Table 51 (Continued)

SUMMARY OF ELECTROCARDIOGRAPHIC FINDINGS PRESTUDY AND DURING THE STUDY

Patient Number	Tx*	Prestudy 12-lead ECG	Baseline	During Study Changes
504C	ST	First degree AV block. Q-waves present.	None	Occasional PVCs noted throughout entire study period.
505C	ST	Occasional PVCs. First degree AV block. Right bundle branch block. Q-waves present.	None	Occasional PACs noted throughout entire study period.
506C		Q-waves present.	None	None
507C	ST	Non-specific ST-T wave changes.	None	Left bundle branch block present postinduction, lasting for approximately one minute.
601	P	J-point depression in leads II, III, AVF, V_5 and V_6. Biphasic T-waves in leads III and AVF.	None	None
602	P	Occasional PVCs. Non-specific ST-T wave changes in leads V_4-V_6. Q-waves in inferior and anterior leads.	None	Occasional PACs noted throughout entire study period.
605	E	Elevated ST-segments in leads V_2 and V_3. Inverted T-waves in leads II, III, AVF, V_5 and V_6. Q-waves in leeds III and V_2.	None	None
606	E	Inverted T-waves in lead III. Q-waves in lead III.	None	Rare PACs noted for 29 mintues prior to start of study drug infusion.
608	P	T-wave inverted in three leads.	None	None
609	P	T-wave inverted in lead AVL. Q-waves in leads AVL and V_2-V_6.	None	None
610	E	Sinus bradycardia.	None	Rare PACs noted from start of study drug infusion until two mintes after aortic dissection.
611	P	Inverted T-waves in leads III, V_2 and AVF.	None	Rare PVCs noted throughout entire study period.
613	E	Inverted T waves in lead AVL. Micro Q-waves in leads V_2 -V_4.	None	Rare PVCs noted from two minutes after start of study drug infusion until end of aortic dissection.

* 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
614	P	Inverted T-waves in leads III, AVL and V_4-V_6.	None	Frequent PVCs noted throughout entire study period. ST-segment depression noted at six mintues postinduction, not responding to treatment with diazepam (Valium 10 mg in divided doses). Study discontinued 13 minutes later due to persistence of ST-segment depression. Further treatment with intravenous nitroglycerin and propranolol (Inderal 1.5 mg) was instituted. Total duration of ST-segment depression was 57 minutes.
616	P	PVCs. First degree AV block.	Frequent PVC's	Frequent PVCs noted throughout entire study period. A further increase in frequency was noted six minutes post-induction, in combination with high pulmonary filling pressures and a low cardiac output. Diazepam (Valium 15 mg in divided doses) was administered for treatment of arrhythmias, and fentanyl and enflurane for hypertension. PVCs subsided thereafter, however the study was discontinued due to persistent pulmonary hypertension.
617	P	Inverted T-waves in leads III and AVF. Q-waves in leads III and AVF.	None	None
619	E	First degree AV block. Depressed ST-segments in leads V_4 and V_5. Inverted T-waves in leads III, AVR and AVF.	None	None
620	E	Inverted T-waves in leads V_1-V_4. Q-waves in leads II, III and AVF.	None	Rare PVCs noted two minutes after start of study drug infusion, lasting for remainder of infusion period.
621	E	Flattened T-waves in lead II. Inverted T-waves in leads III and AVF. Q-waves in lead III.	None	Rare PACs noted two mintes after start of study drug infusion, lasting for remainder of infusion period.
625	E	Inverted T-waves in leads II, III and AVF. Q-waves in leads II, III and AVF.	None	None

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

SCHEMATIC OF CLINICAL DATA INCLUDED FOR EFFICACY ANALYSIS

Patient	Treatment	Infusion Periods							Comments
		Baseline	Induction	Intubation	Skin Incision	Sternotomy	Aortic Dissection	Prebypass	
101	Esmolol	--------	-------->					-------->	Multiple Intubation; SNP*
102	Placebo	--------	---------	---------	--------	---------	-------->		Ephedrine & Phenylephrine
103	Esmolol	--------	---------	---------	--------	---------	-------->		Phenylephrine
104	Placebo	--------	---------	-------->				-------->	SNP
105	Esmolol	--------	---------	---------	--------	---------	-------->		IV NTG** & Phenylephrine
106	Placebo	--------	---------	-------->					Propranolol
107	Esmolol	--------	---------	-------->					SNP & IV NTG
108	Placebo	--------	---------	---------	--------	---------	---------	-------->	
109	Placebo	--------	---------	-------->					SNP
110	Esmolol	--------	---------	---------	--------	---------	---------	-------->	
111	Placebo	--------	---------	---------	--------	---------	-------->		Ephedrine & Phenylephrine
112	Esmolol	--------	---------	-------->					SNP, Ephedrine & Phenylephrine
113	Esmolol	--------	---------	---------	--------	---------	---------	-------->	
114	Placebo	--------	-------->					-------->	SNP
115	Esmolol	--------	---------	-------->			---------	-------->	SNP
116	Placebo	--------	---------	-------->			---------	-------->	SNP
117	Placebo	--------	-------->				no data	available	SNP; Early withdrawal
118	Esmolol	--------	---------	-------->				-------->	SNP
119	Placebo	--------	---------	-------->					SNP
120	Esmolol	--------	---------	---------	--------	---------	---------	-------->	
121	Esmolol	--------	---------	---------	--------	---------	---------	-------->	
122	Placebo	--------	---------	-------->			---------	-------->	Phenylephrine
123	Esmolol	--------	---------	---------	--------	---------	---------	-------->	

* Sodium Nitroprusside
** Intravenous Nitroglycerin
--> Represents data included for efficacy analysis.

Figure 1 (continued)

SCHEMATIC OF CLINICAL DATA INCLUDED FOR EFFICACY ANALYSIS

		Infusion Periods							
Patient	Treatment	Baseline	Induction	Intubation	Skin Incision	Sternotomy	Aortic Dissection	Prebypass	Comments
201	Placebo	No effi	cacy anal	ysis					Propranolol before study
202	Esmolol	-------->			---------	----------	----------	-------->	Phenylephrine
203	Esmolol	---------	---------	----------	---------	--------->		-------->	IV NTG**
204	Placebo	---------	---------	----------	---------	----------	----------	-------->	
205	Placebo	---------	---------	----------	---------	--------->			SNP*
206	Esmolol	---------	---------	----------	-------->		no data	available	Propranolol
201C	Standard	---------	---------	--------->					IV NTG & Propranolol
302	Placebo	---------	---------	----------	---------	----------	----------	-------->	
303	Placebo	---------	---------	----------	---------	----------	----------	-------->	
304	Esmolol	---------	---------	----------	---------	----------	----------	-------->	
305	Placebo	---------	---------	----------	---------	----------	----------	-------->	
306	Esmolol	---------	---------	----------	---------	----------	----------	-------->	
307	Placebo	---------	---------	----------	---------	--------->			Propranolol
308	Esmolol	---------	---------	----------	---------	----------	----------	-------->	
309	Esmolol	---------	---------	----------	---------	--------->			SNP
310	Placebo	---------	---------	----------	---------	----------	----------	-------->	
311	Placebo	---------	---------	----------	---------	----------	----------	-------->	
312	Esmolol	---------	---------	----------	---------	----------	----------	-------->	
314	Esmolol	---------	---------	----------	---------	----------	----------	-------->	
315	Placebo	---------	---------	----------	---------	----------	---------->		Propanolol
316	Placebo	---------	--------->						IV NTG & Propranolol
317	Placebo	---------	---------	----------	---------	----------	----------	-------->	
318	Esmolol	---------	---------	----------	---------	----------	----------	-------->	

* Sodium Nitroprusside
** Intravenous Nitroglycerin
--> Represents data included for effi[illegible]s

S21

Figure 1 (continued)

SCHEMATIC OF CLINICAL DATA INCLUDED FOR EFFICACY ANALYSIS

Patient	Treatment	Time Periods							Comments
		Baseline	Induction	Intubation	Skin Incision	Sternotomy	Aortic Dissection	Prebypass	
319	Esmolol	--------	---------	---------	--------	---------	---------	-------->	
320	Placebo	--------	-------->						Propranolol
321	Esmolol	--------	---------	---------	--------	---------	---------	-------->	
322	Esmolol	--------	---------	---------	--------	---------	---------	-------->	
301C	Standard	--------	-------->						Propranolol
302C	Standard	--------	---------	---------	--------	---------	---------	-------->	
303C	Standard	--------	---------	---------	--------	--------->			IV NTG** & Propranolol
304C	Standard	--------	-------->			---------	---------	-------->	IV NTG
305C	Standard	--------	-- ------	---------	-----	---------	---------	-------->	
306C	Standard	--------	----- ---	---------	-------	---------	---------	-------->	
307C	Standard	--------	---------	---------	------	--------->		-------->	IV NTG
308C	Standard	--------	---------	---------	--------	--------->			Propranolol
309C	Standard	--------	---------	---------	--------	--------->		-------->	IV NTG
310C	Standard	--------	---------	---------	--------	---------	---------	-------->	
501	Placebo	--------	-------->		------->		---------	-------->	Topical Cetacaine, Halothane > 2 MAC
502	Placebo	------->						-------->	Halothane > 2 MAC, Trimethaphan
503	Esmolol	--------	---------	---		---------	---------	-------->	
504	Esmolol	--------	---------	---		---------	--------->		Ephedrine
506	Placebo	------->							IV NTG
507	Esmolol	--------	---------	---		---------	---------	-------->	
508	Placebo	--------	---------	---		---------	---------	-------->	
509	Placebo	No effi	cacy anal	ysis					SNP* through baseline
510	Esmolol	--------	-------->					-------->	IV NTG

* Sodium Nitroprusside
** Intravenous Nitroglycerin
--> Represents data included for efficacy only

(Table 1 Continued)

SCHEMATIC OF CLINICAL DATA INCLUDED FOR EFFICACY ANALYSIS

Patient	Treatment	Infusion Periods							Comments
		Baseline	Induction	Intubation	Skin Incision	Sternotomy	Aortic Dissection	Prebypass	
511	Placebo	No efficacy analysis							SNP° through baseline
512	Esmolol	-------->						-------->	
513	Placebo	-------->				-------->		-------->	Halothane >2 MAC, IV NTG°°, Infusion ran out
514	Esmolol	-------->						-------->	
515	Esmolol	-------->							IV NTG
516	Placebo	-------->				-------->		-------->	SNP
501C	Standard	-------->						-------->	Halothane > 2 MAC
502C	Standard	-------->							Propranolol
503C	Standard	No efficacy analysis							IV NTG through baseline
504C	Standard	-------->						-------->	
505C	Standard	No efficacy analysis							IV NTG through baseline
506C	Standard	No efficacy analysis							IV NTG through baseline
507C	Standard	-------->						-------->	IV NTG
601	Placebo	-------->	-------->				-------->	no data available	Multiple intubation
602	Placebo	-------->	-------->				-------->	no data available	
603	Esmolol	-------->	-------->				-------->	no data available	
604	Esmolol	-------->	-------->				-------->	no data available	
605	Esmolol	-------->	-------->				-------->	no data available	
606	Esmolol	-------->	-------->				-------->	no data available	
608	Placebo	-------->	-------->				-------->	no data available	

° Sodium Nitroprusside
°° Intravenous Nitroglycerin
--> Represents data included for efficacy analysis

I (continued)

INCLUDED FOR EFFICACY ANALYSIS

Patient	Treatment	Baseline	Ind	Intubation	Sternotomy	Aortic Dissection	Prebypass	Comments
609	Placebo	-------->	-------->	-------->	-------->	-------->	no data available	
610	Esmolol	-------->	-------->	-------->	-------->	-------->	no data available	
611	Placebo	-------->	-------->	-------->	-------->	-------->	no data available	
612	Esmolol	-------->	-------->	-------->	-------->	-------->	no data available	Multiple intubation
613	Esmolol	-------->	-------->	-------->	-------->	-------->	no data available	
614	Placebo	-------->	-------->	-------->	illable	-------->	no data available	Multiple intubation; patient withdrawn - ADR
616	Placebo	-------->	-------->	-------->	no	data	available	Patient withdrawn - ADR
617	Placebo	-------->	-------->	-------->	-------->	-------->	no data available	
618	Placebo	-------->	-------->	-------->	-------->	-------->	no data available	
619	Esmolol	-------->	-------->	-------->	-------->	-------->	no data available	
62	Esmolol	-------->	-------->	-------->	-------->	no data	available	Patient withdrawn - ADR
6	Esmolol	-------->	-------->	-------->	-------->	-------->	no data available	
6	Esmolol	-------->	-------->	-------->	-------->	-------->	no data available	

--- presents data included for

FIGURE 2

Heart Rate
± standard error)

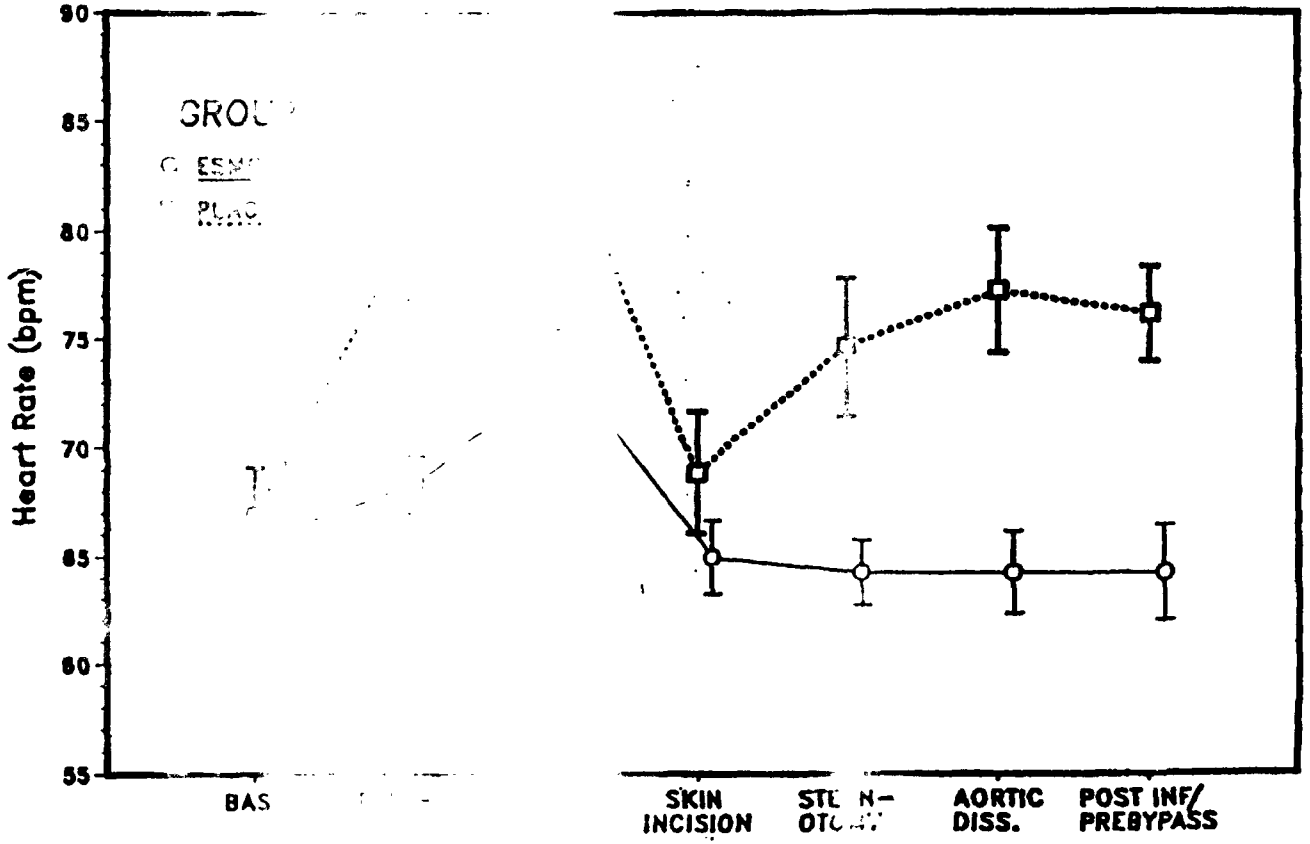
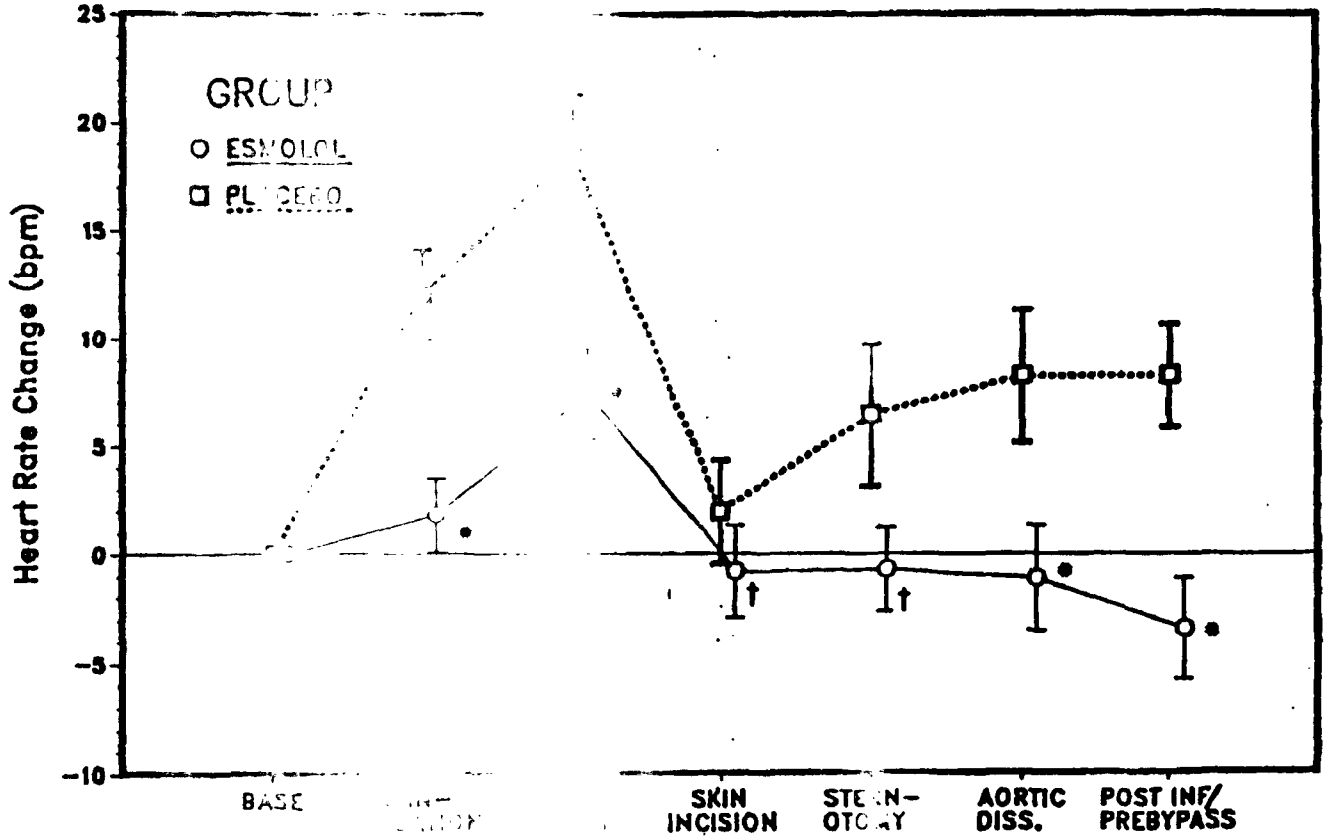


FIGURE 3

Changes From Baseline
n ± standard error)



* *Esmolol is significantly lower than p... with respect to change (p<0.05).*
† *Not tested due to ca... myocardial n... tion.*

FIGURE 4

Blood Pressure
± standard error)

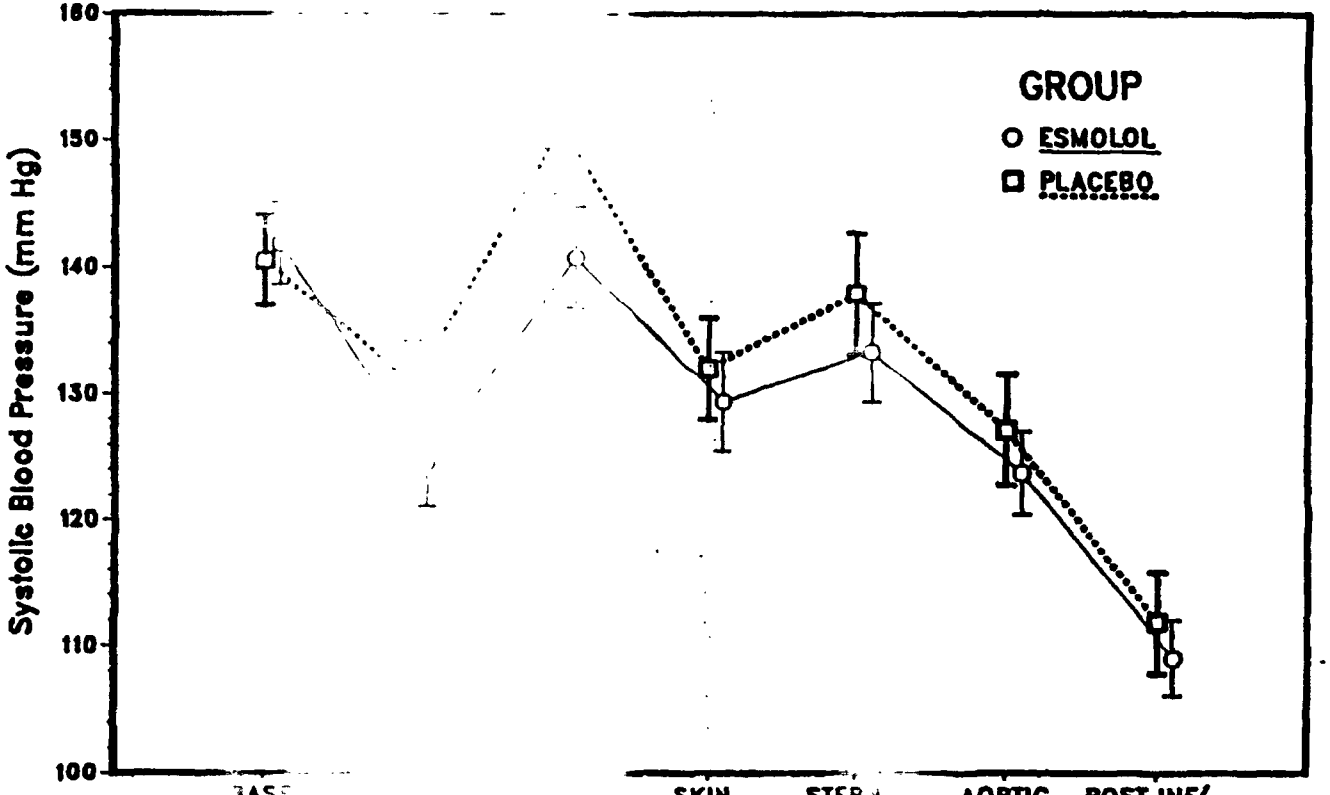
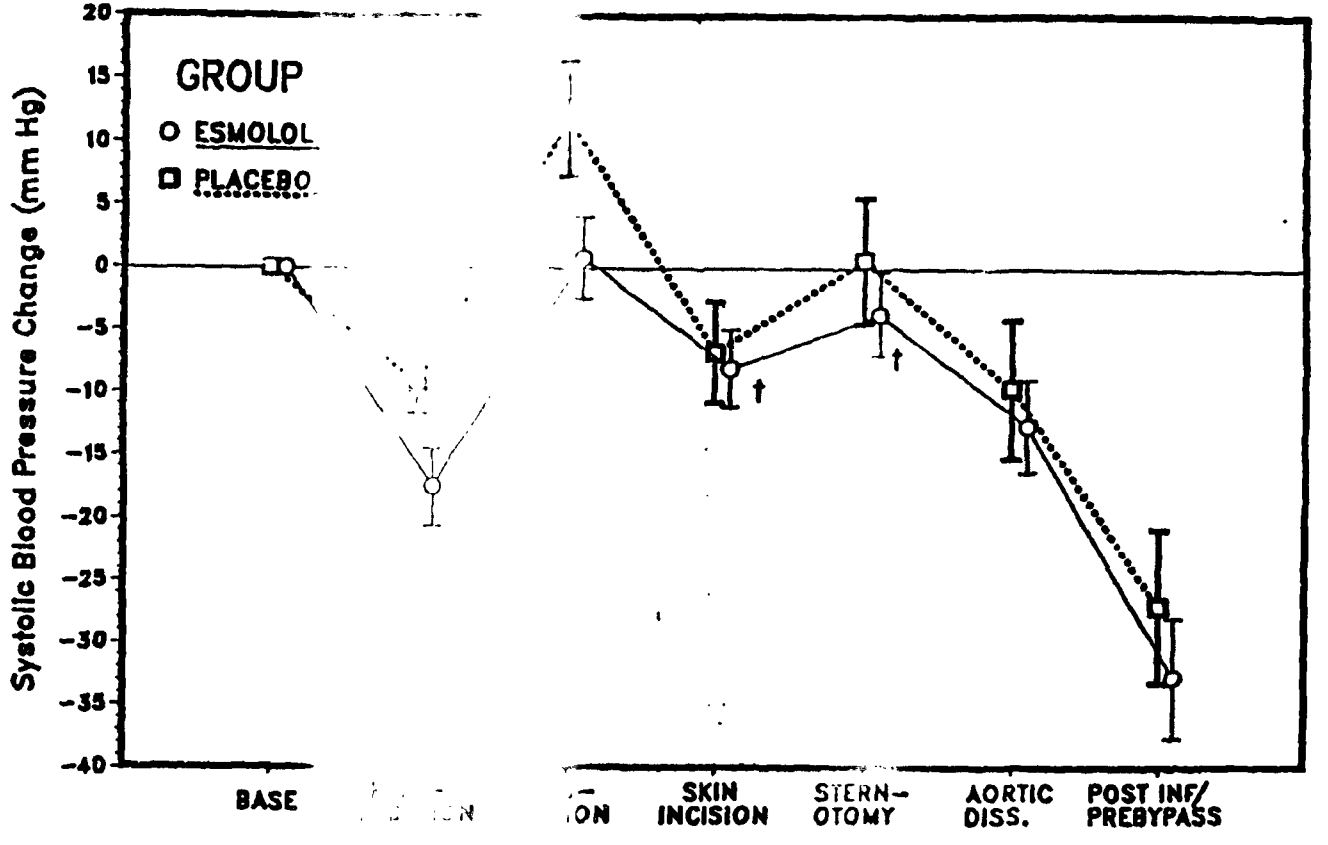


FIGURE 5

Systolic Blood Pressure Changes From Baseline
(Mean ± standard error)



† Not tested due to center by treatment interaction.

FIGURE 6

te–Pressure Product
mean ± standard error)

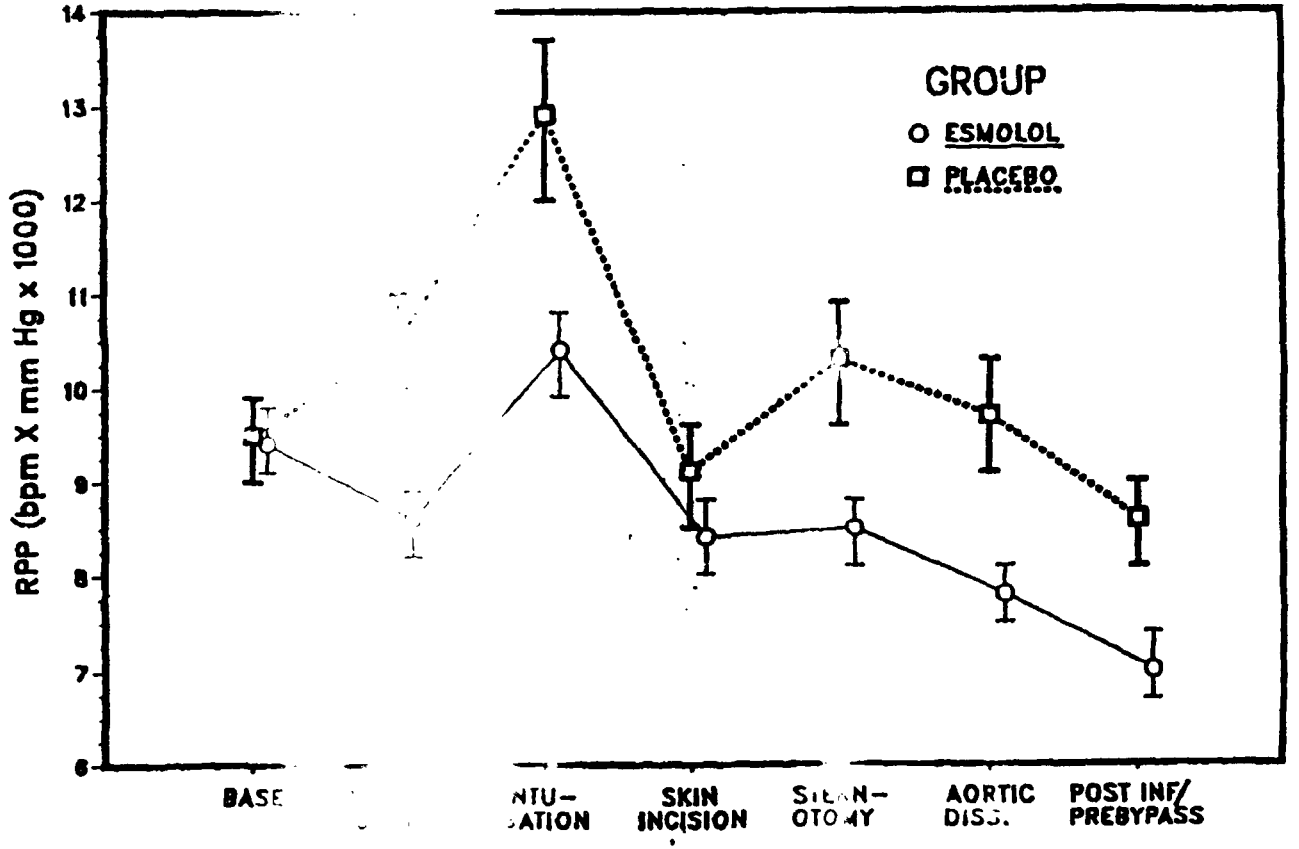
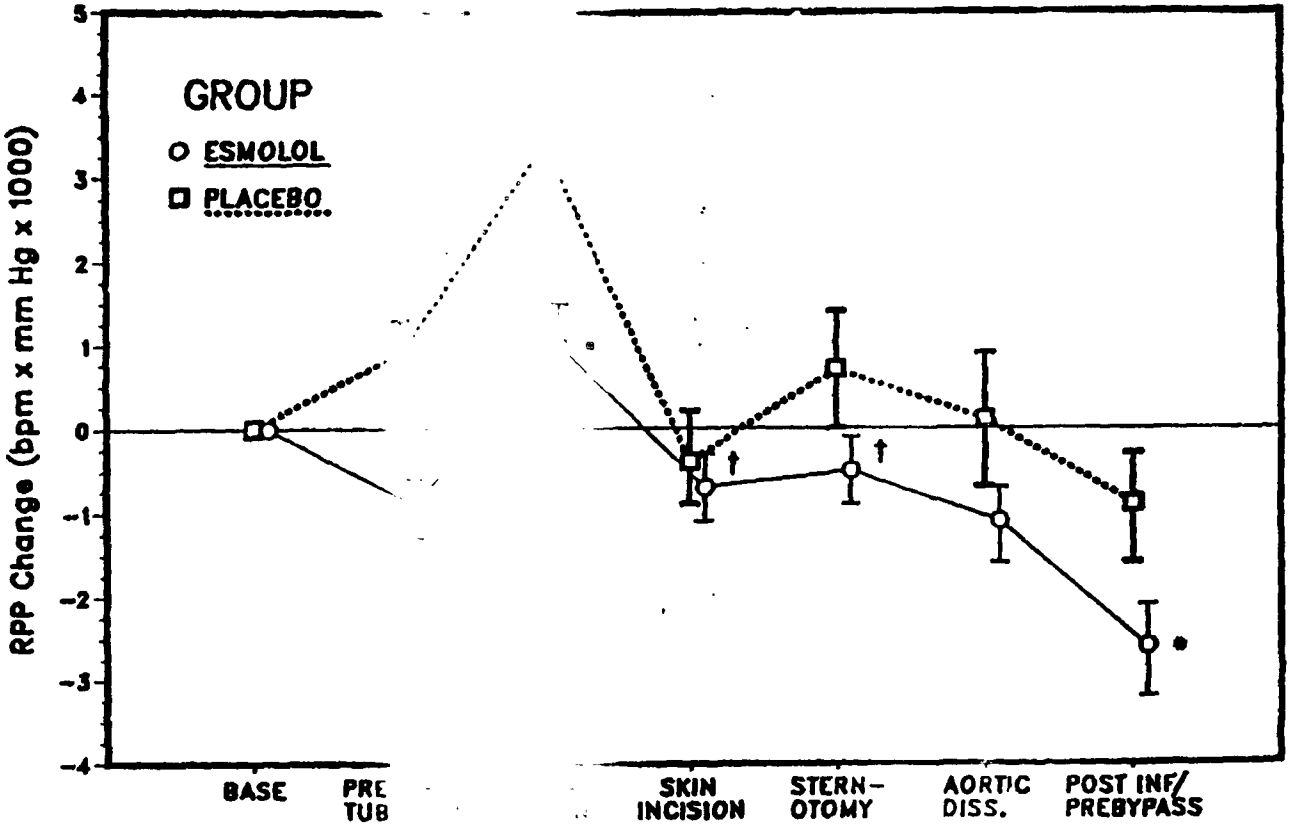


FIGURE 7

Rate–Pressure Product Changes From Baseline
(mean ± standard error)



* *Esmolol is significantly lower ... with respect to change ($p<0.05$).*
† *Not tested due to center by treat... tion.*

FIGURE 8

olic Blood Pressure
an ± standard error)

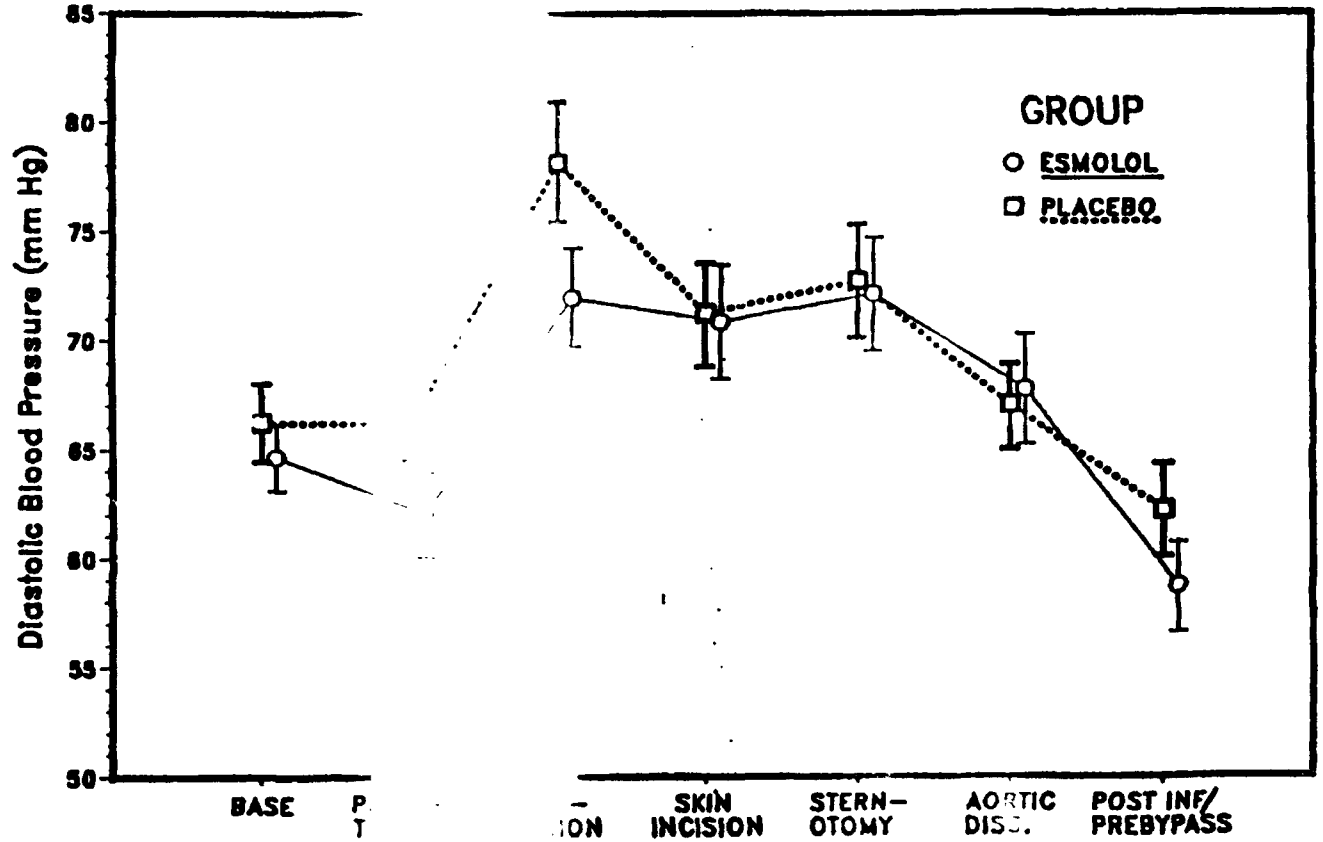
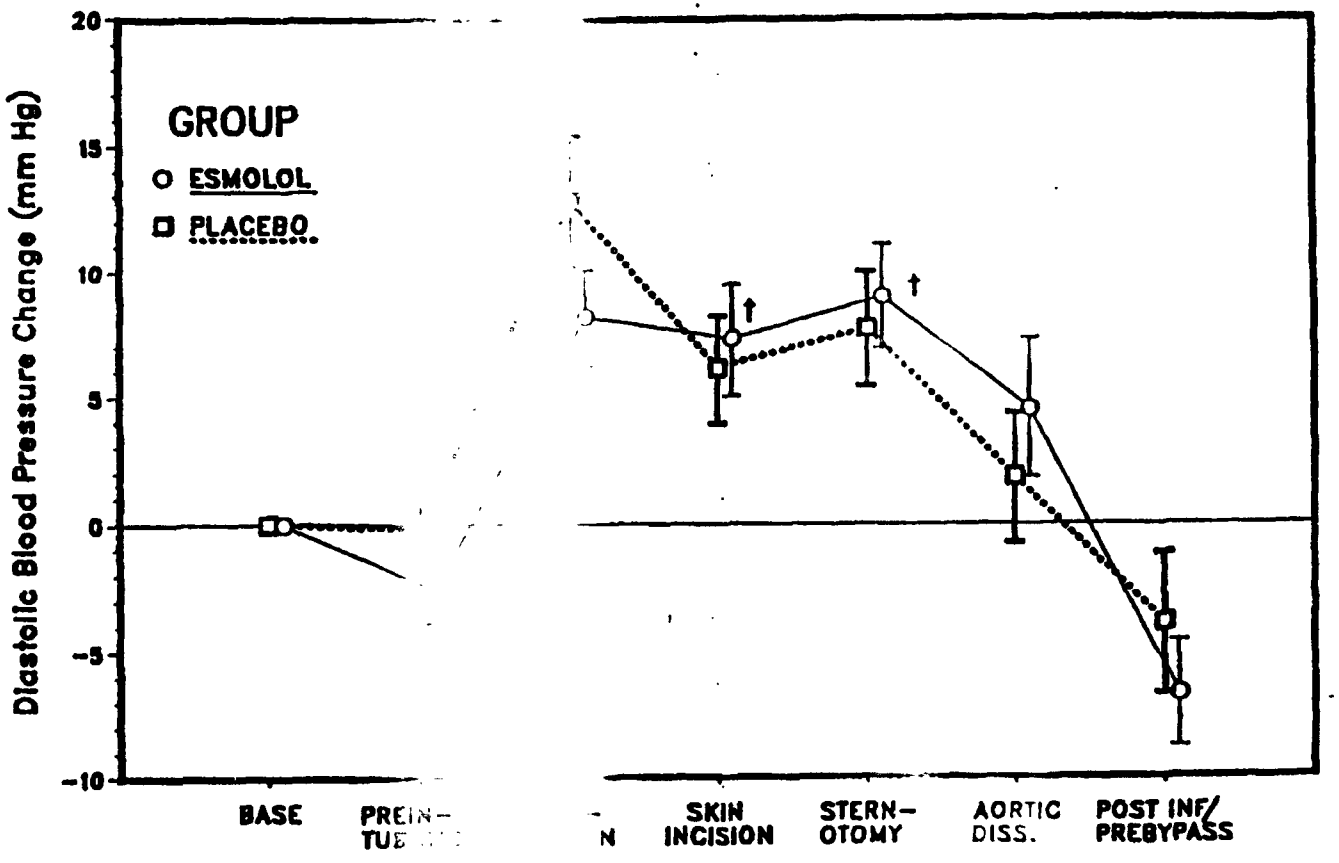


FIGURE 9

Diastolic Blood Pressure Changes From Baseline
(mean ± standard error)



† *Not tested due to center by tre* *ction.*

FIGURE 10

. Arterial Pressure
an ± standard error)

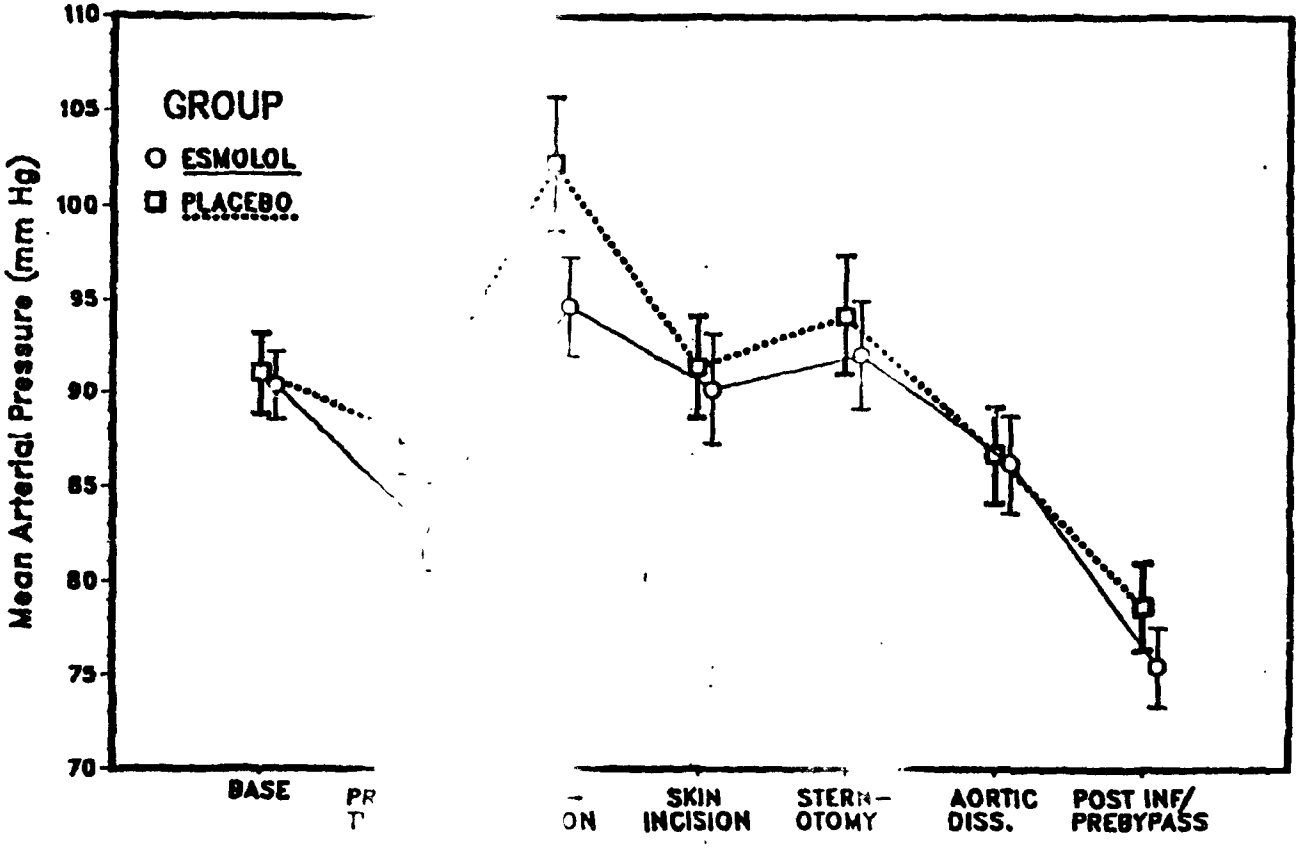
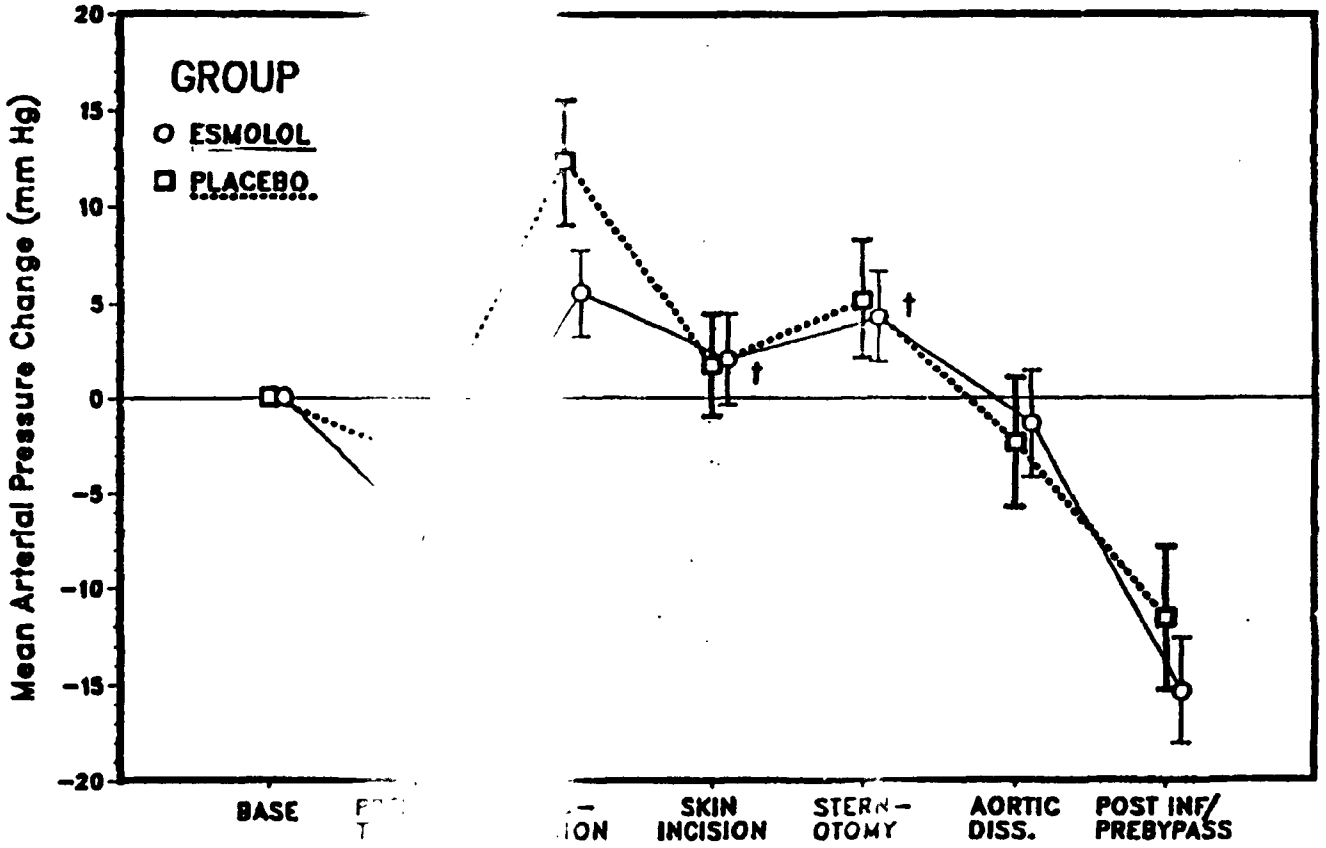


FIGURE 11

Mean Arterial Pressure Changes From Baseline
(Mean ± standard error)



† *Not tested due to center by t[illegible]action.*

FIGURE 12

Heart Rate

Standard Therapy Patients

...an ± standard error)

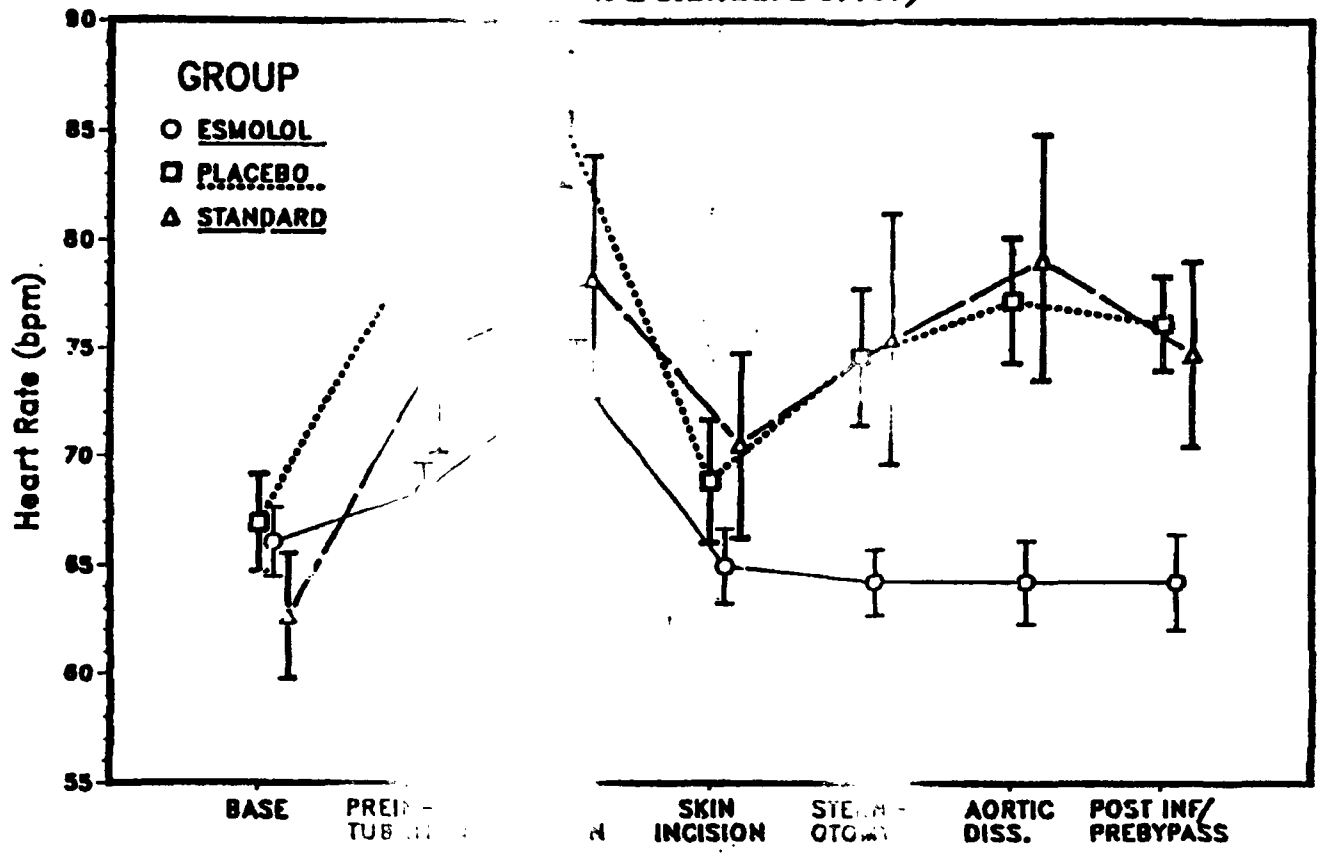
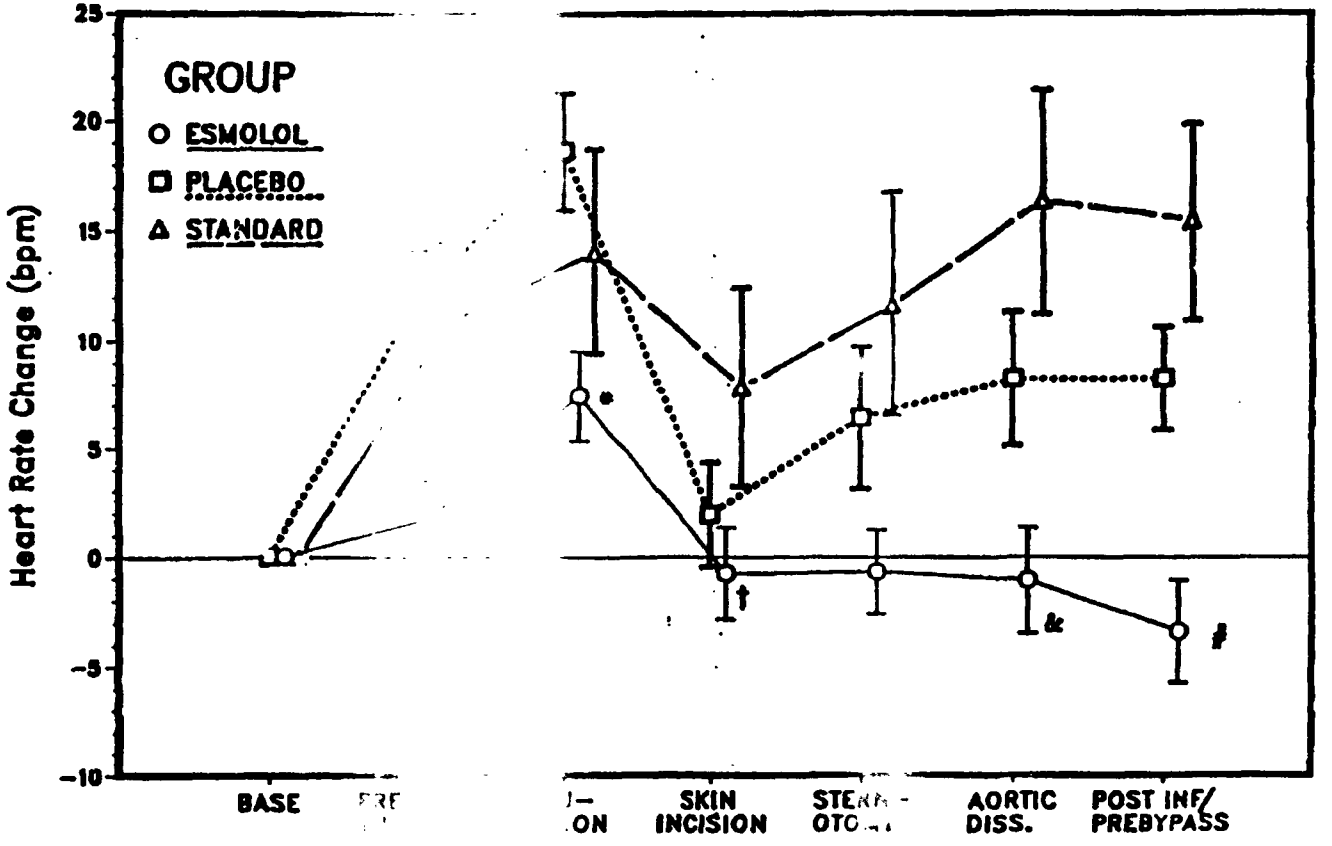


FIGURE 13

H[illegible]e Changes From Baseline
I[illegible]g Standard Therapy Patients
[illegible]ean ± standard error)



* Esmolol is significantly lower [illegible] respect to change ($p<0.05$).
# Esmolol is significantly lower [illegible] standard therapy with respect to change ($p<0.05$)
& Esmolol is significantly lower [illegible] therapy with respect to change ($p<0.05$).
† Not tested due to center by trea[illegible]n.

FIGURE 14

olic Blood Pressure
Standard Therapy Patients
ean ± standard error)

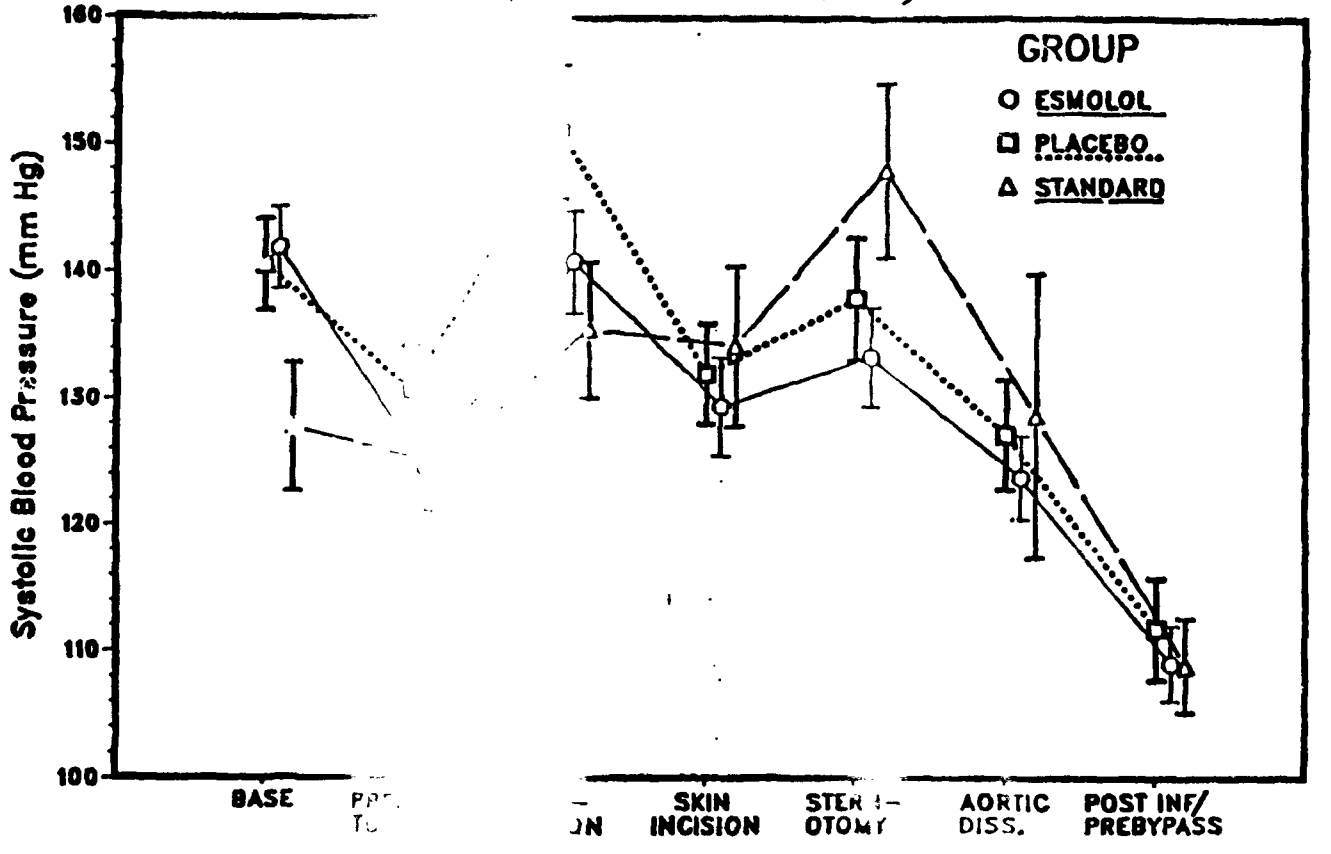


FIGURE 18

Hea[illegible]te: All Patients
(± standard error)

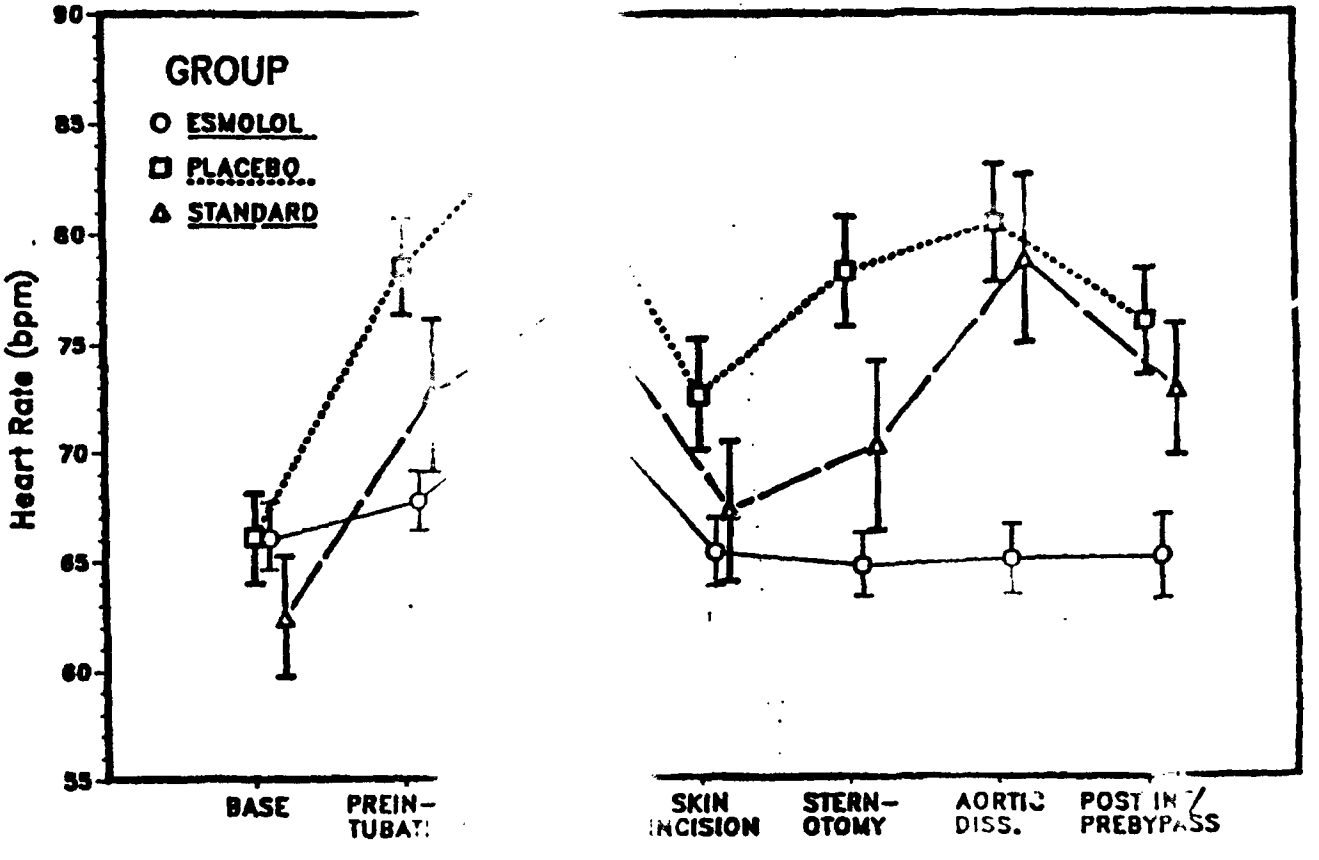
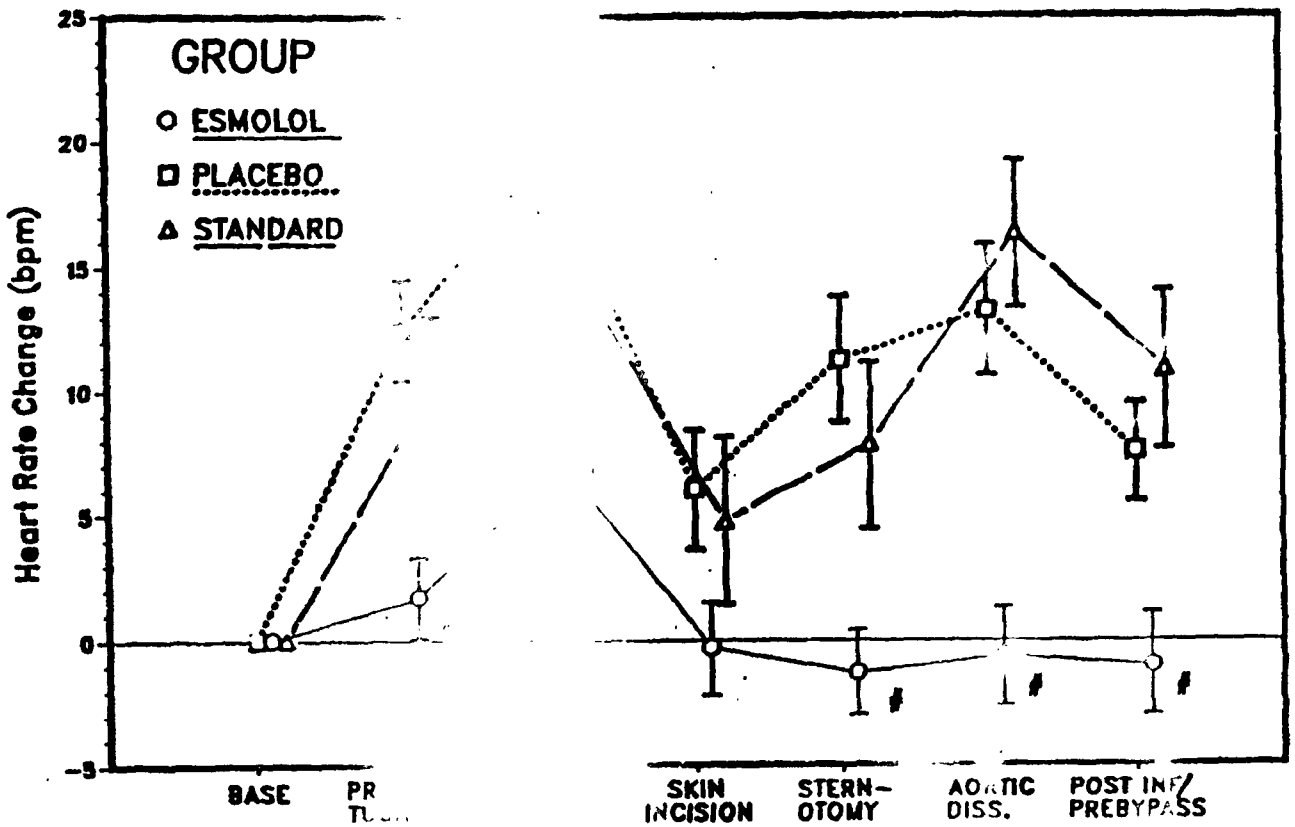


FIGURE 19

Heart Rate C... From Baseline: All Patients
± standard error)



 # Esmolol is significantly lower th... ...standard therapy with respect to change (p<0.05).

FIGURE 20

l Pressure: All Patients
± standard error)

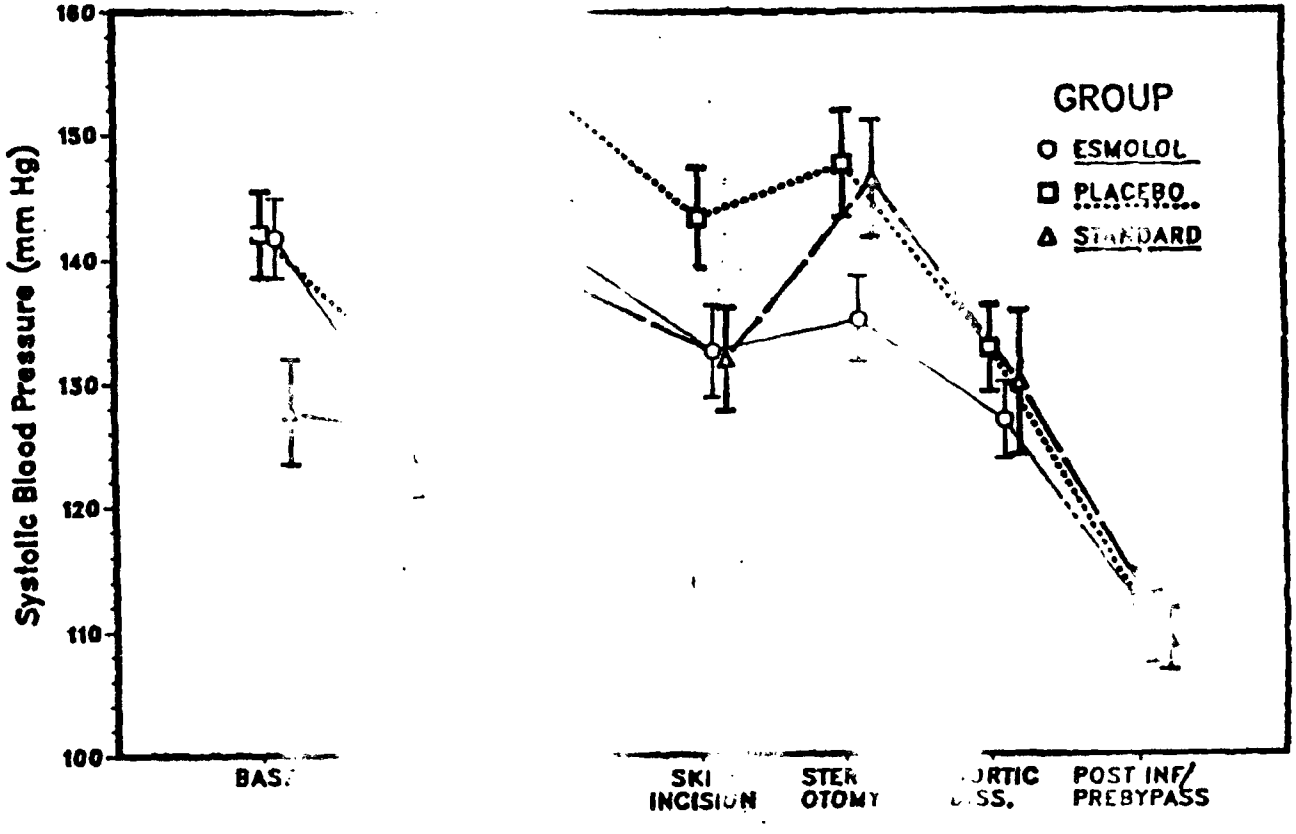
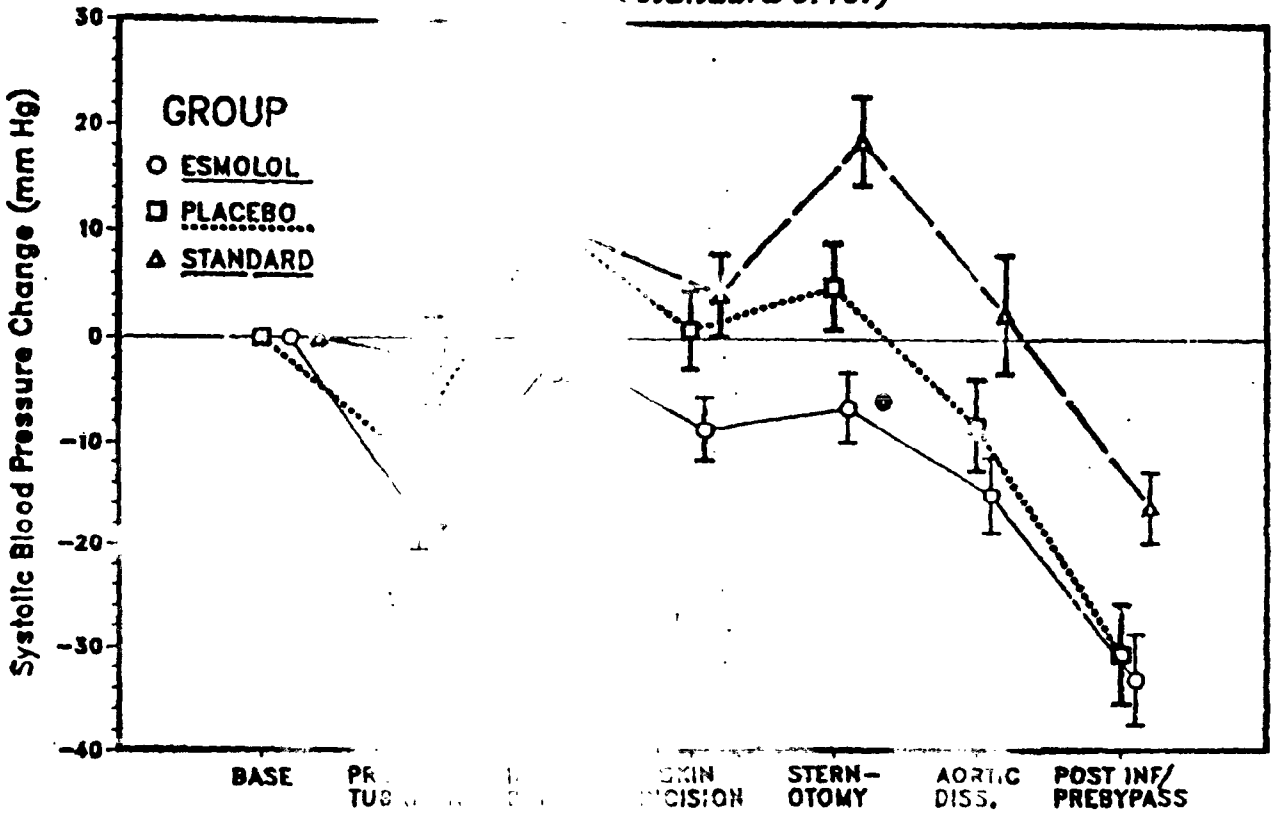


FIGURE 21

Systolic Blood [illegible]ure Changes From Baseline:
[illegible]ll Patients
([illegible] standard error)

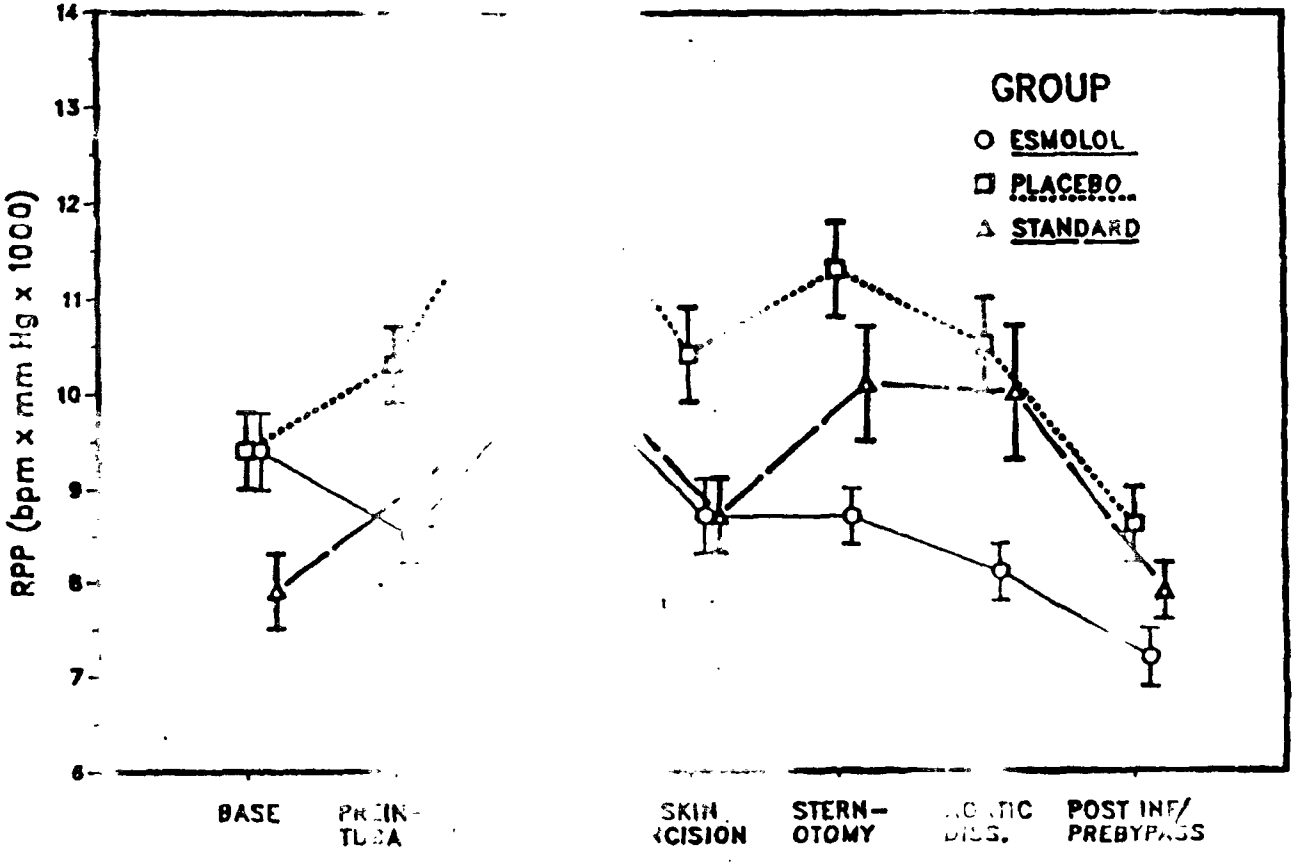


‡ *Esmolol is significantly lower*
‡ *Esmolol and placebo are sign.*
● *Esmolol is significantly lower with respect to change (p<0.05,*

standard therapy with respect to change (p<0.05).
standard therapy with respect to change (p<0.05).
placebo is significantly lower than standard therapy

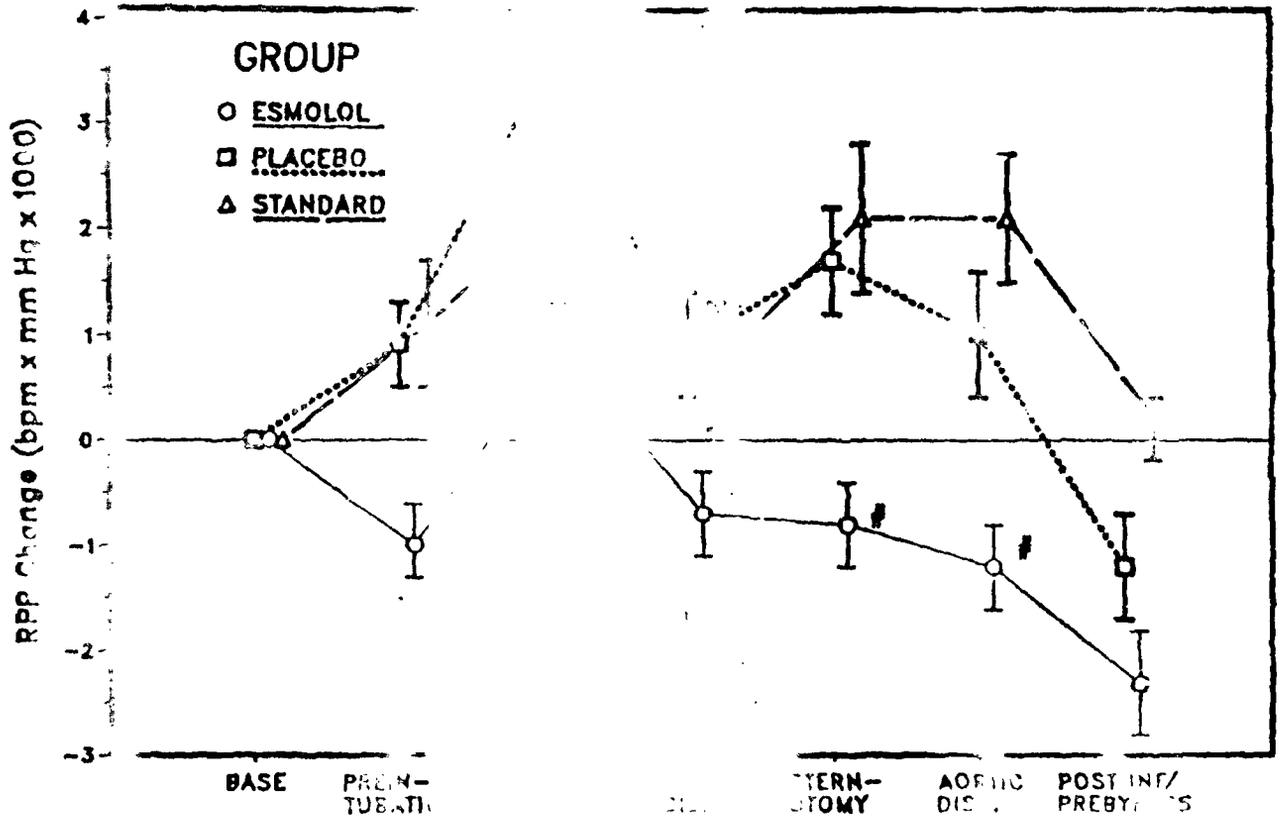
URE 22

ssure Product:
Patients
tandard error)



URE 23

Rate–Press… … ct Changes From Baseline:
Pati…nts
tan… …d error)



 # Esmolol … significantly lower tha… … with respect to change (p<0.05).

APPENDIX I

ANESTHETIC TECHNIQUES USED AT EACH CENTER

Appendix I

ANESTHETIC TECHNIQUES USED AT EACH CENTER*

Center 1 (University of Alabama, Birmingham, AL):

A. Premedication (60-90 minutes prior to induction of anesthesia)
   1. diazepam 0.15 mg/kg po
   2. morphine sulfate 0.1 mg/kg IM
   3. scopolamine 0.3-0.4 mg IM

B. Induction
   1. diazepam 0.5 mg/kg IV
   2. pancuronium 0.1 mg/kg IV
   3. nitrous oxide in oxygen 50:50

C. Maintenance
   1. enflurane INH as needed

Center 2 (University of Kansas, Kansas City, KS):

A. Premedication
   1. lorazepam 2 mg po (the night before surgery)
   2. lorazepam 2-4 mg po (90 minutes prior to induction of anesthesia)

B. Induction
   1. lorazepam 2 mg IV (optional)
   2. fentanyl 50 mcg/kg IV
   3. pancuronium 2 mg IV
   4. pancuronium 0.1 mg/kg IV

C. Maintenance
   1. fentanyl 0.5 mcg/kg/min IV

Center 3 (Emory University Hospital, Atlanta, GA):

A. Premedication (60-90 minutes prior to induction of anesthesia)
   1. lorazepam 0.05 mg/kg po
   2. morphine sulfate 0.1 mg/kg IM

B. Induction
   1. fentanyl 50 mcg/kg IV (over 20 minutes)
   2. pancuronium 0.08-0.1 mg/kg IV

C. Maintenance
   1. fentanyl 0.3 mcg/kg/min IV

* Center 4 (University of Iowa Hospitals and Clinics, Iowa City, IA) is not discussed due to early withdrawal from study participation prior to entering any patients.

Appendix I (continued)

ANESTHETIC TECHNIQUES USED AT EACH CENTER

Center 5 (V.A. Medical Center, Miami, FL):

A. Premedication (60-90 minutes prior to induction of anesthesia)
   1. diazepam 0.15 mg/kg po
   2. morphine sulfate 0.1 mg/kg IM
   3. scopolamine 0.3-0.4 mg IM

B. Induction
   1. fentanyl 50 mcg/kg IV
   2. pancuronium 0.1 mg/kg IV

C. Maintenence
   1. halothane INH as needed
   2. fentanyl IV as needed

Center 6 (Mt. Sinai Medical Center, New York, NY):

A. Premedication (60-90 minutes prior to induction of anesthesia)
   1. diazepam 0.1 mg/kg po
   2. morphine sulfate 0.1 mg/kg IM
   3. scopolamine 0.4 mg IM

B. Induction
   1. fentanyl 50-100 mcg/kg IV
   2. pancuronium 0.15 mg/kg IV

C. Maintenance
   1. fentanyl IV as needed
   2. enflurane INH as needed

APPENDIX V

SUMMARY OF PRESTUDY 12-LEAD ELECTROCARDIOGRAPHIC FINDINGS

Appendix V

SUMMARY OF PRESTUDY 12-LEAD ELECTROCARDIOGRAPHIC FINDINGS

PATIENT NUMBER	DESCRIPTION OF FINDINGS
101	T-wave inversion in inferior leads.
103	Non-specific ST-T wave abnormalities.
105	Non-specific ST-segment abnormality.
106	Right bundle branch block.
107	Inverted T-waves in leads II, III and AVF compatible with inferior infarct (age undetermined).
108	Non-specific ST-T wave changes. Evidence of old infero-lateral myocardial infarction.
109	Non-specific ST-T wave abnormalities. Evidence of inferior infarct (age undetermined).
110	ST-T wave abnormality consistent with inferior lateral ischemia.
111	Non-specific ST-segment abnormality.
113	Inverted T-waves in anterolateral chest leads.
114	Prolonged QT interval or TU fusion.
118	Elevated ST-segments and inverted T-waves in anterior lateral chest leads compatible with anterior lateral ischemia.
119	Non-specific T-wave abnormality.
122	Non-specific ST-segment abnormality.
123	ST-T wave changes compatible with lateral ischemia.
203	Q-waves in leads III and AVF; possible old inferior myocardial infarction.
205	1 mm ST-segment depression. T-wave inversion in leads II, III and AVF.
206	Inverted T-waves in leads V_5 and V_6.
201C	Non-diagnostic inferior ST-segment changes (<1 mm elevation). Inverted T-waves in inferior leads.

Appendix V (continued)

SUMMARY OF PRESTUDY 12-LEAD ELECTROCARDIOGRAPHIC FINDINGS

PATIENT NUMBER	DESCRIPTION OF FINDINGS
302	Non-specific ST-T wave changes.
303	Non-specific ST-T wave changes.
304	Evidence of old inferior myocardial infarction.
305	Right bundle branch block.
306	Non-specific ST-T wave changes.
309	Non-specific ST-T wave changes.
310	Septal Q-waves.
311	Non-specific ST-T wave changes.
315	Non-specific ST-T wave changes.
316	Non-specific ST-T wave changes.
317	Inferior Q-waves.
318	T-wave inversion in inferior leads.
320	Non-specific ST-T wave changes.
302C	Possible old inferior myocardial infarction.
303C	Non-specific ST-T wave changes.
304C	Non-specific ST-T wave changes.
305C	Right bundle branch block.
306C	Septal Q-waves.
307C	Non-specific ST-T wave changes.
308C	Non-specific ST-T wave changes.
310C	Non-specific ST-T wave changes.
501	First degree atrioventricular (AV) block. Incomplete right bundle branch block. Ischemic changes in all leads. T-wave inversion in inferior leads.

Appendix V (continued)

SUMMARY OF PRESTUDY 12-LEAD ELECTROCARDIOGRAPHIC FINDINGS

PATIENT NUMBER	DESCRIPTION OF FINDINGS
502	Non-specific ST-T wave changes.
503	Non-specific ST-T wave changes.
504	Non-specific ST-T wave changes.
506	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.
507	Q-waves in lead III; small Q-wave in lead AVF.
508	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.
509	ST-segment elevation consistent with post-myocardial infarction.
510	Intra-atrial conduction delay. Incomplete right bundle branch block.
511	First degree AV block. Right bundle branch block. Left anterior hemiblock. Peaked ST-segments.
513	First degree AV block. Evidence of old inferior wall myocardial infarction.
515	Incomplete left bundle branch block. Inverted T-waves. Q-waves present.
516	Non-specific ST-T wave change
501C	Minor ST-T wave changes.
502C	First degree AV block. Minor ST-T wave changes.
503C	First degree AV block. Inverted T-waves in lead I; flattened T-waves in leads II, V_4 and V_5.
504C	First degree AV block. Q-waves present.
505C	Occasional PVCs. First degree AV block. Right bundle branch block. Q-waves present.
506C	Q-waves present.
507C	Non-specific ST-T wave changes.

Appendix V (continued)

SUMMARY OF PRESTUDY 12-LEAD ELECTROCARDIOGRAPHIC FINDINGS

PATIENT NUMBER	DESCRIPTION OF FINDINGS
601	J-point depression in leads II, III, AVF, V_5 and V_6. Biphasic T-waves in leads III and AVF.
602	Occasional PVCs. Non-specific ST-T wave changes in leads V_4-V_6. Q-waves in inferior and anterior leads.
605	Elevated ST-segments in leads V_2 and V_3. Inverted T-waves in leads II, III, AVF, V_5 and V_6. Q-waves in leads III and V_2.
606	Inverted T-waves in lead III. Q-waves in lead III.
608	Inverted T-waves in lead III. Q-waves in lead III.
609	Inverted T-waves in lead AVL. Q-waves in leads I, AVL and V_2-V_6.
611	Inverted T-waves in leads III, V_2 and AVF.
613	Inverted T-waves in lead AVL. Micro Q-waves in leads V_2-V_4.
614	Inverted T-waves in leads III, AVL and V_4-V_6.
616	PVCs. First degree AV block.
617	Inverted T-waves in leads III and AVF. Q-waves in leads III and AVF.
619	First degree AV block. Depressed ST-segments in leads V_4 and V_5. Inverted T-waves in leads III, AVF and AVF.
620	Inverted T-waves in leads V_{1-4}. Q-waves in leads II, III and AVF.
621	Flattened T-waves in lead II. Inverted T-waves in leads III and AVF. Q-waves in lead III.
625	Inverted T-waves in leads II, III and AVF. Q-waves in leads II, III and AVF.

Appendix A_2 Study 8052-84-56

EFFECT OF ESMOLOL VERSUS PLACEBO ON HEMODYNAMICS AND MYOCARDIAL ISCHEMIA DURING SPECIFIED SURGICAL STIMULI IN ANESTHETIZED CORONARY REVASCULARIZATION PATIENTS

PROTOCOL #8052-84-56

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MEDICAL SUMMARY

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Figure 1

SCHEMATIC OF HEART RATE AND BLOOD PRESSURE DATA INCLUDED FOR EFFICACY ANALYSIS

Treatment	Patient	INFUSION PERIOD*							Comments
		Initial Infusion	Induction	Intubation	Skin Incision	Sternotomy	Aortic Dissection	Pre Bypass	
Esmolol	101	--------	---------	----------	--------	---------	----------	----->	
Esmolol	102	--------	---------	--------->		---------	----------	----->	Skin incision period clinical observation time off protocol schedule
Placebo	103	--------	---------	----------	--------	---------	----------	----->	
Placebo	104	--------	---------	----------	--------	---------	----------	----->	
Esmolol	105	--------	---------	----------	--------	---------	----------	----->	
Placebo	106	--------	-------->		------->		----------	----->	Intubation period isoflurane dose increase >2.30%. Sternotomy period clinical observation time off protocol schedule
Placebo	107	--------	-------->		------	---------	----------	----->	Intubation period isoflurane induction dose >2.30%. Skin incision period study minutes 0 & 1 isoflurane dose decrease >2.30%
Placebo	110	--------	---------	----------	--------	---------	----------	----->	
Esmolol	111	--------	---------	----------	--------	---------	- --------	----->	
Esmolol	112	--------	---------	----------	------->			----->	Difficult and prolonged sternotomy. Esmolol discontinuation during aortic dissection
Esmolol	113	------->			--------	--------->			Phenylephrine administration
Placebo	114								Patient excluded because nitroglycerin (sl) given before and during initial infusion period
Placebo	115	--------	---------	--------->			----------	----->	Ephedrine administration
Esmolol	116	--------	---------	----------	--------	---------	----------	----->	
Esmolol	117	--------	-------->		--------	---------	----------	----->	Induction period study minutes 4 & 5 and intubation period isoflurane induction dose >2.30%

* Periods containing dotted lines were included for efficacy analysis.

Figure 1 (continued)

SCHEMATIC OF HEART RATE AND BLOOD PRESSURE DATA INCLUDED FOR EFFICACY ANALYSIS

Treatment	Patient	INFUSION PERIOD*							Comments
		Initial Infusion	Induction	Intubation	Skin Incision	Sternotomy	Aortic Dissection	Pre Bypass	
Placebo	118	---------	------>		---------	----------	----------	----->	Induction period study minutes 4 & 5 and intubation period isoflurane induction dose >2.30%
Placebo	120	---------	----------	----------	---------	----------	----------	----->	
Esmolol	121	---------	----------	----------	---------	----------	----------	----->	
Placebo	122	---------	----------	----------	---------	----------	----------	----->	
Placebo	123	---------	--------->		---------	----------	----------	----->	Intubation started prior to induction of anesthesia completed
Esmolol	124	---------	----------	----------	---------	----------	---------->		Phenylephrine administration
Placebo	125	---------	---------	---------->		----------	----------	----->	Skin incision period isoflurane dose increase >2.30%
Esmolol	126	---------	----------	----------	---------	--------->			Aortic dissection and pre-bypass periods isoflurane restart dose >2.30%
Placebo	127	---------	----------	----------	---------	----------	----------	----->	
Esmolol	128	---------	----------	----------	---------	--------->		----->	Aortic dissection period clinical observation time off protocol schedule
Placebo	129	---------	----------	----------	---------	----------	----------	----->	
Placebo	130	---------	----------	----------	---------	----------	---------->		Phenylephrine, ephedrine, and nitroglycerin administration
Esmolol	131	---------	----------	----------	---------	----------	----------	----->	
Esmolol	132	---------	--------->		---------	----------	----------	----->	Multiple intubation
Esmolol	133	---------	----------	----------	---------	----------	-------->		Aortic dissection period minute 5 and pre-bypass phenylephrine administration

* Periods containing dotted lines were included for efficacy analysis.

Table 3A

SUMMARY OF DEMOGRAPHIC AND PRESTUDY CLINICAL DATA,
FOR ALL PATIENTS BY TREATMENT GROUP

		Mean ± SD		Min	Max	N[a]
Age (years)	ESMOLOL	57.6	8.0	46.0	77.0	15
	PLACEBO	56.0	8.3	42.0	67.0	15
Height (cm)	ESMOLOL	170.7	5.7	157.0	177.0	15
	PLACEBO	172.3	6.3	163.0	183.0	15
Weight (kg)	ESMOLOL	75.2	8.7	64.0	97.0	15
	PLACEBO	76.9	13.3	61.0	113.0	15
BSA (m2)	ESMOLOL	1.9	0.1	1.7	2.1	15
	PLACEBO	1.9	0.2	1.7	2.3	15
Heart Rate (bpm)	ESMOLOL	62.9	8.1	50.0	75.0	15
	PLACEBO	58.3	8.5	46.0	75.0	15
SBP (mm Hg)	ESMOLOL	129.0	17.1	105.0	160.0	15
	PLACEBO	130.3	18.9	110.0	160.0	15
DBP (mm Hg)	ESMOLOL	81.0	11.1	60.0	100.0	15
	PLACEBO	79.0	10.9	60.0	90.0	15
Resp (/min)	ESMOLOL	13.2	1.3	12.0	16.0	13
	PLACEBO	13.9	2.6	12.0	20.0	14
Temp (^{o}C)	ESMOLOL	36.8	0.3	36.0	37.0	15
	PLACEBO	36.7	0.4	36.0	37.0	14

[a] Respiratory rate was not recorded for Patients 102, 114, and 133. Body temperature was not recorded for Patient 114.

Note: No significant differences were found between the esmolol and placebo treatment groups ($p \geq 0.05$).

Table 3B

Demographic Data (NYHA Class, ASA Class, Sex, Race, Smoking History and Alcohol Use)

Group	NYHA Class		ASA Class		Sex		Race	Smoker		Alcohol Use		
	III	IV	III	IV	M	F	Cauc	Yes	No	Never	Occas	Freq
ESMOLOL	15	0	15	0	13	2	15	5	10	1	12	2
PLACEBO	14	1	14	1	14	1	15	3	12	0	11	4

Note: No significant differences were found between the esmolol and placebo treatment groups ($p \geq 0.05$).

Table 4

SUMMARY OF PRESTUDY STRESS ELECTROCARDIOGRAPHIC TESTING DATA

		Mean	± SD	Min	Max	N
HR Rest (bpm)	ESMOLOL	64.5	10.7	44.0	77.0	8
	PLACEBO	65.5	13.0	53.0	92.0	11
HR Peak (bpm)	ESMOLOL	117.7	23.8	80.0	165.0	12
	PLACEBO	116.7	20.5	86.0	147.0	12
SBP Rest (mm Hg)	ESMOLOL	129.8	16.3	104.0	154.0	8
	PLACEBO	130.0	18.4	100.0	160.0	11
SBP Peak (mm Hg)	ESMOLOL	154.0	24.4	108.0	196.0	11
	PLACEBO	160.5	17.7	135.0	190.0	11
DBP Rest (mm Hg)	ESMOLOL	81.0	8.8	68.0	100.0	8
	PLACEBO	79.5	10.1	60.0	90.0	11
DBP Peak (mm Hg)	ESMOLOL	85.5	12.9	60.0	110.0	11
	PLACEBO	86.0	12.6	70.0	110.0	10
RPP Rest	ESMOLOL	8.3	2.5	5.7	11.9	5
	PLACEBO	8.6	2.3	5.4	12.0	10
RPP Peak	ESMOLOL	17.6	4.8	9.7	27.8	11
	PLACEBO	18.4	4.3	14.4	27.9	11

Note: No significant differences were found between the esmolol and placebo treatment groups ($p \geq 0.05$).

Table 5A

Incidence of Ischemia

Event	Patient Number	
	Placebo	Esmolol
Induction	114, 115	
Intubation	114, 115	
Aortic Dissection	127*, 130*	128*, 131
Post-Aortic Dissection	118*	

* Classified as having an ischemic episode by the blinded cardiologist during the reevaluation of Holter recordings.

NOTE: No significant treatment group differences were found with respect to the proportion of patients having an ischemic episode in either the initial or reevaluation ($p \geq 0.05$).

Table 5B

Proportion of Patients Having PVCs During Each Study-Event

Event	Group (# of PVCs)	
	Esmolol	Placebo
Baseline	3/15	4/15
Insertion of Monitor[a]	13/15	12/15
Infusion Start	4/15	5/15
Induction Start	1/15	4/15
Intubation	2/15	2/15
Skin Incision	1/15	1/15
Sternotomy	4/15	3/15
Aortic Dissection*	9/15	14/15

[a] Prior to study drug infusion.

* A significantly greater proportion of patients in the placebo group had at least one PVC in comparison with the esmolol group ($p < 0.05$).

Table 6

Heart Rate and Systolic Blood Pressure with Maximum Changes from Baseline for Efficacy Patients by Event

	Group	BASELINE			INTUBATION			SKIN INCISION			STERNOTOMY			AORTIC DISSEC.		
		Mean	±SEM	N[b]	Mean	±SEM	N	Mean	±SEM	N	Mean	±SEM	N	Mean	±SEM	N
HR (bpm)	Esmolol	54.6	2.2	15	67.7	2.6	12	66.1	2.2	14	64.4	2.1	14	62.0	2.1	11
	Placebo	52.0	1.4	14	67.4	2.8	10	60.3	2.6	13	61.6	1.7	12	63.9	2.5	14
HR Change	Esmolol				15.0	3.1	12	10.5	3.2	14	9.5	2.8	14	7.8	2.5	11
	Placebo				14.3	2.3	10	8.1	2.4	13	8.9	2.0	12	11.9	2.3	14
Comparison of Change[a]			N.S.			N.S.			N.S.			N.S.			N.S.	
SBP (mm Hg)	Esmolol	146.0	6.3	15	138.5	3.7	12	132.3	3.7	14	128.6	3.7	14	123.6	3.2	11
	Placebo	133.8	6.3	14	137.3	7.6	10	131.2	4.7	13	139.8	6.4	12	125.8	3.2	14
SBP Change	Esmolol				-2.5	5.5	12	-13.5	5.9	14	-16.4	5.7	14	-26.4	7.2	11
	Placebo				6.4	4.0	10	-3.1	4.4	13	4.2	4.0	12	-8.0	6.7	14
Comparison of Change[a]			N.S.			N.S.			N.S.			E<P**			N.S.	

[a] N. S. indicates no significant difference between the esmolol and placebo treatment groups ($p \geq 0.05$), P = Placebo, E = Esmolol 300 mcg/kg/min, * $p<0.05$, ** $p<0.01$.

[b] Due to exclusion of partial data, the sample size varied during the study.

Table 7

Diastolic, Mean Arterial Blood Pressure, and Rate-Pressure Product with Maximum Changes from Baseline for Efficacy Patients by Event

		BASELINE			INTUBATION			SKIN INCISION			STERNOTOMY			AORTIC DISSEC.		
	Group	Mean	±SEM	N[b]	Mean	±SEM	N	Mean	±SEM	N	Mean	±SEM	N	Mean	±SEM	N
DBP (mm Hg)	Esmolol	73.4	2.7	15	77.3	3.4	12	76.1	3.3	14	74.9	2.8	14	72.2	3.7	11
	Placebo	68.3	2.2	14	71.1	3.0	10	71.9	2.4	13	78.8	3.3	12	74.7	2.8	14
DBP Change	Esmolol				4.4	2.7	12	3.2	2.7	14	1.8	1.8	14	-2.3	2.8	11
	Placebo				5.2	2.0	10	2.9	2.7	13	10.1	3.3	12	6.4	3.4	14
Comparison of Change[a]			N.S.			N.S.			N.S.			E<P*			N.S.	
MAP (mm Hg)	Esmolol	97.6	3.6	15	97.7	3.2	12	94.6	3.0	14	92.2	2.9	14	89.2	3.2	11
	Placebo	90.1	3.3	14	93.0	4.3	10	91.4	2.9	13	98.8	4.2	12	91.8	2.7	14
MAP Change	Esmolol				2.0	3.5	12	-2.8	3.5	14	-4.9	3.0	14	-10.4	4.0	11
	Placebo				5.4	2.5	10	0.8	3.0	13	7.7	3.4	12	1.5	4.2	14
Comparison of Change[a]			N.S.			N.S.			N.S.			E<P*			N.S.	
RPP	Esmolol	8.0	0.5	15	9.3	0.4	12	8.7	0.4	14	9.1	0.3	14	7.4	0.3	11
	Placebo	7.0	0.3	14	9.1	0.6	10	7.8	0.4	13	8.4	0.3	12	7.8	0.4	14
RPP Change	Esmolol				1.9	0.5	12	0.8	0.6	14	0.2	0.4	14	-0.7	0.5	11
	Placebo				2.2	0.5	10	0.8	0.5	13	1.3	0.4	12	0.8	0.5	14
Comparison of Change[a]			N.S.			N.S.			N.S.			N.S.			E<P*	

[a] N.S. indicates no significant difference between the esmolol and placebo treatment groups ($p \geq 0.05$), P = Placebo, E = Esmolol 300 mcg/kg/min, * $p<0.05$, ** $p<0.01$.

[b] Due to exclusion of partial data, the sample size varied during the study.

Table 10

Heart Rate and Systolic Blood Pressure with Maximum Changes from Baseline for All Patients by Event

		BASELINE			INTUBATION			SKIN INCISION			STERNOTOMY			AORTIC DISSEC.		
Group		Mean	±SEM	N	Mean	±SEM	N	Mean	±SEM	N	Mean	±SEM	N	Mean	±SEM	N
HR (bpm)	Esmolol	54.6	2.2	15	67.8	2.2	15	64.9	2.4	15	64.7	1.9	15	63.1	1.7	15
	Placebo	51.9	1.3	15	65.9	2.2	15	60.1	2.2	15	62.2	1.6	15	63.9	2.3	15
HR Change	Esmolol				13.2	2.8	15	10.4	3.0	15	10.2	2.7	15	8.5	2.6	15
	Placebo				14.0	2.0	15	8.2	2.1	15	10.4	1.9	15	12.0	2.1	15
Comparison of Change[a]			N.S.			N.S.			N.S.			N.S.			N.S.	
SBP (mmHg)	Esmolol	146.0	6.3	15	137.9	3.1	15	132.8	3.5	15	130.2	3.8	15	123.9	2.4	15
	Placebo	134.3	5.9	15	138.1	6.7	15	133.2	4.3	15	140.8	5.8	15	125.7	3.0	15
SBP Change	Esmolol				-8.2	5.9	15	-13.2	5.5	15	-15.8	5.3	15	-22.1	5.9	15
	Placebo				3.8	3.6	15	-1.1	4.1	15	6.2	4.1	15	-8.6	6.3	15
Comparison of Change[a]			N.S.			N.S.			N.S.			E<P**			N.S.	

[a] N.S. indicates no significant difference between the esmolol and placebo treatment groups ($p \geq 0.05$). P = Placebo, E = Esmolol 300 mcg/kg/min, * $p<0.05$, ** $p<0.01$.

Table 12

Summary of MAC Units* for All Patients, by Event

	Event											
	INDUCTION			INTUBATION			SKIN INC			STERNOTOMY			AORTIC DIS		
	MAC Units			MAC Units			MAC Units			MAC Units			MAC Units		
Group	Mean	±SEM	N	Mean	±SEM	N	Mean	±SEM	N	Mean	±SEM	N	Mean	±SEM	N
Esmolol	0.43	0.29	15	1.51	1.06	15	0.60	0.32	15	1.43	0.66	15	0.87	0.45	15
Placebo	0.40	0.29	15	1.85	0.75	15	0.67	0.30	15	2.78	0.72	15	2.23	0.73	15
Comparison[a]	N.S.			N.S.			N.S.			N.S.			N.S.		

[a] N.S. indicates no significant differences between the esmolol and placebo treatment groups ($p \geq 0.05$).

* MAC units = % inspired isoflurane/1.15% x minutes of isoflurane administration.

Table 14

Summary of Prescribed Medications for All Patients, by Treatment Group

	Medication (Prescribed Dose)																	
	Scopolamine (0.4 mg/kg)			Morphine (0.1 mg/kg)			Fentanyl (load) (40 mcg/kg)			Fentanyl (main.) (0.4 mcg/kg/min)			Pancuronium (0.1 mg/kg)			Isoflurane (initial dose, %)		
Group	MEAN ±	SEM	N	MEAN ±	SEM	N	MEAN ±	SEM	N	MEAN ±	SEM	N	MEAN ±	SEM	N	MEAN ±	SEM	N
ESMOLOL	0.35	0.01	15	0.13	0.00	15	39.99	0.09	15	0.40	0.00	15	0.10	0.00	15	1.68	0.29	11
PLACEBO	0.36	0.01	15	0.13	0.01	15	40.00	0.00	15	0.40	0.00	15	0.10	0.00	15	1.91	0.31	11
Comparison[a]	N.S.			N.S.			N.S.			N.S.			N.S.			N.S.		

[a] N.S. indicates no significant difference between the esmolol and placebo treatment groups ($p \geq 0.05$).

Table 16

SUMMARY OF ADVERSE EFFECTS, BY PATIENT

PATIENT NUMBER	ADVERSE EFFECT	TREATMENT	ONSET DOSE (MCG/KG/MIN)	ONSET PERIOD	DURATION (MIN)	SEVERITY	ACTION TAKEN	ATTRIB. TO DRUG	OUTCOME
113	HYPOTENSION	ESMOLOL	300	INDUCTION	2	MILD	PHENYLEPHRINE 125 MCG GIVEN	NO	RECOVERED
	HYPOTENSION	ESMOLOL	300	POST STERNOTOMY	2-3	MILD	PHENYLEPHRINE 125 MCG GIVEN	NO	RECOVERED
	HYPOTENSION	ESMOLOL	300	AORTIC DISSECTION	4-5	MILD	PHENYLEPHRINE 100 MCG GIVEN	NO	RECOVERED
115	HYPOTENSION	PLACEBO	NA	POST INTUBATION	2	MILD	EPHEDRINE 2.5 MCG GIVEN	REMOTELY	RECOVERED
123	HYPOTENSION	PLACEBO	NA	INDUCTION	3	MOD	INTUBATED EARLY	POSSIBLY	RECOVERED
124	HYPOTENSION	ESMOLOL	300	ATRIAL CANNULATION	1	MILD	PHENYLEPHRINE 125 MCG GIVEN	NO	RECOVERED
128	HYPOTENSION	ESMOLOL	POST INFUSION	ATRIAL CANNULATION	22	MOD	NONE	REMOTELY	RECOVERED
	ATRIAL FIBRILLATION	ESMOLOL	POST INFUSION	ATRIAL CANNULATION	22	MOD	NONE	REMOTELY	RECOVERED
130	HYPOTENSION/ MYOCARDIAL ISCHEMIA	PLACEBO	NA	ATRIAL CANNULATION	11	MOD	PHENYLEPHRINE 125 MCG, EPHEDRINE 5 MG, NITROGLYCERIN 3 MCG/KG/MIN GIVEN	NO	RECOVERED
133	HYPOTENSION	ESMOLOL	300	AORTIC DISSECTION	2	MOD	PHENYLEPHRINE 125 MCG GIVEN	NO	RECOVERED

Table 21

PATIENTS WITH HEMODYNAMIC VALUES BEYOND SAFETY CHECK POINTS,
BY TREATMENT GROUP AND PERIOD

	Esmolol Group Patient Number	Placebo Group Patient Number	Periods* During Which Values Noted
Heart Rate <45 bpm	102		Base, Min 5 Inf
		106	Min 5 Inf, Pre Ind
	111		Base, Min 5 Inf, Pre Ind
		123	Min 5 Inf, Pre Ind
Total # Pts	2	2	
Systolic Blood Pressure <90 mm Hg		123	Pre Int
Total # Pts	0	1	
Diastolic Blood Pressure <50 mm Hg		123	Pre Int
	129		Pre Ind, Pre Int
Total # Pts	1	1	
Cardiac Index <2.0 L/min/m^2		104	AoD
	105		SK In
	113		Stern
		115	AoD
	117		Stern, AoD
		120	Pre Ind, SK In, Stern
		122	SK In, Stern
		123	Pre Ind, Stern
		125	AoD
	126		Base, Pre Ind
		127	SK In, AoD
		129	Pre Ind
	131		AoD
	133		AoD
Total # Pts	6	8	
PCWP >20 mm Hg	105		Int
		107	Int
		125	Int
	126		Base, Pre Ind
	128		AoD
Total # Pts	3	2	

* See footnote on next page.

* Abbreviations used for periods: Base = baseline, Min 5 Inf = minute 5 of infusion, Pre Ind = preinduction, Pre Int = preintubation, Int = intubation, SK In = skin incision, Stern = sternotomy, AoD = aortic dissection

Note: This evaluation was done only for the periods when complete hemodynamic measurements were taken. Patients who had HR <45 bpm, SBP <90 mm Hg, or DBP <50 mm Hg at other measurement times were not included.

APPENDIX V

CLINICAL DATA OF PATIENTS WHO EXHIBITED ST-SEGMENT CHANGES INDICATIVE OF MYOCARDIAL ISCHEMIA ACCORDING TO PROTOCOL CRITERIA

PATIENT NUMBER/INITIALS: 114/

AGE/SEX: 53/M

TREATMENT GROUP: Placebo

HISTORY:
1. Anterior wall myocardial infarction (1984)
2. Unstable angina (1984)
3. Single kidney (congenital) with normal renal function
4. Hearing impairment

AVERAGE BASELINE HEART RATE: 50 bpm
AVERAGE BASELINE BLOOD PRESSURE: 144/67 mm Hg

PRIOR MEDICATIONS:

1. Nifedipine 20 mg p.o.
2. Metoprolol 50 mg p.o.
3. Isosorbide 5 mg sublingual
4. Nitroglycerin 0.3 mg sublingual
5. Morphine 10 mg i.v.
6. Hyoscine 0.3 mg i.v.
7. Cefazolin 1000 mg i.v.
8. Heparin 5000 units subcutaneous
9. Dipyridamole 100 mg p.o.

CLASSIFIED AS HAVING ISCHEMIA BY BLINDED CARDIOLOGIST? No

DETAILS:
1. General Comments: The prestudy 12-lead electrocardiogram was normal. The patient received sublingual nitroglycerin three minutes prior to, and again four minutes after, the start of placebo infusion.

2. ST-segment Changes: ST-segment elevation of 1 mm was found on the Holter recording (channel 1) following induction of anesthesia. This ST-segment elevation persisted seven minutes, starting four minutes prior to intubation and lasting three minutes after intubation.

3. Arrhythmias: The Holter recording showed occasional ventricular extrasystoles with complex arrhythmias during placement of the Swan-Ganz catheter (one three-beat salvo) and at aortic dissection (one ventricular couplet).

PATIENT NUMBER/INITIALS: 115/

AGE/SEX: 64/M

TREATMENT GROUP: Placebo

HISTORY: 1. Myocardial infarction (1964)
2. Angina (1964)

AVERAGE BASELINE HEART RATE: 50 bpm
AVERAGE BASELINE BLOOD PRESSURE: 128/59 mm Hg

PRIOR MEDICATIONS:

1. Propranolol (Inderal®) 20 mg p.o.
2. Morphine 10 mg i.m.
3. Scopolamine 0.4 mg i.m.
4. Heparin 5000 units subcutaneous
5. Cefazolin 500 mg i.m.

CLASSIFIED AS HAVING ISCHEMIA BY BLINDED CARDIOLOGIST? No

DETAILS:

1. General Comments: The prestudy 12-lead electrocardiogram showed isoelectric T-waves and also Q-waves, the latter of which were present in leads II, III, AVF, and V_1 - V_3.

2. ST-segment Changes: ST-segment elevation of 0.5 mm to 1 mm was seen on the Holter record throughout a 31 minute baseline recording period. This degree of ST-segment elevation continued through the initial placebo infusion period (except for a ten second period when the ST-segment returned to isoelectric) until induction of anesthesia. Following anesthesia induction, there was an increase in ST-segment elevation of approximately 1 mm (i.e., 1.5-2 mm) which occurred approximately two minutes before intubation and persisted for two minutes after intubation.

3. Arrhythmias: The Holter recording showed intermittent episodes of junctional rhythm that were as slow as 41 bpm and were associated with ST-segment changes. The patient had one six beat salvo of ventricular tachycardia around the period of Swan-Ganz catheter insertion. Occasional ventricular extrasystoles and intermittent supraventricular arrhythmias were also noted.

PATIENT NUMBER/INITIALS: 118/

AGE/SEX: 54/M

TREATMENT GROUP: Placebo

HISTORY: 1. Myocardial infarction (1968)
2. Hypertension (1968)

AVERAGE BASELINE HEART RATE: 50 bpm
AVERAGE BASELINE BLOOD PRESSURE: 171/79 mm Hg

PRIOR MEDICATIONS:

1. Propranolol 40 mg p.o. b.i.d.
2. Isosorbide dinitrate (Isordil®) 20 mg p.o. q.i.d.
3. Lorazepam (Ativan®) 1 mg p.o. x 1
4. Morphine 10 mg i.m. x 1
5. Scopolamine 0.3 mg i.m. x 1
6. Heparin 5000 units subcutaneous x 1
7. Cefazolin 1000 mg i.m. x 1

CLASSIFIED AS HAVING ISCHEMIA BY BLINDED CARDIOLOGIST? Yes

DETAILS: 1. General Comments: There were no abnormal findings on the prestudy 12-lead electrocardiogram and the course of the study was uneventful except that isoflurane was given for hypertension through most of the study period.

2. ST-segment Changes: ST-segment elevation of 0.5 to 1 mm was noted at baseline and throughout the Holter record. This degree of ST-segment elevation persisted unchanged through the study until seven minutes after the completion of aortic dissection when an increase to 2-2.5 mm was noted. This increase in ST-segment elevation during placebo infusion was associated with surgical manipulation of the heart.

3. Arrhythmias: Complex ventricular arrhythmias were found on the Holter record at the time that ST-segment elevation increased to 2-2.5 mm. Occasional supraventricular arrhythmias were noted at different periods throughout the record.

PATIENT NUMBER/INITIALS: 127/

AGE/SEX: 54/M

TREATMENT GROUP: Placebo

HISTORY:
1. Myocardial infarction (1984)
2. Angina on minimal exertion (1984)
3. Jaundice (1962)

AVERAGE BASELINE HEART RATE: 49 bpm
AVERAGE BASELINE BLOOD PRESSURE: 111/66 mm Hg

PRIOR MEDICATIONS:

1. Nifedipine 20 mg p.o. t.i.d.
2. Metoprolol 50 mg p.o. b.i.d.
3. Morphine 10 mg i.m. x 1
4. Scopolamine 0.4 mg i.m. x 1
5. Heparin 5000 units subcutaneous x 1
6. Dipyridamole (Persantine®) 100 mg p.o. t.i.d.
7. Cefazolin (Kefzol®) 500 mg i.m. x 1

CLASSIFIED AS HAVING ISCHEMIA BY BLINDED CARDIOLOGIST? Yes

DETAILS:
1. General Comments: The prestudy 12-lead electrocardiogram was normal and the course of the study was uneventful except that isoflurane was given for hypertension.

2. ST-segment Changes: The ST-segments recorded on the Holter monitor were normal at baseline and remained so until one minute after aortic dissection when ST-segment elevation of 1 mm was noted. This episode of ST-segment elevation lasted ten seconds.

3. Arrhythmias: Complex ventricular arrhythmias were seen on the Holter record during aortic dissection. Supraventricular arrhythmias occurred during insertion of the monitoring lines and again at atrial cannulation.

PATIENT NUMBER/INITIALS: 128/

AGE/SEX: 60/M

TREATMENT GROUP: Esmolol

HISTORY: 1. Myocardial infarction (1981)
2. Angina (1978)

AVERAGE BASELINE HEART RATE: 56 bpm
AVERAGE BASELINE BLOOD PRESSURE: 115/69 mm Hg

PRIOR MEDICATIONS:

1. Nifedipine 20 mg p.o. q.i.d.
2. Propranolol 50 mg p.o. q.i.d.
3. Isosorbide dinitrate (Isordil®) 20 mg p.o. q.i.d.
4. Morphine 10 mg i.m. x 1
5. Scopolamine 0.4 mg i.m. x 1
6. Heparin 5000 units subcutaneous
7. Cefazolin (Kefzol®) 500 mg i.m. x 1

CLASSIFIED AS HAVING ISCHEMIA BY BLINDED CARDIOLOGIST? Yes

DETAILS: 1. General Comments: The prestudy 12-lead electrocardiogram showed flattening of T-waves in leads II and AVF, and Q-waves in leads II, III and AVF. This patient exhibited adverse reactions prebypass and complications postbypass. Three minutes after esmolol infusion was discontinued the patient's systolic blood pressure dropped from 120 to 80-85 mm Hg. This hypotension occurred around the time of atrial cannulation. At this time, pulmonary capillary wedge pressure increased from 14 to 20-22 mm Hg and cardiac output decreased from 4.6 L/min to 4.1 L/min. Difficulty was experienced weaning the patient from bypass despite inotropic support. Following insertion of an intraaortic balloon pump, the patient was successfully terminated from bypass using the balloon pump. An episode of ventricular fibrillation occurred during closure of the sternum. Ten minutes after successful defibrillation the patient developed a nodal rhythm and hypotension (BP= 60/30 mm Hg) unresponsive to inotropes, pacing, and the intraaortic balloon pump. Intravenous nitroglycerin was then administered which resulted in a return to normal sinus rhythm and normalization of blood pressure. The investigator suspected that the patient sustained myocardial damage prebypass at the time that hypotension and atrial fibrillation occurred resulting in the difficulty in weaning from bypass.

2. ST-segment Changes: The ST-segments were normal at baseline and throughout the Holter record until the end of aortic dissection when ST-elevation of 1 to 1.5 mm occurred (channel 1).

3. Arrhythmias: Complex ventricular arrhythmias and supraventricular arrhythmias were seen during insertion of the Swan-Ganz catheter and at aortic dissection.

4. Other Holter Findings: Intermittent changes in intraventricular conduction, indicative of right bundle branch block, were observed from the period following anesthesia induction until post sternotomy.

PATIENT NUMBER/INITIALS: 130/

AGE/SEX: 65/M

TREATMENT GROUP: Placebo

HISTORY:
1. Myocardial infarction (two in 1968)
2. Hypertension
3. Angina with decreased exercise tolerance
4. Nephrolithiasis (1974)
5. Benign prostatic hypertrophy

AVERAGE BASELINE HEART RATE: 46 bpm
AVERAGE BASELINE BLOOD PRESSURE: 162/81 mm Hg

PRIOR MEDICATIONS:

1. Nifedipine 10 mg p.o. t.i.d.
2. Propranolol 40 mg p.o. t.i.d.
3. Morphine 10 mg i.m. x 1
4. Scopolamine 0.4 mg i.m. x 1
5. Heparin 5000 units subcutaneous x 1
6. Cefazolin 500 (Kefzol®) mg i.m. x 1

CLASSIFIED AS HAVING ISCHEMIA BY BLINDED CARDIOLOGIST? Yes

DETAILS: 1. General Comments: The following were noted on the prestudy 12-lead electrocardiogram: poor R-wave progression in leads V_1 - V_3, ST-segment sloping in leads I, AVL, and V_2-V_6, compatible with ischemia, inverted T-waves in leads I, AVL, and V_2 - V_6. Biphasic T-wave in lead V_6, Q-waves in leads II, III, and AVF. This patient exhibited hypotension (blood pressure 85/50 mm Hg) secondary to blood loss during aortic dissection and atrial cannulation. This hypotension was associated with myocardial ischemia (V-waves and pulmonary hypertension). The patient was treated with saline and vasopressors for the hypotension and intravenous nitroglycerin for the myocardial ischemia. Hypotension persisted approximately 11 minutes. There were surgical problems at the time of bypass and norepinephrine and phentolamine were required to wean the patient from bypass. The patient did not have increased cardiac enzymes in the recovery room.

2. ST-segment Changes: The patient had ST-segment depression of 1.5 to 1.75 mm at baseline and throughout the Holter recording, except for an increase in ST-depression of 0.5 mm for one minute that occurred three minutes after the start of anesthesia induction, and an increase in ST-segment depression of 1 mm that occurred 13 minutes after the end of aortic dissection and persisted for four minutes (channel 1).

3. Arrhythmias: Complex ventricular arrhythmias were noted on the Holter recording during Swan-Ganz catheter insertion and sternal spreading and supraventricular arrhythmias occurred during aortic dissection.

PATIENT NUMBER/INITIALS: 131/

AGE/SEX: 56/M

DRUG GROUP: Esmolol

HISTORY:
1. Myocardial infarction (1971)
2. No angina but positive stress test
3. Peptic ulcer disease (1977)
4. Middle ear surgery (1983)

AVERAGE BASELINE HEART RATE: 53 bpm
AVERAGE BASELINE BLOOD PRESSURE: 117/64 mm Hg

PRIOR MEDICATIONS:

1. Nifedipine 10 mg p.o. q.i.d.
2. Metoprolol 100 mg p.o. b.i.d.
3. Morphine 10 mg i.m. x 1
4. Scopolamine 0.4 mg i.m. x 1
5. Heparin 5000 units subcutaneous x 1
6. Cefazolin 500 mg i.m. x 1

CLASSIFIED AS HAVING ISCHEMIA BY BLINDED CARDIOLOGIST? No

DETAILS:
1. General Comments - The patient's prestudy electrocardiogram was normal and the patient had an uneventful study course.

2. ST-segment Changes - The ST-segment was normal at baseline and throughout the Holter records except for ST-segment elevation of 0.75 to 1 mm that occurred six minutes after aortic dissection and persisted for six minutes. This ST-segment elevation was associated with a loss in QRS voltage during surgical lifting of the heart.

3. Arrhythmias - Complex ventricular and supraventricular arrhythmias occurred on the Holter record during Swan-Ganz catheter insertion and aortic dissection and cannulation.

FIGURE 2

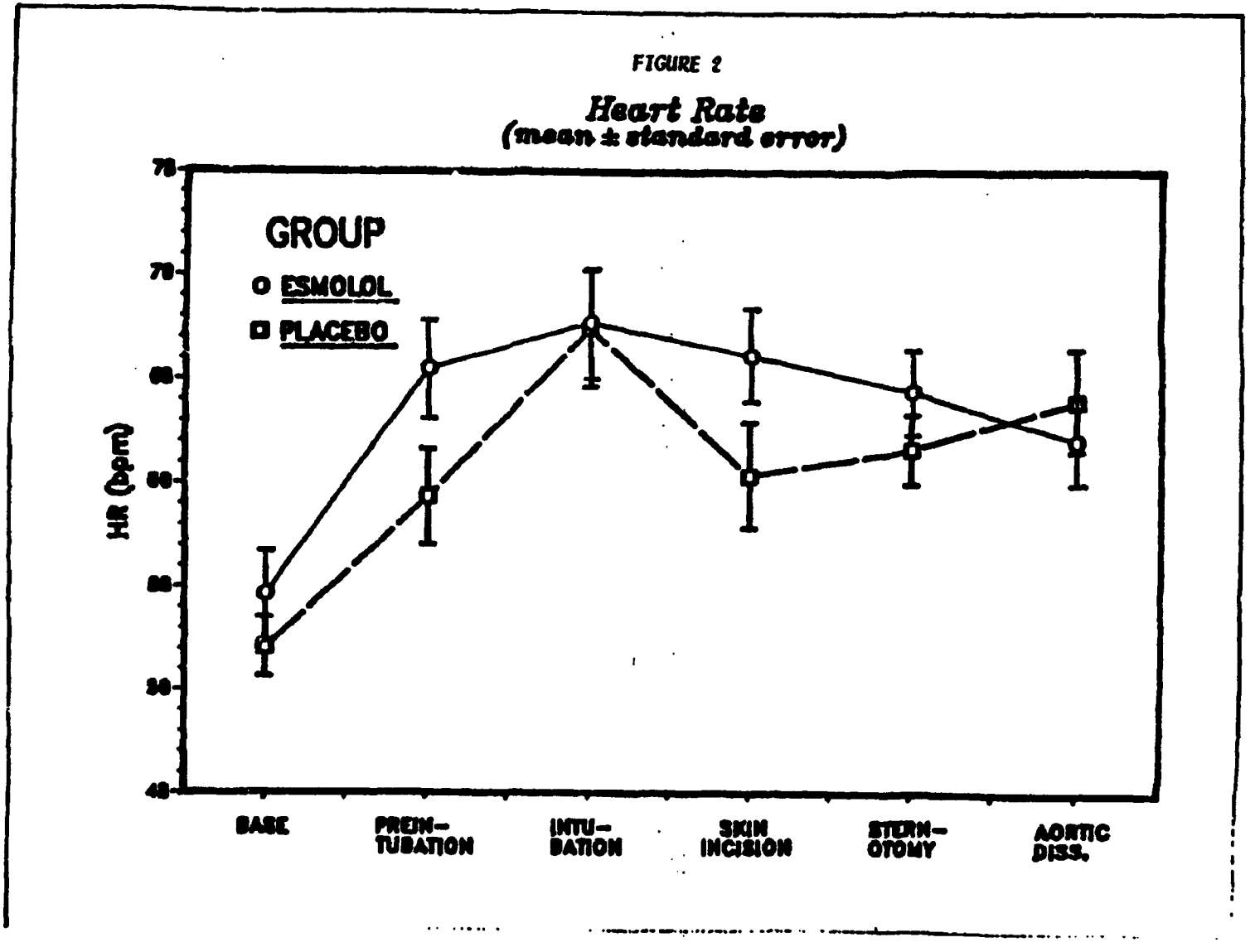

Heart Rate
(mean ± standard error)
GROUP
ESMOLOL
PLACEBO
HR (bpm)
70
60
50
BASE
PREIN-TUBATION
INTU-BATION
SKIN INCISION
STERN-OTOMY
AORTIC DISS.

FIGURE 3

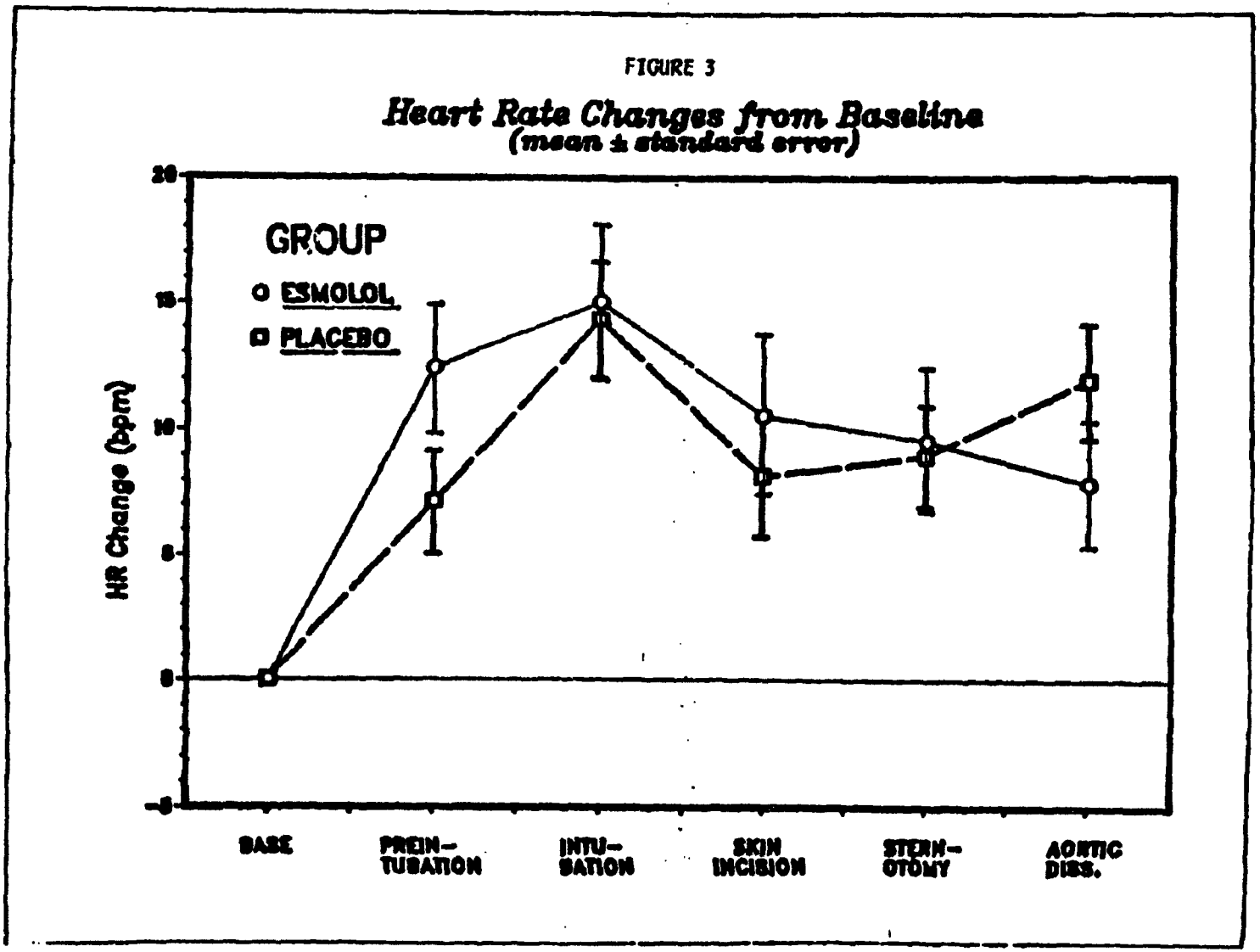

Heart Rate Changes from Baseline
(mean ± standard error)
GROUP
ESMOLOL
PLACEBO
HR Change (bpm)
20
15
10
5
0
-5
BASE
PREIN-TUBATION
INTU-BATION
SKIN INCISION
STERN-OTOMY
AORTIC DISS.

FIGURE 4

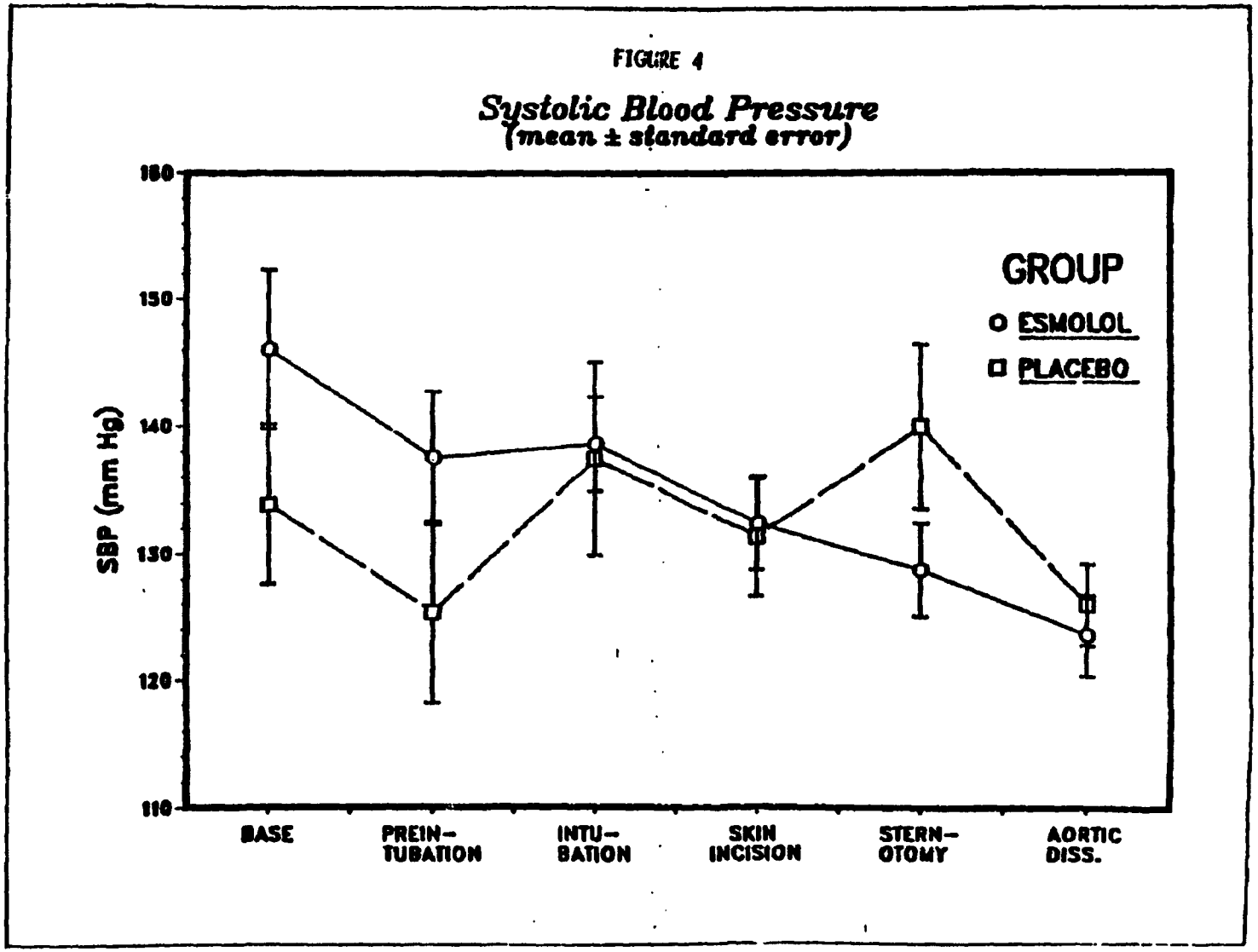
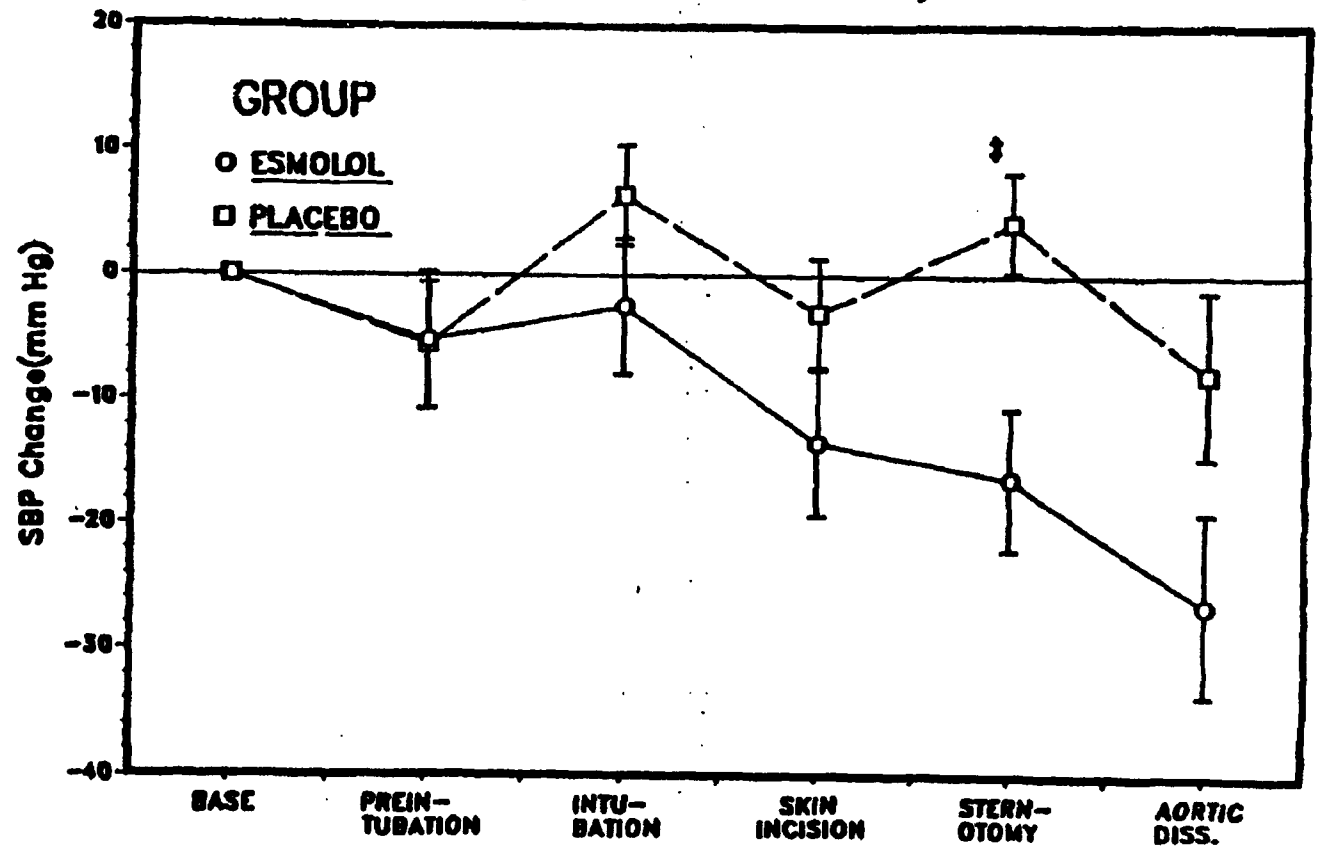

Systolic Blood Pressure
(mean ± standard error)
SBP (mm Hg)
160
150
140
130
120
110
GROUP
ESMOLOL
PLACEBO
BASE
PREIN-
TUBATION
INTU-
BATION
SKIN
INCISION
STERN-
OTOMY
AORTIC
DISS.

FIGURE 5

Systolic Blood Pressure Changes from Baseline
(mean ± standard error)



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

FIGURE 6

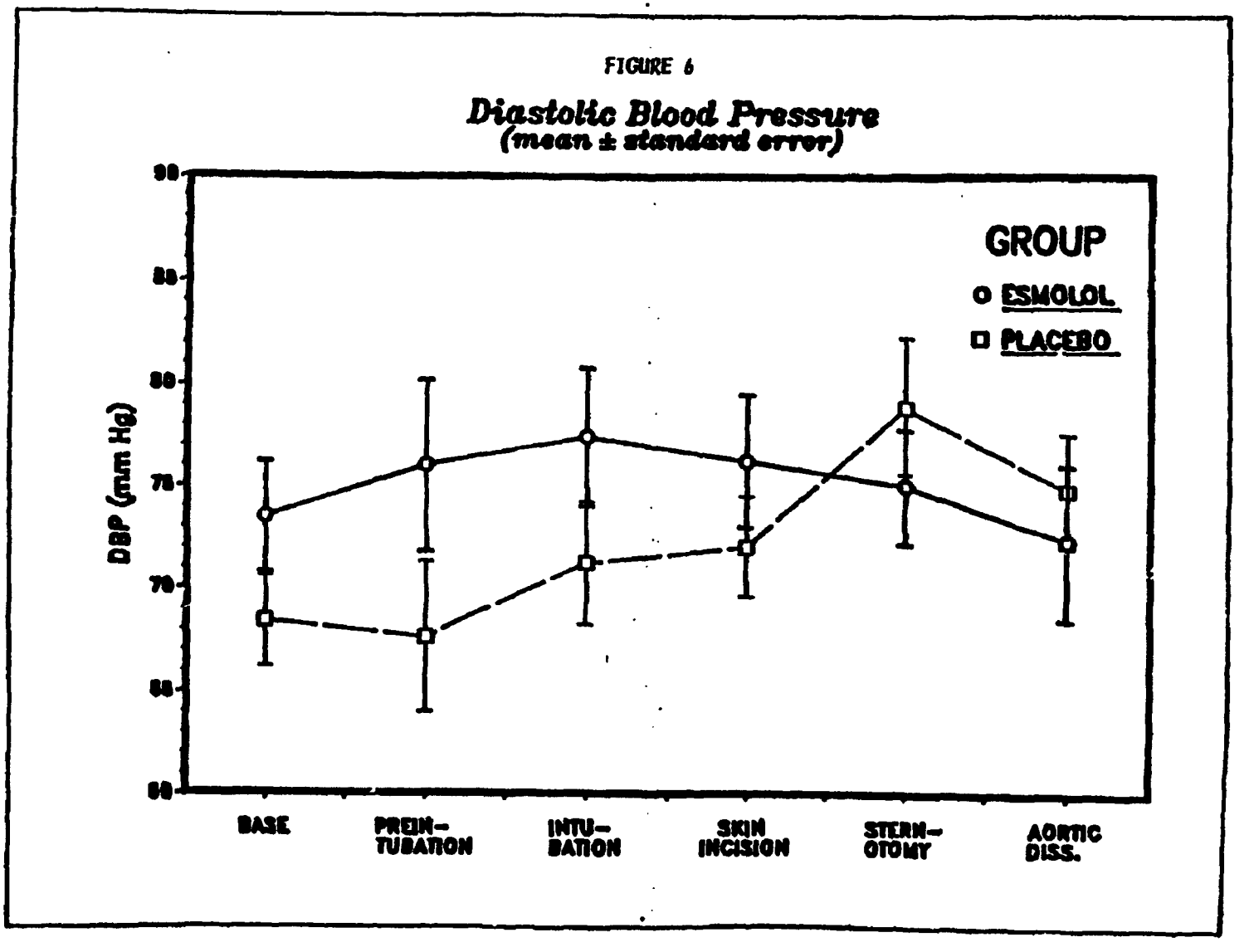
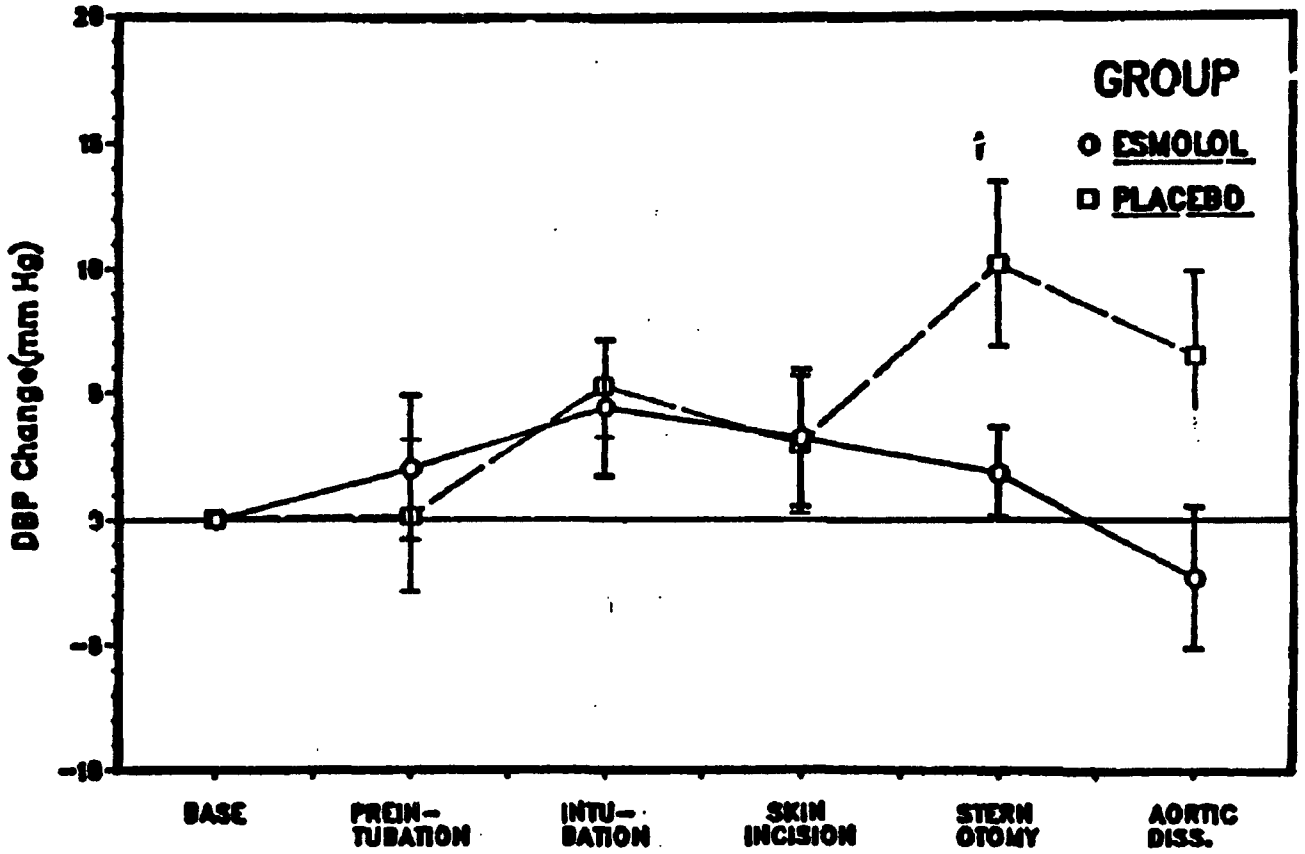

Diastolic Blood Pressure
(mean ± standard error)
GROUP
ESMOLOL
PLACEBO
DBP (mm Hg)
BASE
PREIN-TUBATION
INTU-BATION
SKIN INCISION
STERN-OTOMY
AORTIC DISS.

FIGURE 1

Diastolic Blood Pressure Changes from Baseline
(mean ± standard error)



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

Figure 8

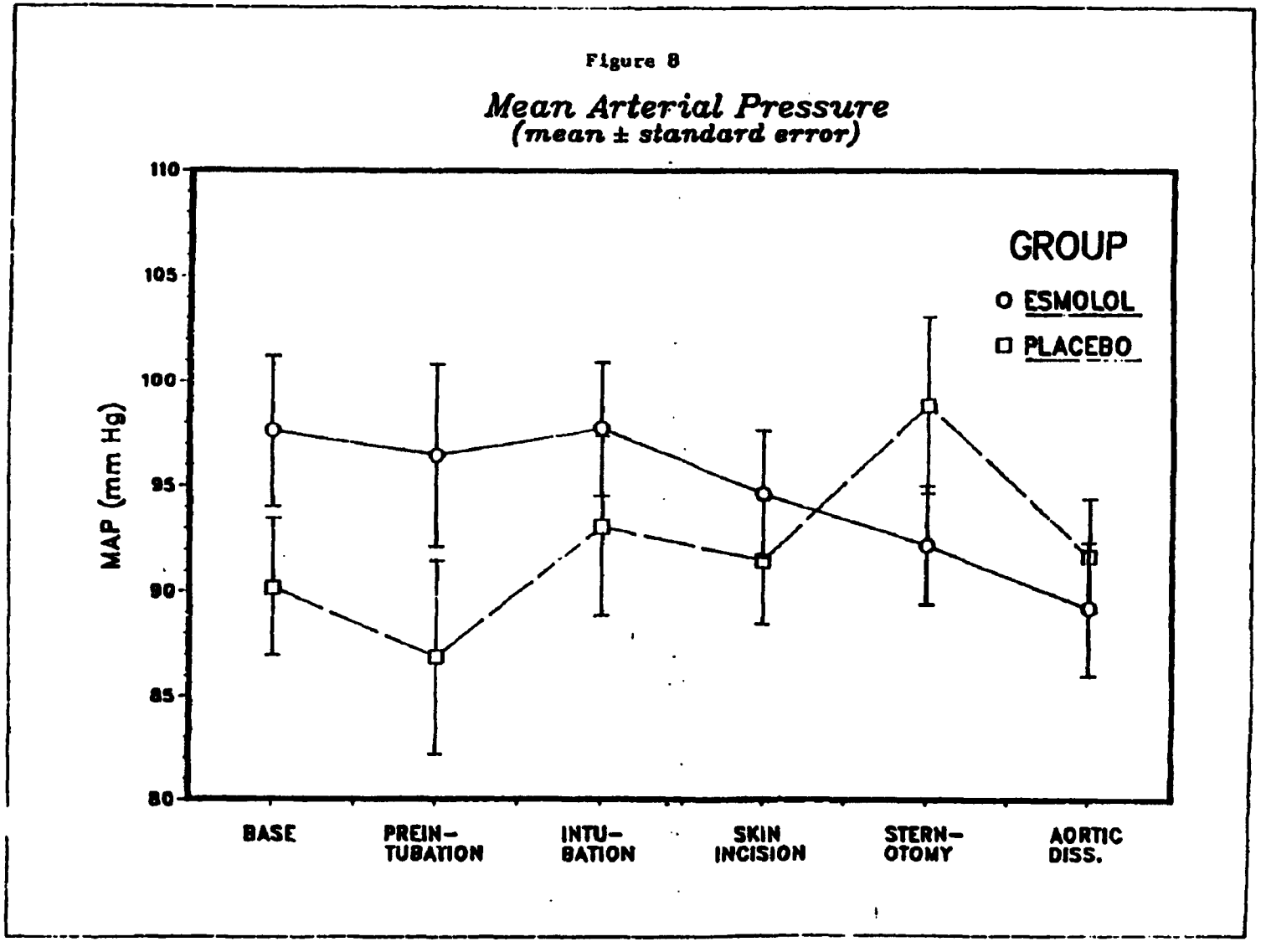
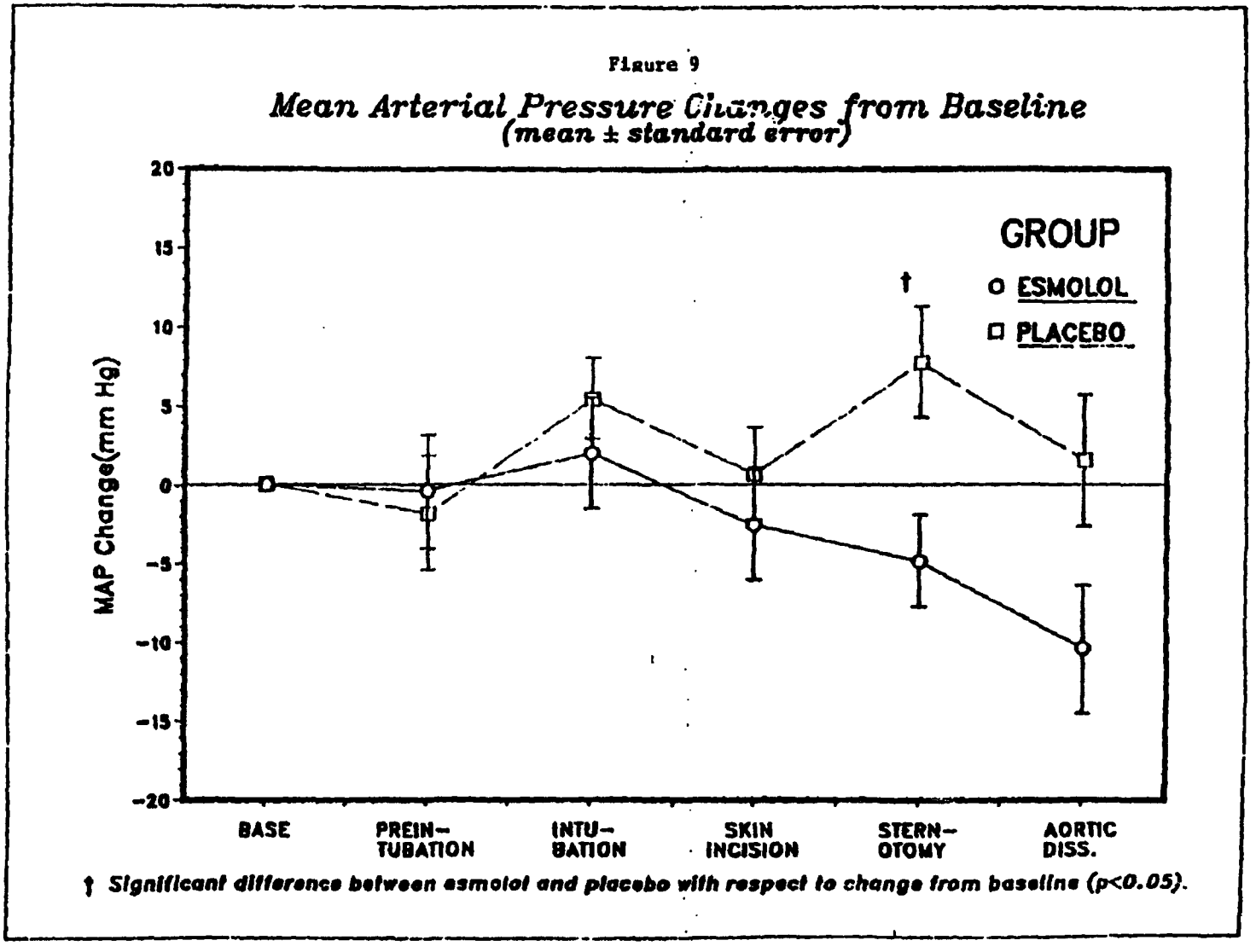

Mean Arterial Pressure
(mean ± standard error)
MAP (mm Hg)
110
105
100
95
90
85
80
GROUP
ESMOLOL
PLACEBO
BASE
PREIN-
TUBATION
INTU-
BATION
SKIN
INCISION
STERN-
OTOMY
AORTIC
DISS.

Figure 9



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

FIGURE 10

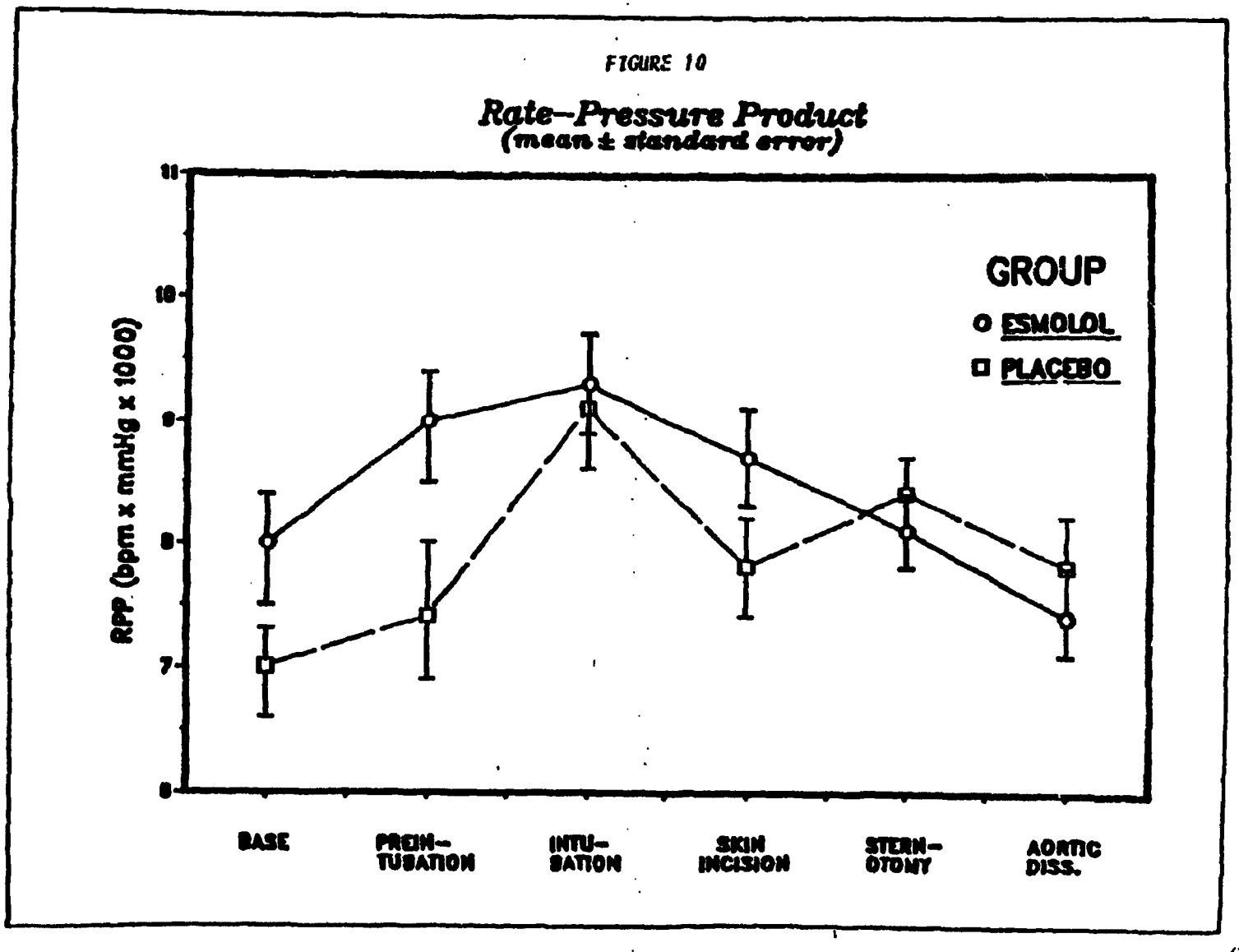
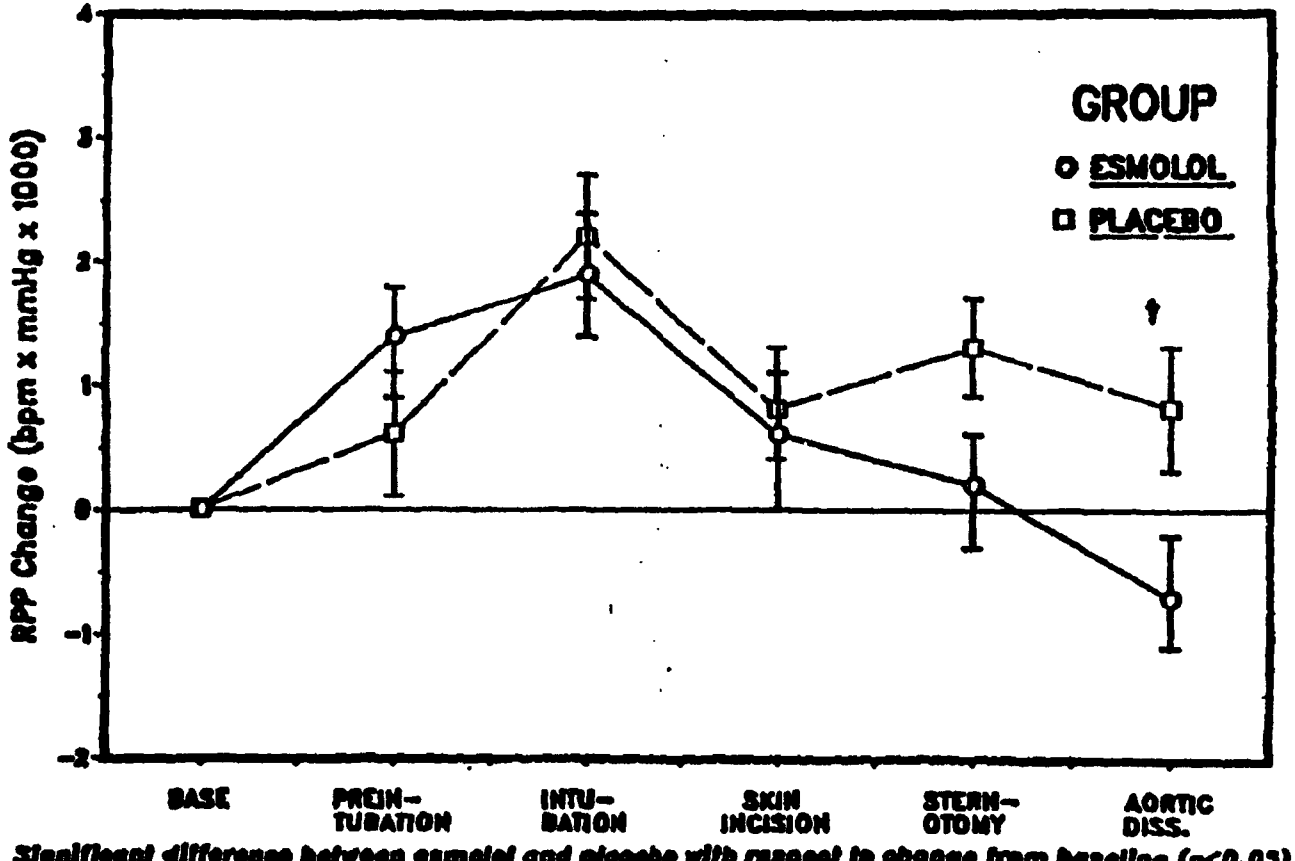

Rate–Pressure Product
(mean ± standard error)
RPP (bpm x mmHg x 1000)
11
10
9
8
7
6
GROUP
ESMOLOL
PLACEBO
BASE
PREIN–TUBATION
INTU–BATION
SKIN INCISION
STERN–OTOMY
AORTIC DISS.

FIGURE 11

Rate–Pressure Product Changes from Baseline
(mean ± standard error)



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

FIGURE 12

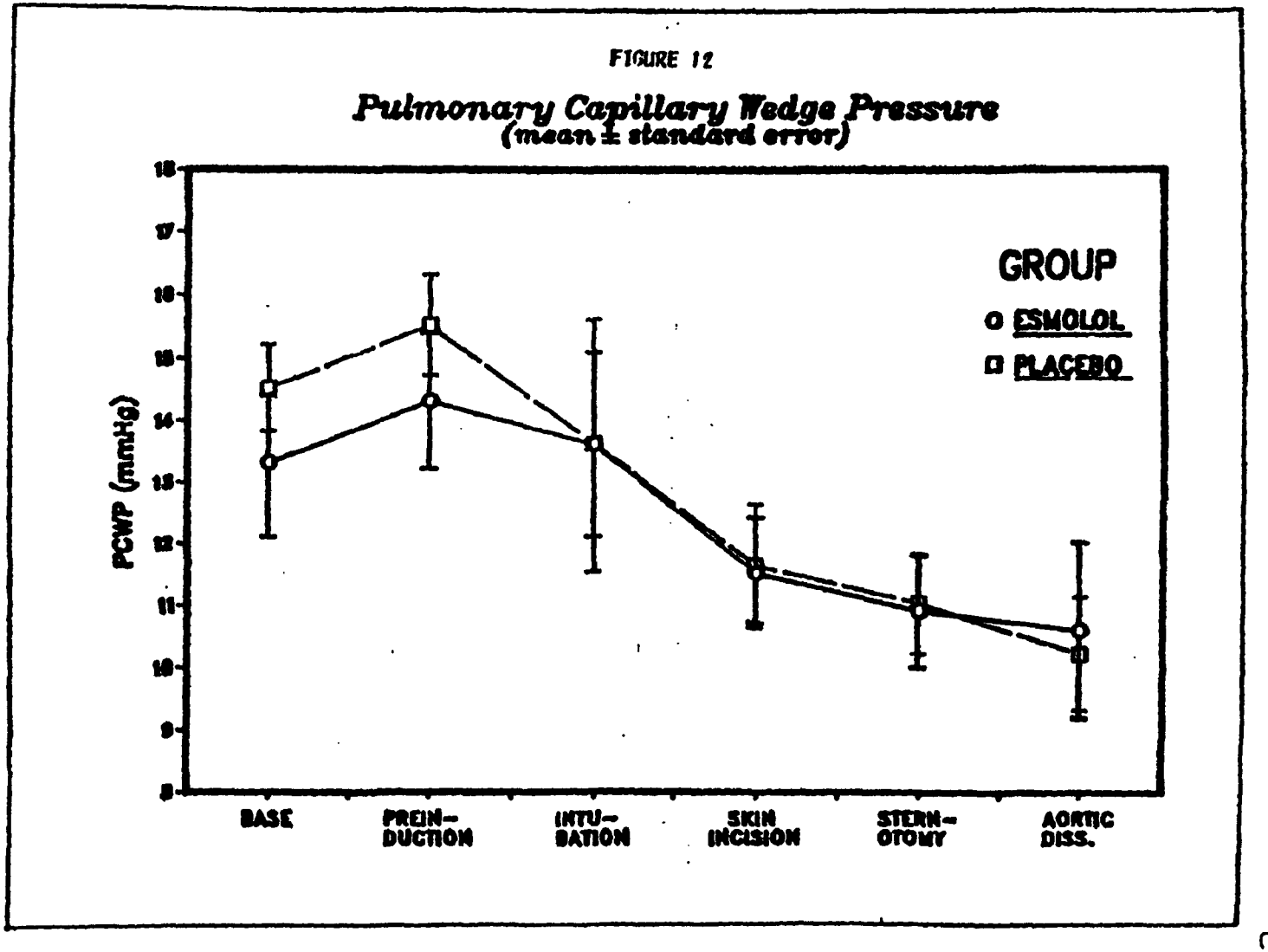

Pulmonary Capillary Wedge Pressure
(mean ± standard error)
PCWP (mmHg)
GROUP
ESMOLOL
PLACEBO
BASE
PREIN-DUCTION
INTU-BATION
SKIN INCISION
STERN-OTOMY
AORTIC DISS.

FIGURE 13

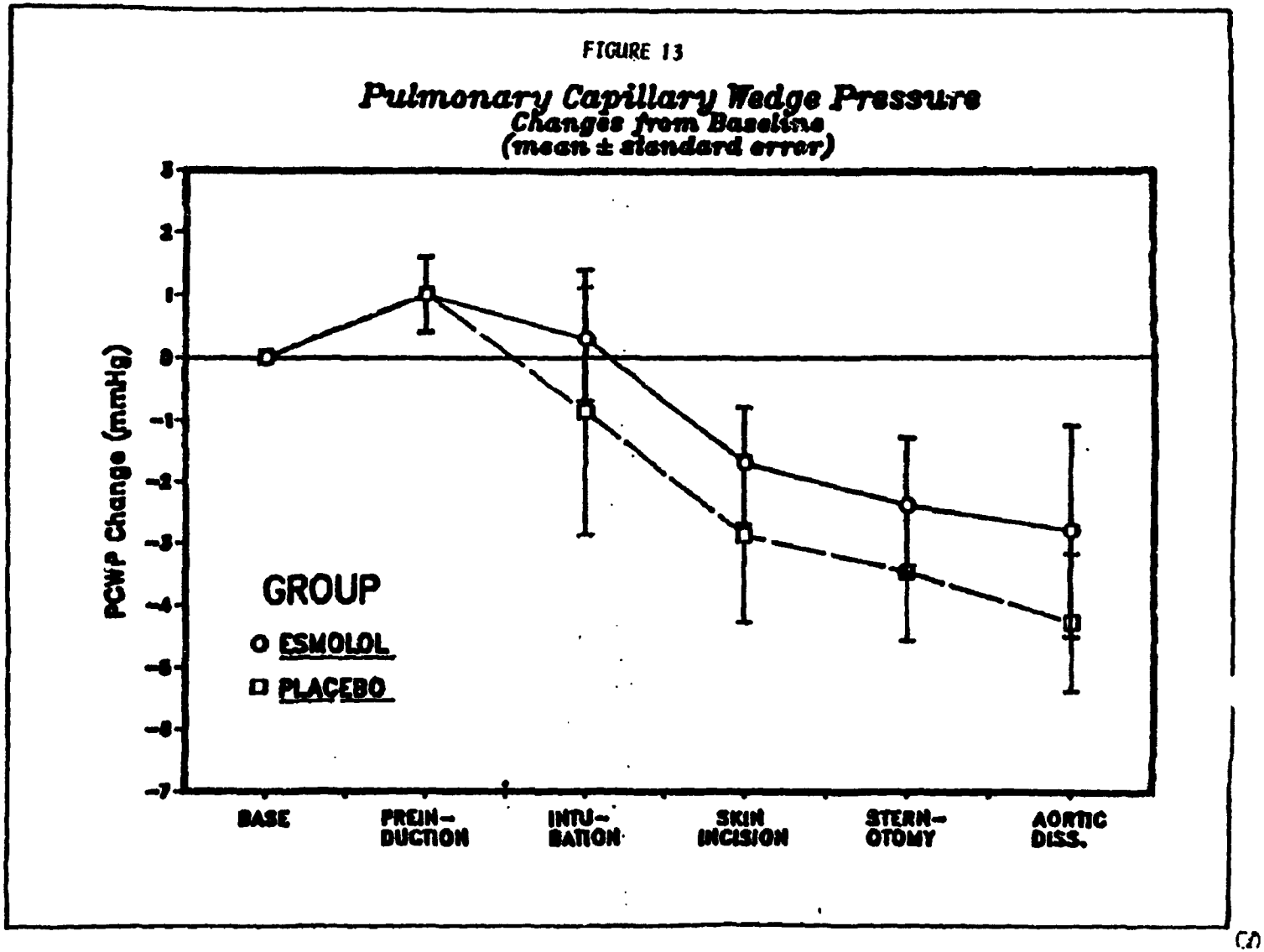

Pulmonary Capillary Wedge Pressure
Changes from Baseline
(mean ± standard error)
PCWP Change (mmHg)
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
GROUP
ESMOLOL
PLACEBO
BASE
PREIN-DUCTION
INTU-BATION
SKIN INCISION
STERN-OTOMY
AORTIC DISS.

Figure 14

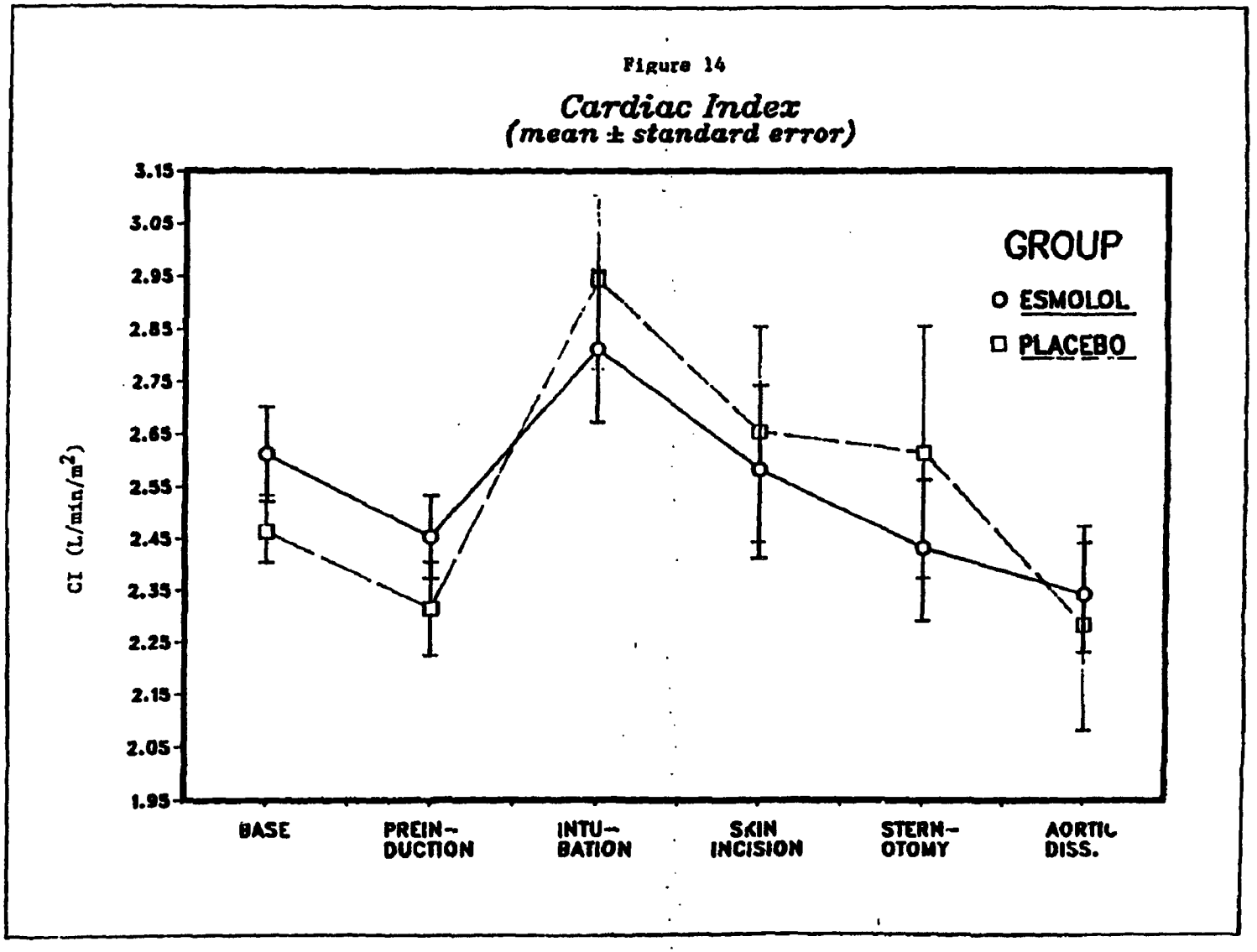

Cardiac Index
(mean ± standard error)
CI (L/min/m²)
3.15
3.05
2.95
2.85
2.75
2.65
2.55
2.45
2.35
2.25
2.15
2.05
1.95
GROUP
ESMOLOL
PLACEBO
BASE
PREIN-DUCTION
INTU-BATION
SKIN INCISION
STERN-OTOMY
AORTIC DISS.

Figure 15

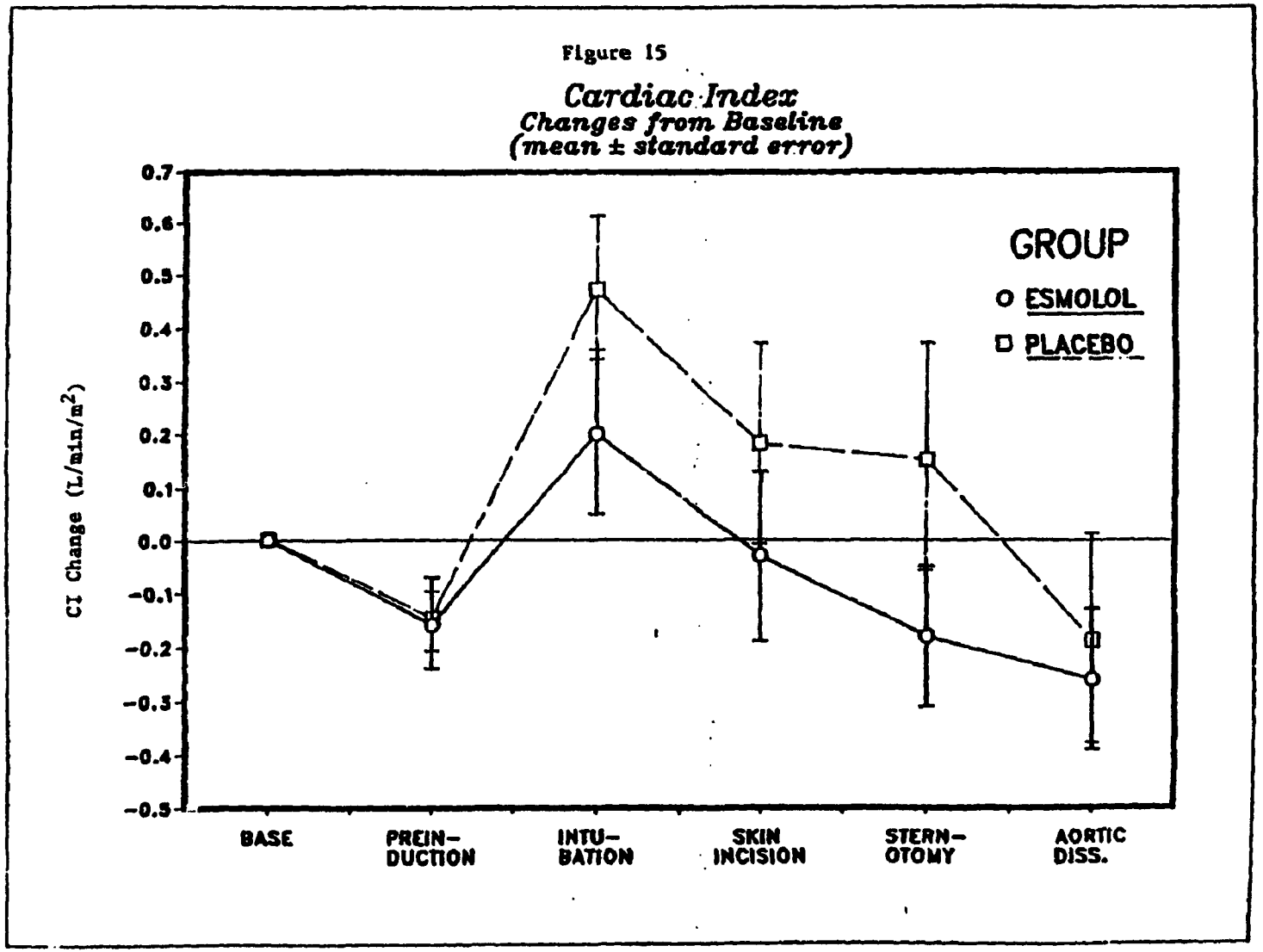

Cardiac Index
Changes from Baseline
(mean ± standard error)
CI Change (L/min/m²)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
-0.4
-0.5
GROUP
ESMOLOL
PLACEBO
BASE
PREIN-DUCTION
INTU-BATION
SKIN INCISION
STERN-OTOMY
AORTIC DISS.

Figure 16

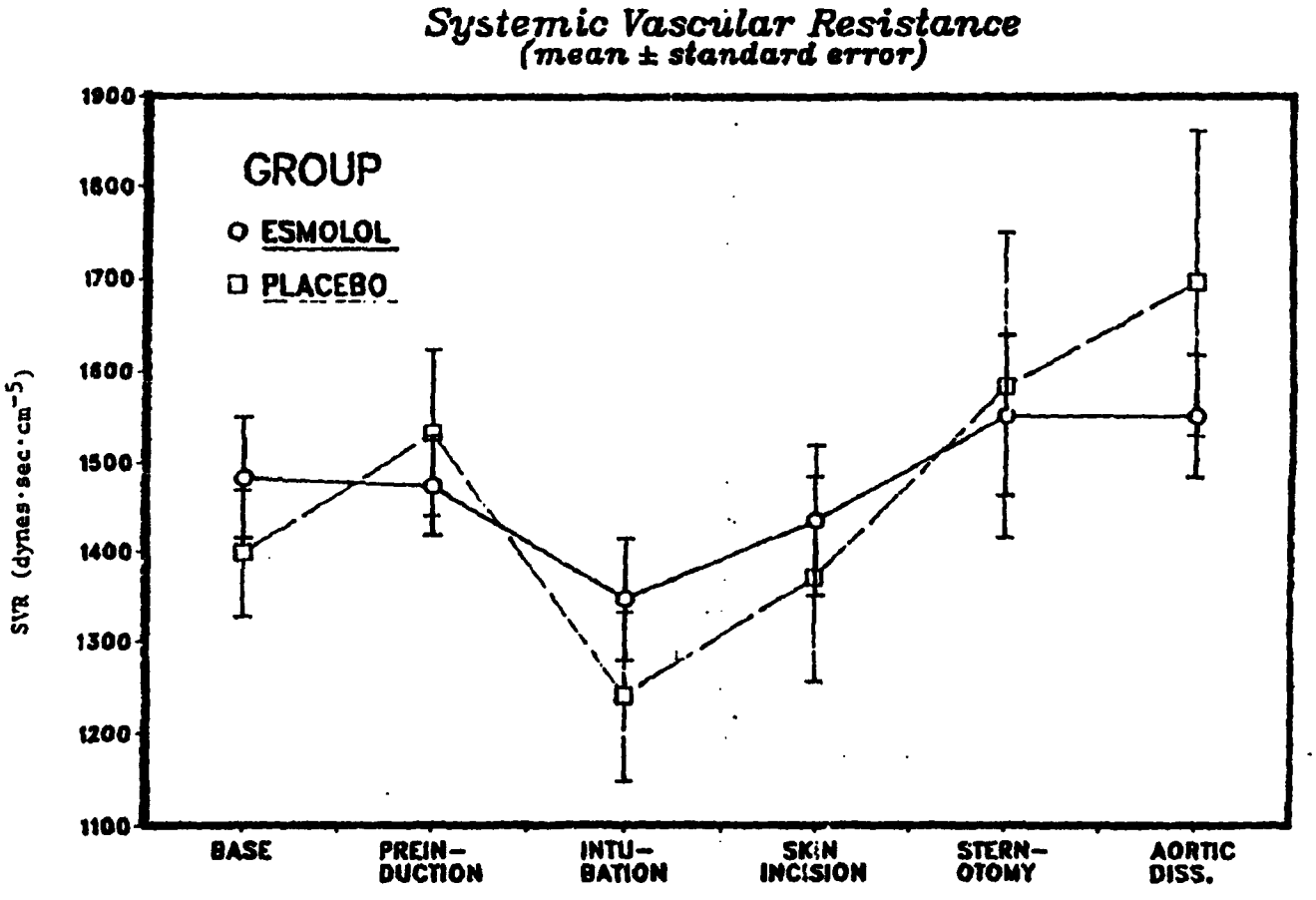
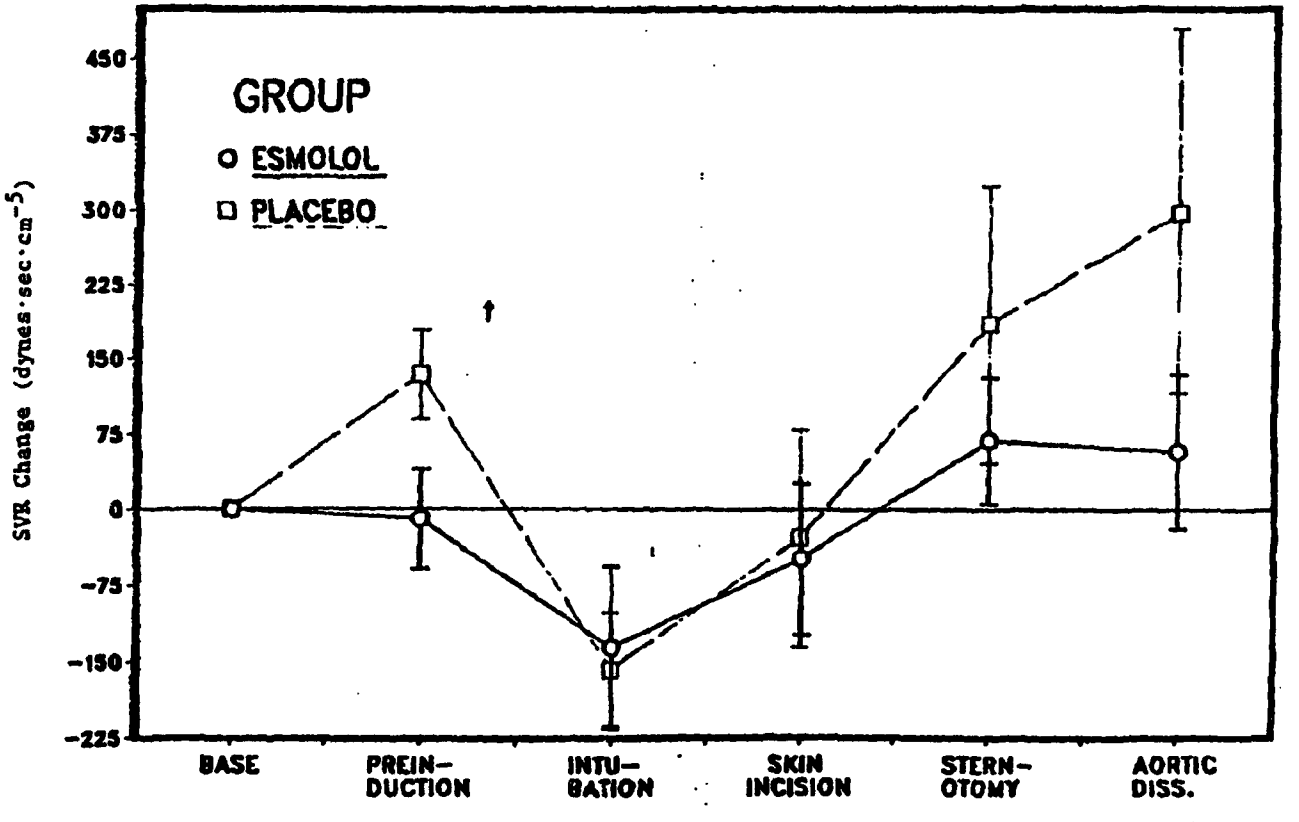

Systemic Vascular Resistance
(mean ± standard error)
GROUP
ESMOLOL
PLACEBO
SVR (dynes·sec·cm⁻⁵)
1900
1800
1700
1600
1500
1400
1300
1200
1100
BASE
PREIN-DUCTION
INTU-BATION
SKIN INCISION
STERN-OTOMY
AORTIC DISS.

Figure 17

Systemic Vascular Resistance
Changes from Baseline
(mean ± standard error)



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