Table 12 (continued)

New Table

Diastolic and Mean Arterial Blood Pressures and Rate-Pressure Product with Changes from Baseline, at 10 and 15 Minutes Postinfusion, for "Efficacy Patients" Treated with Esmolol or Placebo

Study #8052-83-49

		POST INF 10			POST INF 15		
		Mean ± SEM		N	Mean ± SEM		N
	Group						
DBP (mmHg)	Esmolol	47.5	22.5	2	56.5	1.5	2
	Placebo	98.0	-	1	70.0	-	1
DBP Change	Esmolol	-17.7	23.7	2	-8.7#	0.3	2
	Placebo	30.7	-	1	2.7	-	1
Comparison of Change[a]			N.T.			N.T.	
MAP (mmHg)	Esmolol	68.3	23.3	2	85.0	3.0	2
	Placebo	112.0	-	1	87.7	-	1
MAP Change	Esmolol	-38.8	31.8	2	-21.9	5.5	2
	Placebo	15.2	-	1	-9.1	-	1
Comparison of Change[a]			N.T.			N.T.	
RPP	Esmolol	7.4	1.4	2	8.9	0.3	2
	Placebo	16.0	-	1	12.9	-	1
RPP Change	Esmolol	-8.7	5.4	2	-7.2	3.7	2
	Placebo	3.4	-	1	0.4	-	1
Comparison of Change[a]			N.T.			N.T.	

# Indicates significant change from baseline ($p<0.05$).

[a] N.T. Not tested due to small sample size.

study #8052-83-49

Table 27

Heart Rate and Systolic Blood Pressure with Changes from Baseline, by Period, for "All Patients" Treated with Esmolol or Placebo

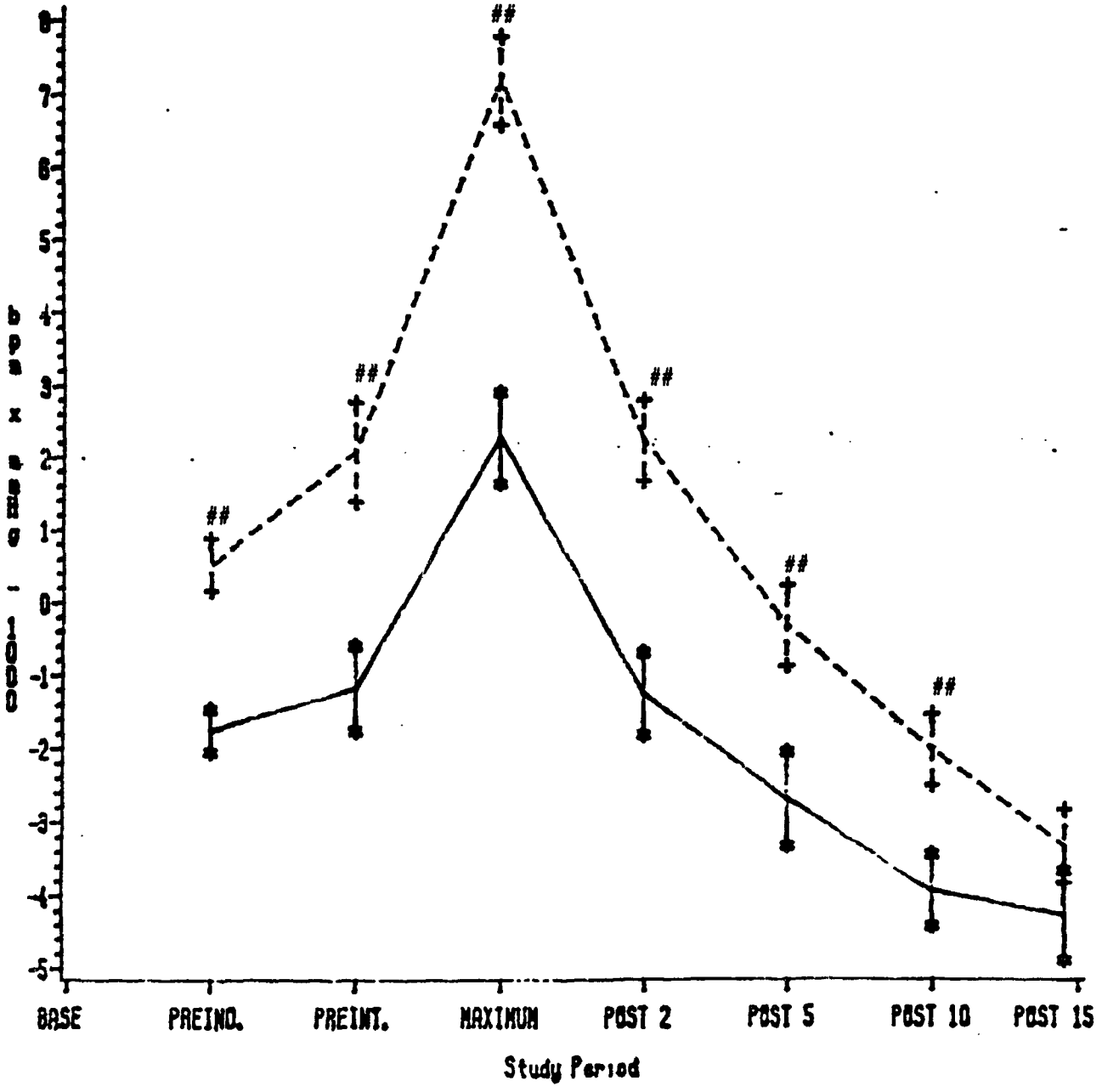
		BASELINE	PREINDUCTION	PREINTUBATION	MAXIMUM	POST INF 2	POST INF 5
		MEAN ± SEM N	MEAN ± SEM N	MEAN ± SEM N	MEAN ± SEM N	MEAN ± SEM N[b]	MEAN ± SEM N[b]
Group							
HR (bpm)	Esmolol	75.3 2.3 37	66.6 2.0 37	74.0 2.2 37	85.4 2.5 37	70.6 2.1 37	71.1 1.8 37
	Placebo	79.0 2.2 37	78.1 2.2 37	88.3 2.4 37	108.7 2.4 37	88.8 2.6 36	84.8 2.6 36
HR Change	Esmolol		-8.7# 1.0 37	-1.3 1.9 37	10.0 2.4 37	-4.7# 1.9 37	-4.2# 1.7 37
	Placebo		-1.0 1.1 37	9.3# 1.7 37	27.7 2.4 37	9.9# 3.1 36	5.9 2.9 36
Comparison of Change[a]		N.S.	P>E**	P>E**	P>E**	P>E**	P>E**
SBP (mm Hg)	Esmolol	181.9 4.4 37	176.6 5.3 37	143.3 4.6 37	187.1 4.4 37	138.4 5.3 37	124.9 4.1 37
	Placebo	170.8 4.3 37	173.4 4.2 37	151.6 5.7 37	217.8 5.1 37	141.8 7.0 37	131.8 5.2 37
SBP Change	Esmolol		-5.3 5.0 37	-38.6# 4.7 37	5.1 5.3 37	-43.6# 5.7 37	-57.0# 4.7 37
	Placebo		2.6 2.2 37	-19.2# 5.3 37	47.0 5.0 37	-28.9# 7.3 37	-39.0# 5.3 37
Comparison of Change[a]		N.S.	N.S.	P>E**	P>E**	N.S.	P>E*

\# Indicates significant change from baseline ($p<0.05$). Maximum change from baseline was not tested for significance.

a N.S. indicates no significant difference between the esmolol and placebo treatment groups (actual values used for baseline comparisons, change from baseline used for comparison at subsequent periods, $p \geq 0.05$).
P = Placebo, E = Esmolol 300 mcg/kg/min, * $p<0.05$, ** $p<0.01$

b POST INF 2 & 5 HR was not retrievable for Patient #607.

ASA III & IV (8052-84-51B)
Rate Pressure Product Changes from Baseline for All Patients

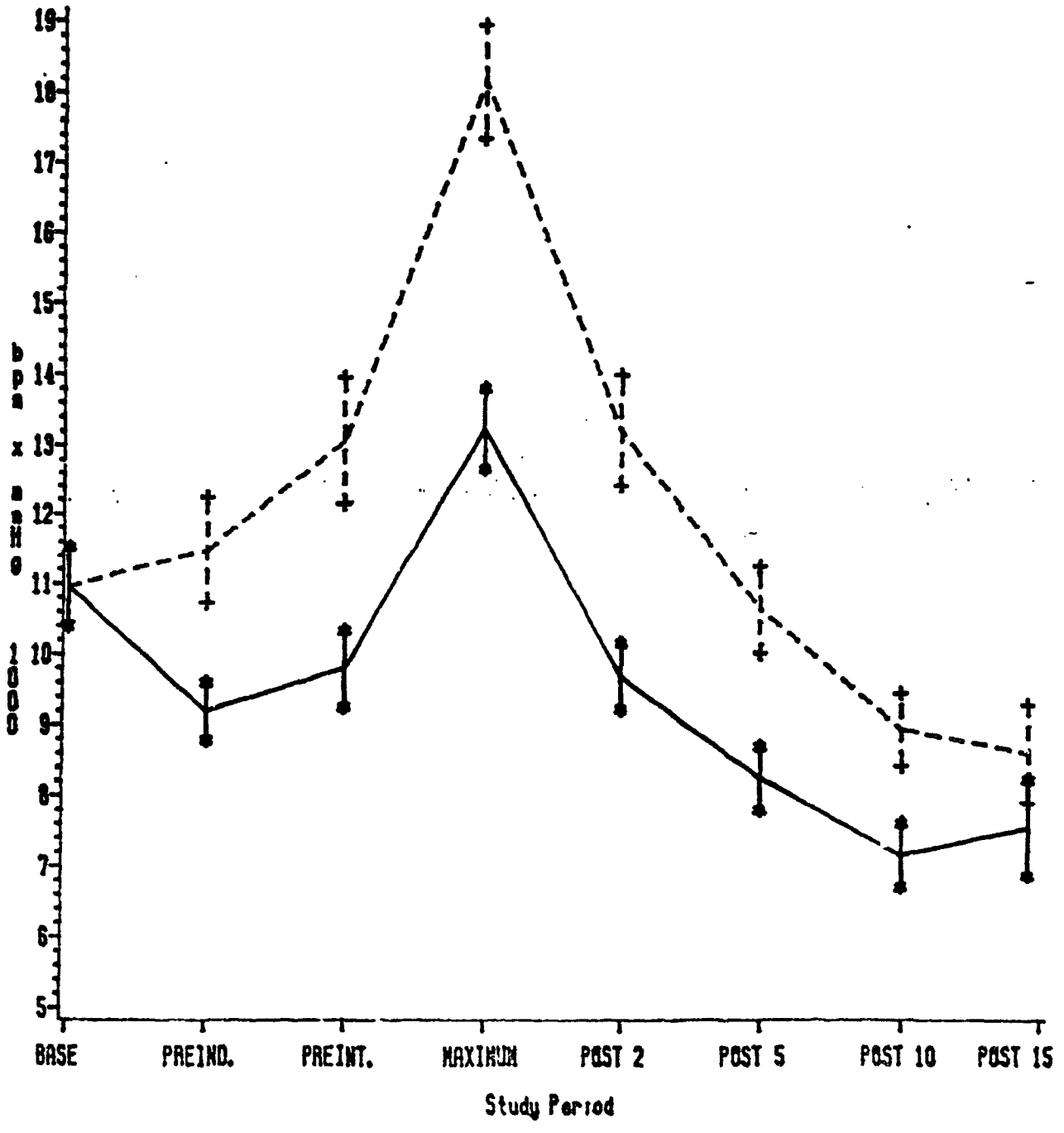


Esmolol ●—●—●

Placebo +—+—+

Significant difference between esmolol and placebo with respect to change from baseline ($p < 0.01$).

ASA III & IV (8052–84–51B)
Rate Pressure Product for All Patients

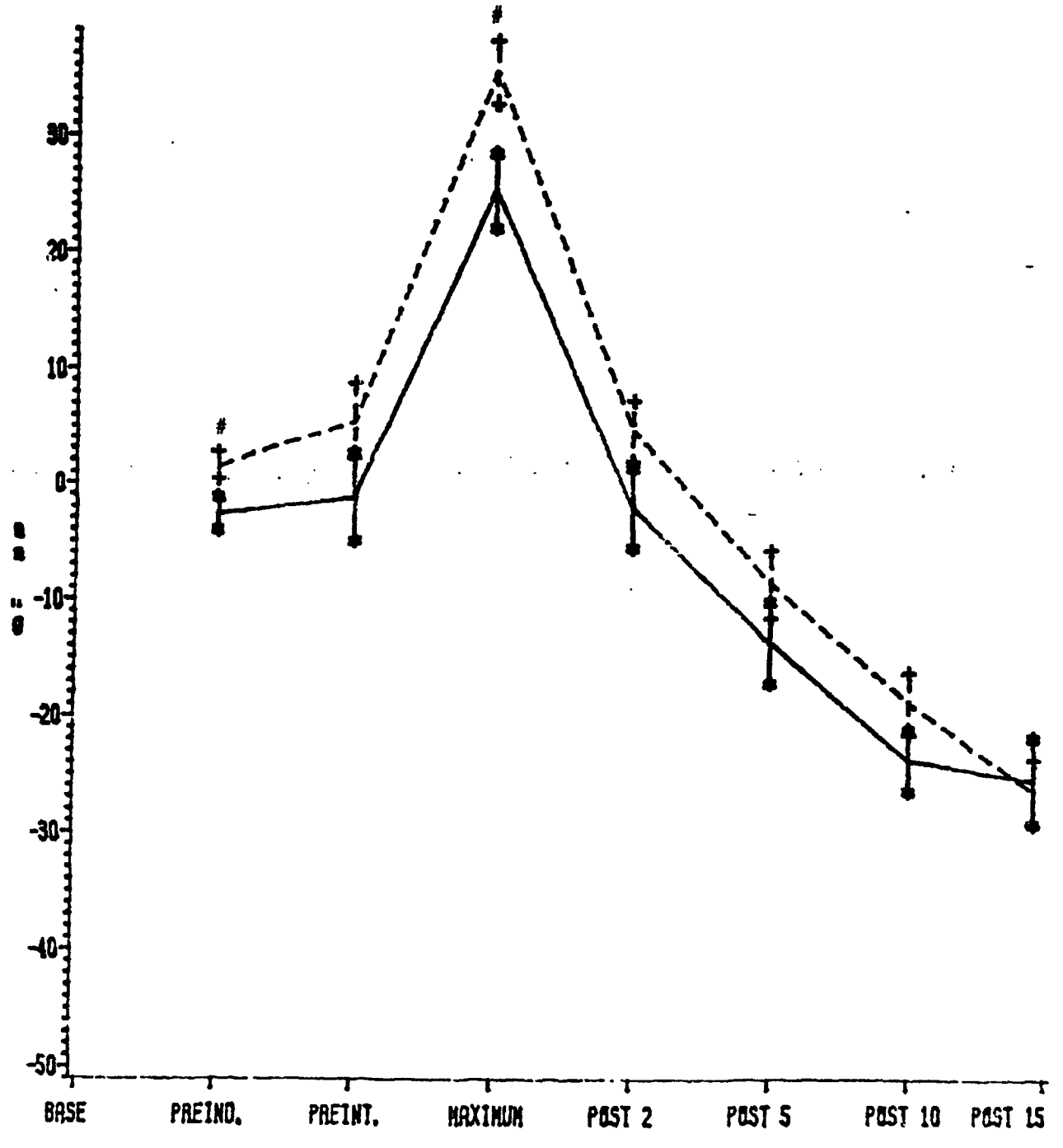


Esmolol *—*—*

Placebo +—+—+

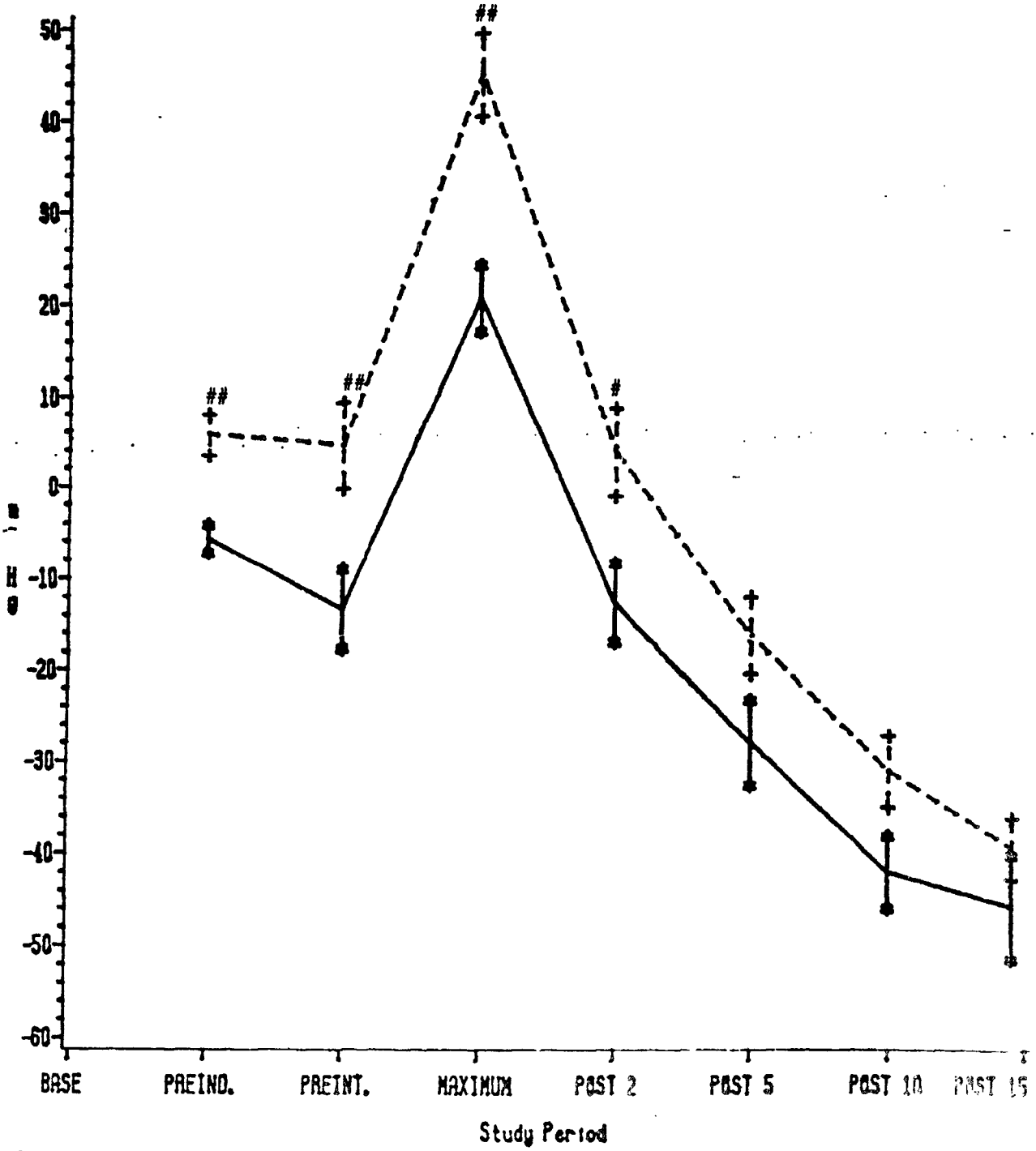
– [illegible] baseline ($p < 0.05$).

ASA III & IV (8052-84-51B)
Mean Arterial Blood Pressure Changes from Baseline for All Patients



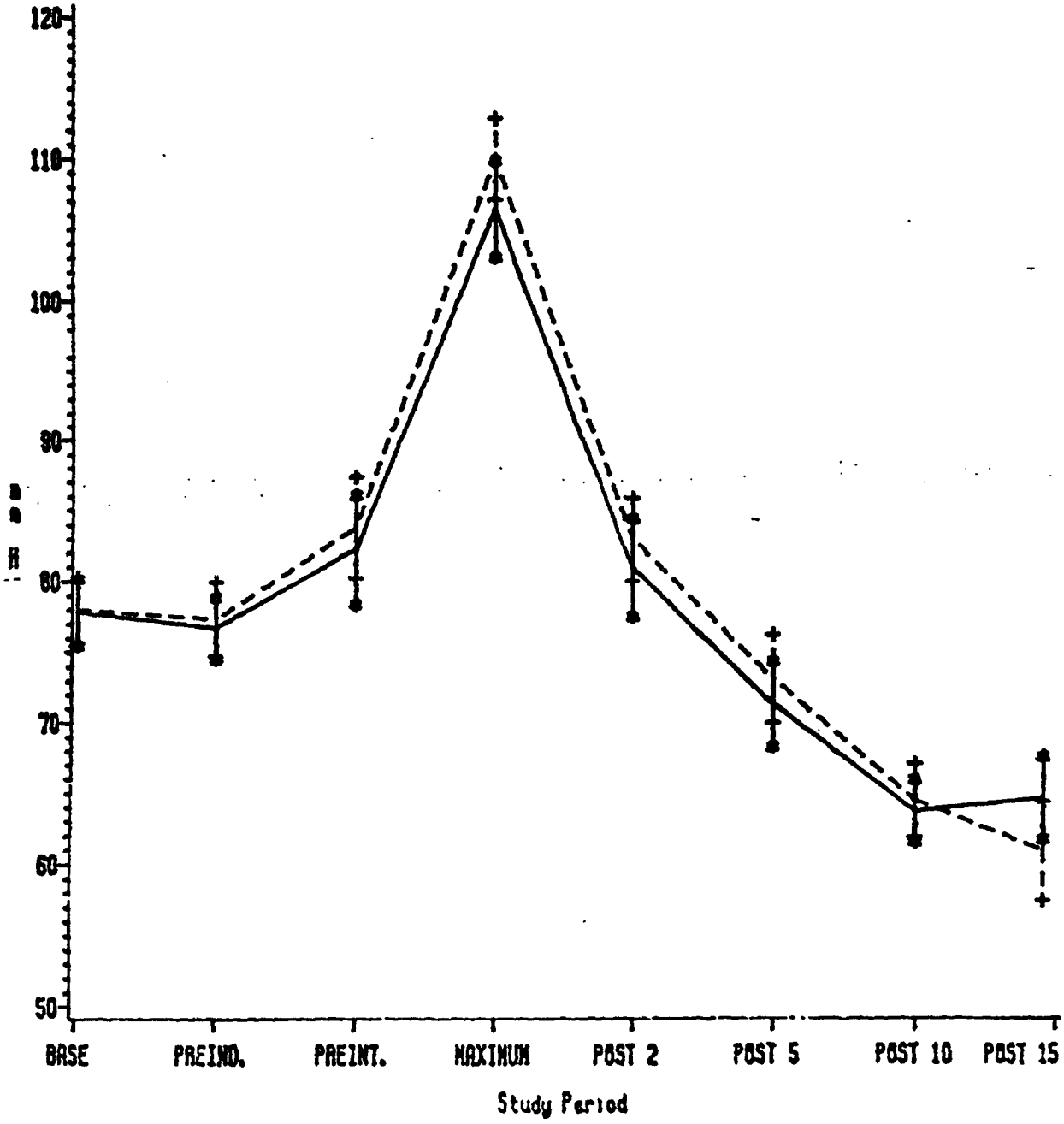
\# Significant difference between esmolol and placebo with respect to change from baseline ($p < 0.05$).

ASA III & IV (8052-84-51B)
Systolic Blood Pressure Changes from Baseline for All Patients



\# Significant difference between esmolol and placebo with respect to change from baseline ($p < 0.05$).

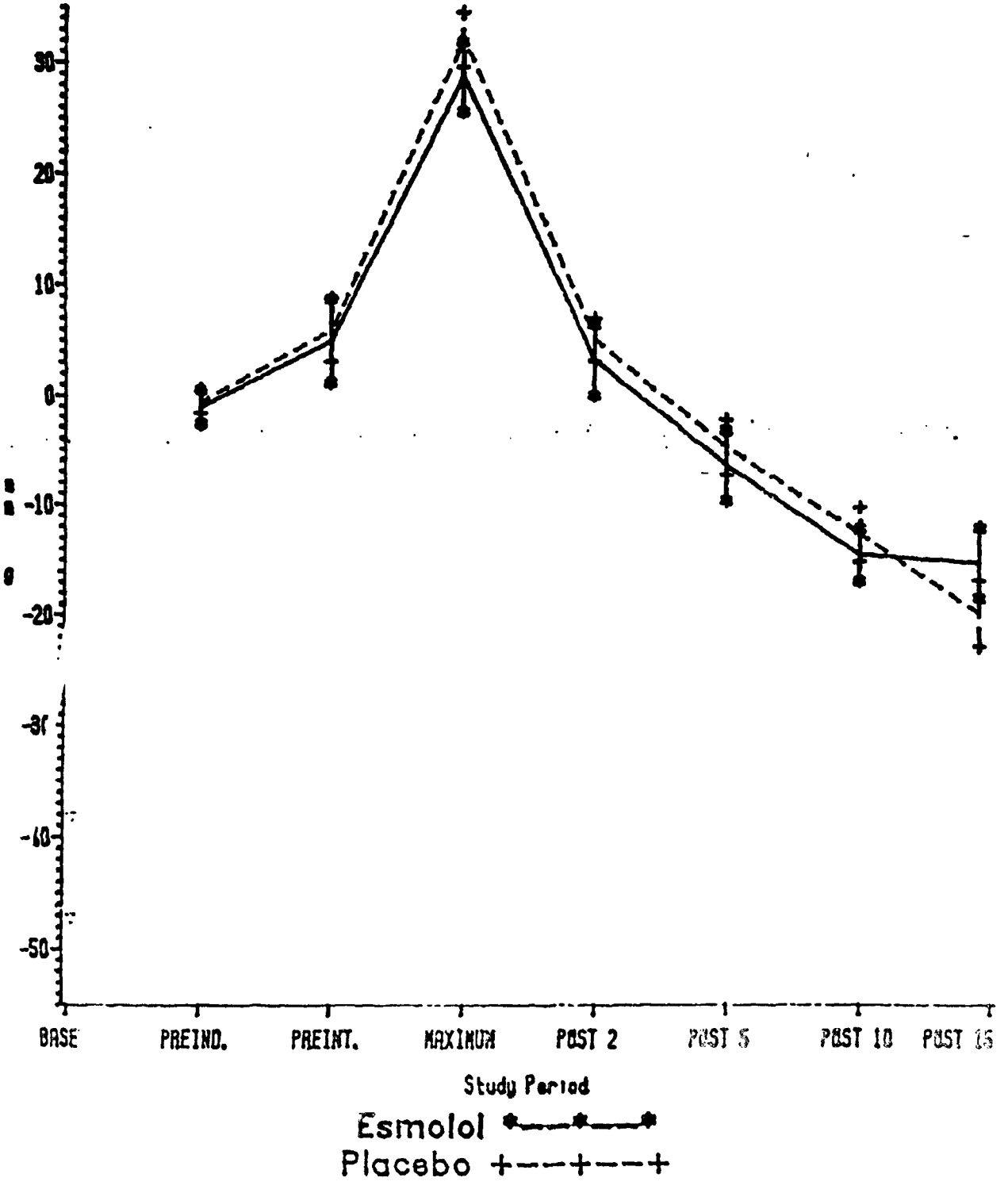
ASA III & IV (8052-84-51B)
Diastolic Blood Pressure for All Patients



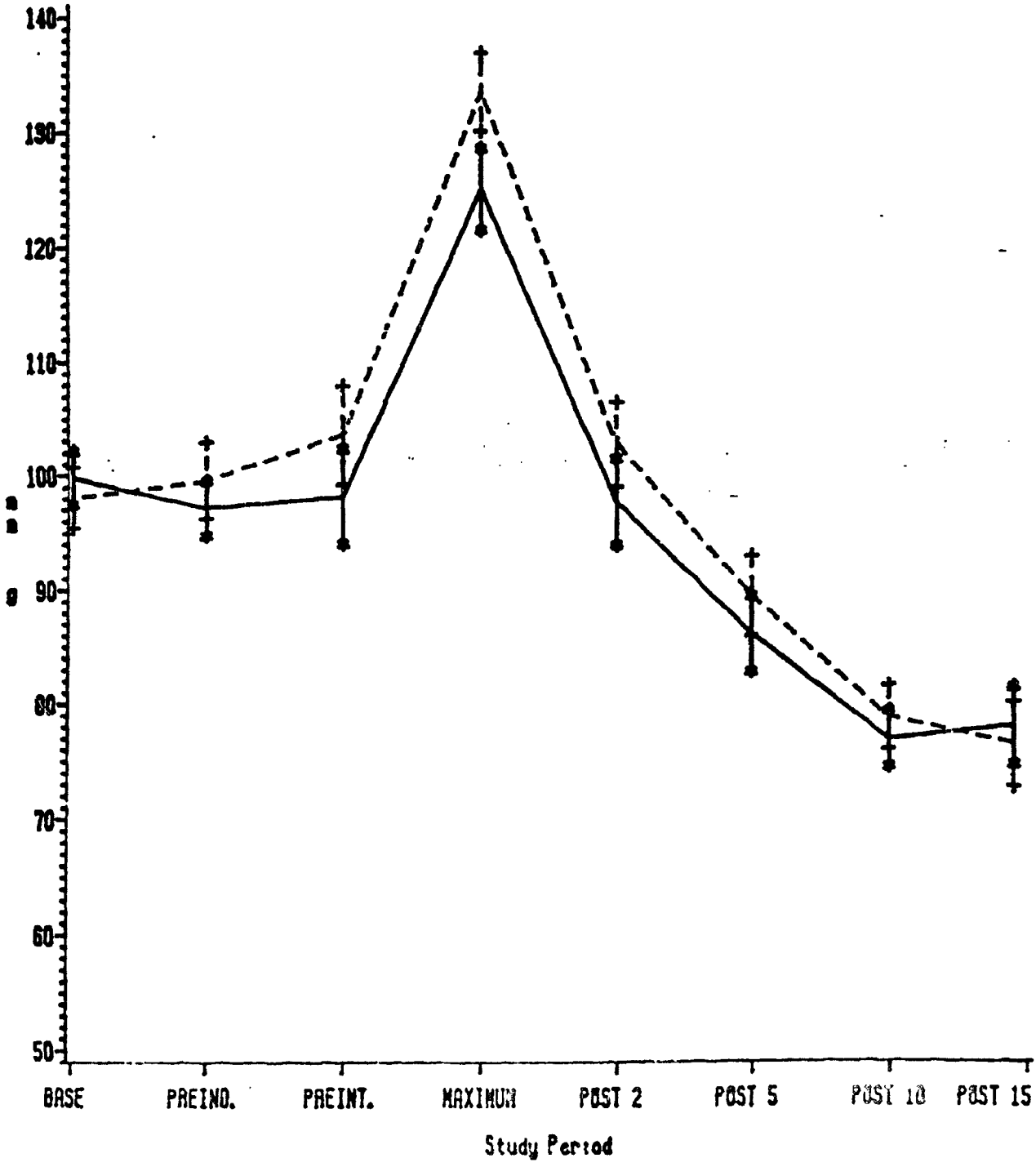
Esmolol *——*——*

Placebo +--+--+

ASA III & IV (8052-84-51B)
Diastolic Blood Pressure Changes from Baseline for All Patients



ASA III & IV (8052-84-51B)
Mean Arterial Blood Pressure for All Patients



ASA III & IV (8052–84–51B)
Systolic Blood Pressure for All Patients

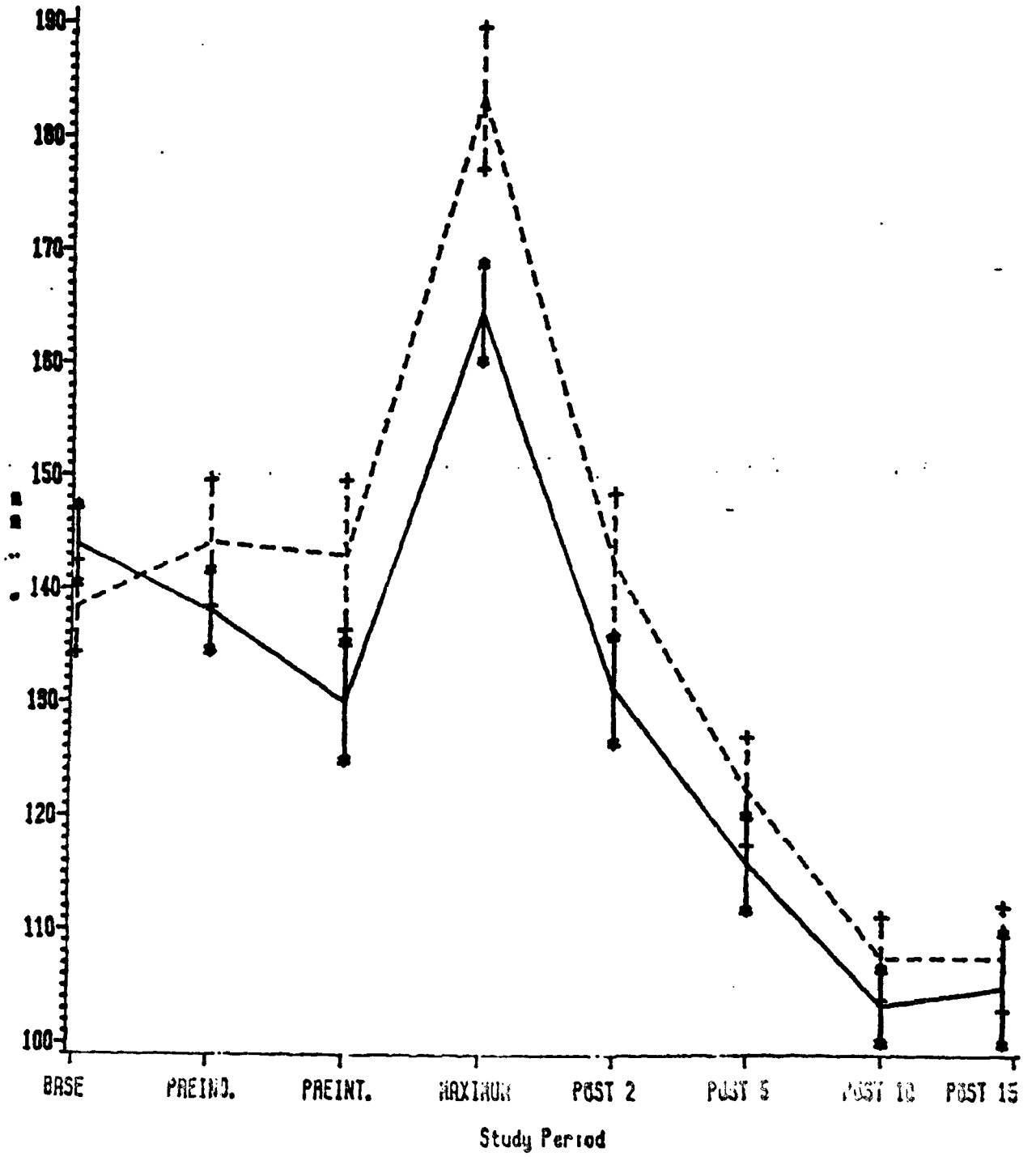


Table 27 (continued)

Heart Rate and Systolic Blood Pressure with Changes from *Baseline, by Period, for "All Patients" Treated with Esmolol or Placebo*

		POST INF 10			POST INF 15		
		MEAN	± SEM	N[b]	MEAN	± SEM	N[b]
Group							
HR (bpm)	Esmolol	71.2	1.9	37	71.1	2.3	37
	Placebo	83.3	3.1	36	80.0	2.9	36
HR Change	Esmolol	-4.2	2.1	37	-4.2	2.3	37
	Placebo	4.5	3.2	36	1.1	2.9	36
Comparison of Change[a]		P>E*			N.S.		
SBP (mm Hg)	Esmolol	121.9	3.7	37	133.3	4.4	37
	Placebo	131.0	4.8	36	133.8	4.4	36
SBP Change	Esmolol	-60.0#	4.3	37	-48.6#	4.8	37
	Placebo	-39.0#	5.5	36	-36.3#	5.3	36
Comparison of Change[a]		P>E**			N.S.		

\# Indicates significant change from baseline ($p<0.05$). Maximum change from baseline was not tested for significance.

a N.S. Indicates no significant difference between the esmolol and placebo treatment groups (actual values used for baseline comparisons, change from baseline used for comparison at subsequent periods, $p>0.05$).
P = Placebo, E = Esmolol 300 mcg/kg/min, * $p<0.05$, ** $p<0.01$

b POST INF 10 & 15 HR & SBP were not retrievable for Patient #607.

Table 28

Diastolic Blood Pressure, Mean Arterial Blood Pressure, and Rate-Pressure Product with Changes from Baseline, by Period, for "All Patients" Treated with Esmolol or Placebo

		BASELINE	PREINDUCTION	PREINTUBATION	MAXIMUM	POST INF 2	POST INF 5
		MEAN ± SEM N	MEAN ± SEM N	MEAN ± SEM N[b]	MEAN ± SEM N	MEAN ± SEM N[c]	MEAN ± SEM N[c]
Group							
DBP (mm Hg)	Esmolol	77.7 2.3 37	77.2 2.6 37	75.2 3.0 37	101.2 2.9 37	71.1 2.6 37	66.3 2.5 37
	Placebo	75.7 2.1 37	76.9 2.4 37	78.1 3.3 36	114.9 3.3 37	75.6 4.4 37	71.4 3.2 37
DBP Change	Esmolol		-0.5 1.6 37	-2.5 2.6 37	23.5 2.8 37	-6.6# 2.5 37	-11.4# 2.2 37
	Placebo		1.2 1.3 37	2.1 2.8 36	39.2 2.5 37	-0.1 4.0 37	-4.3 2.2 37
Comparison of Change[a]		N.S.	N.S.	N.S.	P>E**	N.S.	P>E*
MAP (mm Hg)	Esmolol	112.4 2.8 37	110.3 3.2 37	97.9 3.3 37	128.9 3.2 37	93.5 3.3 37	85.8 2.8 37
	Placebo	107.4 2.5 37	109.0 2.7 37	103.4 3.9 36	147.9 3.6 37	97.7 5.2 37	91.5 3.8 37
MAP Change	Esmolol		-2.1 2.6 37	-14.6# 3.2 37	16.5 3.4 37	-18.9# 3.4 37	-28.6# 2.9 37
	Placebo		1.6 1.4 37	-4.7 3.5 36	40.5 3.2 37	-9.7 4.9 37	-15.9# 3.1 37
Comparison of Change[a]		N.S.	N.S.	P>E*	P>E**	N.S.	P>E*
RPP	Esmolol	13.7 0.5 37	11.8 0.5 37	10.6 0.4 37	15.2 0.7 37	9.9 0.5 37	8.9 0.4 37
	Placebo	13.5 0.5 37	13.5 0.5 37	13.5 0.7 37	22.4 0.8 37	13.0 0.9 36	11.1 0.6 36
RPP Change	Esmolol		-2.0# 0.4 37	-3.1# 0.5 37	1.5 0.8 37	-3.8# 0.7 37	-4.8# 0.6 37
	Placebo		0.0 0.3 37	-0.0 0.6 37	8.9 0.9 37	-0.4 1.0 36	-2.3# 0.8 36
Comparison of Change[a]		N.S.	P>E**	P>E**	P>E**	P>E**	P>E*

\# Indicates significant change from baseline ($p<0.05$). Maximum change from baseline was not tested for significance.

[a] N.S. Indicates no significant difference between the esmolol and placebo treatment groups (actual values used for baseline comparisons, change from baseline used for comparison at subsequent periods, $p \geq 0.05$).
P = Placebo, E = Esmolol 300 mcg/kg/min, * $p<0.05$, ** $p<0.01$

[b] Preintubation DBP was not retrievable for Patient #226.

[c] POST INF 2 & 5 RPP was not retrievable for Patient #607.

Table 28 (continued)

Diastolic Blood Pressure, Mean Arterial Blood Pressure, and Rate-Pressure Product Changes from Baseline, by Period, for "All Patients" Treated with Esmolol or Placebo

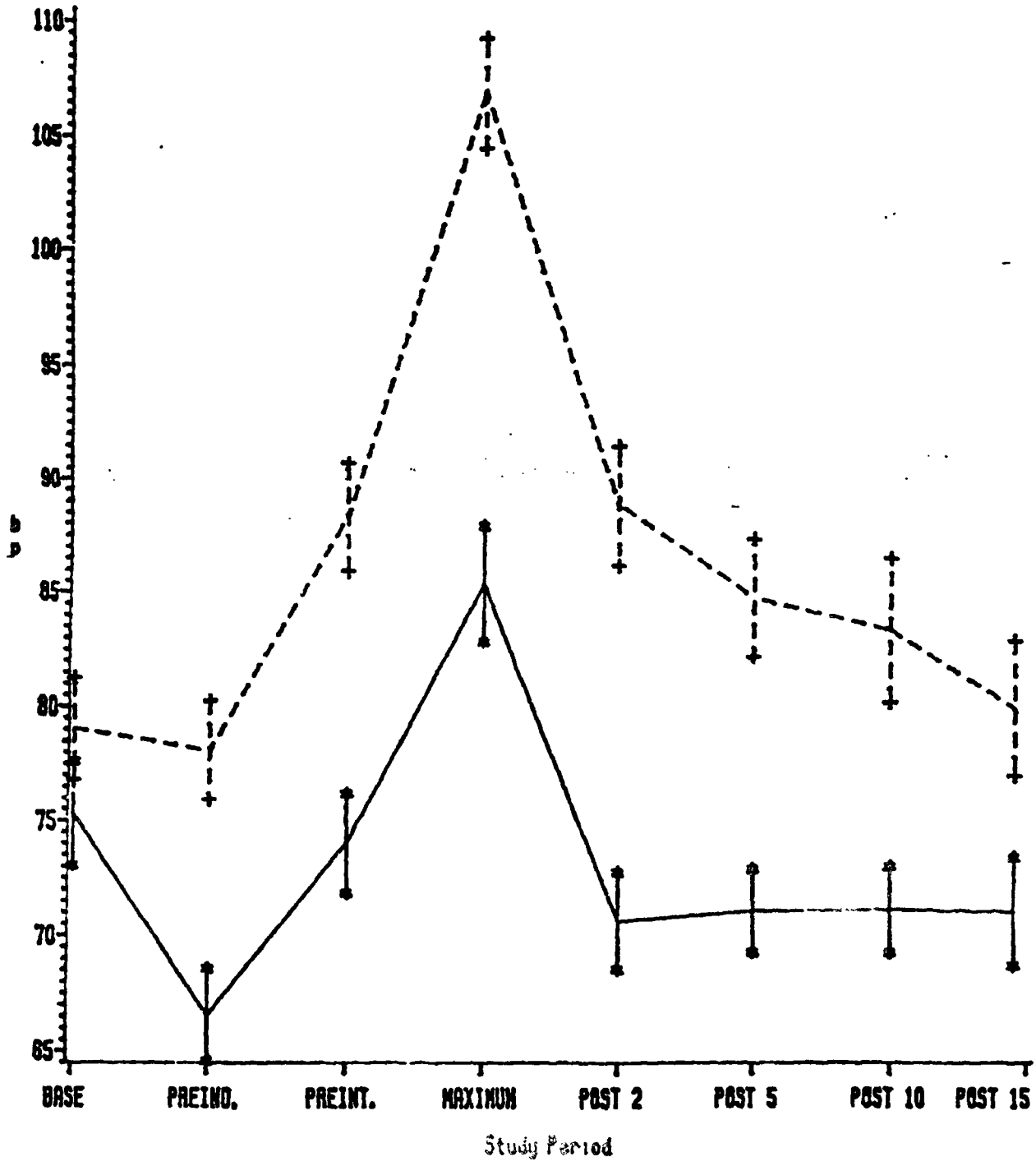
		POST INF 10	POST INF 15
		MEAN ± SEM N[b]	MEAN ± SEM N[b]
	Group		
DBP (mm Hg)	Esmolol	67.2 2.3 37	70.2 2.6 37
	Placebo	70.7 2.6 36	70.9 1.8 36
DBP Change	Esmolol	-10.5# 2.4 37	-7.4# 2.1 37
	Placebo	-4.3 2.4 36	-4.1 2.1 36
Comparison of Change[a]		N.S.	N.S.
MAP (mm Hg)	Esmolol	85.4 2.6 37	91.3 3.0 37
	Placebo	90.8 3.2 36	91.9 2.5 36
MAP Change	Esmolol	-27.0# 3.0 37	-21.2# 2.8 37
	Placebo	-15.9# 3.2 36	-14.8# 3.0 36
Comparison of Change[a]		P>E*	N.S.
RPP	Esmolol	8.7 0.3 37	9.5 0.5 37
	Placebo	11.0 0.7 36	10.7 0.8 36
RPP Change	Esmolol	-5.0# 0.6 37	-4.2# 0.6 37
	Placebo	-2.4# 0.8 36	-2.7# 0.7 36
Comparison of Change[a]		P>E*	N.S.

\# Indicates significant change from baseline ($p<0.05$). Maximum change from baseline was not tested for significance.

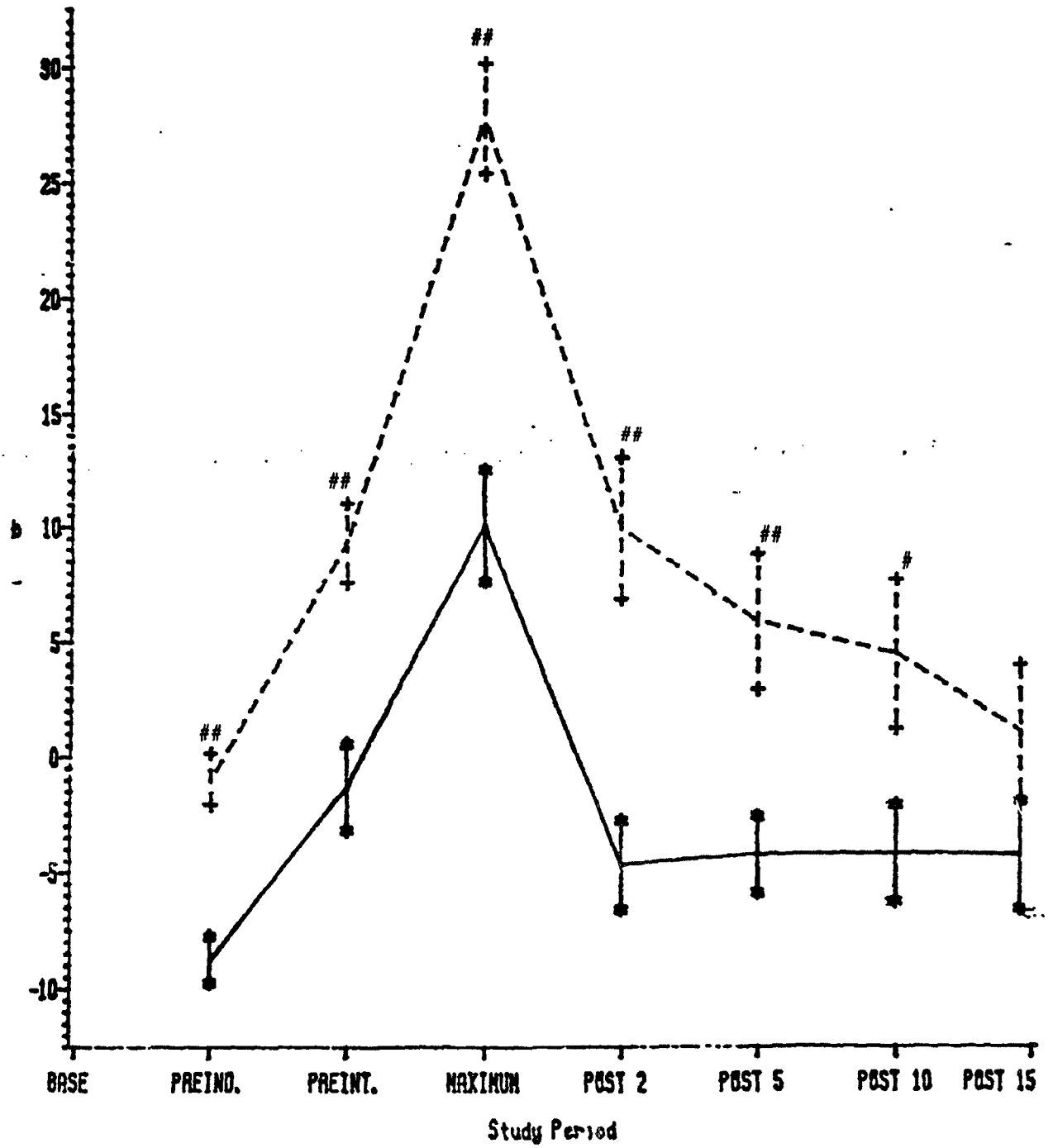
a N.S. Indicates no significant difference between the esmolol and placebo treatment groups (actual values used for baseline comparisons, change from baseline used for comparison at subsequent periods, $p \geq 0.05$).
P = Placebo, E = Esmolol 300 mcg/kg/min, * $p<0.05$, ** $p<0.01$

b POST INF 10 & 15 DBP, MAP and RPP were not retrievable for Patient #607.

CAROTID (8052-83-49)
Heart Rate for All Patients



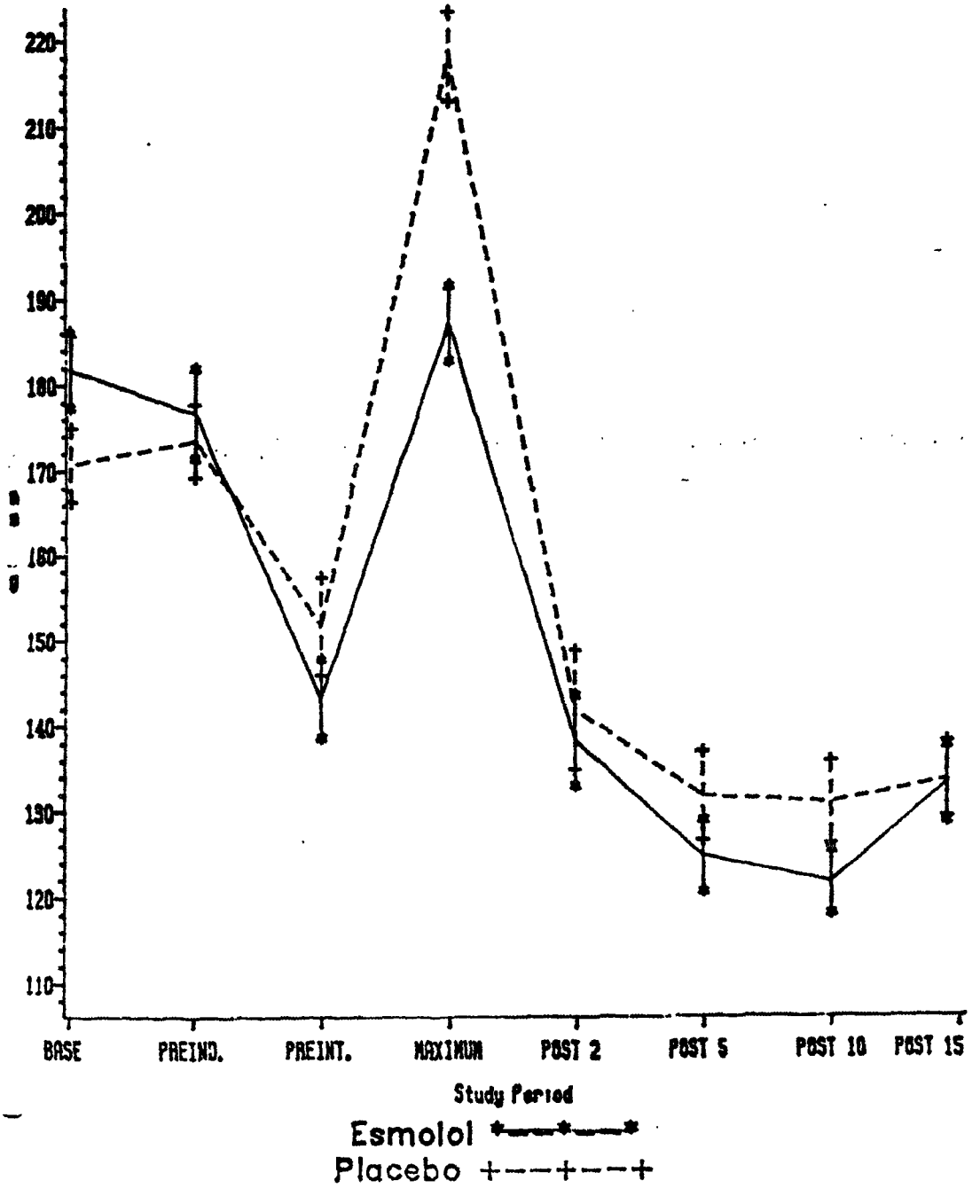
CAROTID (8052-83-49)
Heart Rate Changes from Baseline for All Patients



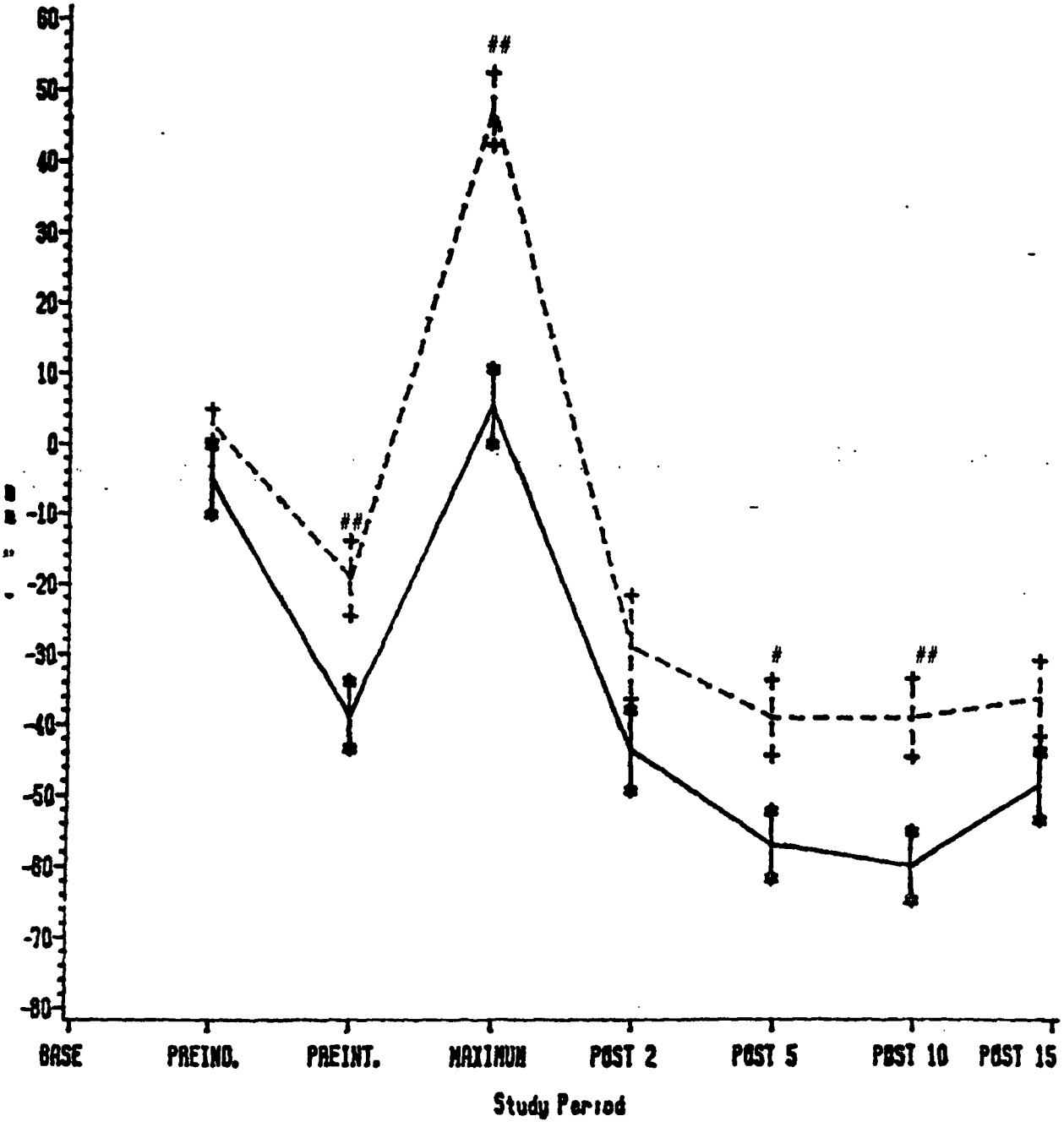
\# Significant difference between esmolol and placebo with respect to change from baseline ($p < 0.05$).

\## $p < 0.01$.

CAROTID (8052-83-49)
Systolic Blood Pressure for All Patients



CAROTID (8052-83-49)
Systolic Blood Pressure Changes from Baseline for All Patients



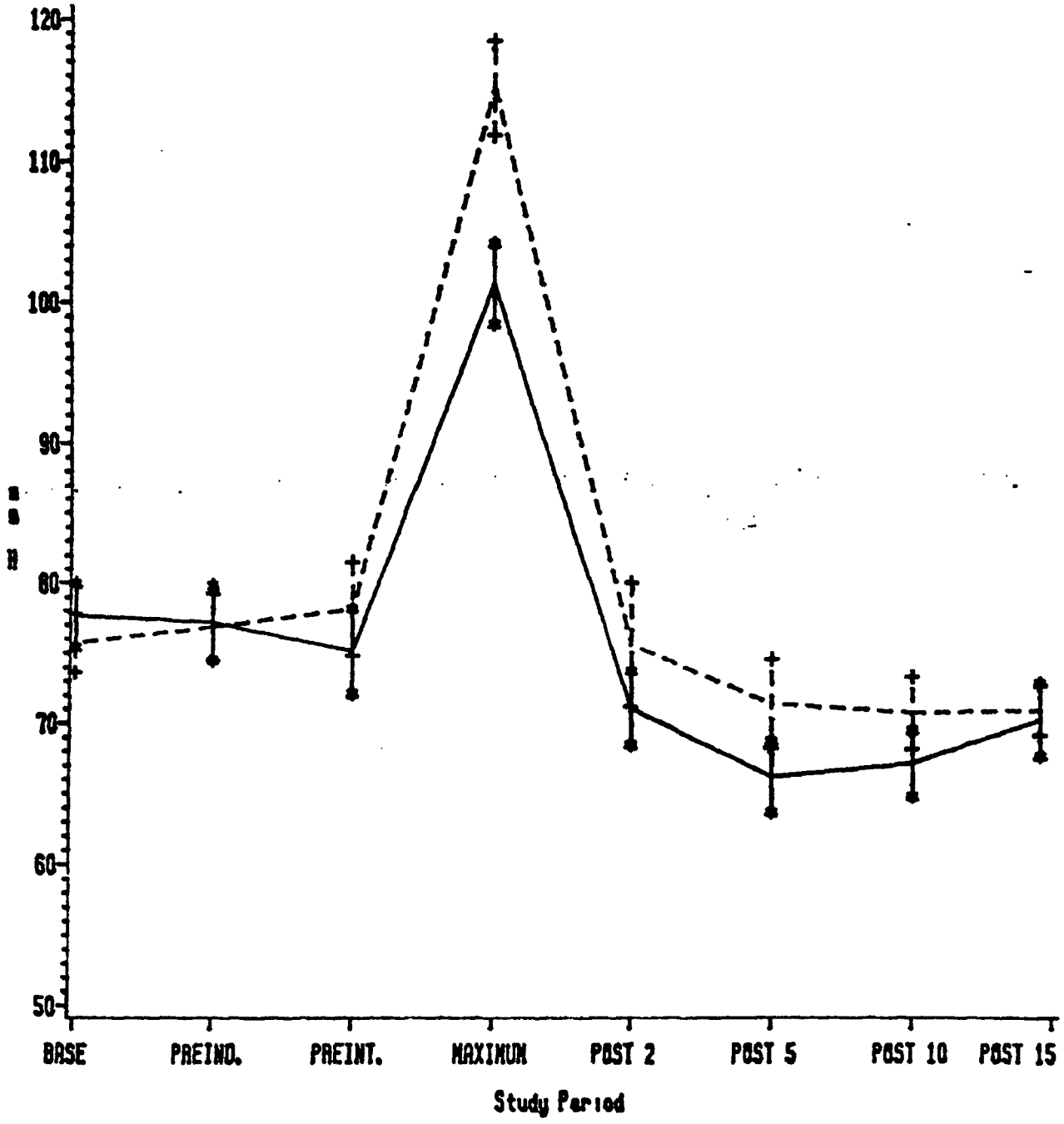
Esmolol

Placebo

\# Significant difference between esmolol and placebo with respect to change from baseline ($p < 0.05$).

\## $p < 0.01$.

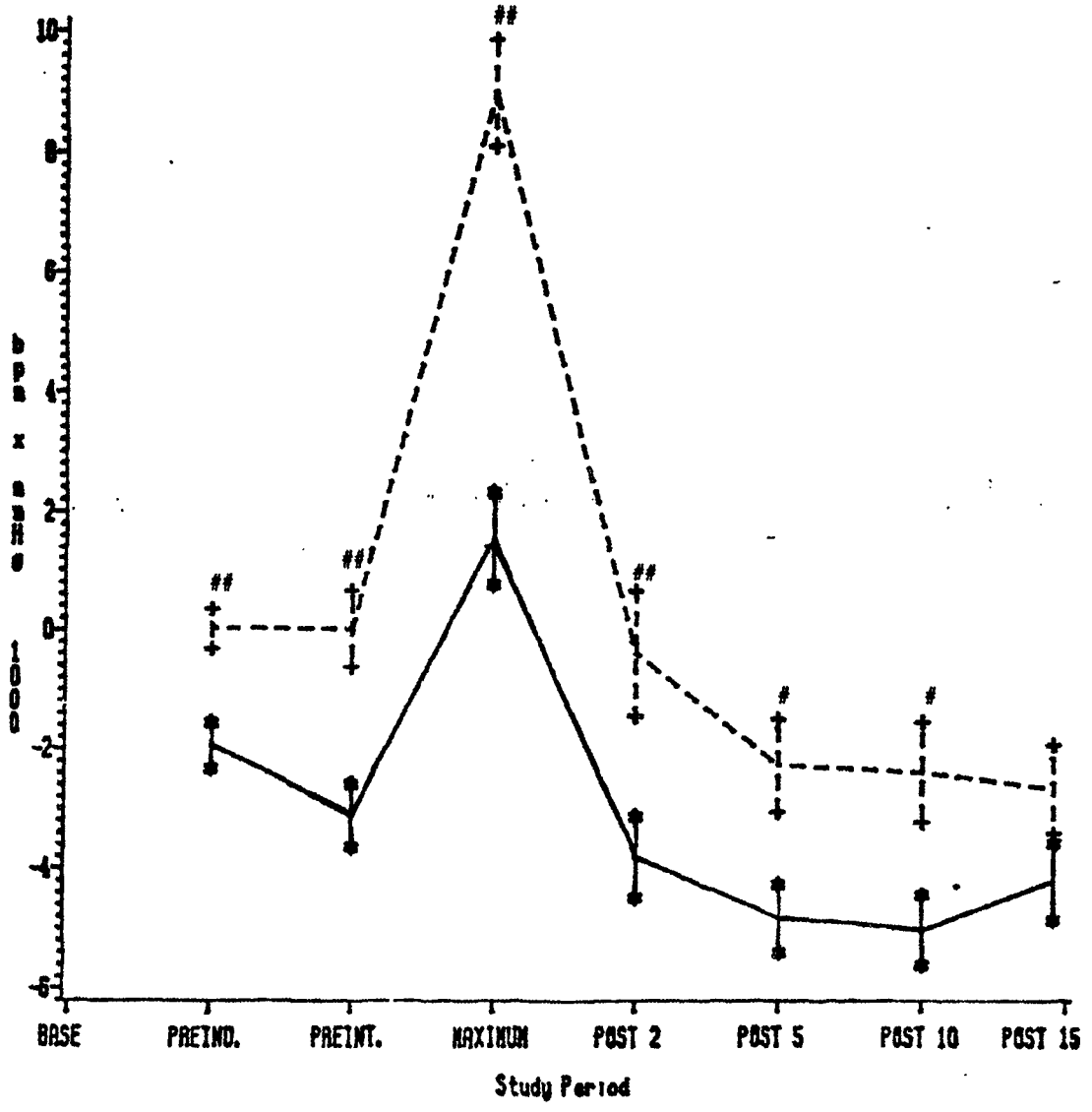
CAROTID (8052-83-49)
Diastolic Blood Pressure for All Patients



Esmolol *---*---*

Placebo +---+---+

CAROTID (8052-83-49)
Rate Pressure Product Changes from Baseline for All Patients



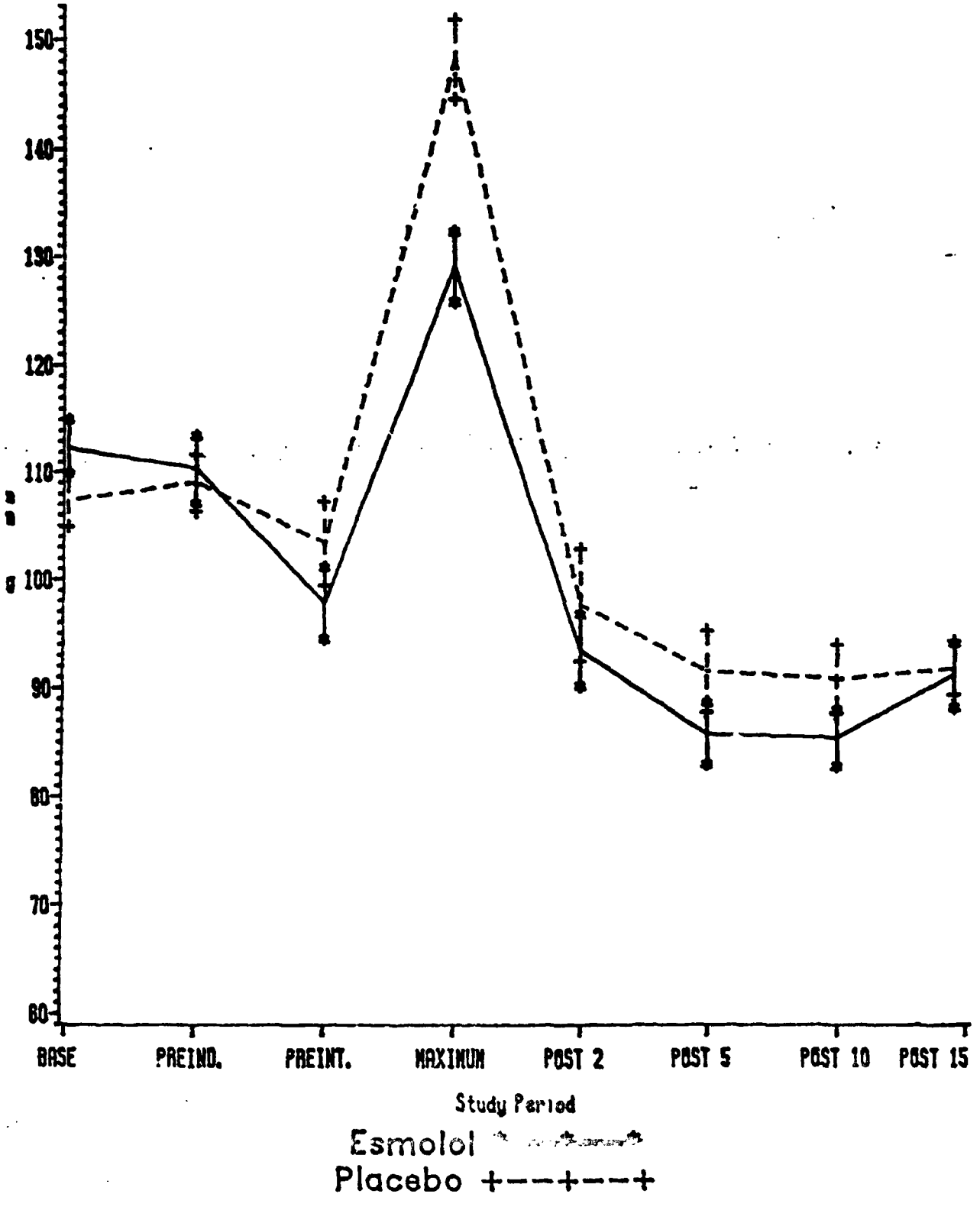
Esmolol ●——●——●

Placebo +——+——+

\# Significant difference between esmolol and placebo with respect to change from baseline ($p < 0.05$).

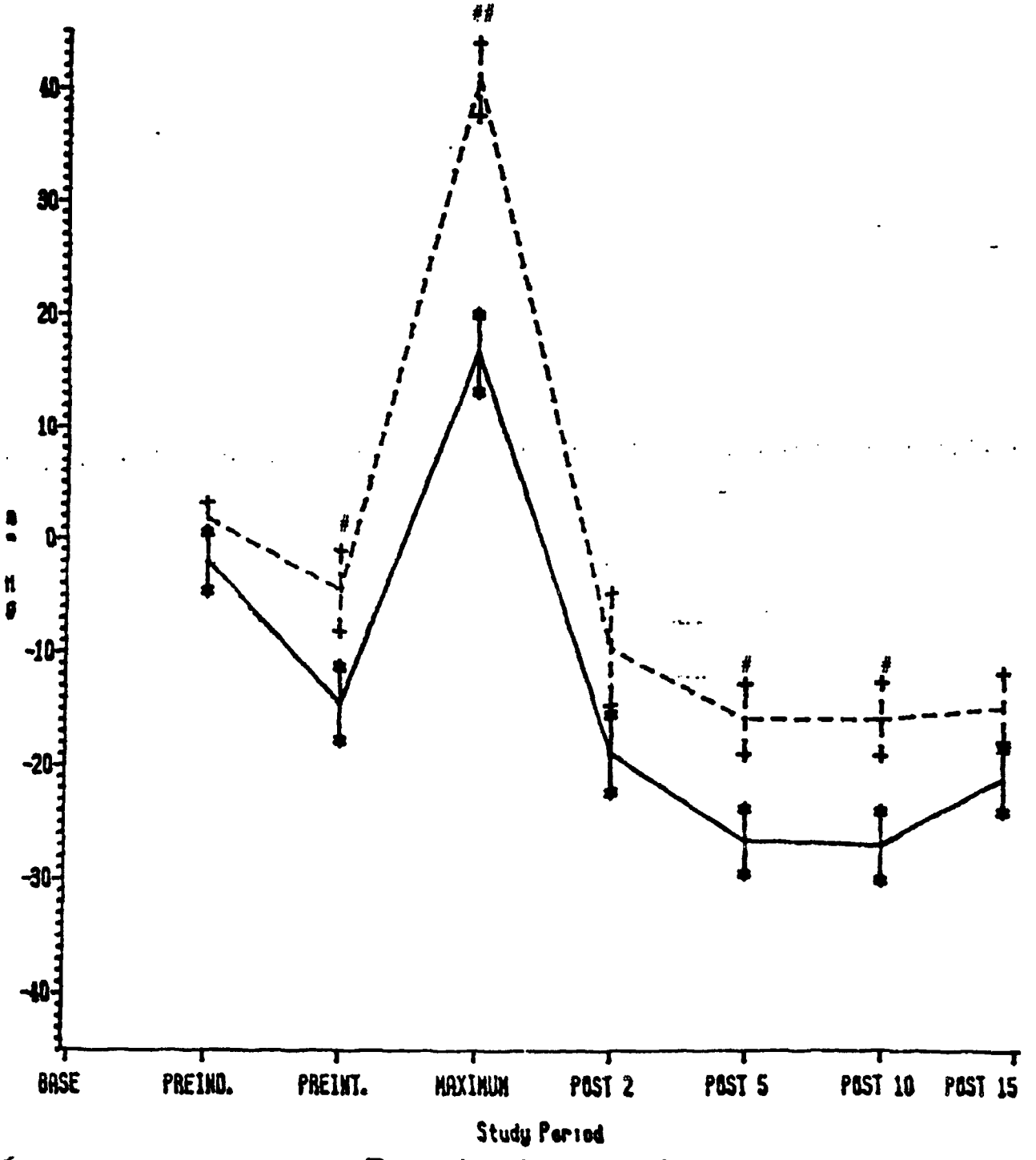
\## $p < 0.01$.

CAROTID (8052-83-49)
Mean Arterial Blood Pressure for All Patients



CAROTID (8052-83-49)

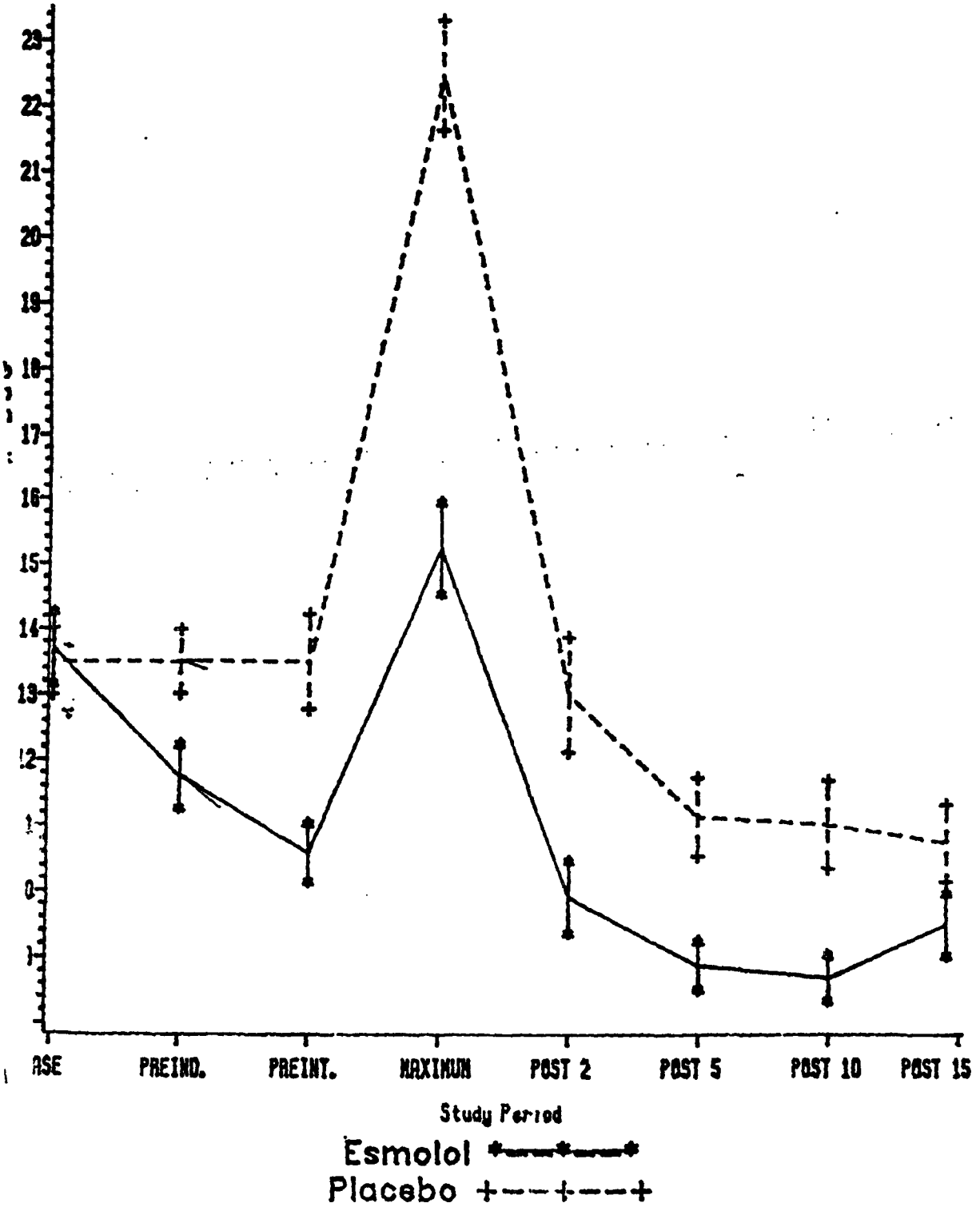
Mean Arterial Blood Pressure Changes from Baseline for All Patients



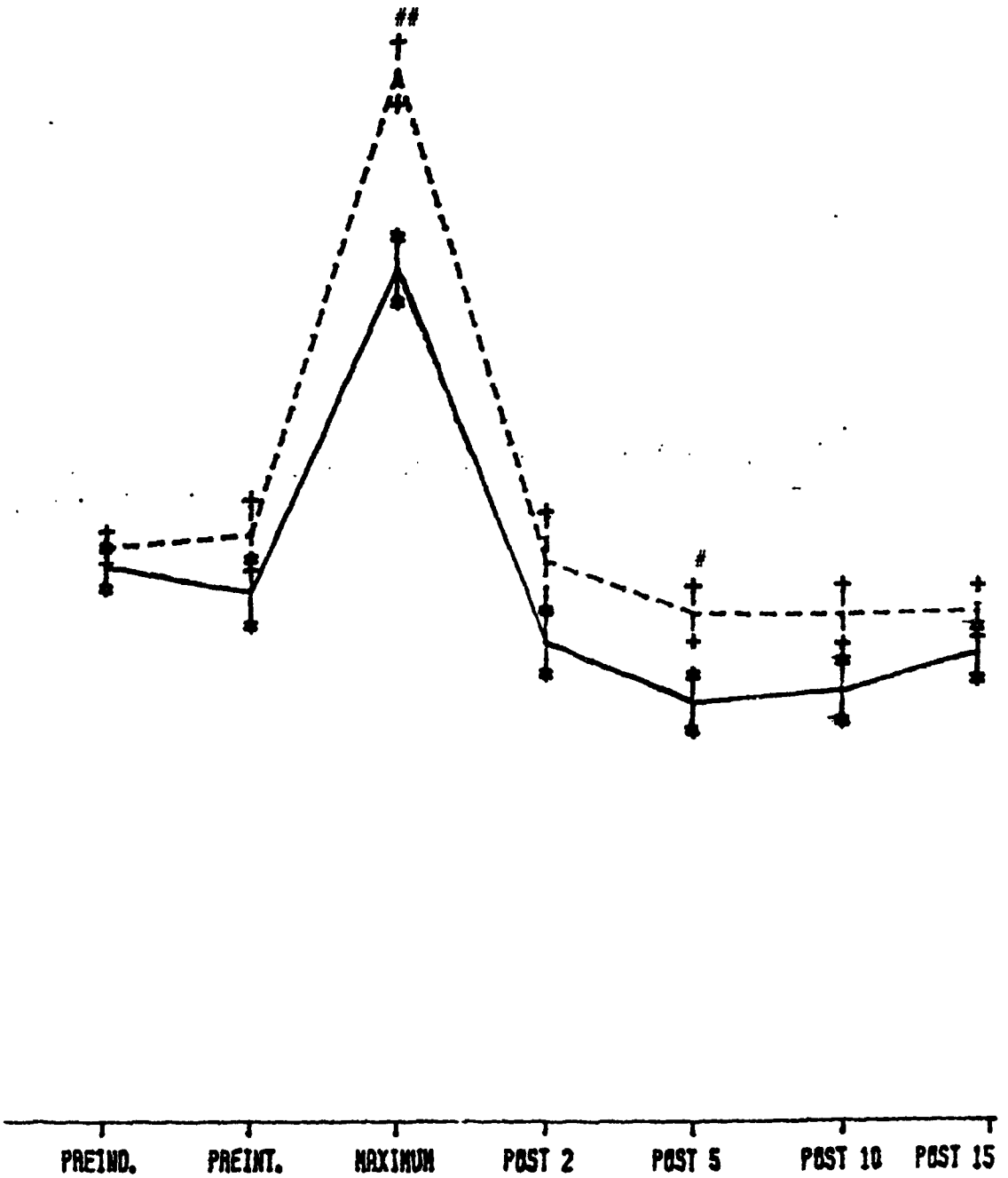
\# Significant difference between esmolol and placebo with respect to change from baseline ($p < 0.05$).

\## $p < 0.01$.

CAROTID (8052-83-49)
Rate Pressure Product for All Patients



CAROTID (8052-83-49)
iastolic Blood Pressure Changes from Baseline for All Patients



\# Significant difference between esmolol and placebo with respect to change from baseline ($p < 0.05$).

\## $p < 0.01$.

Appendix A1 Study 8052-83-27

EFFECT OF ESMOLOL VERSUS PLACEBO ON HEART RATE AND BLOOD PRESSURE DURING SPECIFIED SURGICAL STIMULI IN ANESTHETIZED CORONARY REVASCULARIZATION PATIENTS: A MULTICENTER TRIAL

Protocol #8052-83-27

Investigators and Institutions

Robert Berger, M.D.	V. A. Medical Center	Miami, FL
Colleen Henling, M.D.	University of Alabama	Birmingham, AL
Carl Hug, M.D.	Emory University Hospital	Atlanta, GA
Joel Kaplan, M.D.	Mt. Sinai Medical Center	New York, NY
Steven Tosone, M.D.	University of Kansas	Kansas City, KS

MEDICAL SUMMARY

Sponsor:

American Critical Care
1600 Waukegan Road
McGaw Park, Illinois 60085

The identity of the contents of the ampuls was printed inside of the sealed label. At the conclusion of study participation, the unopened label was attached to the patient's case report form. In the event of a serious adverse effect or other emergency requiring medical intervention, the investigator had the option of opening the sealed label to identify the study medications. If the seal on the label was broken, the investigator had to sign and date the opened label before attaching it to the case report form.

The boxes were used sequentially in the order of the patient number printed on the label. Each investigative center was assigned 40 patient numbers, starting from 100 series (e.g. Center 1: 101, 102; Center 2: 201, 202). Center 4 was never issued drug and these medications were assigned to Center 6 who started numbering patients from 601. For details of patient numbers used at each site, see Table 3. For details regarding patient numbers not used, see Table 4.

4.4 Drug Preparation

Esmolol or its placebo was diluted prior to administration, in Dextrose (5%) Injection, USP, yielding a concentration of 10 mg/mL.

4.5 Infusion Pump

Infusion rates of esmolol or its placebo were controlled by an intravenous infusion pump capable of delivering a stable and sufficient volume to infuse esmolol or its placebo predictably and as scheduled. The infusion pumps used in the study were IMED volumetric pumps (IMED Corporation, San Diego, California), Model No. 927. The infusion pumps were calibrated at the study sites before the study was initiated, and checked throughout the study period to assure proper functioning.

5. PATIENT SELECTION

Patients were selected for this study according to the following entrance criteria:

5.1 Inclusion Criteria

a. Either males or non-pregnant females (as confirmed by a negative pregnancy test or corroboration of nonchildbearing potential), 21

years of age or older.

b. Patients were those scheduled to undergo general anesthesia for elective coronary revascularization surgery. They may or may not have been on beta blocker or calcium channel blocker therapy, however, these drugs were not to be given on the morning of the study. (Only those patients belonging to the standard therapy group received their morning dose of beta or calcium channel blocker.)

c. All patients signed an informed consent form prior to study participation.

5.2 Exclusion Criteria

a. Females who were pregnant.

b. Atrial fibrillation or flutter.

c. AV conduction block greater than first degree.

d. Myocardial infarction within one month prior to the study.

e. History of congestive heart failure that precluded therapy with a beta-adrenergic blocking drug.

f. Systolic blood pressure less than 100 mm Hg or diastolic less than 50 mm Hg, or cardiogenic shock.

g. Severe renal or hepatic failure.

h. History of bronchial asthma or bronchospasm that precluded therapy with a beta-adrenergic blocking drug.

i. Clinically significant metabolic or electrolyte abnormalities.

j. History of drug allergy or idiosyncracy to beta-adrenergic blocking drugs.

k. Patients who had received the beta blocker nadolol within five days prior to the study.

l. Patients (except for those patients who were part of the standard therapy group) who received a dose of beta blocker or calcium channel blocker the morning of surgery.

m. Patients who had received digoxin. Other oral or intravenous cardiovascular medications (e.g., quinidine, procainamide) could be continued provided their doses remained fixed throughout the study period.

n. Patients who had received adrenergic-augmenting drugs (including monoamine oxidase inhibitors) or adrenergic-depleting drugs (i.e. guanethidine or reserpine) during the six week period prior to entry into the study. The original protocol also excluded patients who received centrally acting antihypertensive drugs during this same time period; however Amendment #2, dated August 21, 1984, changed this to allow study patients to receive antihypertensive agents such as clonidine and methyldopa.

o. Experimental drug administration within the previous two weeks, or proportionately longer if the drug had a long half-life.

6. **EFFICACY ASSESSMENT**

Efficacy in this study was defined as the attenuation of increases in heart rate, blood pressure and rate-pressure product by esmolol in comparison to placebo during the following events: intubation, chest skin incision, sternotomy, and aortic dissection. In addition, the frequency and amount of supplemental anesthesia and additional therapeutic agents required to control heart rate and blood pressure in the esmolol and placebo-treated groups were compared.

Primary efficacy analysis included only the patients randomized to the esmolol or placebo groups. The primary purpose of analysis was to compare the two treatment groups with respect to the maximum changes observed in heart rate, systolic, diastolic and mean arterial blood pressures, and rate-pressure product from the baseline period to the time periods surrounding intubation, chest skin incision, sternotomy, and aortic dissection. Also included in the primary analysis was the comparison of frequency and amount of supplemental anesthesia and the use of nitroglycerin, nitroprusside and propranolol to control heart rate and blood pressure between the esmolol and placebo treatment groups.

Secondary purposes of analysis included a comparison of changes in the hemodynamic variables between the randomized patients and the

mean arterial blood pressures could not be statistically tested at skin incision and sternotomy (Table 11 and 12).

10.2.2 Analysis of Maximum Changes in Hemodynamic Variables from Baseline for Individual Centers

Tables 14 through 17 provide the data for maximum changes from baseline at each surgical event for the 81 randomized "efficacy patients", by center. In Center 1, the average maximum increases of HR, SBP, MAP and RPP from baseline were significantly lower in the esmolol-treated group than in the placebo-treated group at intubation. In contrast the average maximum changes in SBP and MAP were significantly lower in the placebo-treated patients as compared to the esmolol-treated patients during skin incision and aortic dissection. No significant treatment effects were found for Center 1 during sternotomy.

Centers 2 and 3 (pooled) showed significantly lower average maximum changes of heart rate for the esmolol-treated patients in comparison with the placebo-treated patients at all four surgical events and for rate-pressure product during arotic dissection. No significant differences in average maximum changes of the remaining hemodynamic variables were found between the two treatment groups at the four surgical events. No significant differences for any of the five hemodynamic variables were detected between the treatment groups in either Centers 5 or 6.

The different patterns of maximum changes for the five hemodynamic variables for Center 1 compared to the other centers at events like skin incision and aortic dissection confirmed the finding of center and treatment interaction. Therefore, to assess the contribution of Center 1 on the pooled analysis, a separate analysis was conducted on Centers 2, 3, 5 and 6 without Center 1 (Tables 14 through 17). These data followed very closely with the overall pooled results. Therefore, although Center 1 showed significant differences among centers for hemodynamic variables its contribution was only minimal in determining the overall pooled treatment effect.

10.2.3 Clinically Significant Increases in Heart Rate and Systolic Blood Pressure

Adverse effects on the balance between myocardial oxygen demand versus supply in patients

Table 1

LIST OF INVESTIGATORS AND
NUMBER OF PATIENTS ENROLLED

CENTER NUMBER	INVESTIGATOR AND INSTITUTION	NUMBER OF PATIENTS ENROLLED	ENTRY DATES
1	Colleen Henling, M.D. University of Alabama, Birmingham Birmingham, Alabama	23	9/15/84- 1/23/85
2	Steven Tosone, M.D. University of Kansas Kansas City, Kansas	7	9/17/84- 1/23/85
3	Carl Hug, M.D. Emory University Hospital Atlanta, Georgia	30	8/28/84- 12/11/84
4*	John Tinker, M.D. University of Iowa Hospitals and Clinics Iowa City, Iowa	0	-
5	Robert Berger, M.D.** Veterans Administration Medical Center Miami, Florida	22	7/30/84- 12/11/84
6	Joel Kaplan, M.D. Mount Sinai Medical Center New York, New York	20	10/4/84- 2/20/85

* Center 4 withdrew from participation in the study prior to submitting for Institutional Review Board approval.

** Principal Investigator was changed from Robert Berger, M.D. to Everard deLisser, M.D. on December 1, 1984.

Table 2

SCHEDULE OF OBSERVATIONS

time (minutes)	Prestudy Evaluation Period	Preinfusion Baseline Period	Esmolol/Placebo Infusion Period																						CPB◆	
			induction*					intubation									skin incision** sternotomy aortic dissection									
		-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	-1	0	1	2	3	4	5	-1	0
Informed Consent	X																									
Medical History	X																									
Physical Examination	X																									
12-lead ECG	X																									
Cardiac Cath Data (if available)	X																									
Rest and Exercise Stress Test Data (if available)	X																									
Heart Rate (II/V_5***)		X	X	X					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood Pressure		X	X	X					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

◆ If time lapse between induction and intubation was greater than three minutes, heart rate and blood pressure continued to be obtained at one-minute intervals.

◆◆ Heart rate and blood pressure was continuously recorded at one-minute intervals between skin incision and sternotomy.

◆◆◆ Electrocardiographic leads II or V_5 were monitored continuously for ST-segment changes and occurrence of arrhythmias during the entire study period.

◆ CPB = cardiopulmonary bypass

Table 5

DERIVATION OF "ALL PATIENTS", "EFFICACY PATIENTS", AND RANDOMIZED "EFFICACY PATIENTS" IN THE STUDY

"All Patients"	102	43 Esmolol 41 Placebo 18 Standard Therapy
Excluded from Efficacy Analysis	6	(#201, 509, 511) Placebo (#503C, 505C, 506C) Standard Therapy
"Efficacy Patients"	96	43 Esmolol 38 Placebo 15 Standard Therapy
Randomized "Efficacy Patients"	81	43 Esmolol 38 Placebo

TABLE 8: SUMMARY OF "ALL PATIENTS" AT EACH PHASE OF THE STUDY

	Randomized						Nonrandomized		
	Esmolol (Number of Patients)			Placebo (Number of Patients)			Standard Therapy (Number of Patients)		
	Ineligible	Eligible	Total Exclusion	Ineligible	Eligible	Total Exclusion	Ineligible	Eligible	Total Exclusion
Prestudy Evaluation		43			41			18	
Baseline		43			38	1[a] 2[b]		15	3[b]
Induction	2[c]	41		2[c] 1[g]	35		2[b]	13	
Intubation	3[c] 2[d]	38		6[c] 2[d] 1[g] 1[h]	28		4[c]	11	
Chest Skin Incision	7[c]	36		12[c] 1[f]	25		4[c]	11	
Sternotomy	8[c]	35		12[c] 2[f] 1[g]	23		4[c] 1[g]	10	
Aortic Dissection	9[c] 1[f]	33		12[c] 1[e] 2[f] 1[j]	22		8[c]	7	
Prebypass	8[c] 1[f] 10[i]	24		11[c] 2[f] 7[i] 1[j]	17		5[c]	10	

[a] Propranolol administered 2 hours before induction (Patient #201)
[b] No baseline data available due to administration of sodium nitroprusside (SNP) (Patients #509 and 511) or intravenous nitroglycerin (IV NTG) (Patients #503C, 505C, and 506C) during baseline period.
[c] Medical intervention (Patients #101, 102, 103, 104, 105, 106, 107, 109, 111, 112, 114, 115, 116, 117, 118, 119, 122, 202, 203, 205, 206, 201C, 307, 309, 315, 316, 320, 301C, 303C, 304C, 307C, 308C, 309C, 502, 504, 506, 510, 513, 515, 516, 502C and 507C).
[d] Multiple intubation (Patients #101, 601, 612, and 614).
[e] Allotment of study drug exhausted (Patient #513).
[f] Patient withdrawn - ADR (Patients #614, 616, and 620).
[g] Anesthetic administration at > 2 MAC (Patients #501, 502 and 501C).
[h] Topical anesthetic (Patient #501).
[i] Center 6 did not collect prebypass observations.
[j] Patient withdrawn - investigator's decision (Patient #117).

Table 7

LIST OF PATIENTS EXCLUDED FROM EFFICACY ANALYSIS

Patient Number	Treatment Group	Demographic Data			Baseline Average Data		Reason For Exclusion From Efficacy Analysis
		Sex	Age (yrs)	Weight (kg)	Heart Rate (bpm)	Blood Pressure (mm Hg)	
201	Placebo	F	60	60.2	60	148/64	Propranolol administered 2 hours prior to induction
509	Placebo	M	60	75	46	161/68	Sodium Nitroprusside Infused Through Baseline Period
511	Placebo	M	63	65	61	176/70	Sodium Nitroprusside Infused Through Baseline Period
503C	Control	M	74	73	64	131/53	Intravenous Nitroglycerin Infused Through Baseline Period
505C	Control	M	50	95	77	129/65	Intravenous Nitroglycerin Infused Through Baseline Period
506C	Control	M	52	75	45	124/65	Intravenous Nitroglycerin Infused Through Baseline Period

TABLE 9

SUMMARY OF PRESTUDY CLINICAL DATA BY CENTER,
EFFICACY ELIGIBLE, EFFICACY INELIGIBLE AND "ALL PATIENTS"

Variable	Group	Mean	S.D.	Min	Max	N
Heart Rate (bpm)	Center 1	65.7	11.2	48.0	83.0	23
	Centers 2 & 3	65.9	11.9	48.0	104.0	37
	Center 5	61.1	7.9	50.0	78.0	19[c]
	Center 6	67.7	12.4	50.0	90.0	20
	Eligible[a]	65.4	11.3	48.0	104.0	94[c]
	Ineligible[b]	63.4	9.8	50.0	72.0	5[c]
	All Patients	**65.3**	**11.2**	**48.0**	**104.0**	**99[c]**
SBP (mm Hg)*	Center 1	122.7	14.2	110.0	164.0	23
	Centers 2 & 3	122.7	15.6	100.0	178.0	37
	Center 5	125.6	12.6	100.0	150.0	22
	Center 6	115.5	11.9	100.0	140.0	20
	Eligible[a]	121.1	14.0	100.0	178.0	96
	Ineligible[b]	135.0	10.5	120.0	150.0	6
	All Patients	121.9	14.2	100.0	178.0	102
DBP (mm Hg)	Center 1	76.3	14.0	50.0	118.0	23
	Centers 2 & 3	77.6	9.7	60.0	100.0	37
	Center 5	72.8	9.3	50.0	92.0	22
	Center 6	70.6	7.5	60.0	80.0	20
	Eligible[a]	**75.0**	**10.7**	**50.0**	**118.0**	**96**
	Ineligible[b]	**73.3**	**10.3**	**60.0**	**90.0**	**6**
	All Patients	74.9	10.7	50.0	118.0	102

[a] Patients eligible for efficacy analysis.
[b] Patients ineligible for efficacy analysis.
[c] Heart rate measurement was not obtained for Patients #508, 510, and 511.
* Mean values of systolic blood pressure for eligible and ineligible patients were significantly different ($p < 0.05$).

Table 10

Summary of Demographic and Prestudy Clinical Data,
by Treatment Group for "All Patients"

Variable	Treatment*	Mean ± S.D.	Min	Max	N
Age (years)	All Esmolol	59.0 9.8	36.0	77.0	43
	All Placebo	57.0 8.9	38.0	76.0	40[a]
	All Standard	57.7 9.4	38.0	74.0	17[a]
Height (cm)	All Esmolol	172.7 10.2	149.0	195.0	43
	All Placebo	173.1 8.4	152.0	188.0	41
	All Standard	173.4 9.1	150.0	190.0	18
Weight (kg)	All Esmolol	82.6 13.3	46.0	112.0	43
	All Placebo	83.0 13.2	60.2	117.2	41
	All Standard	82.1 16.4	43.0	120.0	18
BSA (m2)	All Esmolol	2.0 0.2	1.4	2.4	43
	All Placebo	2.0 0.2	1.6	2.4	41
	All Standard	2.0 0.2	1.3	2.5	18
Temperature (°C)	All Esmolol	36.7 0.4	36.0	37.8	43
	All Placebo	36.9 0.5	36.0	39.0	41
	All Standard	36.6 0.4	36.0	37.0	18
Heart Rate (bpm)	All Esmolol	65.1 12.0	48.0	104.0	42[b]
	All Placebo	67.7 10.8	50.0	88.8	39[b]
	All Standard	60.7 9.3	50.0	83.0	18
SBP (mm Hg)	All Esmolol	120.7 14.2	100.0	178.0	43
	All Placebo	122.9 15.5	100.0	164.0	41
	All Standard	122.6 11.0	100.0	140.0	18
DBP (mm Hg)	All Esmolol	73.4 9.5	50.0	95.0	43
	All Placebo	76.2 12.9	60.0	118.0	41
	All Standard	75.6 7.2	60.0	84.0	18

[a] Birthdate was not obtained for Patients #307 and 304C.
[b] Heart rate was not obtained for Patients #508, 510, and 511.
* For all variables, mean values were not significantly different among treatment groups ($p>0.05$).

Table 11

HEART RATE AND SYSTOLIC BLOOD PRESSURE WITH CHANGES FROM BASELINE, BY PERIOD, FOR "EFFICACY PATIENTS" TREATED WITH ESMOLOL OR PLACEBO

		BASELINE			PREINTUBATION			INTUBATION			SKIN INCISION[a]			STERNOTOMY[a]			AORTIC DISSECTION			POSTINF./PRE-BYPASS		
	Treatment Group	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N
HR (bpm)	Esmolol	66.0	1.6	43	68.3	1.3	41	73.7	1.7	38	64.9	1.7	36	64.2	1.5	35	64.2	1.9	33	64.2	2.2	24
	Placebo	66.9	2.2	38	79.2	2.4	35	85.5	3.1	28	68.8	2.8	25	74.6	3.2	23	77.2	2.9	23	76.1	2.2	17
HR Change	Esmolol				1.8	1.7	41	7.4	2.1	38	-0.8	2.1	36	-0.7	1.9	35	-1.1	2.4	33	-3.4	2.3	24
	Placebo				12.0#	2.1	35	18.6	2.7	28	1.9	2.4	25	6.4	3.3	23	8.2	3.1	23	8.2#	2.4	17
Comparison of Change[b]					P > E			P > E			N.T.			N.T.			P > E			P > E		
SBP (mmHg)	Esmolol	141.8	3.2	43	124.4	3.5	41	140.7	4.0	38	129.3	3.9	36	133.3	3.9	35	123.7	3.3	33	109.0	3.0	24
	Placebo	140.5	3.6	38	130.6	3.4	35	151.0	5.3	28	131.9	4.0	25	137.9	4.8	23	127.1	4.4	23	111.8	4.0	17
SBP Change	Esmolol				-17.6#	3.0	41	0.8	3.3	38	-8.1	3.1	36	-3.7	3.4	35	-12.7	3.7	33	-32.7#	4.9	24
	Placebo				-9.4#	2.4	35	11.8	4.8	28	-6.8	4.1	25	0.6	5.0	23	-9.7	5.6	23	-27.0#	6.2	17
Comparison of Change[b]					N.S.			N.S.			N.T.			N.T.			N.S.			N.S.		

a Significant center by treatment interaction was detected for the change of all variables at the skin incision and sternotomy periods ($p < 0.05$).

\# Indicates significant change from baseline ($p < 0.05$). Maximum change from baseline was not tested for significance at intubation, skin incision, sternotomy, and aortic dissection.

b N.S. Indicates no significant difference among treatment groups ($p \geq 0.05$).
E = Esmolol, P = Placebo
N.T. Not tested due to center by treatment interaction.

Table 13

SUMMARY OF BASELINE OBSERVATIONS FOR "EFFICACY PATIENTS", BY CENTER AND TREATMENT GROUP

		HR bpm		SBP mm Hg		DBP mm Hg		MAP mm Hg		RPP		
Center[a]	Treatment Group	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	N
1	Esmolol	67.5	2.2	150.0	6.9	80.3	3.6	90.2	4.4	10.2	0.7	12
	Placebo	70.7	3.7	150.7	6.9	66.5	3.2	94.5	4.2	10.7	0.8	11
	Pooled	69.0	2.1	150.3	4.8	63.3	2.5	92.3	3.0	10.4	0.5	23
2 & 3	Esmolol	70.6	3.6	140.5	5.9	87.7	2.7	92.0	3.3	10.0	0.7	13
	Placebo	71.3	4.0	139.4	6.0	68.8	4.4	92.4	4.8	10.1	1.0	12
	Pooled	70.9	2.8	140.0	4.1	68.3	2.5	92.2	2.8	10.0	0.6	25
5	Esmolol	58.7	2.8	139.0	6.9	65.1	3.8	89.8	4.4	8.2	0.7	7
	Placebo	63.6	4.9	136.3	11.6	62.8	3.3	87.3	5.3	8.5	0.5	6
	Pooled	61.0	2.7	137.8	6.2	64.1	2.5	88.6	3.3	8.3	0.4	13
6	Esmolol	63.7	3.2	138.1	5.5	65.2	2.1	88.8	2.8	8.7	0.7	11
	Placebo	58.5	4.0	132.4	5.4	64.5	1.5	87.2	2.4	7.9	0.8	9
	Pooled	61.4	2.5	134.4	3.8	64.9	1.3	88.1	1.8	8.3	0.5	20
Pooled (2&3,5,6)	Esmolol	65.5	2.1	138.6	3.4	66.3	1.6	90.4	1.9	9.1	0.4	31
	Placebo	65.3	2.6	136.4	4.0	66.1	2.1	89.5	2.5	9.0	0.5	27
Comparison[b]		N.S.		N.S.		N.S.		N.S.		N.S.		
Pooled (All)	Esmolol	66.0	1.6	141.8	3.2	84.6	1.5	90.3	1.8	9.4	0.4	43
	Placebo	66.9	2.2	140.5	3.6	66.2	1.8	91.0	2.2	9.5	0.5	38
Comparison[c]		N.S.		N.S.		N.S.		N.S.		N.S.		

a Significant difference among centers for HR and RPP (Centers 1, 2&3 > 5 and 6).
b Comparison among treatment groups for pooled data (Centers 2&3, 5, and 6).
c Comparison among treatment groups for pooled data (all centers).
N.S. Indicates no significant difference among treatment groups ($p \geq 0.05$).

Note: No significant difference among treatment groups was detected by each center.

Table 14

MAXIMUM CHANGES FROM BASELINE DURING INTUBATION FOR "EFFICACY PATIENTS", BY CENTER AND TREATMENT

		HR Change		SBP Change		DBP Change		MAP Change		RPP Change		
Center[a]	Treatment Group	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	N
1	Esmolol	10.0	3.1	8.6	3.3	17.7	2.5	14.6	2.5	1.9	0.5	11
	Placebo	23.5	5.6	33.8	8.8	25.5	4.6	28.3	6.0	6.5	1.1	9
	Pooled	16.1	3.3	20.0	5.1	21.2	2.6	20.8	3.3	4.0	0.8	20
Comparison[b]		P > E		P > E		N.S.		P > E		P > E		
2 & 3	Esmolol	3.6	3.7	1.1	6.1	9.0	3.3	5.8	3.9	0.6	0.9	12
	Placebo	19.0	4.0	3.1	5.6	7.4	3.0	5.9	3.7	2.5	0.8	10
	Pooled	10.6	3.1	2.0	4.1	8.3	2.2	5.8	2.61	.4	0.6	22
Comparison[b]		P > E		N.S.		N.S.		N.S.		N.S.		
5	Esmolol	13.7	3.4	-1.1	13.3	0.1	5.0	-0.5	7.6	1.7	0.8	5
	Placebo	9.2	7.8	-3.7	9.3	9.7	12.7	5.1	11.7	0.6	1.6	2
	Pooled	12.4	3.0	-1.9	9.4	2.9	4.8	1.1	5.91	.4	0.7	7
Comparison[b]		N.S.		N.S.		N.S.		N.S.		N.S.		
8	Esmolol	5.9	5.3	-7.0	6.8	0.8	2.9	-2.0	4.1	0.2	1.1	10
	Placebo	14.6	5.5	0.6	4.4	5.1	2.4	2.8	2.7	1.7	1.0	7
	Pooled	9.5	3.9	-3.9	4.4	2.9	2.0	-0.0	2.7	0.9	0.8	17
Comparison[b]		N.S.		N.S.		N.S.		N.S.		N.S.		

(Continued)

Table 14 (Continued)

MAXIMUM CHANGES FROM BASELINE DURING INTUBATION FOR "EFFICACY PATIENTS", BY CENTER AND TREATMENT

		HR Change		SBP Change		DBP Change		MAP Change		RPP Change		
Center[a]	Treatment Group	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	N
Pooled (2&3,5,6)	Esmolol	6.4	2.7	-2.3	4.3	4.3	2.1	1.7	2.7	0.7	0.6	27
	Placebo	16.3	3.0	1.5	3.4	6.8	2.0	4.7	2.3	2.0	0.6	19
Comparison[c]		N.S.		N.S.		N.S.		N.S.		N.S.		
Pooled (All)	Esmolol	7.4	2.1	0.8	3.3	8.2	1.9	5.5	2.2	1.0	0.4	38
	Placebo	18.6	2.7	11.8	4.6	12.8	2.6	12.3	3.2	3.4	0.7	28
Comparison[d]		P > E		N.S.		N.S.		N.S.		P > E		

a Significant difference among centers for SBP, DBP, MAP, and RPP changes (Centers 1 > 2&3, 5, 6).
b Comparison among treatment groups for each center.
c Comparison among treatment groups for pooled data (Centers 2&3, 5, and 6).
d Comparison among treatment groups for pooled data (all centers).
N.S. Indicates no significant difference among treatment groups ($p \geq 0.05$).
E = Esmolol, P = Placebo

Table 15

MAXIMUM CHANGES FROM BASELINE DURING SKIN INCISION FOR "EFFICACY PATIENTS", BY CENTER AND TREATMENT

		HR Change		SBP Change		DBP Change		MAP Change		RPP Change		
Center[a]	Treatment Group	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	N
1	Esmolol	1.2	5.8	3.2	5.3	22.0	5.8	15.7	5.3	0.3	1.0	7
	Placebo	-9.6	2.8	-31.0	11.3	-1.0	5.7	-11.0	7.4	-3.9	1.5	3
	Pooled	-2.0	4.4	-7.1	7.0	15.1	5.5	7.7	5.8	-1.0	1.0	10
Comparison[b]		N.S.		E > P		E > P		E > P		N.S.		
2 & 3	Esmolol	-4.9	2.6	-3.8	5.0	9.2	3.2	4.6	3.4	-0.9	0.6	13
	Placebo	6.4	4.3	1.4	5.5	9.2	3.5	6.5	4.0	0.7	0.7	10
	Pooled	-0.0	2.6	-1.4	3.7	9.2	2.3	5.4	2.5	-0.2	0.5	23
Comparison[b]		P > E		N.S.		N.S.		N.S.		N.S.		
5	Esmolol	9.5	4.3	-9.5	6.9	3.3	3.0	-1.0	4.2	0.5	0.6	5
	Placebo	-0.2	2.1	-6.8	11.6	11.6	5.7	5.4	7.4	-0.2	0.8	4
	Pooled	5.2	2.9	8.3	6.0	7.0	3.1	1.9	3.9	0.2	0.5	9
Comparison[b]		N.S.		N.S.		N.S.		N.S.		N.S.		
6	Esmolol	-1.8	3.9	-19.9	5.8	-2.6	2.8	-8.4	3.6	-1.5	0.8	11
	Placebo	1.5	4.8	-7.9	6.8	2.0	3.1	-1.4	4.2	-0.5	0.9	8
	Pooled	-0.4	2.9	-14.8	4.5	-0.6	2.0	-5.5	2.8	-1.1	0.8	19
Comparison[b]		N.S.		N.S.		N.S.		N.S.		N.S.		

(Continued)

Table 15 (Continued)

MAXIMUM CHANGES FROM BASELINE DURING SKIN INCISION FOR "EFFICACY PATIENTS", BY CENTER AND TREATMENT

		HR Change		SBP Change		DBP Change		MAP Change		RPP Change		
Center[a]	Treatment Group	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	N
Pooled (2&3,5,6)	Esmolol	-1.3	2.2	-10.8	3.5	3.7	2.0	-1.3	2.4	-0.9	0.4	29
	Placebo	3.4	2.6	-3.5	4.0	7.0	2.3	3.4	2.7	0.1	0.5	22
Comparison[c]		N.S.		N.S.		N.S.		N.S.		N.S.		
Pooled (All)	Esmolol	-0.8	2.1	-8.1	3.1	7.3	2.3	2.0	2.4	-0.7	0.4	36
	Placebo	1.9	2.4	-6.8	4.1	6.1	2.1	1.7	2.7	-0.4	0.5	25
Comparison[d]		N.T.		N.T.		N.T.		N.T.		N.T.		

a Significant center and treatment interaction; no test was performed for center effect.
b Comparison among treatment groups for each center.
c Comparison among treatment groups for pooled data (Centers 2&3, 5, and 6).
d Comparison among treatment groups for pooled data (all centers).
N.S. Indicates no significant difference among treatment groups ($p \geq 0.05$).
E = Esmolol, P = Placebo
N.T. Not tested due to significant center and treatment interaction.

Table 18

MAXIMUM CHANGES FROM BASELINE DURING STERNOTOMY FOR "EFFICACY PATIENTS", BY CENTER AND TREATMENT

		HR Change		SBP Change		DBP Change		MAP Change		RPP Change		
Center[a]	Treatment Group	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	N
1	Esmolol	-1.3	5.5	-2.7	5.7	18.5	5.4	11.0	5.2	-0.6	0.9	7
	Placebo	-11.6	6.9	-33.0	18.5	0.3	8.6	-10.8	11.9	-4.2	2.3	3
	Pooled	-4.3	4.4	-11.8	7.7	13.1	5.1	4.5	5.7	-1.7	1.0	10
Comparison[b]		N.S.		N.S.		N.S.		N.S.		N.S.		
2 & 3	Esmolol	-2.7	2.7	3.3	5.2	11.8	3.0	8.1	3.4	-0.3	0.6	12
	Placebo	13.9	4.6	13.7	5.7	11.7	3.8	12.1	4.2	2.6	0.8	10
	Pooled	4.8	3.1	8.0	3.9	11.7	2.3	10.0	2.6	1.0	0.5	22
Comparison[b]		P > E		N.S.		N.S.		N.S.		P > E		
5	Esmolol	8.3	3.4	8.1	8.0	10.7	2.5	9.7	4.2	1.2	0.3	5
	Placebo	4.2	5.7	9.3	10.3	13.4	6.5	11.6	6.8	1.4	1.3	3
	Pooled	6.8	2.8	8.5	5.9	11.8	2.7	10.4	3.4	1.3	0.5	8
Comparison[b]		N.S.		N.S.		N.S.		N.S.		N.S.		
6	Esmolol	-2.3	3.7	-17.3	6.0	-0.9	2.9	-6.8	3.9	-1.4	0.8	11
	Placebo	4.4	5.8	-7.6	5.4	2.7	2.0	-0.8	3.0	-0.1	1.1	7
	Pooled	0.3	3.2	-13.5	4.3	0.5	2.0	-4.5	2.7	-0.9	0.6	18
Comparison[b]		N.S.		N.S.		N.S.		N.S.		N.S.		

(Continued)

Table 16 (Continued)

MAXIMUM CHANGES FROM BASELINE DURING STERNOTOMY FOR "EFFICACY PATIENTS", BY CENTER AND TREATMENT

		HR Change		SBP Change		DBP Change		MAP Change		RPP Change		
Center[A]	Treatment Group	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	N
Pooled (2&3,5,6)	Esmolol	-0.6	2.0	-3.9	4.0	6.6	2.1	2.5	2.6	-0.5	0.4	28
	Placebo	9.1	3.2	-5.6	4.2	8.8	2.4	7.5	2.8	1.4	0.6	20
Comparison[C]		N.S.		N.S.		N.S.		N.S.		N.S.		
Pooled (All)	Esmolol	-0.7	1.9	-3.7	3.4	9.0	2.1	4.2	2.4	-0.5	0.4	35
	Placebo	6.4	3.3	0.6	5.0	7.7	2.3	5.1	3.1	0.7	0.7	23
Comparison[D]		N.T.		N.T.		N.T.		N.T.		N.T.		

a Significant center and treatment interaction; no test was performed for center effect.
b Comparison among treatment groups for each center.
c Comparison among treatment groups for pooled data (Centers 2&3, 5, and 6).
d Comparison among treatment groups for pooled data (all centers.
N.S. Indicates no significant difference among treatment groups ($p \geq 0.05$).
E = Esmolol, P = Placebo
N.T. Not tested due to significant center and treatment interaction.

Table 17

MAXIMUM CHANGES FROM BASELINE DURING AORTIC DISSECTION FOR "EFFICACY PATIENTS, BY CENTER AND TREATMENT

		HR Change		SBP Change		DBP Change		MAP Change		RPP Change		
Center[a]	Treatment Group	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	N
1	Esmolol	-1.6	7.5	-7.9	4.8	15.0	5.7	7.3	4.9	-1.1	1.1	8
	Placebo	1.7	7.1	-29.4	9.5	-0.1	3.0	-10.3	4.7	-2.3	2.0	5
	Pooled	-0.3	5.2	-16.2	5.3	9.2	4.1	0.6	4.2	-1.6	1.0	13
Comparison[b]		N.S.		E > P		N.S.		E > P		N.S.		
2 & 3	Esmolol	-3.0	3.1	-2.0	6.1	6.2	2.8	3.3	3.8	-0.6	0.7	10
	Placebo	14.7	4.8	4.6	12.4	7.2	6.6	5.9	8.3	2.0	1.5	8
	Pooled	4.8	3.4	0.9	6.3	6.6	3.2	4.5	4.1	0.5	0.8	18
Comparison[b]		P > E		N.S.		N.S.		N.S.		N.S.		
5	Esmolol	8.9	4.4	-9.9	6.2	8.3	9.7	1.4	7.4	0.1	0.5	5
	Placebo	15.0	6.9	0.2	0.5	2.3	1.9	1.2	1.6	1.5	0.8	3
	Pooled	11.2	3.7	-6.1	4.2	6.1	5.9	1.3	4.5	0.6	0.5	8
Comparison[b]		N.S.		N.S.		N.S.		N.S.		N.S.		
6	Esmolol	-4.0	3.7	-28.6	7.4	-7.3	3.4	-14.5	4.6	-2.3	0.8	10
	Placebo	2.5	5.4	-16.3	5.4	-3.3	1.9	-7.8	2.9	-1.0	0.9	7
	Pooled	-1.3	3.1	-23.5	5.0	-5.7	2.2	-11.7	3.0	-1.8	0.6	17
Comparison[b]		N.S.		N.S.		N.S.		N.S.		N.S.		

(Continued)

Table 17 (Continued).

MAXIMUM CHANGES FRO BASELINE DURING AORTIC DISSECTION FOR "EFFICACY PATIENTS", BY CENTER AND TREATMENT

		HR Change		SBP Change		DBP Change		MAP Change		RPP Change		
Center[a]	Treatment Group	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	N
Pooled (2&3,5,6)	Esmolol	-1.0	2.3	-14.2	4.6	1.2	2.9	-4.2	6.2	-1.2	0.5	25
	Placebo	10.0	3.4	-4.3	6.1	2.3	3.1	-0.2	4.0	0.8	0.8	18
Comparison[c]		P > E		N.S.		N.S.		N.S.		P > E		
Pooled (All)	Esmolol	-1.1	2.4	-12.7	3.7	4.5	2.7	-1.4	2.8	-1.1	0.4	33
	Placebo	8.2	3.1	-9.7	5.6	1.8	2.5	-2.4	3.4	0.1	0.8	23
Comparison[d]		P > E		N.S.		N.S.		N.S.		N.S.		

a Significant difference among centers for SBP change (Centers 2&3 > 6);
Significant difference among centers for DBP and MAP changes (Centers 1, 2&3, 5 > 6).
b Comparison among treatment groups for each center.
c Comparison among treatment groups for pooled data (Centers 2&3, 5, and 6).
d Comparison among treatment groups for pooled data (all centers).
N.S. Indicates no significant difference among treatment groups ($p \geq 0.05$).
E = Esmolol, P = Placebo.

Table 18

NUMBER OF PATIENTS EXHIBITING CLINICALLY SIGNIFICANT HEART RATE AND SYSTOLIC BLOOD PRESSURE MAXIMA, BY SURGICAL EVENT

Center	Treatment Group	Intubation					Skin Incision[a]				Sternotomy[a]				Aortic Dissection[b]		
		HR≥100	SBP≥180	HR≥100 or SBP≥180	HR≥100 and SBP≥180	N	HR≥100	SBP≥180	HR≥100 or SBP≥180	N	HR≥100	SBP≥180	HR≥100 or SBP≥180	N	HR≥100	HR≥100 or SBP≥180	N
1	Esmolol	0	1	1	0	11	0	0	0	7	0	0	0	7	0	0	8
	Placebo	4	6	6	4	9	0	0	0	3	0	0	0	3	0	0	5
2 & 3	Esmolol	1	2	2	1	12	0	1	1	13	0	1	1	12	0	0	10
	Placebo	2	0	2	0	10	1	0	1	10	2	1	3	10	0	0	8
5	Esmolol	0	0	0	0	5	0	0	0	5	0	0	0	5	0	0	5
	Placebo	0	0	0	0	2	0	0	0	4	0	0	0	3	1	1	3
6	Esmolol	0	0	0	0	10	0	0	0	11	0	0	0	11	0	0	10
	Placebo	0	0	0	0	7	0	0	0	8	0	0	0	7	0	0	7
Pooled	Esmolol	1	3	3	1	38	0	1	1	36	0	1	1	35	0	0	33
	Placebo	6	6	8	4	28	1	0	1	25	2	1	3	23	1	1	23
Comparison[c]		P > E	N.S.	P > E	N.S.		N.S.	N.S.	N.S.		N.S.	N.S.	N.S.		N.S.	N.S.	

[a] No incidences occurred for patients with both HR ≥ 100 bpm and SBP ≥ 180 mm Hg.
[b] No incidences occurred for patients with SBP ≥ 180 mm Hg or HR ≥ 100 bpm and SBP ≥ 180 mm Hg.
[c] N.S. indicates no significant difference between the esmolol and placebo treatment groups ($p \geq 0.05$).
P = Placebo, E = Esmolol.

Table 19

NUMBER OF PATIENTS EXHIBITING CLINICALLY SIGNIFICANT RATE-PRESSURE PRODUCT MAXIMA, BY SURGICAL EVENT

Center	Treatment Group	Intubation RPP ≥ 12 YES	Intubation RPP ≥ 12 NO	Intubation N	Skin Incision RPP ≥ 12 YES	Skin Incision RPP ≥ 12 NO	Skin Incision N	Sternotomy RPP ≥ 12 YES	Sternotomy RPP ≥ 12 NO	Sternotomy N	Aortic Dissection RPP ≥ 12 YES	Aortic Dissection RPP ≥ 12 NO	Aortic Dissection N
1	Esmolol	3	8*	11	1	6	7	0	7	7	0	8	8
	Placebo	9	0	9	0	3	3	0	3	3	1	4	5
2 & 3	Esmolol	3	9*	12	2	11	13	2	10	12	1	9*	10
	Placebo	7	3	10	3	7	10	4	6	10	6	2	8
5	Esmolol	1	4	5	0	5	5	0	5	5	0	5	5
	Placebo	0	2	2	0	4	4	0	3	3	1	2	3
6	Esmolol	2	8	10	0	11	11	0	11	11	0	10	10
	Placebo	0	7	7	0	8	8	0	7	7	0	7	7
Pooled	Esmolol	9	29	38	3	33	36	2	33	35	1	32	33
	Placebo	16	12	28	3	22	25	4	19	23	8	15	23
Comparison[a]		P > E			N.S.			N.S.			P > E		

[a] Comparison between the esmolol and placebo groups for pooled data.
N.S. Indicates no significant difference between the esmolol and placebo groups ($p \geq 0.05$).
P = Placebo, E = Esmolol.

* Significant difference between the two treatment groups for the corresponding center and event ($p < 0.05$).

Table 20

NUMBER OF PATIENTS EXHIBITING RATE-PRESSURE PRODUCT IN EXCESS OF ISCHEMIC THRESHOLD, BY SURGICAL EVENT

		INTUBATION	SKIN INCISION	STERNOTOMY	AORTIC DISSECTION	
Center	Group	Incidence/ Sample Size	Incidence/ Sample Size	Incidence/ Sample Size	Incidence/ Sample Size	No. of Patients With Peak RPP
1	Esmolol	0 0	0 0	0 0	0 0	1
	Placebo	2 2	0 1	0 1	0 1	2
2 & 3	Esmolol	0 2	0 3	0 2	0 1	3
	Placebo	0 1	0 1	0 1	0 1	1
5	Esmolol	0 4	0 4	0 4	0 4	4
	Placebo	0 2	0 3	1 3	1 3	5
6	Esmolol	0 1	0 2	0 2	0 2	2
	Placebo	0 1	0 2	0 2	0 2	2
Pooled*	Esmolol	0 7	0 9	0 8	0 7	10
	Placebo	2 6	0 7	1 7	1 7	10

* No significant differences were found between the esmolol and placebo treatment groups with respect to the incidence of RPP exceeding ischemic threshold during the study ($p > 0.05$).

Table 21

SUMMARY OF [illegible]E MAC UNITS[a] OF SUPPLEMENTAL ANESTHESIA, BY CENTER AND TREATMENT GROUP

Center[b]	Treatment Group	MAC Units		
		Mean	SEM	N
1	Esmolol	36.7	6.5	12
	Placebo	53.7	9.9	11
3	Esmolol	7.7	5.2	10
	Placebo	21.5	5.2	10
5	Esmolol	16.8	7.6	7
	Placebo	35.2	13.8	8
6	Esmolol	6.5	2.5	11
	Placebo	14.3	6.0	9
Pooled[c]	Esmolol	17.7	3.4	40
	Placebo	32.0	5.0	38

[a] MAC units = (% of inspired inhalation anesthetic/MAC for the inhalation agent) x minutes of inhalation agent administration.

[b] No center by treatment interaction;

[c] Significant difference among centers ($p < 0.05$) (Centers 1 > 3, 5 and 6);
Significant difference between treatment groups for pooled data ($p < 0.05$).

Table 22

SUMMARY OF MAC UNITS FOR ENFLURANE AND HALOTHANE ADMINISTRATIONS, BY CENTER AND EVENT

Center[a]	Treatment Group	Induction			Intubation			Int/Inc[b]			Skin Incision			Sternotomy			Aortic Dissection		
		Mean	SEM	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N
1	Esmolol	0.0	0.0	12	0.1	0.1	12	8.3	2.7	12	1.8	0.5	12	3.6	0.4	12	2.7	0.4	12
	Placebo	0.2	0.2	11	1.0	0.4	11	10.4	4.3	11	1.9	0.3	11	4.0	0.5	11	3.6	0.7	10
3	Esmolol	0.0	0.0	10	0.0	0.0	10	0.0	0.0	10	0.1	0.1	10	0.6	0.6	10	0.8	0.6	10
	Placebo	0.0	0.0	10	1.0	0.6	10	0.0	0.0	10	0.8	0.6	10	1.2	0.6	10	1.5	0.5	10
5	Esmolol	2.6	1.5	7	1.1	0.4	7	2.5	1.6	7	0.4	0.3	7	1.3	0.7	7	0.5	0.3	7
	Placebo	1.0	1.6	8	2.2	1.1	8	4.3	2.9	8	1.0	0.6	8	6.2	4.0	8	1.9	0.9	8
6	Esmolol	0.0	0.0	11	0.0	0.0	11	0.9	0.7	11	0.3	0.2	11	0.4	0.3	11	0.2	0.2	10
	Placebo	1.0	1.0	9	0.5	0.3	9	3.0	2.6	8	0.6	0.4	8	1.3	0.6	7	0.5	0.3	7
Pooled[c]	Esmolol	0.5	0.3	40	0.2	0.1	40	3.2	1.0	40	0.7	0.2	40	1.6	0.3	40	1.2	0.3	39
	Placebo	0.9	0.4	38	1.2	0.3	38	4.7	1.6	37	1.2	0.2	37	3.2	0.9	36	2.0	0.4	35

[a] No significant center and treatment interaction at any study periods;
Significant differences among centers (Centers 5 > 1, 3, and 6) at induction and intubation ($p < 0.05$);
Significant differences among centers (Centers 1 > 3, 5, and 6) at int/inc[b], skin incision, and aortic dissection ($p < 0.05$);
Significant differences among centers (Centers 1 and 5 > 3 and 6) at sternotomy ($p < 0.05$);

[b] Indicates a time interval between end of intubation and pre skin incision.

[c] Significant difference between treatment groups (placebo > esmolol) for the pooled data at intubation and aortic dissection ($p<0.05$).

Table 23

NUMBER OF PATIENTS REQUIRING SUPPLEMENTAL ANESTHESIA

Treatment Group[a]	Enflurane and Halothane Usage NO	YES	N
Esmolol	15	25	40
Placebo	7	31	38

[a] No significant differences were found between the esmolol and placebo treatment groups with respect to the frequency of distribution of enflurane and halothane usage (p=0.052).

Table 24

NUMBER OF PATIENTS REQUIRING SUPPLEMENTAL ANESTHESIA BY SURGICAL EVENT

Event	Treatment Group	Enflurane and Halothane Usage		N[c]
		NO	YES	
Induction	Esmolol	37	3	40
	Placebo	33	5	38
Intubation	Esmolol	34	6[a]	40
	Placebo	23	15	38
Intubation/ Skin Incision[b]	Esmolol	24	16	40
	Placebo	23	14	37
Skin Incision	Esmolol	23	17	40
	Placebo	19	18	37
Sternotomy	Esmolol	20	20	40
	Placebo	14	22	36
Aortic Dissection	Esmolol	23	16	39
	Placebo	13	22	35

[a] Significant differences were found between the esmolol and placebo treatment groups with respect to frequency of enflurane and halothane usage during intubation ($p < 0.05$).

[b] Indicates a time interval between end of intubation and pre skin incision.

[c] Due to the missing values for some patients, the sample size did not remain constant during the study.

Table 25

NUMBER OF PATIENTS WITHIN MAXIMUM ENFLURANE DOSE RANGES BY SURGICAL EVENT

Event[a]	Treatment Group	Maximum Dose of Enflurane					N[c]
		0 to 0.5%	0.5 to 1%	1 to 1.5%	1.5 to 2%	≥ 2%	
Induction	Esmolol	33	0	0	0	0	33
	Placebo	28	1	0	0	1	30
Intubation	Esmolol	31	2	0	0	0	33
	Placebo	19	5	2	4	0	30
Intubation-Skin Incision[b]	Esmolol	21	6	6	0	0	33
	Placebo	14	2	7	5	1	29
Skin Incision	Esmolol	21	5	6	1	0	33
	Placebo	14	2	6	6	1	29
Sternotomy	Esmolol	19	4	7	3	0	33
	Placebo	11	4	7	6	0	26
Aortic Dissection	Esmolol	18	6	4	4	0	32
	Placebo	13	3	4	7	0	27

[a] Significant differences were found between the esmolol and placebo treatment groups with respect to frequency distributions of maximum enflurane doses during intubation and between end of intubation and pre skin incision ($p < 0.05$).

[b] Indicates the time interval between end of intubation and pre skin incision.

[c] Due to the missing values for some patients, the sample size did not remain constant during the study.

Table 26

NUMBER OF PATIENTS WITHIN MAXIMUM HALOTHANE DOSE RANGES BY SURGICAL EVENT

Event[a]	Treatment Group	Maximum Dose of Halothane					N
		0 to 0.5%	0.5 to 1%	1 to 1.5%	1.5 to 2%	≥ 2%	
Induction	Esmolol	5	1	1	0	0	7
	Placebo	5	1	0	2	0	8
Intubation	Esmolol	6	0	1	0	0	7
	Placebo	5	2	0	1	0	8
Intubation/ Skin Incision[b]	Esmolol	7	0	0	0	0	7
	Placebo	6	2	0	0	0	8
Skin Incision	Esmolol	7	0	0	0	0	7
	Placebo	7	1	0	0	0	8
Sternotomy	Esmolol	6	1	0	0	0	7
	Placebo	5	0	1	1	1	8
Aortic Dissection	Esmolol	7	0	0	0	0	7
	Placebo	6	1	1	0	0	8

a No tests were performed due to small sample sizes.
b Indicates the time interval between end of intubation and pre skin incision.

Table 27

NUMBER OF PATIENTS REQUIRING NITROPRUSSIDE AND NITROGLYCERIN ADMINISTRATION DURING THE STUDY PERIOD

Center	Treatment Group	Nitroprusside		Nitroglycerin		Nitroprusside or Nitroglycerin		Propranolol		
		YES	NO	YES	NO	YES	NO	YES	NO	N
1	Esmolol	5	7	3	9	7	5	0	12	12
	Placebo	7	4	0	11	7	4	1	10	11
2	Esmolol	0	3	2	1	2	1	1	2	3
	Placebo	2	1	1	2	2	1	0	3	3
3	Esmolol	1	9	0	10	1	9	0	10*	10
	Placebo	1	9	1	9	2	8	4	6	10
2 & 3 (Pooled)	Esmolol	1	12	2	11	3	10	1	12	13
	Placebo	3	10	2	11	4	9	4	9	13
5	Esmolol	0	7	3	4	3	4	0	7	7
	Placebo	3	5	4	4	5	3	0	8	8
6	Esmolol	0	11	0	11	0	11	0	11	11
	Placebo	0	9	2	7	2	7	1	8	9
Pooled	Esmolol	6	37*	8	35	13	30	1	42*	43
	Placebo	13	28	8	33	18	23	6	35	41

* Significant difference between esmolol and placebo groups ($p < 0.05$).

Table 28

NUMBER OF PATIENTS REQUIRING NITROGLYCERIN OR NITROPRUSSIDE ADMINISTRATION BY TREATMENT GROUP AND SURGICAL EVENT

Period[a]	Treatment Group	Nitroprusside		Nitroglycerin		Nitroprusside or Nitroglycerin		N
		YES	NO	YES	NO	YES	NO	
Induction	Esmolol	0	42	2	41	2	41	43
	Placebo	2	39	3	38	4	37	41
Intubation	Esmolol	0	43	2	41	2	41	43
	Placebo	3	38	4	37	6	35	41
Intubation/ Incision[b]	Esmolol	3	40[c]	2	41	5	38[d]	43
	Placebo	8	33	3	38	11	30	41
Skin Incision	Esmolol	5	38	2	41	7	36	43
	Placebo	7	33	3	37	10	30	40
Sternotomy	Esmolol	4	39	4	39	8	35	43
	Placebo	7	32	4	35	11	39	39
Aortic Dissection	Esmolol	4	37[e]	2	39	6	35[e]	41
	Placebo	10	28	4	34	13	25	38

a Data not available for one, two, and five patients at skin incision, sternotomy, and aortic dissection respectively.
b Indicates the time interval between end of intubation and pre skin incision periods.
c Patient distributions of nitroprusside at intubation/incision[b] (p=0.083).
d Patient distributions of nitroglycerin or nitroprusside at intubation/incision[b] (p=0.067).
e Patient distributions of nitroprusside at aortic dissection (p=0.051).
• Significant difference between esmolol and placebo groups ($p < 0.05$).

Table 29

HEART RATE AND SYSTOLIC BLOOD PRESSURE WITH CHANGES FROM BASELINE, BY EVENT
FOR ESMOLOL, PLACEBO AND STANDARD THERAPY "EFFICACY PATIENTS"

		BASELINE			PREINTUBATION			INTUBATION			SKIN INCISION[a]			STERNOTOMY			AORTIC DISSECTION			POSTINF./PRE-BYPASS		
	Treatment Group	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N
HR (bpm)	Esmolol	66.0	1.8	43	68.3	1.3	41	73.7	1.7	38	64.9	1.7	36	64.2	1.5	35	64.2	1.9	33	64.2	2.2	24
	Placebo	66.9	2.2	38	79.2	2.4	35	85.5	3.1	28	68.8	2.8	25	74.8	3.2	23	77.2	2.9	23	76.1	2.2	17
	Standard	62.6	2.5	15	74.8	4.7	13	78.2	5.8	11	70.5	4.3	11	75.4	5.8	10	79.1	5.7	7	74.7	4.3	10
HR Change	Esmolol				1.8	1.7	41	7.4	2.1	38	-0.8	2.1	36	-0.7	1.9	35	-1.1	2.4	33	-3.4	2.3	24
	Placebo				12.0[#]	2.1	35	18.6	2.7	28	1.9	2.4	25	6.4	3.3	23	8.2	3.1	23	8.2[#]	2.4	17
	Standard				10.8[#]	3.6	13	14.0	4.6	11	7.8	4.6	11	11.6	5.1	10	16.3	5.1	7	15.4[#]	4.4	10
Comparison of Change[b]					P, S > E			P > E			N.T.			N.S.			S > E			S, P > E		
SBP (mm)	Esmolol	141.8	3.[illegible]	43	124.4	3.5	41	140.7	4.0	38	129.3	3.9	36	133.3	3.9	35	123.7	3.3	33	109.0	3.0	24
	Placebo	140.5	3.[illegible]	38	130.6	3.4	35	151.0	5.3	28	131.9	4.0	25	137.9	4.8	23	127.1	4.4	23	111.8	4.0	17
	Standard	127.7	5.[illegible]	15	124.7	5.3	13	135.4	5.3	11	134.1	6.3	11	148.0	6.9	10	128.6	11.2	7	108.9	3.7	10
SBP Change	Esmolol				-17.6[#]	3.0	41	0.8	3.3	38	-8.1	3.1	36	-3.7	3.4	35	-12.7	3.7	33	-32.7[#]	4.9	24
	Placebo				-9.4[#]	2.4	35	11.8	4.6	28	-6.8	4.1	25	0.6	5.0	23	-9.7	5.6	23	-27.0[#]	6.2	17
	Standard				-1.7	4.6	13	10.1	4.9	11	10.6	4.9	11	24.3	5.6	10	2.6	8.3	7	-15.9[#]	5.5	10
Comparison of Change[b]					S > E			N.S.			N.T.			N.S.			N.S.			N.S.		

[a] Significant center by treatment interaction was detected for the change of all variables at the skin incision period ($p < 0.05$).

[#] Indicates significant change from baseline ($p < 0.05$). Maximum change from baseline was not tested for significance at intubation, skin incision, sternotomy, and aortic dissection.

[b] N.S. Indicates no significant difference among treatment groups ($p \geq 0.05$).
E = Esmolol, P = Placebo, S = Standard
N.T. Not tested due to center by treatment interaction.

Table 36

HEART RATE AND SYSTOLIC BLOOD PRESSURE WITH CHANGES FROM BASELINE, FOR ALL PATIENTS, BY EVENT

		BASELINE			PRE-INTUBATION			INTUBATION			SKIN INCISION			STERNOTOMY			AORTIC DISSECTION			POSTINF./PRE-BYPASS[a]		
	Group	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N
HR (bpm)	Esmolol	66.0	1.6	43	67.7	1.4	43	73.1	1.6	43	65.3	1.5	42	64.7	1.4	43	65.0	1.6	41	65.1	1.9	31
	Placebo	66.1	2.1	41	78.5	2.2	41	85.5	2.5	41	72.5	2.6	40	78.2	2.5	39	80.4	2.7	38	75.9	2.5	31
	Standard	62.4	2.8	18	72.6	3.5	18	77.2	3.8	18	67.2	3.2	18	70.2	3.9	18	78.7	3.8	18	72.7	3.0	17
HR Change	Esmolol				1.7	1.6	43	7.0	1.9	43	-0.3	1.8	42	-1.3	1.7	43	-0.6	2.0	41	-1.0	2.1	31
	Placebo				12.4#	2.1	41	19.5	2.2	41	6.0	2.4	40	11.2	2.6	39	13.2	2.7	36	7.5#	2.0	31
	Standard				10.1#	2.9	18	14.8	3.1	18	4.7	3.4	18	7.8	3.3	18	16.3	2.9	18	10.8#	3.2	17
Comparison of Change[b]					P,S > E			P,S > E			N.S.			P,S > E			S,P > E			S,P > E		
SBP (mmHg)	Esmolol	141.8	3.2	43	134.1	3.3	43	140.8	4.0	43	132.6	3.7	42	135.2	3.5	43	127.0	3.1	41	110.4	2.8	31
	Placebo	142.1	3.5	41	150.8	3.1	41	153.2	4.5	41	143.3	4.0	40	147.6	4.3	39	132.8	3.5	38	112.2	2.8	31
	Standard	127.7	4.2	18	125.5	4.5	18	137.6	4.4	18	131.9	4.2	18	146.4	4.7	18	130.0	5.8	18	109.4	2.5	17
SBP Change	Esmolol				-7.7#	2.9	43	-1.0	3.1	43	-8.7	3.0	42	-6.8	3.3	43	-15.1	3.7	41	-33.2#	4.3	31
	Placebo				8.3#	2.4	41	11.1	3.6	41	0.8	3.7	40	4.9	4.1	39	-8.4	4.4	38	-30.8#	4.8	31
	Standard				-1.2	4.2	18	9.8	3.7	18	4.2	3.8	18	18.7	4.2	18	2.3	5.8	18	-16.4#	3.6	17
Comparison of Change[b]					S > P,E			P,S > E			N.S.			S > P > E			N.S.			N.S.		

Notes: No significant center by treatment interaction was detected for the change of any variables at any event ($p \geq 0.05$).

[a] Data not available for patients from Center 6 at prebypass, after end of infusion.

[b] N.S. Indicates no significant difference among treatment groups ($p \geq 0.05$).

\# Indicates significant change from baseline ($p < 0.05$). Maximum change from baseline at intubation, skin incision, sternotomy, and aortic dissection was not tested for significance.

E = Esmolol, P = Placebo, S = Standard Therapy

Table 37

DIASTOLIC, MEAN ARTERIAL BLOOD PRESSURE, AND RATE-PRESSURE PRODUCT WITH CHANGES FROM BASELINE FOR ALL PATIENTS

		BASELINE			PREINTUBATION			INTUBATION			SKIN INCISION			STERNOTOMY			AORTIC DISSECTION			POSTINF./PRE-BYPASS[a]		
	Group	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N
DBP (mmHg)	Esmolol	64.6	1.5	43	62.3	1.8	43	71.8	2.0	43	72.6	2.4	42	73.8	2.2	43	69.4	2.3	41	59.4	2.0	31
	Placebo	66.3	1.6	41	65.9	1.5	41	78.8	2.1	41	76.5	2.2	40	78.4	2.2	39	69.3	1.9	38	60.4	1.7	31
	Standard	63.3	2.1	18	66.2	2.6	18	71.2	2.7	18	71.8	2.6	18	77.3	3.1	18	68.8	2.9	18	60.1	1.6	17
DBP Change	Esmolol				-2.3	1.3	43	7.2	1.8	43	8.0	2.3	42	9.2	1.8	43	4.9	2.5	41	-4.5	2.2	31
	Placebo				-0.4	1.1	41	12.5	1.9	41	10.3	1.9	40	12.0	2.0	39	3.4	2.1	38	-5.8[#]	2.1	31
	Standard				2.9	1.9	18	7.9	1.9	18	8.5	1.9	18	13.9	2.3	18	5.5	2.2	18	-2.2	1.8	17
Comparison of Change[b]					N.S.			P > E			N.S.			N.S.			N.S.			N.S.		
MAP (mmHg)	Esmolol	90.3	1.8	43	82.9	2.2	43	94.6	2.5	43	92.5	2.8	42	93.8	2.5	43	88.4	2.4	41	76.4	2.1	31
	Placebo	91.5	2.1	41	87.5	1.9	41	103.3	2.8	41	98.5	2.7	40	101.1	2.8	39	90.1	2.3	38	77.7	1.8	31
	Standard	84.8	2.6	18	86.0	3.1	18	92.8	3.2	18	91.5	2.9	18	99.4	3.4	18	89.0	3.6	18	76.5	1.5	17
MAP Change	Esmolol				-7.4[#]	1.7	43	4.2	2.1	43	2.3	2.4	42	3.5	2.1	43	-2.0	2.7	41	-14.1[#]	2.7	31
	Placebo				-4.0[#]	1.3	41	11.8	2.4	41	8.9	2.4	40	9.2	2.5	39	-0.9	2.8	38	-14.1[#]	2.8	31
	Standard				1.2	2.5	18	8.0	2.3	18	6.7	2.3	18	14.6	2.7	18	4.2	3.1	18	-7.0[#]	2.1	17
Comparison of Change[b]					S > E			P > E			N.S.			N.S.			N.S.			N.S.		
RPP	Esmolol	9.4	0.4	43	8.5	0.3	43	10.3	0.5	43	8.7	0.4	42	8.7	0.3	43	8.1	0.3	41	7.2	0.3	31
	Placebo	9.4	0.4	41	10.3	0.4	41	12.9	0.6	41	10.4	0.5	40	11.3	0.5	39	10.5	0.5	38	8.6	0.4	31
	Standard	7.9	0.4	18	9.1	0.5	18	10.4	0.6	18	8.7	0.4	18	10.1	0.6	18	10.0	0.7	18	7.[illegible]	0.3	17
RPP Change	Esmolol				-1.0[#]	0.3	43	0.9	0.4	43	-0.7	0.4	42	-0.8	0.4	43	-1.2	0.4	41	-2.3[#]	0.5	31
	Placebo				0.9[#]	0.4	41	3.5	0.5	41	0.9	0.5	40	1.7	0.5	39	1.0	0.6	38	-1.2[#]	0.5	31
	Standard				1.1	0.6	18	2.4	0.6	18	0.7	0.6	18	2.1	0.7	18	2.1	0.6	18	0.2	0.4	17
Comparison of Change[b]					S, P > E			P, S > E			N.S.			S, P > E			S, P > E			N.S.		

Note: No significant center by treatment interaction was detected for the change of any variables at any event ($p \geq 0.05$).

a Data not available for patients from Center 6 at prebypass, after end of infusion.

b N.S. Indicates no significant difference among treatment groups ($p \geq 0.05$).

# Indicates significant change from baseline ($p < 0.05$). Maximum change from baseline at intubation, skin incision, sternotomy, and aortic dissection was not tested for significance.

E = Esmolol, P = Placebo, S = Standard Therapy

Table 38

SUMMARY OF BASELINE OBSERVATIONS FOR ALL PATIENTS, BY CENTER AND TREATMENT GROUP

		HR bpm		SBP mm Hg		DBP mm Hg		MAP mm Hg		RPP		
Center[a]	Group	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	N
1	Esmolol	67.5	2.2	150.0	6.9	60.3	3.6	90.2	4.4	10.2	0.7	12
	Placebo	70.7	3.7	150.7	6.9	66.5	3.2	94.5	4.2	10.7	0.8	11
	Pooled	69.0	2.1	150.3	4.8	63.3	2.5	92.3	3.0	10.4	0.5	23
2 & 3	Esmolol	70.6	3.6	140.5	5.9	67.7	2.7	92.0	3.3	10.0	0.7	13
	Placebo	70.4	3.8	140.1	5.6	68.5	4.1	92.3	4.4	10.0	0.9	13
	Standard	66.1	3.3	128.4	6.3	64.4	3.1	85.7	3.8	8.4	0.5	11
	Pooled	69.2	2.1	136.8	3.4	67.0	1.9	90.2	2.2	9.5	0.4	37
5	Esmolol	58.7	2.8	139.0	6.9	65.1	3.8	89.8	4.4	8.2	0.7	7
	Placebo	61.1	4.2	144.3	10.1	64.3	2.6	91.0	4.6	8.8	0.5	8
	Standard	56.6	4.1	126.6	5.0	61.7	2.4	83.4	2.9	7.2	0.7	7
	Pooled	58.9	2.1	137.0	4.6	63.7	1.7	88.2	2.4	8.0	0.4	22
6	Esmolol	63.7	3.2	136.1	5.5	65.2	2.1	88.8	2.8	8.7	0.7	11
	Placebo	58.5	4.0	132.4	5.4	64.5	1.5	87.2	2.4	7.9	0.8	9
	Pooled	61.4	2.5	134.4	3.8	64.9	1.3	88.1	1.8	8.3	0.5	20
Pooled (2&3,5,6)	Esmolol	65.5	2.1	138.6	3.4	66.3	1.6	90.4	1.9	9.1	0.4	31
	Placebo	64.4	2.5	138.9	3.9	66.2	1.9	90.4	2.4	9.0	0.5	30
	Standard	62.4	2.8	127.7	4.2	63.3	2.1	84.8	2.6	7.9	0.4	18
Comparison[b]		N.S.		N.S.		N.S.		N.S.		N.S.		
Pooled (All)	Esmolol	68.0	1.6	141.8	3.2	64.6	1.5	90.3	1.8	9.4	0.4	43
	Placebo	66.1	2.1	142.1	3.5	66.3	1.6	91.5	2.1	9.4	0.4	41
	Standard	62.4	2.8	127.7	4.2	63.3	2.1	84.8	2.6	7.9	0.4	18
Comparison[c]		N.S.		P,E > S		N.S.		N.S.		N.S.		

[a] Significant difference among the centers for HR (Centers 1 and 2&3 > 5, 6) and RPP (Centers 1 > 5, 6); No significant difference among the treatment groups by center.

[b] Comparison among treatment groups for pooled data (Centers 2&3, 5, and 6).

[c] Comparison among treatment groups for pooled data (all centers).

N.S. Indicates no significant difference among the treatment groups ($p \geq 0.05$).

E = Esmolol, P = Placebo, S = Standard Therapy

Table 39

MAXIMUM CHANGES FROM BASELINE FOR ALL PATIENTS DURING INTUBATION BY CENTER AND TREATMENT

		HR Change		SBP Change		DBP Change		MAP Change		RPP Change		
Center[a]	Group	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	N
1	Esmolol	9.8	2.9	8.0	3.1	16.3	2.7	13.5	2.6	1.9	0.4	12
	Placebo	23.9	4.8	35.0	8.1	25.5	4.0	28.7	5.3	6.7	0.9	11
	Pooled	16.6	3.1	20.9	5.0	20.7	2.5	20.8	3.2	4.2	0.7	23
Comparison[b]		P > E		P > E		N.S.		P > E		P > E		
2&3	Esmolol	2.7	3.5	-1.3	6.1	8.4	3.1	4.7	3.8	0.3	0.9	13
	Placebo	19.6	3.2	5.2	4.7	8.6	2.3	7.3	3.0	2.9	0.7	13
	Standard	13.1	4.4	12.0	5.5	9.0	2.7	9.2	3.4	2.5	0.8	11
	Pooled	11.7	2.4	5.0	3.2	8.7	1.5	7.0	1.9	1.9	0.5	37
Comparison[b]		P > E		N.S.		N.S.		N.S.		N.S.		
5	Esmolol	11.0	3.1	-7.0	10.2	-1.1	3.7	-3.3	5.7	0.9	0.8	7
	Placebo	15.6	6.2	0.7	3.0	9.8	3.1	6.5	2.8	2.0	1.0	8
	Standard	17.4	4.2	6.5	4.2	6.1	2.4	6.1	2.9	2.3	0.9	7
	Pooled	14.7	2.7	0.1	3.7	5.2	2.0	3.2	2.4	1.8	0.5	22
Comparison[b]		N.S.		N.S.		N.S.		N.S.		N.S.		
6	Esmolol	6.6	4.9	-6.6	6.1	1.2	2.7	-1.6	3.8	0.4	1.0	11
	Placebo	17.2	4.6	-0.2	3.6	4.7	1.9	2.3	2.2	1.9	0.8	9
	Pooled	11.4	3.5	-3.7	3.7	2.8	1.7	0.2	2.3	1.0	0.7	20
Comparison[b]		N.S.		N.S.		N.S.		N.S.		N.S.		

(Continued)

Table 39 (Continued)

MAXIMUM CHANGES FROM BASELINE FOR ALL PATIENTS DURING INTUBATION, BY CENTER AND TREATMENT

		HR Change		SBP Change		DBP Change		MAP Change		RPP Change		
Center[a]	Group	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	N
Pooled (2&3,5,6)	Esmolol	5.9	2.4	-4.5	3.9	3.7	1.9	0.6	2.4	0.5	0.5	31
	Placebo	17.8	2.5	2.4	2.4	7.8	1.4	5.6	1.6	2.3	0.5	30
	Standard	14.8	3.1	9.8	3.7	7.9	1.9	8.0	2.3	2.4	0.6	18
Comparison[c]		P, S > E		S > E		N.S.		N.S.		S, P > E		
Pooled (All)	Esmolol	7.0	1.9	-1.0	3.1	7.2	1.8	4.2	2.1	0.9	0.4	43
	Placebo	19.5	2.2	11.1	3.6	12.5	1.9	11.8	2.4	3.5	0.5	41
	Standard	14.8	3.1	9.8	3.7	7.9	1.9	8.0	2.3	2.4	0.6	18
Comparison[d]		P, S > E		P, S > E		P>E		P>E		P, S > E		

a Significant differences in SBP, DBP, MAP, and RPP changes (Centers 1 > 2&3, 5 and 6).
b Comparison among treatment groups for each center.
c Comparison among treatment groups for pooled data (Centers 2&3, 5, and 6).
d Comparison among treatment groups for pooled data (all centers).
N.S. Indicates no significant difference among treatment groups.
E = Esmolol, P = Placebo, S = Standard Therapy

Table 40

MAXIMUM CHANGES FROM BASELINE FOR ALL PATIENTS DURING SKIN INCISION, BY CENTER AND TREATMENT

Center[a]	Group	HR Change Mean	HR Change SEM	SBP Change Mean	SBP Change SEM	DBP Change Mean	DBP Change SEM	MAP Change Mean	MAP Change SEM	RPP Change Mean	RPP Change SEM	N
1	Esmolol	2.2	4.0	2.3	6.7	20.0	5.6	12.6	5.8	-0.0	0.6	11
	Placebo	11.8	6.2	2.8	9.6	13.5	4.5	10.0	6.1	2.1	1.4	11
	Pooled	7.0	3.8	0.2	5.7	16.8	3.6	11.3	4.1	1.0	0.8	22
Comparison[b]		N.S.		N.S.		N.S.		N.S.		N.S.		
2 & 3	Esmolol	-4.9	2.6	-3.6	5.0	9.2	3.2	4.6	3.4	-0.9	0.6	13
	Placebo	6.8	3.5	1.3	4.8	9.4	3.1	6.6	3.6	0.8	0.6	13
	Standard	2.0	4.4	3.9	5.3	6.3	2.0	5.2	2.9	0.4	0.8	11
	Pooled	1.3	2.1	0.4	2.8	8.4	1.6	5.5	1.8	0.1	0.4	37
Comparison[b]		N.S.		N.S.		N.S.		N.S.		N.S.		
5	Esmolol	8.6	3.5	-10.6	5.4	3.3	2.0	-1.4	3.0	0.0	0.5	7
	Placebo	1.3	4.4	6.2	8.5	15.4	3.2	11.4	4.8	0.6	0.7	8
	Standard	8.9	5.2	4.6	5.6	12.0	3.6	8.9	3.8	1.2	1.0	7
	Pooled	5.4	2.5	0.3	4.1	10.5	2.0	6.5	2.5	0.6	0.4	22
Comparison[b]		N.S.		N.S.		P > E		N.S.		N.S.		
6	Esmolol	-1.3	3.9	-19.9	5.8	-2.6	2.6	-8.4	3.6	-1.5	0.8	11
	Placebo	1.5	4.6	-7.9	6.8	2.0	3.1	-1.4	4.2	-0.5	0.9	8
	Pooled	-0.4	2.8	-14.8	4.5	-0.6	2.0	5.5	2.8	-1.1	0.6	19
Comparison[b]		N.S.		N.S.		N.S.		N.S.		N.S.		

(Continued)

Table 40 (Continued)

MAXIMUM CHANGES FROM BASELINE FOR ALL PATIENTS DURING SKIN INCISION, BY CENTER AND TREATMENT

Center[a]	Group	HR Change Mean	HR Change SEM	SBP Change Mean	SBP Change SEM	DBP Change Mean	DBP Change SEM	MAP Change Mean	MAP Change SEM	RPP Change Mean	RPP Change SEM	N
Pooled (2&3,5,6)	Esmolol	-1.2	2.0	-11.0	3.3	3.7	1.9	-1.4	2.2	-0.9	0.4	31
	Placebo	3.8	2.3	0.1	3.7	9.0	2.0	5.7	2.5	0.4	0.4	29
	Standard	4.7	3.4	4.2	3.8	8.5	1.9	6.7	2.3	0.7	0.6	18
Comparison[c]		N.S.		S, P > E		N.S.		N.S.		N.S.		
Pooled (All)	Esmolol	-0.3	1.8	-8.7	3.0	8.0	2.3	2.3	2.4	-0.7	0.4	42
	Placebo	6.0	2.4	0.8	3.7	10.3	1.9	6.9	2.4	0.9	0.5	40
	Standard	4.7	3.4	4.2	3.8	8.5	1.9	6.7	2.3	0.7	0.6	18
Comparison[d]		N.S.		N.S.		N.S.		N.S.		N.S.		

a Significant difference in DBP change among centers (Centers 1 and 5 > 6);
Significant difference in MAP change among centers (Centers 1, 2&3, and 5 > 6).
b Comparison among treatment groups for each center.
c Comparison among treatment groups for pooled data (Centers 2&3, 5, and 6).
d Comparison among treatment groups for pooled data (all centers).
N.S. Indicates no significant difference among treatment groups ($p \geq 0.05$).
E = Esmolol, P = Placebo, S = Standard Therapy

Table 41

MAXIMUM CHANGES FROM BASELINE FOR ALL PATIENTS DURING STERNOTOMY, BY CENTER AND TREATMENT

Center[a]	Group	HR Change Mean	HR Change SEM	SBP Change Mean	SBP Change SEM	DBP Change Mean	DBP Change SEM	MAP Change Mean	MAP Change SEM	RPP Change Mean	RPP Change SEM	N
1	Esmolol	-3.1	3.9	-13.3	7.3	15.3	3.8	5.4	4.6	-1.5	0.8	12
	Placebo	9.8	6.0	-2.8	10.4	13.4	4.3	7.7	6.2	1.2	1.5	11
	Pooled	3.1	3.7	-8.3	6.2	14.4	2.8	6.5	3.8	-0.2	0.9	23
Comparison[b]		N.S.		N.S.		N.S.		N.S.		N.S.		
2 & 3	Esmolol	-3.0	2.5	2.2	4.9	11.7	2.8	7.8	3.1	-0.4	0.5	13
	Placebo	13.1	3.8	11.2	5.5	12.2	3.3	11.5	3.8	2.3	0.7	13
	Standard	8.6	5.3	22.8	5.4	12.8	2.5	14.8	3.3	2.6	1.0	11
	Pooled	8.1	2.5	11.5	3.3	12.2	1.6	11.7	2.0	1.4	0.5	37
Comparison[b]		P, S > E		S > E		N.S.		N.S.		S, P > E		
5	Esmolol	6.6	2.7	5.4	6.1	10.1	1.8	8.5	3.1	0.9	0.4	7
	Placebo	15.9	5.1	16.4	8.0	17.8	4.4	16.6	5.1	3.0	0.7	8
	Standard	6.5	2.7	12.4	6.5	15.7	4.5	14.4	4.7	1.3	0.6	7
	Pooled	10.0	2.3	11.6	4.0	14.7	2.2	13.3	2.6	1.8	0.4	22
Comparison[b]		N.S.		N.S.		N.S.		N.S.		P > E		
6	Esmolol	-2.3	3.7	-17.3	6.0	-0.9	2.9	-6.8	3.9	-1.4	0.8	11
	Placebo	4.4	5.8	-7.6	5.4	2.7	2.0	-0.8	3.0	-0.1	1.1	7
	Pooled	0.3	3.2	-13.5	4.3	0.5	2.0	-4.5	2.7	-0.9	0.6	18
Comparison[b]		N.S.		N.S.		N.S.		N.S.		N.S.		

(Continued)

Table 41 (Continued)

MAXIMUM CHANGES FROM BASELINE FOR ALL PATIENTS DURING STERNOTOMY BY CENTER AND TREATMENT

Center[a]	Group	HR Change Mean	HR Change SEM	SBP Change Mean	SBP Change SEM	DBP Change Mean	DBP Change SEM	MAP Change Mean	MAP Change SEM	RPP Change Mean	RPP Change SEM	N
Pooled (2&3,5,6)	Esmolol	-0.6	1.0	-4.0	3.6	6.9	1.9	2.8	2.4	-0.5	0.4	31
	Placebo	11.7	2.7	8.0	4.0	11.4	2.2	9.9	2.6	1.9	0.5	28
	Standard	7.8	3.3	18.7	4.2	13.9	2.3	14.6	2.7	2.1	0.7	18
Comparison[c]		P, S > E		S> P > E		N.S.		N.S.		S, P > E		
Pooled (All)	Esmolol	-1.3	1.7	-6.6	3.3	9.2	1.8	3.5	2.1	-0.8	0.4	43
	Placebo	11.2	2.6	4.9	4.1	12.0	2.0	9.2	2.5	1.7	0.5	39
	Standard	7.8	3.3	18.7	4.2	13.9	2.3	14.6	2.7	2.1	0.7	18
Comparison[d]		P, S > E		S > P > E		N.S.		N.S.		S, P > E		

a Significant difference in SBP and RPP changes (Centers 5 and 2&3 > 1 and 6); Significant difference in DBP and MAP changes (Centers 1, 2&3, and 5 > 6).
b Comparison among treatment groups for each center.
c Comparison among treatment groups for pooled data (Centers 2&3, 5, and 6).
d Comparison among treatment groups for pooled data (all centers).
N.S. Indicates no significant difference among treatment groups ($p \geq 0.05$).
E = Esmolol, P = Placebo, S = Standard Therapy

Table 42

MAXIMUM CHANGES FROM BASELINE FOR ALL PATIENTS DURING AORTIC DISSECTION, BY CENTER AND TREATMENT

Center[a]	Treatment Group	HR Change Mean	HR Change SEM	SBP Change Mean	SBP Change SEM	DBP Change Mean	DBP Change SEM	MAP Change Mean	MAP Change SEM	RPP Change Mean	RPP Change SEM	N
1	Esmolol	0.0	4.7	-14.7	7.6	14.0	5.2	4.4	5.8	-1.3	0.9	12
	Placebo	10.6	5.7	-12.8	8.0	7.3	3.2	0.5	4.7	0.4	1.4	10
	Pooled	4.8	3.7	-13.8	5.4	11.0	3.2	2.6	3.7	-0.5	1.8	22
Comparison[b]		N.S.		N.S.		N.S.		N.S.		N.S.		
2 & 3	Esmolol	-3.2	2.8	-3.8	6.3	7.3	2.5	3.5	3.4	-0.8	0.6	12
	Placebo	18.3	4.6	5.2	8.9	6.5	5.2	5.4	6.3	2.6	1.2	13
	Standard	17.5	3.5	12.4	7.1	7.5	3.2	8.9	4.1	3.0	0.9	11
	Pooled	10.8	2.7	4.4	4.4	7.1	2.2	5.8	2.8	1.6	0.6	36
Comparison[b]		P, S > E		N.S.		N.S.		N.S.		S, P > E		
5	Esmolol	7.5	3.2	-16.0	6.5	2.6	7.7	-4.3	6.4	-0.4	0.6	7
	Placebo	17.7	4.3	-17.8	9.2	-0.7	2.3	-6.8	4.6	1.0	0.6	8
	Standard	14.4	5.4	-13.6	5.4	2.4	2.5	-3.0	3.1	0.6	0.5	7
	Pooled	13.4	2.6	-15.8	4.1	1.3	2.6	-4.8	2.7	0.4	0.3	22
Comparison[b]		N.S.		N.S.		N.S.		N.S.		N.S.		
6	Esmolol	-4.0	3.7	-28.6	7.4	-7.3	3.4	-14.5	4.6	-2.3	0.8	10
	Placebo	2.5	5.4	-16.3	5.4	-3.3	1.9	-7.8	2.9	-1.0	0.9	7
	Pooled	-1.3	3.1	-23.5	5.0	-5.7	2.2	-11.7	3.0	-1.9	0.8	17
Comparison[b]		N.S.		N.S.		N.S.		N.S.		N.S.		

(Continued)

Table 42 (Continued)

MAXIMUM CHANGES FROM BASELINE FOR ALL PATIENTS DURING AORTIC DISSECTION, BY CENTER AND TREATMENT

Center[a]	Treatment Group	HR Change Mean	HR Change SEM	SBP Change Mean	SBP Change SEM	DBP Change Mean	DBP Change SEM	MAP Change Mean	MAP Change SEM	RPP Change Mean	RPP Change SEM	N
Pooled (2&3,5,6)	Esmolol	-0.9	2.0	-15.3	4.3	1.1	2.6	-4.6	2.9	-1.2	0.4	29
	Placebo	14.2	3.0	-6.8	5.4	2.0	2.6	-1.4	3.4	1.2	0.7	28
	Standard	16.3	2.9	2.3	5.6	5.5	2.2	4.2	3.1	2.1	0.6	18
Comparison[c]		S, P > E		N.S.		N.S.		N.S.		S, P > E		
Pooled (All)	Esmolol	-0.6	2.0	-15.1	3.7	4.9	2.5	-2.0	2.7	-1.2	0.4	41
	Placebo	13.2	2.7	-8.4	4.4	3.4	2.1	-0.9	2.8	1.0	0.6	38
	Standard	16.3	2.9	2.3	5.6	5.5	2.2	4.2	3.1	2.1	0.6	18
Comparison[d]		S, P > E		N.S.		N.S.		N.S.		S, P > E		

a Significant difference in SBP change (Centers 2&3 > 1, 5, and 6;
Significant difference in DBP change (Centers 1, > 5 and 6);
Significant difference in MAP change (Centers 3 > 5 and 6);
Significant difference in RPP change (Centers 3 > 1 and 6).

b Comparison among treatment groups for each center.

c Comparison among treatment groups for pooled data (Centers 2&3, 5, and 6).

d Comparison among treatment groups for pooled data (all centers).

N.S. Indicates no significant difference among treatment groups ($p \geq 0.05$).

E = Esmolol, P = Placebo, S = Standard Therapy

Table 43

SUMMARY STATISTICS FOR SELECTED TIME INTERVALS

Center	Treatment Group	DURATION OF BYPASS[a] (MINUTES) Mean	SEM	MIN	MAX	DURATION OF VENTILATION[b] (HOURS) Mean	SEM	MIN	MAX	DURATION OF INTUBATION[c] (HOURS) Mean	SEM	MIN	MAX	N
1	Esmolol	76.2	5.6	36.2	123.2	11.8	1.1	7.6	16.8	14.8	1.2	10.5	21.0	12
	Placebo	86.4	8.3	38.7	139.7	12.5	1.7	7.3	22.7	15.5	1.7	10.2	25.1	11
2 & 3	Esmolol	103.7	11.0	48.0	192.0	18.0	2.1	4.0	38.0	23.3	2.2	10.3	45.7	13
	Placebo	96.7	6.6	55.0	131.0	26.5	6.2	4.0	91.3	31.3	6.2	9.3	96.0	13
5	Esmolol	130.9	7.0	102.0	152.0	33.0	7.3	18.0	67.6	38.1	7.4	22.4	72.7	7
	Placebo	149.2	15.0	88.0	204.0	17.1	1.9	10.3	24.8	22.4	2.0	14.1	30.5	8
6	Esmolol	68.2	13.0	12.0	172.0	22.0	2.8	15.6	49.8	26.9	3.4	18.9	51.9	11
	Placebo	81.4	22.0	40.0	221.0	21.1	1.2	17.0	28.8	26.7	2.8	19.3	46.1	9
Pooled	GROUP													
	Esmolol	91.4	6.0	12.0	192.0	19.7	1.8	4.0	67.6	24.3	2.0	10.3	72.7	43
	Placebo	100.8	7.3	38.7	221.0	19.7	2.2	4.0	91.3	24.3	2.3	9.3	96.0	41

[a] Significant difference by treatment interaction ($p < 0.05$).
[b] Significant center by treatment interaction ($p < 0.05$).
[c] Significant center by treatment interaction ($p < 0.05$).

Table 50.

SUMMARY OF ADVERSE EFFECTS, BY PATIENT

Patient Number	Adverse Effect	Onset of Adverse Effect Period	Treatment (drug)	Dosage (mcg/kg/min)	Time*	Duration (min)	Severity	Attrib. To Study Drug	Action	Outcome of Action	Outcome to Date
118	Urticaria	Post-Infusion	Esmolol	0	3-4 hr	Unknown	Mild	Not Drug Related	None	Resolved	Recovered
316	Cardiac Arrest	Post-Infusion	Placebo	0	3-4 hr	Unknown	Severe	Not Drug Related	Open Chest Cardiac Massage Emergency Operation	Restarted Heart	Recovered
603	Hypotension	Infusion	Esmolol	200	41 min	1	Moderate	Remote	Neosynephrine 40 mcg	Recovered	Recovered
614	ST-Segment Depression	Infusion	Placebo	0	11 min	57	Moderate	Possible	Valium given & Study Dc'd. Propranolol then given & IV NTG started	Recovered	Recovered
616	Pulmonary Hypertension	Infusion	Placebo	0	11 min	50	Moderate	Possible	Valium, Fentanyl, Enflurane, & IV NTG Given, Study Dc'd.	Recovered	Recovered
620	Hypotension	Infusion	Esmolol	200	1 hr	5	Moderate	Possible	Study Dc'd. Ephedrine 5 mg	Recovered	Recovered
301C	Ischemic ECG Changes	NA	NA (Standard Therapy)	NA	approx. 10 min.	19	Severe	NA	IV NTG & Enflurane	Recovered	Recovered
305C	Broncho-spasm	NA	NA (Standard) Therapy)	NA	approx. 10 m...	120	Moderate	NA	Aminophyl-line Albuterol, & Terbut-taline	Recovered	Recovered

* Relative to start of infusion.

** Loading dose for 300 mcg/kg/min infusion.

NA Not applicable because patient was in the Standard Therapy Control Group.

Table 51

SUMMARY OF ELECTROCARDIOGRAPHIC FINDINGS PRESTUDY AND DURING THE STUDY

Patient Number	Tx*	Prestudy 12-lead ECG	Baseline	During Study Changes
101	E	T-wave inversion inferior leads.	One PVC.	None
102	P	General evaluation: abnormal.	None	One PVC noted just prior to and two minutes after start of infusion. One PAC noted at minutes four, five, and six of aortic dissection, associated with pericardial stay stitches and left atrial catheter placement.
103	E	Non-specific ST-T wave abnormalities.	None	One PAC noted in conjunction with left atrial catheter placement.
104	P	General evaluation: abnormal.	1 mm ST-segment depression at five minutes prior to start of infusion.	ST-segment depression recurred at intubation, progressing to a more pronounced ST-segment depression (i.e., 2 mm) in addition to T-wave inversion by four minutes post-intubation. Two more episodes of 1 mm ST-segment depression in conjunction with T-wave inversion were noted during the infusion period, in the absence of any surgical stimulus, however. 1 mm ST-segment depression plus T-wave inversion recurred at chest incision, progressing to 2 mm depression by sternotomy. Three minutes post-sternotomy, ST-segment depression returned to 1 mm and T-waves were normal. ST-segments also normalized by time of aortic dissection. Only PACs were noted at end of aortic dissection.
105	E	Non-specific ST-segment abnormality.	None	Short run of ventricular tachycardia noted during aortic dissection when heart was touched while opening pericardium.
106	P	Right bundle branch block.	One PVC noted at three minutes prior to leg incision.	None
107	E	Inverted T-waves in leads II, III and AVF compatible with inferior infarct (age undetermined).	None	One PVC noted just prior to start of infusion. Two PACs noted during right atrial retraction for insertion of left atrial catheter. A third PAC was noted during the infusion, in the absence of any surgical stimulus, however.
108	P	Non-specific ST-T wave changes. Evidence of old interolateral myocardial infarction.	None	One PVC noted one minute after leg incision. Two PACs noted during right atrial retraction for insertion of left atrial line, with one PAC occurring during insertion of atrial purse string.

* E = Esmolol, P = Placebo, ST = Standard Therapy

Table 5: (Continued)

SUMMARY OF ELECTROCARDIOGRAPHIC FINDINGS PRESTUDY AND DURING THE STUDY

Patient Number	Tx*	Prestudy 12-lead ECG	Baseline	During Study Changes
109	P	Non-specific ST-T wave abnormalities. Evidence of inferior infarct (age undetermined).	None	One PVC and one PAC noted just prior to leg incision and during left atrial catheter insertion, respectively.
110	E	ST-T wave abnormality consistent with inferior lateral ischemia.	None	One PVC noted three minutes postintubation and five minutes into aortic dissection while inserting a pericardial stay stitch.
111	P	Non-specific ST-segment abnormality.	None	One PVC noted during aortic dissection.
112	E	General evaluation: abnormal. Sinus bradycardia.	None	Rare PACs noted three minutes after aortic dissection (one PAC), at time of heparinization (two PACs), and during left atrial catheter placement (three PACs).
113	E	Inverted T-waves in anterolateral chest leads.	None	Once PAC noted one minute after aortic dissection.
114	P	Prolonged QT interval or TU fusion.	None	None
117	P	General evaluation: normal.	None	Transient atrial fibrillation noted during left atrial catheter placement.
118	E	Elevated ST-segments and inverted T-waves in anterior lateral chest leads compatible with anterior lateral ischemia.	None	Rare PVCs noted nine minutes postintubation (two PACs), four minutes post-sternotomy (one PAC), and prior to heparinization (one PVC).
119	P	Non-specific T-wave abnormality.	1 mm ST-segment elevation noted throughout baseline and during first five minutes of infusion.	Progressed to a more pronounced ST-segment elevation (i.e., 2 mm) upon induction, lasting for five minutes. By one minute postintubation, ST-segments had returned to a 1 mm elevation. By two minutes postintubation, the ST-segments were normal. Immediately after aortic dissection, three isolated PACs and one PVC were noted.
120	E	General evaluation: normal.	One PVC noted, associated with a coughing spell.	One PAC noted at one minute after aortic dissection and during cross clamping. A third PAC occurred during the infusion, in the absence of a surgical stimulus, however.
121	E	General evaluation: normal.	None	Atrial arrhythmias noted for two minutes during left atrial catheter placement.
122	P	Non-specific ST-segment abnormality.	None	One PAC noted during insertion of atrial purse string.

* E = Esmolol, P = Placebo, ST = Standard Therapy

Table 51 (Continued)

Summary of Electrocardiographic Findings Prestudy and During the Study

Patient Number	Tx[a]	Prestudy 12-lead ECG	Baseline	During Study Changes
123	E	ST-T wave changes compatible with lateral ischemia.	None	One PAC noted one minute after aortic dissection, with one PVC occurring during insertion of atrial purse string.
203	E	Q-waves in leads III and AVF, possible old inferior myocardial infarction.	None	None
205	P	1 mm ST-segment depression, T-wave inversion in leads II, III and AVF.	None	None
206	E	Sinus bradycardia.	None	None
201C	ST	Inferior T-wave inverted, non diagnosed inferior ST changes < 1 mm elevation.	None	None
501	P	First degree atrioventricular (AV) block. Incomplete right bundle branch block. Ischemia changes in all leads. T-wave inversion in inferior leads.	Occasional PVCs	Occasional PVCs at minutes three and four postinduction. Ventricular bigeminy noted in conjunction with left leg incision, sternotomy, and prior to cardiopulmonary bypass. Frequent PVCs had also been noted prior to aortic dissection.
502	P	Non-specific ST-T wave changes.	None	None
503	E	Non-specific ST-T wave changes.	None	None
504	E	Non-specific ST-T wave changes.	None	Significant ST-segment depression (i.e., 5 mm) noted after aortic cannulation. Treated with immediate initiation of cardiopulmonary bypass, thus lasted only eight minutes. It must also be noted that the patient had a similar episode during a stress test prior to surgery.
506	P	ST-segment depression in lead V_5. Inverted T-waves in leads III, AVF, V_2 and V_3. Evidence of old anterior septal wall myocardial infarction.	None	Rare PACs with aberrant conduction noted during left leg incision. Occasional PACs (some with and some without aberrancy) and PVCs noted during sternotomy. Frequent PACs and PVCs noted during aortic dissection.

[a] E = Esmolol, P = Placebo, ST = Standard Therapy

Table 51 (Continued)

SUMMARY OF ELECTROCARDIOGRAPHIC FINDINGS PRESTUDY AND DURING THE STUDY

Patient Number	Tx*	Prestudy 12-lead ECG	Baseline	During Study Changes
507	E	Q-waves in lead III. Small Q-wave in lead AVF.	None	None
508	P	Premature ventricular contractions (PVCs). Inverted T-waves in leads II, III, AVF and V_6, all compatible with recent myocardial infarction. Q-waves in lead III.	None	Two PACs noted within a 30-second period during aortic dissection.
509	P	ST-segment elevation consistent with post-myocardial infarction.	None	Rare multifocal PVCs noted on induction.
510	E	Intra-atrial conduction delay. Incomplete right bundle branch block.	None	Rare PVCs noted in conjunction with sternotomy and insertion of aortic purse strings prior to aortic dissection.
511	P	First degree AV block. Right bundle branch block. Left anterior hemiblock. Peaked ST-segments.	None	Flipped T-waves noted on intubation, normalizing by sternotomy. Duration of episode was 36 minutes. ST-segment elevation noted with use of Favaloro Spreader post-sternotomy, normalizing just prior to cardiopulmonary bypass. Duration of episode was 23 minutes.
513	P	First degree AV block. Evidence of old inferior wall myocardial infarction.	None	None
514	E	General evaluation: normal.	None	ST-segment depression (2 mm) noted three and four minutes postinduction and at time of mammary artery dissection. Rare PACs noted during aortic dissection.
515	E	Incomplete left bundle branch block. Inverted T-waves. Q-waves present.	None	None
516	P	Non-specific ST-T wave changes.	None	Occasional PVCs and PACs noted for three minutes post-sternotomy.
501C	ST	Minor ST-T wave changes.	None	None
502C	ST	First degree block. Minor ST-T wave changes.	None	None
503C	ST	First degree AV block. Inverted T-waves in lead I, flattened T-waves in leads II, V_4 and V_5.	None	Inverted T-waves noted throughout entire study period. (It must also be noted that inverted T-waves were present during the prestudy 12-lead ECG.) ST-segment depression noted five minutes postinduction, lasting until cardiopulmonary bypass for a total of 82 minutes.

* E = Esmolol, P = Placebo, ST = Standard Therapy