The dose schedules relative to intubation for the 3 esmolol groups were as follows.

Infusion Time	Brevibloc Group 100 mcg/kg/min	200 mcg/kg/min	300 mcg/kg/min
Minute 1	500 mcg/kg/min	500 mcg/kg/min	500 mcg/kg/min
Minute 2	100 mcg/kg/min	500 mcg/kg/min	500 mcg/kg/min
Minute 3	100 mcg/kg/min	200 mcg/kg/min	500 mcg/kg/min
	Intubation	Intubation	Intubation
Minute 4	100 mcg/kg/min	200 mcg/kg/min	300 mcg/kg/min
Minute 5	100 mcg/kg/min	200 mcg/kg/min	300 mcg/kg/min
Minute 6	100 mcg/kg/min	200 mcg/kg/min	300 mcg/kg/min
Minute 7	100 mcg/kg/min	200 mcg/kg/min	300 mcg/kg/min

Heart rate and blood pressure were measured at periodic intervals for all patients throughout the study. Hemodynamic measurements from a pulmonary artery catheter were also obtained in 55% (23/42) of the patients. In addition, plasma catecholamine levels and esmolol blood levels were determined to evaluate their possible relationship to the efficacy of esmolol.

Study Results

The efficacy results for the primary variables (heart rate and blood pressure) and rate pressure product (RPP) are provided in Tables 8, 9, 12 and 13.

Table 8

HEART RATE (BPM) AT VARIOUS STAGES OF THE STUDY

DOSAGE MCG/KG/MIN		BASELINE	POST INDUCTION	PRE INTUBATION	MAXIMUM	POST INFUSION 1 MIN	POST INFUSION 5 MIN
CONTROL	HR	76.0±4.0 (9)	82.0±4.8 (9)	84.3±3.7 (9)	104.4±6.2 (9)	93.3±4.4 (3)	91.0±3.0 (3)
	CHANGE		12.3±3.2* (9)	13.0±3.6* (9)	33.9±5.5* (9)	14.0±7.6 (3)	14.0±14.0 (2)
E 100	HR	69.2±2.8 (10)	81.7±1.6 (10)	79.7±3.2 (10)	89.4±3.7 (10)	88.0±2.2 (7)	88.0±3.5 (5)
	CHANGE		12.5±3.1* (10)	9.5±4.1 (10)	20.2±4.9*(10)	9.3±4.6 (7)	16.0±3.0* (5)
E 200	HR	69.6±3.9 (9)	81.1±3.9 (9)	79.0±5.0 (9)	86.4±2.8 (9)	83.2±4.1 (5)	87.5±3.2 (4)
	CHANGE		11.6±3.2 (9)	6.2±3.8 (9)	16.9±3.2* (9)	16.8±3.3* (5)	21.8±3.3* (4)
E 300	HR	68.1±4.3 (10)	77.6±3.6 (10)	71.0±2.6 (10)	84.8±2.1 (10)	81.6±2.3 (10)	80.7±2.4 (6)
	CHANGE		9.5±2.7* (10)	3.7±3.2 (10)	15.9±3.8*(10)	13.5±3.7*(10)	12.5±3.9 (6)
Comparison of Changes		N.S	N.S	N.S.	N.S.	N.S.	N.S.

* Indicates significant change from the corresponding baseline ($p<0.05$).

N.S. Indicates mean changes are not statistically different among the four groups ($p\geq0.05$).

Numbers in parenthesis indicate number of patients.

Data represent Mean ± SEM.

E = enalol

Table 9

SYSTOLIC BLOOD PRESSURE (mm Hg) AND CHANGE FROM BASELINE IN CONTROL GROUP AND FOLLOWING VARIOUS DOSES OF ESMOLOL

DOSAGE MCG/KG/MIN		BASELINE	POST INDUCTION	PRE INTUBATION	MAXIMUM	POST INFUSION 1 MIN	POST INFUSION 5 MIN
CONTROL	SBP	147.4±7.3 (9)	142.0±9.8 (9)	141.4±9.2 (9)	191.0±9.4 (9)	152.0±11.3 (3)	150.0±10.0 (2)
	CHANGE		-4.6±5.8 (9)	-6.0±5.7 (9)	44.4±10.4*(9)	10.3±4.9 (3)	7.5±7.5 (2)
E 100	SBP	141.0±5.5 (10)	127.3±7.2 (10)	114.4±5.7 (9)	172.6±5.0 (9)	140.3±14.1 (4)	133.0±4.0 (3)
	CHANGE		-14.5±5.2*(10)	-27.6±5.6* (9)	30.6±9.4* (9)	6.0±10.4 (4)	-0.3±5.4 (3)
E 200	SBP	148.4±7.2 (9)	129.3±5.2 (9)	110.3±5.1 (9)	163.3±9.6 (9)	141.2±5.9 (3)	137.5±1.5 (4)
	CHANGE		-17.1±5.2* (9)	-33.0±5.9* (9)	16.0±4.8* (9)	7.4±2.3* (3)	8.5±1.0 (4)
E 300	SBP	130.0±5.7 (10)	122.0±7.7 (10)	105.2±5.7 (10)	136.2±5.8 (10)	140.5±9.0 (10)	141.3±5.7 (6)
	CHANGE		-8.0±5.1 (10)	-24.8±5.3*(10)	25.2±5.8*(10)	10.5±7.0* (10)	12.3±5.9 (6)
Comparison of Changes		N.S.	N.S.	Control ≠ E 100, ≠ E 200, ≠ E 300	N.S.	N.S.	N.S.

* Indicates significant change from the corresponding baseline ($p<0.05$).

N.S. Indicates mean changes are not statistically different among the four groups ($p\geq0.05$).

Numbers in parenthesis indicate number of patients.

Data represent Mean ± SEM.

E = enalol

Table 12

RATE-PRESSURE PRODUCT AND CHANGE FROM BASELINE IN CONTROL GROUP AND FOLLOWING VARIOUS DOSES OF ESMOLOL

DOSAGE MCG/KG/MIN		BASELINE	POST INDUCTION	PRE INTUBATION	MAXIMUM	POST INFUSION 1 MIN	POST INFUSION 5 MIN
CONTROL	RPP	10.4±0.9 (9)	11.6±0.8 (9)	11.8±0.7 (9)	19.8±1.1 (9)	14.0±1.8 (3)	14.2±1.8 (2)
	CHANGE		1.3±0.6 (9)	1.5±0.8 (9)	9.4±1.9* (9)	3.2±0.6 (3)	2.0±1.5 (2)
E 100	RPP	9.8±0.8 (10)	10.3±1.1 (10)	8.3±0.7 (9)	14.8±0.9 (9)	11.1±0.7 (6)	11.8±0.5 (3)
	CHANGE		0.6±0.9 (10)	-1.6±0.6* (9)	4.7±1.0* (9)	1.7±0.9 (6)	2.1±1.5 (3)
E 200	RPP	10.2±0.8 (9)	10.4±0.9 (9)	8.4±0.7 (9)	13.9±1.0 (9)	12.8±1.0 (9)	12.8±0.7 (6)
	CHANGE		0.3±1.0 (9)	-1.8±1.0 (9)	3.8±1.1* (9)	3.0±0.9* (9)	3.4±1.0* (6)
E 300	RPP	9.8±0.9 (10)	9.8±0.9 (10)	7.3±0.6 (10)	13.1±1.0 (10)	12.3±1.0 (10)	11.4±0.8 (6)
	CHANGE		0.7±0.6 (10)	-1.3±0.7 (10)	4.1±0.7*(10)	3.3±0.7*(10)	2.0±1.2 (6)
Comparison of Changes		N.S.	N.S.	Control > E100, E200, E300	Control > E100, E200, E300	N.S.	N.S.

* Indicates significant change from the corresponding baseline ($p<.05$).

N.S. Indicates mean changes are not statistically different among the four groups ($p\geq.05$).

Numbers in parenthesis indicate number of patients.

Data represent Mean ± SEM.

E = esmolol

Table 13

MAXIMUM CHANGE IN HEART RATE, BLOOD PRESSURE AND RATE PRESSURE PRODUCT FROM BASELINE TO POST INTUBATION

GROUP	HR	SBP	DBP	MAP	RPP
Control (N=9)	33.9±6.5	44.4±10.4	32.1±5.3	36.2±6.5	9.4±1.5
E 100 (N=10)	20.2±4.9	30.6±9.4	28.8±4.6	29.4±6.1	4.7±1.4
E 200 (N=9)	16.9±5.2	16.9±4.8	23.6±3.6	20.7±3.8	3.8±1.1
E 300 (N=10)	15.9±3.8	26.2±5.8	25.5±4.1	25.7±4.6	4.1±0.7
Comparison of Changes	N.S.	N.S.	N.S.	N.S.	Control > E100, E200, E300

N.S. Indicates mean changes are not statistically different among the four groups ($p\geq0.05$).

Data represent Mean ± SEM.

E = esmolol (mcg/kg/min)

A. Heart Rate

The maximum change from baseline to post intubation is shown in Table 13. As can be seen in this table, the stimulus of endotracheal intubation produced a significant increase in the heart rate from the baseline values. Treatment with esmolol produced blunting of this response (Tables 8 and 13). The differences between the control and esmolol treated groups with respect to mean increases in heart rate approached but did not reach statistical significance (p=0.07). A clear dose response relationship between the dose of esmolol and the effect on intubation induced changes in hemodynamics was not seen, although a dose response pattern was observed with respect to heart rate: the 300 mg/kg/min dose of esmolol appeared to be more effective than the lower two doses of esmolol.

B. Systolic Blood Pressure

Maximum post intubation increases (changes from the baseline) in SBP were lower in magnitude for the esmolol treated patients when compared to the control patients, though the differences did not reach statistical significance. Actual maximum SBP following intubation was significantly higher in the control and esmolol 100 mcg/kg/min groups, than in the esmolol 200 and 300 mcg/kg/min groups, suggesting the blunting effect of esmolol at the 200 and 300 mcg/kg/min dose levels (see Table 9 and 13).

C. Secondary Variables

No significant differences were detected between study groups for the variables DBP and MAP with respect to maximum changes from baseline or on actual maximal values.

D. RPP

RPP alone among the efficacy variables exhibited a statistically significant difference between the four study groups with respect to maximum change from baseline following intubation. See Tables 12 and 13.

E. Clinically Significant Increases in Heart Rate and Blood Pressure

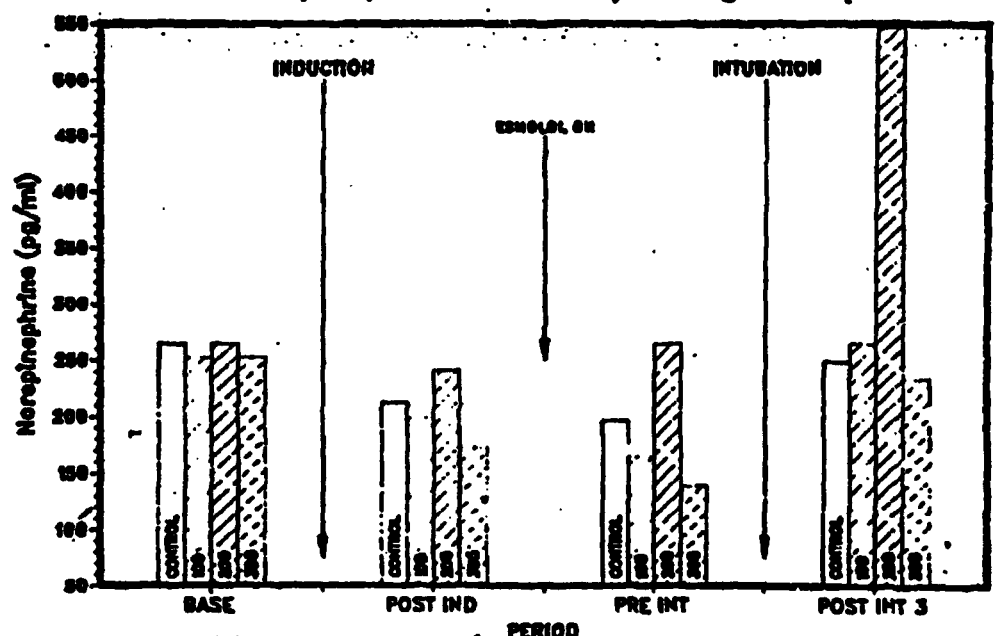
Since adverse effects due to the imbalance between myocardial oxygen demand vs supply in patients with coronary artery disease will be related to the maximum values of heart rate and blood pressure obtained by particular patients following intubation, the sponsor tabulated the number of patients in the three esmolol dosage groups and one control group in terms of increases in heart rate and blood pressure that would be considered clinically significant in this patient population. For the purposes of this analysis, systolic blood pressure greater than 180 mm Hg and heart rate greater than 100 bpm were selected as the significant levels. In summary the number of patients exhibiting elevations of heart rate and/or systolic blood pressure was lower in all of the esmolol groups than in the control groups.

F. Variables Possibly Related to Efficacy

Since the effects of intubation on heart rate and blood pressure are generally believed to be adrenergically mediated, plasma catecholamine (norepinephrine, epinephrine) levels were measured in an attempt to correlate these levels with the intubation induced changes and following the administration of esmolol. This data is presented in Figures 6 and 7 and Table 19.

Figure 6

Norepinephrine Levels, by Dosage Group



100 = Esmolol 100 mcg/kg/min
200 = Esmolol 200 mcg/kg/min
300 = Esmolol 300 mcg/kg/min

Figure 7

Epinephrine Levels, by Dosage Group

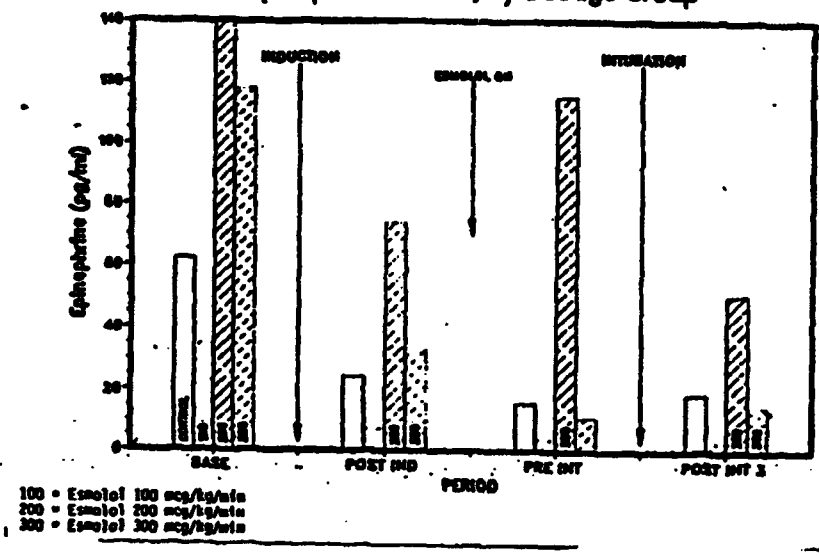


Table 19

MEAN PLASMA NOREPINEPHRINE AND EPINEPHRINE LEVELS

VAR	DOSAGE	BASE	N	POST IND	N	PRE INT	N	POST INT 3	N
NOREPI (pg/ml) N.S.	Control	264.1	(7)	211.4	(7)	195.6	(7)	248.0	(4)
	E 100	252.2	(8)	188.9	(8)	184.1*	(8)	265.0	(5)
	E 200	264.3	(6)	240.6	(6)	264.1	(7)	545.8	(4)
	E 300	253.2	(10)	172.6	(10)	138.9	(10)	234.0	(10)
EPI (pg/ml) N.S.	Control	62.1	(7)	24.2*	(7)	15.8*	(7)	18.8*	(4)
	E 100	34.8	(8)	7.1*	(8)	3.6*	(8)	3.0*	(5)
	E 200	138.6	(6)	73.6	(6)	114.8	(6)	90.3	(3)
	E 300	117.7	(10)	32.8	(10)	11.1*	(10)	15.0*	(10)

* Indicates mean value is significantly different than the corresponding baseline mean ($p<0.05$).

NMA - no measureable amount.

N.S. Indicates no significant difference among the four groups at any of the four periods (actual values used for baseline comparisons, change from baseline used for subsequent comparisons, $p>0.05$).

Numbers in parentheses represent ranges.

E = esmolol (mcg/kg/min)

Epi = Epinephrine

Norepi = Norepinephrine

Although the sponsor interprets the data to suggest that the levels of norepinephrine increased after the stimulus of intubation, careful analysis of this data however does not really support this conclusion. Rather it appears that for norepinephrine, there were not significant changes from baseline except for the esmolol 200 group. However, for epinephrine, all groups exhibited significant change from baseline including the post intubation period. For both norepinephrine and epinephrine there were no significant differences between the groups. Thus it is difficult to interpret whether esmolol had any effect on circulating levels of catecholamines (epinephrine) since levels of epinephrine were already depressed prior to the esmolol infusion (post induction). It is not clear what effect methodological problems might have had on the results obtained. Nevertheless, because of the scatter in the data especially for the esmolol 200 mg/kg/min group, it is probably not possible to make any definitive conclusion from this data. Thus, the sponsor's contention that the administration of esmolol attenuated the intubation induced heart rate and blood pressure response only without effecting norepinephrine levels is not clear from the data.

Safety Results

Only one adverse effect was reported by the investigator (hypotension exhibited by one patient). This occurred prior to the initiation of the esmolol infusion and was treated with phenylephrine. In summary, although a clear dose response relationship between the dose of esmolol and the effect on intubation induced changes in hemodynamics was not seen, a dose response trend was observed with respect to heart rate and blood pressure: 300 mcg/kg/min dose of esmolol appeared to more effect than the lower two doses. Based on the data obtained on circulating levels of catecholamines, it is not possible to make any definitive conclusions regarding their relationship to the efficacy of esmolol and the hemodynamic changes observed.

Addendum to 8052-82-21

The sponsor indicates that after the stimulus of intubation all four groups exhibited an elevation of the norepinephrine levels. However, if one uses the prestudy baseline period for a comparison, rather than the preintubation period there is no significant change in the plasma norepinephrine levels. However, the data can be interpreted to indicate that esmolol while attenuating the intubation induced heart rate and blood pressure response, does not appear to effect significantly norepinephrine levels.

Study 8052-83-44

Study Objective

To compare four treatment groups: esmolol 100, 200, and 300 and placebo with respect to the effect on increases observed in heart rate and systolic blood pressure following the stimulus of endotracheal intubation and safety in patients anesthetized with thiopental. A secondary objective was to compare the plasma catecholamines and esmolol levels between the groups and assess their relationship to heart rate.

Study Design and Number of Patients

This was a nonrandomized, open label study in noncardiac surgery patients. Forty all patients entered the study and of these patients, 35 were classified as efficacy patients; placebo group n=7, esmolol 100 n=8, esmolol 200 n=9, esmolol 300 n=11. Analysis of the effect of esmolol on heart rate and blood pressure was restricted to the 35 "efficacy patients."

Treatment Plan and Test Parameters for Safety and/or Efficacy

The study consisted of 4 periods: a prestudy evaluation period, a 5-minute preinfusion baseline period, a 10 minute study drug infusion period, and 30 minute post infusion (followup). The patients were assigned to one of three study treatment groups in a nonrandom manner. The dosage schedules in these groups were as follows.

Treatment Groups

Time in Minutes	Placebo (D5W) mL/kg/hr	Brevibloc 100 mcg/kg/min	Brevibloc 200 mcg/kg/min	Brevibloc 300 mcg/kg/min
1	1.0	500*	500*	500*
2	1.0	100	500*	500*
3	1.0	100	200	500*
4	1.0	100	200	500*
5	1.0	100	200	300
6	1.0	100	200	300
7	1.0	100	200	300
8	1.0	100	200	300
9	1.0	100	200	300
10	1.0	100	200	300

*Loading dose to rapidly achieve steady state blood level.

Anesthesia was induced with thiopental (3-4 mg/kg IV) at minute four of the esmolol infusion.

Heart rate and blood pressure were measured at periodic intervals for all patients throughout the study. In addition, plasma catecholamine levels and blood levels of esmolol were also determined.

Study Results

The major findings are summarized in Table 6 (heart rate), 7 (systolic blood pressure) and 10 (rate pressure product).

TABLE 7

SUMMARY OF SYSTOLIC BLOOD PRESSURE (MM HG) AND SYSTOLIC BLOOD PRESSURE CHANGES FOR "EFFICACY PATIENTS"

DOSAGE		BASE MEAN ± SEM	N	PREINDUCTION MEAN ± SEM	N	PREINTUBATION MEAN ± SEM	N	MAXIMUM MEAN ± SEM	N	POST INF 5 MEAN ± SEM	N	POST INF 15 MEAN ± SEM	N
PLACEBO	SBP	142.3 ± 8.5	7	143.9 ± 6.4	7	145.7 ± 10.3	7	202.3 ± 12.6	7	129.1 ± 7.2	7	108.4 ± 6.5	5
	CHANGE			1.6 ± 1.6	7	3.5 ± 15.8	7	60.0* ± 9.7	7	-13.1 ± 7.4	7	-46.0* ± 8.4	5
100†	SBP	159.9 ± 8.1	8	164.6 ± 7.9	8	165.6 ± 11.4	8	200.6 ± 8.4	8	132.1 ± 9.3	8	107.8 ± 5.5	4
	CHANGE			4.7 ± 6.6	8	5.7 ± 12.5	8	46.7* ± 9.2	8	-27.8 ± 11.8	8	-41.2 ± 8.7	4
200†	SBP	154.7 ± 8.3	9	157.8 ± 10.1	9	137.2 ± 10.9	9	174.0 ± 8.8	9	119.3 ± 5.9	9	119.1 ± 8.9	8
	CHANGE			3.1 ± 5.2	9	-17.5* ± 7.1	9	19.3* ± 6.9	9	-35.3* ± 7.6	9	-35.5 ± 11.0*	8
300†	SBP	151.1 ± 8.5	11	148.9 ± 6.6	11	138.8 ± 8.5	11	179.1 ± 8.4	11	118.6 ± 7.2	11	105.0 ± 5.0	10
	CHANGE			-2.2 ± 3.2	11	-13.1 ± 6.4	11	28.0* ± 4.8	11	-32.5* ± 6.0	11	-46.0 ± 7.1*	10
COMPARISON OF CHANGE		N.S.		N.S.		N.S.		Placebo> 200, 300		N.S.		N.S.	

† Somatol dose (mcg/kg/min)

* Indicates significant change from baseline ($p \leq 0.05$).

N.S. Indicates no significant changes between groups ($p > 0.05$).

(Actual values used for baseline comparisons).

TABLE 8

SUMMARY OF HEART RATE (BPM) AND HEART RATE CHANGES FOR "EFFICACY PATIENTS"

DOSAGE		BASE MEAN ± SEM	N	PREINDUCTION MEAN ± SEM	N	PREINTUBATION MEAN ± SEM	N	MAXIMUM MEAN ± SEM	N	POST INF 5 MEAN ± SEM	N	POST INF 15 MEAN ± SEM	N
PLACEBO	HR	88.9 ± 5.0	7	93.7 ± 5.0	7	94.9 ± 6.3	7	117.0 ± 6.4	7	98.4 ± 4.7	7	88.8 ± 5.1	5
	CHANGE			3.8 ± 2.9	7	5.0 ± 5.9	7	27.1* ± 5.5	7	8.6 ± 5.6	7	5.8 ± 5.3	5
100†	HR	88.1 ± 6.4	8	83.1 ± 3.5	8	83.8 ± 3.0	8	91.6 ± 4.1	8	80.3 ± 5.5	8	82.0 ± 3.3	4
	CHANGE			-17.0* ± 3.0	8	3.5 ± 6.8	8	11.5 ± 5.9	8	0.2 ± 6.1	8	-0.1 ± 9.5	4
200†	HR	82.1 ± 3.9	9	78.2 ± 4.8	9	89.3 ± 5.8	9	105.0 ± 6.1	9	87.7 ± 4.4	9	77.4 ± 3.0	8
	CHANGE			-5.8* ± 1.4	9	7.3 ± 4.4	9	22.8* ± 4.5	9	5.8 ± 4.2	9	-1.8 ± 4.7	8
300†	HR	83.1 ± 5.3	11	69.4 ± 4.6	11	81.8 ± 3.7	11	94.2 ± 3.0	11	78.5 ± 4.2	11	76.4 ± 3.4	10
	CHANGE			-19.7* ± 1.9	11	-1.4 ± 4.0	11	11.1 ± 5.4	11	-3.5 ± 6.8	11	-2.6 ± 4.2	10
COMPARISON OF CHANGE		N.S.		Placebo> 100, 200, 300		N.S.		N.S.		N.S.		N.S.	

† Somatol dose (mcg/kg/min)

* Indicates significant change from baseline ($p \leq 0.05$).

N.S. Indicates no significant changes between groups ($p > 0.05$).

(Actual values used for baseline comparisons).

TABLE 10

SUMMARY OF RATE-PRESSURE PRODUCT AND RATE-PRESSURE PRODUCT CHANGES FOR "EFFICACY PATIENTS"

		BASE			PREINDUCTION			PREINTUBATION			MAXIMUM			POST INF 5			POST INF 10		
DOSAGE		MEAN	± SEM	N	MEAN	± SEM	N	MEAN	± SEM	N	MEAN	± SEM	N	MEAN	± SEM	N	MEAN	± SEM	N
PLACEBO	RPP	12.9	1.0	7	13.6	1.2	7	14.3	2.0	7	22.5	1.9	7	12.6	0.8	7	8.9	0.7	5
	CHANGE				0.7	0.5	7	1.4	1.9	7	9.6*	1.4	7	-0.3	0.8	7	-5.0*	1.2	5
100[1]	RPP	12.8	1.3	8	10.5	1.0	8	14.0	1.2	8	17.8	1.3	8	10.7	1.2	8	8.9	0.6	4
	CHANGE				-2.4*	0.7	8	1.0	1.6	8	4.9*	1.1	8	-2.3	1.0	8	-3.6	2.6	4
200[1]	RPP	12.8	1.0	9	12.1	1.1	9	12.5	1.6	9	17.6	1.2	9	10.5	0.7	9	8.4	1.1	6
	CHANGE				-0.7	0.6	9	-0.3	1.0	9	5.0*	0.8	9	-2.3	1.1	9	-3.0	1.4	6
300[1]	RPP	12.3	1.2	11	10.4	0.8	11	11.5	1.2	11	16.6	1.0	11	9.5	0.8	11	8.0	0.5	10
	CHANGE				-2.4*	0.6	11	-1.2	0.8	11	3.9*	1.1	11	-3.3*	1.3	11	-4.8*	1.0	10
COMPARISON OF CHANGE		N.S.			Placebo > 100, 300			N.S.			Placebo > 100, 200, 300			N.S.			N.S.		

[1] Esmolol dose (mcg/kg/min).

* Indicates significant change from baseline ($p \leq 0.05$).

N.S. Indicates no significant changes between groups ($p > 0.05$).

(Actual values used for baseline comparisons).

A. Heart Rate

The three esmolol dosage groups (100, 200 and 300 mcg/kg/min) exhibited smaller mean increases in heart rate after intubation when compared to the placebo group (see Table 6). The net mean change (23 vs (11 at 100) in the esmolol 200 mcg/kg/min groups deviates from the expected dose response effect. Hence, HR does not order re increasing doses of esmolol.

B. Systolic Blood Pressure

In the esmolol 200 and 300 mcg/kg/min dosage groups, a significant decrease after intubation, of the increase in systolic blood pressure was seen in comparison to the placebo group (see Table 7). The systolic blood pressure in the esmolol 300 mcg/kg/min group showed a mean increase of 28 vs (19 at 200) which again deviates from the expected dose response effect. Hence SBP doesn't order re increasing doses of esmolol.

C. Rate Pressure Product

The rate pressure product (which the sponsor claims is an indicator of myocardial oxygen consumption) showed a greater increase in the placebo group than in the 3 esmolol groups (see Table 10). However, RPP doesn't order re increasing doses of esmolol.

D. Following intubation a significantly greater number of patients in the placebo group demonstrated heart rates greater than 100 bpm and systolic blood pressure greater than 180 mm Hg compared to the esmolol groups.

E. Increases in catecholamines were observed as a result of endotracheal intubation in the placebo and three esmolol groups (see Table 25 for changes in plasma norepinephrine from baseline). Hence, the increases in catecholamines following endotracheal intubation were unaffected by esmolol.

TABLE 25

PLASMA NOREPINEPHRINE AND EPINEPHRINE LEVELS IN EFFICACY PATIENTS

VARIABLE	ESMOLOL DOSAGE MCG/KG/MIN	PREANESTHESIA MEAN ± SEM	MIN	MAX	N	POST LARYNGOSCOPY MIN 3 MEAN ± SEM	MIN	MAX	N	CHANGES FROM PREANESTHESIA TO POST INTUBATION MEAN ± SEM	MIN	MAX	N
NOREPI pg/ml (NS)	Placebo	270.7 84.5			6	440.1 160.9			7	200.6 140.9			6
	100	363.6 96.3			7	496.9 165.3			8	182.6 169.2			7
	200	147.6 17.2			9	337.6 75.3			9	189.8* 65.8			9
	300	180.4 32.8			10	399.8 115.2			11	224.4 127.8			10
EPI pg/ml (NS)	Placebo	29.4 14.4			7	41.6 16.8			7	12.1 24.9			7
	100	66.1 33.2			7	65.5 27.2			8	-0.1 14.8			7
	200	52.8 14.8			9	66.7 28.7			9	13.8 34.6			9
	300	61.6 19.4			10	49.3 13.9			11	-17.1 12.8			10
NOREPI + EPI pg/ml (NS)	Placebo	311.5 78.4			6	481.7 176.5			7	214.7 187.3			6
	100	429.7 86.9			7	563.4 164.0			8	196.4 196.9			7
	200	200.7 25.6			9	404.2 102.1			9	203.6 97.4			9
	300	222.8 35.9			10	448.8 116.8			11	207.3 130.5			10

* Indicates significant change from preanesthesia ($p \leq 0.05$).

(NS) Indicates no significant changes between groups ($p > 0.05$).

NOREPI = Norepinephrine

EPI = Epinephrine

Safety Results and Summary

Safety was assessed in all the patients entering the study esmolol n=30 and placebo n=10. No adverse effects were reported in this study. In summary, the rank order of the described effect i.e., HR and SBP is lost implying there is no clear effect of esmolol on these parameters.

Study 8052-83-45

Study Objective

To compare four treatment groups (placebo and esmolol 100, 200 and 300 mcg/kg/min) with respect to changes observed in HR and SBP following endotracheal intubation in patients anesthetized with ketamine.

Study Design and Number of Patients

This was a nonrandomized, open label study in noncardiac surgical patients. 41 all patients entered the study and of these 34 were classified as "efficacy patients": control group n=9; esmolol 100 n=8; esmolol 200 n=10, esmolol 300 n=7. Seven all patients were excluded from the analysis. Thus analysis of efficacy patients was based on 34 patients whereas safety was based on the data for all 41 patients.

Treatment Plan and Test Parameters for Safety and/or Efficacy

The study consisted of four periods.

1. Prestudy evaluation period.
2. Preinfusion baseline period.
3. Study drug infusion period.
4. Post infusion (follow up) period.

The study drug dose was administered according to the same schedule as in 8052-83-44.

Anesthesia was induced at minute four of the infusion with ketamine (0.5-1.0 mg/kg IV).

Heart rate and blood pressure measurements were obtained periodically for all patients throughout the study. Similar to the other two studies, plasma catecholamine levels and esmolol levels were also monitored.

Study Results

The overall findings are summarized in Table 6 (heart rate), Table 7 (systolic blood pressure), Table 10 (rate pressure product) and Table 24 (plasma catechol levels).

TABLE 6

SUMMARY OF HEART RATE (BPM) AND HEART RATE CHANGES FOR "EFFICACY PATIENTS"

DOSAGE		BASE			PREINDUCTION			PREINTUBATION			MAXIMUM**			POST INF 5		
		MEAN ± SEM		N	MEAN ± SEM		N	MEAN ± SEM		N	MEAN ± SEM		N	MEAN ± SEM		N
PLACEBO	HR	83.4	5.4	9	83.0	5.6	9	96.8	6.5	9	113.0	5.9	9	103.0	5.7	3
	CHANGE				-0.4	1.5	9	13.4*	4.1	9	29.6	4.6	9	14.6	7.4	3
100[1]	HR	81.6	4.0	8	74.9	3.3	8	81.1	3.2	8	97.9	4.8	8	82.3	6.1	4
	CHANGE				-6.7	3.4	8	-0.5	2.9	8	11.3	4.7	8	2.0	4.8	4
200[1]	HR	85.4	2.8	10	73.0	2.8	10	78.2	2.6	10	88.6	3.0	10	71.0		1
	CHANGE				-12.4*	1.6	10	-7.7*	2.2	10	1.2	2.5	10	-20.5		1
300[1]	HR	78.8	6.2	7	69.3	5.3	7	69.4	5.7	7	77.0	5.2	7	72.5	9.5	4
	CHANGE				-9.4*	2.8	7	-9.3*	2.8	7	-1.7	5.0	7	-7.2	5.1	4
COMPARISON OF CHANGE		N.S.			Placebo> 200, 300			Placebo> 100, 200, 300			Placebo> 100,200,300			Not Tested		

[1] Esmolol dose (mcg/kg/min)
* Indicates significant change from baseline ($p<0.05$).
** Maximum change from baseline was not tested for significance.
N.S. Indicates no significant changes between groups (actual values used for baseline comparisons, change from baseline used for subsequent comparisons, $p>0.05$).

TABLE 7

SUMMARY OF SYSTOLIC BLOOD PRESSURE (MM HG) AND SYSTOLIC BLOOD PRESSURE CHANGES FOR "EFFICACY PATIENTS"

DOSAGE		BASE			PREINDUCTION			PREINTUBATION			MAXIMUM**			POST INF 5		
		MEAN ± SEM		N	MEAN ± SEM		N	MEAN ± SEM		N	MEAN ± SEM		N	MEAN ± SEM		N
PLACEBO	SBP	150.4	8.3	9	153.6	8.9	9	170.2	8.3	9	193.6	9.6	9	142.3	13.9	3
	CHANGE				3.1	1.5	9	19.8	10.6	9	43.1	12.4	9	7.4	19.7	3
100[1]	SBP	147.2	10.7	8	142.3	12.2	8	139.9	10.3	8	171.8	10.0	8	117.5	17.1	4
	CHANGE				-4.9	3.1	8	-7.3	6.5	8	24.6	6.6	8	-73.7	16.7	4
200[1]	SBP	153.0	8.2	10	157.1	7.0	10	158.2	9.1	10	184.0	8.8	10	121.0		1
	CHANGE				-1.7	2.8	10	2.4	5.1	10	32.7	7.6	10	-88.0		1
300[1]	SBP	141.3	8.0	7	133.3	8.2	7	135.6	7.0	7	157.7	11.4	7	103.3	8.8	6
	CHANGE				-8.0*	2.8	7	-5.7	4.1	7	11.4	7.6	7	-33.0*	3.4	6
COMPARISON OF CHANGE		N.S.			Placebo> 100,300			N.S.			N.S.			Not Tested		

[1] Esmolol dose (mcg/kg/min)
* Indicates significant change from baseline ($p<0.05$).
** Maximum change from baseline was not tested for significance.
N.S. Indicates no significant changes between groups (actual values used for baseline comparisons, change from baseline used for subsequent comparisons, $p>0.05$).

TABLE 10

SUMMARY OF RATE PRESSURE PRODUCT AND RATE PRESSURE PRODUCT CHANGES FOR "EFFICACY PATIENTS"

DOSAGE		BASE MEAN ± SEM	N	PREINDUCTION MEAN ± SEM	N	PREINTUBATION MEAN ± SEM	N	MAXIMUM** MEAN ± SEM	N	POST INF 5 MEAN ± SEM	N
PLACEBO	RPP	12.5 0.9	9	12.7 1.0	9	10.3 1.1	9	21.4 1.4	9	14.8 1.5	3
	CHANGE			0.2 0.3	9	3.8* 1.4	8	9.0 1.8	9	2.6 2.8	3
100†	RPP	12.1 1.2	8	10.9 1.3	8	11.3 0.9	8	19.6 0.9	8	9.7 1.5	4
	CHANGE			-1.2 0.6	8	-0.8 0.9	8	3.4 1.1	8	-1.9 1.9	4
200†	RPP	13.2 1.0	10	11.2 0.7	10	12.3 0.9	10	15.9 1.1	10	8.6	1
	CHANGE			-2.0* 0.4	10	-0.9 0.5	10	2.7 0.8	10	-8.6	9
300†	RPP	11.0 0.7	7	9.1 0.6	7	9.2 0.4	7	11.6 1.1	7	7.3 0.8	4
	CHANGE			-1.8* 0.5	7	-1.8* 0.5	7	0.6 1.2	7	-3.2* 0.6	4
COMPARISON OF CHANGE		N.S.		Placebo> 100,200,300		Placebo> 100,200,300		Placebo> 100, 200, 300		Not Tested	

† Constat dose (mcg/kg/min)
* Indicates significant change from baseline ($p \leq 0.05$).
** Maximum change from baseline was not tested for significance.
N.S. Indicates no significant changes between groups (actual values used for baseline comparisons, change from baseline used for subsequent comparisons, $p > 0.05$).

TABLE 24

PLASMA NOREPINEPHRINE AND EPINEPHRINE LEVELS IN EFFICACY PATIENTS

VARIABLE	ESMOLOL DOSAGE MCG/KG/MIN	PREANESTHESIA MEAN ± SEM	MIN	MAX	N	POST LARYNGOSCOPY MIN 3 MEAN ± SEM	MIN	MAX	N	CHANGES FROM PREANESTHESIA TO POST INTUBATION MEAN ± SEM	MIN	MAX	N
NOREPI pg/ml (NS)	Placebo	336.4 73.9	118	672	9	553.1 71.3	288	948	9	218.7* 21.8	128	314	9
	100	170.8 23.4	80	306	8	376.0 85.9	134	900	8	205.3* 84.6	54	594	8
	200	270.0 48.1	68	728	10	455.2 117.4	118	1138	10	185.2* 77.3	-200	726	10
	300	408.3 85.9	272	884	7	599.7 58.4	288	774	7	191.4 103.3	-308	942	7
EPI pg/ml (NS)	Placebo	48.1 7.7	5	74	9	49.2 12.0	5	130	9	3.1 13.1	-28	182	9
	100	74.0 21.3	5	176	8	39.9 8.5	5	78	8	-34.1 17.1	-118	23	8
	200	55.6 14.7	5	130	10	77.7 33.1	5	308	10	21.9 28.4	-78	188	10
	300	44.1 7.8	5	70	7	48.0 15.8	5	128	7	4.9 12.6	-29	58	7
NOREPI + EPI pg/ml (NS)	Placebo	382.8 79.1	173	734	9	602.3 74.3	342	1018	9	219.8* 32.8	100	416	9
	100	244.8 39.6	141	482	8	415.9 89.2	210	960	8	171.1* 51.1	41	478	8
	200	325.8 74.6	71	824	10	532.9 148.7	169	1440	10	207.1 96.8	-182	914	10
	300	452.4 88.7	237	916	7	648.7 99.8	293	898	7	196.3 109.2	-278	971	7

* Indicates significant change from preanesthesia ($p \leq 0.05$).
(NS) Indicates no significant changes between groups ($p > 0.05$).
NOREPI = Norepinephrine
EPI = Epinephrine

A. Heart Rate

Esmolol treated patients showed a significant blunting of the increase in heart rate observed following endotracheal intubation when compared to the placebo treated patients (see Table 6). Although not statistically significant, there was a trend towards dose dependency with higher doses of esmolol resulting in lesser increases in heart rate.

B. Systolic Blood Pressure

No significant differences were observed in the maximum changes from baseline during endotracheal intubation between different esmolol dosage groups for SBP. SBP did not order re increasing doses of esmolol (Table 7).

C. The rate pressure product showed results similar to that for heart rate, with greater increases in rate pressure product seen in the placebo group than in the three esmolol groups. Moreover, the results for the RPP showed a nonsignificant dose response trend (see Table 10).

D. Elevations in catecholamines were observed as a result of endotracheal intubation (see Table 24). However because of large variability in the data only few of the changes were significant. There were no significant differences between treatment groups for plasma norepinephrine, epinephrin., or the sum of the two (see Table 24). In addition there were no significant differences between groups for the changes in these variables from preinduction to postintubation.

E. There was also a significant correlation between the blood level of esmolol and the blunting of the heart rate increases observed during endotracheal intubation. Esmolol reached steady state levels at four minutes after the initiation of the infusion.

Safety Results

Safety was assessed in all the patients entering the study. One patient treated with esmolol (300 mcg/kg/min) developed an adverse effect. This patient exhibited bradycardia (heart rate of around 40 bpm) 3 minutes after the infusion was discontinued and hypotension (80/40 mm Hg) 13 minutes after discontinuing esmolol. In summary, although a clear dose response relationship between the dose of esmolol and the effect on intubation induced changes in hemodynamics was not seen, a dose response trend was observed with respect to heart rate. However, the rank order response of SBP was lost suggesting that esmolol had no effect on this parameter.

Conclusion

In conclusion, all four studies were probably too small to establish a statistically significant dose response relationship. A positive trend was noted in the SVT study in that the largest dosage given (300 mcg/kg/min) appeared to be most effective. However, no clear cut effect or dose related trend was demonstrated in two of the three perioperative studies. In addition, in all studies the overall incidence of adverse effects was very small. Accordingly, the sponsor then selected the 300 mcg/kg/min dosage for the controlled perioperative clinical studies, see Controlled Clinical Studies.

Addendum to the Clinical Pharmacology (Section I)

The following material (appendices 1C, 1D, 1E) represents new or revised pharmacokinetic (PK) and pharmacodynamic (PD) data submitted by the sponsor at the request of the FDA. Initial review of the original NDA submission identified deficiencies and/or problems in the Clinical Pharm data base.

Since much of this information cuts across several related studies and appears to be generally applicable to the basic PK model and PD profile previously described in the initial medical review, this new information will be discussed and analyzed as a whole in this addendum.

Issue #1: Quantitation limits (analytical sensitivity) of esmolol and acid metabolite blood assays. The table below provides the range of detection for esmolol (e.g. [redacted] ng/ml in 8052-81-01 to [redacted] ng/ml in 8052-82-07). In the majority of studies, the limit of detection was [redacted] ng/mL.

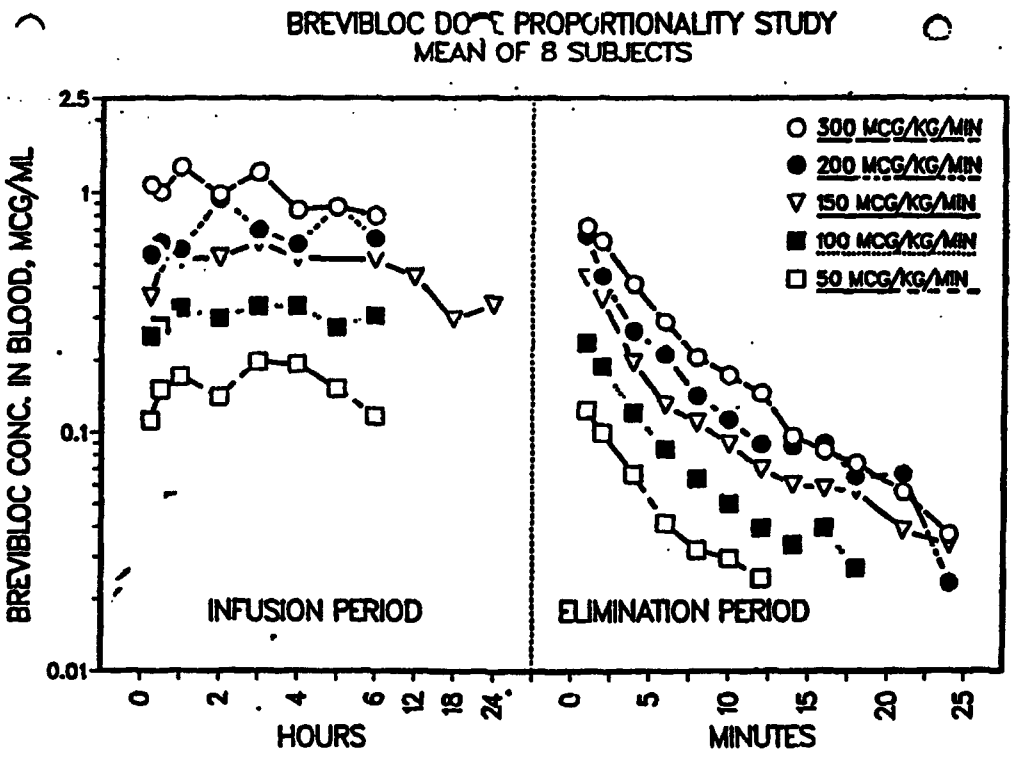
Quantitation Limits of Brevibloc and Metabolite Blood Assays

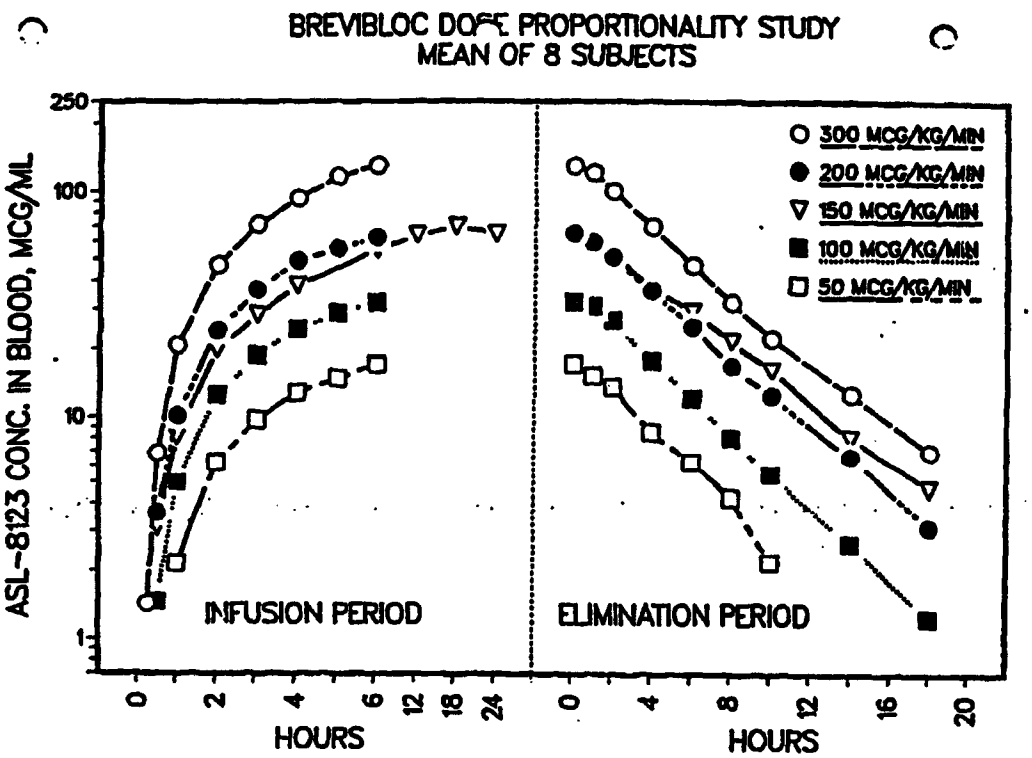
Study Number	Brevibloc, ng/ml	ASL-8123, ng/ml
8052-81-01	2.5*	1
8052-81-02	5*	1
8052-81-03	10**	1
8052-82-07	100**	1
8052-82-09	25**	1
8052-82-10	50	1
8052-82-12	50**	1
8052-82-13	50	1
8052-82-14-02	50	1
8052-82-15	25	1
8052-82-21	50	1
8052-83-25	50	1
8052-83-27-06	50	1
8052-83-38	50	1
8052-83-39	50	1
8052-83-43	50	1
8052-83-44	50	1
8052-83-45	50	1
8052-84-50	50	1
8052-84-58	50	1
8052-84-61	25	1

Notes: All Brevibloc assays done by HPLC-UV unless noted * GC-MS or ** GC-ECD.
All ASL-8123 assays done by HPLC-UV.
Details of assay procedures maybe found in Volume 3.11 of this submission.

Issue #2: Linearity of the terminal elimination half-life of esmolol and ASL-8123.

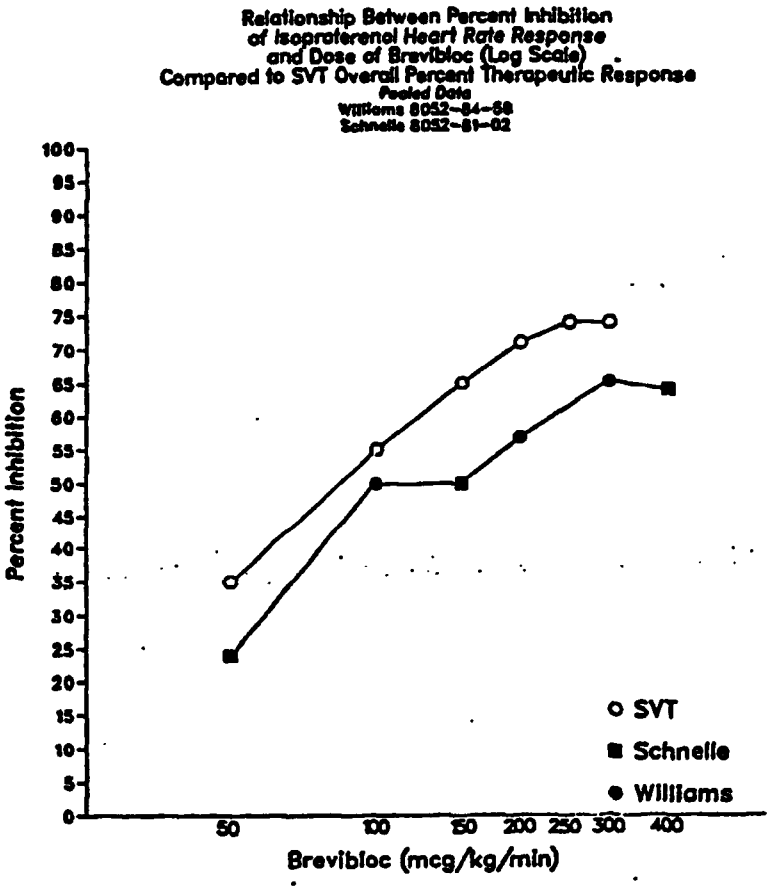
The overall impression of the data (Studies 01, 02, 03, 09) providing (a) individual subject plots and (b) mean plots (for Study 09) re log blood conc vs time for esmolol is that the elimination phase is consistent with "pseudo" first order kinetics (see appendix IC). Clearly one doesn't find the classic "linear" pattern which is the sine quo non of a true first order reaction. This contrasts with the same plots for the acid metabolite (ASL-8123) which does show a true linear pattern (see the two figures below for this comparison).





Since enzymatic metabolism per se doesn't preclude linear kinetics, the data could support the idea that (a) the concentration of the enzyme (nonspecific esterase) is not the crucial factor here and (b) the rate of metabolism is dependent on the concentration of esmolol, i.e., "pseudo" first order reaction.

Issue #3: Dose-response relationship (Studies 43 and 58) of inhibition of isoproterenol induced tachycardia. The new data plots (percent beta blockade vs log (dose, time and blood levels of esmolol) tend to support the analysis provided in the body of the medical review (see Appendix 1D). However, some resolution to the problem is provided in the figure below which compares the dose response in SVT (clinical efficacy trials) to the percent inhibition of tachycardia (pharmacodynamic beta blockade studies).



The above data supports the following:

(1) The 50-200 dose range is at the lower end of the dose response curve and at the 300 dose one has reached the plateau or maximum response.

(2) The clinical response in the SVT (which showed a dose response effect) reasonably well parallels the isoproterenol inhibition curve.

(3) These data tend to reinforce each other.

(4) The sponsor's assertion is probably correct that exercise-induced tachycardia is a clinically more relevant model [vs isoproterenol induced tachycardia] in comparing the potency and effects of cardioselective (esmolol) and non-selected beta blockers (inderal) at the heart.

Issue #4: Methanol Blood Levels as a function of esmolol dose and duration

Since the metabolism of esmolol yields methanol (a potentially toxic metabolite) the safety of this compound needs to be carefully monitored (see Appendix 1E). Review of this data supports the sponsor's contention that methanol levels remain below toxic levels.

Appendix 1A - Pharmacokinetic Modeling

BREVIBLOC® (esmolol hydrochloride)

DOSING REGIMEN DETERMINATION

Following the completion of Study No. 8052-81-02 in which varying doses of esmolol were infused intravenously in eight subjects and the blood levels determined, a computer modeling system was developed to predict blood levels based on varying infusion regimens. Based on these data and with subsequent analysis it was determined that the optimum dosing regimen would require an initial loading dose followed by a maintainence dose designed to rapidly produce the desired steady state blood levels.

This regimen was then incorporated in the subsequent studies designed to establish the safety and efficacy of esmolol hydrochloride.

Following is a report entitled, "Design of Dosing Regimen for Brevibloc Efficacy," describing the kinetic information used and the computer predicted blood level curves for the selected dosing regimens.

DESIGN OF DOSING REGIMEN FOR BREVIBLOC EFFICACY

Purpose: To design a dosing regimen that will allow rapid establishment of steady state blood concentrations and when desired cause rapid transition from the steady state blood concentration of one dose to the steady state of the following dose.

It is desirable to have a dosing regimen that will, in effect, either cause a staircase type pattern in blood and tissue concentrations or one that will cause rapid transition to a single level. Simple infusion of the various doses will require too long for the tissues and blood to reach a steady state. Because of the concentration of propylene glycol in the early formulation, bolus dosing was not considered at this time.

The data from eight normal male subjects have been used to determine the pharmacokinetic parameters of esmolol following a two hour infusion at 400 mcg/kg/min.(1) The blood values, following similar dosing with either 50 or 150 mcg/kg/min, were too low to allow meaningful pharmacokinetic analyses of the data. The calculated parameters for esmolol be summarized as follows:

$\alpha = 0.364\ min^{-1}$, $T_{1/2,\alpha} = 2.03$ min, $\beta = 0.085\ min^{-1}$, $T_{1/2,\beta}$ 9.19 min, $k_{10} = 0.310\ min^{-1}$, $k_{12} = 0.038\ min^{-1}$, $k_{21} = 0.101\ min^{-1}$ $V\beta = 3.43$ l/kg and $Vc = 0.867$ l/kg. Total clearance averaged 285 ml/kg/min and steady state blood concentrations averaged 1.59 mcg/ml after two hours of infusions of esmolol at 400 mcg/kg/min. The equation for blood concentrations using an infusion and assuming: a) primary metabolism via hydrolysis of the ester, to the extent of 90% or more; b) a two compartment model; and c) linear kinetics of distribution and elimination can be described by an established model(1,2) as follows:

$$C = ko\ \frac{(k_{21}-\alpha)(1-e^{\alpha T})}{V_c\ \alpha\ (\alpha-\beta)}\ e^{-\alpha T} + \frac{k_o\ (\beta-k_{21})(1-e^{\beta T})}{Vc\ \beta\ (\alpha-\beta)}\ e^{-\beta T}$$

This equation describes the time course of drug in the blood during infusion and after cessation of infusion. While infusion is continuing, T=t and varies with time. When infusion ceases, T becomes a constant corresponding to the time infusion was stopped. In this equation, k_{21} is the rate constant going from the peripheral compartment to the central compartment. Since $\alpha \times \beta = k_{10} \times k_{21}$, the equation above can be rewritten as:

$$C = \frac{k_o}{V_c\ k_{10}}\ \frac{(\beta-k_{10})(1-e^{\alpha T})}{(\alpha-\beta)}\ e^{-\alpha t} + \frac{(k_{10}-\alpha)(1-e^{\beta T})}{(\alpha-\beta)}\ e^{-\beta t}$$

Using these equations and the calculated values for α, β, V_c, and k_{10} given above, the plasma concentrations, at any given time during or following infusion, can be calculated. Summing these concentrations for several different infusions for each time point, gives us a model to approximate the plasma profile with time.

These equations have been incorporated into a basic computer program so that multiple analysis of different rates and times of infusions can be summed. The following figures show the predicted blood concentration profiles for dosing regimes with and without a short loading dose prior to the maintenance dose expected to be used in clinical trials. Figure 1 shows the doses given for a fifteen minute period each progressing in 50 mcg/kg/min increments from 50 to 300 mcg/kg/min. Table 1 shows the percent of steady state achieved after 5 minutes with and without the loading dose at each level. As can be seen, a five minute interval is sufficient to establish near steady state conditions with the loading dose. Some studies may have a longer or shorter maintenance period than the 15 minute period shown but the same general pattern will be observed. Figure 2 depicts the simulated plasma concentration versus time profiles of esmolol using a dosing regime in which some doses are not tested. Thus a longer loading dose is required to make the rapid transition to the next higher steady state level. Again, it is demonstrated that a proper dosing regimen involving a loading dose, followed by a given dose, can produce desirable blood levels. Also shown are the lower predicted levels that would result if no loading doses were given.

Figure 3 depicts the regime used to make a single rapid transition to the steady state of 3 doses (100, 200 and 300 mcg/kg/min). Here again the duration of the loading dose must be adjusted in accordance with the desired steady state level and the absence of the loading dose results in a prolonged time to achieve steady state. Numerous such schemas can be predicted for individual situations but these figures are representation of regimens used in clinical studies.

Table 1

Comparison of Dosing Regimens After Five Minutes of Constant Infusion

Infusion Rate mcg/kg/min	Predicted Steady State Blood Level mcg/mL	Blood Level at 5 min	
		With The Loading Dose[a,b]	Without The Loading Dose[b]
50	0.186	0.253 (136)	0.138 (74.2)
100	0.372	0.435 (117)	0.305 (82.0)
150	0.558	0.605 (108)	0.480 (86.0)
200	0.744	0.773 (104)	0.660 (88.7)

a A loading dose of 500 mcg/kg/min was given during the first 1.0 minutes of infusion.
b Values given in parentheses denote percent of steady state value

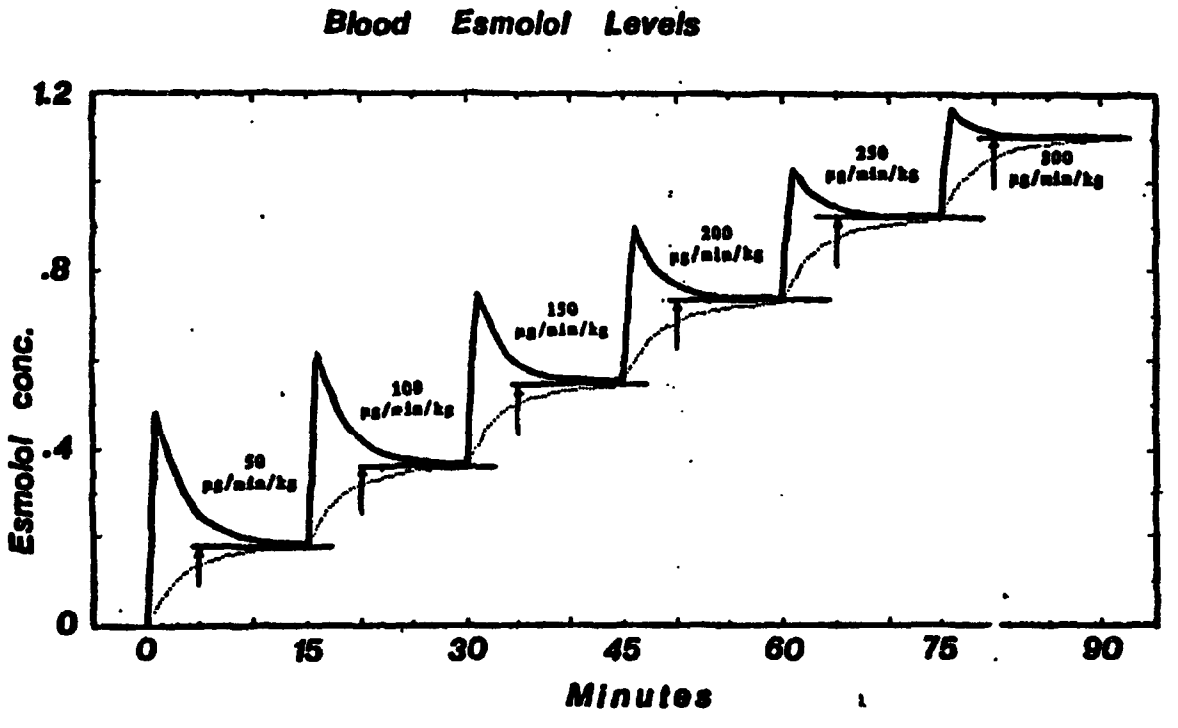


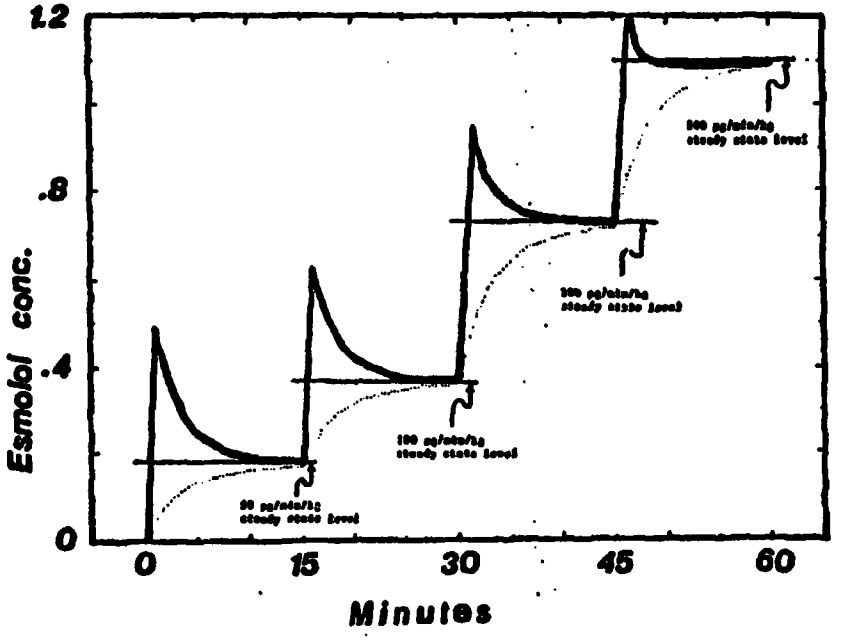
Figure 1

——— 14 min. infusions at each dose level proceeded by a 1.0 min loading dose at 300 µg/min/kg

..... 15 min. infusions at each dose without any loading dose

lines at arrows denote steady state levels for each dose

Blood Esmolol Levels



solid line:	1.0 min at 500 µg/min/kg 14 min at 50 µg/min/kg	1 min at 500 µg/min/kg 14 min at 100 µg/min/kg	1.5 min at 500 µg/min/kg 13.5 min at 200 µg/min/kg	1.5 min at 500 µg/min/kg 13.5 min at 300 µg/min/kg
dotted line:	15 min at 50 µg/min/kg	15 min at 100 µg/min/kg	15 min at 200 µg/min/kg	15 min at 300 µg/min/kg

Figure 2

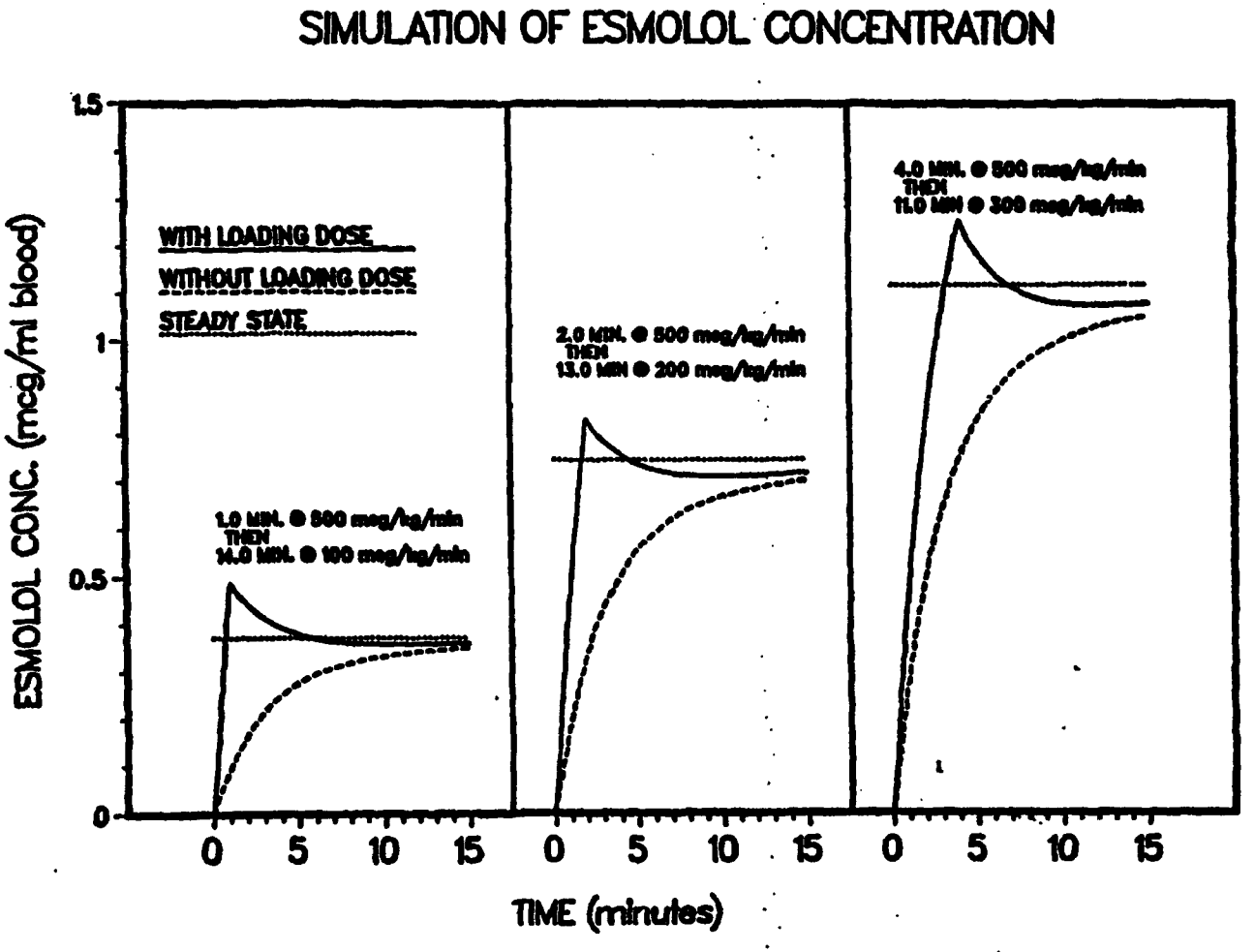

SIMULATION OF ESMOLOL CONCENTRATION
ESMOLOL CONC. (mcg/ml blood)
1.5
1
0.5
0
WITH LOADING DOSE
WITHOUT LOADING DOSE
STEADY STATE
1.0 MIN. @ 500 mcg/kg/min
THEN
14.0 MIN. @ 100 mcg/kg/min
2.0 MIN. @ 500 mcg/kg/min
THEN
13.0 MIN @ 200 mcg/kg/min
4.0 MIN. @ 500 mcg/kg/min
THEN
11.0 MIN @ 300 mcg/kg/min
0 5 10 15
0 5 10 15
0 5 10 15
TIME (minutes)

Figure 3

REFERENCES

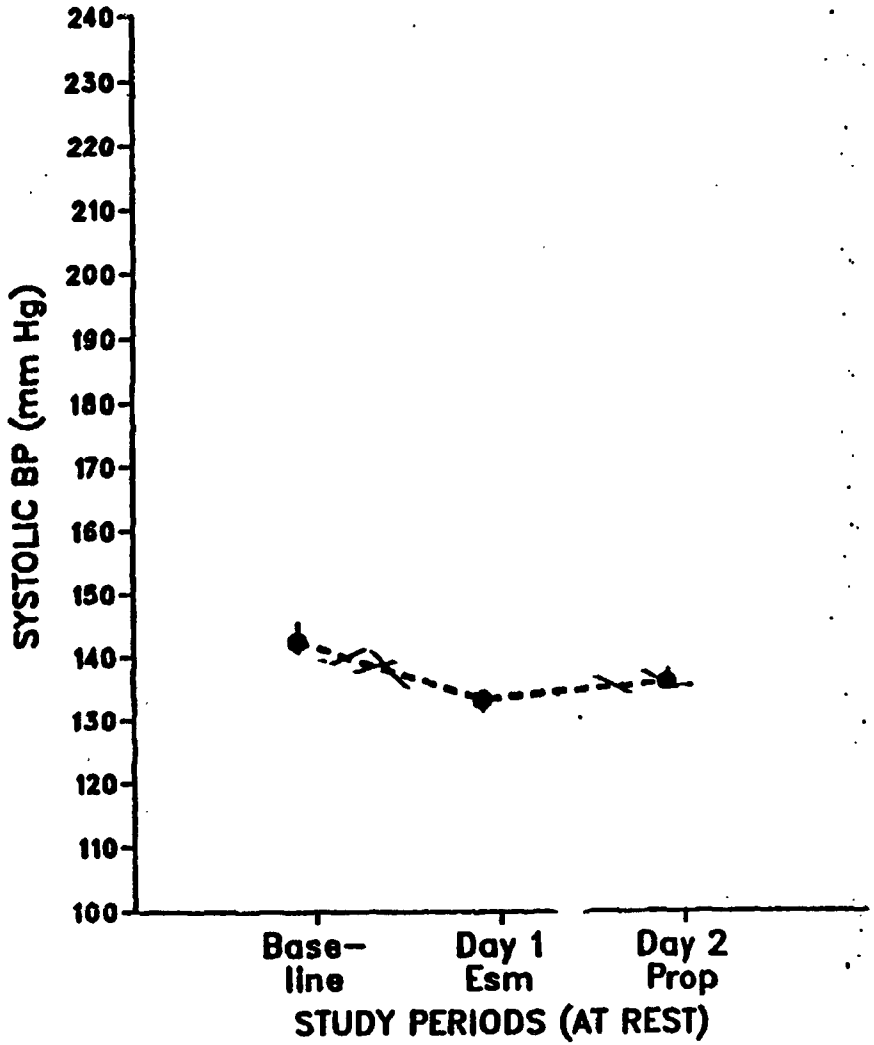
1. Sum, C.Y. and Yacobi, A.Y.: Pharmacokinetics of ASL-8052 and ASL-8123 in Human Tolerance and Beta Blocking Activity of ASL-8052 in Normal Volunteers (1982) ACC Central File, Document #100-82-00057.

2. Gibaldi, M. and Perrier, D., Drugs and the Pharmaceutical Sciences, Vol. 1, Pharmacokinetics, Swarbrick, J. (ed), New York, Marcel Dekker, 1975, pp. 70-71.

Appendix 1B - Key Hemodynamic Variables

Study 15

ISKANDRIAN (8052-82-15) – SYSTOLIC BP
DRUG SEQUENCE: ESMOLOL/PROPRANOLOL

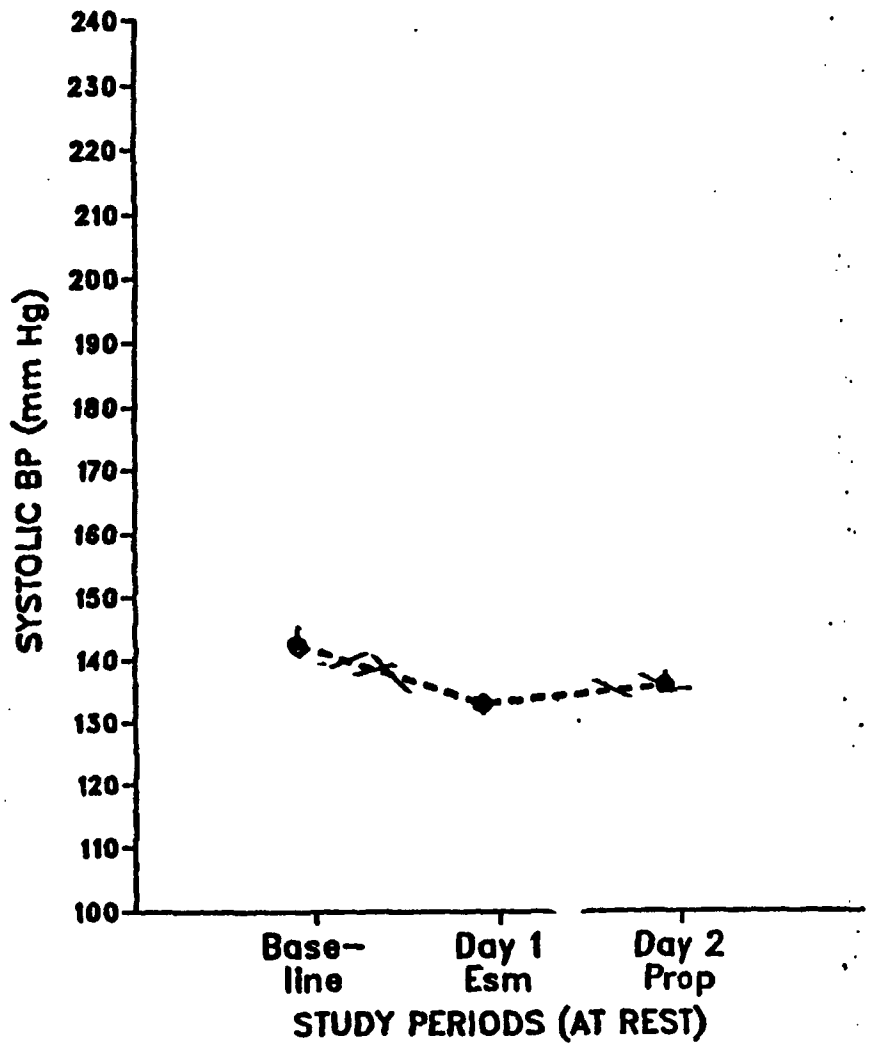


PATIENT

● MEAN (SEM)

Study 15

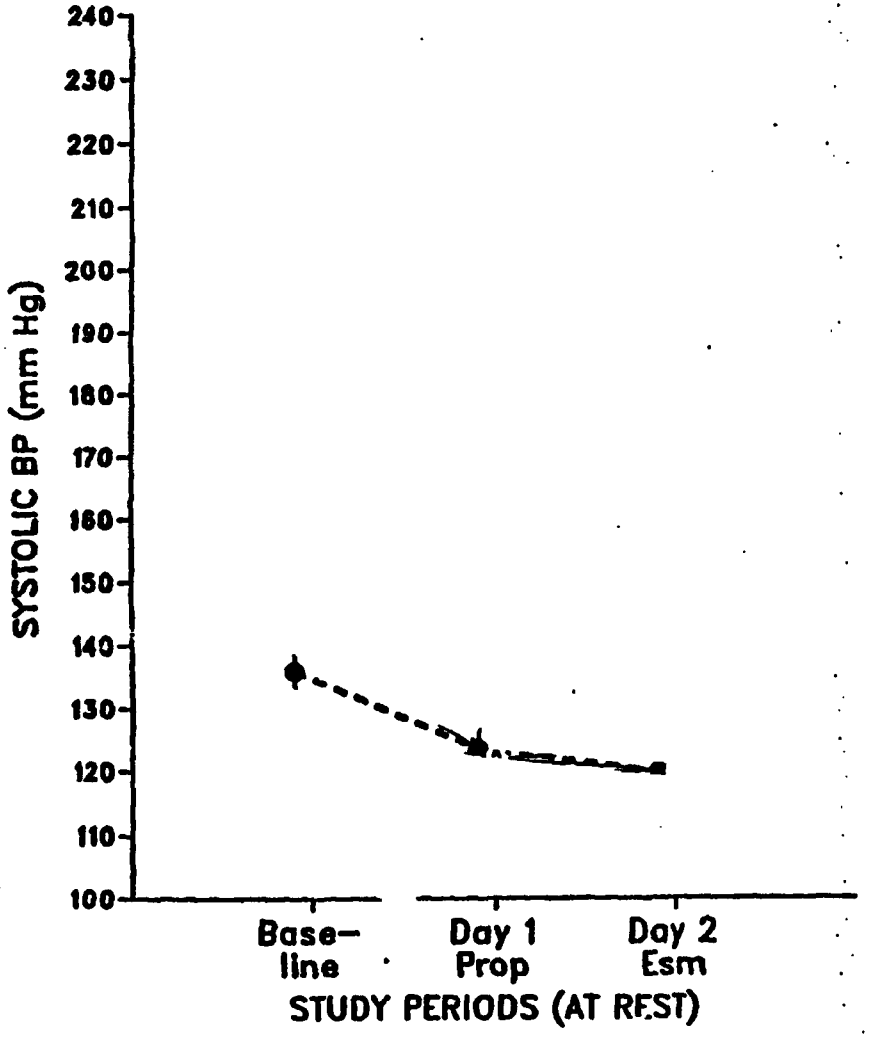
ISKANDRIAN (8052-82-15) – SYSTOLIC BP
DRUG SEQUENCE: ESMOLOL/PROPRANOLOL



PATIENT

● MEAN (SEM)

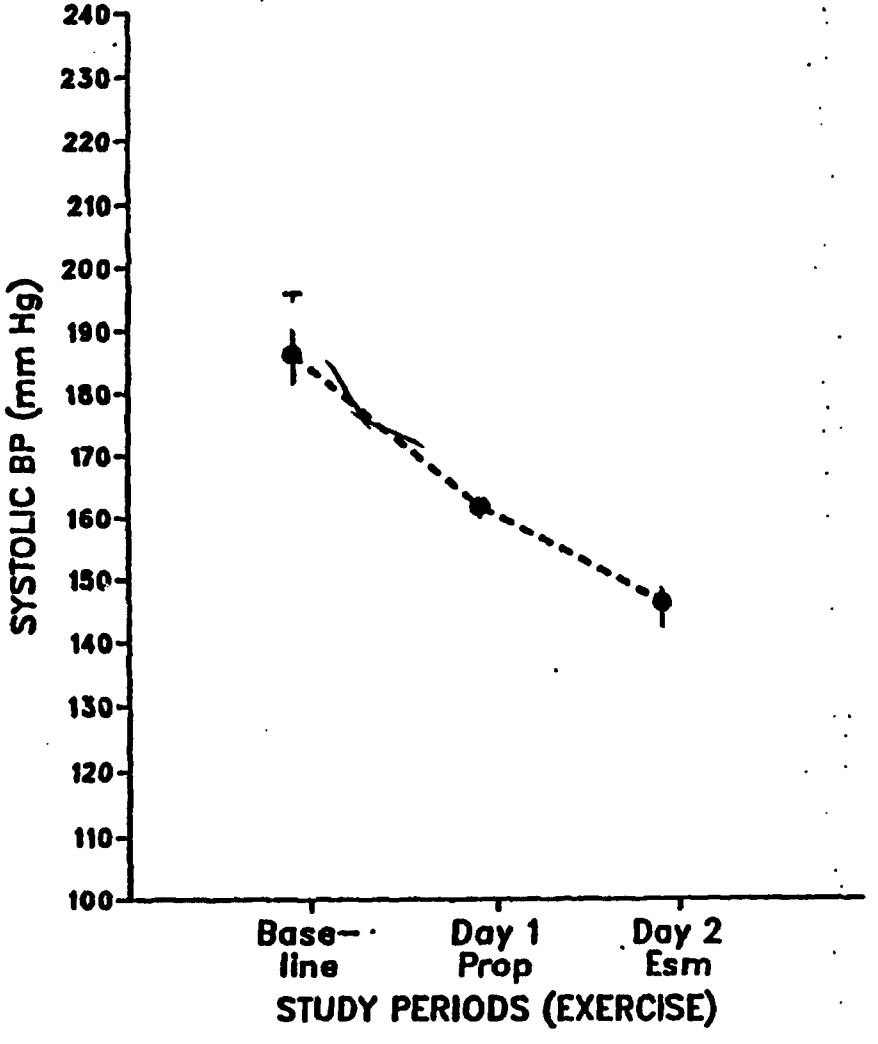
ISKANDRIAN (8052–82–15) – SYSTOLIC BP
DRUG SEQUENCE: PROPRANOLOL/ESMOLOL



PATIENT

● MEAN (SEM)

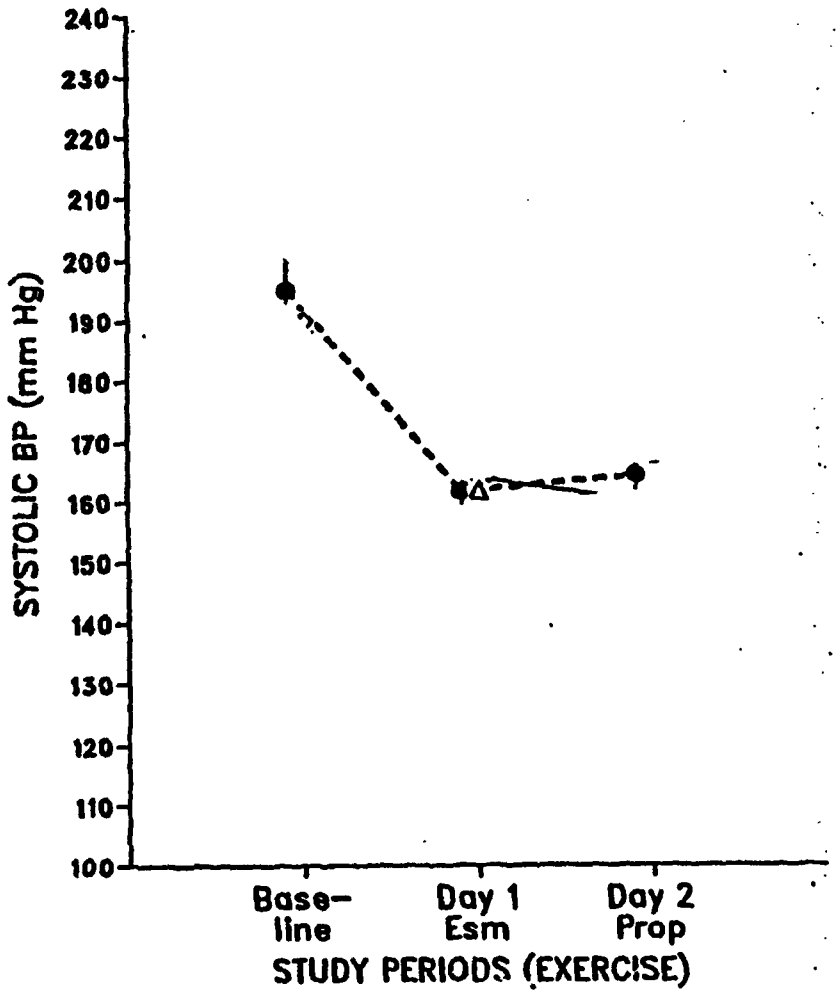
ISKANDRIAN (8052–82–15) – SYSTOLIC BP
DRUG SEQUENCE: PROPRANOLOL/ESMOLOL



PATIENT

● MEAN (SEM)

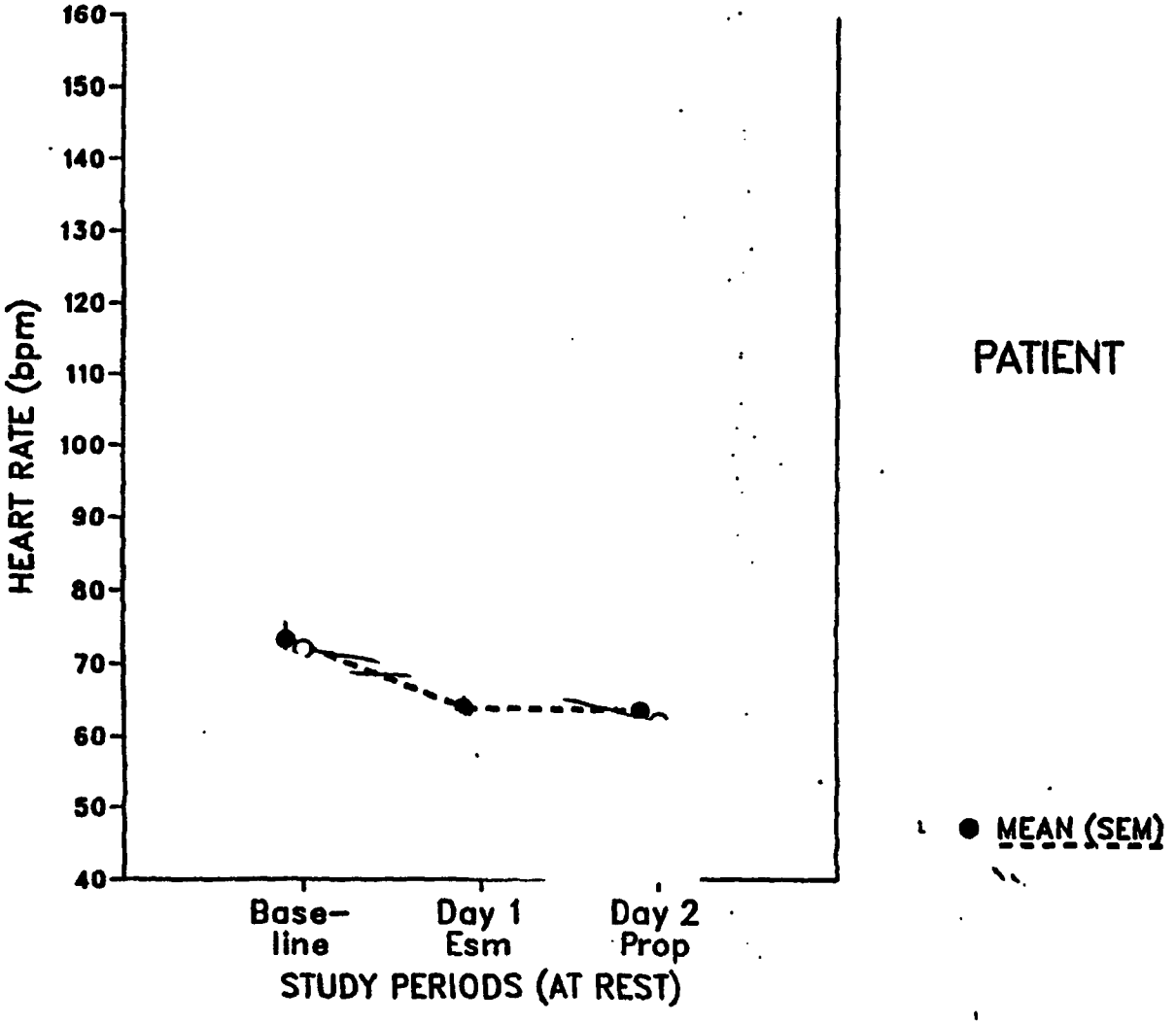
ISKANDRIAN (8052-82-15) - SYSTOLIC BP
DRUG SEQUENCE: ESMOLOL/PROPRANOLOL



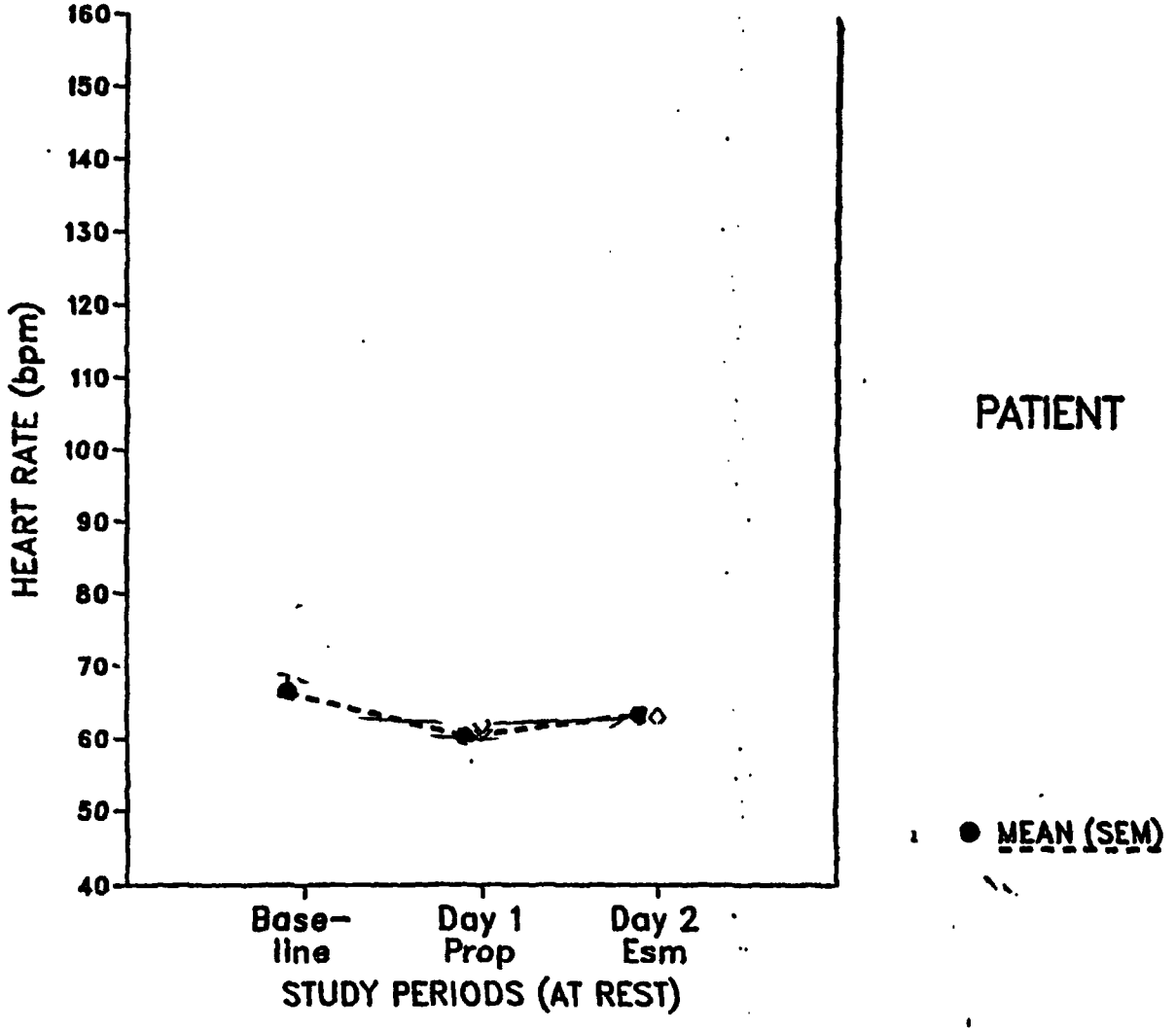
PATIENT

● MEAN (SEM)

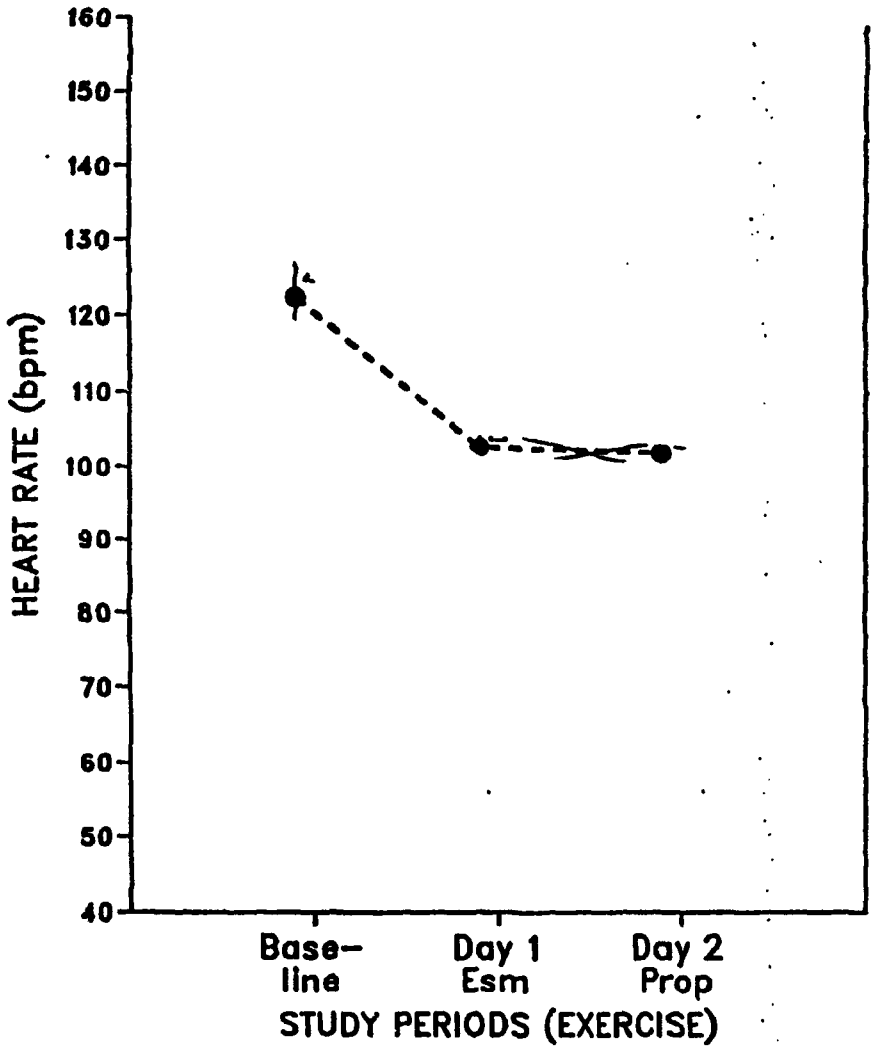
ISKANDRIAN (8052–82–15) : HEART RATE
DRUG SEQUENCE: ESMOLOL/PROPRANOLOL



ISKANDRIAN (8052-82-15) HEART RATE
DRUG SEQUENCE: PROPRANOLOL/ESMOLOL



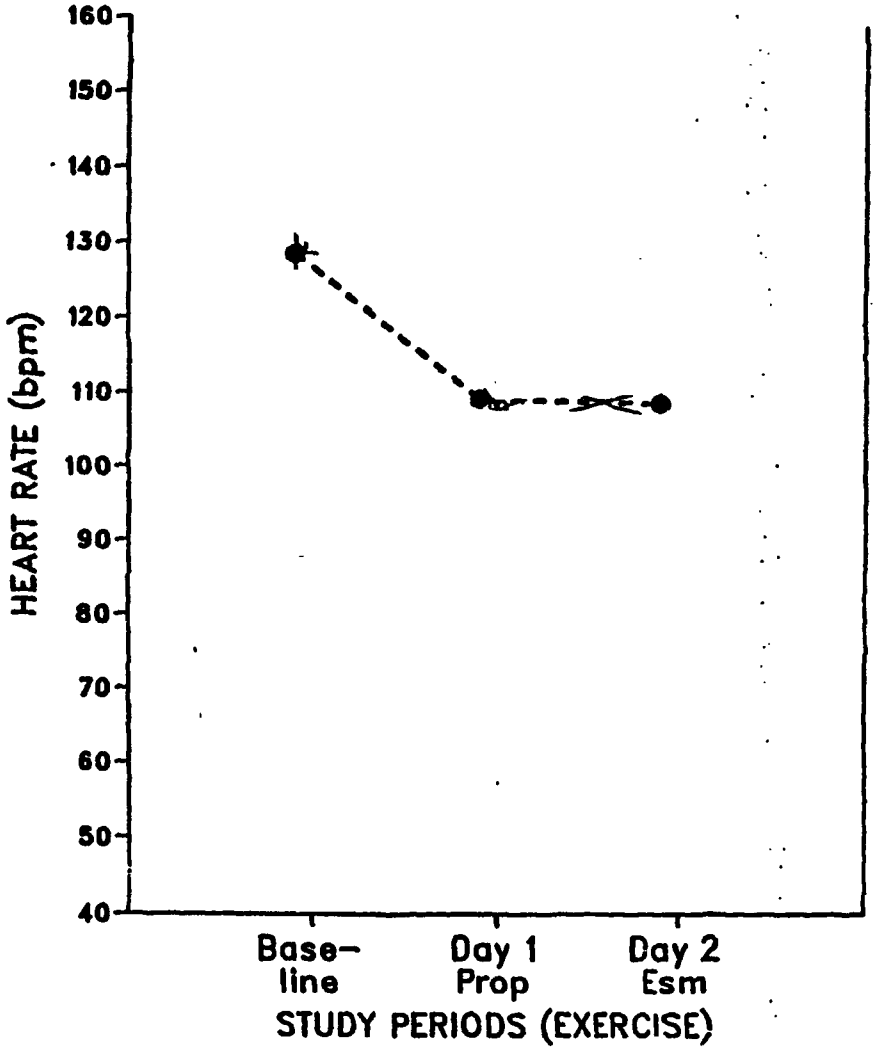
ISKANDRIAN (8052-82-15) HEART RATE
DRUG SEQUENCE: ESMOLOL/PROPRANOLOL



PATIENT

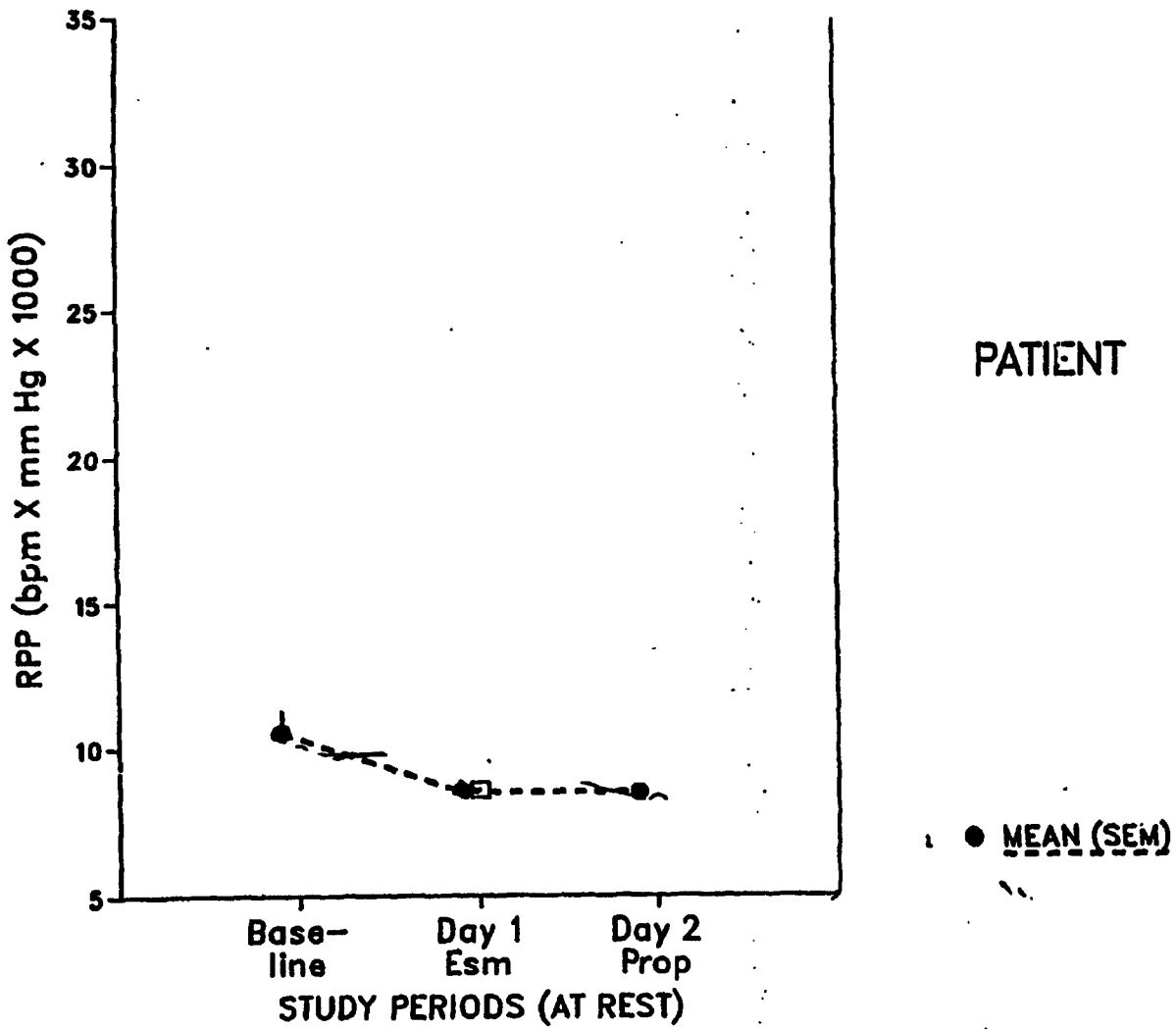
● MEAN (SEM)

ISKANDRIAN (8052–82–15) HEART RATE
DRUG SEQUENCE: PROPRANOLOL/ESMOLOL

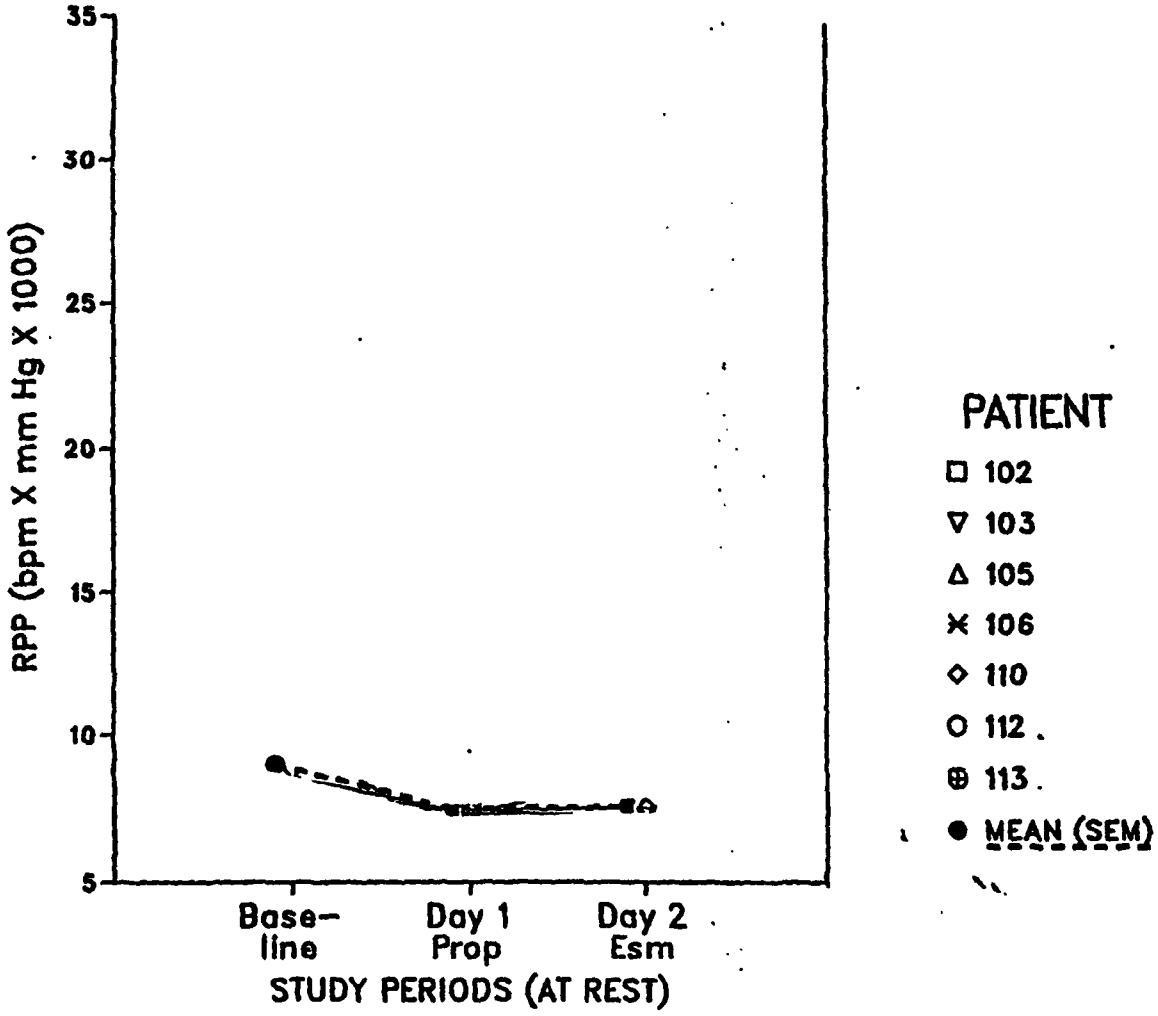


PATIENT
- □ 102
- ▽ 103
- △ 105
- ✕ 106
- ◇ 110
- ○ 112
- ⊕ 113
- ● MEAN (SEM)

ISKANDRIAN (8052-82-15) – RATE PRESSURE PRODUCT
DRUG SEQUENCE: ESMOLOL/PROPRANOLOL



ISKANDRIAN (8052–82–15) – RATE PRESSURE PRODUCT
DRUG SEQUENCE: PROPRANOLOL/ESMOLOL



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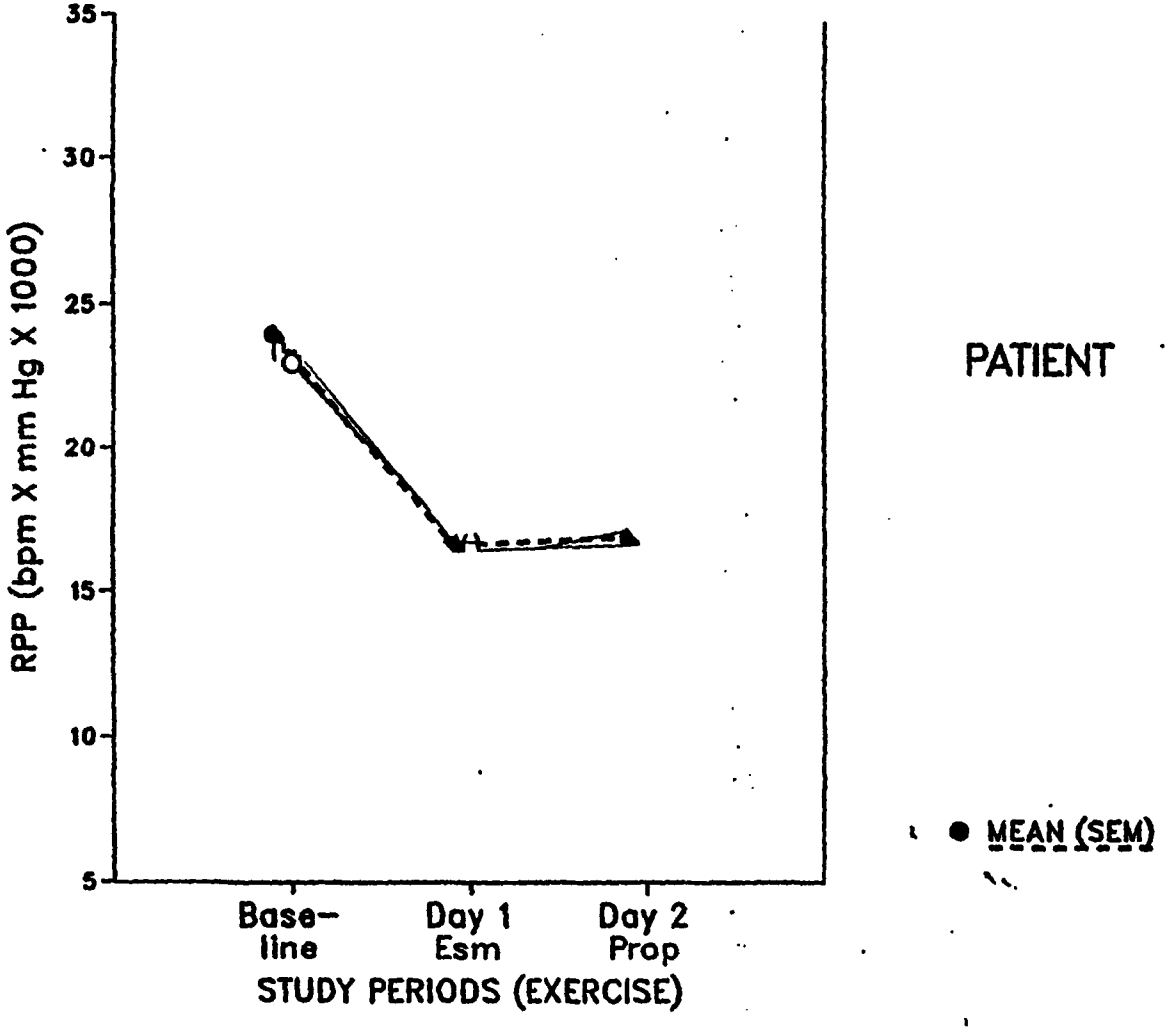
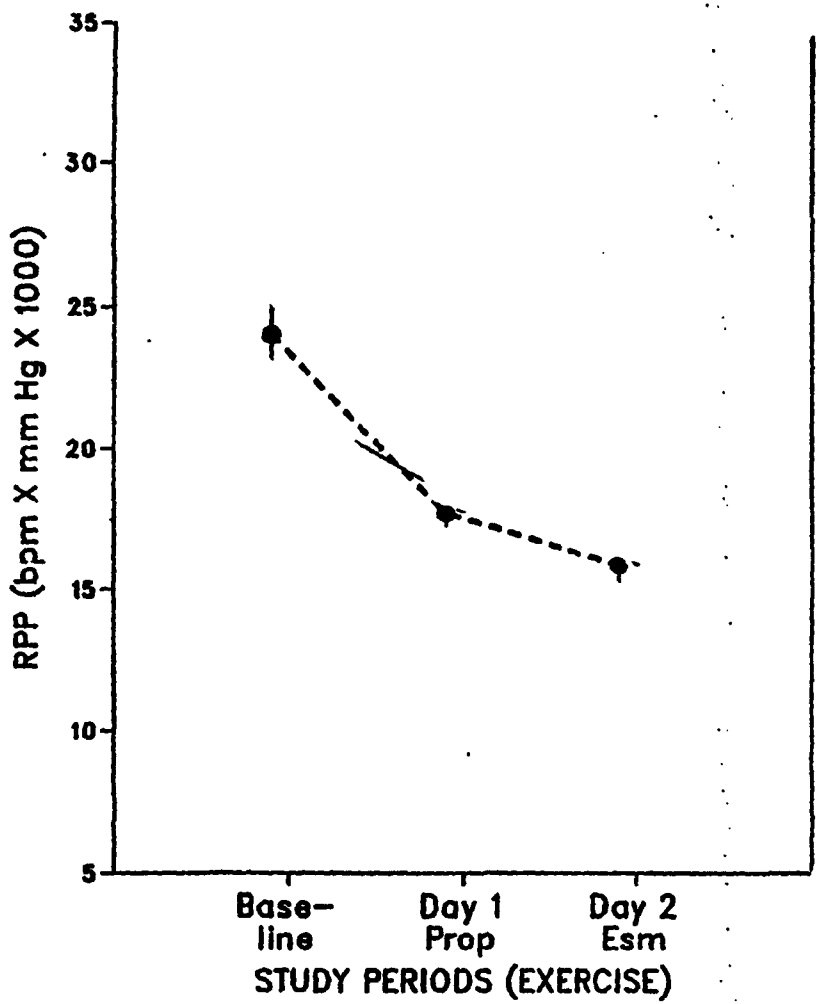
DRUG SEQUENCE: ESMOLOL/PROPRANOLOL



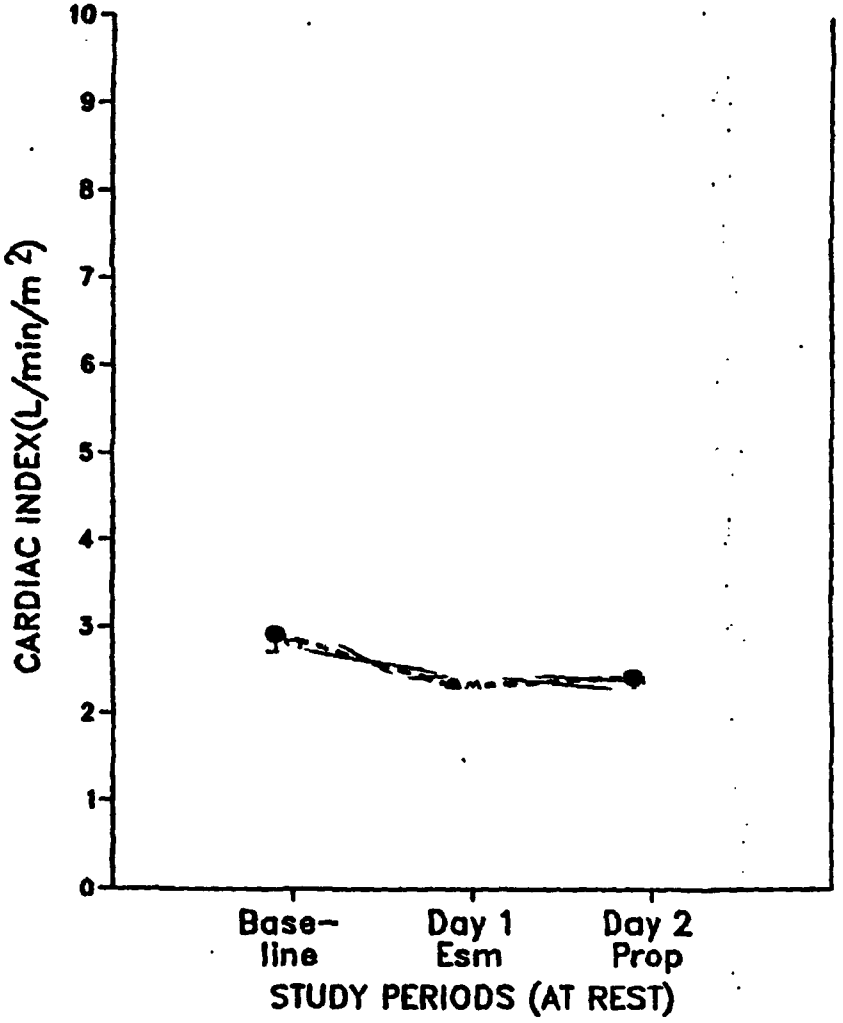
ISKANDRIAN (8052-82-15) – RATE PRESSURE PRODUCT
DRUG SEQUENCE: PROPRANOLOL/ESMOLOL



PATIENT

● MEAN (SEM)

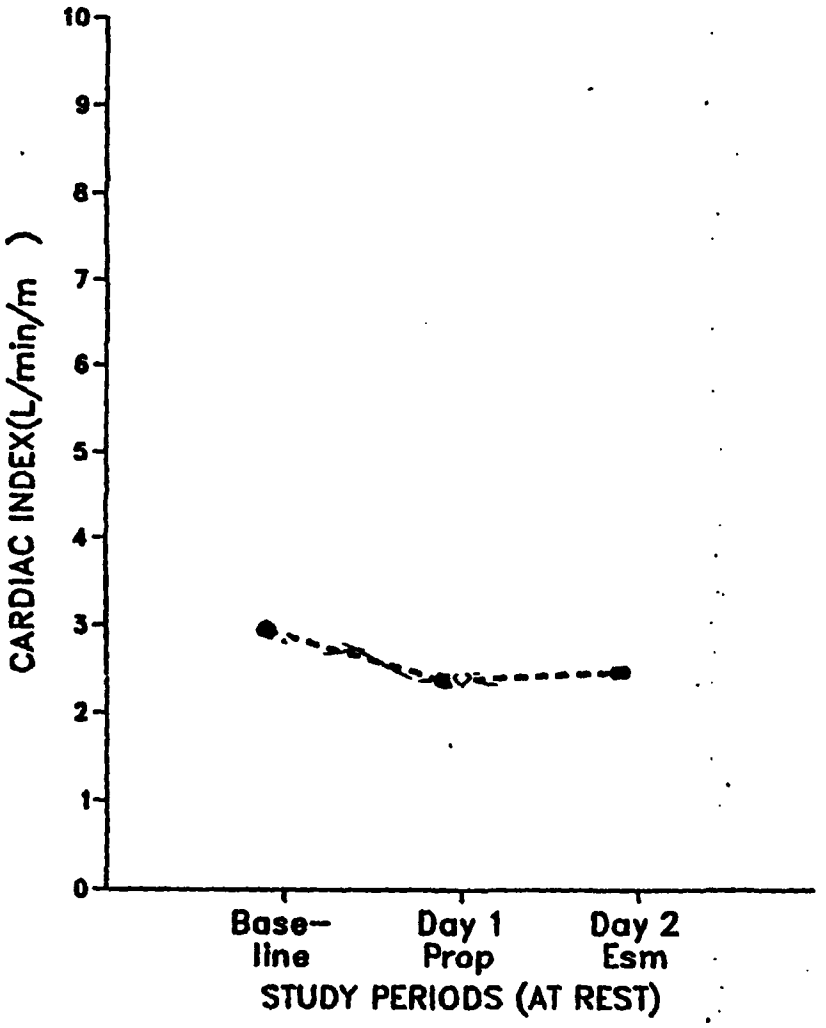
ISKANDRIAN (8052-82-15) - CARDIAC INDEX
DRUG SEQUENCE: ESMOLOL/PROPRANOLOL



PATIENT

● MEAN (SEM)

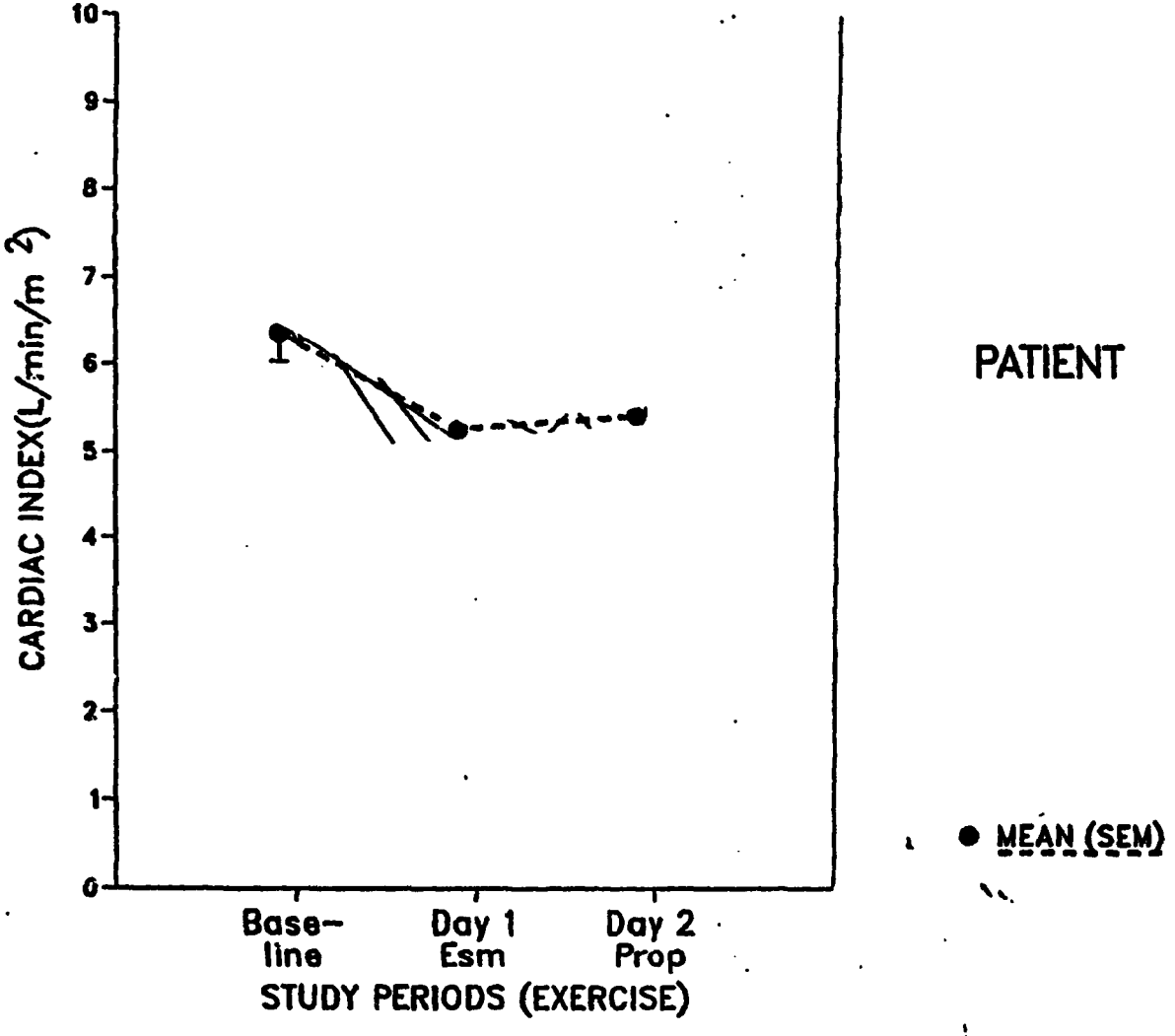
ISKANDRIAN (8052-82-15) - CARDIAC INDEX
DRUG SEQUENCE: PROPRANOLOL/ESMOLOL



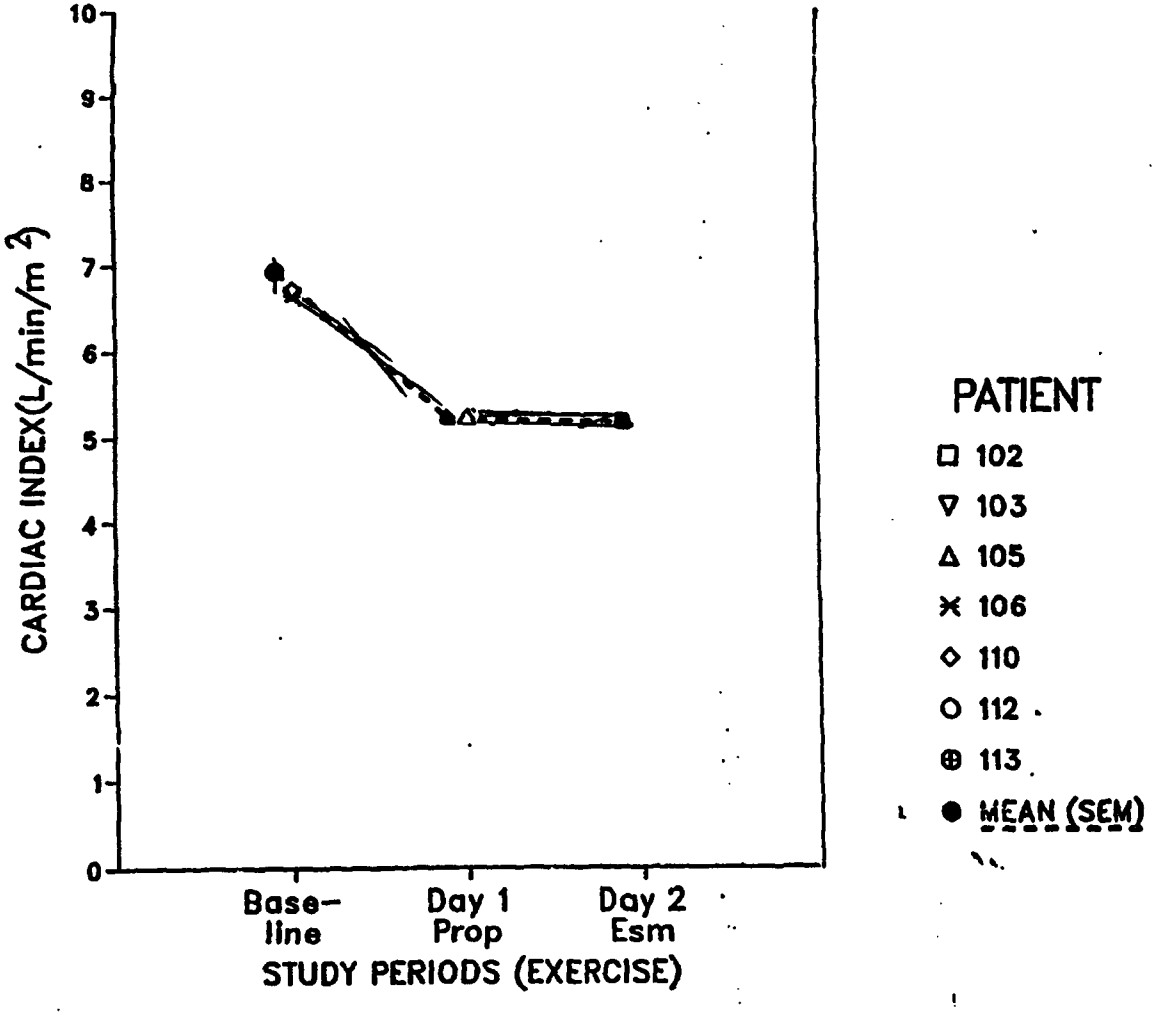
PATIENT

● MEAN (SEM)

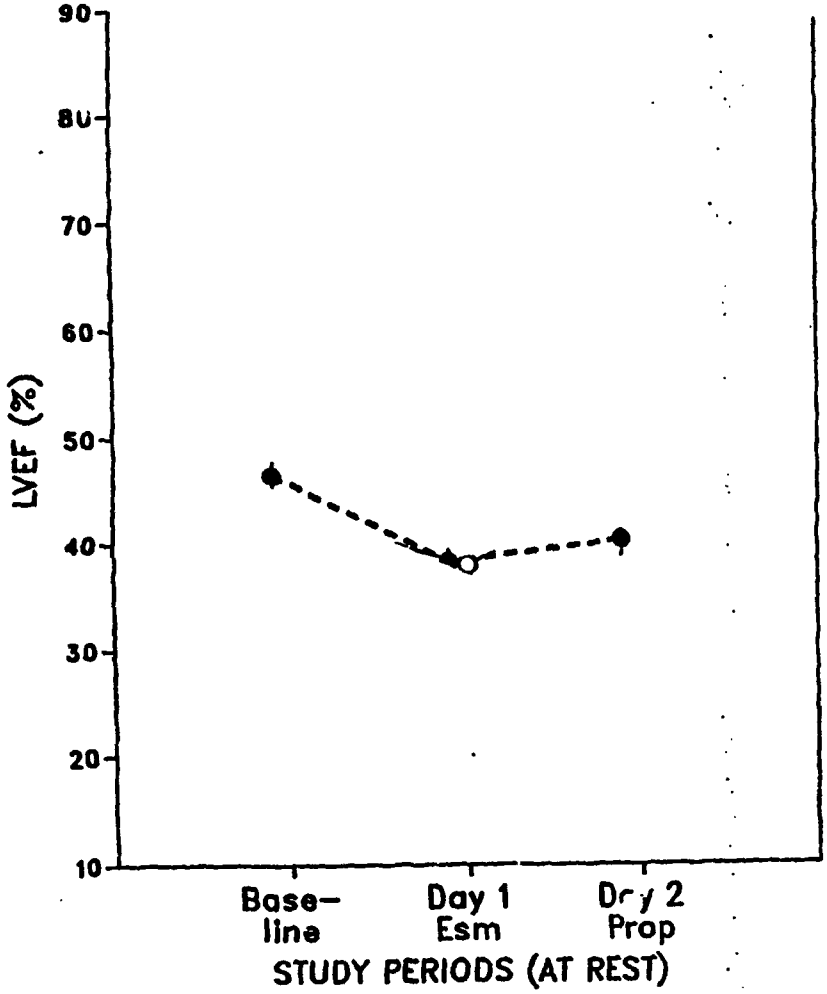
ISKANDRIAN (8052-82-15) - CARDIAC INDEX
DRUG SEQUENCE: ESMOLOL/PROPRANOLOL



ISKANDRIAN (8052-82-15) - CARDIAC INDEX
DRUG SEQUENCE: PROPRANOLOL/ESMOLOL



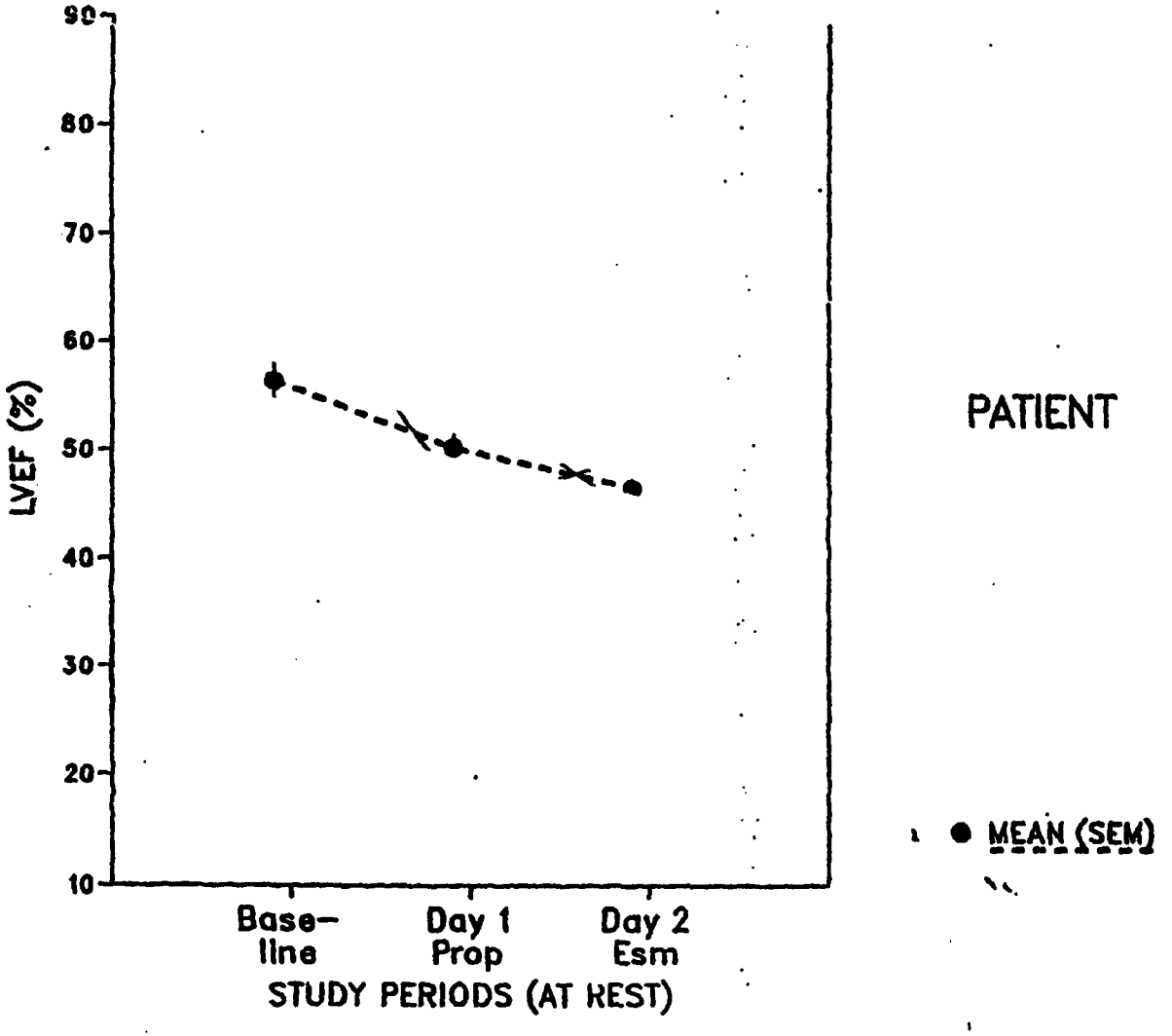
ISKANDRIAN (8052–82–[illegible] – LVEF
DRUG SEQUENCE: ESMOLOL/PROPRANOLOL



PATIENT

● MEAN (SEM)

ISKANDRIAN (8052–82–[illegible] – LVEF
DRUG SEQUENCE: PROPRANOLOL/ESMOLOL



ISKANDRIAN (8052–82[illegible]) – LVEF

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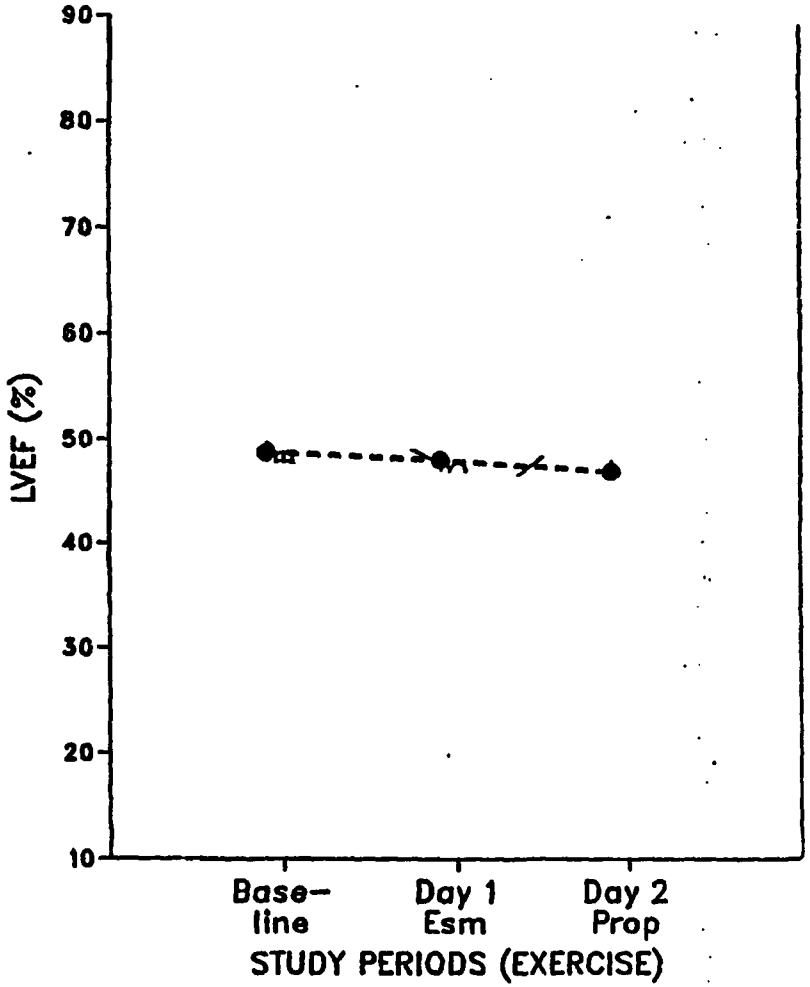

PATIENT

● MEAN (SEM)

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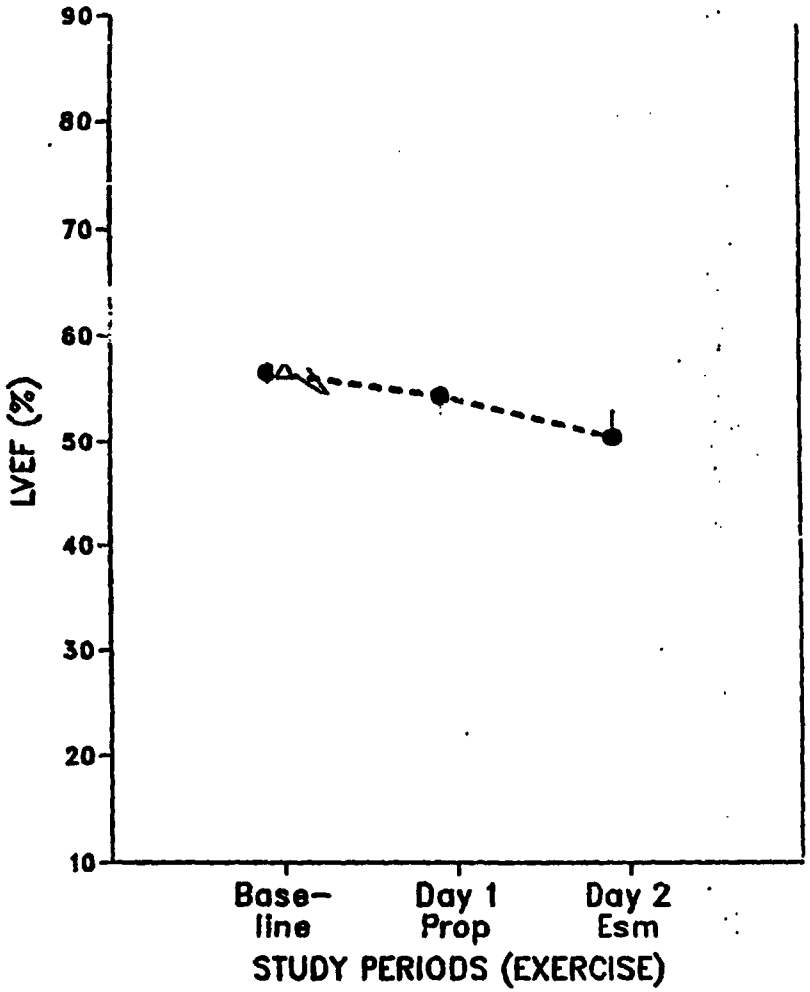
DRUG SEQUENCE: PROPRANOLOL/ESMOLOL

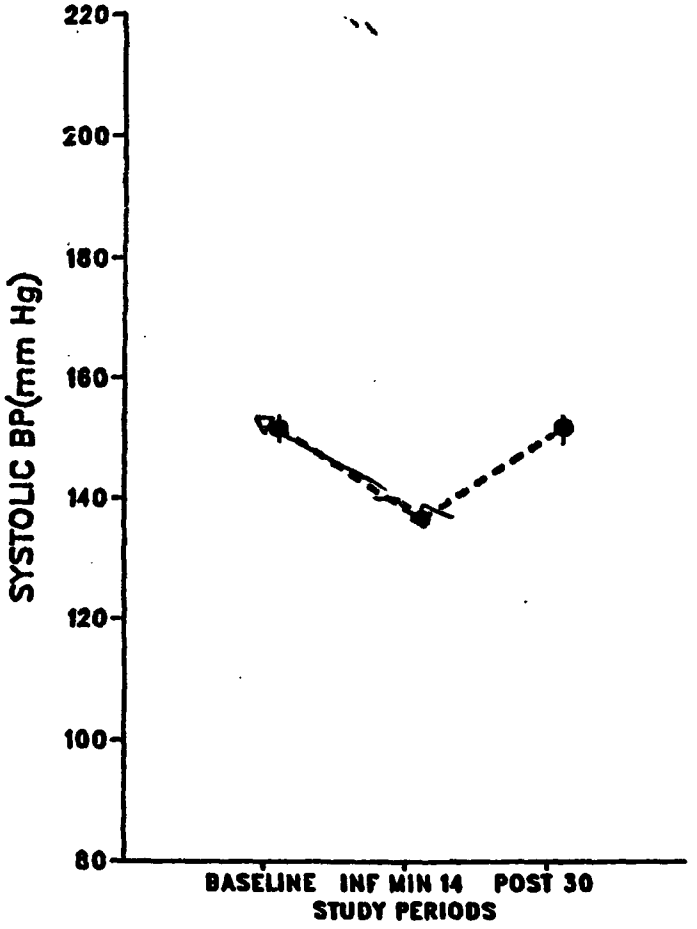


PATIENT

● MEAN (SEM)

Study 14

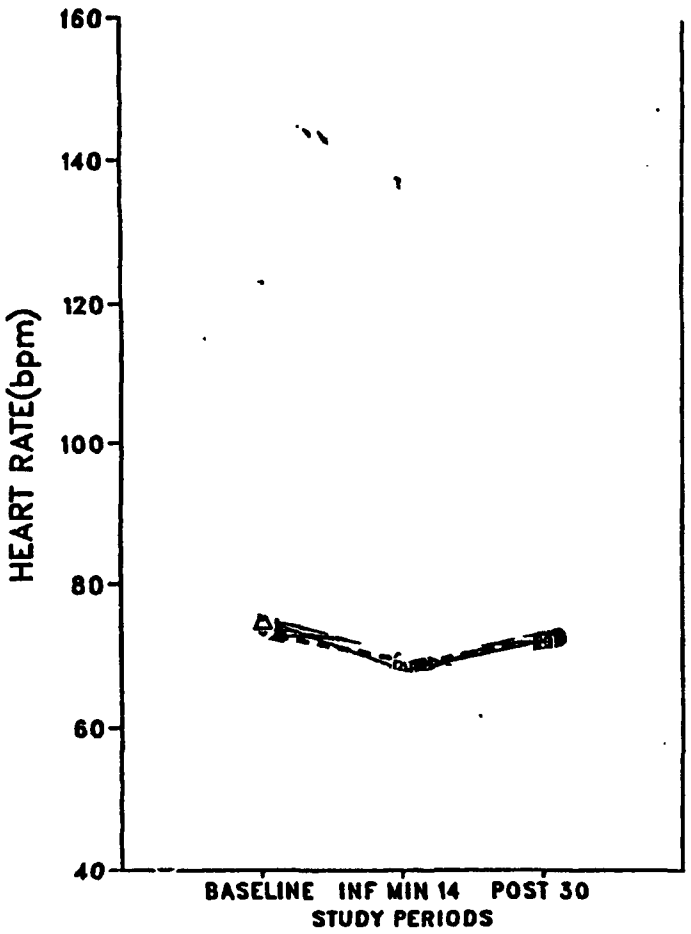
ASKENAZI (8052–82–14) – SYSTOLIC BP



PATIENT

● MEAN (SEM)

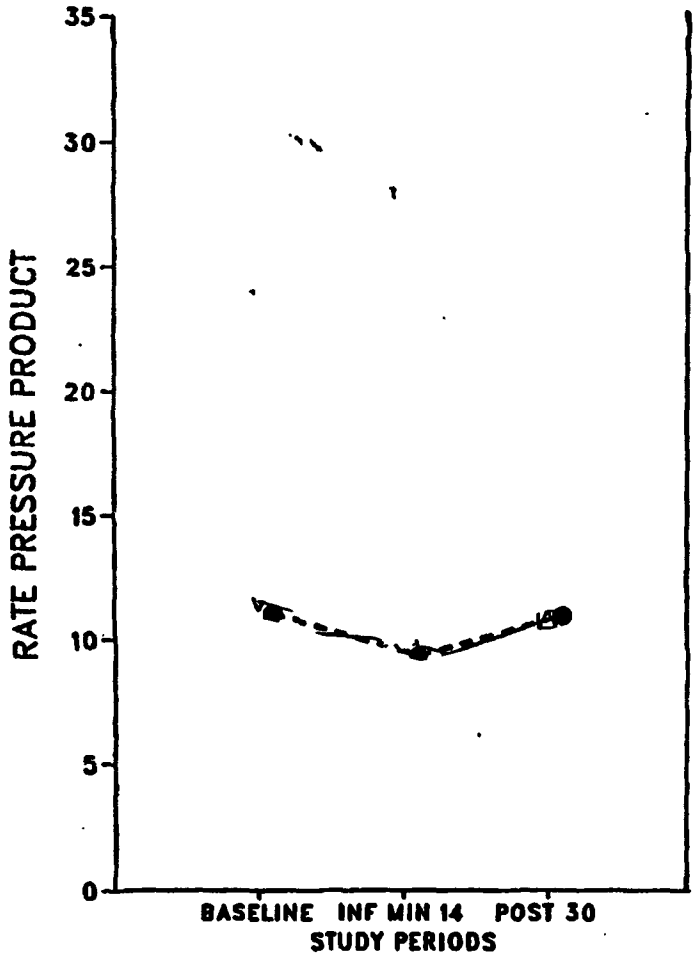
ASKENAZI (8052–82–14) – HEART RATE



PATIENT

● MEAN (SEM)

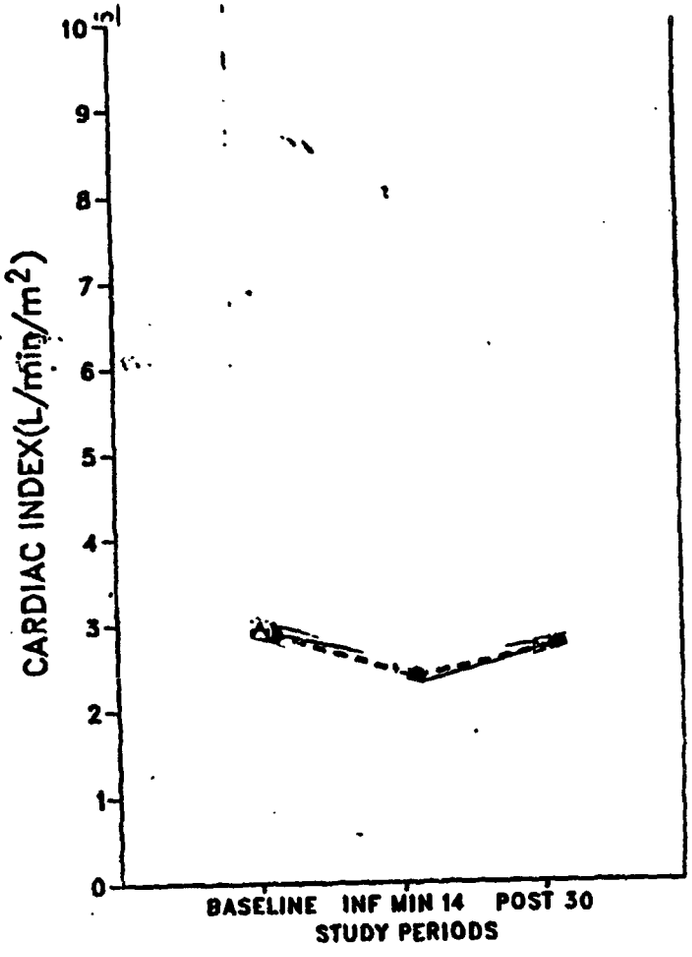
ASKENAZI (8052-82-14) - RATE PRESSURE PRODUCT



PATIENT

● MEAN (SEM)

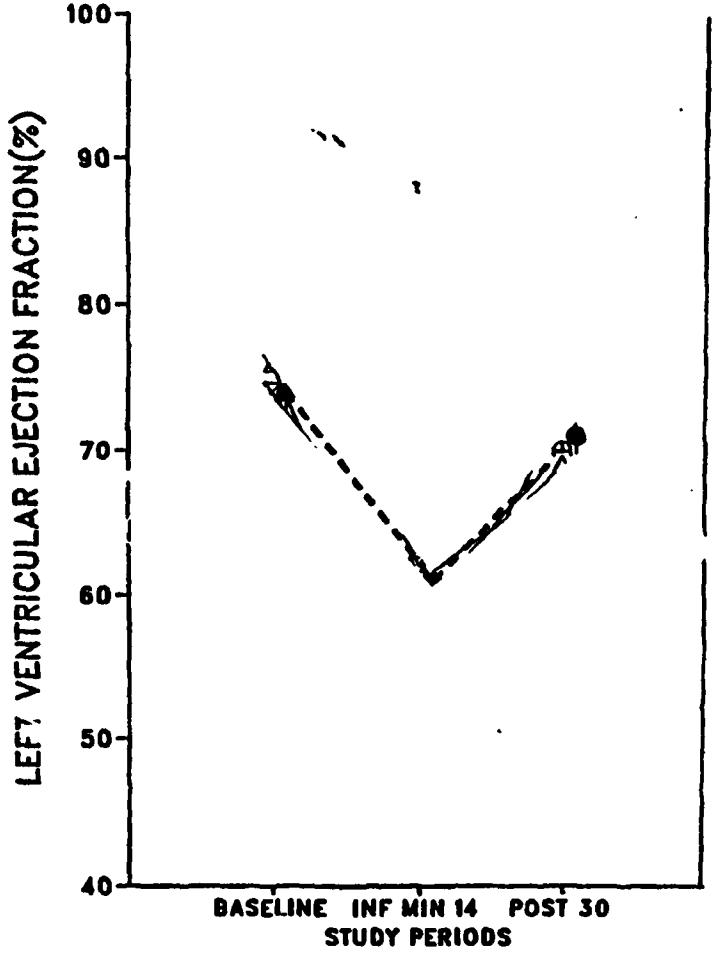
ASKENAZI (8052–82–14) – CARDIAC INDEX



PATIENT

● MEAN (SEM)

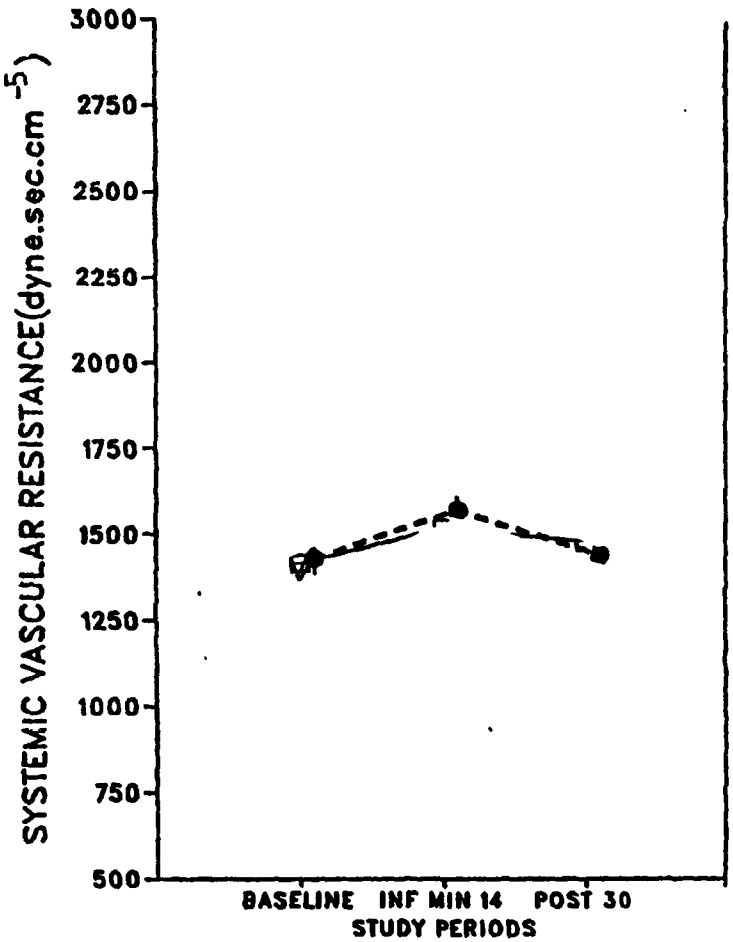
ASKENAZI (8052–82–14) – LVEF



PATIENT

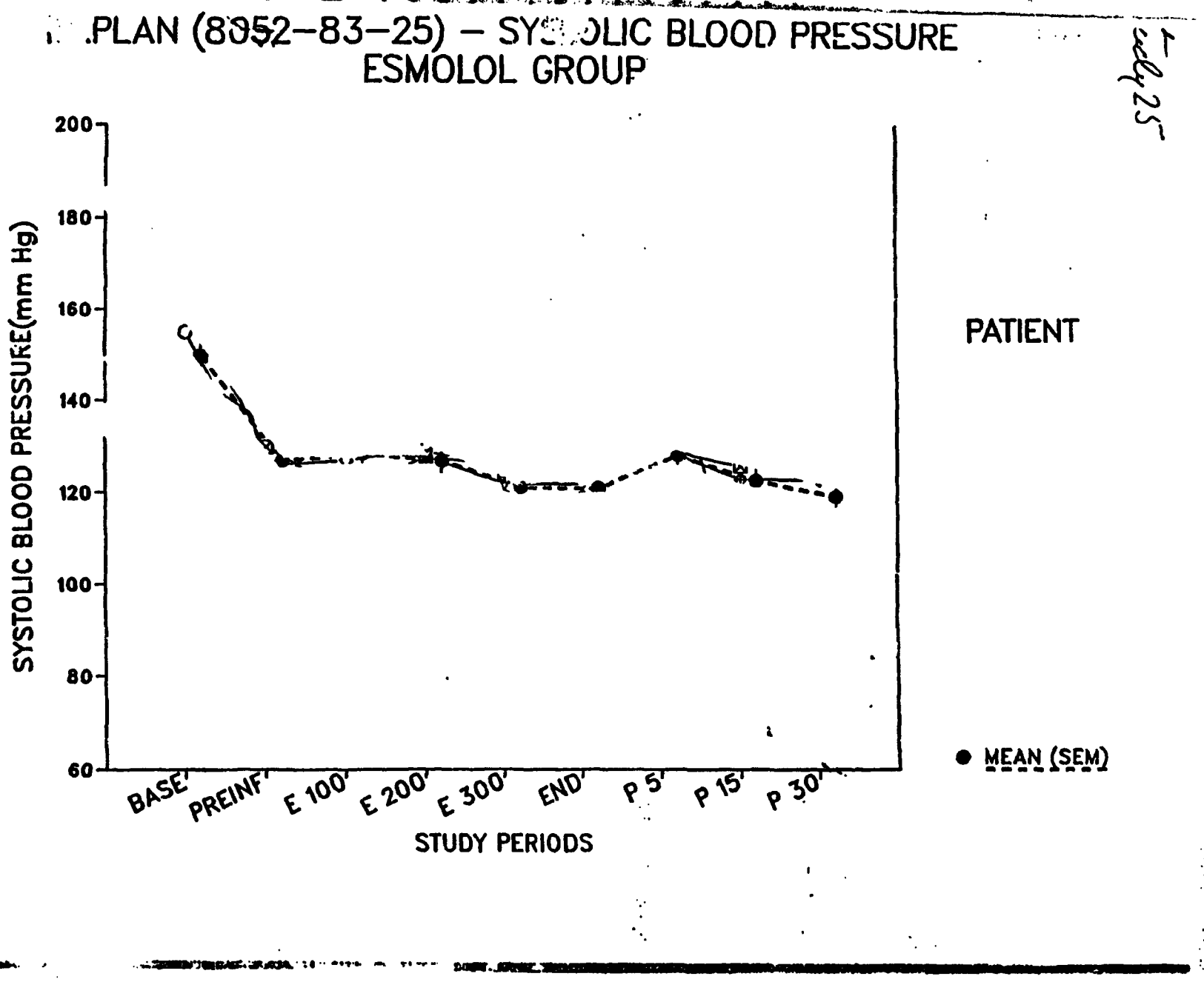
● MEAN (SEM)

ASKENAZI (8052-82-14) - SVR

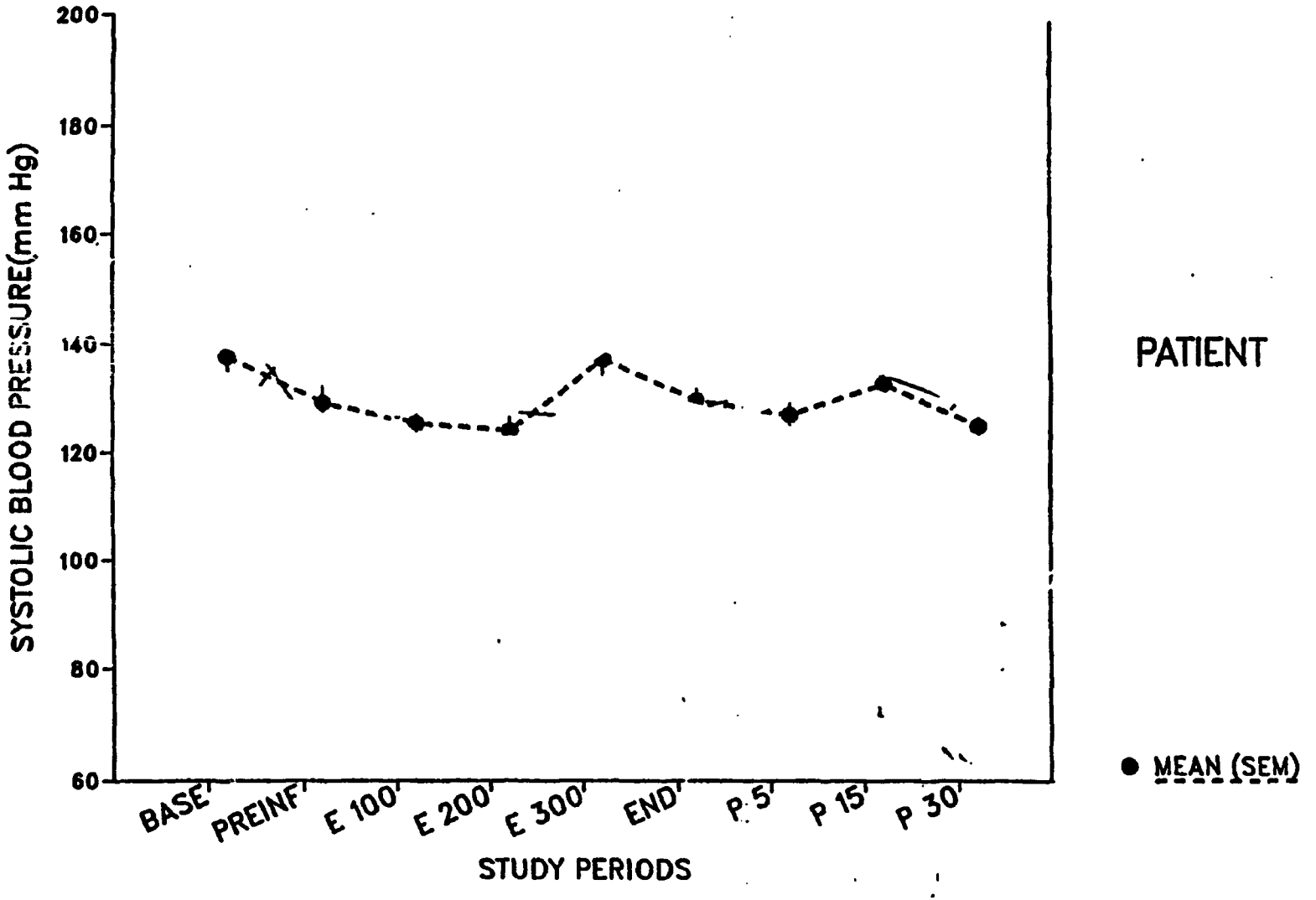


PATIENT

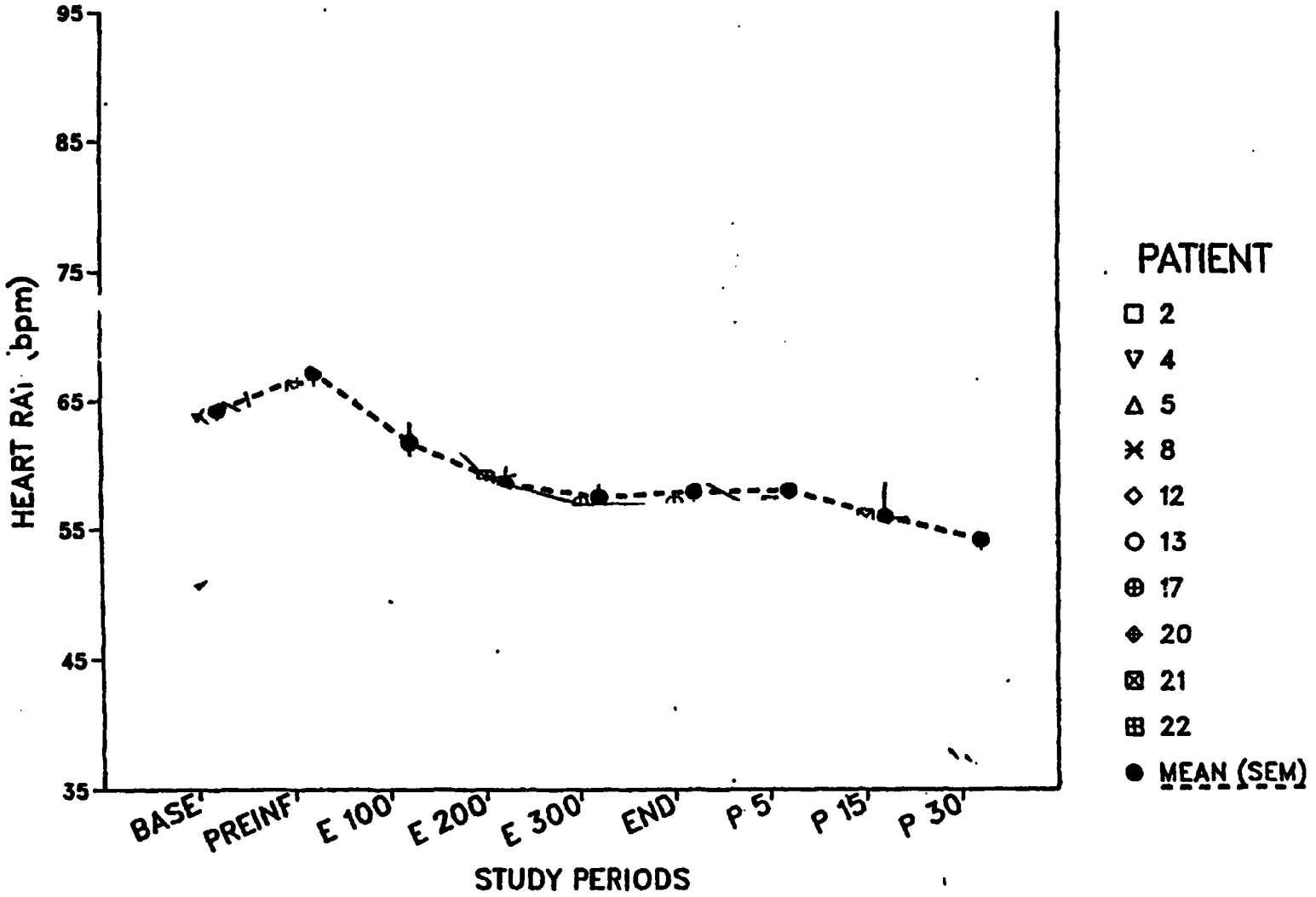
● MEAN (SEM)


PLAN (8352-83-25) – SYSTOLIC BLOOD PRESSURE
ESMOLOL GROUP
July 25
SYSTOLIC BLOOD PRESSURE(mm Hg)
200
180
160
140
120
100
80
60
BASE'
PREINF'
E 100'
E 200'
E 300'
END'
P 5'
P 15'
P 30'
STUDY PERIODS
PATIENT
MEAN (SEM)

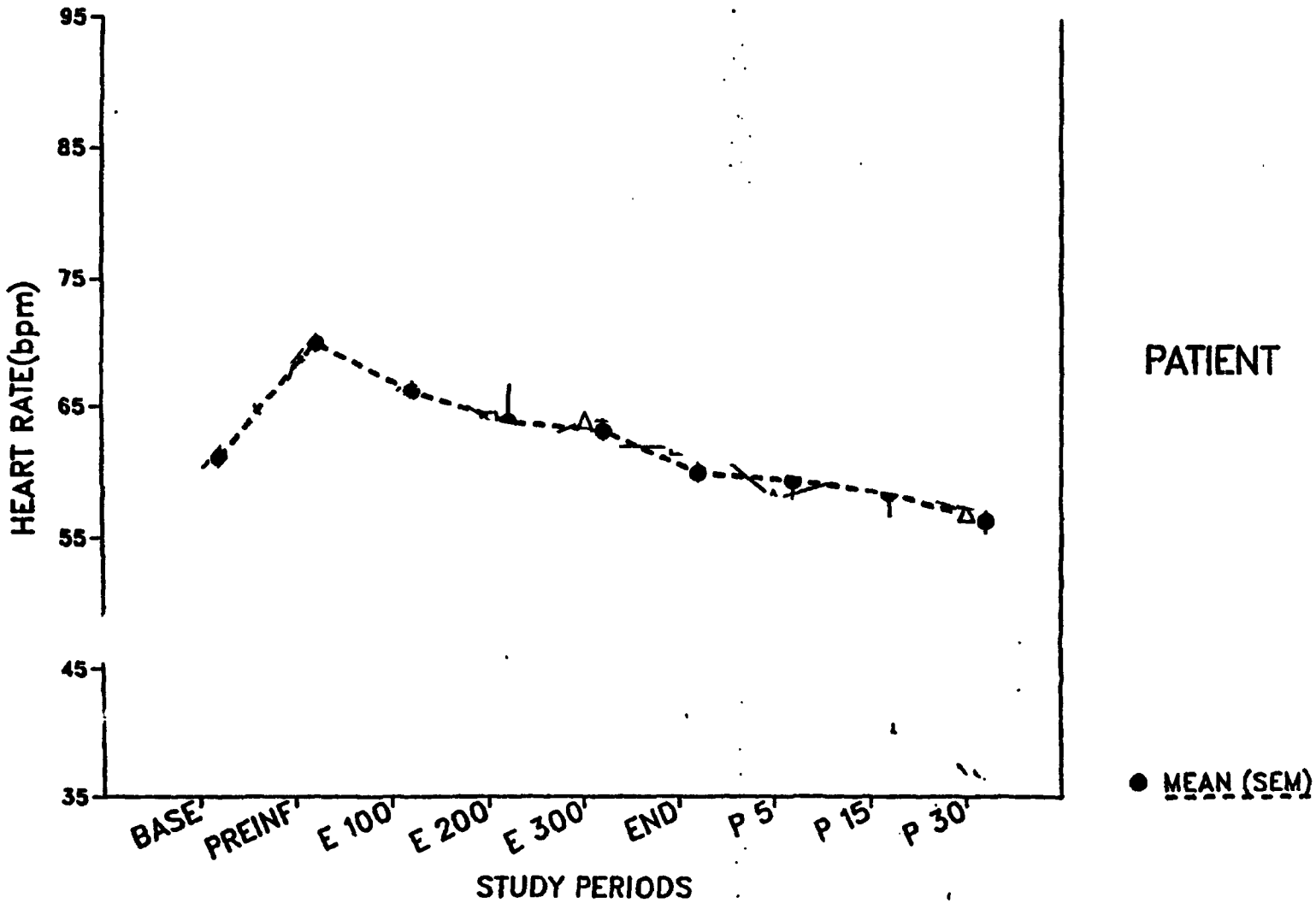
KAPLAN (8052–83–25) – SYSTOLIC BLOOD PRESSURE
PLACEBO GROUP



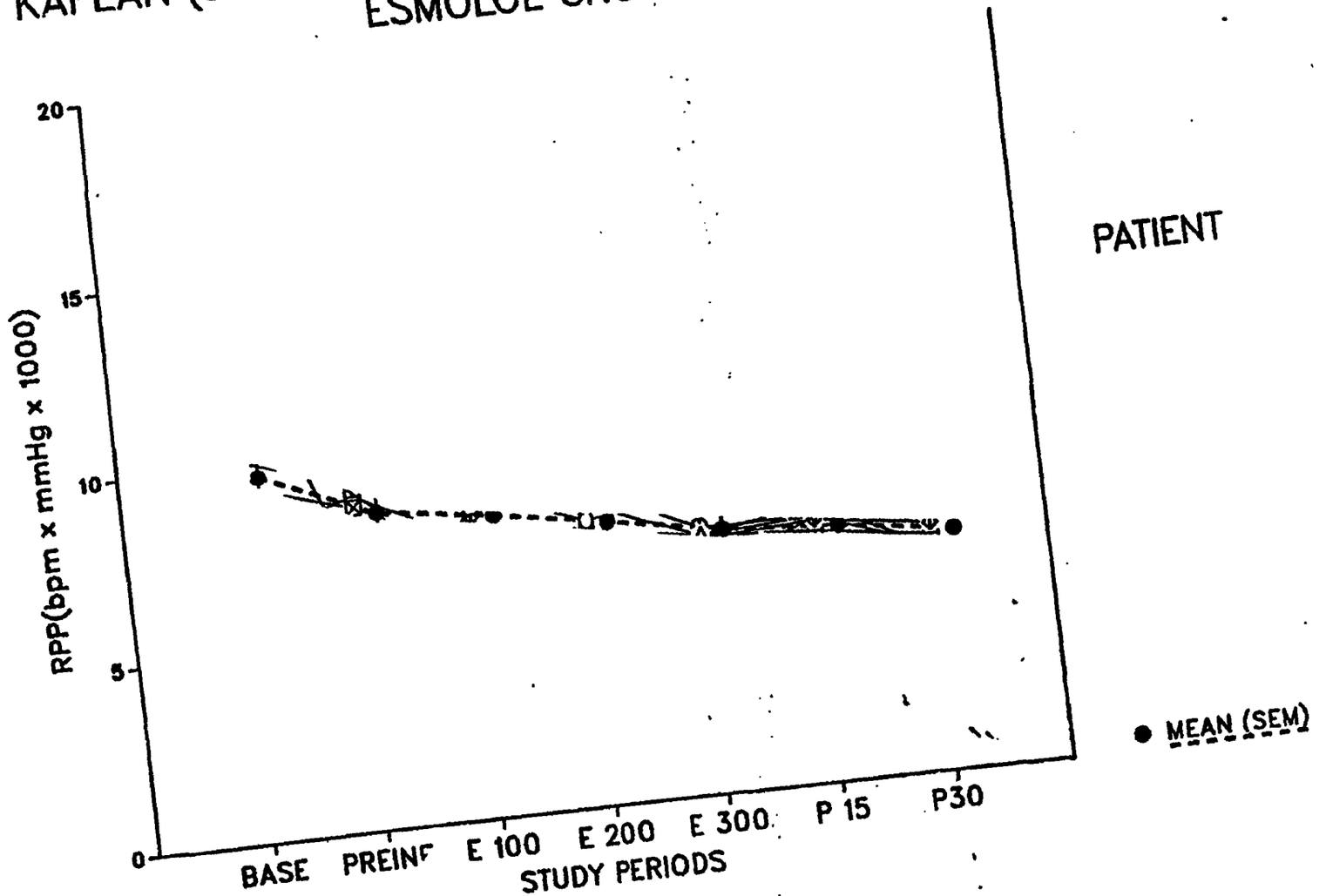
KAPLAN (8052-83-25) – HEART RATE
ESMOLOL GROUP



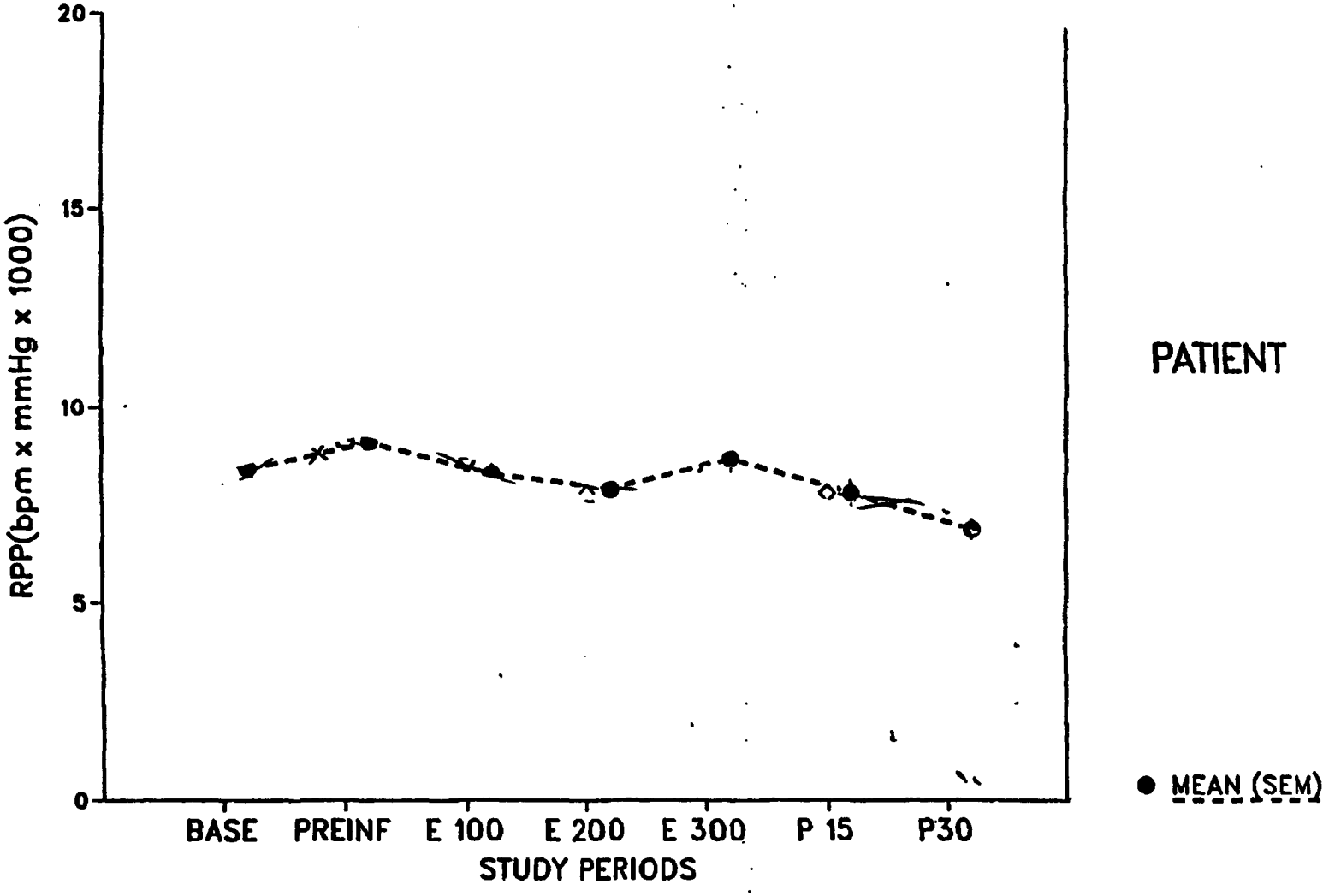
KAPLAN (8052-83-25) – HEART RATE
PLACEBO GROUP



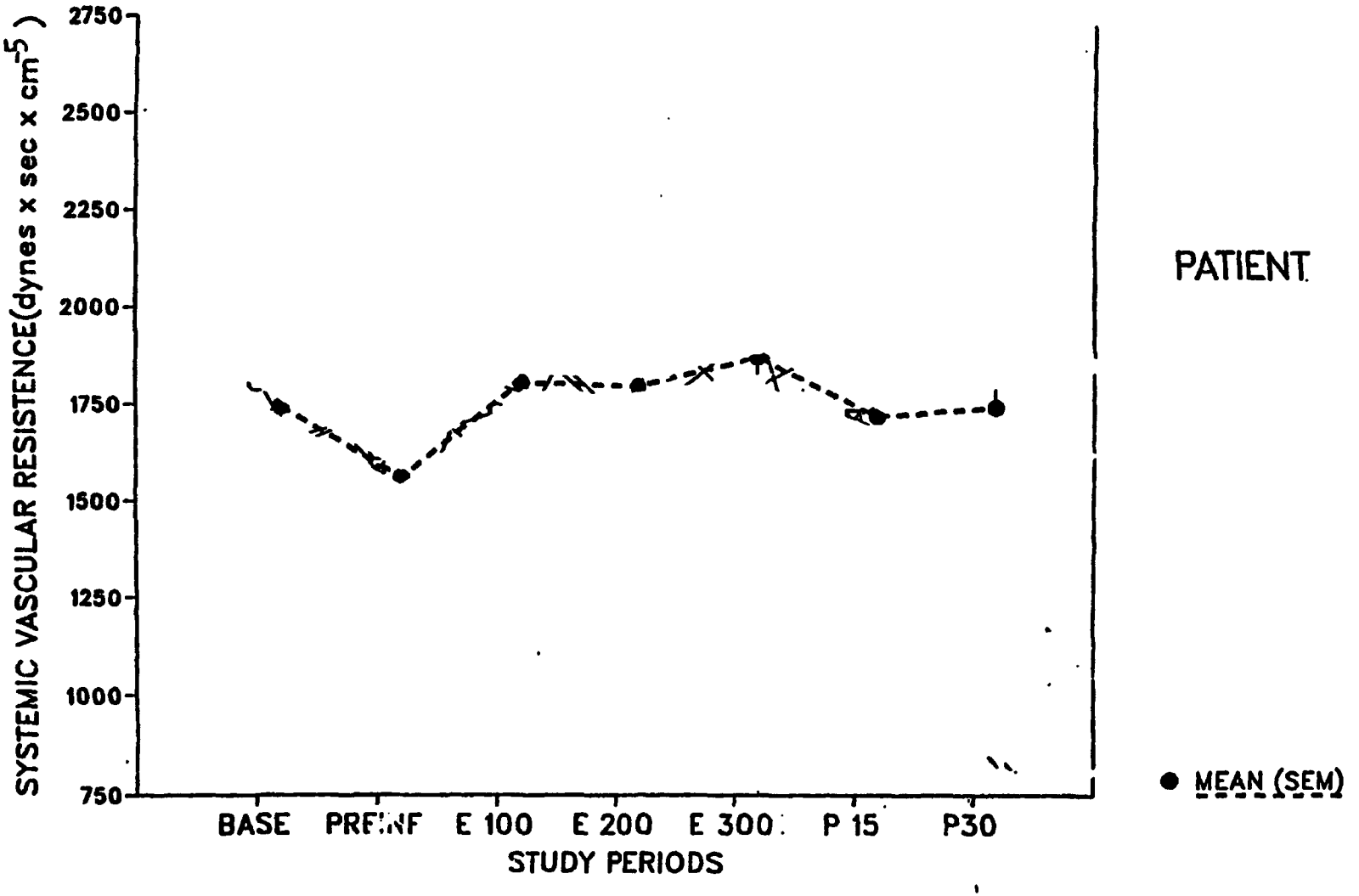
KAPLAN (8052-83-25) - RATE PRESSURE PRODUCT
ESMOLOL GROUP



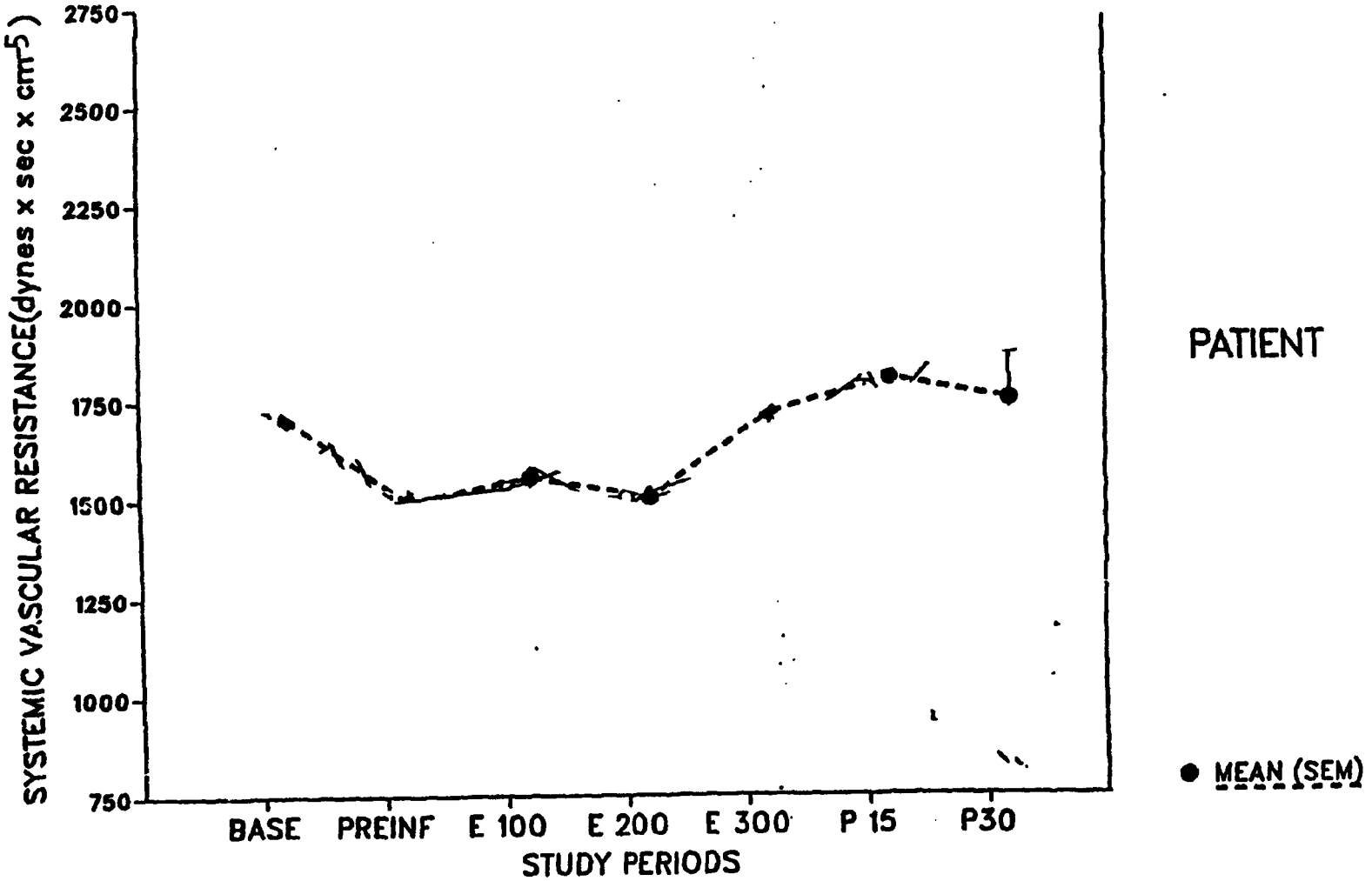
KAPLAN (8052-83-25) - RATE PRESSURE PRODUCT
PLACEBO GROUP

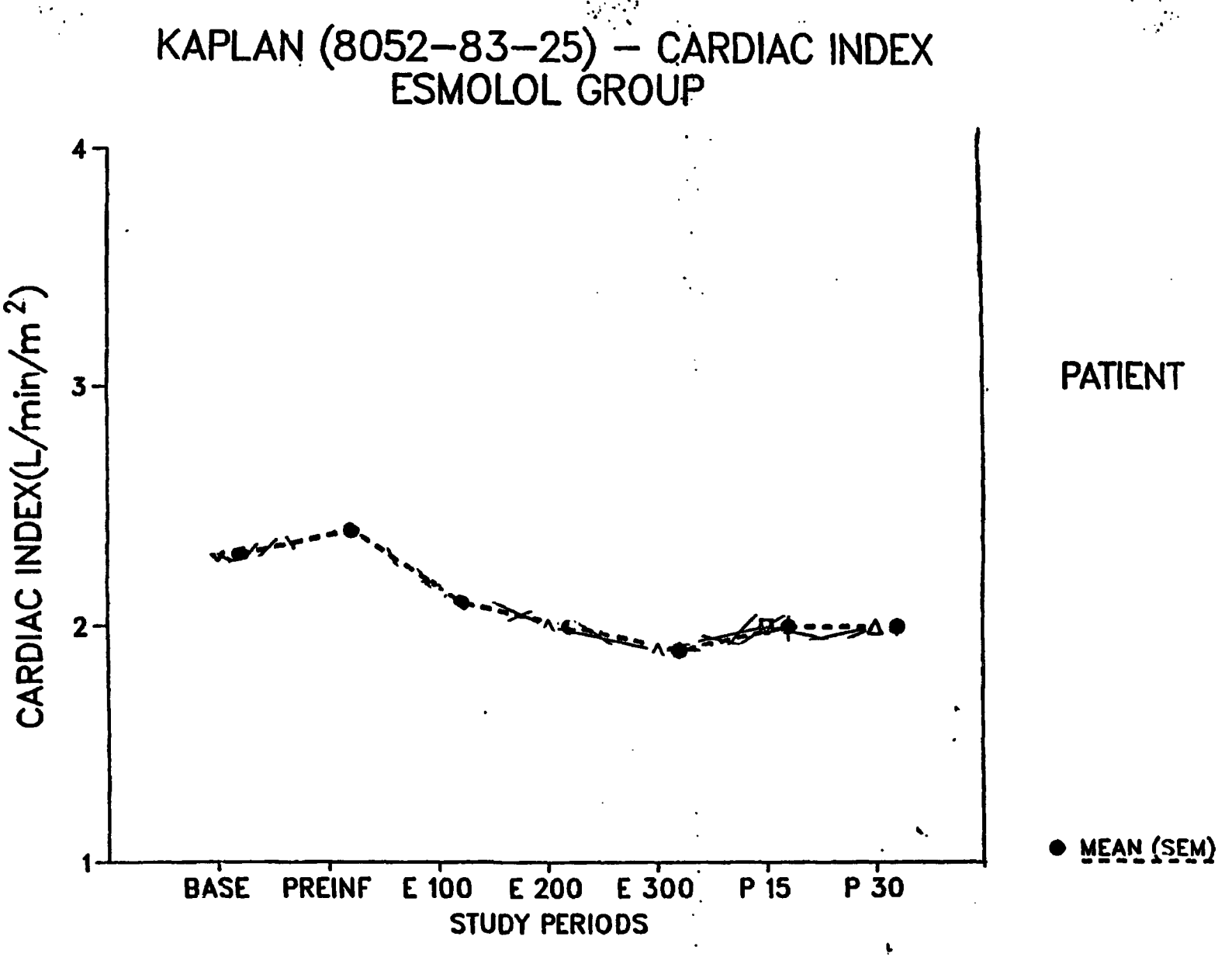


KAPLAN (8052–83–25) – SVR
ESMOLOL GROUP

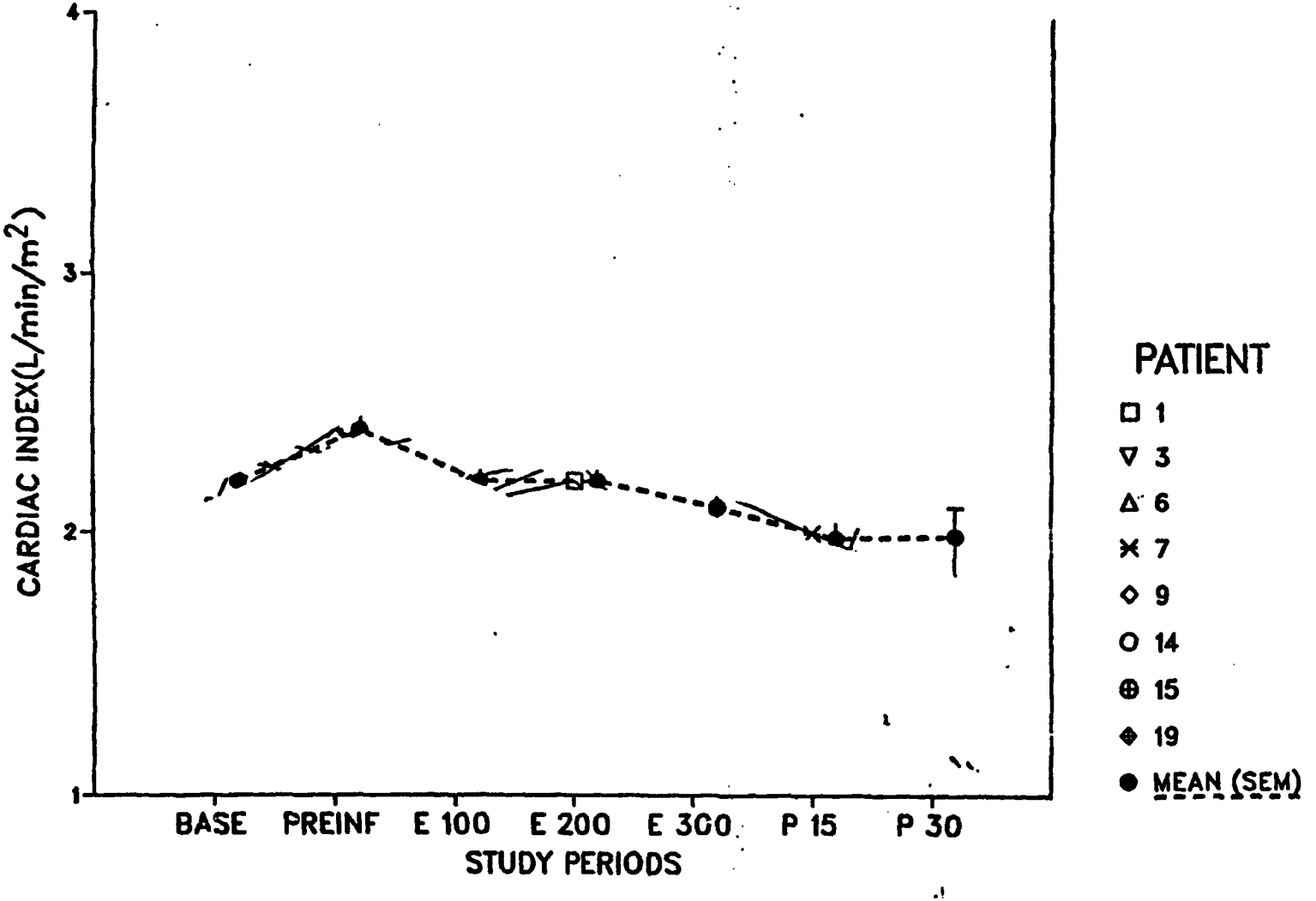


KAPLAN (8052-83-25) - SVR
PLACEBO GROUP




KAPLAN (8052-83-25) - CARDIAC INDEX
ESMOLOL GROUP
CARDIAC INDEX(L/min/m 2)
4
3
2
1
BASE
PREINF
E 100
E 200
E 300
P 15
P 30
STUDY PERIODS
PATIENT
MEAN (SEM)

KAPLAN (8052-83-25) - CARDIAC INDEX
PLACEBO GROUP



Appendix 1C - Blood Concentration X Time Plots for Esmolol and Its Acid Metabolite

Study No 1

12 Pages

Redacted

Study # 2

16 Pages

Redacted

Study #3

23 Pages

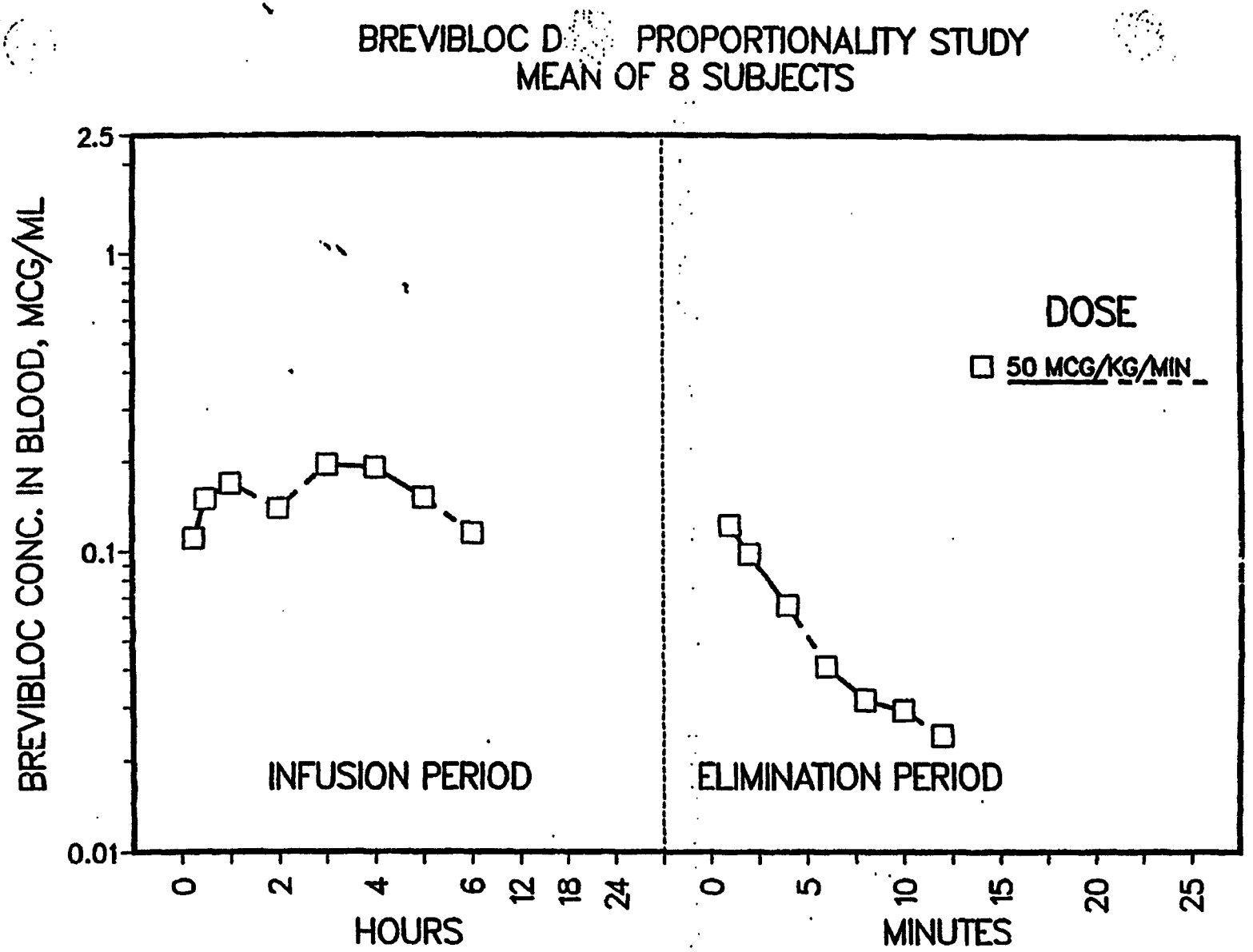
Redacted

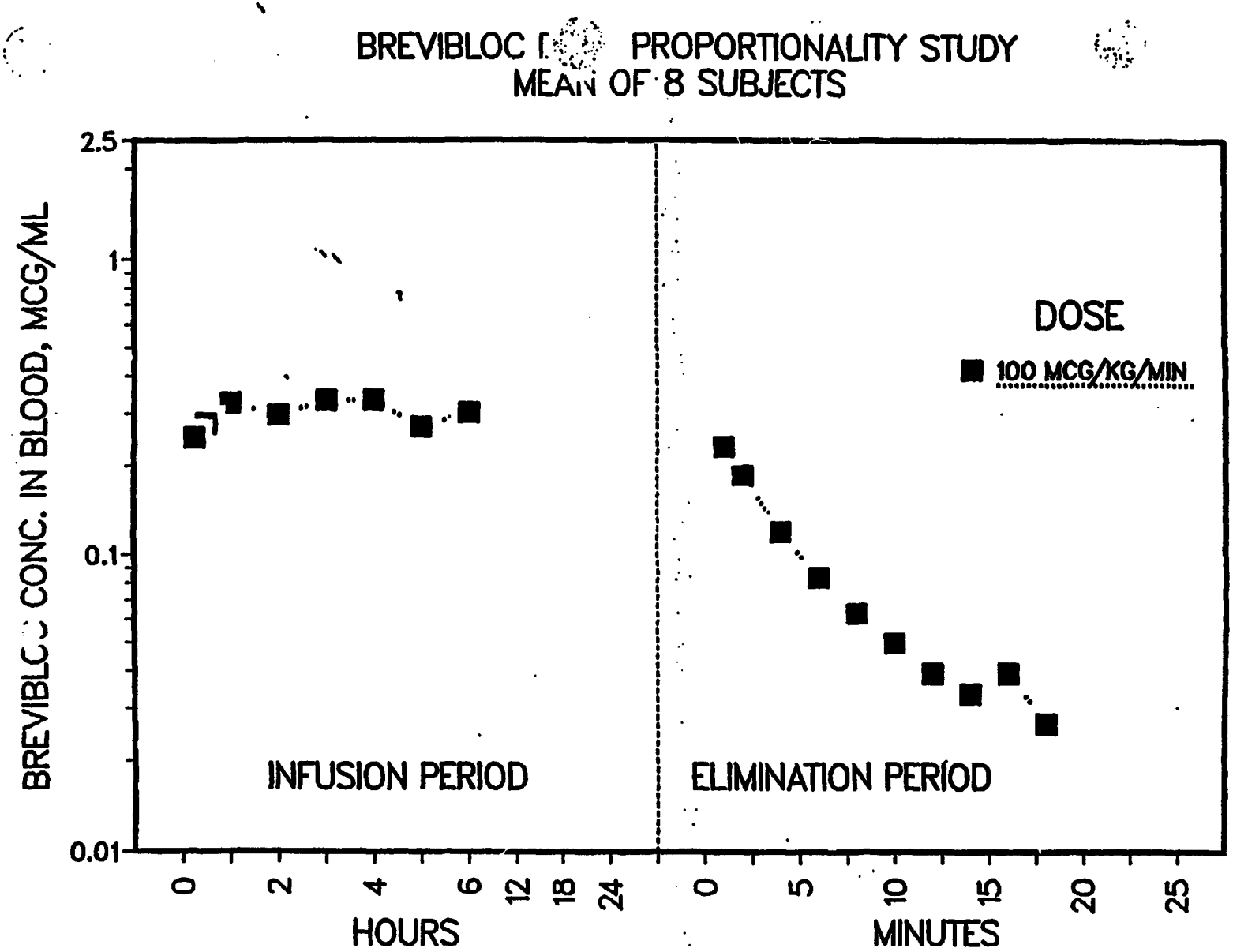
Study #9

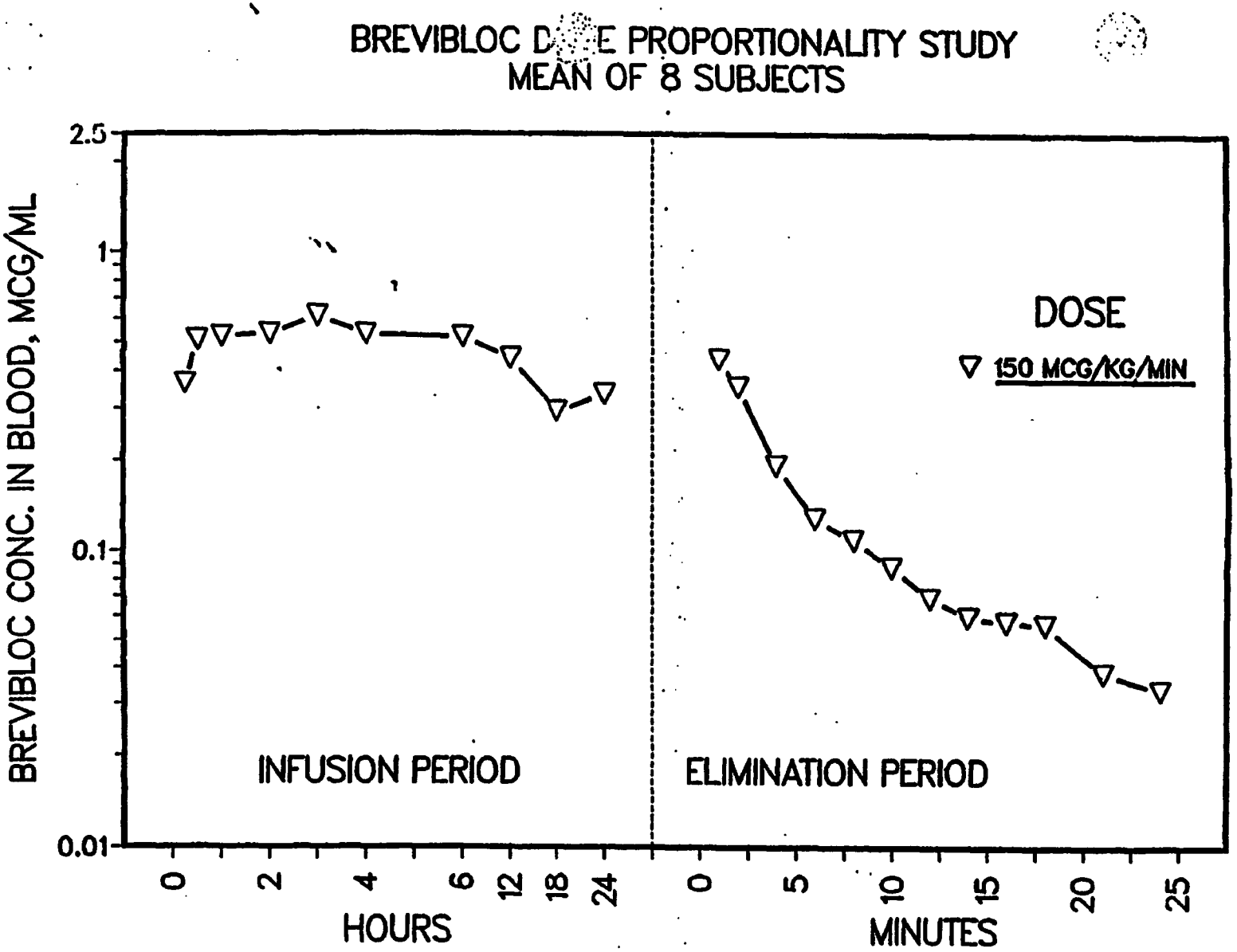
13 Pages

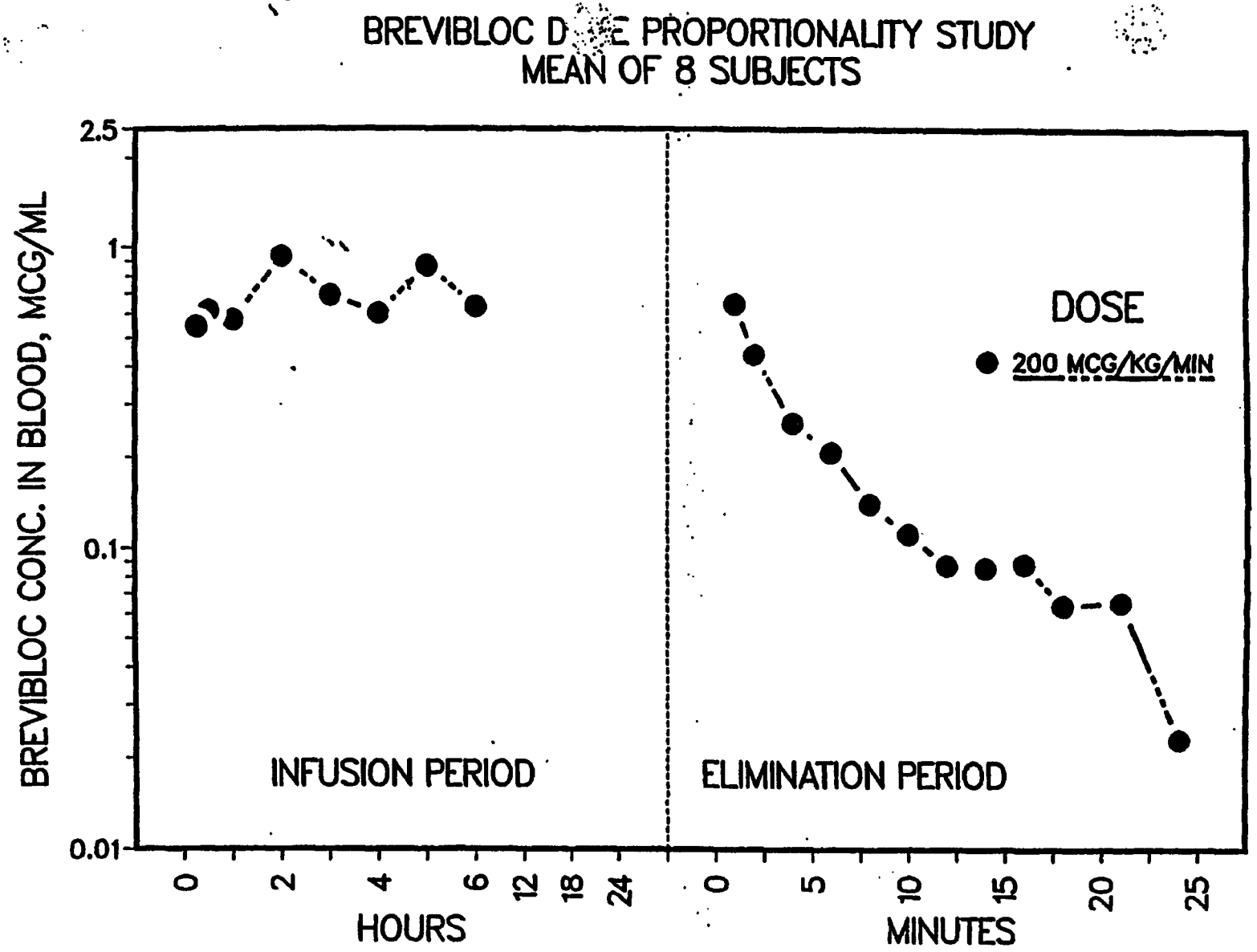
Redacted

Study 09


BREVIBLOC D PROPORTIONALITY STUDY
MEAN OF 8 SUBJECTS
BREVIBLOC CONC. IN BLOOD, MCG/ML
2.5
1
0.1
0.01
DOSE
50 MCG/KG/MIN
INFUSION PERIOD
ELIMINATION PERIOD
0
2
4
6
12
18
24
HOURS
0
5
10
15
20
25
MINUTES


BREVIBLOC PROPORTIONALITY STUDY
MEAN OF 8 SUBJECTS
BREVIBLOC CONC. IN BLOOD, MCG/ML
2.5
1
0.1
0.01
DOSE
100 MCG/KG/MIN
INFUSION PERIOD
ELIMINATION PERIOD
0
2
4
6
12
18
24
HOURS
0
5
10
15
20
25
MINUTES


BREVIBLOC DOSE PROPORTIONALITY STUDY
MEAN OF 8 SUBJECTS
BREVIBLOC CONC. IN BLOOD, MCG/ML
2.5
1
0.1
0.01
DOSE
150 MCG/KG/MIN
INFUSION PERIOD
ELIMINATION PERIOD
0
2
4
6
12
18
24
HOURS
0
5
10
15
20
25
MINUTES


BREVIBLOC D E PROPORTIONALITY STUDY
MEAN OF 8 SUBJECTS
BREVIBLOC CONC. IN BLOOD, MCG/ML
2.5
1
0.1
0.01
DOSE
200 MCG/KG/MIN
INFUSION PERIOD
ELIMINATION PERIOD
0
2
4
6
12
18
24
HOURS
0
5
10
15
20
25
MINUTES