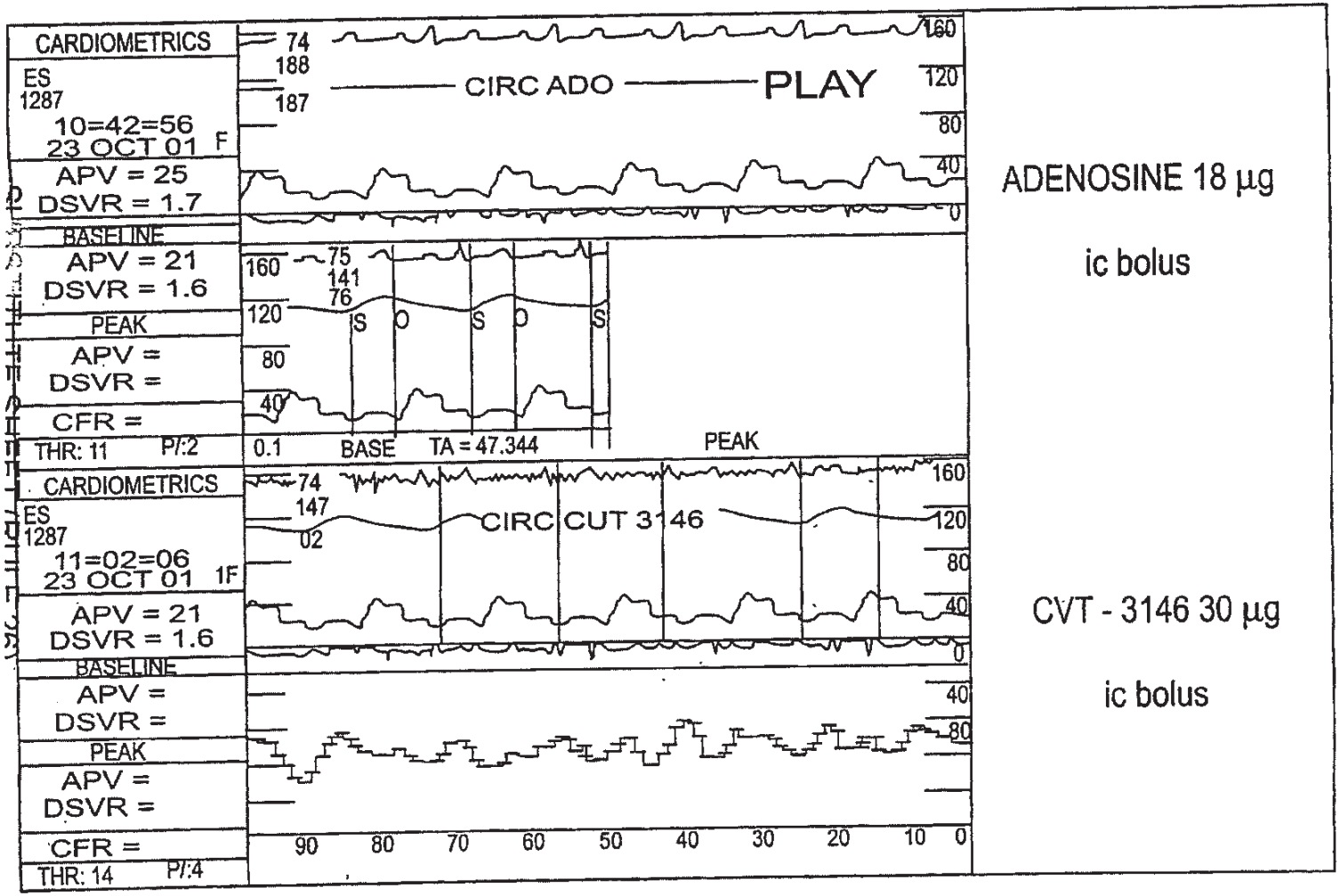

CARDIOMETRICS
ES
1287
10=42=56
23 OCT 01 F
APV = 25
DSVR = 1.7
BASELINE
APV = 21
DSVR = 1.6
PEAK
APV =
DSVR =
CFR =
THR: 11 P/:2
74
188
187
CIRC ADO
PLAY
160
120
80
40
0
ADENOSINE 18 µg
ic bolus
160
120
80
40
75
141
76
S
O
S
O
S
0.1
BASE
TA = 47.344
PEAK
CARDIOMETRICS
ES
1287
11=02=06
23 OCT 01 1F
APV = 21
DSVR = 1.6
BASELINE
APV =
DSVR =
PEAK
APV =
DSVR =
CFR =
THR: 14 P/:4
74
147
02
CIRC CUT 3146
160
120
80
40
0
CVT - 3146 30 µg
ic bolus
40
80
90
80
70
60
50
40
30
20
10
0

FIG. 1

1/7

Dose-Dependent Increase in Peak Flow Velocity Caused by CVT-3146

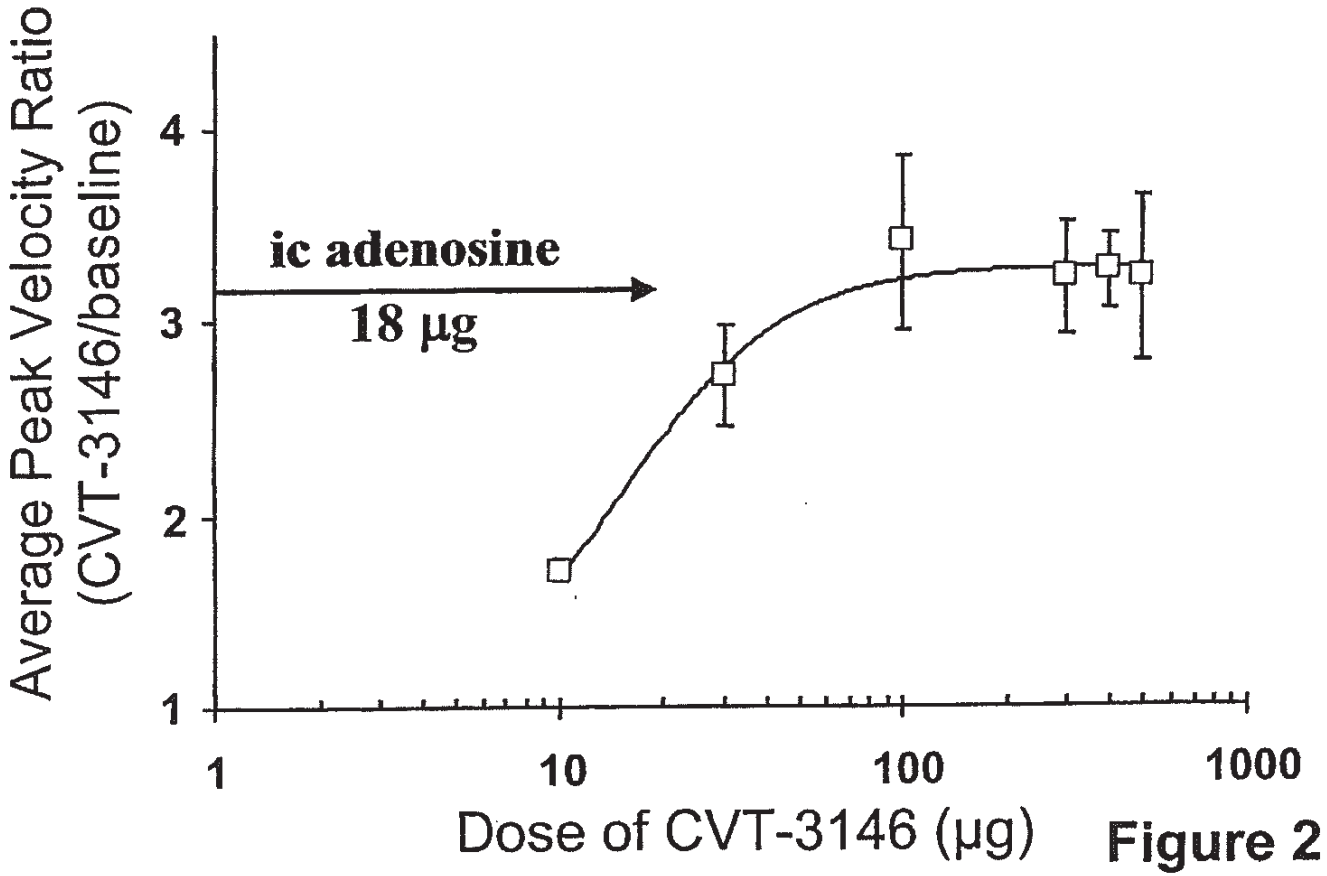


Figure 2

CVT-3146 and Coronary Flow Velocity

Duration of Effect:

Dose (n)	Duration ≥2.5 Baseline Mean ± SEM
10 μg (4)	0
30 μg (4)	0
100 μg (3)	0.2 ± 0.2 minutes
300 μg (4)	2.2 ± 1.3 minutes
400 μg (8)	2.8 ± 0.8 minutes
500 μg (4)	2.9 ± 1.3 minutes

Figure 3

Time Course of APV Ratio (CVT-3146 400 µg)

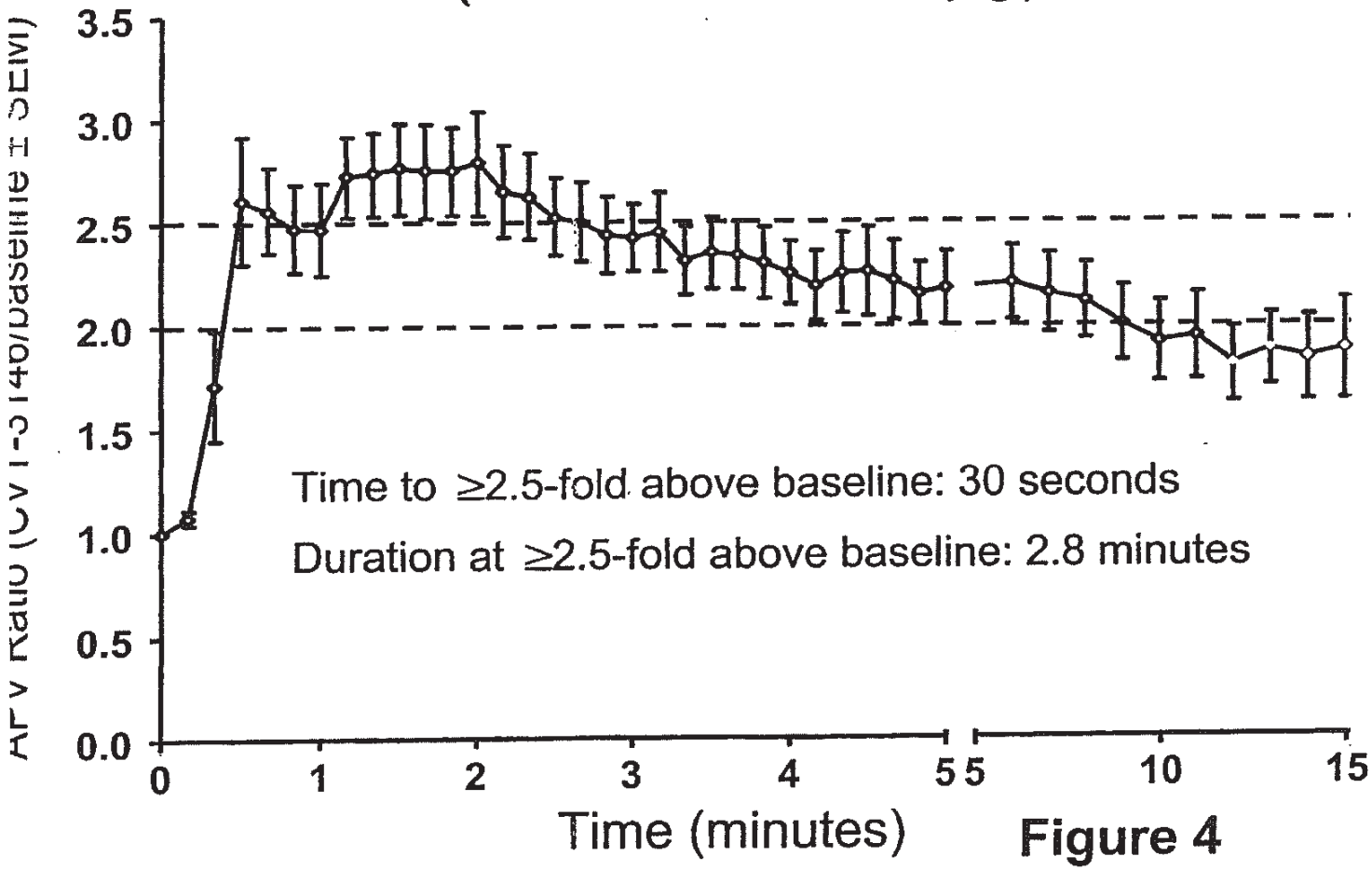


Figure 4

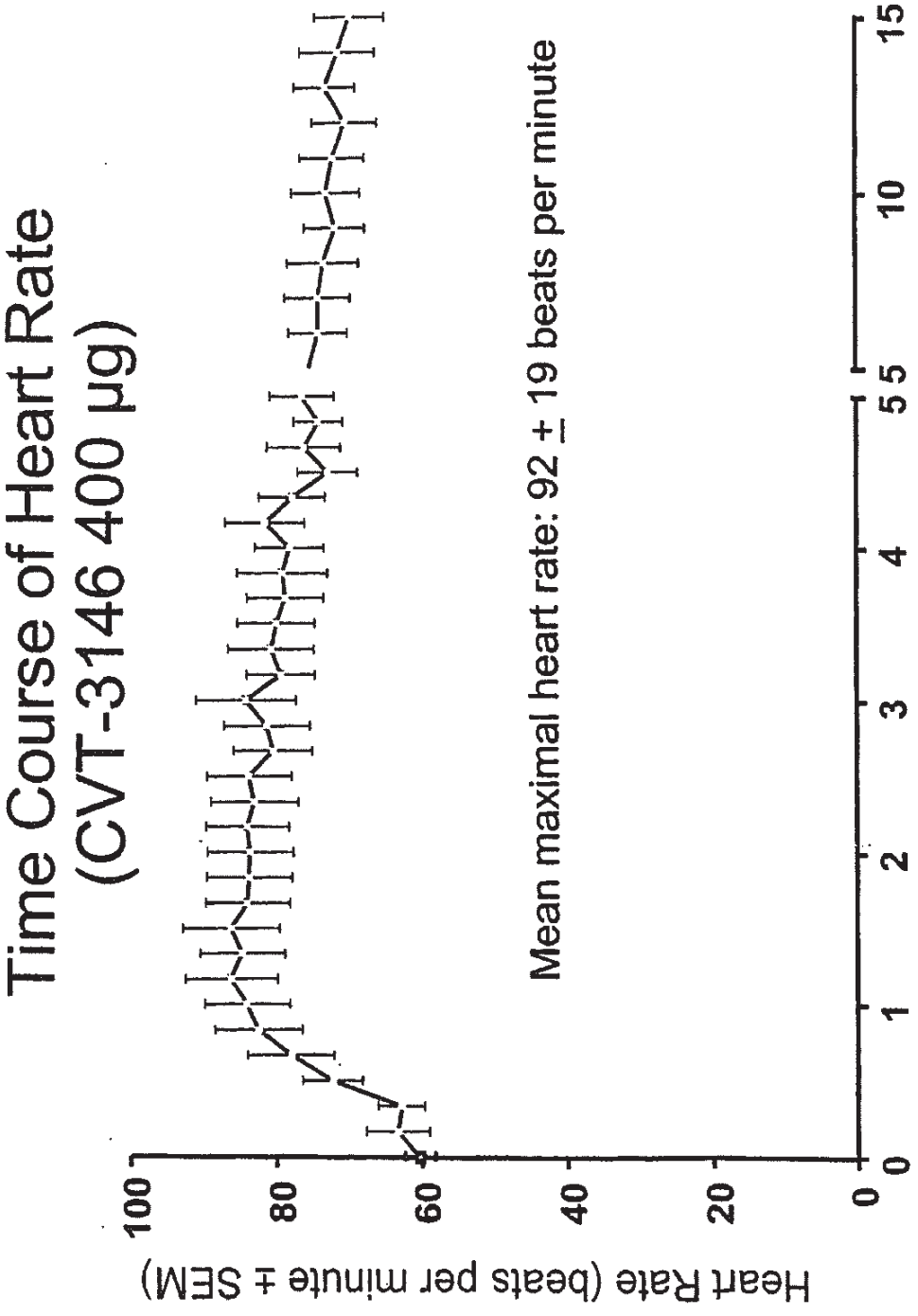

Time Course of Heart Rate
(CVT-3146 400 µg)
Mean maximal heart rate: 92 ± 19 beats per minute
Heart Rate (beats per minute ± SEM)
100
80
60
40
20
0
0
1
2
3
4
5
5
10
15
Time (minutes)

Figure 5

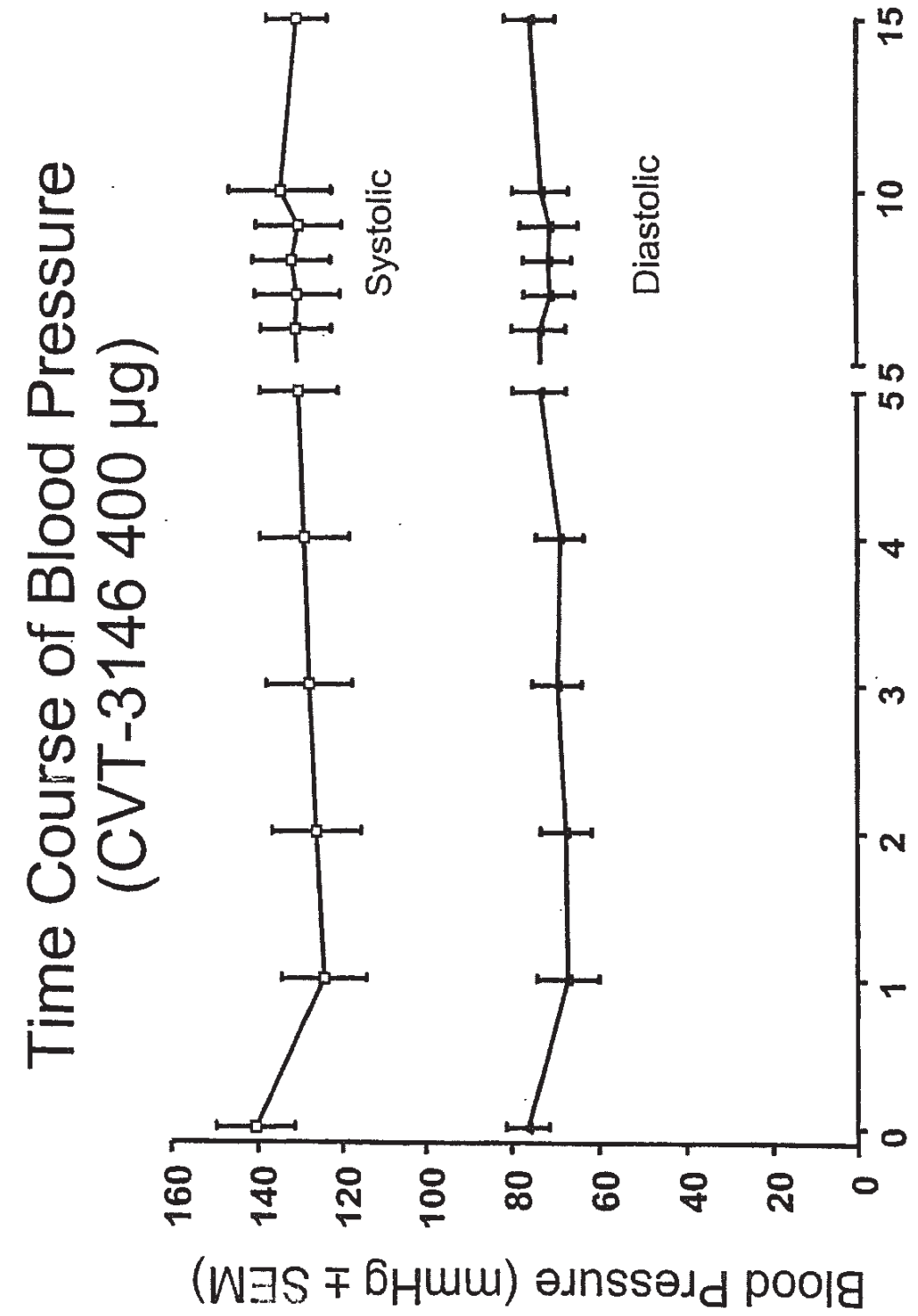

Time Course of Blood Pressure
(CVT-3146 400 µg)
Blood Pressure (mmHg ± SEM)
160
140
120
100
80
60
40
20
0
Systolic
Diastolic
0
1
2
3
4
5
5
10
15
Time (minutes)

Figure 6

All Drug-Related Adverse Events Were Mild and Transient

Adverse Event	All Doses (n = 36)	400 µg (n = 9)
chest discomfort	3	3
increased heart rate	3	1
hypotension	2	2
flushing	2	1
shortness of breath	2	0
funny taste in mouth	1	0
sensation in mouth, sinus, and chest	1	0
headache	1	0
tingling in hands	1	1
heart racing	1	1
bradycardia	1	1
lightheadedness	1	1
cough	1	0
nausea and vomiting	1	0

Figure 7

Figure 8

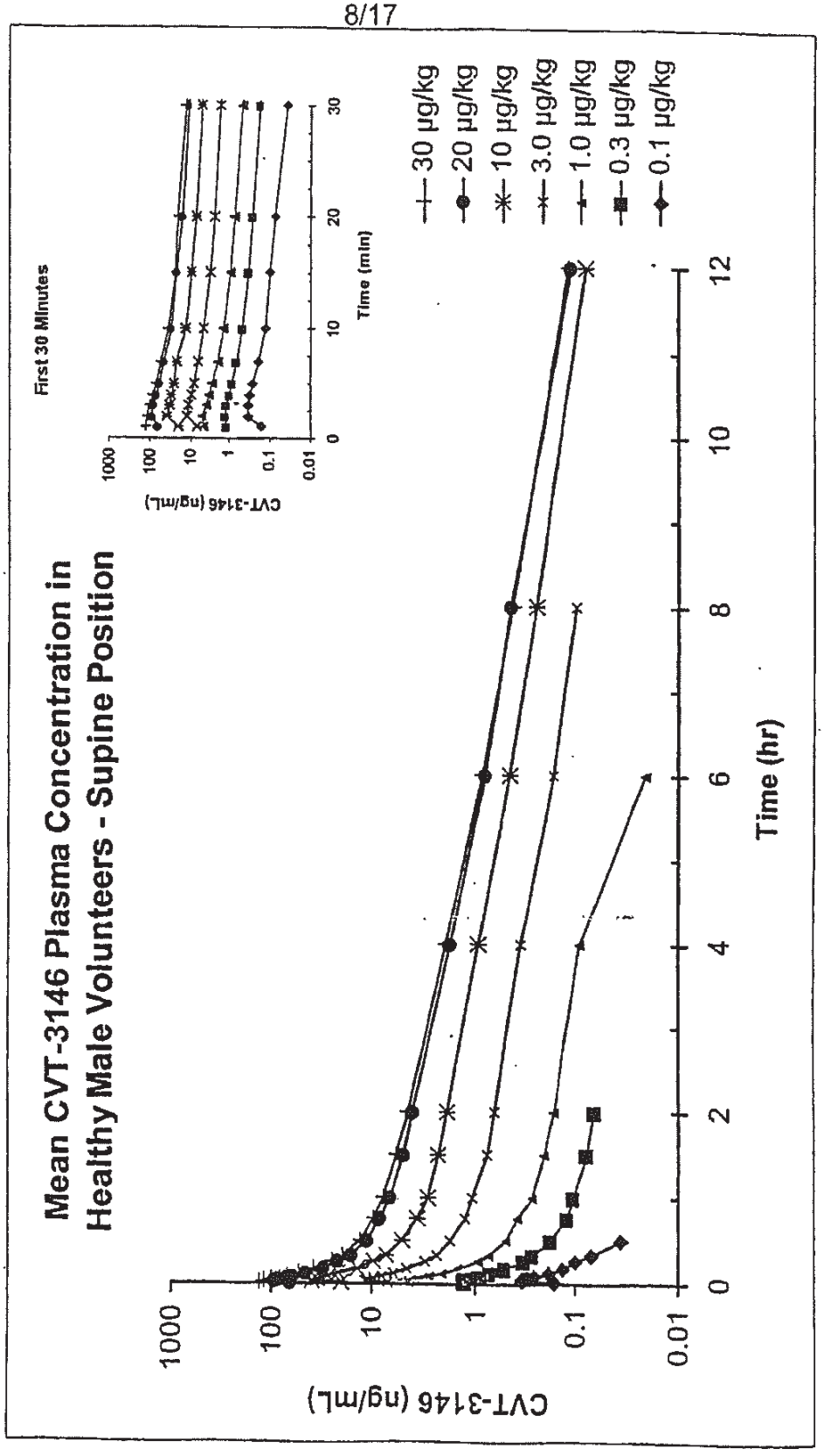

Mean CVT-3146 Plasma Concentration in Healthy Male Volunteers - Supine Position
CVT-3146 (ng/mL)
Time (hr)
30 µg/kg
20 µg/kg
10 µg/kg
3.0 µg/kg
1.0 µg/kg
0.3 µg/kg
0.1 µg/kg
First 30 Minutes
Time (min)

Figure 9

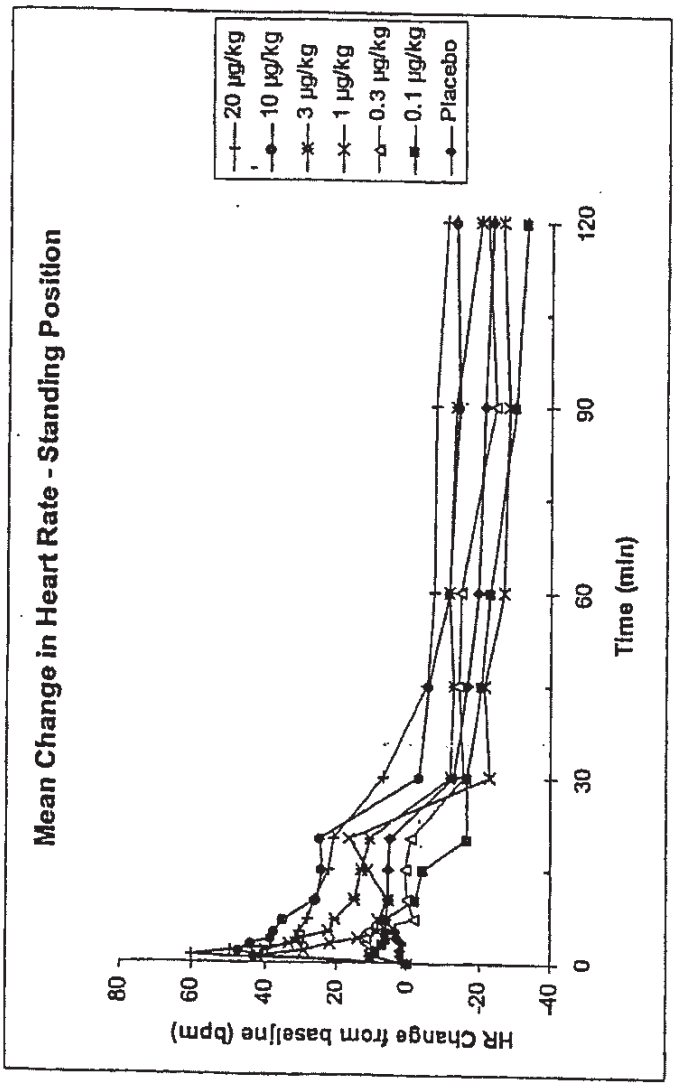

Mean Change in Heart Rate - Standing Position
HR Change from baseline (bpm)
Time (min)
20 µg/kg
10 µg/kg
3 µg/kg
1 µg/kg
0.3 µg/kg
0.1 µg/kg
Placebo
80
60
40
20
0
-20
-40
0
30
60
90
120

Figure 10

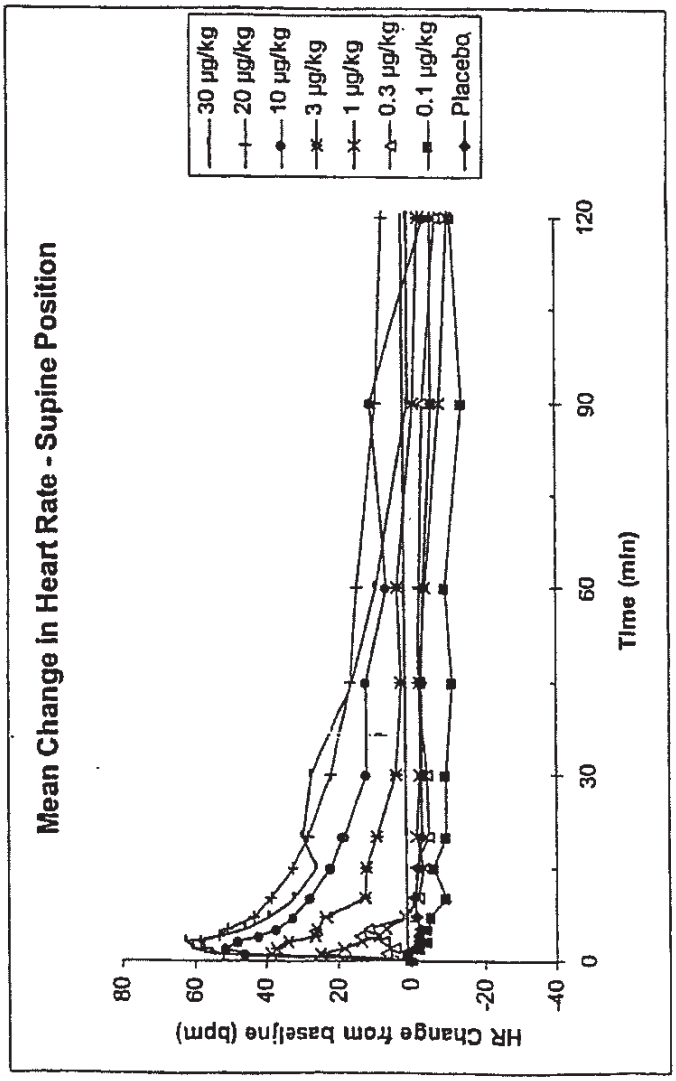

Mean Change in Heart Rate - Supine Position
30 µg/kg
20 µg/kg
10 µg/kg
3 µg/kg
1 µg/kg
0.3 µg/kg
0.1 µg/kg
Placebo
HR Change from baseline (bpm)
80
60
40
20
0
-20
-40
0
30
60
90
120
Time (min)

Figure 11

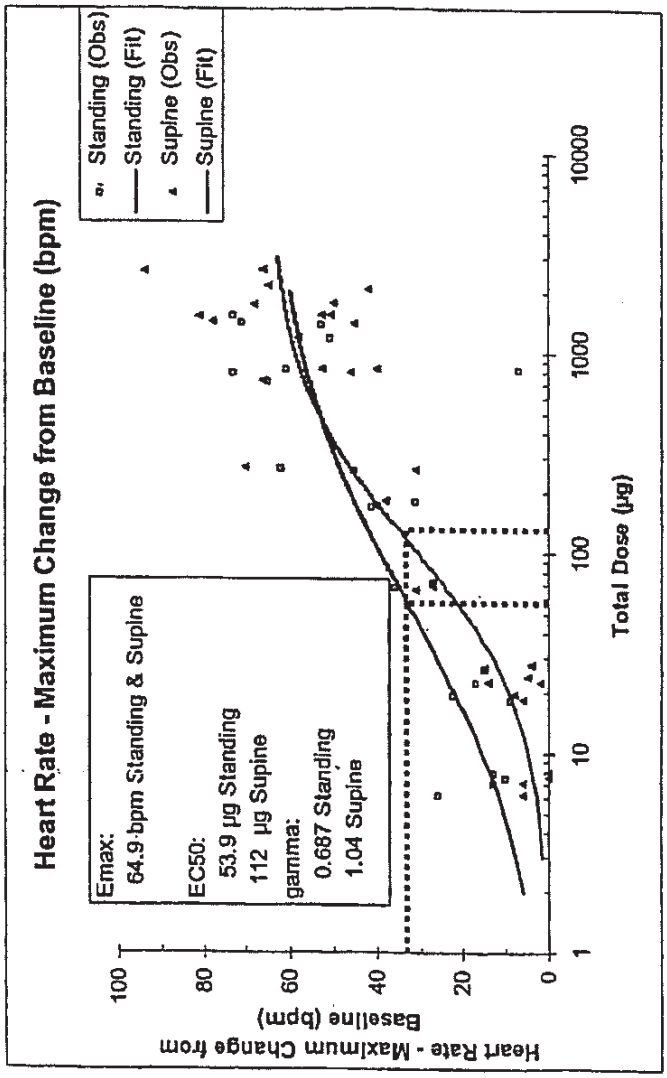

Heart Rate - Maximum Change from Baseline (bpm)
Emax:
64.9 bpm Standing & Supine
EC50:
53.9 µg Standing
112 µg Supine
gamma:
0.687 Standing
1.04 Supine
Standing (Obs)
Standing (Fit)
Supine (Obs)
Supine (Fit)
Heart Rate - Maximum Change from Baseline (bpm)
100
80
60
40
20
0
1
10
100
1000
10000
Total Dose (µg)

Figure 12

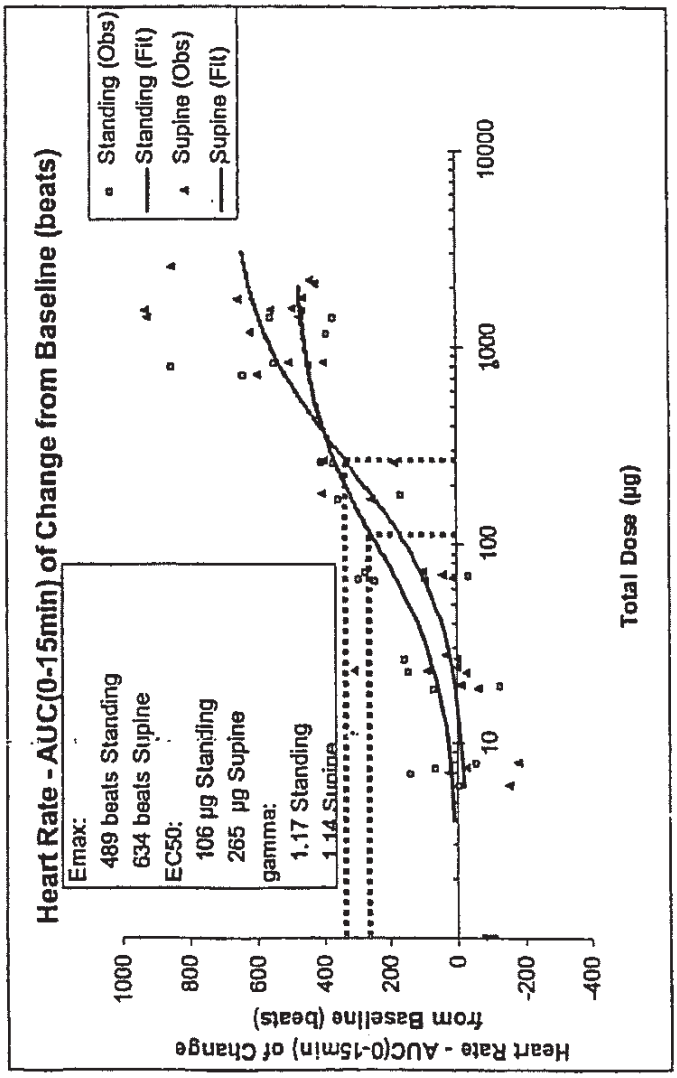

Heart Rate - AUC(0-15min) of Change from Baseline (beats)
Emax:
489 beats Standing
634 beats Supine
EC50:
106 µg Standing
265 µg Supine
gamma:
1.17 Standing
1.14 Supine
Standing (Obs)
Standing (Fit)
Supine (Obs)
Supine (Fit)
Heart Rate - AUC(0-15min) of Change from Baseline (beats)
1000
800
600
400
200
0
-200
-400
10
100
1000
10000
Total Dose (µg)

Figure 13

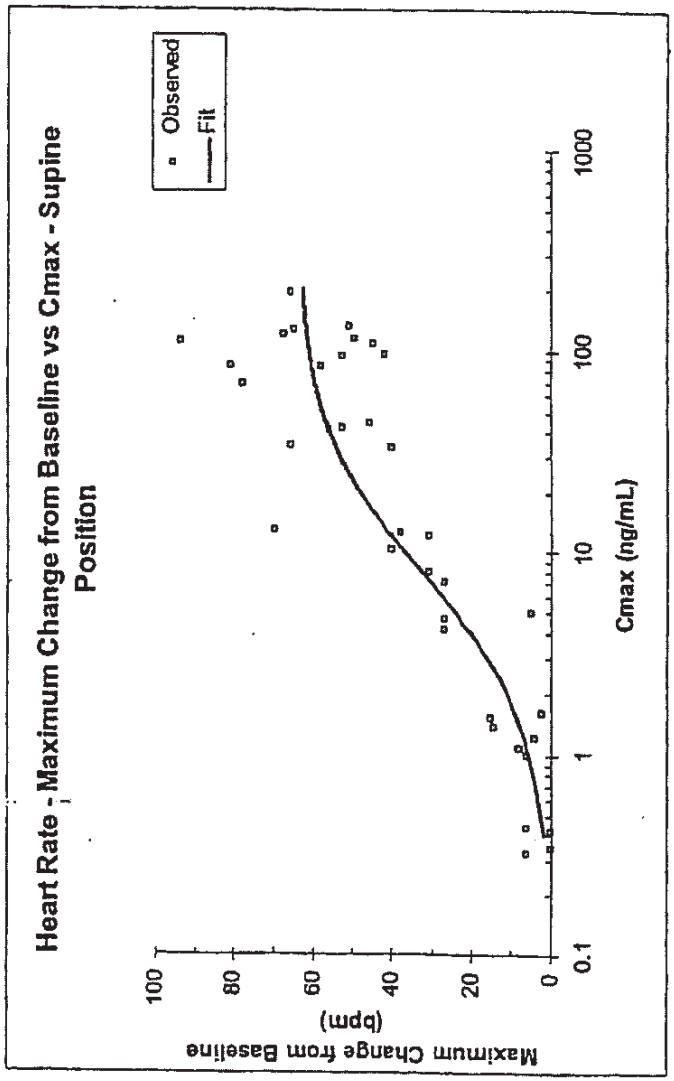

Heart Rate - Maximum Change from Baseline vs Cmax - Supine Position
Observed
Fit
Maximum Change from Baseline (bpm)
100
80
60
40
20
0
0.1
1
10
100
1000
Cmax (ng/mL)

Figure 14

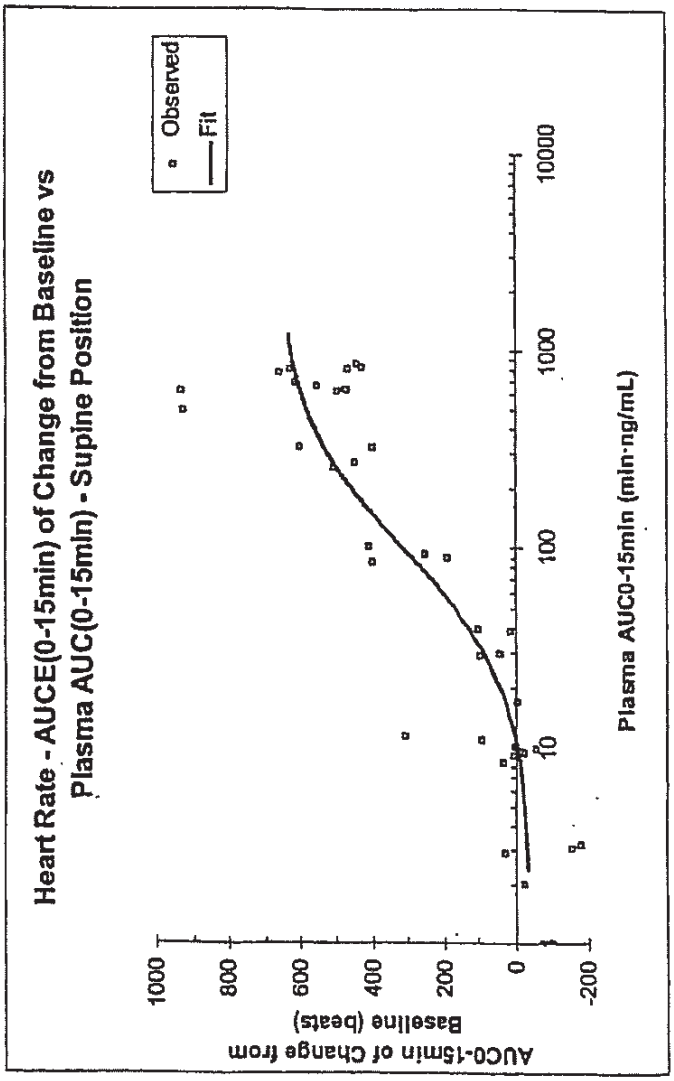
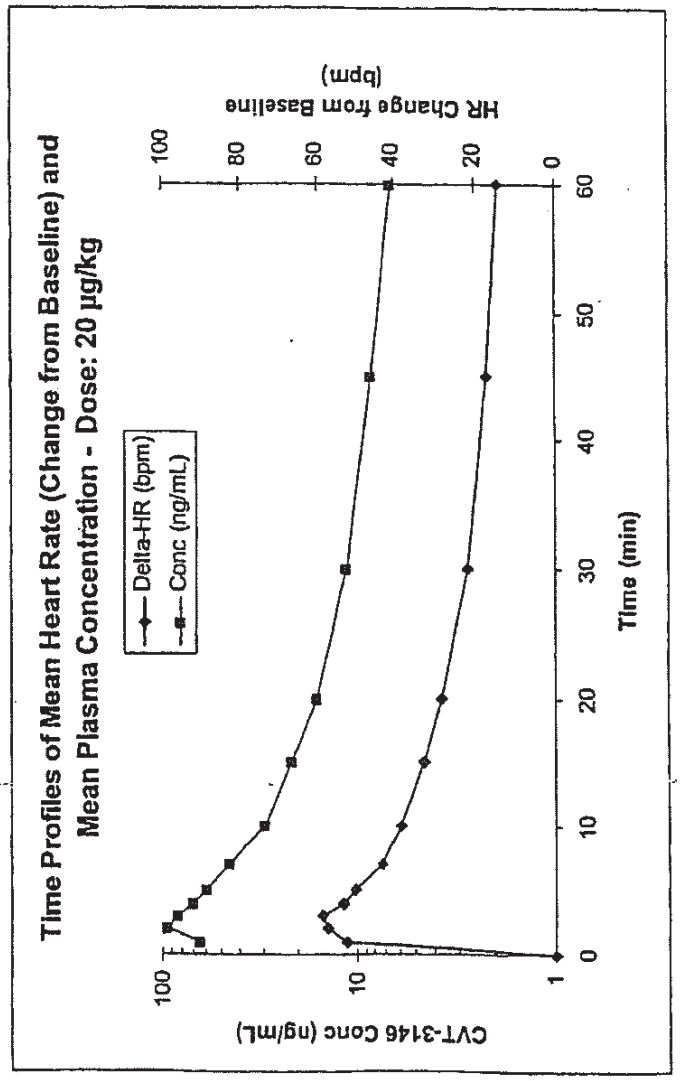

Heart Rate - AUCE(0-15min) of Change from Baseline vs Plasma AUC(0-15mln) - Supine Position
Observed
Fit
AUC0-15min of Change from Baseline (beats)
1000
800
600
400
200
0
-200
10
100
1000
10000
Plasma AUC0-15min (min·ng/mL)

Figure 15


Time Profiles of Mean Heart Rate (Change from Baseline) and Mean Plasma Concentration - Dose: 20 µg/kg
Delta-HR (bpm)
Conc (ng/mL)
HR Change from Baseline (bpm)
CVT-3146 Conc (ng/mL)
Time (min)
0
20
40
60
80
100
1
10
100
0
10
20
30
40
50
60

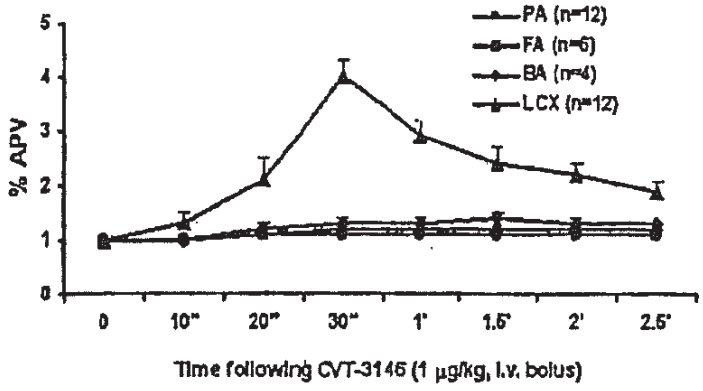


Figure 16

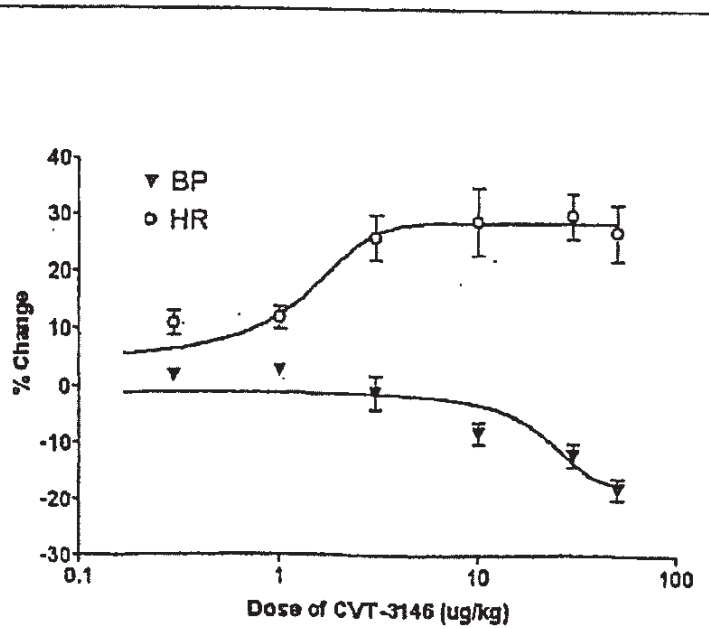


Figure 17

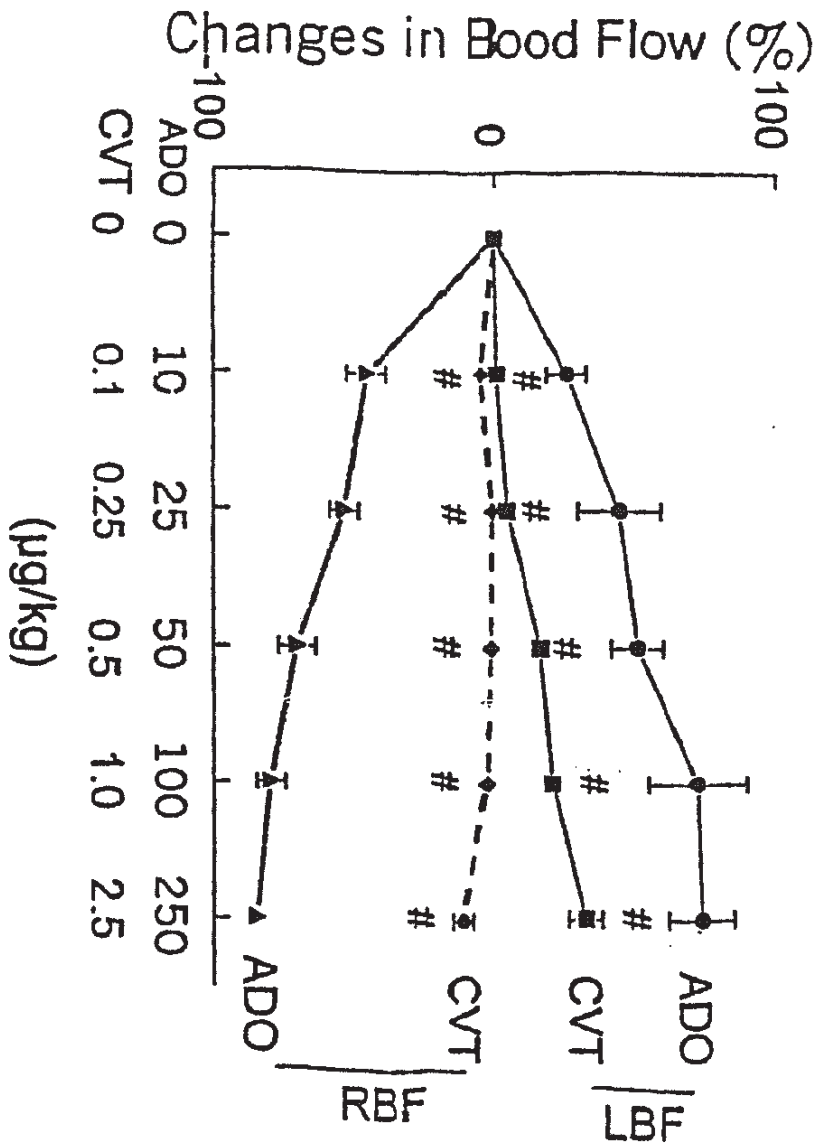

Changes in Blood Flow (%)
-100
0
100
ADO 0
CVT 0
0
10
25
50
100
250
0.1
0.25
0.5
1.0
2.5
(μg/kg)
ADO
CVT
CVT
ADO
RBF
LBF

Figure 18