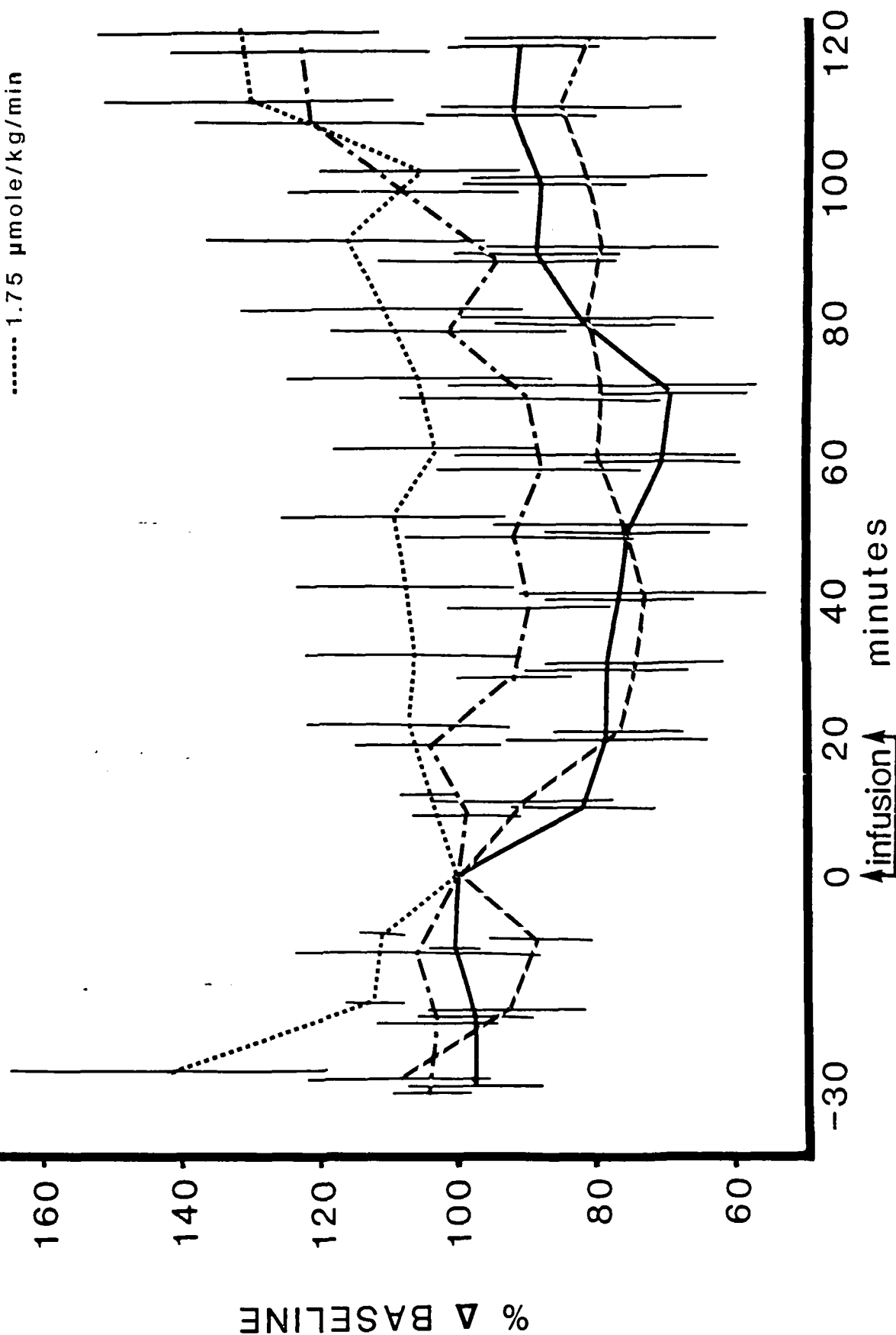


figure 20A PULMONARY WEDGE PRESSURE

WR-6026

— PO_4 buffer
 - - - 1.0 $\mu\text{mole/kg/min}$
 - . - . 2.5 $\mu\text{mole/kg/min}$
 4.0 $\mu\text{mole/kg/min}$

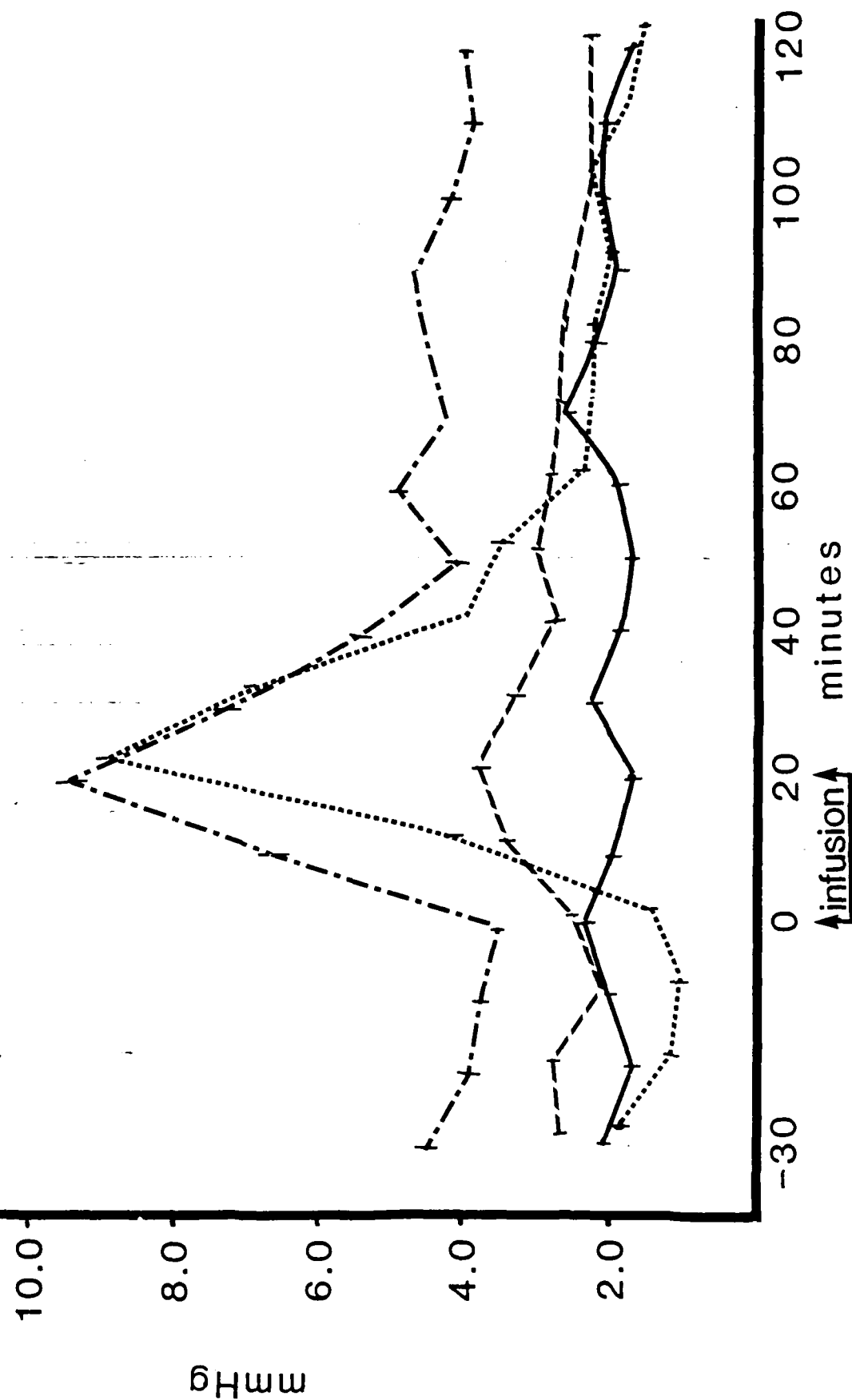


figure 20B

PULMONARY WEDGE PRESSURE

Primaquine

— PO_4 buffer
- - - 0.50 $\mu\text{mole/kg/min}$
- - - 1.00 $\mu\text{mole/kg/min}$
..... 1.75 $\mu\text{mole/kg/min}$

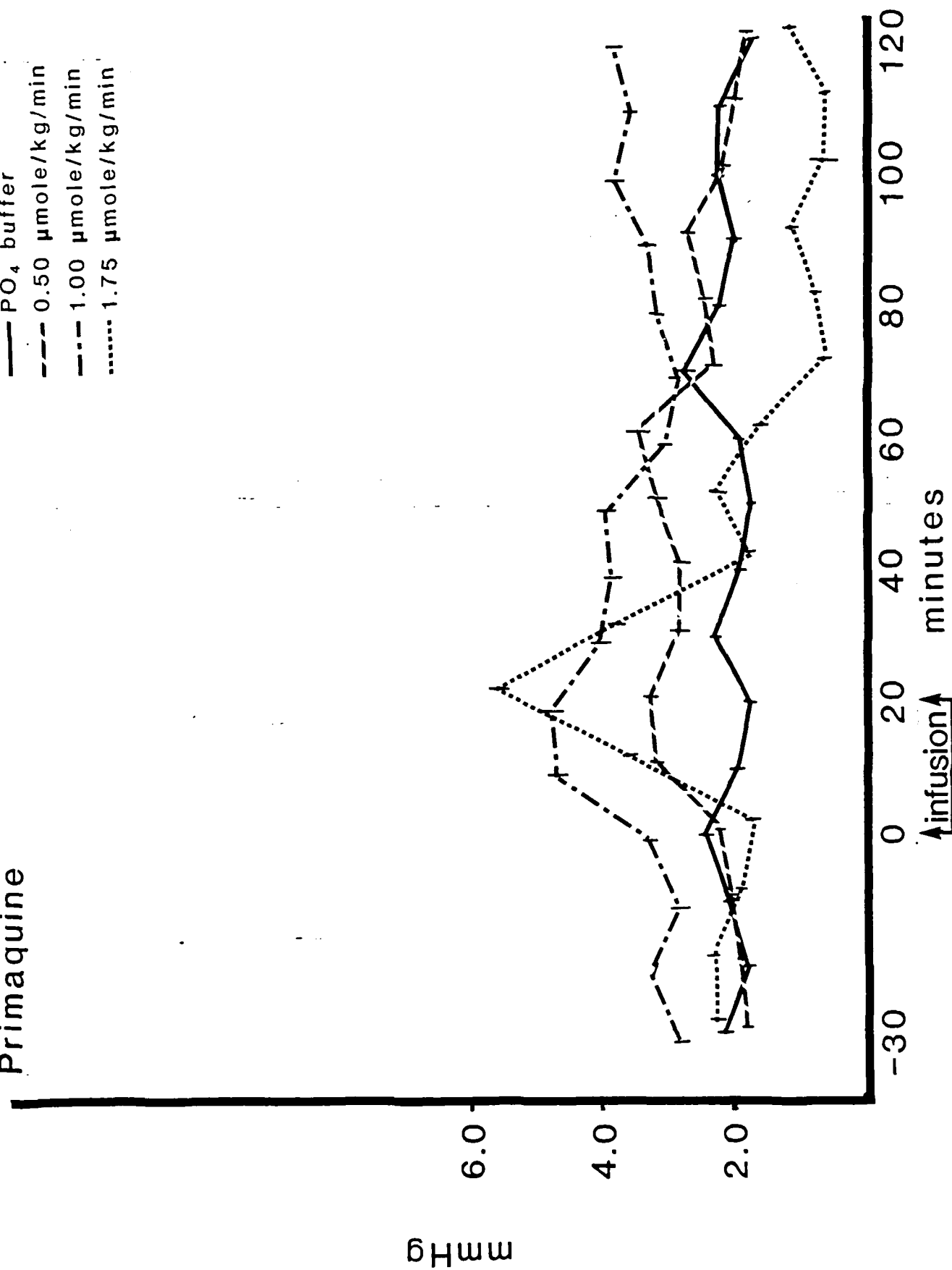
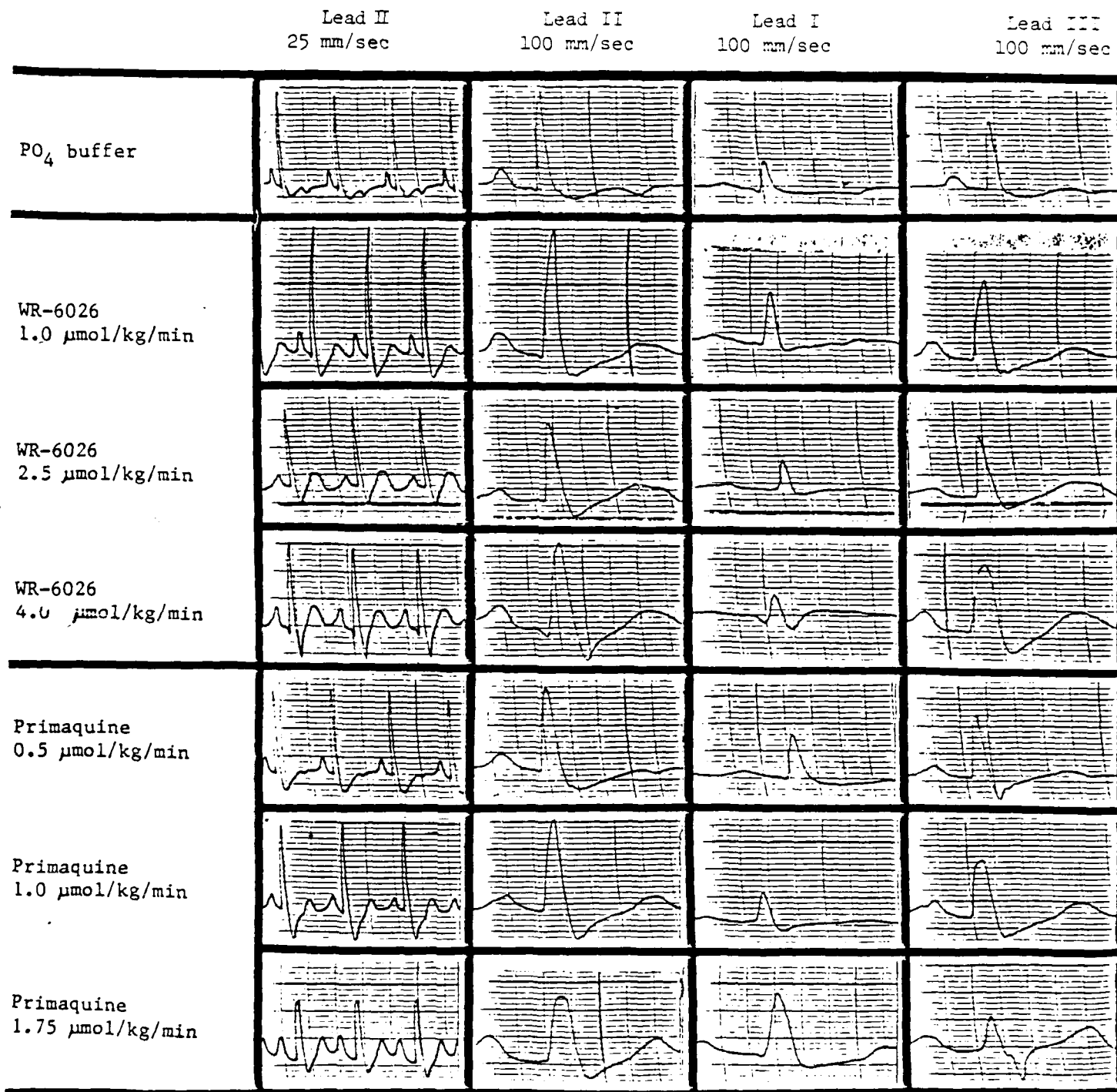


Fig. 21

Representative EKG tracings
at +20 minutes

1 mv = 1 cm



APPENDIX E
Variable Recordings

Tracing 1 A

Heart Rate
beats/min

Time = 0

WR-6026 @ 6.0 units/H/min. for 20 min.

Time = 0

-100

11/1/62

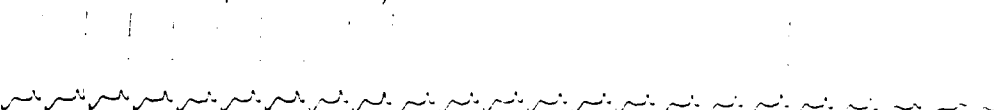
-50

25 mm/min

EKG

Lead II

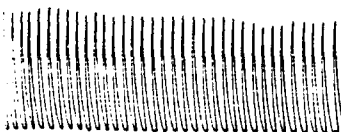
25 mm/sec



II

Tidal Volume
ml/breath

-200



Arterial Blood Pressure mm Hg

-100



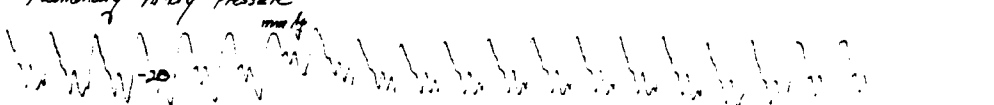
-0

Intrapleural pressure

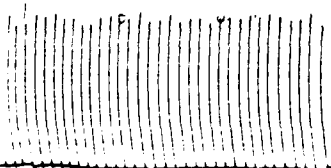


Pulmonary Artery Pressure mm Hg

-0



-20 Compliance cu



Resistance cu

-5

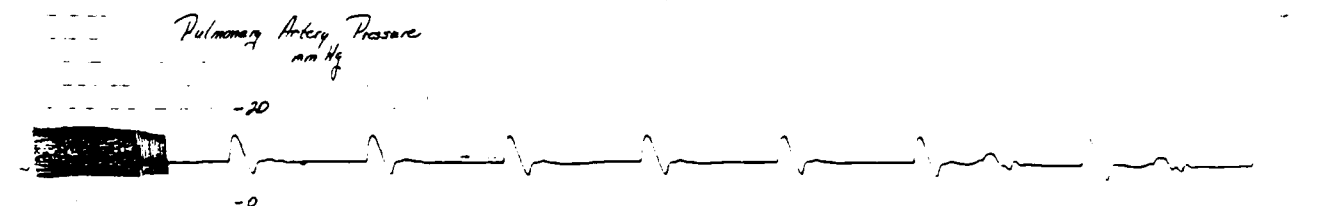
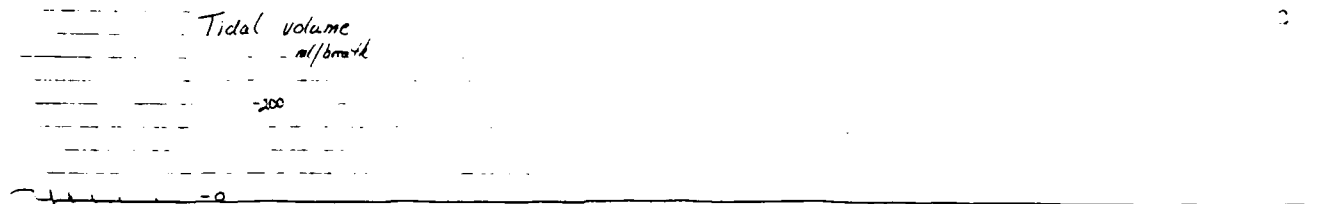
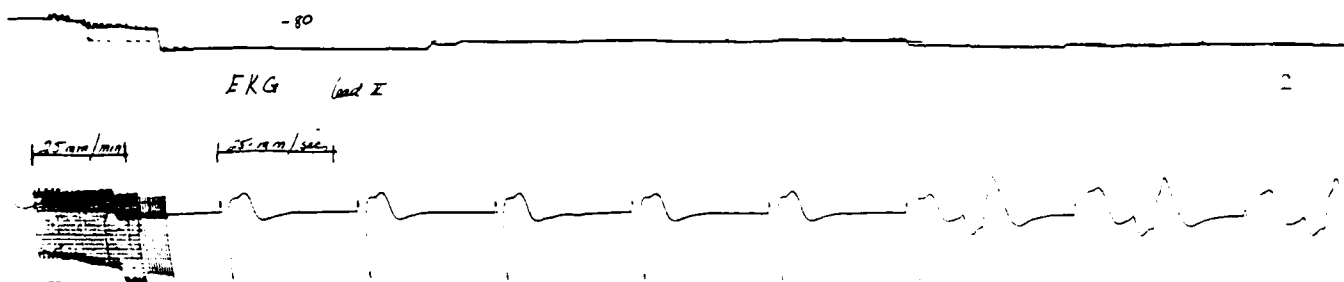


Time = +10

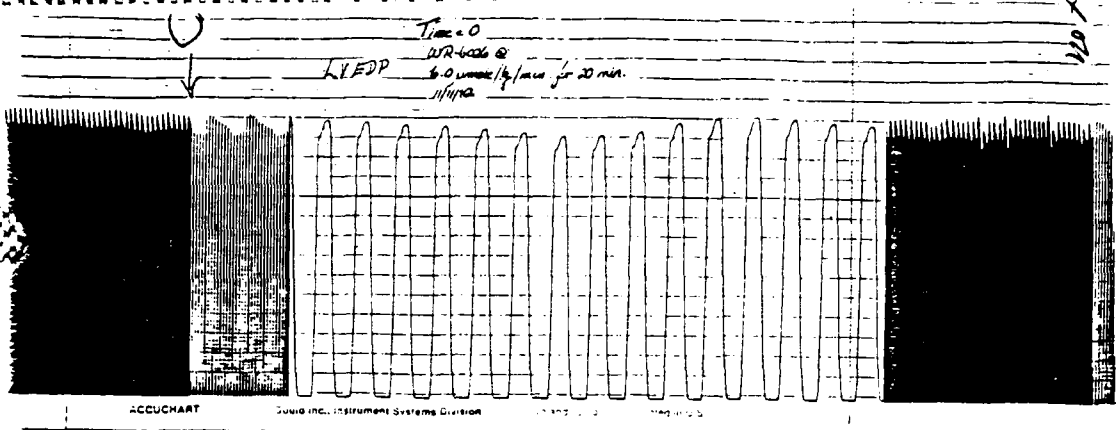
Heart rate
beats/min.
-160

Time = 20 min
WR 626 @ 6.0, made 1/2 min for 20 min.
4/1/72

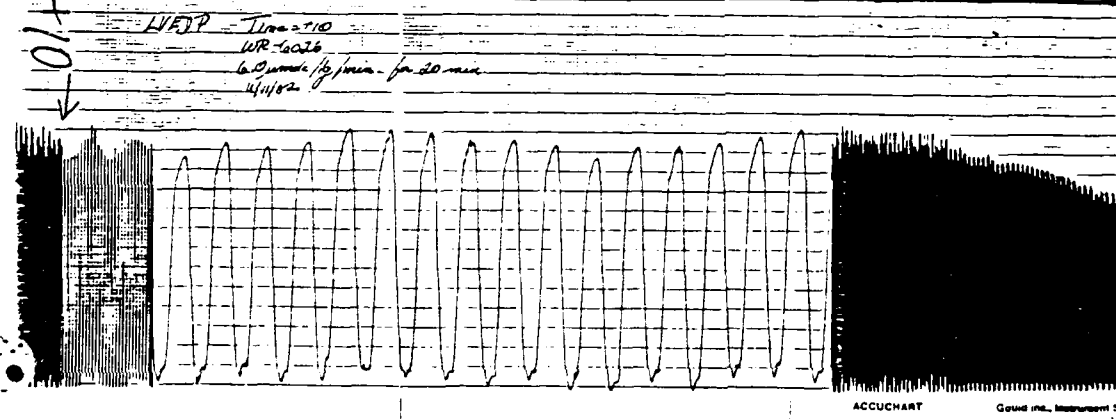
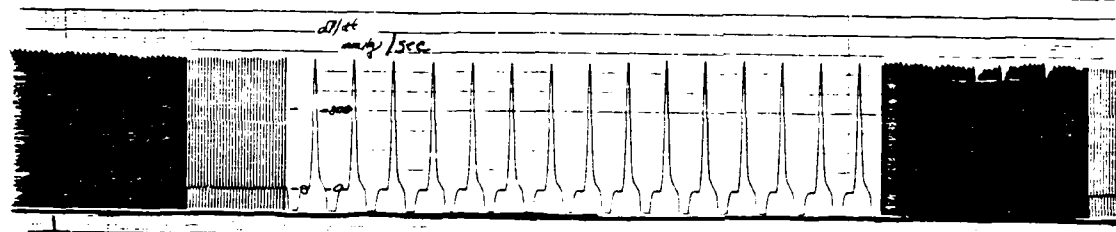
Tracing 1 C
Time = 120



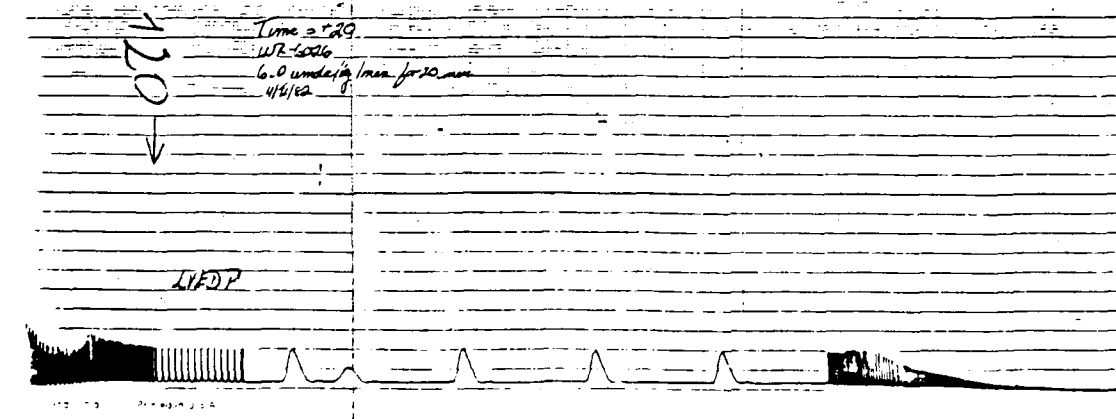
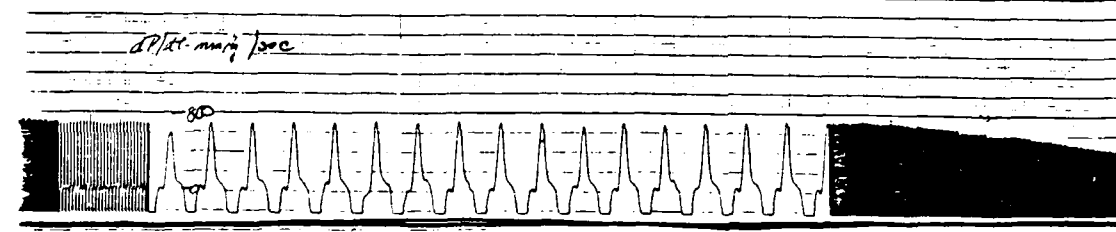
Tracing 1 D



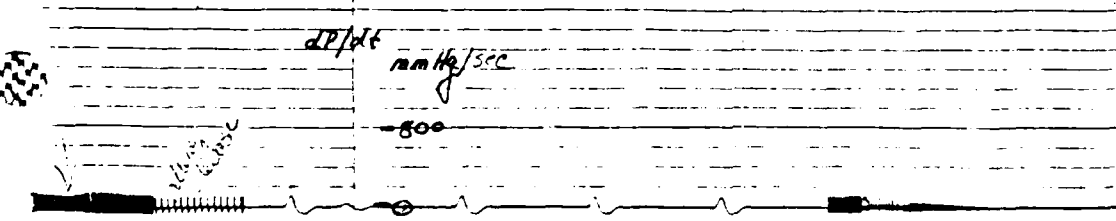
Time = 0



Time = +10



Time = +20



Heart Rate
beats/min

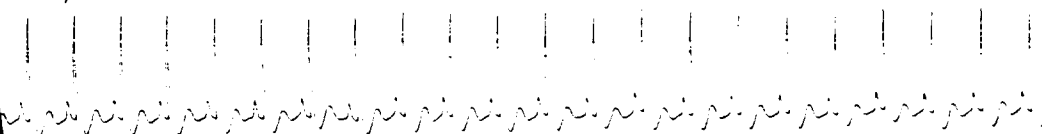
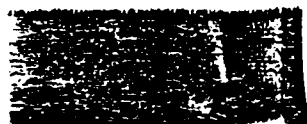
-160

Time = 0
Tintinapua
2.0 cm/sec / 4 mm for 30 min
2/23/83

Tracing 2 A
Time = 0

-80

35 mm/min
EKG lead II
25 mm/sec

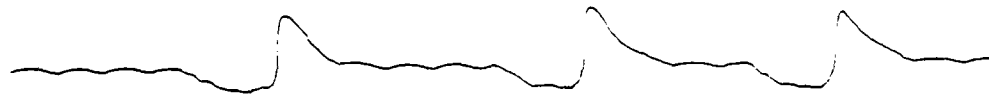
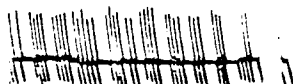


Tidal Volume
ml/ breath

-200

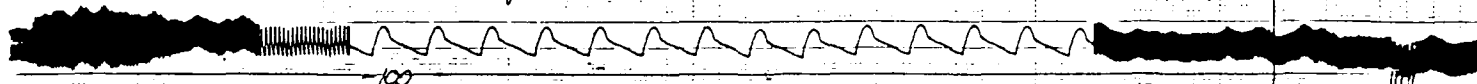


Intrapleural Pressure



ABP mmHg

-100



-20

Pulmonary Artery Pressure mmHg

-20



Heart Rate
beats/min

-160

Time = +10

Temperature

2.0 units/kg/min for 20 min
2/23/83

Tracing 2B

Time = +10

EKG lead II

25 mm/sec

25 mm/sec

Tidal Volume
ml/breath

-200

Intrapleural Pressure

ABP

mm Hg

-0

Pulmonary Artery Pressure mm Hg

-20

-0

ing 2 D

Tracing 2C

Time = +20

Heart Rate
(not triggering due to
arrhythmias) -160

Time = +20

-80

EKG lead II

= 0

1.25 mm/sec

Volume
cal 11
200

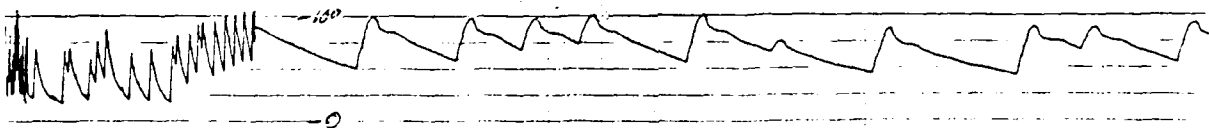


Intracranial pressure



= +10

173D



nc = +20

Pulmonary Artery Pressure mmHg

AD-A194 390

STUDY OF THE EFFECTS OF DRUGS UPON THE CARDIOVASCULAR
AND RESPIRATORY SYSTEMS(U) TENNESSEE UNIV CENTER FOR
THE HEALTH SCIENCES MEMPHIS R W CALDWELL ET AL.

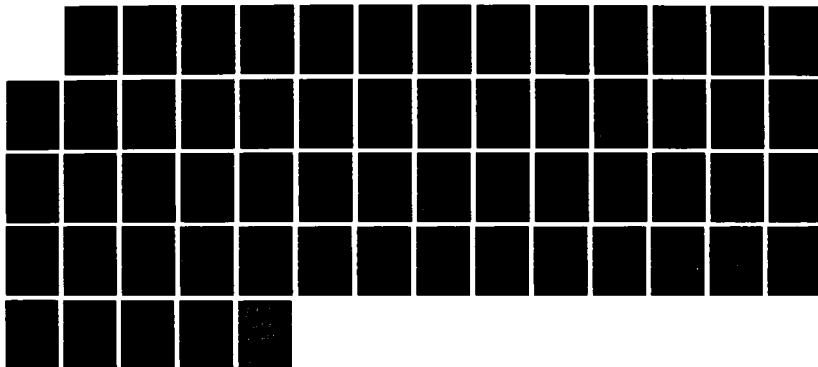
2/2

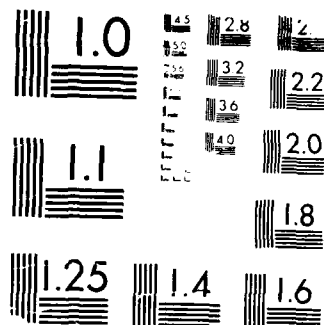
UNCLASSIFIED

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F/G 6/15

NL





MICROCOPY RESOLUTION TEST CHART

10-1000

APPENDIX F

Tabulated Data

- Note: (1) Numerical entries under time represents minutes
(2) For definitions of column heading abbreviations see Appendix A

DR. 9-4-88 WT 10.91 kg
 DOSE 4 ml/min for 120 min DATE 12/6/83

DOSE 4.0 ml/min for 150 min																				
TIME	T	RESP	M	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	P _{O₂}	A	P _{CO₂}	P _H	P _{O₂}	P _{CO₂}	P _H	HCT
30	43.0	4.0	1.42	5.0	5.0	100	144	1.67	5600	5.0	57.5	16.47	50.6	51.2	7.247	38.9	53.0	7.247	37.2	
20	51.0	4.0	1.44	5.0	5.0	100	144	1.56	3500	4.0	54.0	15.38								
10	44.0	4.0	1.40	5.0	5.0	100	140	1.51	3400	4.0	54.0	13.91								
0	46.0	4.0	1.84	5.0	5.5	100	148	1.50	3200	5.0	52.5	12.67	67.2	48.7	55.8	7.216	51.1	55.8	7.216	37.0
10	44.0	5.0	1.60	5.0	5.0	100	140	1.49	3200	5.0	14.0	9.40								
20	44.0	5.5	1.48	5.0	5.0	100	144	1.66	3000	5.5	11.5	6.93	69.0	42.5	49.1	7.262	51.6	49.1	7.262	38.0
30	45.0	5.0	1.65	5.0	5.0	100	147	1.61	3300	4.0	9.5	5.90								
40	45.0	5.5	1.40	5.0	5.0	100	144	1.54	3100	4.0	9.0	5.84	70.6	45.1	47.8	7.272	49.0	47.8	7.272	38.7
50	44.0	5.5	1.58	5.0	4.5	100	144	1.63	3200	4.0	9.0	5.56								
60	42.0	6.2	1.88	5.0	4.0	100	143	1.51	4000	4.5	8.0	4.97	11.1	56.0	45.3	7.299	48.8	45.3	7.299	40.5
70	54.0	9.0	1.45	5.0	4.0	100	144	1.61	2400	4.5	9.0	5.54								
80	42.0	5.5	1.40	5.0	6.5	100	144	1.49	3100	3.5	16.0	11.11	51.6	43.0	47.8	7.290	49.2	47.8	7.290	41.5
90	47.0	5.0	1.85	5.0	6.0	100	152	1.67	3300	4.0	18.0	4.77								
100	50.0	5.0	1.50	5.0	6.5	100	144	1.44	3300	5.0	17.0	14.91	50.4	46.9	44.1	7.263	46.8	44.1	7.263	40.3
110	49.0	5.0	1.45	5.0	7.0	100	144	1.44	3600	5.0	17.5	16.2								
120	48.0	5.5	1.44	5.0	6.5	100	144	1.44	3400	4.0	17.5	15.53	59.2	42.8	41.3	7.264	47.4	41.3	7.264	39.2

DRUG Pop-buffa WT 9.09kg

DOSE 4ml/min for 20min DATE 10/18/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	A P _{O2}	A P _{CO2}	A PH	V P _{O2}	V P _{CO2}	V PH	HCT
-30	2.0	15	1.0	15	15	145/100	100	1.0	1.0	1.0	1.0	8.64	57.8	27.2	74.2	39.1	45.5	7.25	64.2
-20	2.0	10	1.0	15	15	145/100	100	1.0	1.0	1.0	1.0	10.0	57.8	27.2	74.2	39.1	45.5	7.25	64.2
-10	2.0	10	1.0	15	15	145/100	100	1.0	1.0	1.0	1.0	11.1	57.8	27.2	74.2	39.1	45.5	7.25	64.2
0	2.0	10	1.0	15	15	145/100	100	1.0	1.0	1.0	1.0	12.0	57.8	27.2	74.2	39.1	45.5	7.25	64.2
10	2.0	10	1.0	15	15	145/100	100	1.0	1.0	1.0	1.0	12.0	57.8	27.2	74.2	39.1	45.5	7.25	64.2
20	2.0	14.0	1.0	14.0	14.0	145/100	100	1.0	1.0	1.0	1.0	12.0	57.8	27.2	74.2	39.1	45.5	7.25	64.2
30	2.0	14.0	1.0	14.0	14.0	145/100	100	1.0	1.0	1.0	1.0	12.0	57.8	27.2	74.2	39.1	45.5	7.25	64.2
40	2.0	14.0	1.0	14.0	14.0	145/100	100	1.0	1.0	1.0	1.0	12.0	57.8	27.2	74.2	39.1	45.5	7.25	64.2
50	2.0	14.0	1.0	14.0	14.0	145/100	100	1.0	1.0	1.0	1.0	12.0	57.8	27.2	74.2	39.1	45.5	7.25	64.2
60	2.0	14.0	1.0	14.0	14.0	145/100	100	1.0	1.0	1.0	1.0	12.0	57.8	27.2	74.2	39.1	45.5	7.25	64.2
70	2.0	14.0	1.0	14.0	14.0	145/100	100	1.0	1.0	1.0	1.0	12.0	57.8	27.2	74.2	39.1	45.5	7.25	64.2
80	2.0	14.0	1.0	14.0	14.0	145/100	100	1.0	1.0	1.0	1.0	12.0	57.8	27.2	74.2	39.1	45.5	7.25	64.2
90	2.0	14.0	1.0	14.0	14.0	145/100	100	1.0	1.0	1.0	1.0	12.0	57.8	27.2	74.2	39.1	45.5	7.25	64.2
100	2.0	14.0	1.0	14.0	14.0	145/100	100	1.0	1.0	1.0	1.0	12.0	57.8	27.2	74.2	39.1	45.5	7.25	64.2
110	2.0	14.0	1.0	14.0	14.0	145/100	100	1.0	1.0	1.0	1.0	12.0	57.8	27.2	74.2	39.1	45.5	7.25	64.2
120	2.0	14.0	1.0	14.0	14.0	145/100	100	1.0	1.0	1.0	1.0	12.0	57.8	27.2	74.2	39.1	45.5	7.25	64.2

DRUG PO₂-buffer WT 10-21 kg

DOSE nothing for 22 min DATE 7/16/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	DR/DT	PWP	PAP	PVR	A P _{O₂}	A P _{CO₂}	A PH	V P _{O₂}	V P _{CO₂}	V PH	HCT
-30	17	16.5	1.1	1	1	115	115	1.47	160	0.0	1.0	5.00	81.2	58.8	74.4	74.4	44.0	7.375	35.7
-20	17	17.5	1.45	1	1	115	115	1.34	800	-0.5	7.0	5.00							
-10	17	16.0	1.1	1	1	115	115	1.24	800	-1.0	6.5	5.34							
0	17	22.5	1.87	1	1	115	115	1.24	800	-1.0	6.0	4.84	81.1	58.8	74.4	74.4	44.0	7.375	35.7
10	17	16.5	1.1	1	1	115	115	1.14	800	-1.0	6.0	5.26	81.0	58.8	74.4	74.4	44.0	7.375	35.7
20	17	45.5	1.1	1	1	115	115	1.13	800	-	6.0	6.10	88.0	58.8	74.4	74.4	44.0	7.375	35.7
30	17	17.5	1.1	1	1	115	115	1.08	800	-	6.5	6.02	88.0	58.8	74.4	74.4	44.0	7.375	35.7
40	17	59.5	1.1	1	1	115	115	1.50	800	-	7.5	5.71	88.0	58.8	74.4	74.4	44.0	7.375	35.7
50	17	11.0	1.1	1	1	115	115	1.02	800	-	8.0	5.57	88.0	58.8	74.4	74.4	44.0	7.375	35.7
60	17	43.5	1.1	1	1	115	115	1.28	800	-	8.0	5.13	88.0	58.8	74.4	74.4	44.0	7.375	35.7
70	17	49.5	1.1	1	1	115	115	1.47	800	-	7.0	4.56	88.0	58.8	74.4	74.4	44.0	7.375	35.7
80	17	45.0	1.1	1	1	115	115	1.24	800	-	6.0	4.84	88.0	58.8	74.4	74.4	44.0	7.375	35.7
90	17	44.0	1.1	1	1	115	115	1.07	800	-	5.5	5.14	88.0	58.8	74.4	74.4	44.0	7.375	35.7
100	17	44.5	1.1	1	1	115	115	1.06	800	-	5.5	5.13	88.0	58.8	74.4	74.4	44.0	7.375	35.7
110	17	46.5	1.1	1	1	115	115	1.11	800	-	5.5	4.95	88.0	58.8	74.4	74.4	44.0	7.375	35.7
120	17	45.5	1.1	1	1	115	115	1.06	800	-	5.5	5.13	88.0	58.8	74.4	74.4	44.0	7.375	35.7

Drug Ph. buffer WT 12.27kg

DOSE 4ml/min for 20 min DATE 6/30/83

TIME	T	RFS _D	MV	C	D	ABP	HR	CO	DP/DT	PWP	PAP	PVR	A P _{O₂}	A P _{CO₂}	A PH	V P _{O₂}	V P _{CO₂}	V PH	HCT
-30	3.0	2.5	1.18	4.0	2.0	110	135	1.20	800	1.5	12.5	6.55	66.6	41.4	7.23	41.0	46.4	7.283	59.7
-20	3.0	2.5	1.18	4.0	2.0	110	135	1.20	800	1.5	12.5	5.58							
-10	4.0	2.5	1.18	4.0	4.5	110	135	1.40	840	1.5	11.0	7.86							
0	4.0	3.0	1.44	4.0	8.0	110	140	1.22	800	2.0	11.0	8.53	65.8	45.0	7.265	46.5	49.1	7.245	41.0
10	3.0	3.0	1.41	4.0	5.0	110	130	1.18	740	1.0	10.5	8.50							
20	2.0	4.0	1.34	4.0	4.0	110	124	1.01	690	1.5	9.0	9.00	86.5	35.4	7.315	42.5	42.5	7.280	42.3
30	3.0	5.5	1.62	4.0	3.0	110	130	1.07	640	0.5	7.5	7.04							
40	3.0	6.5	1.62	4.0	3.0	110	134	1.08	640	0.5	7.0	6.48	91.4	35.6	7.335	42.9	41.5	7.306	40.7
50	3.0	9.0	1.43	4.0	4.0	110	130	1.00	640	1.5	7.5	6.95							
60	4.0	10.5	1.52	4.0	4.0	110	140	1.54	700	0.5	8.0	5.14	95.3	34.1	7.264	40.6	38.9	7.235	40.8
70	3.0	7.5	1.18	4.0	7.0	110	124	1.68	700	0.5	8.0	4.76							
80	3.0	7.0	1.14	4.0	3.0	110	118	1.62	640	0.0	7.5	4.63	95.1	34.4	7.233	35.5	36.9	7.307	41.2
90	3.0	9.5	1.18	6.0	3.0	110	118	1.28	640	0.0	7.0	5.47							
100	3.0	8.5	1.18	6.0	3.0	110	118	1.30	640	0.0	6.5	5.42	89.3	34.1	7.335	44.9	35.8	7.211	48.8
110	3.0	7.5	1.18	6.0	3.0	110	118	1.25	640	0.0	6.5	5.23							
120	3.0	7.5	1.18	6.0	3.0	110	118	1.26	640	0.0	6.0	6.25	92.1	34.1	7.365	44.5	34.1	7.234	45.0

DRUG PO4-buffer WT 10.15kg

DOSE Amiloride 2.2mg DATE 6/28/83

TIME	TV	RSP	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	A P _{O2}	A P _{CO2}	A PH	V P _{O2}	V P _{CO2}	V PH	Hct
-30	6.0	6.0	1.56	24.0	1.5	112/70	120	1.44	2.0	2.5	14.0	9.12	76.5	52.8	73.7	45.4	37.9	7.306	42.8
-20	6.0	6.0	1.56	24.0	1.5	112/70	122	1.55	2.40	2.5	15.0	9.87							
-10	6.0	6.0	1.56	24.0	1.5	112/70	120	1.50	2.0	2.0	15.0	10.00							
0	6.0	6.0	1.56	24.0	1.5	112/70	122	1.41	2.0	2.5	15.0	10.64	80.7	53.1	73.7	47.6	37.2	7.342	43.7
10	6.0	6.0	1.59	24.0	1.5	112/70	122	1.52	2.0	2.5	14.5	8.32							
20	6.0	6.0	1.56	24.0	1.5	112/70	122	1.51	2.0	2.5	11.5	8.58	85.9	51.0	73.62	45.4	36.1	7.335	43.7
30	6.0	6.0	1.56	24.0	1.5	112/70	124	1.52	2.40	1.0	11.0	7.02							
40	6.0	6.0	1.56	24.0	1.5	112/70	124	1.57	2.40	2.5	11.0	8.16	92.7	57.9	74.0	47.5	38.1	7.379	46.0
50	6.0	6.0	1.56	24.0	1.5	112/70	124	1.52	2.40	0.0	12.0	7.84							
60	6.0	6.0	1.56	24.0	1.5	112/70	124	1.57	2.40	0.5	12.0	9.45	91.1	57.1	73.95	48.6	39.9	7.341	47.0
70	6.0	6.0	1.56	24.0	1.5	112/70	124	1.52	2.40	-1.0	12.0	9.87							
80	6.0	6.0	1.56	24.0	1.5	112/70	124	1.55	2.40	1.0	11.0	9.75	94.4	54.7	74.13	49.1	41.4	7.371	50.3
90	6.0	6.0	1.56	24.0	1.5	112/70	124	1.51	2.40	0.5	12.0	9.93							
100	6.0	6.0	1.56	24.0	1.0	112/70	122	1.52	2.40	3.0	12.0	8.45	88.7	56.1	73.71	49.0	49.8	7.359	47.7
110	6.0	6.0	1.56	24.0	1.0	112/70	124	1.56	2.40	2.5	10.0	10.42							
120	6.0	6.0	1.56	24.0	1.5	112/70	124	1.58	2.40	1.0	12.2	7.56	85.2	57.8	73.83	47.4	42.7	7.359	45.5

DRUG NR 6026 WT 12.04 kg
 DOSE 10 mg/kg/min DATE 1/6/84

TIME	T	RESP	M	C	R	ABD	HR	CO	DP/DT	PWP	PAP	PVR	PO ₂	PCO ₂	PH	PO ₂	PCO ₂	PH	HCT
-30	200	50	2.0	22	-	100	176	556	50	155	1200	39.1	51.7	51.7	7.20	22.4	55.6	7.217	45.3
-20	35	35	1.5	21	-	100	200	500	30	165	800	20.5							
-10	35	40	1.5	20	-	100	216	508	30	150	700	20.1							
0	30	45	1.5	20	-	100	218	506	35	140	600	20.5	71.8	71.8	7.265	45.1	51.7	7.236	41.0
10	70	50	2.0	20	-	100	224	500	60	140	500	20.5							
20	75	60	2.0	20	-	100	224	500	60	140	500	20.5	63.2	42.8	7.289	48.5	14.2	7.285	40.7
30	70	40	1.5	20	-	100	220	508	70	130	500	20.5							
40	75	40	1.5	20	-	100	220	500	50	140	500	20.5	57.8	41.1	7.254	43.0	17.9	7.243	45.7
50	70	50	1.5	20	-	100	220	500	50	130	600	20.5							
60	50	60	2.0	20	-	100	222	504	50	150	800	20.5	55.1	41.1	7.250	53.5	18.9	7.264	46.8
70	50	50	1.5	20	-	100	220	500	50	165	800	20.5							
80	50	50	1.5	20	-	100	220	500	55	140	800	20.5	45.1	41.2	7.246	49.1	61.0	7.174	50.0
90	50	50	1.5	20	-	100	220	500	55	140	800	20.5							
100	40	55	1.5	20	-	100	220	500	30	140	700	20.5	48.4	43.7	7.162	21.0	65.6	7.144	48.3
110	40	45	1.2	20	-	100	220	500	55	110	800	20.5							
120	40	50	1.0	20	-	100	220	500	50	80	600	20.5	48.7	42.4	7.172	46.6	61.7	7.155	45.0

DRUG WR-6026 WT 8.52g

DOSE 10mg/kg DATE 4/18/83

DOSE ~~25mg/kg~~ DATE 11/18/83																								
TIME	T	RESP	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	A	P _{O₂}	A	P _{CO₂}	A	P _H	P _{O₂}	V	P _{CO₂}	V	P _H	HCT
-30	5.0	4.5	1.17	2.0	1.2	5.5	136	1.38	300	5.0	11.5	7.28	71.1	42.2	44.6	42.5	7.37	7.37	6.29	44.6	6.29	37.5		
-20	5.0	4.5	1.12	2.0	1.2	5.5	134	1.40	300	5.0	8.0	5.00												
-10	5.0	4.5	1.04	1.0	1.0	5.5	142	1.34	3100	5.0	10.0	7.14												
0	5.0	4.5	1.04	2.0	1.0	5.5	140	1.36	3000	3.0	11.0	7.05	77.1	51.7	45.6	56.5	7.345	7.345	7.300	45.6	7.300	40.5		
10	5.0	5.0	1.22	1.0	1.0	5.5	136	1.38	3100	5.0	15.0	8.49												
20	5.0	6.5	1.49	1.0	1.0	5.5	144	1.40	3110	5.0	13.0	8.12	92.8	45.1	44.3	54.5	7.348	7.348	7.311	44.3	7.311	38.0		
30	5.0	7.5	1.28	1.0	1.0	5.5	144	1.40	3130	4.0	9.0	5.84												
40	5.0	8.5	1.27	1.0	1.0	5.5	144	1.40	3130	4.5	9.0	5.66	75.1	51.1	45.1	40.0	7.353	7.353	7.285	45.1	7.285	40.7		
50	5.0	10.0	1.20	1.0	1.0	5.5	144	1.40	3120	4.0	4.0	5.00												
60	5.0	8.5	1.01	1.0	1.0	5.5	144	1.40	3120	4.0	9.2	5.36	74.1	53.0	47.6	45.5	7.349	7.349	7.274	47.6	7.274	41.0		
70	5.0	9.5	1.20	1.0	1.0	5.5	144	1.40	3100	4.0	9.0	5.34												
80	5.0	10.0	1.10	1.0	1.0	5.5	144	1.40	3140	4.0	7.0	4.74	74.1	47.9	48.6	44.4	7.345	7.345	7.246	48.6	7.246	40.5		
90	5.0	9.5	1.04	1.0	1.0	5.5	144	1.40	3140	5.5	7.0	4.95												
100	5.0	8.5	1.05	1.0	1.0	5.5	144	1.40	3140	5.0	7.0	4.89	64.1	34.9	53.6	45.1	7.342	7.342	7.246	53.6	7.246	41.0		
110	5.0	8.5	1.04	1.0	1.0	5.5	144	1.40	3140	4.0	6.5	6.15												
120	5.0	8.5	1.14	1.0	1.0	5.5	144	1.40	3140	5.0	0.5	5.28	74.1	34.9	53.6	45.1	7.342	7.342	7.246	53.6	7.246	41.0		

DRUG WR-606 WT 1091g

DOSE 1g/ml/kg/min DATE 10/27/83

TIME	T	RESP	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	PO ₂	A	PH	PO ₂	PCO ₂	PH	HCT
-30	240	20.0	1.00	18.0	5.5	117/75	140	2.00	600	1.0	6.5	3.25	51.3	61.8	1.120	19.3	66.8	7.128	42.8
-20	180	23.5	1.21	18.0	6.5	117/75	148	1.81	610	1.0	5.5	3.04							
-10	220	8.5	1.52	18.0	5.5	117/70	140	1.93	600	1.0	5.5	2.85							
0	220	2.0	1.76	18.0	6.5	117/70	130	2.08	640	1.0	6.0	2.88	51.9	61.8	1.125	16.1	76.8	7.061	43.3
10	220	4.5	1.61	18.0	6.5	117/70	142	1.27	670	1.0	6.0	2.64							
20	220	16.5	1.75	18.0	6.5	117/70	144	2.34	680	1.0	5.0	2.11	44.6	71.0	7.069	23.3	79.9	7.042	43.0
30	220	14.0	1.75	18.0	6.5	117/70	144	1.94	680	1.0	5.0	2.32							
40	220	11.5	1.64	17.0	6.5	117/70	144	1.84	680	1.0	5.5	2.49	57.9	61.8	1.090	36.8	82.3	7.048	42.5
50	220	14.0	1.64	17.0	6.5	117/70	144	1.73	670	1.0	5.5	3.32							
60	220	14.0	1.64	17.5	6.5	117/70	144	1.66	670	1.0	5.0	3.21	57.5	63.0	1.117	41.3	76.5	7.059	41.2
70	220	14.0	1.64	18.0	6.5	117/70	144	1.66	670	1.0	5.0	3.21							
80	220	14.0	1.64	18.0	6.5	117/70	144	1.60	680	1.0	6.0	2.75	57.6	63.0	7.121	41.3	75.8	7.083	40.5
90	220	14.0	1.64	18.0	6.5	117/70	144	1.58	680	1.0	6.0	3.80							
100	220	14.0	1.64	18.0	6.5	117/70	144	1.64	680	1.0	6.0	3.66	61.5	57.4	7.117	42.9	74.1	7.047	40.0
110	220	14.5	1.64	18.0	6.5	117/70	144	1.62	680	1.0	6.0	3.75							
120	220	14.0	1.64	18.0	6.5	117/70	144	1.56	680	1.0	6.5	4.17	64.1	57.5	7.119	44.4	64.8	7.164	37.2

DRUG WUR 6026 WT 8.18 kg

DOSE 6.0 mg/kg DATE 4/8/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	DR/DT	PWP	PAP	PVR	A P _{O2}	A P _{CO2}	A PH	V P _{O2}	V P _{CO2}	V PH	HCT
-30	1.0	12	1.0	0	0	100	120	1.0	5.75	0.0	6.0	5.5	83.5	31.3	7.35	41.0	41.2	7.365	30.5
-20	1.0	12	1.0	0	0	100	120	1.0	5.75	0.0	5.0	5.0	83.5	31.3	7.35	41.0	41.2	7.365	30.5
-10	1.0	12	1.0	0	0	100	120	1.0	5.75	0.0	4.5	4.5	83.5	31.3	7.35	41.0	41.2	7.365	30.5
0	1.0	12	1.0	0	0	100	120	1.0	5.75	0.0	4.5	4.5	83.5	31.3	7.35	41.0	41.2	7.365	30.5
10	1.0	12	1.0	0	0	100	120	1.0	5.75	0.0	5.0	5.0	83.5	31.3	7.35	41.0	41.2	7.365	30.5
20	1.0	12	1.0	0	0	100	120	1.0	5.75	0.0	6.0	4.90	91.9	34.0	7.355	51.4	48.8	7.353	30.0
30	1.0	12	1.0	0	0	100	120	1.0	5.75	0.0	5.0	4.40	91.9	34.0	7.355	51.4	48.8	7.353	30.0
40	1.0	12	1.0	0	0	100	120	1.0	5.75	0.0	5.0	4.40	91.9	34.0	7.355	51.4	48.8	7.353	30.0
50	1.0	12	1.0	0	0	100	120	1.0	5.75	0.0	5.0	4.40	91.9	34.0	7.355	51.4	48.8	7.353	30.0
60	1.0	12	1.0	0	0	100	120	1.0	5.75	0.0	6.0	6.0	87.1	35.8	7.321	51.6	46.7	7.300	30.3
70	1.0	12	1.0	0	0	100	120	1.0	5.75	0.0	4.5	5.0	87.1	35.8	7.321	51.6	46.7	7.300	30.3
80	1.0	12	1.0	0	0	100	120	1.0	5.75	0.0	4.0	5.0	87.1	35.8	7.321	51.6	46.7	7.300	30.3
90	1.0	12	1.0	0	0	100	120	1.0	5.75	0.0	4.5	5.0	87.1	35.8	7.321	51.6	46.7	7.300	30.3
100	1.0	12	1.0	0	0	100	120	1.0	5.75	0.0	4.5	5.0	87.1	35.8	7.321	51.6	46.7	7.300	30.3
110	1.0	12	1.0	0	0	100	120	1.0	5.75	0.0	5.0	4.40	87.1	35.8	7.321	51.6	46.7	7.300	30.3
120	1.0	12	1.0	0	0	100	120	1.0	5.75	0.0	5.0	4.40	87.1	35.8	7.321	51.6	46.7	7.300	30.3

DRUG WR-6026 WT 9.77kg
 DOSE 1.0mg/kg/min DATE 8/30/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	A P _{O2}	A P _{CO2}	A PH	V P _{O2}	V P _{CO2}	V PH	HCT
-30						112/75	132	1.88	5400	3.0	12.5	6.65	58.9	45.4	7.50	49.7	48.0	7.204	44.3
-20						112/75	124	1.74	5600	5.0	13.0	7.30							
-10						112/75	132	1.84	5100	4.5	13.0	6.72							
0				0	8	112/75	124	1.66	5600	5.0	14.0	7.25	51.6	47.8	7.188	48.3	48.1	7.193	46.2
10				0		112/75	124	1.62	5600	5.0	11.0	6.40	61.0	43.7	7.225	46.1	44.5	7.239	46.7
20				0	8	112/75	124	1.76	5600	6.0	11.0	7.05	87.4	51.8	7.221	44.7	42.4	7.205	44.5
30				0		112/75	124	1.58	5600	5.5	9.5	5.97							
40				0	17	112/75	124	1.55	5600	5.0	8.0	5.16	13.2	51.8	7.230	42.8	44.5	7.209	44.5
50				0		112/75	124	1.61	5600	4.0	12.5	5.12							
60				0	8	112/75	124	1.14	5600	5.5	7.5	4.11	13.2	51.8	7.230	42.8	44.5	7.209	44.5
70				0		112/75	124	1.67	5600	5.0	8.0	4.11							
80				0	8	112/75	124	1.17	5600	5.0	8.5	5.12	44.0	41.7	7.235	41.9	41.9	7.204	44.7
90				0	5	112/75	124	1.68	5600	4.0	10.0	6.08							
100				5		112/75	124	1.51	5600	4.0	9.5	6.08	63.9	41.7	7.238	41.2	41.8	7.202	44.5
110				5		112/75	124	1.51	5600	4.0	9.0	7.50							
120				0		112/75	124	1.51	5600	4.0	9.2	6.58	58.4	41.7	7.231	41.2	41.8	7.207	44.5

DRUG WR-6026 WT 13.64kg
 DOSE 40mg/kg DATE 8/16/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	A P _{O2}	A P _{CO2}	A PH	V P _{O2}	V P _{CO2}	V PH	HCT
-30	5.0	5.0	2.0	0		102	144	1.44	144	1.5	11.5	4.96	83.1	4.5	7.71	48.1	50.5	7.576	33.5
-20	5.0	5.0	2.0	0		104	140	1.40	140	1.5	11.0	5.05	83.1	4.5	7.71	48.1	50.5	7.576	33.5
-10	5.0	5.0	2.0	0		104	140	1.40	140	1.5	11.0	5.05	83.1	4.5	7.71	48.1	50.5	7.576	33.5
0	5.0	5.0	2.0	0		104	140	1.40	140	1.5	11.0	5.05	83.1	4.5	7.71	48.1	50.5	7.576	33.5
10	5.0	5.0	2.0	0		104	140	1.40	140	1.5	11.0	5.05	83.1	4.5	7.71	48.1	50.5	7.576	33.5
20	5.0	5.0	2.0	0		104	140	1.40	140	1.5	11.0	5.05	83.1	4.5	7.71	48.1	50.5	7.576	33.5
30	5.0	5.0	2.0	0		104	140	1.40	140	1.5	11.0	5.05	83.1	4.5	7.71	48.1	50.5	7.576	33.5
40	5.0	5.0	2.0	0		104	140	1.40	140	1.5	11.0	5.05	83.1	4.5	7.71	48.1	50.5	7.576	33.5
50	5.0	5.0	2.0	0		104	140	1.40	140	1.5	11.0	5.05	83.1	4.5	7.71	48.1	50.5	7.576	33.5
60	5.0	5.0	2.0	0		104	140	1.40	140	1.5	11.0	5.05	83.1	4.5	7.71	48.1	50.5	7.576	33.5
70	5.0	5.0	2.0	0		104	140	1.40	140	1.5	11.0	5.05	83.1	4.5	7.71	48.1	50.5	7.576	33.5
80	5.0	5.0	2.0	0		104	140	1.40	140	1.5	11.0	5.05	83.1	4.5	7.71	48.1	50.5	7.576	33.5
90	5.0	5.0	2.0	0		104	140	1.40	140	1.5	11.0	5.05	83.1	4.5	7.71	48.1	50.5	7.576	33.5
100	5.0	5.0	2.0	0		104	140	1.40	140	1.5	11.0	5.05	83.1	4.5	7.71	48.1	50.5	7.576	33.5
110	5.0	5.0	2.0	0		104	140	1.40	140	1.5	11.0	5.05	83.1	4.5	7.71	48.1	50.5	7.576	33.5
120	5.0	5.0	2.0	0		104	140	1.40	140	1.5	11.0	5.05	83.1	4.5	7.71	48.1	50.5	7.576	33.5

DROG WR 6026 WT 1284g

DOSE 25mg/kg DATE 1/9/84

TIME	T	RESP	MV	C	R	ABP	HR	CO	DR/DI	PWP	PAP	PVR	APO ₂	PCO ₂	PH	PV	PCO ₂	PH	HCT
-30	35	50	120	20	-	100	150	120	500	60	18.5	10.8	57.2	40.8	7.41	42.6	49.7	7.264	50.3
-20	30	50	120	20	-	100	150	120	500	60	18.5	10.8	57.2	40.8	7.41	42.6	49.7	7.264	50.3
-10	30	50	120	20	-	100	150	120	500	60	18.5	10.8	57.2	40.8	7.41	42.6	49.7	7.264	50.3
0	35	60	120	20	-	100	150	120	500	60	18.5	10.8	57.2	40.8	7.41	42.6	49.7	7.264	50.3
10	35	60	120	20	-	100	150	120	500	60	18.5	10.8	57.2	40.8	7.41	42.6	49.7	7.264	50.3
20	35	60	120	20	-	100	150	120	500	60	18.5	10.8	57.2	40.8	7.41	42.6	49.7	7.264	50.3
30	35	60	120	20	-	100	150	120	500	60	18.5	10.8	57.2	40.8	7.41	42.6	49.7	7.264	50.3
40	35	60	120	20	-	100	150	120	500	60	18.5	10.8	57.2	40.8	7.41	42.6	49.7	7.264	50.3
50	35	60	120	20	-	100	150	120	500	60	18.5	10.8	57.2	40.8	7.41	42.6	49.7	7.264	50.3
60	35	60	120	20	-	100	150	120	500	60	18.5	10.8	57.2	40.8	7.41	42.6	49.7	7.264	50.3
70	35	60	120	20	-	100	150	120	500	60	18.5	10.8	57.2	40.8	7.41	42.6	49.7	7.264	50.3
80	35	60	120	20	-	100	150	120	500	60	18.5	10.8	57.2	40.8	7.41	42.6	49.7	7.264	50.3
90	35	60	120	20	-	100	150	120	500	60	18.5	10.8	57.2	40.8	7.41	42.6	49.7	7.264	50.3
100	35	60	120	20	-	100	150	120	500	60	18.5	10.8	57.2	40.8	7.41	42.6	49.7	7.264	50.3
110	35	60	120	20	-	100	150	120	500	60	18.5	10.8	57.2	40.8	7.41	42.6	49.7	7.264	50.3
120	35	60	120	20	-	100	150	120	500	60	18.5	10.8	57.2	40.8	7.41	42.6	49.7	7.264	50.3

DRUG NR-6026 VV1 10.0 kg
 DOSE 2.5 mg/kg DATE 12/8/83

TIME	T	RESP	Z	C	R	ABD	HR	CO	DR/DT	PWP	PAP	PVR	PO ₂	PCO ₂	PH	PO ₂	PCO ₂	PH	HCT
30	30	90	3.42	40	62	100/10	160	1.82	4400	5.0	16.0	8.79	77.8	40.8	7.37	44.0	44.8	7.289	33.7
20	30	100	3.0	40	50	100/10	160	1.81	4500	4.5	15.0	8.29							
10	30	95	3.32	46	50	100/10	160	2.09	4300	5.0	15.0	10.53							
0	40	70	3.27	40	60	100/10	170	1.83	4400	5.0	20.0	10.93	75.1	42.2	7.37	44.5	45.8	7.262	33.2
10	35	110	4.27	186	50	100/10	175	1.80	4930	7.0	16.5	9.17							
20	30	550	5.20	160	10	100/10	170	1.58	2030	11.0	17.5	11.08	85.2	37.2	7.35	47.4	44.0	7.275	33.0
30	30	550	5.28	180	25	100/10	170	1.78	5700	9.0	13.5	8.54							
40	30	550	5.20	180	15	100/10	170	1.71	5400	7.0	13.5	7.89	86.1	35.6	7.35	42.6	42.1	7.285	33.7
50	30	530	5.15	20	15	100/10	170	1.60	4200	6.5	13.0	8.12							
60	30	550	5.80	216	20	100/10	170	1.52	1200	6.0	13.0	8.55	82.9	34.0	7.34	40.5	40.8	7.303	37.0
70	30	545	7.27	220	25	100/10	170	1.05	1830	7.0	12.0	11.43							
80	30	545	6.40	220	20	100/10	170	1.04	1850	7.0	11.5	11.06	82.8	34.6	7.34	32.5	44.9	7.274	38.5
90	30	550	6.30	206	15	100/10	170	1.10	1900	7.5	13.5	14.85							
100	30	550	6.30	200	25	100/10	170	1.11	2000	6.0	12.0	11.88	81.4	36.9	7.37	21.2	46.5	7.258	36.5
110	30	550	6.21	202	15	100/10	170	1.02	2000	5.0	13.0	12.74							
120	30	575	5.77	200	15	100/10	170	0.96	1400	4.0	12.5	13.22	86.2	34.0	7.38	35.6	46.6	7.273	35.0

URUG MR 6026 VV 1 7.32kg

DOSE 25 mg/kg/10 min DATE 11/22/83

TIME	T	R _{SP}	M	C	D	ABD	HR	CO	DP/DT	PWP	PAP	PVR	A _{P_{O2}}	A _{P_{CO2}}	A _{PH}	V _{P_{O2}}	V _{P_{CO2}}	V _{PH}	HCT
-30	40	3.0	1.0	110	74	115	140	162	1500	1.0	16.0	988	60.3	55.1	135.9	43.3	56.6	7.262	73.3
-20	40	4.5	1.0	125	76	130/120	144	146	1500	2.5	18.0	1370							
-10	40	3.0	1.0	125	75	120/115	148	132	1450	2.5	17.0	1288							
0	40	4.5	1.5	125	75	120/115	146	126	1400	2.5	17.5	1208	58.7	55.8	120.3	32.1	62.9	7.190	44.8
10	40	6.0	1.5	125	75	120	144	146	1500	6.0	15.0	904							
20	40	9.5	1.5	120	70	120	140	171	1400	7.0	15.0	817	91.6	43.2	128.2	57.8	48.5	7.266	45.0
30	40	7.0	1.5	150	78	120	140	167	1425	6.0	13.5	823							
40	40	4.5	1.5	155	74	120	140	172	1400	5.5	13.0	942	78.5	46.8	126.0	53.7	51.5	7.249	45.0
50	40	4.5	1.7	130	75	120	140	157	1600	6.0	13.0	942							
60	40	5.5	1.5	122	78	120	140	150	1500	5.5	12.5	992	65.5	52.0	120.5	46.5	54.4	7.288	46.0
70	40	4.0	1.5	130	74	120	140	160	1400	5.0	13.0	1083							
80	40	4.0	1.5	130	74	120	140	160	1500	4.0	12.0	928	66.8	54.1	125.3	44.2	61.2	7.211	48.2
90	40	4.5	1.5	120	76	120	140	160	1500	3.5	11.0	873							
100	40	4.5	1.5	120	78	120	140	160	1500	3.5	11.5	1008	71.8	51.5	124.1	42.8	62.7	7.215	47.8
110	40	4.5	1.5	120	78	120	140	160	1500	4.0	11.0	1134							
120	40	4.5	1.5	120	78	120	140	160	1500	4.5	10.0	940	81.5	48.0	126.2	40.1	62.6	7.213	47.0

DRUG WR-6026 WT 10.23 kg

DOSE 25 mg/kg/min DATE 10/19/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	A P _{O2}	A P _{CO2}	A PH	V P _{O2}	V P _{CO2}	V PH	HCT
-30	2.5	70	0	0	0	120	70	1.54	1000	0.0	10.0	5.61	-	-	-	-	-	-	-
-20	2.5	70	0	0	0	120	66	1.58	1000	10	10.5	5.53	-	-	-	-	-	-	-
-10	2.5	70	0	0	0	120	62	1.56	1000	10	10.5	5.54	-	-	-	-	-	-	-
0	2.5	70	0	0	0	120	62	1.50	1000	10	9.0	6.00	62.0	7.2	7.21	57.8	57.2	7.28	43.5
10	2.5	70	0	0	0	120	61	1.50	1000	10	9.0	6.00	62.0	7.2	7.21	57.8	57.2	7.28	43.5
20	2.5	70	0	0	0	120	60	1.43	1000	10	8.0	6.00	44.9	7.2	7.23	55.5	56.4	7.22	38.8
30	2.5	70	0	0	0	120	60	1.44	1000	10	8.0	6.00	44.9	7.2	7.23	55.5	56.4	7.22	38.8
40	2.5	70	0	0	0	120	60	1.44	1000	10	8.0	6.00	44.9	7.2	7.23	55.5	56.4	7.22	38.8
50	2.5	70	0	0	0	120	60	1.44	1000	10	8.0	6.00	44.9	7.2	7.23	55.5	56.4	7.22	38.8
60	2.5	70	0	0	0	120	60	1.44	1000	10	8.0	6.00	44.9	7.2	7.23	55.5	56.4	7.22	38.8
70	2.5	70	0	0	0	120	60	1.44	1000	10	8.0	6.00	44.9	7.2	7.23	55.5	56.4	7.22	38.8
80	2.5	70	0	0	0	120	60	1.44	1000	10	8.0	6.00	44.9	7.2	7.23	55.5	56.4	7.22	38.8
90	2.5	70	0	0	0	120	60	1.44	1000	10	8.0	6.00	44.9	7.2	7.23	55.5	56.4	7.22	38.8
100	2.5	70	0	0	0	120	60	1.44	1000	10	8.0	6.00	44.9	7.2	7.23	55.5	56.4	7.22	38.8
110	2.5	70	0	0	0	120	60	1.44	1000	10	8.0	6.00	44.9	7.2	7.23	55.5	56.4	7.22	38.8
120	2.5	70	0	0	0	120	60	1.44	1000	10	8.0	6.00	44.9	7.2	7.23	55.5	56.4	7.22	38.8

DRUG WLR 6026 WT 9.77kg
 DOSE 2.5 mg/kg DATE 10/14/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	A P _{O2}	A P _{CO2}	A PH	V P _{O2}	V P _{CO2}	V PH	HCT
-30	3.0	15	0.2	-	-	100	70	1.2	1000	8.5	8.0	5.14	101.5	55.6	7.35	88.6	46.5	7.3/2	55.3
-20	3.0	15	0.2	-	-	100	70	1.4	1000	9.0	9.0	6.29	101.5	55.6	7.35	88.6	46.5	7.3/2	55.3
-10	3.0	15	0.2	-	-	100	70	1.4	1000	9.5	9.5	4.67	101.5	55.6	7.35	88.6	46.5	7.3/2	55.3
0	3.0	15	0.2	-	-	100	70	1.5	1000	10.0	10.0	4.67	101.5	55.6	7.35	88.6	46.5	7.3/2	55.3
10	3.0	15	0.2	-	-	100	70	1.7	1000	10.0	10.0	7.95	101.5	55.6	7.35	88.6	46.5	7.3/2	55.3
20	3.0	15	0.2	-	-	100	70	1.7	1000	10.0	10.0	7.95	101.5	55.6	7.35	88.6	46.5	7.3/2	55.3
30	3.0	15	0.2	-	-	100	70	1.7	1000	10.0	10.0	7.95	101.5	55.6	7.35	88.6	46.5	7.3/2	55.3
40	3.0	15	0.2	-	-	100	70	1.7	1000	10.0	10.0	7.95	101.5	55.6	7.35	88.6	46.5	7.3/2	55.3
50	3.0	15	0.2	-	-	100	70	1.7	1000	10.0	10.0	7.95	101.5	55.6	7.35	88.6	46.5	7.3/2	55.3
60	3.0	15	0.2	-	-	100	70	1.7	1000	10.0	10.0	7.95	101.5	55.6	7.35	88.6	46.5	7.3/2	55.3
70	3.0	15	0.2	-	-	100	70	1.7	1000	10.0	10.0	7.95	101.5	55.6	7.35	88.6	46.5	7.3/2	55.3
80	3.0	15	0.2	-	-	100	70	1.7	1000	10.0	10.0	7.95	101.5	55.6	7.35	88.6	46.5	7.3/2	55.3
90	3.0	15	0.2	-	-	100	70	1.7	1000	10.0	10.0	7.95	101.5	55.6	7.35	88.6	46.5	7.3/2	55.3
100	3.0	15	0.2	-	-	100	70	1.7	1000	10.0	10.0	7.95	101.5	55.6	7.35	88.6	46.5	7.3/2	55.3
110	3.0	15	0.2	-	-	100	70	1.7	1000	10.0	10.0	7.95	101.5	55.6	7.35	88.6	46.5	7.3/2	55.3
120	3.0	15	0.2	-	-	100	70	1.7	1000	10.0	10.0	7.95	101.5	55.6	7.35	88.6	46.5	7.3/2	55.3

DRUG WR-6026 WT 12.73 kg

DOSE 25 mg/kg DATE 8/11/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	A P _{O2}	A P _{CO2}	A PH	V P _{O2}	V P _{CO2}	V PH	HCT
-30	50	25	1.0	15.5	6.8	110	155	1.32	1520	1.0	9.0	5.92	21.7	55.9	1.338	51.1	58.0	7.312	43.8
-20	50	25	1.0	14.8	6.8	105	156	1.63	1520	0.5	9.5	5.64							
-10	50	25	1.0	14.0	6.8	105	156	1.70	1320	0.5	10.0	5.88							
0	50	25	1.0	14.5	6.8	105	164	1.85	1080	0.5	8.0	4.32	22.5	44.5	1.538	45.0	56.8	7.227	42.5
10	50	25	1.0	14.5	6.8	105	164	1.46	920	1.5	7.5	5.14							
20	50	25	1.0	14.0	6.8	105	164	1.52	740	2.0	7.0	4.60	24.3	26.5	1.437	46.3	43.2	7.422	40.8
30	50	25	1.0	14.0	6.8	105	164	1.40	740	1.0	6.0	4.28							
40	50	25	1.0	14.0	6.8	105	164	1.54	280	1.5	7.0	4.54	28.5	45.5	1.511	49.7	44.2	7.540	42.0
50	50	25	1.0	14.0	6.8	105	164	1.49	280	1.5	7.5	5.00							
60	50	25	1.0	14.0	6.8	105	164	1.55	280	1.5	7.0	5.18	15.1	40.4	1.448	48.4	43.4	7.325	42.0
70	50	25	1.0	14.0	6.8	105	164	1.22	280	0.0	5.5	4.54							
80	50	25	1.0	14.1	6.8	105	164	1.51	280	2.5	6.0	4.58	20.5	41.6	1.484	43.8	41.7	7.414	42.8
90	50	25	1.0	14.0	6.8	105	164	1.44	280	2.0	7.0	4.80							
100	50	25	1.0	14.0	6.8	105	164	1.34	280	1.5	7.0	5.00	23.1	47.8	1.407	46.4	43.1	7.306	50.5
110	50	25	1.0	14.0	6.8	105	164	1.42	280	0.0	6.0	4.60							
120	50	25	1.0	14.0	6.8	105	164	1.30	280	1.0	7.5	5.20	27.7	45.5	1.511	42.5	43.5	7.323	40.0

DRUG 14-typhoid WT 1304g

DOSE 100mg/100ml DATE 11/9/83

TIME	TV	R _{ESP}	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	A _{P_{O₂}}	A _{P_{CO₂}}	A _{PH}	V _{P_{O₂}}	V _{P_{CO₂}}	V _{PH}	HCT
-30	5.5	6.0	5.67	0.0	0.0	107/60	504	2.57	500	0.0	12.0	0.0	55.0	43.1	7.54	44.8	50.2	7.27	37.0
-20	5.0	5.0	5.66	0.0	0.0	107/60	184	2.53	450	0.0	11.0	0.0							
-10	5.0	6.0	5.50	0.0	0.0	107/60	170	2.50	400	0.0	10.0	0.0							
0	5.0	6.0	5.0	0.0	0.0	107/60	150	2.51	400	0.0	10.0	0.0	66.1	47.5	7.78	47.7	53.2	7.26	39.2
10	5.0	6.0	5.0	0.0	0.0	107/60	140	2.41	400	0.0	10.0	0.0							
20	5.0	6.0	5.0	0.0	0.0	107/60	141	2.48	400	0.0	10.0	0.0	77.3	46.2	7.72	47.8	50.6	7.27	37.5
30	5.0	6.0	5.0	0.0	0.0	107/60	140	2.48	400	0.0	10.0	0.0	78.0	45.5	7.74	47.7	51.6	7.26	38.5
40	5.0	6.0	5.0	0.0	0.0	107/60	140	2.49	400	0.0	10.0	0.0							
50	5.0	6.0	5.0	0.0	0.0	107/60	140	2.51	400	0.0	10.0	0.0							
60	5.0	6.0	5.0	0.0	0.0	107/60	141	2.4	400	0.0	10.0	0.0	77.7	44.1	7.70	47.7	50.8	7.27	39.8
70	5.0	6.0	5.0	0.0	0.0	107/60	140	1.84	400	0.0	10.0	0.0							
80	5.0	6.0	5.0	0.0	0.0	107/60	140	1.81	400	0.0	10.0	0.0	78.7	40.5	7.54	42.9	49.7	7.26	40.7
90	5.0	6.0	5.0	0.0	0.0	107/60	140	1.64	400	0.0	10.0	0.0							
100	5.0	6.0	5.0	0.0	0.0	107/60	140	1.60	400	0.0	10.0	0.0	73.1	42.0	7.52	42.1	49.7	7.26	42.0
110	5.0	6.0	5.0	0.0	0.0	107/60	140	1.58	400	0.0	10.0	0.0							
120	5.0	6.0	5.0	0.0	0.0	107/60	140	1.56	400	0.0	10.0	0.0	60.8	48.1	7.52	41.6	53.4	7.26	41.0



●

TIME	T	R _{ESP}	MV	C	R	ABP	HR	CO	DR/DI	PWP	PAP	PVR	P _{O₂}	A	P _{CO₂}	A	P _H	P _{O₂}	V	P _H	HCT
30	280	45	126	285	6.8	250/135	156	1.71	3500	3.0	250	1462	55.7	48.4	7.259	36.7	52.5	7.244	38.2		
20	325	41.5	137	275	8.0	227/120	156	1.70	3400	2.5	210	1235									
10	295	40	122	250	9.0	227/135	140	1.66	3100	3.5	19.5	1175									
0	300	45	135	250	9.0	227/120	140	1.52	3100	1.5	170	1118	67.3	42.3	7.281	37.7	51.0	7.242	40.7		
10	160	21.5	258	19.0	1.5	240/105	160	1.80	3400	5.5	14.5	806									
20	165	27.5	344	13.5	1.5	227/75	151	1.28	1700	10.0	20.0	1542	75.5	38.8	7.294	45.8	43.9	7.261	43.5		
30	165	31.5	341	14.5	1.5	197/100	151	1.40	1710	5.5	15.5	1107									
40	160	31.0	372	15.0	1.5	157/105	119	1.38	1900	6.0	16.0	1159	69.8	42.5	7.266	47.8	48.8	7.253	46.7		
50	170	28.5	342	16.0	2.0	170/100	120	1.35	1900	6.0	17.0	1259									
60	160	30.5	366	18.0	1.5	170/100	128	1.32	1950	5.0	14.5	1248	72.9	45.3	7.264	45.1	50.2	7.238	48.0		
70	165	27.0	398	18.0	1.5	157/95	127	1.16	2000	2.5	11.0	948									
80	165	23.0	288	17.0	1.5	170/95	130	1.08	1900	3.5	11.0	1018	71.1	43.2	7.280	41.4	53.4	7.245	49.3		
90	165	27.5	316	15.5	1.5	157/95	128	0.98	1800	4.0	12.0	1224									
100	170	29.0	319	16.0	0.8	145/105	130	0.99	1900	4.0	12.0	1212	73.4	41.1	7.285	36.8	53.9	7.240	50.5		
110	115	28.0	322	14.0	0.7	145/100	120	0.90	1900	4.0	11.0	1222									
120	115	26.5	305	15.0	1.0	145/105	140	0.82	1900	4.5	11.5	1402	75.2	41.4	7.247	33.3	52.6	7.244	50.0		

DRUG NR 6026 WT 12.01kg

DOSE 40mg/kg/hr DATE 12/7/83

DOSE 40 mg/ml / 1g hour 12/1/83																						
TIME	T	RESP	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	A	P _{O₂}	A	P _H	A	P _{O₂}	V	P _H	V	HCT
30	4.0	6.5	5.73	14.0	6.0	117/110	150	2.06	0.00	5.5	35.0	12.14	50.6	48.4	1.224	56.5	7.188	36.0				
20	4.0	5.5	5.36	13.0	6.5	114/105	116	1.74	5.00	4.5	21.0	12.07										
10	4.0	6.0	5.32	16.0	10.0	114/110	102	1.72	5.200	2.0	5.10	11.73										
0	4.0	5.0	5.12	14.0	12.1	115/110	114	1.63	5.300	5.5	42.0	10.93	59.9	48.1	7.255	56.1	7.196	34.8				
10	5.0	6.0	5.40	17.0		114/110	132	1.95	1.700	7.5	53.0	11.42										
20	5.0	7.5	3.15	16.0	5.5	115/110	118	1.04	2.00	15.0	53.0	8.52	71.7	43.1	7.267	54.3	7.211	36.7				
30	5.0	7.5	3.37	16.0	5.5	115/110	110	1.18	9.50	11.5	17.0	14.41										
40	5.0	7.5	4.03	14.0	5.0	115/110	110	1.52	1.500	7.0	62.5	8.52	62.2	42.6	1.270	58.8	7.226	36.5				
50	5.0	7.5	4.77	14.0	1.0	115/110	114	1.70	1.350	6.0	62.5	8.33										
60	5.0	7.5	5.12	13.0	5.5	117/110	120	1.32	1.400	5.0	13.0	8.55	76.2	39.1	7.322	50.3	7.236	40.0				
70	5.0	7.5	5.12	13.0	5.5	115/110	114	1.65	1.500	5.0	13.5	8.53										
80	5.0	7.5	5.18	14.0	4.0	115/110	120	1.54	1.550	4.5	14.0	8.09	81.8	34.9	7.344	46.1	7.281	41.3				
90	5.0	7.5	5.55	14.0	1.0	115/110	120	1.42	1.600	3.0	11.5	8.10										
100	5.0	7.5	4.90	13.0	1.0	115/110	120	1.27	1.550	2.0	14.0	9.58	72.8	36.5	7.353	44.8	7.278	42.5				
110	5.0	7.5	4.93	14.0		115/110	124	1.24	1.550	2.5	11.5	8.58										
120	5.0	7.5	5.76	13.0	1.0	115/110	140	1.26	1.500	1.5	11.0	8.13	63.7	37.5	7.315	47.4	7.268	43.0				

DRUG WAR 6026 WT 277kg

DOSE 40mg/kg DATE 4/23/83

TIME	T	RESP	MV	C	R	ABP	HR	CO	DR/DT	PWP	PAP	PVR	A P _{O2}	A P _{CO2}	A PH	V P _{O2}	V P _{CO2}	V PH	HCT
-30	5.7	15.5	16.5	14.5	1.5	175/90	196	2.01	3550	40	25.0	5.97	79.4	33.4	14.3	44.4	36.9	7.385	36.5
-20	5.4	15.0	15.4	14.0	1.5	175/90	196	1.98	3500	35	25.0	5.97	79.4	33.4	14.3	44.4	36.9	7.385	36.5
-10	5.0	14.0	15.0	14.0	1.5	175/90	196	1.98	3500	35	25.0	5.97	79.4	33.4	14.3	44.4	36.9	7.385	36.5
0	5.0	14.5	15.5	14.5	1.5	175/90	196	1.98	3500	35	25.0	5.97	79.4	33.4	14.3	44.4	36.9	7.385	36.5
10	5.0	14.5	15.5	14.5	1.5	175/90	196	1.98	3500	35	25.0	5.97	79.4	33.4	14.3	44.4	36.9	7.385	36.5
20	5.0	14.5	15.5	14.5	1.5	175/90	196	1.98	3500	35	25.0	5.97	79.4	33.4	14.3	44.4	36.9	7.385	36.5
30	5.0	14.5	15.5	14.5	1.5	175/90	196	1.98	3500	35	25.0	5.97	79.4	33.4	14.3	44.4	36.9	7.385	36.5
40	5.0	14.5	15.5	14.5	1.5	175/90	196	1.98	3500	35	25.0	5.97	79.4	33.4	14.3	44.4	36.9	7.385	36.5
50	5.0	14.5	15.5	14.5	1.5	175/90	196	1.98	3500	35	25.0	5.97	79.4	33.4	14.3	44.4	36.9	7.385	36.5
60	5.0	14.5	15.5	14.5	1.5	175/90	196	1.98	3500	35	25.0	5.97	79.4	33.4	14.3	44.4	36.9	7.385	36.5
70	5.0	14.5	15.5	14.5	1.5	175/90	196	1.98	3500	35	25.0	5.97	79.4	33.4	14.3	44.4	36.9	7.385	36.5
80	5.0	14.5	15.5	14.5	1.5	175/90	196	1.98	3500	35	25.0	5.97	79.4	33.4	14.3	44.4	36.9	7.385	36.5
90	5.0	14.5	15.5	14.5	1.5	175/90	196	1.98	3500	35	25.0	5.97	79.4	33.4	14.3	44.4	36.9	7.385	36.5
100	5.0	14.5	15.5	14.5	1.5	175/90	196	1.98	3500	35	25.0	5.97	79.4	33.4	14.3	44.4	36.9	7.385	36.5
110	5.0	14.5	15.5	14.5	1.5	175/90	196	1.98	3500	35	25.0	5.97	79.4	33.4	14.3	44.4	36.9	7.385	36.5
120	5.0	14.5	15.5	14.5	1.5	175/90	196	1.98	3500	35	25.0	5.97	79.4	33.4	14.3	44.4	36.9	7.385	36.5

DRUG NR 6026 WT 11.57 kg

DOSE 20 mg/kg DATE 10/26/83

TIME	T	RESP	MV	C	R	ABD	HR	CO	DP/DT	PWP	PAP	PVR	A P _{O2}	A P _{CO2}	A PH	V P _{O2}	V P _{CO2}	V PH	HCT
30	310	22	6.3	50	1.0	17/105	180	1.98	3400	5.0	60	6.86	740	42.4	7.33	40.9	47.3	7.315	33.3
20	310	20	6.12	50	1.5	17/105	156	1.90	3300	1.5	12.0	6.32							
10	350	8.5	6.20	540	1.5	17/105	156	1.78	3300	1.0	11.0	6.18							
0	300	8.5	6.50	500	1.5	17/105	180	1.79	3300	1.5	11.0	6.14	688	41.2	7.33	41.5	46.7	7.296	31.5
10	370	4.5	6.1	410	2.0	17/105	176	1.68	1900	5.0	16.0	7.69							
20	365	12.0	4.3	500	1.5	17/105	156	1.44	1050	7.0	19.0	13.19	71.1	37.0	7.34	44.7	59.9	7.319	40.5
30	350	12.0	4.35	400	1.6	17/105	148	1.36	1335	7.0	16.1	2.09							
40	370	12.0	4.6	500	1.0	17/105	178	1.73	1650	5.0	13.0	7.43	76.1	33.8	7.32	44.7	40.4	7.323	35.8
50	370	12.0	4.18	400	1.5	17/105	178	1.60	1800	3.5	12.2	5.66							
60	370	14.5	5.0	410	2.0	17/105	150	1.07	1925	3.0	11.0	4.83	72.9	31.9	7.386	32.3	38.9	7.363	34.5
70	375	14.5	5.00	350	2.0	17/105	168	1.02	3300	2.0	9.0	4.88							
80	370	14.5	7.25	400	1.0	17/105	255	1.53	3330	3.0	11.0	5.53	75.1	31.7	7.32	33.9	36.9	7.369	36.8
90	370	16.0	7.80	440	1.5	17/105	177	1.56	3750	2.0	11.5	4.87							
100	370	18.0	5.88	440	2.0	17/105	181	1.52	3730	3.0	13.0	6.44	71.7	31.7	1.389	38.9	6.1	7.368	38.0
110	380	17.5	5.55	500	2.0	17/105	170	1.52	3450	2.0	11.5	6.01							
120	370	17.0	5.61	400	1.0	17/105	184	1.37	3350	1.0	13.0	6.70	71.5	31.7	1.392	37.3	57.9	7.362	42.2

DROG UR 6026 WT 8.64 kg

DOSE 4.0 mg/kg DATE 8/4/83

TIME	T	RESP	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	A P _{O2}	A P _{CO2}	A PH	V P _{O2}	V P _{CO2}	V PH	HCT
-30	22.2	40	4.5	17.8	22.8	78	161	1.89	400	0	8.0	4.03	65.5	57.4	7.36	46.4	42.1	7.203	21.5
-20	22.0	40	4.5	18.2	22.8	78	160	1.66	420	-1.5	8.5	5.12							
-10	22.4	40	4.5	18.1	22.8	78	161	1.64	430	0	7.0	4.27							
0	22.0	40	4.5	18.2	22.8	78	161	1.50	430	0	6.0	4.00	67.5	55.1	7.467	53.9	46.1	7.185	26.0
10	22.0	40	4.5	18.2	22.8	78	161	1.47	430	1.0	7.0	4.76							
20	22.0	40	4.5	18.2	22.8	78	161	1.57	430	4.0	9.0	5.36	72.9	52.1	7.290	41.9	58.6	7.244	36.7
30	22.0	40	4.5	18.2	22.8	78	161	1.64	430	1.0	8.0	4.88							
40	22.0	40	4.5	18.2	22.8	78	161	1.65	430	-1.0	7.5	4.54	66.3	54.2	7.279	47.5	59.3	7.230	27.5
50	22.0	40	4.5	18.2	22.8	78	161	1.44	430	-1.0	6.0	4.11							
60	22.0	40	4.5	18.2	22.8	78	161	1.31	430	-1.5	5.5	4.30	63.1	54.8	7.262	55.5	41.0	7.182	27.8
70	22.0	40	4.4	18.9	22.8	78	161	1.30	430	1.5	4.5	5.57							
80	22.0	40	4.4	18.9	22.8	78	161	1.32	430	2.0	4.5	5.64	71.1	55.4	7.285	53.9	45.3	7.189	27.0
90	22.0	40	4.4	18.9	22.8	78	161	1.15	430	2.0	4.0	5.48							
100	22.0	40	4.4	18.9	22.8	78	161	1.15	430	2.0	4.5	5.12	71.2	54.1	7.287	55.1	45.3	7.177	25.0
110	22.0	40	4.4	18.8	22.8	78	161	1.14	430	1.5	4.5	5.04							
120	22.0	40	4.4	18.8	22.8	78	161	1.14	430	1.5	4.5	5.04							

Drug WR-6026 WT 9.54kg

Dose 40mg/kg/min DATE 9/15/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	A P _{O2}	A P _{CO2}	A PH	V P _{O2}	V P _{CO2}	V PH	HCT
-30						16.7/11.0	127	1.55	5.5	0.5	0.5	17.7	7.5	45.6	74.5	74.5	46.5	71.4	50.3
-20						16.5/11.5	125	1.48	5.5	0.0	0.0	17.0							
-10					0.8	16.1/11.0	127	1.44	5.0	0.0	0.0	16.9							
0						15.9/10.0	132	1.51	5.0	0.5	0.5	16.5	83.5	42.9	74.5	74.5	42.5	71.9	51.5
10				0		15.5/10.0	127	1.52	5.0	0.0	0.5	16.2							
20				0		15.4/10.0	126	1.50	8.0	0.0	0.0	15.5	84.6	40.1	74.5	74.5	42.5	71.5	51.5
30						15.2/10.0	125	1.50	7.0	0.0	0.0	15.5							
40					0	15.0/10.0	125	1.51	7.5	0.0	0.0	15.4	84.4	39.0	74.5	74.5	42.0	71.5	50.3
50						14.8/10.0	125	1.50	7.0	0.0	0.0	15.1							
60						14.6/10.0	125	1.47	7.0	0.0	0.0	15.0	83.0	39.0	74.5	74.5	42.0	71.1	50.3
70						14.4/10.0	125	1.42	7.0	0.0	0.5	14.6							
80						14.2/10.0	127	1.52	7.0	0.0	0.0	14.6	82.5	38.6	74.5	74.5	42.0	71.5	50.3
90				1		14.0/10.0	127	1.08	7.0	0.5	0.4	14.5							
100						13.8/10.0	124	1.5	7.5	0.5	0.5	14.1	81.5	37.5	74.5	74.5	42.0	71.5	50.3
110						13.6/10.0	110	1.5	7.5	0.5	0.5	13.5							
120						13.4/10.0	110	1.46	7.5	0.5	0.5	13.0	81.0	37.0	74.5	74.5	42.0	71.5	50.3

Drug: Levamisole 100 mg WT 10.33g
 DOSE 0.5 mg/kg body weight DATE 11/2/84

TIME	T	RESP	MV	C	R	ABP	HR	CO	DR/DI	PWP	PAP	PVR	A P _{O2}	A P _{CO2}	A PH	V P _{O2}	V P _{CO2}	V PH	HCT
30	1.0	10	1.0	1.0	1.0	100/50	80	1.71	300	3.5	17.5	10.0	65.8	46.9	7.37	45.1	51.2	7.317	49.0
20	1.0	10	1.0	1.0	1.0	100/50	80	1.71	300	3.5	15.0	8.57							
10	1.5	10	1.0	1.0	1.0	100/50	80	1.95	300	4.0	14.0	7.18							
0	1.5	10	1.0	1.0	1.0	100/50	80	2.05	300	4.0	15.0	7.32	77.6	41.2	7.312	51.4	46.3	7.344	50.0
10	1.5	10	1.0	1.0	1.0	100/50	80	2.05	300	5.5	14.5	6.42							
20	1.5	10	1.0	1.0	1.0	100/50	80	2.05	300	6.0	15.0	6.41	74.6	41.2	7.348	45.0	46.6	7.457	49.7
30	1.5	10	1.0	1.0	1.0	100/50	80	2.05	300	6.0	12.5	6.48							
40	1.5	10	1.0	1.0	1.0	100/50	80	2.05	300	4.0	11.5	5.44	65.5	37.9	7.341	44.2	43.8	7.335	51.7
50	1.5	10	1.0	1.0	1.0	100/50	80	2.05	300	4.5	11.0	7.01							
60	1.0	10	1.0	1.0	1.0	100/50	80	2.05	300	4.0	17.5	5.03	73.7	37.8	7.332	44.9	44.2	7.402	57.3
70	1.0	10	1.0	1.0	1.0	100/50	80	2.05	300	4.0	11.0	6.35							
80	1.0	10	1.0	1.0	1.0	100/50	80	2.05	300	3.5	11.5	6.42	70.4	37.4	7.335	44.2	43.5	7.332	48.4
90	1.0	10	1.0	1.0	1.0	100/50	80	2.05	300	4.0	11.0	6.45							
100	1.0	10	1.0	1.0	1.0	100/50	80	2.05	300	5.0	11.0	7.38	64.5	37.5	7.332	44.2	43.5	7.332	48.5
110	1.0	10	1.0	1.0	1.0	100/50	80	2.05	300	5.0	11.5	8.10							
120	1.0	10	1.0	1.0	1.0	100/50	80	2.05	300	5.0	11.5	7.86				40.4	44.2	7.332	48.5

DRUG Imagaine 4.5g WT 9.45 kg

DOSE 0.5 mg/kg/min DATE 12/13/83

DOSE 0.5 mg/kg/min DATE 12/13/83																								
TIME	T	RESP	MV	C	R	ABD	HR	CO	DP/DT	PWP	PAP	PVR	A	P _{O₂}	A	P _{CO₂}	A	P _H	P _{O₂}	V	P _{CO₂}	P _H	V	HCT
30	5.5	32.0	4.57	18.0	5.5	10/110	168	1.76	850	5.0	13.0	7.39	89.7	37.0	7.36	7.9	43.3	7.36	7.9	43.3	7.36	7.36	35.3	
20	5.5	34.0	5.84	19.0	5.5	10/105	164	1.85	850	5.0	12.5	6.76												
10	5.5	34.0	5.84	19.0	5.5	10/110	164	1.94	400	4.5	13.0	6.70												
0	5.5	18.0	4.59	9.0	5.0	10/105	164	1.70	400	5.0	13.0	7.65	72.0	37.8	7.36	46.4	39.0	7.27	46.4	39.0	7.27	39.0	39.0	
10	5.5	34.5	5.76	17.0	-	10/100	152	1.69	600	4.5	12.0	7.10												
20	5.5	35.5	7.31	37.0	-	10/100	158	1.49	300	4.0	11.0	7.58	80.3	30.5	7.38	38.6	35.3	7.38	38.6	35.3	7.38	35.3	35.3	
30	1.5	41.0	6.57	5.70	-	10/100	115	1.15	300	5.0	10.0	8.70												
40	1.5	39.5	5.97	5.40	-	10/105	120	1.20	1850	7.0	13.0	10.83	70.6	37.4	7.20	44.0	39.0	7.20	44.0	39.0	7.20	39.0	39.0	
50	1.5	36.5	6.57	5.60	-	10/100	120	1.10	2050	6.5	12.5	10.78												
60	1.5	33.0	5.17	5.60	-	10/100	94	0.90	1600	6.0	11.5	11.98	66.9	40.9	7.20	47.7	40.0	7.20	47.7	40.0	7.20	40.0	40.0	
70	1.5	38.0	5.89	5.80	-	10/100	88	0.91	1700	6.0	11.5	12.64												
80	1.5	41.0	6.57	5.80	-	10/105	88	0.94	1450	5.0	9.5	10.11	70.6	40.4	7.20	50.2	41.0	7.20	50.2	41.0	7.20	41.0	41.0	
90	1.5	37.5	6.19	5.50	-	10/100	88	1.04	1450	5.0	9.5	9.13												
100	1.5	34.5	5.86	16.0	-	10/100	88	1.06	1600	4.0	10.0	9.43	74.1	36.8	7.20	49.3	40.0	7.20	49.3	40.0	7.20	40.0	40.0	
110	1.5	33.0	5.54	14.0	-	10/105	88	1.04	1650	3.5	10.0	9.65												
120	1.5	31.0	6.20	15.0	-	10/100	96	1.11	1800	3.0	8.5	7.66	75.3	35.9	7.20	49.8	40.5	7.20	49.8	40.5	7.20	40.5	40.5	

Drug: Amphetamine WT 16.68 kg
 Dose: 25 mg/kg DATE 4/8/83

TIME	T _V	R _{ESP}	M _V	C	R	ABP	HR	CO	DR/DI	PWP	PAP	PVR	P _{O₂}	P _{CO₂}	PH	P _{O₂}	P _{CO₂}	PH	HCT
30	5.0	5.5	1.5	16.0	1.5	110	170	1.8	1.0	4.0	42.0	6.5	80.1	59.5	7.35	41.2	47.9	7.20	39.4
20	5.0	5.0	1.5	16.0	1.5	110	170	1.8	1.0	4.0	42.0	6.5	80.1	59.5	7.35	41.2	47.9	7.20	39.4
10	5.0	4.5	1.5	16.0	1.5	110	170	1.8	1.0	4.0	42.0	6.5	80.1	59.5	7.35	41.2	47.9	7.20	39.4
0	5.0	4.5	1.5	16.0	1.5	110	170	1.8	1.0	4.0	42.0	6.5	80.1	59.5	7.35	41.2	47.9	7.20	39.4
10	5.0	5.0	1.5	16.0	1.5	110	170	1.8	1.0	4.0	42.0	6.5	80.1	59.5	7.35	41.2	47.9	7.20	39.4
20	5.0	5.5	1.5	16.0	1.5	110	170	1.8	1.0	4.0	42.0	6.5	80.1	59.5	7.35	41.2	47.9	7.20	39.4
30	5.0	5.5	1.5	16.0	1.5	110	170	1.8	1.0	4.0	42.0	6.5	80.1	59.5	7.35	41.2	47.9	7.20	39.4
40	5.0	6.0	1.5	16.0	1.5	110	170	1.8	1.0	4.0	42.0	6.5	80.1	59.5	7.35	41.2	47.9	7.20	39.4
50	5.0	6.5	1.5	16.0	1.5	110	170	1.8	1.0	4.0	42.0	6.5	80.1	59.5	7.35	41.2	47.9	7.20	39.4
60	5.0	7.0	1.5	16.0	1.5	110	170	1.8	1.0	4.0	42.0	6.5	80.1	59.5	7.35	41.2	47.9	7.20	39.4
70	5.0	7.5	1.5	16.0	1.5	110	170	1.8	1.0	4.0	42.0	6.5	80.1	59.5	7.35	41.2	47.9	7.20	39.4
80	5.0	8.0	1.5	16.0	1.5	110	170	1.8	1.0	4.0	42.0	6.5	80.1	59.5	7.35	41.2	47.9	7.20	39.4
90	5.0	8.5	1.5	16.0	1.5	110	170	1.8	1.0	4.0	42.0	6.5	80.1	59.5	7.35	41.2	47.9	7.20	39.4
100	5.0	9.0	1.5	16.0	1.5	110	170	1.8	1.0	4.0	42.0	6.5	80.1	59.5	7.35	41.2	47.9	7.20	39.4
110	5.0	9.5	1.5	16.0	1.5	110	170	1.8	1.0	4.0	42.0	6.5	80.1	59.5	7.35	41.2	47.9	7.20	39.4
120	5.0	10.0	1.5	16.0	1.5	110	170	1.8	1.0	4.0	42.0	6.5	80.1	59.5	7.35	41.2	47.9	7.20	39.4

DRUG Alprostadil 100 µg WT 15.23 kg

DOSE 0.5 µg/kg/min DATE 10/14/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	A P _{O2}	A P _{CO2}	A PH	V P _{O2}	V P _{CO2}	V PH	HCT
-30	1.5	1.5	1.0	1.0	1.0	110	110	1.60	1.00	0.5	7.0	4.9	94.5	44.9	73.3	47.5	49.1	7.306	33.7
-20	1.5	1.5	1.0	1.0	1.0	110	110	1.70	1.00	0.0	7.0	4.9	94.5	44.9	73.3	47.5	49.1	7.306	33.7
-10	1.5	1.5	1.0	1.0	1.0	110	110	1.70	1.00	0.0	7.0	4.9	94.5	44.9	73.3	47.5	49.1	7.306	33.7
0	1.5	1.5	1.0	1.0	1.0	110	110	1.70	1.00	0.0	7.0	4.9	94.5	44.9	73.3	47.5	49.1	7.306	33.7
10	1.5	1.5	1.0	1.0	1.0	110	110	1.70	1.00	0.0	7.0	4.9	94.5	44.9	73.3	47.5	49.1	7.306	33.7
20	1.5	1.5	1.0	1.0	1.0	110	110	1.70	1.00	0.0	7.0	4.9	94.5	44.9	73.3	47.5	49.1	7.306	33.7
30	1.5	1.5	1.0	1.0	1.0	110	110	1.70	1.00	0.0	7.0	4.9	94.5	44.9	73.3	47.5	49.1	7.306	33.7
40	1.5	1.5	1.0	1.0	1.0	110	110	1.70	1.00	0.0	7.0	4.9	94.5	44.9	73.3	47.5	49.1	7.306	33.7
50	1.5	1.5	1.0	1.0	1.0	110	110	1.70	1.00	0.0	7.0	4.9	94.5	44.9	73.3	47.5	49.1	7.306	33.7
60	1.5	1.5	1.0	1.0	1.0	110	110	1.70	1.00	0.0	7.0	4.9	94.5	44.9	73.3	47.5	49.1	7.306	33.7
70	1.5	1.5	1.0	1.0	1.0	110	110	1.70	1.00	0.0	7.0	4.9	94.5	44.9	73.3	47.5	49.1	7.306	33.7
80	1.5	1.5	1.0	1.0	1.0	110	110	1.70	1.00	0.0	7.0	4.9	94.5	44.9	73.3	47.5	49.1	7.306	33.7
90	1.5	1.5	1.0	1.0	1.0	110	110	1.70	1.00	0.0	7.0	4.9	94.5	44.9	73.3	47.5	49.1	7.306	33.7
100	1.5	1.5	1.0	1.0	1.0	110	110	1.70	1.00	0.0	7.0	4.9	94.5	44.9	73.3	47.5	49.1	7.306	33.7
110	1.5	1.5	1.0	1.0	1.0	110	110	1.70	1.00	0.0	7.0	4.9	94.5	44.9	73.3	47.5	49.1	7.306	33.7
120	1.5	1.5	1.0	1.0	1.0	110	110	1.70	1.00	0.0	7.0	4.9	94.5	44.9	73.3	47.5	49.1	7.306	33.7

DRUG Propofol 1.0% WT 2.54 kg

DOSE 0.5 mg/kg/min DATE 8/25/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	DR/DT	PWP	PAP	PVR	A P _{O2}	A P _{CO2}	A PH	V P _{O2}	V P _{CO2}	V PH	HCT
-30	12.5	7.0	1.26	4.0	3.2	110/70	184	2.06	2350	0.0	25.0	12.4	87.0	48.6	7.249	42.1	61.6	7.240	37.0
-20	12.5	6.5	1.10	4.0	2.9	110/70	184	1.92	2700	0.0	24.0	12.50							
-10	12.5	7.0	1.20	4.0	1	110/70	180	1.96	2300	0.0	22.0	11.73							
0	12.5	7.0	1.20	4.0	4	110/70	176	1.94	2500	-0.5	21.0	10.82	68.5	48.1	7.235	50.2	44.2	7.235	38.2
10	12.5	7.5	1.22	4.0	6.5	110/70	158	1.65	1700	0.0	15.5	9.59	84.1	43.7	7.260	51.7	48.2	7.228	37.2
20	12.5	10.0	1.20	4.0	7.0	110/70	152	1.72	1550	0.0	8.5	5.59	84.1	43.7	7.260	51.7	48.2	7.228	37.2
30	14.5	9.5	1.57	5.0	6.5	110/70	142	1.52	1675	-0.5	6.0	3.95	85.8	42.7	7.271	47.5	48.3	7.258	38.5
40	14.5	10.0	1.55	4.0	6.0	110/70	140	1.52	1600	-1.0	6.0	3.95	85.8	42.7	7.271	47.5	48.3	7.258	38.5
50	14.5	8.5	1.25	4.0	1	110/70	152	1.48	1450	-0.5	6.5	4.39							
60	14.5	7.5	1.22	4.0	7	110/70	140	1.46	1400	0.0	7.5	5.14	55.7	49.6	7.212	49.0	49.7	7.198	38.0
70	14.5	8.0	1.40	5.0	1	110/70	144	1.43	1420	-1.0	6.0	4.20							
80	14.5	9.0	1.48	5.0	7	110/70	148	1.42	1400	-0.5	6.0	4.22	85.6	43.7	7.252	52.1	51.1	7.228	38.2
90	14.0	12.5	1.00	5.0	7.9	110/70	148	1.33	1250	-0.5	6.0	4.57							
100	14.0	13.0	1.25	5.0	7	110/70	142	1.12	1150	-1.0	5.0	4.46	88.9	42.7	7.281	44.3	49.3	7.240	37.5
110	14.0	15.5	1.30	4.0	12	110/70	142	1.16	925	-1.5	4.0	3.77							
120	14.0	16.0	1.25	5.0	11	110/70	144	1.12	975	-1.5	3.5	3.40	91.4	34.5	7.321	42.8	45.9	7.250	36.3

DRUG Lorazepam 4.5 mg WT 11.82 kg

DOSE 0.5 mg/kg DATE 8/23/97

TIME	TV	RESP	MV	C	R	ABP	HR	CO	DR/DT	PWP	PAP	PVR	A P _{O2}	A P _{CO2}	A PH	V P _{O2}	V P _{CO2}	V PH	HCT
-30				8			72	1.77	1.00	95	13.0	7.47	80.5	40.5	7.51	38.8	44.5	7.273	31.0
-20							72	1.62	1.00	95	13.0	7.52							
-10							74	1.56	1.00	95	13.0	7.41							
0							72	1.43	1.00	95	13.0	7.59	61.4	49.0	7.54	35.7	42.1	7.211	33.8
10				8			72	1.53	1.00	95	9.0	6.77							
20							71	1.52	1.00	95	9.0	6.72	73.8	47.9	7.538	43.5	51.2	7.204	33.5
30							74	1.42	1.00	95	9.0	6.77							
40							72	1.42	1.00	95	9.0	6.72	75.1	47.5	7.527	44.1	56.1	7.219	37.0
50				0			72	1.42	1.00	95	9.0	6.72							
60							72	1.42	1.00	95	9.0	6.72	88.7	57.8	7.548	41.1	50.5	7.230	37.0
70				8			72	1.42	1.00	95	9.0	6.72							
80							72	1.42	1.00	95	9.0	6.72	86.1	57.7	7.549	51.8	50.6	7.221	38.8
90				5			72	1.42	1.00	95	9.0	6.72							
100							72	1.42	1.00	95	9.0	6.72	87.3	55.8	7.542	54.2	51.9	7.219	40.0
110				4			72	1.42	1.00	95	9.0	6.72							
120							72	1.42	1.00	95	9.0	6.72	92.7	54.5	7.542	56.5	49.5	7.222	42.0

DRUG Propofol 1% in 100% EtOH WT 4.094g

DOSE 10 mg/kg/min DATE 1/10/84

TIME	T	RESP	MV	C	R	ABP	HR	CO	DR/DI	PWP	PAP	PVR	P _{O2}	P _{CO2}	PH	P _{O2}	P _{CO2}	PH	HCT
30	33.5	40	1.07	2.15	4.4	75.55	150	4.45	2300	5.0	17.0	700	45.4	53.4	7.238	74.8	52.3	7.248	44.2
20	34.0	35	1.25	2.10	8.0	77.35	70	4.52	1800	6.0	17.0	726							
10	30.5	35	1.17	2.15	12.5	75.55	50	4.50	2200	6.0	16.5	7.17							
0	30.0	35	1.57	2.18	13.5	77.55	40	4.78	2300	0.0	17.0	6.85	63.3	46.4	7.270	44.1	53.2	7.247	45.8
10	30.0	45	1.06	2.52	7.1	77.50	160	4.16	2000	9.0	17.0	8.05							
20	35	55	1.07	2.49	7.0	77.50	170	3.10	1950	1.0	17.0	8.10	78.2	41.9	7.277	45.4	50.6	7.260	44.3
30	30.5	45	1.27	2.52	22.0	77.45	110	2.20	2100	7.0	13.0	5.72							
40	30.0	45	1.17	2.51	6.5	77.40	120	2.30	2100	7.0	13.0	5.65	67.7	43.2	7.290	46.0	48.8	7.274	45.5
50	30.0	55	1.25	2.51	7.0	77.45	160	2.52	2200	9.0	13.5	5.52							
60	30	50	1.35	2.67	5.0	77.40	170	2.51	2200	7.0	15.0	5.18	77.7	40.7	7.316	44.3	47.0	7.288	47.2
70	30	55	1.0	2.67	7.0	77.40	170	2.66	2200	7.0	15.0	4.82							
80	30.5	55	1.02	2.42	7.5	77.40	170	2.52	2200	6.0	16.5	4.77	71.7	44.7	7.296	44.2	45.9	7.300	48.2
90	34.0	55	1.86	2.0	7.0	77.45	170	2.53	2300	0.0	11.0	4.42							
100	40.5	45	1.02	2.67	7.0	77.40	120	2.28	2100	6.5	16.0	5.77	71.2	42.9	7.300	50.0	45.1	7.300	48.0
110	30.0	50	1.33	2.20	9.5	77.45	170	1.77	2100	7.0	11.0	5.76							
120	30.5	55	2.07	2.21	5.7	77.40	170	1.76	2000	7.0	11.5	6.55	73.2	41.9	7.319	47.3	45.1	7.314	48.2

DRUG Trimethoprim-HCl WT 47.32g

DOSE 60mg/kg/min DATE 12/22/83

DOSE 10mg/kg/min DATE 4/22/83																						
TIME	TV	RSP	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	P _{O₂}	A	P _{CO₂}	PH	P _{O₂}	V	P _{CO₂}	PH	V	HCT
30	32.5	4.5	1.46	37.3	8.5	145/50	144	2.05	2550	4.0	26.0	12.86	65.5	48.9	38.3	7.16	38.3	38.3	7.16	40.5		
20	38.0	4.0	1.12	31.1	17.5	135/50	120	2.09	2600	5.5	28.5	13.64										
10	31.5	4.5	1.37	32.8	24.6	140/55	116	2.10	2800	5.0	27.0	12.86										
0	31.0	4.0	1.16	34.0	27.4	140/50	124	1.97	2800	5.0	28.0	14.21	59.3	54.0	31.5	7.15	31.5	38.5	7.09	41.8		
10	31.0	5.0	1.50	31.7	18.4	119/40	148	1.98	2300	6.0	27.5	13.89										
20	32.0	6.0	1.97	32.6	15.8	117/40	148	1.94	2100	6.0	25.0	12.89	63.2	57.4	42.9	7.16	42.9	42.9	7.12	37.5		
30	32.5	7.0	1.82	29.9	16.2	116/35	142	1.86	2300	5.0	27.5	14.78										
40	32.0	5.5	1.82	30.6	13.1	117/30	132	1.82	2000	4.0	23.0	12.64	62.4	53.2	40.2	7.16	40.2	40.2	7.13	37.8		
50	32.5	5.5	1.89	24.8	12.1	116		1.68	1850	4.5	22.0	13.10										
60	32.5	6.0	1.96	29.5	11.5	114/30	126	1.70	1700	4.0	18.5	10.88	73.5	42.6	37.9	7.23	37.9	37.9	7.16	36.8		
70	32.5	8.0	2.14	29.5	14.2	116/40	140	1.57	1750	3.5	16.0	12.68										
80	32.5	8.0	3.14	21.0	15.0	117/45	144	1.57	1725	4.0	14.0	8.82	76.1	42.0	36.5	7.21	36.5	36.5	7.20	34.0		
90	32.5	9.5	3.11	28.5	14.9	117/45	132	1.52	1800	3.5	14.0	9.21										
100	32.0	1.0	3.21	25.6	13.0	115	144	1.63	1800	4.0	21.0	12.27	62.6	42.1	38.1	7.21	38.1	38.1	7.21	34.3		
110	32.0	5.0	1.77	26.3	12.0	115	124	1.65	1435	4.1	26.0	15.76										
120	32.5	6.0	2.00	25.9	12.2	114/40	132	1.86	1800	5.0	23.0	16.36	65.6	47.6	36.9	7.21	36.9	36.9	7.17	37.2		

UROG Engine to Run VV1 B.18kg

DOSE 100mg/min DATE 4/2/83

TIME	T	RESP	M	C	R	ABP	HR	CO	DR/DT	PWP	PAP	PVR	PO ₂	PCO ₂	PH	PO ₂	PCO ₂	PH	HCT
30	50	20	157	540	25	105/70	108	1.48	1700	5.5	130	8.78	65.4	44.0	7.35	57.9	60.3	7.272	42.5
20	62.5	20	147	540	25	105/70	106	1.52	1800	5.0	138	8.88							
10	62.5	20	149	540	25	105/70	140	1.74	1900	6.0	140	8.04							
0	60	20	154	520	40	105/70	178	1.94	1900	6.0	150	8.15	55.2	51.1	7.26	56.8	56.5	7.260	43.0
10	55	20	153	502	25	105/70	172	2.12	1600	8.0	190	8.96							
20	55	45	157	540	25	105/70	168	1.89	1500	6.0	140	7.41	56.0	50	7.26	41.2	56.0	7.244	43.0
30	55	50	156	560	25	105/70	172	1.82	1400	6.0	140	6.25							
40	55	60	158	540	25	105/70	171	1.77	1100	5.0	140	6.21	51.3	53.1	7.289	55.7	53.7	7.286	45.2
50	55	60	155	540	25	105/70	168	1.80	1600	6.0	140	6.67							
60	580	65	154	520	40	105/70	178	1.68	1500	4.0	150	7.11	97.3	50.7	7.267	59.5	50.7	7.284	44.3
70	55	55	154	540	60	105/70	170	1.54	1400	5.0	135	6.31							
80	55	50	156	540	55	105/70	170	1.46	1400	5.5	140	9.59	73.1	45.5	7.262	53.9	50.8	7.292	45.3
90	55	60	156	500	50	105/70	170	1.66	1300	5.5	140	11.11							
00	55	50	152	140	50	105/70	168	1.66	1100	9.0	140	12.07	66.3	58.2	7.260	53.0	48.5	7.264	44.5
110	42	60	156	140	50	105/70	168	1.55	1100	6.0	142	11.48							
20	41.5	80	151	140	85	105/70	170	1.60	1100	6.0	150	11.67	66.1	50.5	7.260	53.0	50.0	7.251	44.5

DRUG Thiopentone 4.0g WT 22.7kg

DOSE 10mg/kg/min DATE 9/20/83

TIME	TV	RESP	MV	C	R	ABD	HR	CO	DP/DT	PWP	PAP	PVR	A P _{O2}	A P _{CO2}	A PH	V P _{O2}	V P _{CO2}	V PH	HCT
30	570	18	1.5	100	100	100	100	1.5	2.0	12.5	6.0	6.0	86.1	41.8	7.343	40.8	54.4	7.281	27.2
20	570	18	1.5	100	100	100	100	1.5	2.0	13.0	6.31	6.31	91.6	40.7	7.342	50.9	47.0	7.301	29.8
10	570	18	1.5	100	100	100	100	1.5	2.0	11.5	5.42	5.42	84.3	47.0	7.289	47.5	51.6	7.276	30.0
0	570	18	1.5	100	100	100	100	1.5	2.0	14.0	6.54	6.54	81.4	43.7	7.318	44.5	52.3	7.277	28.3
10	570	18	1.5	100	100	100	100	1.5	2.0	15.0	7.69	7.69	81.6	48.4	7.240	44.3	52.7	7.276	28.0
20	570	18	1.5	100	100	100	100	1.5	2.0	16.0	7.80	7.80	70.1	49.8	7.277	43.5	53.1	7.266	28.2
30	570	18	1.5	100	100	100	100	1.5	2.0	15.0	7.84	7.84	89.9	45.6	7.309	35.5	57.3	7.259	29.0
40	570	18	1.5	100	100	100	100	1.5	2.0	13.5	7.46	7.46	11.80	51.9	7.258	38.4	60.1	7.256	28.5
50	570	18	1.5	100	100	100	100	1.5	2.0	14.0	9.21	9.21	12.67	51.9	7.258	38.4	60.1	7.256	28.5
60	570	18	1.5	100	100	100	100	1.5	2.0	16.0	9.76	9.76	11.80	51.9	7.258	38.4	60.1	7.256	28.5
70	570	18	1.5	100	100	100	100	1.5	2.0	16.0	9.76	9.76	11.80	51.9	7.258	38.4	60.1	7.256	28.5
80	570	18	1.5	100	100	100	100	1.5	2.0	16.0	9.76	9.76	11.80	51.9	7.258	38.4	60.1	7.256	28.5
90	570	18	1.5	100	100	100	100	1.5	2.0	16.0	9.76	9.76	11.80	51.9	7.258	38.4	60.1	7.256	28.5
100	570	18	1.5	100	100	100	100	1.5	2.0	16.0	9.76	9.76	11.80	51.9	7.258	38.4	60.1	7.256	28.5
110	570	18	1.5	100	100	100	100	1.5	2.0	16.0	9.76	9.76	11.80	51.9	7.258	38.4	60.1	7.256	28.5
120	570	18	1.5	100	100	100	100	1.5	2.0	16.0	9.76	9.76	11.80	51.9	7.258	38.4	60.1	7.256	28.5

Drug Calcium chloride WT 11.146g
 DOSE 100mg/kg/min DATE 9/13/83

TIME	T _V	R _{ESP}	M _V	C	R	ABP	HR	CO	DR/D _T	PWP	PAP	PVR	A _{P_{O2}}	A _{P_{CO2}}	A _{PH}	V _{P_{O2}}	V _{P_{CO2}}	V _{PH}	HCT
30	1.5	1.1	1.1	0	8	110	110	1.1	0.0	0.0	15.0	83.8	74.8	-	73.57	59.1	-	7.44	-
20	6.5	1.1	1.1	0	8	110	110	1.1	3.00	0.0	12.5	53.0	53.0	-	-	-	-	-	-
10	2.0	1.1	1.1	0	6	110	110	1.1	3.00	1.0	11.5	53.0	53.0	-	-	-	-	-	-
0	1.0	1.0	1.0	0	8	110	110	1.1	3.00	0.0	17.5	77.7	60.1	-	73.08	41.2	-	7.43	-
10	8.0	1.1	1.1	0	8	110	110	1.1	3.00	1.0	13.0	53.0	53.0	-	-	-	-	-	-
20	1.0	1.1	1.1	0	8	110	110	1.1	3.00	1.0	15.5	53.0	53.0	-	73.06	54.9	-	7.425	-
30	1.5	1.1	1.1	0	8	110	110	1.1	3.00	0.5	11.5	53.0	53.0	-	-	-	-	-	-
40	1.5	1.1	1.1	0	8	110	110	1.1	3.00	0.5	9.5	53.0	53.0	-	73.39	32.1	-	7.445	-
50	1.5	1.1	1.1	0	8	110	110	1.1	3.00	0.5	6.0	53.0	53.0	-	-	-	-	-	-
60	1.5	1.1	1.1	0	8	110	110	1.1	3.00	0.5	1.0	53.0	74.0	-	73.0	51.5	-	7.460	-
70	1.5	1.1	1.1	0	8	110	110	1.1	3.00	0.0	7.5	53.0	53.0	-	-	-	-	-	-
80	1.5	1.1	1.1	0	8	110	110	1.1	3.00	1.5	10.0	53.0	60.7	-	73.72	38.8	-	7.447	-
90	1.5	1.1	1.1	0	8	110	110	1.1	3.00	0.5	8.5	43.4	75.2	-	73.2	24.3	-	7.464	-
100	1.5	1.1	1.1	0	8	110	110	1.1	3.00	1.0	4.5	43.4	75.2	-	-	-	-	-	-
110	1.5	1.1	1.1	0	8	110	110	1.1	3.00	1.0	10.5	57.7	60.7	-	-	-	-	-	-
120	1.5	1.1	1.1	0	8	110	110	1.1	3.00	1.0	11.0	60.7	60.7	-	73.40	40.0	-	7.44	-

URV Therapeutic 1.8g WT 0.45 kg
 DOSE 1.0g/mg/kg DATE 8/12/83

TIME	T	RESP	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	A P _{O2}	A P _{CO2}	A PH	V P _{O2}	V P _{CO2}	V PH	HCT
30	300	10	5.1	18.5	11.0	110	144	1.8	100	0.5	13.0	8.25	73.5	41.6	73.2	38.9	47.0	7.449	36.5
20	300	7.5	5.2	16.0	10.5	105	144	1.8	100	0.5	11.5	9.25							
10	300	8.5	5.1	11.8	10.5	105	144	1.8	100	0.5	8.0	12.70							
0	300	9.0	5.1	10.0	10.5	105	144	1.8	100	0.5	7.5	6.82	75.5	42.6	73.7	33.4	52.2	7.233	35.0
10	300	10.5	5.1	10.8	10.5	105	144	1.8	100	0.5	8.0	6.80							
20	300	14.2	5.1	10.0	10.5	105	144	1.8	100	0.5	10.0	7.17	90.7	48.9	73.8	42.1	48.5	7.226	36.0
30	300	16.0	5.1	10.8	10.5	105	144	1.8	100	0.5	9.0	7.56							
40	300	11.0	5.1	10.0	10.5	105	144	1.8	100	0.5	9.5	8.72	16.4	34.8	73.3	41.8	46.3	7.249	36.7
50	300	9.0	5.1	10.0	10.5	105	144	1.8	100	0.5	9.5	9.8							
60	300	12.5	5.1	10.0	10.5	105	144	1.8	100	0.5	8.5	9.44	184.5	51.9	73.3	38.5	43.9	7.232	36.5
70	300	13.5	5.1	10.0	10.5	105	144	1.8	100	0.5	7.5	11.3							
80	300	13.0	5.1	10.0	10.5	105	144	1.8	100	0.5	8.0	10.15	87.9	38.9	73.2	37.5	40.2	7.188	40.5
90	300	13.0	5.1	10.0	10.5	105	144	1.8	100	0.5	1.0	4.11							
00	300	14.0	5.1	10.0	10.5	105	144	1.8	100	0.5	1.0	9.76	97.7	55.5	73.4	44.6	49.3	7.232	37.3
110	300	16.0	5.1	10.0	10.5	105	144	1.8	100	0.5	8.0	10.00							
20	300	13.5	5.1	10.0	10.5	105	144	1.8	100	0.5	7.5	10.14	185.9	54.1	73.8	44.8	46.6	7.218	37.8

Drug: Remoxone-4P4 WT 2.54 kg

Dose 1.25 mg/kg/min DATE 12/21/83

TIME	T _V	RESP	Z	C	R	ABD	HR	CO	DP/DT	PWP	PAP	PVR	A _{Po2}	A _{PCO2}	PH	P _{Po2}	P _{PCO2}	PH	HCT
30	590	5.5	1.60	210	7.5	170/55	164	1.82	2300	4.5	170	9.34	51.1	49.3	7.511	45.3	48.7	7.327	41.2
20	580	6.0	1.74	212	5.0	170/40	140	1.72	2300	6.0	150	8.72							
10	510	4.5	1.40	200	5.5	170/40	160	1.60	2200	4.0	140	8.75							
0	580	6.0	1.68	185	4.0	155/40	150	1.47	2100	3.5	115	7.82	69.3	43.6	7.327	50.1	47.6	7.324	41.5
10	550	9.5	2.31	200	5.5	155/45	168	1.46	1700	6.0	115	7.88							
20	520	14.5	2.19	210	5.1	167/45	152	1.70	1800	8.0	115	6.76	80.5	40.4	7.360	44.4	45.6	7.343	39.0
30	540	16.0	2.76	200	5.0	170/40	160	1.62	2150	5.5	110	6.17							
10	550	9.0	2.07	180	7.0	170/45	144	1.64	1950	4.0	60	7.32	65.0	48.0	7.307	50.0	49.3	7.314	41.3
20	535	8.0	1.88	175	5.5	170/45	166	1.64	2000	-	45	8.84							
30	540	8.0	1.85	170	7.5	170/45	176	1.62	2100	-	140	8.64	75.6	45.6	7.330	51.2	48.3	7.318	41.8
10	545	8.0	1.90	175	8.5	170/45	180	1.50	1850	-	9.5	6.33							
20	560	9.0	2.54	170	7.0	170/40	156	1.37	1700	-	8.0	5.84	74.4	41.1	7.364	48.3	46.5	7.287	41.8
30	540	11.0	2.64	200	6.0	170/45	164	1.25	1500	-	8.0	6.40							
10	530	10.5	2.42	170	6.5	170/40	140	1.18	1475	-	8.5	7.20	75.0	29.5	7.341	46.3	45.1	7.347	41.5
20	510	9.0	1.84	150	1.0	155/40	155	1.11	1250	-	10.0	9.01							
30	500	10.5	2.10	148	1.5	150/40	140	1.12	1200	-	9.5	8.48	76.8	42.4	7.357	46.3	46.5	7.359	41.0

Urag Inequine H₂ P₄ WT 44.2kg

DOSE 125mg/kg DATE 11/30/83

TIME	T	RESP	MV	C	R	ABP	HR	CO	DR/DT	PWP	PAP	PVR	Po ₂	A	Pco ₂	PH	Po ₂	V	PH	Pco ₂	V	HCT
30	89.5	9.5	5.11	6.0	1.0	114	148	1.81	300	4.5	19.0	10.33	71.0	47.0	44.1	7.316	47.5	44.1	7.306			40.0
20	89.0	9.5	5.10	6.0	1.5	115	144	1.94	300	4.5	17.5	9.02										
10	88.5	10.0	5.05	1.0	1.5	117.5	146	1.92	300	4.0	17.0	8.85										
0	88.0	8.5	5.04	1.0	1.5	115.0	142	1.86	300	4.0	16.0	8.60	66.7	45.0	48.9	7.317	57.4	48.9	7.308			40.0
10	88.0	10.0	5.00	1.0	1.5	115	146	1.92	180	6.0	15.0	8.24										
20	88.0	10.5	5.00	1.0	1.5	115	142	1.88	180	7.5	17.5	9.31	71.9	41.6	44.1	7.350	42.8	44.1	7.304			40.0
30	88.0	10.0	5.00	1.0	1.5	114	144	1.90	180	6.0	18.0	10.78										
40	88.0	10.5	5.00	1.0	1.0	115	144	1.90	180	-	51.0	16.65	66.6	50.1	58.7	7.266	56.1	58.7	7.256			42.0
50	88.0	10.5	5.00	1.0	1.5	115	144	1.92	180	-	51.0	12.61										
60	88.0	10.0	5.00	1.0	1.8	115	137	1.86	170	-	56.0	11.83	66.7	47.9	56.2	7.276	54.5	56.2	7.256			42.0
70	88.0	10.0	5.00	1.0	1.0	115	144	1.94	180	-	52.0	16.28										
80	88.0	10.0	5.00	1.0	1.5	115	144	1.94	180	-	19.0	11.73	72.4	44.9	57.7	7.312	56.2	57.7	7.271			41.0
90	88.0	10.0	5.00	1.0	1.0	115	144	1.92	180	-	20.0	12.91										
100	88.0	10.5	5.00	1.0	1.0	115	140	1.90	180	-	19.0	9.69	78.6	58.8	58.5	7.360	56.2	58.5	7.287			37.3
110	88.0	10.0	5.00	1.0	1.0	115	142	1.90	180	-	55.0	15.62										
120	88.0	10.0	5.00	1.0	1.8	115	142	1.94	180	-	55.5	15.88	72.5	44.5	56.6	7.317	55.1	56.6	7.271			37.3

DRUG Insulin H.P.O. WT 9094g
 DOSE 1.75 units/kg DATE 6/20/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	A P _{O2}	A P _{CO2}	A PH	V P _{O2}	V P _{CO2}	V PH	Hct
30	3.1	3.0	1.08	1.0	0.0	100	100	1.80	1.000	1.0	100	5.00	83.3	33.7	73.3	68.9	75.4	7.295	25.8
20	2.1	2.0	1.55	1.0	0.0	100	100	1.70	1.000	1.5	8.0	4.65							
10	2.0	2.0	1.08	1.0	0.0	100	100	1.74	1.000	1.0	0.0	4.60							
0	2.0	2.0	1.00	1.0	0.0	100	100	1.85	1.000	1.0	0.0	5.00	64.0	40.2	73.4	65.0	71.0	7.250	28.0
10	2.0	2.0	1.00	1.0	0.0	100	100	2.05	1.000	1.5	8.0	3.80							
20	2.0	2.0	1.00	1.0	0.0	100	100	2.08	1.000	1.0	8.0	3.80	71.0	41.8	73.5	65.0	71.0	7.250	28.0
30	2.0	2.0	1.00	1.0	0.0	100	100	1.94	1.000	1.0	10.0	5.00							
40	2.0	2.0	1.00	1.0	0.0	100	100	1.86	1.000	1.0	0.0	4.84	74.8	42.8	73.6	65.0	71.0	7.250	28.0
50	2.0	2.0	1.00	1.0	0.0	100	100	1.93	1.000	1.5	9.5	4.71							
60	2.0	2.0	1.00	1.0	0.0	100	100	1.80	1.000	1.5	8.0	4.04	87.8	40.4	73.9	65.0	71.0	7.250	28.0
70	2.0	2.0	1.00	1.0	0.0	100	100	1.82	1.000	1.0	6.5	4.01							
80	2.0	2.0	1.00	1.0	0.0	100	100	1.83	1.000	1.0	8.5	5.09	86.9	41.0	73.8	65.0	71.0	7.250	28.0
90	2.0	2.0	1.00	1.0	0.0	100	100	1.89	1.000	1.0	8.0	5.00							
100	2.0	2.0	1.00	1.0	0.0	100	100	1.82	1.000	1.0	7.0	4.80	90.6	41.0	73.8	65.0	71.0	7.250	28.0
110	2.0	2.0	1.00	1.0	0.0	100	100	1.80	1.000	1.5	9.0	6.00							
120	2.0	2.0	1.00	1.0	0.0	100	100	1.82	1.000	1.5	9.0	5.00	88.1	41.5	73.8	65.0	71.0	7.250	28.0

Drug: Propranolol HCl WT: 10.60 kg

Dose: 1.75 mg/kg/min DATE: 8/24/83

DOSE 1.15 mg/kg/min DATE 2/24/83																			
TIME	TV	RESP	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	A P _{O2}	A P _{CO2}	A PH	V P _{O2}	V P _{CO2}	V PH	HCT
-30	2.0	5.5	1.0	2.2	6	100	100	4.5	1.00	0.5	10.0	7.55	56.4	58.3	71.85	62.5	71.64	31.2	
-20	2.0	5.0	0.5	4.1	5	90	100	1.25	0.75	1.5	10.0	8.00							
-10	2.0	5.0	1.0	3.8	4.0	90	100	3.77	0.70	-1.0	10.0	8.40							
0	2.0	4.0	0.5	4.1	3.5	90	100	4.10	0.70	2.0	8.0	8.00	59.5	61.7	71.62	64.1	71.54	31.7	
10	2.0	4.5	1.0	4.0	3.0	90	100	4.25	0.70	1.0	8.0	7.77	77.2	53.4	71.58	62.1	71.61	27.7	
20	2.0	4.5	1.0	4.0	3.0	90	100	4.25	0.70	2.5	8.0	6.06	81.6	54.4	71.81	62.4	71.57	22.0	
30	2.0	4.5	1.0	4.0	3.0	90	100	4.25	0.70	2.0	8.0	4.25	81.6	54.4	71.81	62.4	71.57	22.0	
40	2.0	4.5	1.0	4.0	3.0	90	100	4.25	0.70	2.0	8.0	4.25	81.6	54.4	71.81	62.4	71.57	22.0	
50	2.0	4.5	1.0	4.0	3.0	90	100	4.25	0.70	2.0	8.0	4.25	81.6	54.4	71.81	62.4	71.57	22.0	
60	2.0	4.0	1.0	4.0	3.0	90	100	4.25	0.70	1.5	6.5	4.1	76.5	54.1	71.47	62.7	71.22	34.7	
70	2.0	4.0	1.0	4.0	3.0	90	100	4.25	0.70	0.5	6.5	4.70	86.7	56.7	71.72	62.0	71.29	24.5	
80	2.0	4.0	1.0	4.5	2.0	90	100	4.25	0.70	0.0	6.0	5.05	84.2	58.5	71.72	62.2	71.27	37.2	
90	2.0	4.0	1.0	4.8	2.0	90	100	4.25	0.70	0.0	6.0	5.05	84.2	58.5	71.72	62.2	71.27	37.2	
100	2.0	4.0	1.0	5.5	5.4	90	100	4.25	0.70	0.0	6.0	5.05	84.2	58.5	71.72	62.2	71.27	37.2	
110	2.0	4.0	1.0	6.0	10.0	90	100	4.25	0.70	0.0	6.0	5.05	84.2	58.5	71.72	62.2	71.27	37.2	
120	2.0	4.0	1.0	6.0	6.0	90	100	4.25	0.70	0.0	6.0	5.05	84.2	58.5	71.72	62.2	71.27	37.2	

DRUG Propofol 1.5% WT 12.73 kg

DOSE 1.25 mg/kg/min DATE 8/19/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	A P _{O2}	A P _{CO2}	A PH	V P _{O2}	V P _{CO2}	V PH	HCT
30	30	12	1.2	0	0	110	110	1.57	700	1.5	13.0	7.47	79.5	44.8	1.271	48.3	45.0	7.252	58.0
20	20	12	1.2	0	0	110	110	1.57	970	1.5	12.0	8.00							
10	10	12	1.2	0	0	110	110	1.42	1040	1.5	10.5	7.39							
0	0	12	1.2	0	0	110	110	1.46	1080	1.5	9.5	6.57	101.2	58.4	1.319	55.7	45.6	7.284	58.5
10	10	12	1.2	0	0	110	110	1.50	1000	1.0	10.0	6.67							
20	20	12	1.2	0	0	110	110	1.52	1110	1.0	9.5	6.09	93.0	57.5	7.313	52.0	46.2	7.276	40.5
30	30	12	1.2	0	0	110	110	1.47	1040	1.5	8.0	5.40							
40	40	12	1.2	0	0	110	110	1.46	1110	1.5	8.0	5.48	81.3	58.4	7.322	48.0	44.8	7.272	41.8
50	50	12	1.2	0	0	110	110	1.47	1110	1.0	6.5	4.78							
60	60	12	1.2	0	0	110	110	1.46	1110	1.5	6.5	4.45	86.3	58.4	7.320	46.8	41.1	7.283	40.2
70	70	12	1.2	0	0	110	110	1.47	1110	1.0	6.5	4.71							
80	80	12	1.2	0	0	110	110	1.47	1110	1.0	6.5	5.16	84.7	58.4	7.320	41.5	41.1	7.291	40.0
90	90	12	1.2	0	0	110	110	1.47	1110	1.5	6.5	4.85							
100	100	12	1.2	0	0	110	110	1.47	1110	1.0	6.5	5.56	77.8	58.4	7.321	54.4	45.8	7.265	40.0
110	110	12	1.2	0	0	110	110	1.47	1110	1.0	7.5	6.41							
120	120	12	1.2	0	0	110	110	1.47	1110	1.0	7.5	7.27	85.1	58.4	7.322	44.7	45.4	7.275	40

APPENDIX G

Blood Chemistry Performance

Data on Performance Evaluation are on file in the Departments of Pharmacology at the University of Tennessee College of Medicine and Walter Reed Army Institute of Research.

APPENDIX H

Certificate of Purity of Primaquine Diphosphate



Chemists Helping Chemists in Research and Industry

aldrich chemical company, inc.

ANALYTICAL DATA

Date January 3, 1983

Our: 16,039-3 Primaquine diphosphate, 99+%, GOLD LABEL

Batch No.: 2429BE

Analytical Results:

Appearance Orange powder

m.p. 205° dec.

b.p.

n_D^{20}

$[\alpha]_D^{20}$

Spectral Data:

I.R. Conforms to structure and standard as illustrated on page 1391 F of Edition III, of "The Aldrich Library of Infrared Spectra".

U.V.

N.M.R.

Assay:

V.P.C.

Titration 100.2% by NaOH titration

Other: The elemental analysis is as follows:

	C	H	N
Theory	39.56	5.98	9.23
Actual	38.47	5.85	9.11

SB/sdb

A. Napiorkowski
Anna Napiorkowski,
Quality Control Manager

SECTION II.

PROTOCOL

Determination of the Involvement of Histamine in the Blood Pressure Response to Liposome Carrier

Introduction

Liposome carrier suspension produces an arterial hypotension when given intravenously. In our recent studies, prior treatment with compound WR-149,024, reported to stabilize histamine-containing cells and antagonize factors which induce histamine release, appeared to reduce this hypotension. These findings have lead to the speculation that histamine is involved in this hypotensive response.

Rationale for Study

If release of histamine from body stores is responsible for the hypotension to liposome injections, a tachyphylaxis should develop as histamine stores are depleted. In dogs with chronically indwelling catheters to measure systemic and pulmonary arterial pressures, we could determine if repeated i.v. bolus injections of a given amount of liposome carrier suspension yield systemic or pulmonary arterial pressure responses which are progressively smaller.

Methods

Two male beagle dogs will be chronically fitted with both a Swan-Ganz balloon-tipped catheter into the pulmonary artery and a polyethylene cannula (PE 260) into the femoral artery to the level of the abdominal aorta. Measurement of pulmonary arterial and wedge pressure and cardiac output will be obtained using the Swan-Ganz catheter with features for thermal dilution determinations. Systemic blood pressure will be measured via the femoral arterial cannula externalized to the nape of the neck. Dogs will be maintained on 100 units/kg/day Na-heparin (s.c.) twice a day to prevent thrombosis. After a seven day period of recovery, the following experiments will be performed.

Dogs will be anesthetized with Na-pentobarbital (30 mg/kg, i.v.) and allowed to reach a steady state of anesthesia at which stable control values can be obtained for pulmonary artery, pulmonary wedge, and systemic blood pressure and heart rate. Bolus i.v. doses of 1.0 ml of liposome carrier will be given via a butterfly-type cannula in a cephalic vein over a period of 10 sec at 20 minute intervals for a total of 5 doses. This dose is a projection to produce a prominent vascular response and will be confirmed during actual experiments. Arterial and pulmonary arterial blood pressure responses to each dose will be monitored continuously. Also to be monitored will be lead II EKG and heart rate. Expanded polygraph recordings (10 sec) will be obtained before and at the point of the greatest vascular response.

Venous blood samples (5 ml) will be taken 1 minute prior to each injection and just prior to the nadir of the depressor response and held in ice. Following rapid separation in a cooled centrifuge, and pH of the plasma (2 ml) will be adjusted to 4-5 with a small volume (~ 100 μ l) of 2.0 M HCl, mixed, and frozen until analysis for histamine. Plasma will be shipped frozen to Burroughs-Wellcome for this analysis.

These beagles will be allowed to recover from the anesthesia and used for a subsequent experiment. A possible secondary experiment, if results of the primary experiment warrant, would be assessment of the effect of histamine receptor blockade (H1 and H2) with chlorpheniramine and cimetidine on the vascular responses to liposome carrier.

Closing note: An alternative or concurrent consideration is the use of the specific histamine-depleting agent, Compound #48/80. We might determine if repeated i.v. administration of this compound with subsequent tachyphalaxis to its hypotensive response yields a preparation which is then unresponsive to liposome carrier.

Robert W. Caldwell, Ph.D.

Clinton B. Nash, Ph.D.

RWC:sbu

SECTION III.

Effects of Carrier Liposomes on the Canine Cardiovascular System.

Methods

Four dogs screened for parasites, in good general health and weighing between 9.6 and 11.2 kg were anesthetized with Na-pentobarbital (30 mg/kg, i.v.) and maintained with doses of 1 to 2 mg/kg as necessary. (See Protocol -- Cardiovascular and Pulmonary Effects of WR-6026•2HCl vs Primaquine•2H₃PO₄.) Two dogs received a test liposome infusion (.3 ml/min for 15 min) via femoral vein with no prior treatment and two dogs received a liposome infusion (.3 ml/min for 15 min) 30 minutes after pretreatment with a symmetrical disulfide WR-149,024 (10 mg/kg, i.v.) The carrier Liposome suspension and WR-149,024 used were furnished by WRAIR. Dogs were fitted with tracheal cannulae and breathed room air. Central aortic blood pressure was measured via left carotid artery using a Statham pressure transducer. Central venous pressure was measured via right external jugular vein using a Gould transducer. Lead II EKG and heart rate were measured continuously using a Grass EKG pre-amplifier and tachometer preamplifier, respectively. Limb EKG leads were recorded at 15 min intervals. A Grass polygraph was used to record all cardiovascular variables. Arterial and venous blood samples were drawn through aforementioned cannulae (carotid and jugular) at 0, +15, +30, +60, +90, and +120 minutes. Six ml of arterial blood and four ml of venous blood were drawn into glass syringes rinsed with Na-heparin. Two ml arterial blood were used for duplicate macrohematocrit (Weintraub). Samples were centrifuged immediately after being drawn and plasma was frozen immediately after centrifugation and stored for future analysis. Variables were measured for 120 minutes from onset of the infusion.

Presentation of Data

Central aortic diastolic blood pressure is expressed as percent of baseline value, with baseline as the value at time zero and equal to 100%. Central venous pressure is expressed as mean values in mmHg. Systolic arterial pressure and pulse pressure are also expressed in mmHg. Heart rate is expressed as beats/min and macrohematocrit is expressed as %cells. All pressure and heart rate values are shown as graphs and/or in tabular form. Macrohematocrit is shown in tabular form. Lead II EKG tracing at 0, +15 and +120 minutes are included for each experiment.

Results

Infusion of liposome with no pretreatment produced a transient depression of diastolic aortic pressure (see fig. and Table 1). In one animal (6/18/84), the decline in pressure was gradual and fairly uniform during the infusion and shortly thereafter. Fifteen minutes after the infusion was over, pressure began to return to its original level. In the other dog given only the liposome test dose (6/1/84), there was a sudden and sharp decrease in blood pressure (within 2.5 min) followed by a sharp rise (+5 min); blood pressure then returned to baseline value (10 min) and stayed within $\pm 10\%$ of baseline until near the end of the experiment (+90 min) when there was a further, but slight drop.

Administration of WR-149,024 caused an immediate and marked decline in diastolic blood pressure in one dog (6/6/84) and almost no apparent effect in the other (6/19/84) (see fig. 2 and Table 1). In the animal which exhibited this marked response to WR-149,024 (6/6/84), infusion of liposome solution had a minimal effect. Diastolic blood pressure fell only slightly towards the end of the experiment on 6/19/84.

Systolic aortic pressure was affected similarly to diastolic pressure in each dog. There was a trend, however, for it to drop more than diastolic pressure during the liposome infusion; pulse pressure was diminished slightly during liposome infusion.

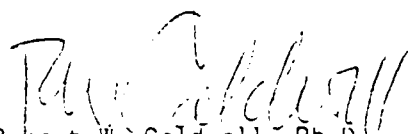
Central venous pressure (CVP) fluctuated during the liposome infusions in dogs which had no pretreatment. After the infusion, one animal's CVP rose (6/19/84) and the other's fell (6/1/84), but neither by a great amount. Central venous pressure was not apparently affected by liposome infusion pretreated with WR-149,024 (6/6/84) and 6/19/84) (see fig. 2 and Table 1).

Administration of WR-149,024 caused a slight, temporary increase in heart rate (see fig. 3 and Table 1) but liposome infusion did not affect any of the animals' heart rates to a significant degree.

EKG records (Lead II) showed no change due to infusion of the Liposome suspension (see fig. 4).

Conclusions

The liposome suspension produces an arterial hypotension when given intravenously. Prior treatment with WR-149,024 appeared to reduce the development of hypotension to liposome infusion. Since one of the reported properties of WR-149,024 is to stabilize histamine-containing cells and antagonize factors which induce histamine release, we may speculate that histamine is involved in this hypotension.


Robert W. Caldwell, Ph.D.
Professor

RWC/ci

FIGURE 1

DIASTOLIC BLOOD PRESSURE

— No Pre-Rx
--- Pre-Rx

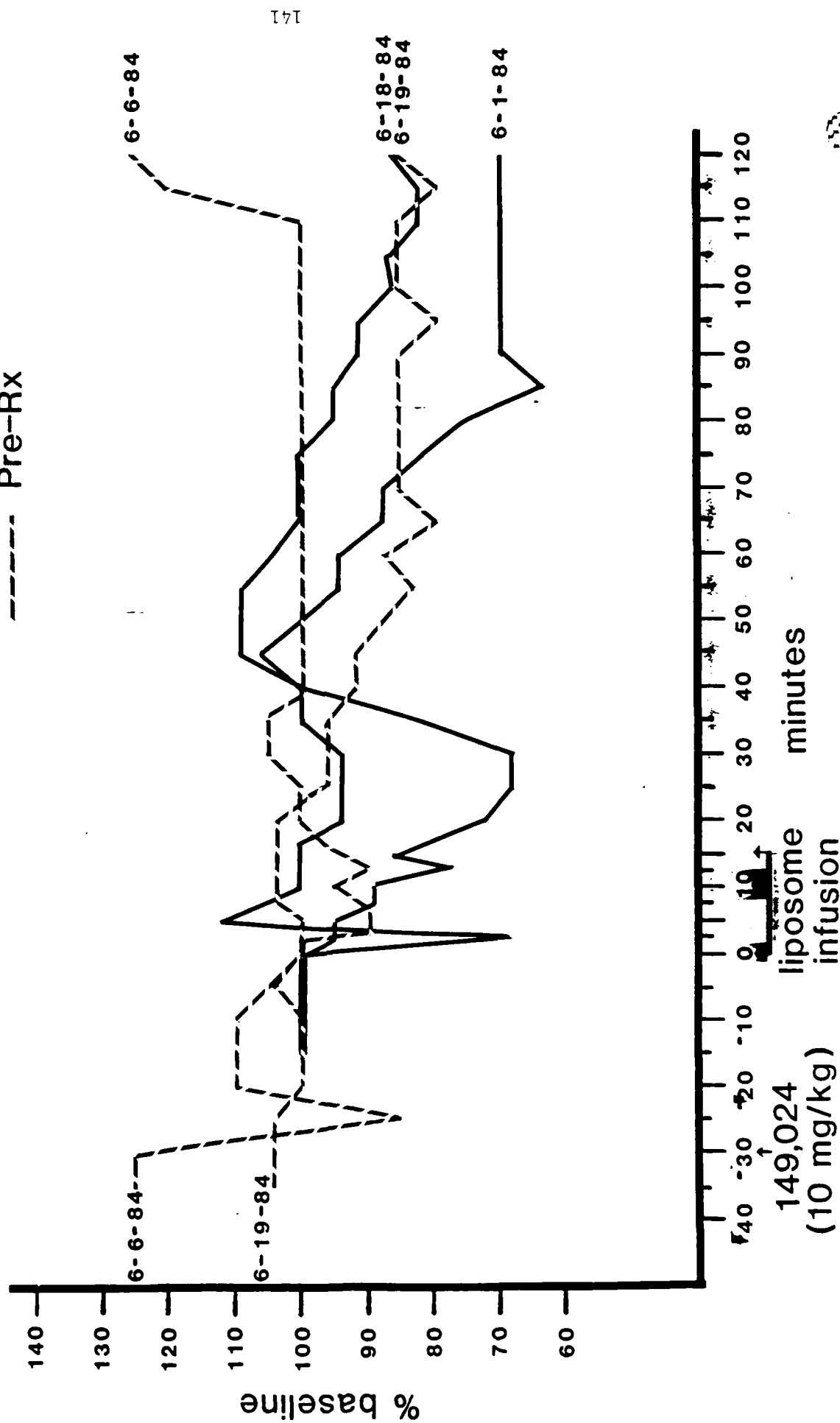


FIGURE 2

MEAN CENTRAL VENOUS PRESSURE

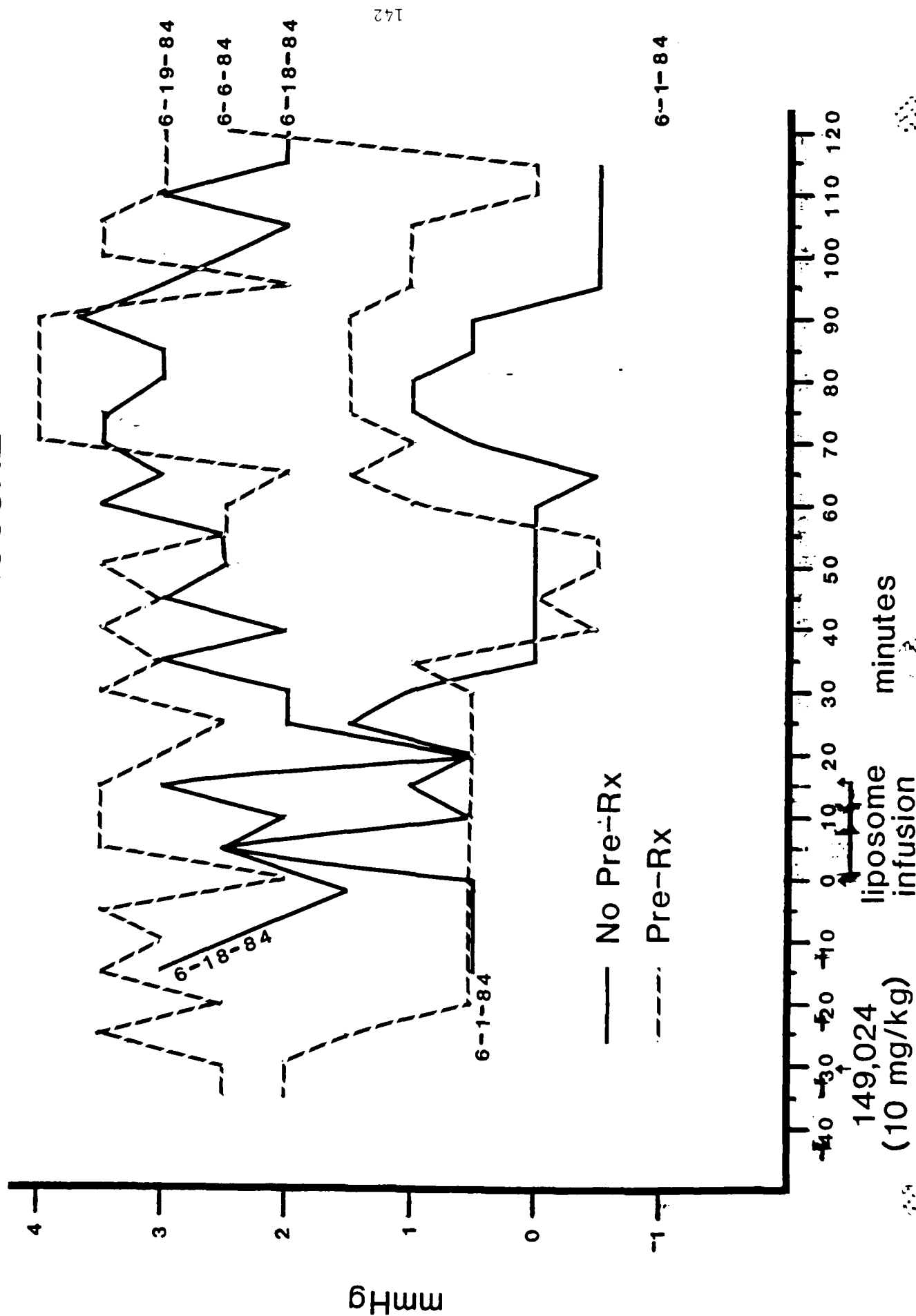


FIGURE 3

HEART RATE

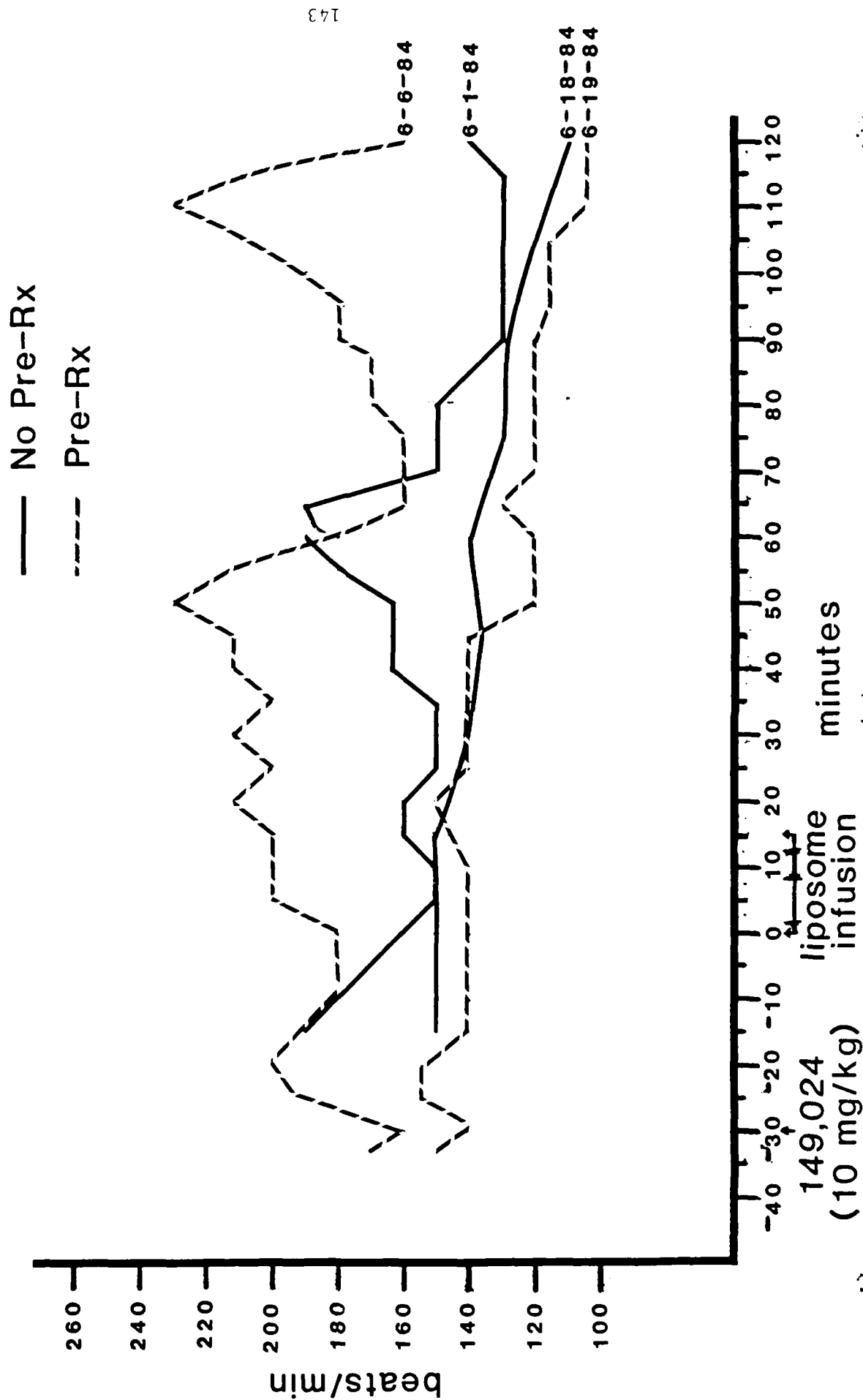


fig.4

Lead II EKG

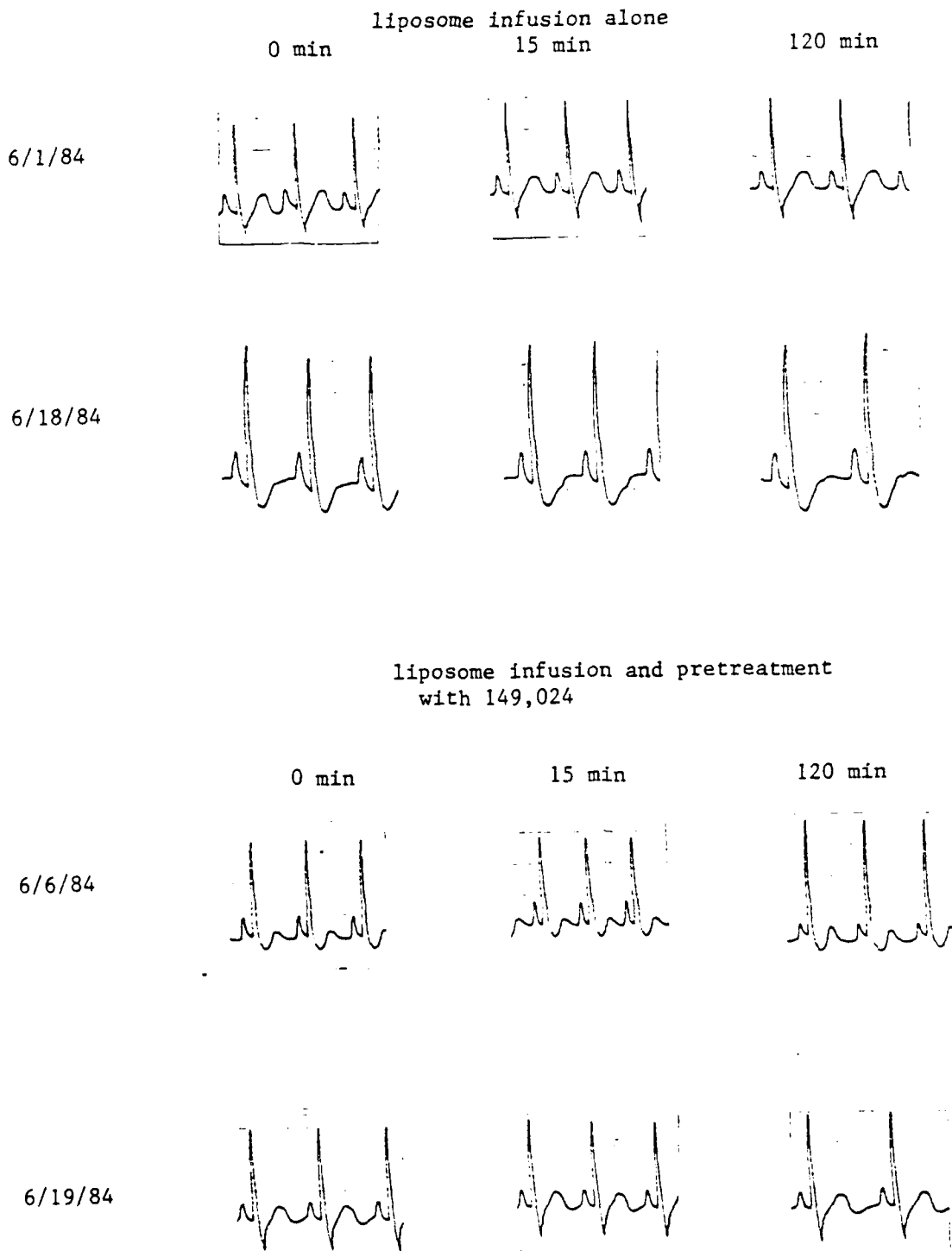


TABLE 1

Minutes	6/1/84				6/8/84				6/16/84				6/19/84			
	DBP	CPP	HR	macro Hct % cells	DBP	CPP	HR	macro Hct % cells	DBP	CPP	HR	macro Hct % cells	DBP	CPP	HR	macro Hct % cells
-35				10.0				11.2								12.4
-30																
-25																
-20																
-15		0.5	190			3.0										
-10		0.5	160	28.5		1.5	150	48								
0	100				100											
2.5	68.75				95.45											
5	112.5	2.5	150		95.45	2.5										
7.5	105				81.82											
10	100	0.5	150		81.82	2.0										
12.5					77.27											
15	100	1.0	160	26	86.36	3.0	150	49								
20	93.75	0.5			72.73	2.5										
25	93.75	1.5	150		64.14	2.0										
30	93.75	1.0	150	25	66.18	2.0	140	47.5								
35	100	0	150		81.82	2.0										
40	100	0	160		100	2.0										
45	106.25	0	160		108.69	3.0	135									
50	100	0	160		109.09	2.5										
55	93.75	0	180		109.09	2.5										
60	93.75	0	140	27	104.54	3.5	140	49								
65	87.5	0.5	190		100	3.0										
70	87.5	0.5	150		100	3.5	130									
75	81.25	1.0	150		100	3.5										
80	75.0	1.0	150		95.45	3.0										
85	62.5	0.5	140		91.45	3.0	130	52.5								
90	68.75	0.5	130	26.5	90.91	3.7										
95	68.75	0.5	130		90.91	3.0										
100	68.75	0.5	130		86.36	2.5										
105	68.75	0.5	130		86.36	2.0	120									
110	68.75	0.5	130		81.82	3.0										
115	68.75	0.5	130		81.82	2.0	110	51								
120	66.75	0.5	140	27	86.36	2.0										
* Liposome infusion (i.v.) from 0 to +15 minutes																

▲ Pre-Rx with WR-149,024 at 10 mg/kg (i.v.)

TABLE 2

minutes	6/11/84	ABP mm Hg	Pulse pressure mm Hg	6/18/84	ABP mm Hg	Pulse pressure mm Hg	6/6/84	ABP mm Hg	Pulse pressure mm Hg	6/19/84	ABP mm Hg	Pulse pressure mm Hg
-35								175/125	50		165/125	40
-30								▲ 175/125	50	▲	165/125	40
-25								160/85	35		150/125	35
-20								160/110	30		155/120	35
-15		110/80	30		160/110	50					155/120	35
-10								160/110	30		160/120	40
0								145/100	45		160/120	40
2.5	*	105/80	25	*	105/110	55	*	125/100	35	*	124/125	40
5		90/55	25		155/105	50		135/90	45		112/110	40
7.5		105/85	20		135/90	45		125/90	35		120/125	35
10		100/80	20		130/90	40		130/95	35		140/125	35
12.5		100/80	20		125/85	40		135/100	35		140/125	35
15		100/80	20		135/95	45		135/95	40		140/125	35
20		100/75	25		135/95	55		135/100	35		160/125	35
25		100/75	25		140/75	65		140/100	40		155/115	40
30		100/75	25		140/75	65		145/105	40		150/115	35
35		105/80	25		140/90	50		140/105	35		150/115	35
40		105/80	25		150/110	40		145/100	45		150/110	40
45		110/85	25		155/120	35		140/100	40		145/110	35
50		115/80	35		155/120	35		145/100	45		145/105	40
55		120/75	45		155/120	35		130/100	50		130/100	30
60		120/75	45		155/115	40		160/100	60		140/135	35
65		110/70	40		155/110	45		150/100	50		125/95	30
70		105/70	35		155/110	45		150/100	50		130/100	30
75		100/65	35		140/110	50		145/100	45		130/100	30
80		95/60	35		135/105	50		145/100	45		125/110	35
85		90/50	40		135/105	50		140/100	40		125/100	25
90		90/55	35		150/100	50		140/100	40		125/100	25
95		95/55	40		150/100	50		135/100	35		120/95	25
100		95/55	40		145/95	50		140/100	40		125/100	25
105		90/55	35		145/95	50		140/100	40		125/100	25
110		95/55	40		135/90	45		140/100	40		120/100	20
115		90/55	35		140/90	50		155/120	35		125/95	20
120		90/55	35		140/95	45		170/125	45		165/110	25

* liposome infusion (0 to +15 min)

▲ Pre-Rx with WR-149,024 @ 10 mg/kg (i.v.)

ABP = arterial blood pressure

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