PROLONGED WEIGHTLESSNESS (300 + days) AND CARDIAC PERFORMANCE IN PRIMATES

I. Neuro-Humoral Mechanisms in the Control of Cardiac and Vascular Performance in Conscious Animals

Progress Report
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PROGRESS REPORT

Summary Statement:

During the past nine (9) months we have continued our studies along the following lines:

I. Further development of techniques for and the instrumentation of dogs and other animals including primates in a manner compatible with the long term survival (300 + days) and periodic study (biweekly) of cardiac dynamics in these conscious and healthy instrumented animals.

II. Studies on the effect of temporary application (1-15 mins.) of lower body negative pressure (LBNP$_{-40}$) of between -30 and -50 mm Hg. on cardiac dynamics.

III. Continued studies on the effect of infusing selected drugs on ventricular performance. An effort was made to determine the "validity" of ventricular function changes in conscious instrumented animals, such as:

A. The validity of using "pacing" of the left ventricle to secure the data for construction of reliable ventricular function curves for conscious instrumented dogs.

B. Evaluation of the reliability of various techniques for identifying myocardial contractility changes.

(1) dP/dt/developed LVP.

(2) Shifts in ventricular function curves.

(3) Changes in mean V_{CF}.

(4) Changes in the end-systolic volume/end-systolic pressure relation.

C. Defining the "typical" effect of constant infusions of norepinephrine, isoproterenol, angiotensin II, methoxamine, phenylephrine on cardiac dynamics in conscious instrumented dogs.

/

IV. Further development of a computer based data acquisition and reduction system.

A. Programs for cardiac cycle definition, calculation of derived variables, and techniques for data reduction involving large samples (4 mins.) containing 200 or more consecutive cardiac cycles.

V. Continued development of a totally implantable package of biosensors for the semicontinuous telemetering of the primary variables, left ventricular pressure, aortic pressure, left ventricular internal diameter, and the left ventricular electrogram. This system is designed to permit studies in conscious primates (chimpanzees).

VI. Initiated studies on the effects of right and left atrial stretch receptor stimulation on myocardial function and renal function in conscious instrumented dogs.

VII. Initiated a systematic study to evaluate the validity of the use of certain popularized non-invasive techniques for evaluating ventricular function by correlating these indices with the hemodynamic information that is derived from the simultaneously monitored primary variables in conscious instrumented dogs.

DETAILED STATEMENT OF PROGRESS

1. Further Development of Techniques for and the Instrumentation of Dogs and Other Animals in a Manner Compatible with the Long Term Survival (300 + days) and Periodic Study (biweekly) of Cardiac Dynamics.

Figure 2 shows a diagram of our usual instrumentation. Table 1 summarizes control data for dogs of this type, taken an average of 101 days after instrumentation. The techniques for instrumenting dogs in this way have been described in the main body of our grant application and published articles. (See section on Publications)

In this area we have concentrated our attack during the past year on monitoring simultaneously the instantaneous changes in ascending aortic flow, left ventricular pressure, aortic pressure, left ventricular internal diameter, left ventricular aorta to apex length, the left atrio-ventricular electrogram, and dP/dt that occur in conscious instrumented dogs throughout each of a series of consecutive cardiac cycles (usually 200 or more). Figure 1 shows a typical analog record of three consecutive cardiac cycles recorded from one such instrumented dog (# 162). This is a portion of a record made from this dog sixty-five (65) days after surgery for instrumentation.

The main purposes of these studies stemmed from the needs; (1) for more precise information concerning the limits and constraints in the use of a single dimensional measurement, specifically left ventricular internal diameter (LVID), for estimating the moment to moment changes in internal volume of the left ventricle, (2) to compare the values for stroke volume obtained using an electromagnetic flowmeter to those calculated from dimensional measurements, (3) to define the changes occuring in the axis ratio left ventricular length (LVL) divided by LVID (LVL/LVID) throughout the cardiac cycle in a number of instrumented conscious dogs both during control periods and under a variety of experimental conditions.

Figure 3 shows a calibrated plot of the dimensional changes - axis ratio (L/D), LVL, LVID, calculated internal volume - along with the changes occuring in aortic and ventricular pressures, and ascending aortic flow for the periods of atrial contraction (AC), isovolumic contraction (IVC), ejection, and rapid filling for a single cardiac cycle recorded from an instrumented dog.

The data in figure 4 was calculated from recordings made on dog #162 of the type shown in figure 1. The relation between the changes in length and changes in internal diameter shown in this data (figs. 3 and 4) are characteristic of our findings. We have data on hundreds of cardiac cycles taken from each of six (6) dogs where length was recorded as shown in figure 1. The data is being collected during control periods and during periods of infusion of various drugs, increasing heart rate by pacing, and rapid infusions of dextran. Thus far it appears that these interventions do not affect the pattern of change in L/D (fig. 4) during ejection.

The relation of change in ventricular length to change in internal diameter during ejection for a single cycle is shown in the lower half of figure 4. When this relation was plotted for each of a large number of (100 +) cardiac cycles in this dog, the average slope of the regression line for the data was found to be 0.4 + 0.014 (S.D.) showing that this slope remained extremely constant. Likewise the slope was not changed by a variety of interventions such as infusions of norepinephrine, isoproterenol, and angiotensin II or pacing the ventricle. The slope of this relation was found to be the same for all the dogs studied so far. These data suggest that the changes in left ventricular length occurring during ejection in healthy conscious dogs are predictable from a knowledge of the simultaneous changes occurring in left ventricular diameter. Although measurements of both LVL and LVID simultaneously is the desired means of utilizing dimensional methods for estimating left ventricular volume changes from moment to moment, the extrapolation of volume changes from measurements of internal diameter alone seems to be feasible, if changes in the length dimension are small and can be predicted from diameter changes during ejection.

We feel that this is an important observation especially since the use of sonarmicrometry has become a popular non-invasive technique for estimating ventricular dimensional and volume changes in man.

We are currently still analyzing this data and evaluating the implications to be derived from them.

We have compared the values for stroke volume derived from aortic flow measurement (electromagnetic flow meter) to the stroke volume calculated from the simultaneously monitored dimensional changes (LVL + LVID) for the same cardiac cycle. With the aid of the computer and a specially developed data reduction program we are able to make these calculations for large numbers of consecutive cardiac cycles while recording from each instrumented animal. There is a good correlation between the values for stroke volume calculated by the two methods. This data is now being collated and summarized. Our results in this regard are in agreement with those of Mitchell and Associates, Bishop and Associates and MacDonald.

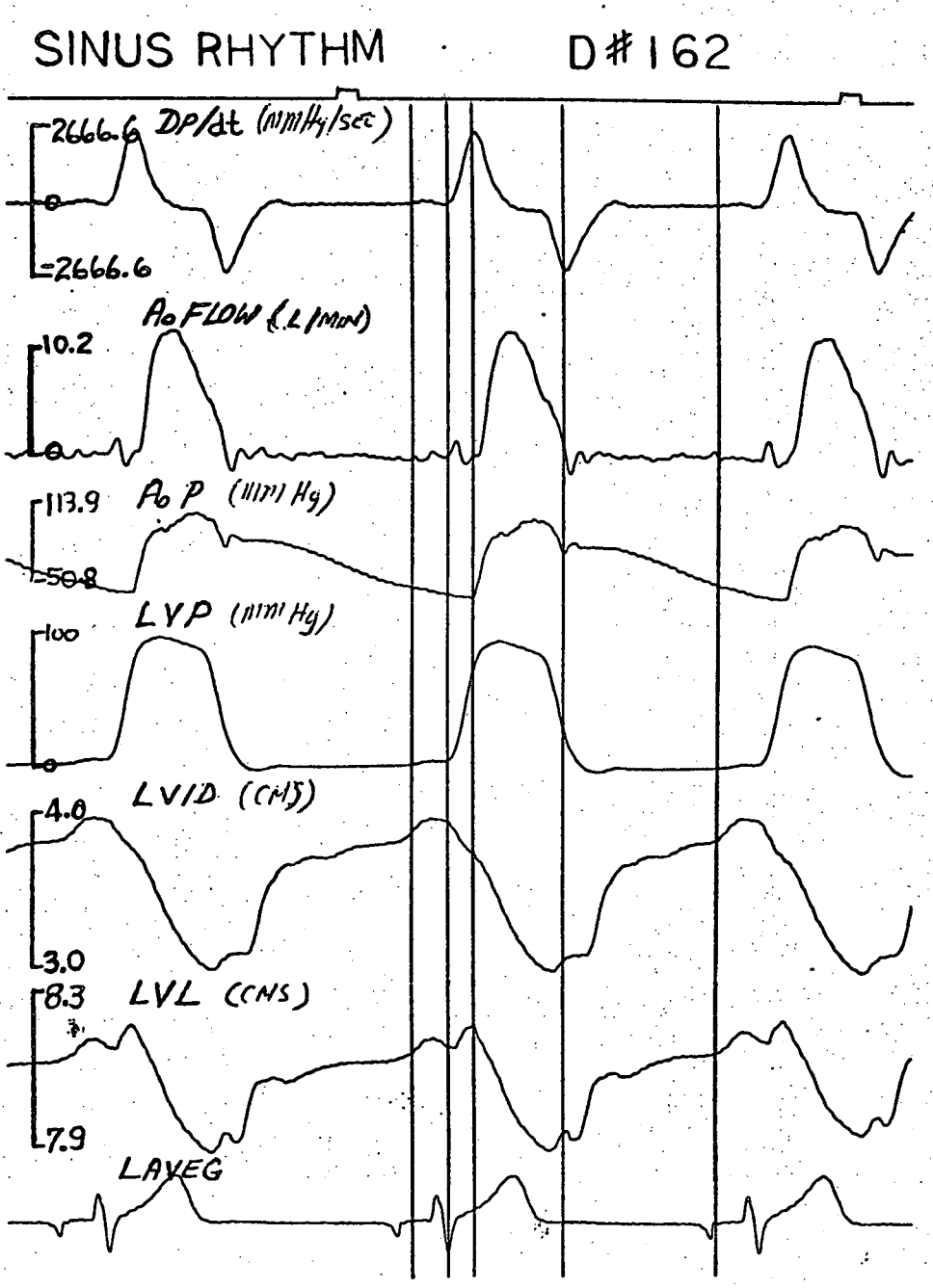
SINUS RHYTHM
D#162
2666.6
DP/dt (MMHg/sec)
-2666.6
Ao FLOW (L/MIN)
10.2
113.9
Ao P (MM Hg)
-50.8
LVP (MM Hg)
100
LVID (CMS)
4.0
3.0
8.3
LVL (CMS)
7.9
LAVEG

FIG. # 1

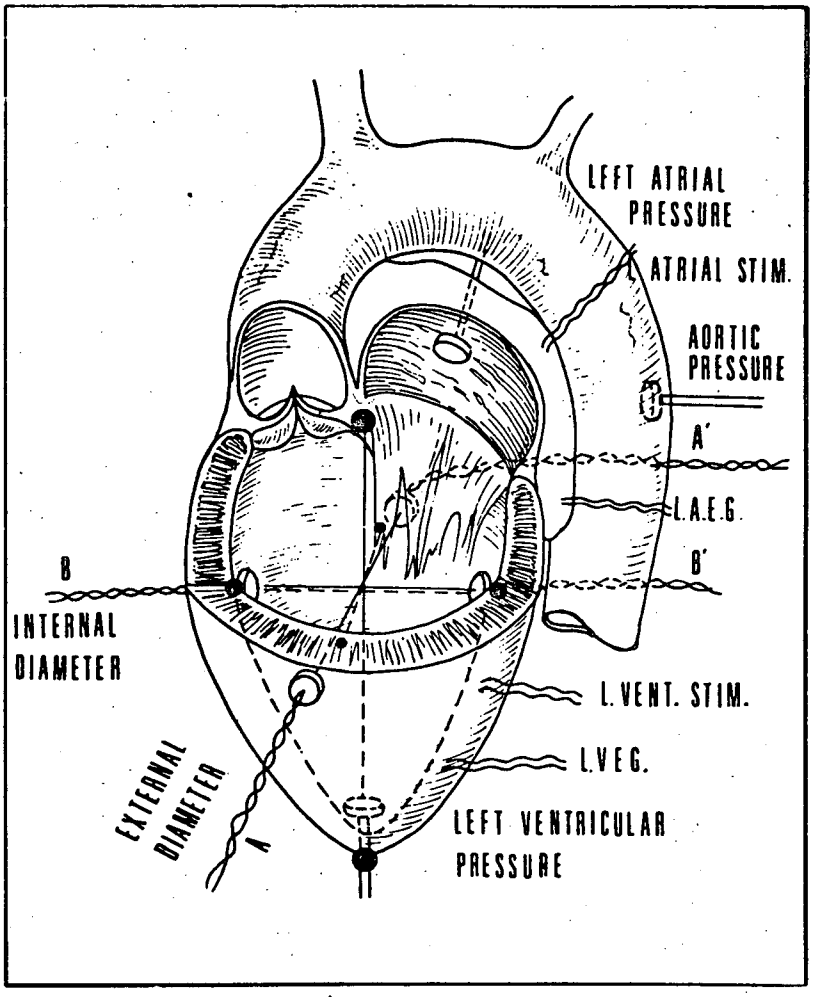
LEFT ATRIAL
PRESSURE
ATRIAL STIM.
AORTIC
PRESSURE
A'
L.A.E.G.
B'
B
INTERNAL
DIAMETER
L. VENT. STIM.
L.V.E.G.
EXTERNAL
DIAMETER
A
LEFT VENTRICULAR
PRESSURE

FIG 2

TABLE I. CONTROL DATA FROM CONSCIOUS INSTRUMENTED DOGS

Dog #	Sex	Wt. Kgs.	Days P. O.	Number of Cycles	Sys. A. P. mm Hg	Diast. A. P. mm Hg	MAP mm Hg	LVEDP mm Hg	H. R. beats/min	CO L/min.	TPR dyne-sec Cm-5	EDV ml.	ESV ml.	SW gm-m	SP gm-m/sec	AWFEI gms	$dp/dt/P_D$ sec^{-1}	P. dp/dt mm Hg/sec	M. Vcf circ/sec	Ej. Fr. %	Ej. T. msec	IVC msec
128	M	24	34	15	127	50	101	1.8	130	3.7	2.1	61	32	47	353	2077	81	2505	1.6	47	133	35
130	M	23.	30	390	123	83	108	-0.5	123	3.3	2.6	53	26	38	262	1835	--	2648	1.6	51	145	41
132	M	25.0	259	150	105	74	93	5.0	100	4.1	1.7	61	19	62	335	1399	92	3534	1.9	59	190	50
133	M	24.5	266	11	138	87	119	12	123	3.3	2.7	48	19	53	456	1921	114	3881	2.6	60	116	36
151	M	26.0	153	360	136	86	113	9.9	94	3.7	2.2	75	35	56	352	2273	64	2486	1.6	54	159	50
154	M	26.0	30	309	131	74	102	8.7	81	3.6	2.1	69	23	67	416	1829	79	2878	2.3	67	161	38
155	M	27.0	145	452	121	92	108	3.9	123	2.5	3.3	62	40	31	218	1902	46	1857	1.0	35	142	49
157	M	24.0	133	425	120	68	94	-3.0	107	2.9	2.6	44	17	54	388	1459	71	2554	2.3	62	139	40
158	M	26.5	28	462	106	66	89	-1.0	67	2.1	3.4	61	27	41	364	1419	64	2317	1.5	51	132	42
159	M	27.5	28	336	113	48	83	-0.7	89	2.5	2.7	57	27	42	261	1573	71	2700	1.5	52	161	40
160	M	24.0	48	304	105	57	80	10.0	83	1.8	3.1	55	31	33	217	1557	61	2321	1.5	43	152	39
162	M	24.0	63	140	121	60	92	6.0	89	1.7	3.9	42	22	32	187	1303	70	2641	1.4	48	171	49
Mean		25.3	101.4	279.5	120.5	70.4	98.5	4.4	100.7	2.9	2.7	57.4	26.5	46.3	317.4	1712.2	67.7	2693.5	1.7	52.4	150.1	42
± S.E.					3.3	4.3	3.5	1.4	5.8	0.2	0.1	2.0	2.0	3.4	24.9	87.6	7.8	156.5	0.1	2.5	5.8	1

All values are the average of the number of consecutive cardiac cycles analyzed

DOG # 162

CHANGES IN AXIS-RATIO VS DIAM.
DURING EJECTION

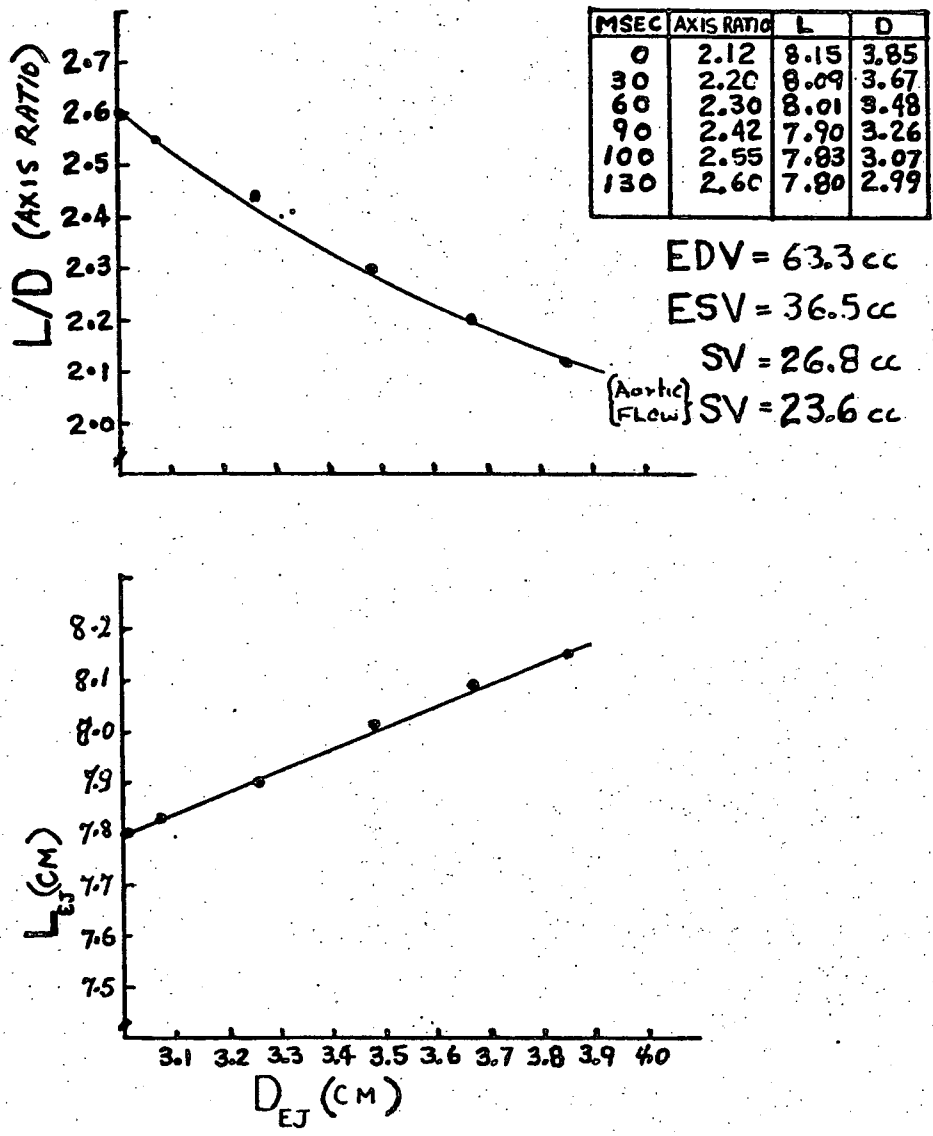

FIG. # 4

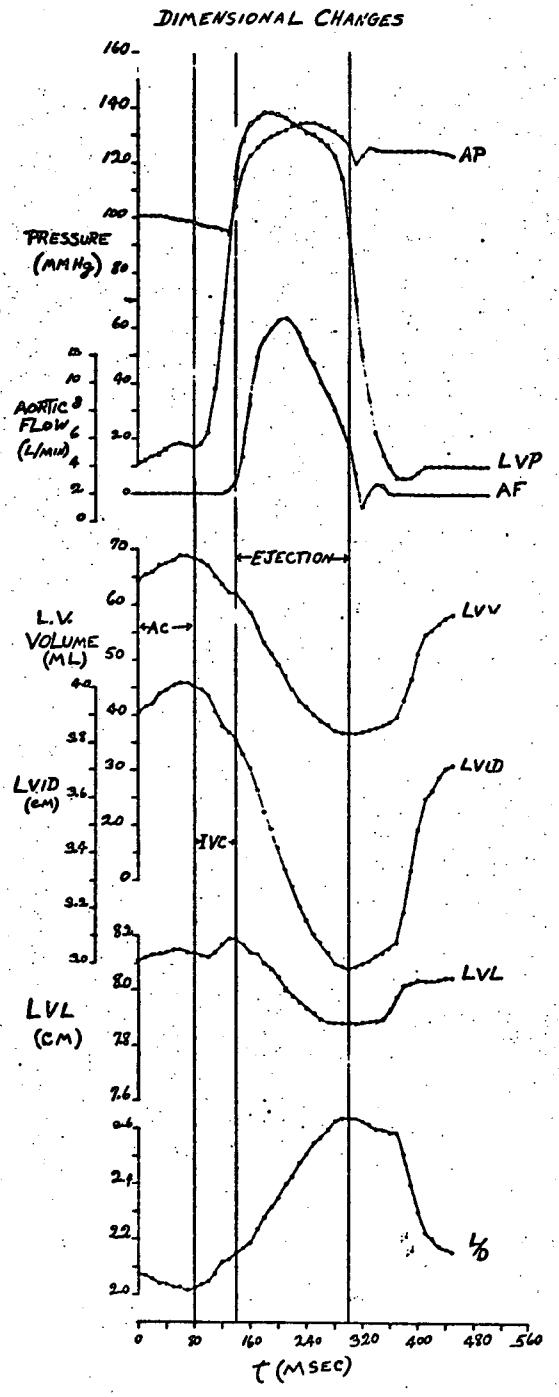
DIMENSIONAL CHANGES
PRESSURE (MMHg)
AP
LVP
AF
AORTIC FLOW (L/MIN)
EJECTION
L.V. VOLUME (ML)
AC
LVV
LVID (CM)
LVID
IVC
LVL (CM)
LVL
L/D
T (MSEC)

FIG. # 3

II. Studies on the Effect of Temporary Application (1-15 mins) of Lower Body Negative Pressure ($LBNP_{-40}$) of Between -30 and -50 mm Hg. on Cardiac Dynamics.

The cardiovascular adjustments to LBNP have been previously studied in humans and anesthetized dogs. However, no studies have been carried out in conscious animals. Recently Nutter, Hurst, and Murray (J. Appl. Physiol. 26: 23, 1969) studied the changes in left ventricular function in intact anesthetized dogs during graded hypovolemia produced by exposure to -30, -60, -90 mm Hg. lower body negative pressure. They observed, in twelve (12) dogs, a linear decrease in left ventricular pressure, max dP/dt, ejection fraction, aortic flow, peak power and stroke work. Of interest was their finding that myocardial contractility, as measured by max dP/dt/isovolumic pressure and max dF/dt to peak flow, was not altered by moderate hypovolemia. We were interested in studying the effects of LBNP in conscious instrumented dogs with the objective of characterizing the responses to LBNP in conscious animals so that it maybe used as a calibrated forcing function on the cardiovascular system; and also to study the effect of various pressor, inotropic and blocking agents on the response of the cardiovascular system to lower body negative pressure.

Five (5) conscious instrumented dogs were subjected to moderate levels (-40 to -50 mm Hg) of lower body negative pressure. A specially constructed lower body negative pressure chamber was made from thick-walled plexiglass and a steel frame. This chamber is capable of withstanding pressures of at least -90 mm Hg. The chamber is fitted with an iris type gum rubber seal. An exhaust is provided at the side which is connected to one or two commercial type vacuum cleaners. An outlet is provided which allows for the measurement of pressures in the chamber when the animal is subjected to lower body negative pressure. The hind quarters of the dog are placed in the box and sealed at the mid-abdominal level when it was desired to expose the animal to LBNP.

Conscious dogs were submitted to LBNP (-40 mm Hg) before and after (1) beta receptor blockade with propranolol (2) mild sedation with Inovar*.

The cardiovascular responses to moderate LBNP in conscious dogs has been found to be variable. Figure 5 shows a recording of the response from dog #151 without sedation. Upon application of LBNP (-45 mm Hg) there is a marked reduction in left ventricular end-diastolic and end-systolic size, a reduction in effective end-diastolic pressure and systolic LV pressure, an initial decrease in aortic systolic and diastolic pressure, an increase in max dP/dt and a marked increase in heart rate. The maintanance of an elevated max dP/dt and gradual return of heart size and aortic pressure is also seen. Analysis of the data for four (4) additional animals is shown in figures 6 through 9 and tables 2 - 5. It can be seen from these data that in all cases there was a reduction in end-diastolic and end-systolic and stroke volumes. The amount of change varied from animal to animal.

*Pitman-Moore, Washington Crossing, New Jersey

The changes in total peripheral resistance (TPR) can be seen in figures 6 through 9. The increase in TPR varies from 4% to 38%. Cardiac output was decreased in all animals by 18 to 30% except in one animal, dog #151 where there was an increase in C.O. by 13%. In the studies, changes in myocardial contractility were estimated from dP/dt with relation to a given developed pressure during the phase of isovolumic contraction ($dP/dt/P_D$) and the mean velocity of circumferential fiber shortening (XV_{CF}) during the phase of ejection. Both of the indices usually show variable increases during the responses to LBNP. Again the changes in heart rate though markedly increased in dog #151 show the same degree of variability from animal to animal in response to LBNP.

Beta receptor blockade was obtained in each animal through administration of enough propranolol (usually 0.5 mg/Kg body wt., I.V.) to block the observed response to standard doses of isoproterenol (usually 10μg) in a single injection. Figures 6, 7, and 10B show the cardiovascular effects of beta-adrenergic blockade in the conscious dog. There is an increase in TPR, and generally an increase in left ventricular end-diastolic size and end systolic size, a decrease in heart rate and no significant changes in myocardial contractility was measured.

The dynamic recording of the response after beta adrenergic blockade is shown in figure 8. There is a uniform decrease in left ventricular end-diastolic and end-systolic volume, a slight decrease in aortic pressure and no change in heart rate, in addition, there is no change in myocardial contractility. However after propranolol most dogs demonstrated an elevation of total peripheral resistance, with a reduction in the ejected fraction and reduction in stroke work at the same level of LBNP as that for the control period.

These preliminary observations would lead to the conclusion that the cardiovascular responses seen to lower body negative pressure appear to be dependent on the level of understanding of autononic nervous activity. For in the conscious dog varied responses were obtained; while in the dog under mild sedation or beta receptor blockade the responses were relatively uniform and similar to those reported for the anesthetized animals. Further studies are being conducted to further understand the responses reported here.

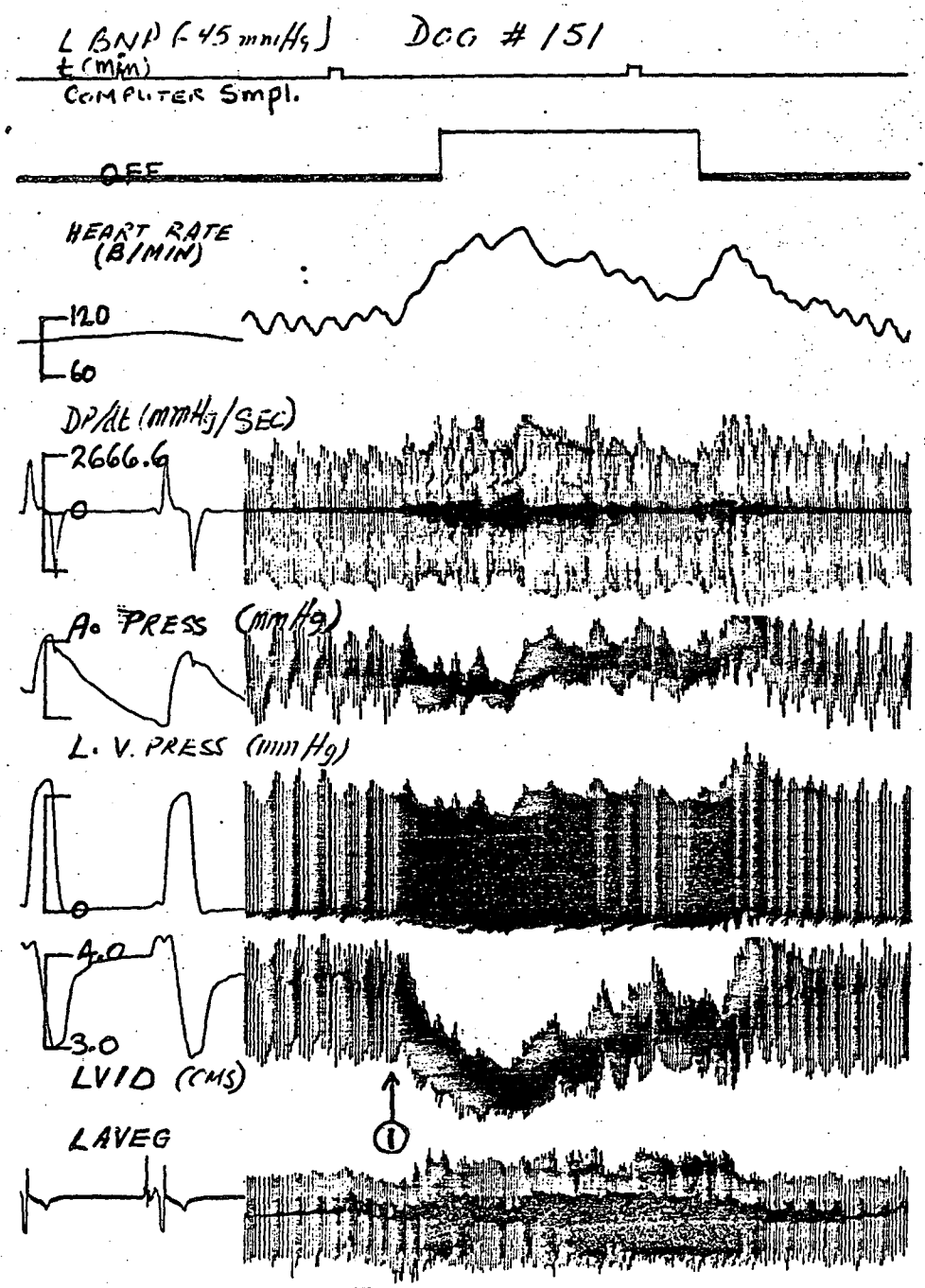
L BNP (-45 mmHg) DOG # 151
t (min)
COMPUTER Smpl.
OFF
HEART RATE (B/MIN)
120
60
DP/dt (mmHg/SEC)
2666.6
0
Ao PRESS (mmHg)
L. V. PRESS (mmHg)
0
4.0
3.0
LVID (CMS)
LAVEG

FIG. # 5

B

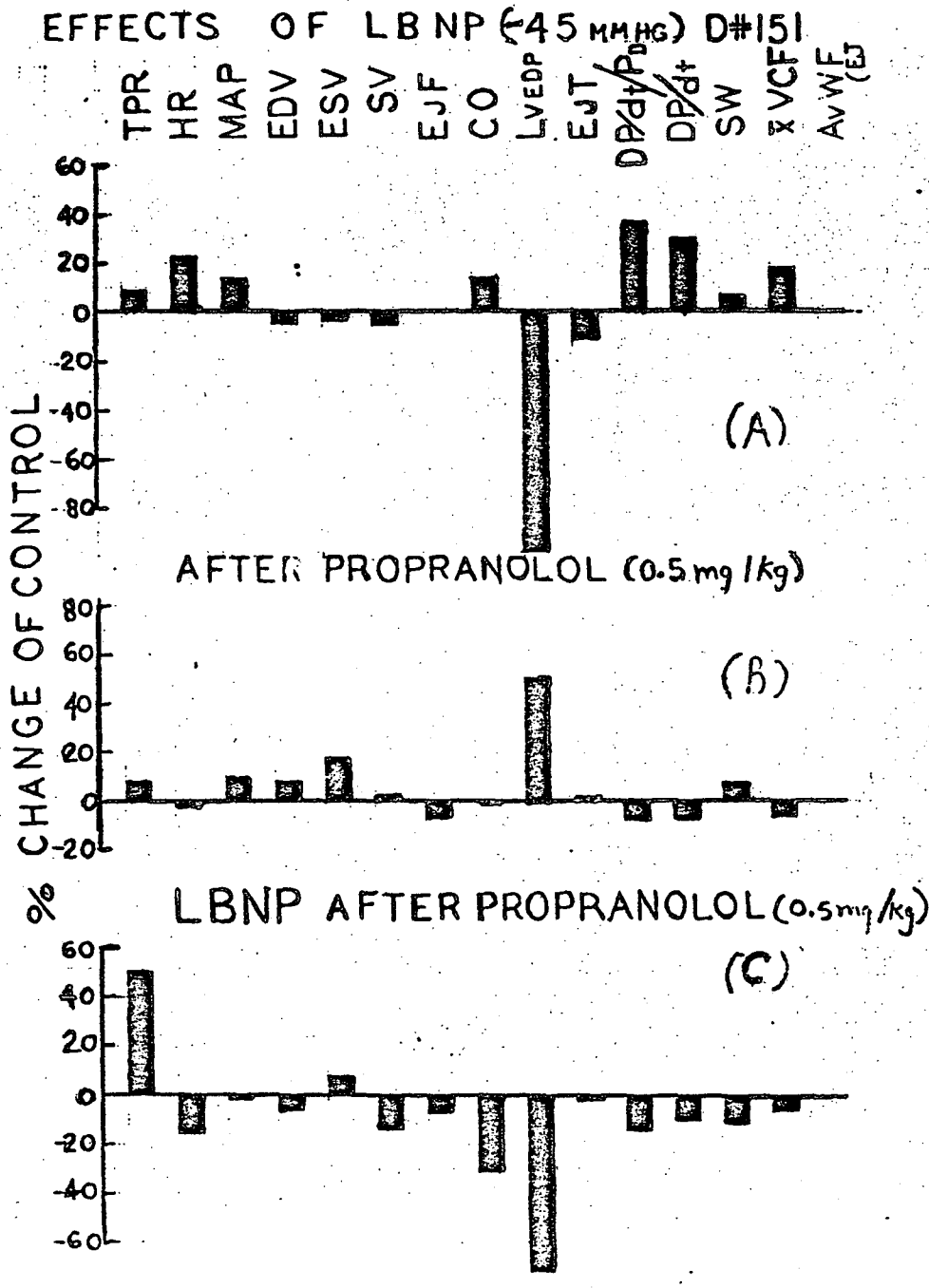
EFFECTS OF LBNP (-45 MM HG) D#151
TPR
HR
MAP
EDV
ESV
SV
EJF
CO
LVEDP
EJT
DP/dt/P0
DP/dt+
SW
X VCF
AV WF (EJ)
60
40
20
0
-20
-40
-60
-80
(A)
AFTER PROPRANOLOL (0.5 mg/kg)
% CHANGE OF CONTROL
80
60
40
20
0
-20
(B)
LBNP AFTER PROPRANOLOL (0.5 mg/kg)
(C)
60
40
20
0
-20
-40
-60

FIG. # 6

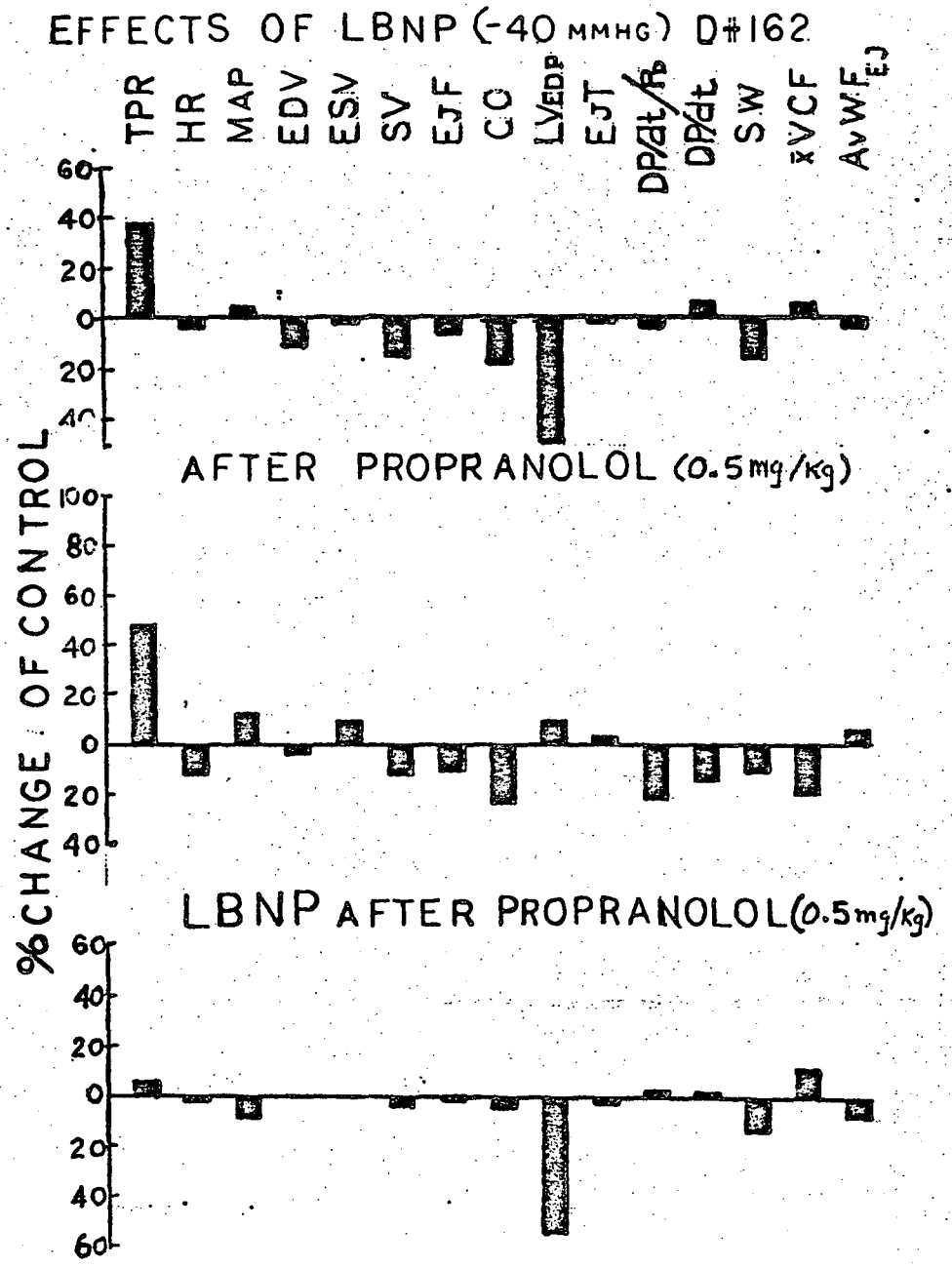
EFFECTS OF LBNP (-40 MMHG) D#162
TPR
HR
MAP
EDV
ESV
SV
EJF
CO
LVEDP
EJT
DP/dt/Rb
DP/dt
S.W
x̄VCF
Av W.F EJ
60
40
20
0
20
40
AFTER PROPRANOLOL (0.5mg/kg)
% CHANGE OF CONTROL
100
80
60
40
20
0
20
40
LBNP AFTER PROPRANOLOL (0.5mg/kg)
60
40
20
0
20
40
60

FIG. # 7

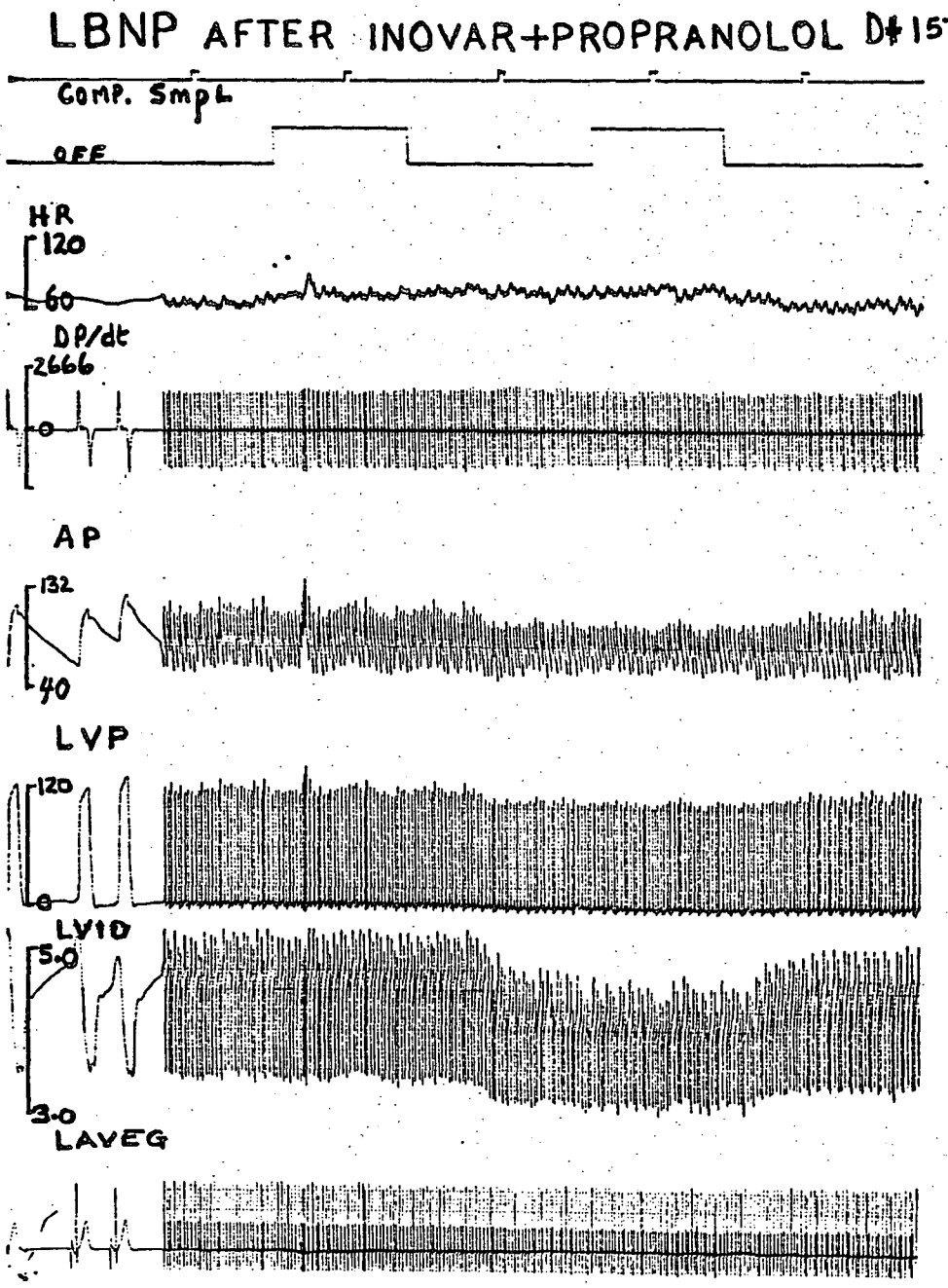
LBNP AFTER INOVAR+PROPRANOLOL D#157
COMP. SMPL
OFF
HR
120
60
DP/dt
2666
0
AP
132
40
LVP
120
0
LVID
5.0
3.0
LAVEG

FIG. # 8

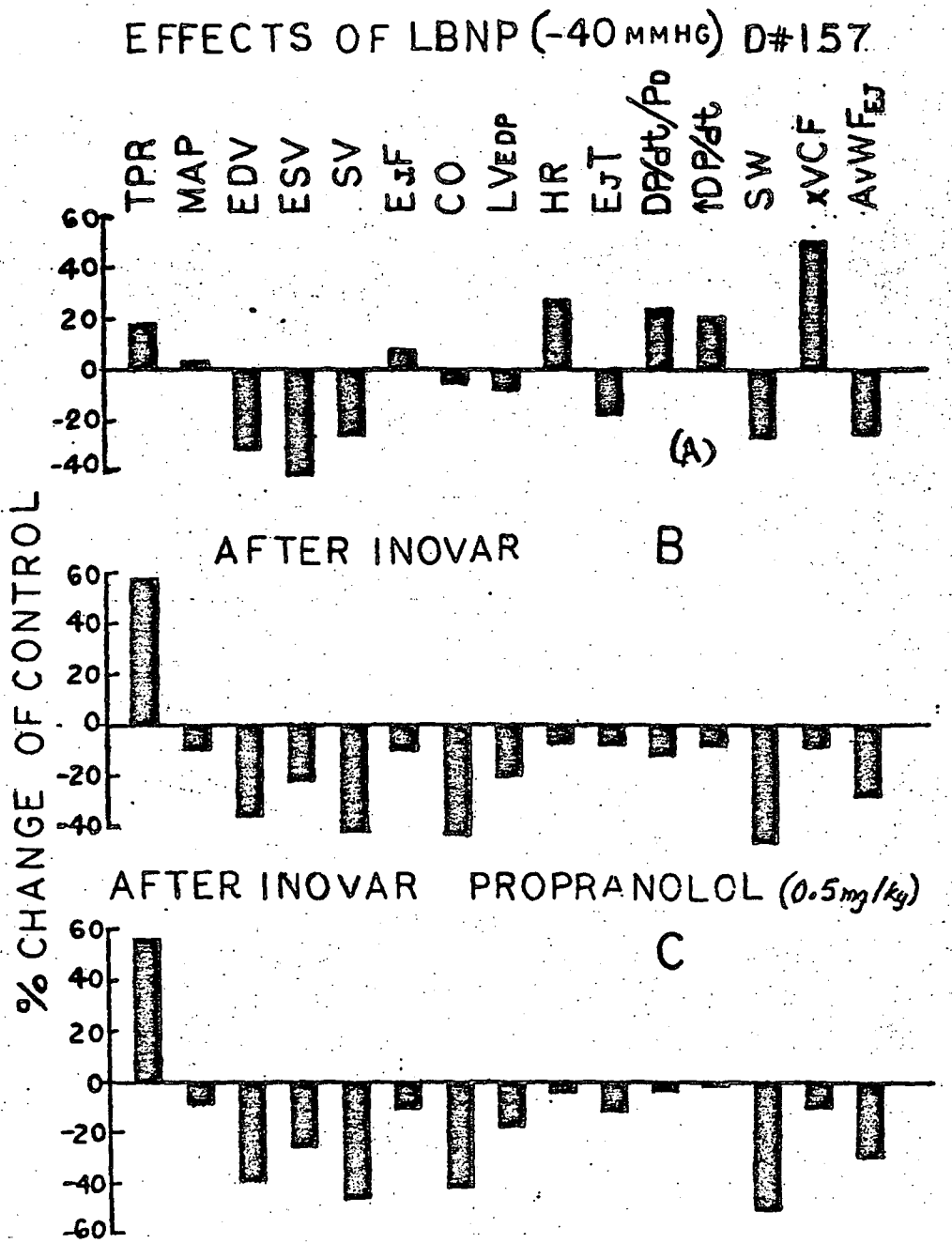
EFFECTS OF LBNP (-40 MMHG) D#157
TPR
MAP
EDV
ESV
SV
EJF
CO
LVEDP
HR
EJT
DP/dt/Po
↑DP/dt
SW
xVCF
AvWFEJ
60
40
20
0
-20
-40
(A)
AFTER INOVAR
B
% CHANGE OF CONTROL
AFTER INOVAR PROPRANOLOL (0.5mg/kg)
C
-60

FIG. # 9

TABLE 2

Effect of LBNP on Cardiac Function Before and After Propranolol - Dog # 151

Variable	Control				After Propranolol			
	Control (C_1)		LBNP		Control (C_2)		LBNP	
	N= 157		N= 188	% C_1	N=74	% C_1	N= 58	% C_2
TPR	2.4		2.6	.8	2.6	8	3.9	50
MAP	128 ±8		145 ±10	13	139 ± 13	9	137 ±9	-1
EDV	65 ±3		62 ± 6	-5	70 ±4	8	66 ± 5	-6
ESV	24 ±2		23 ± 3	-4	28 ±3	17	30 ±2	+7
SV	41 ±3		39 ±5	-5	42 ±3	2	36 ±5	-14
EJF	63 ±3		63 ±4	0	59 ±3	-6	55 ±5	-7
C.O.	3.9		4.4	+13	3.9	0	2.7	-31
LVEDP	8 ±3		0.1 ±5	-99	12 ±3	50	3.0 ± 6	-75
HR	99 ± 16		121 ± 28	+22	96 ± 12	-3	82 ± 24	-15
EJT	171 ± 5		152 ±9	-11	172 ± 4	0.6	170 ±8	-1
$dP/dt/P_D$	79 ±9		108 ±21	37	74 ±9	-6	64 ±9	-14
↑DP/dt	2975 ±75		3855 ±532	30	2753 ± 159	-7	2492 ±213	-10
SW	83 ±7		88 ± 14	6	89 ±7	+7	79 ± 12	-11
VCF	1.7 ±0.1		2.0 ±0.2	18	1.6 ±0.1	-6	1.5 ±0.1	-6

TABLE 3

Effects of LBNP (-45mm Hg) on Cardiac Function - Dog # 155

Variable	Control	LBNP		LBNP after Propranolol	
		N=423	% Control	N=307	% Control
TPR	3.2	5.2	62.5	4.5	40.6
MAP	104 ±12	126.	21.2	147.5	41.8
EDV	63.7 ±7	39.8	-37.5	68.0	6.8
ESV	25.0 ±2	19.2	-23.2	33.0	32.0
SV	38.6 ±7	20.6	-46.6	35.0	-9.3
EJF	60.3 ±5	48.8	-19.1	51.4	-14.8
C.O.	2.5 ±	2.2	-12.0	2.7	8.0
LVEDP	1.6 ±2	-16.2		-5.7	
HR	81.3 ±36	122.	+50.1	85.8	5.5
EJT	184.3 ±	140.5	-24	178.0	-3.3
$DP/dt/P_D$	50 ± 10	67.3	+34	53.2	5.9
↑DP/dt	1970 ±294	2577.0	30.8	21.0	6.8
SW	67.4 ±16	38.6	-42.7	77.0	14.2
$\bar{X}$VCF	18.2 ±1.6	13.2	-27.5	13.9	-23.6
AvWFej	1735 ±248	1423.0	-18.0	2418.6	39.0

TABLE 4

Effect of LBNP on Cardiac Function before and after sedation with Inovar and after Propranolol - Dog # 157

	Control			After Inovar - (1. mg. (IM))				After Propranolol			
	Control #1	LBNP		Control #2		LBNP		Control #3		LBNP	
	N=95*	N=126	$\%C_1$	N=57	$\%C_1$	N=54	$\%C_2$	N=34	$\%C_2$	N=36	$\%C_3$
TPR	1.6	1.9 ±	18.8	1.2	-25	1.9	58.0	1.5	22.5	2.3	56.5
MAP	97.2 ±6	100.1±3	2.9	85.4	-12.1	76.7	-10.2	86.1	1.0	78.5	-8.8
EDV	51.1 ±4	35.3 ±3	-31	92.7	80.6	59.5	-35.8	128.1	38.1	77.8	-39.3
ESV	16.2 ± 1.1	9.4 ±1	-42	23.1	42.5	18.1	-21.6	40.8	76.6	30.3	-25.7
SV	34.9 ±4	25.9 ±3	-25.8	69.6	99.4	41.4	-40.5	87.3	25.4	47.5	-45.6
EJ.F	68.1 ±3	73 ±4	+7.3	74.5	9.4	68.0	-8.7	68.0	-8.7	60.8	-10.6
C.O.	4.3 ±	4.1	-4.6	5.1	18.6	2.9	-43.1	4.0	-21.6	2.3	-42.5
LVEDP	8.0 ±	2.0	-7.5	8.9	11.3	7.1	-20.2	12.9	44.9	10.6	-17.8
HR	129.5 ±25	163.8	26.5	79.6	-38.5	74.3	-6.6	48.9	-38.6	50.6	-3.5
EJ . T	132.8 ±6	109.4	-17.6	153.0	15.8	142.0	-7.2	188.2	23.0	166.5	-11.5
$DP/dt/P_D$	100.7 ±18	124.2	23.8	129.5	28.6	114.0	-12	63.8	-50.7	61.04	-4.3
↑DP/dt	3482 ±213	4248	21.9	4217	21.1	3911.0	-7.2	2478	-41.2	2456	-1.0
SW	56.7 ± 7	41.2	-27.3	107.5	89.6	58.2	-45.9	130.3	+21.2	65.8	-49.5
$\overline{X}$ VCF	29.3 ± 2	43.9	49.8	38.1	30.0	35.6	-6.6	27.9	26.7	25.0	-10.4
Av.WFej.	1325 ±	983	-25.8	1624	22.6	1169	-28.0	2164	33.3	1531	-29.3

* N = Number of consecutive cardiac cycles analyzed by the computer

TABLE 5

Effect of LBNP on Cardiac Function before and after Propranolol - Dog # 162

Variable	Control	$LBNP_1$		$LBNP_2$		AV	Control (C_2 After Propranolol		$LBNP_3$		$LBNP_4$		AV
	N=75(C_1)	N=73	$\%C_1$	N=70	%C	$\%C_1$	N=60	$\%C_1$	N=60	$\%C_2$	N=60	$\%C_2$	$\%C_2$
TPR	2.5	3.3	32	3.6	44	38	3.7	48	3.8	+3	4.0	+8	+6
MAP	91.3±3	95±3	4	95±4	4	4	102±2	12	93±5	-9	95±7	-7	-8
EDV	47.0±1	43±1	-9	41±2	-13	-11	45±1	-4	44±1	0	45±1	0	0
ESV	21.0 ±0.3	21±.3	0	20±.4	-5	-3	23±1	+9	23±.4	0	23±.4	0	0
SV	26.0±1	23±1	-12	21±1	-19	-16	23±1	-12	22±1	-4	22±1	-4	-4
EJF	56.0±1	53±1	-5	51±2	-9	-7	50±1	-11	49±2	-2	50±1	-2	-2
C.O.	2.5±	2.1	-16	2.0	-20	-18	1.9	-24	1.8±	-5	1.8±	-5	-5
LVEDP	11.0±1	7±1	-36	5±2	-55	-50	12±2	+9	5±2	-58	6±2	-50	-54
HR	98.0±8	93±8	-5	95±8	-3	-4	86±8	-12	88±11	+2	83±13	+1	+1
EJT	168 ±8	166±2	-1	163±4	-3	-2	173±3	+3	170±6	-2	175±6	+1	-1
$DP/dt/P_D$	76±9	71±9	-7	75±9	-1	-4	59±5	-22	61±5	+3	60±5	+3	+3
$\hat{}DP/dt$	2660±34	2811±44	+6	2795±6	+5	+6	2272±39	-15	2282±49	+1	2309±85	+1	+1
SW	44±2	39±1	-11	35±3	-21	-16	39±1	-11	34±2	-13	36±1	-8	-11
$\bar{X}VCF$	1.5±0.1	1.6±0.1	+6	1.6±.1	+6	+6	1.2±.1	-20	1.4±.1	+16	1.3±.1	+8	+12
AvWFej	1414±46	1377±35	-3	1346±52	-5	-4	1498±48	+6	1387±65	-7	1426±60	-5	-6

III. Continued studies on the effect of infusing selected drugs on ventricular performance

An effort was made to determine the "validity" of ventricular function changes in conscious instrumented animals, such as:

A. The validity of using "pacing" of the left ventricle to secure the data for construction of reliable ventricular function curves for conscious instrumented dogs.

B. Evaluation of the reliability of various techniques for identifying myocardial contractility changes.

   (1) dP/dt/developed LVP.

   (2) Shifts in ventricular function curves.

   (3) Changes in mean V_{CF}.

   (4) Changes in the end-systolic volume/end-systolic pressure relation.

C. Defining the "typical" effect of constant infusions of norepinephrine, isoproterenol, angiotensin II, methoxamine, phenylephrine on cardiac dynamics in conscious instrumented dogs.

A preliminary survey of the cardiac dynamic effects of single injections and constant infusions of various concentrations of five well known drugs has been made. Summaries of our general observations with examples of our initial data are presented below in five (5) sections. These data are presented only to demonstrate the type of data acquisition and the kind of information that can be secured from our instrumented dogs using the computer and one of the programs for data acquisition and reduction which we are developing.

The purposes of these studies are summarized in our "Summary Statement" above.

NOREPINEPHRINE

Section I

Effect of single injection of norepinephrine (0.4 mgms/kg.)

A classical response to a single intravenous injection of norepinephrine into a conscious instrumented dog is seen in figure 10. This dog was in excellent health and was studied 60 days after surgery for instrumentation. With the aid of our digital computer each cardiac cycle occurring in the interval indicated in figure 10. was analyzed. The data plotted in figure 11 was taken during the recording shown in figure 10. In figure 11 we have plotted the changes occurring in the indicated selected variables for every other cardiac cycle starting with the 90th cardiac cycle from the start of the computer sampling thru the 150th cycle. As a result figure 11 gives a profile of the pattern of change that occurs in the key variables indicative of cardiac and vascular performance in response to a single intravenous injection of a commonly used dose of norepinephrine.

This plot (fig. 11) shows that the norepinephrine injection rapidly increased the myocardial contractility index dP/dt/P, as well as mean arterial pressure. In addition, stroke work (SW), stroke power (SP), and stroke volume (SV) were also increased simultaneously. Total cycle length (TCL) decreased and became constant from cycle to cycle indicating the increase in heart rate. Ejection time (EJT) was significantly decreased while both the average wall force developed within the left ventricle during ejection and the mean velocity of circumferential fiber shortening (mean V_{CF}) increased.

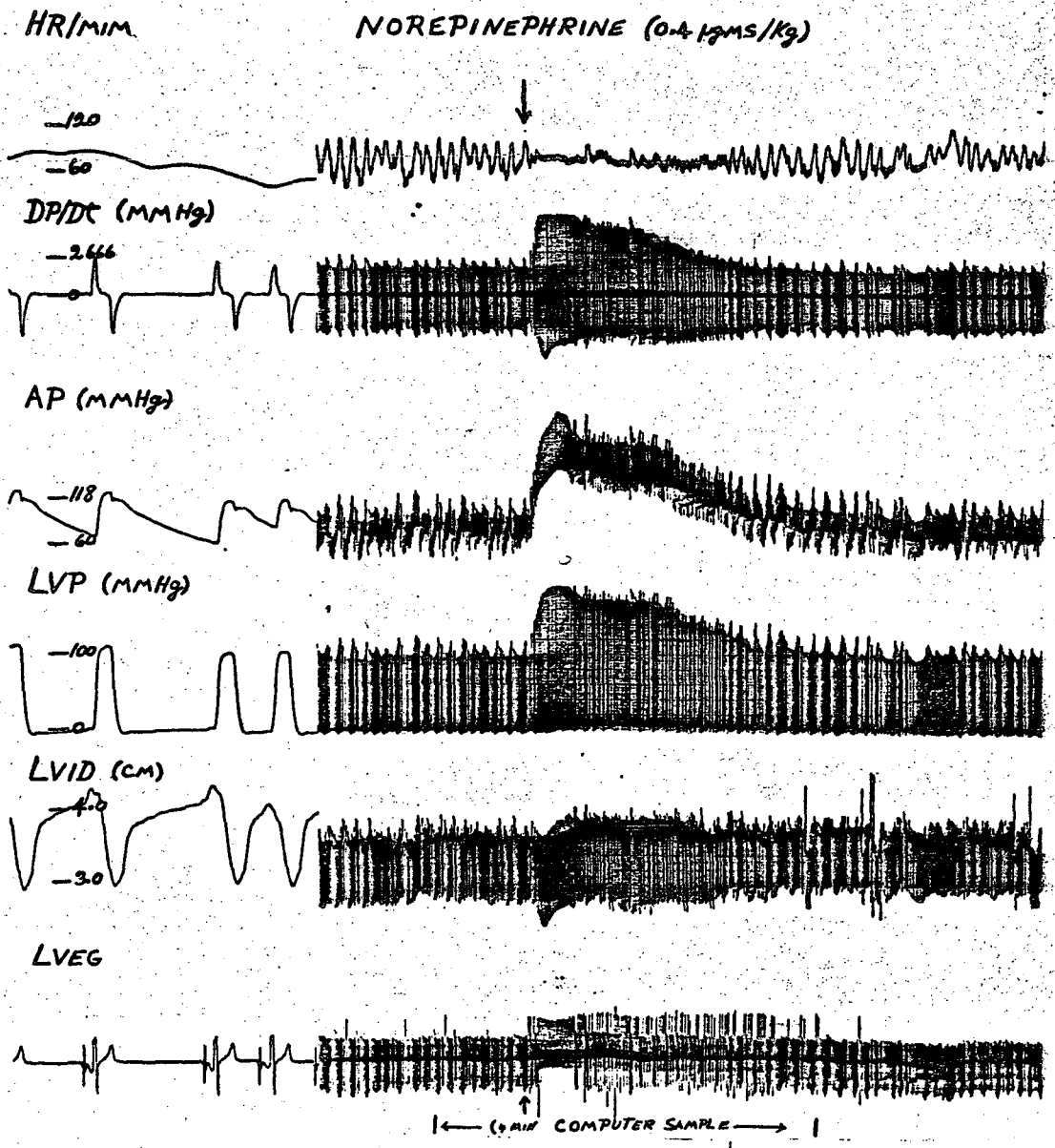
HR/MIM
NOREPINEPHRINE (0.4 µgms/Kg)
120
60
DP/DT (MMHg)
2466
0
AP (MMHg)
118
60
LVP (MMHg)
100
0
LVID (CM)
4.0
3.0
LVEG
1 MIN COMPUTER SAMPLE

FIG. # 10

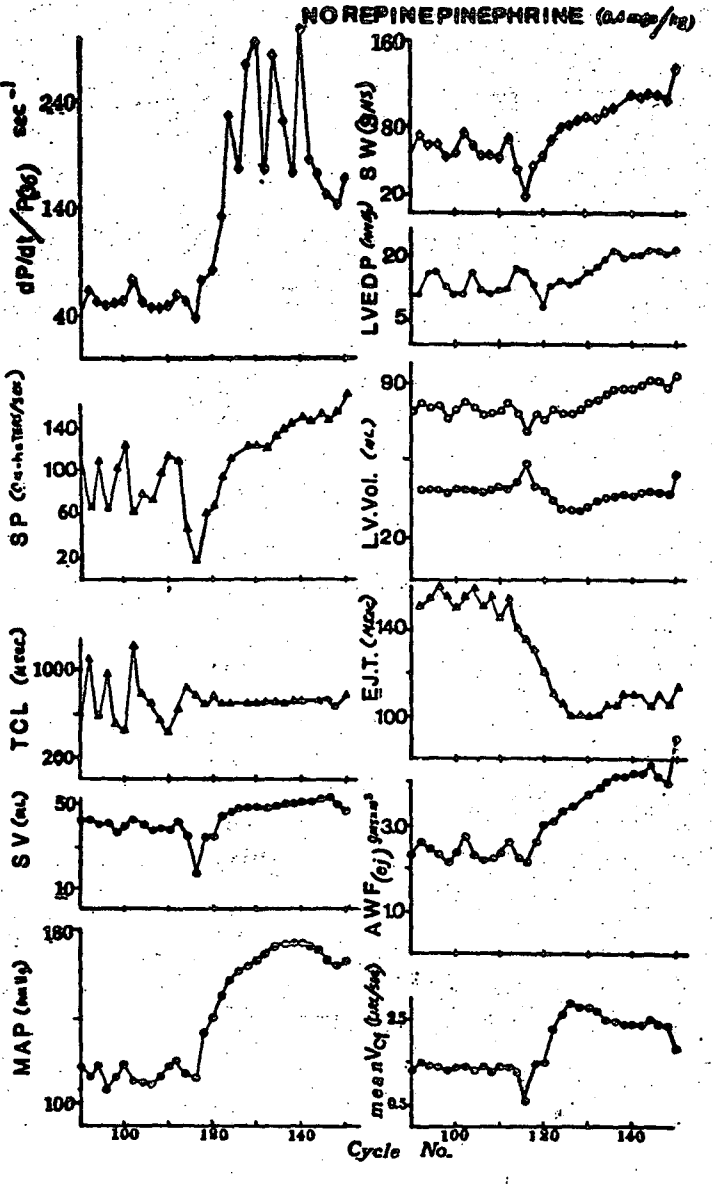
NOREPINEPINEPHRINE
dP/dt
SW
LVEDP
SP
LV.Vol.
TCL
EJT
SV
AWF
MAP
mean VO2
Cycle No.

FIG. # 11

The greater stroke volume produced was achieved as a result of a greater rate of ejection, an increase in myocardial contractility, and more systolic emptying of the left ventricle as well as an increase in total peripheral resistance. These were the primary causes for the significant increase in mean arterial pressure produced by the injection of norepinephrine.

Figure 12 shows a typical recording during a constant infusion of norepinephrine.

Norepinephrine Infusions at Constant Rates

Figure 13 shows the cardiac and circulatory effects of constant infusions of 0.25, 0.5, 1.0, 2.0 and 3.0 micrograms/kilograms/minute of norepinephrine. At the largest dose mean aortic pressure is increased 40% above the control level. This is a typical response. The major effects of norepinephrine infusion are two: First there is an increase in total peripheral resistance at each dose level, which reaches 55% at an infusion rate of 30 μgms/kg/min.; second the rate of rise of ventricular pressure (mm Hg/sec) divided by the developed pressure at 40 mm Hg (dP/dt/lvp (40)) increases significantly with each increase in dose level up to a value of 85% above control when the infusion rate is 3.0 μgms/kg/min. This response is clearly indicative of the potent effect of norepinephrine in causing peripheral arteriolar constriction and increasing myocardial contractility. It is believed that the former is due to the alpha stimulating effect of norepinephrine while the latter is due to beta receptor stimulating effect on ventricular myocardium. Norepinephrine infustions at concentrations above 0.5 μgms/Kg/minute decreased left ventricular

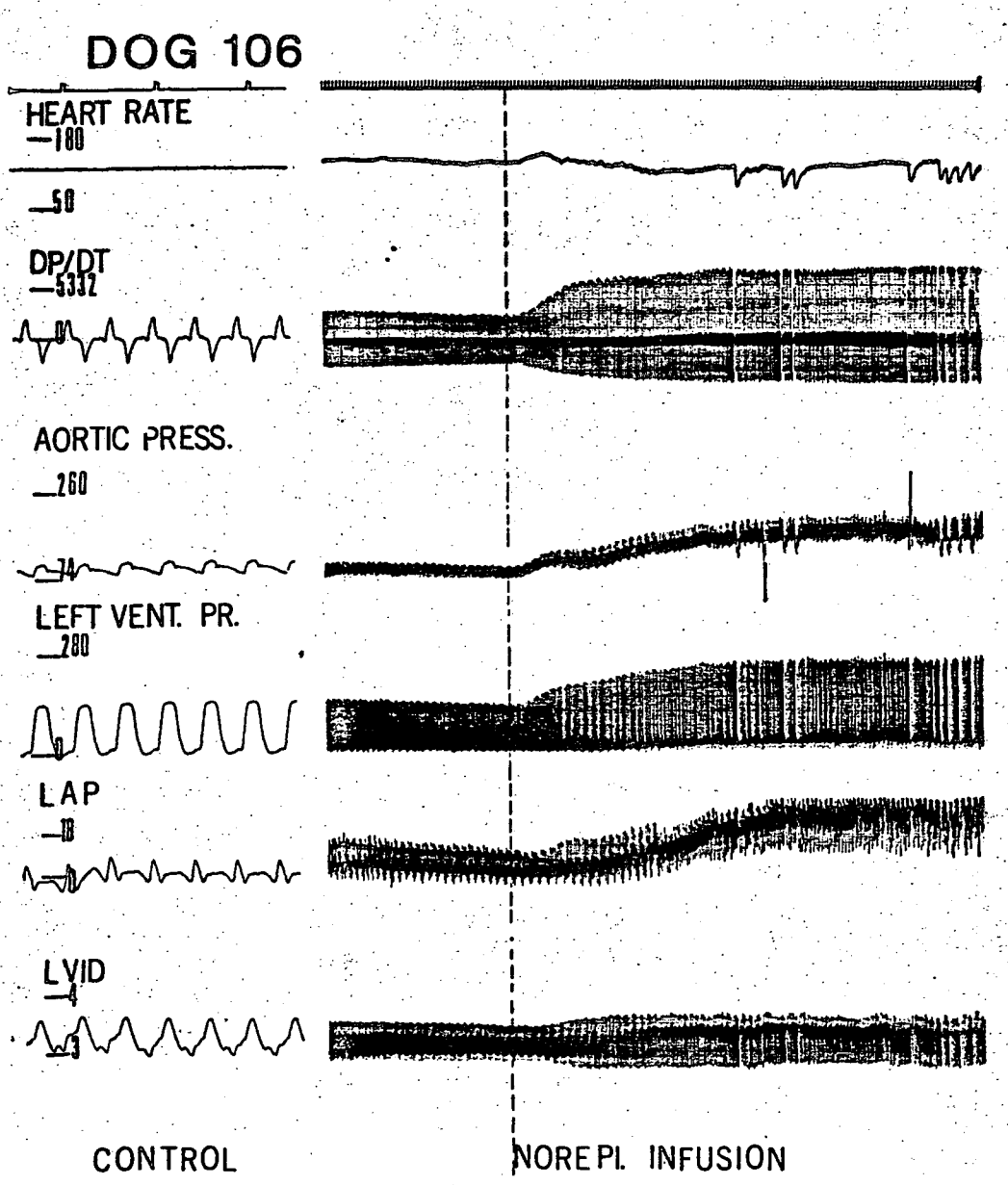
DOG 106
HEART RATE
180
50
DP/DT
5332
0
AORTIC PRESS.
260
0
LEFT VENT. PR.
280
0
LAP
18
0
LVID
4
0
CONTROL
NOREPI. INFUSION

FIG. # 12

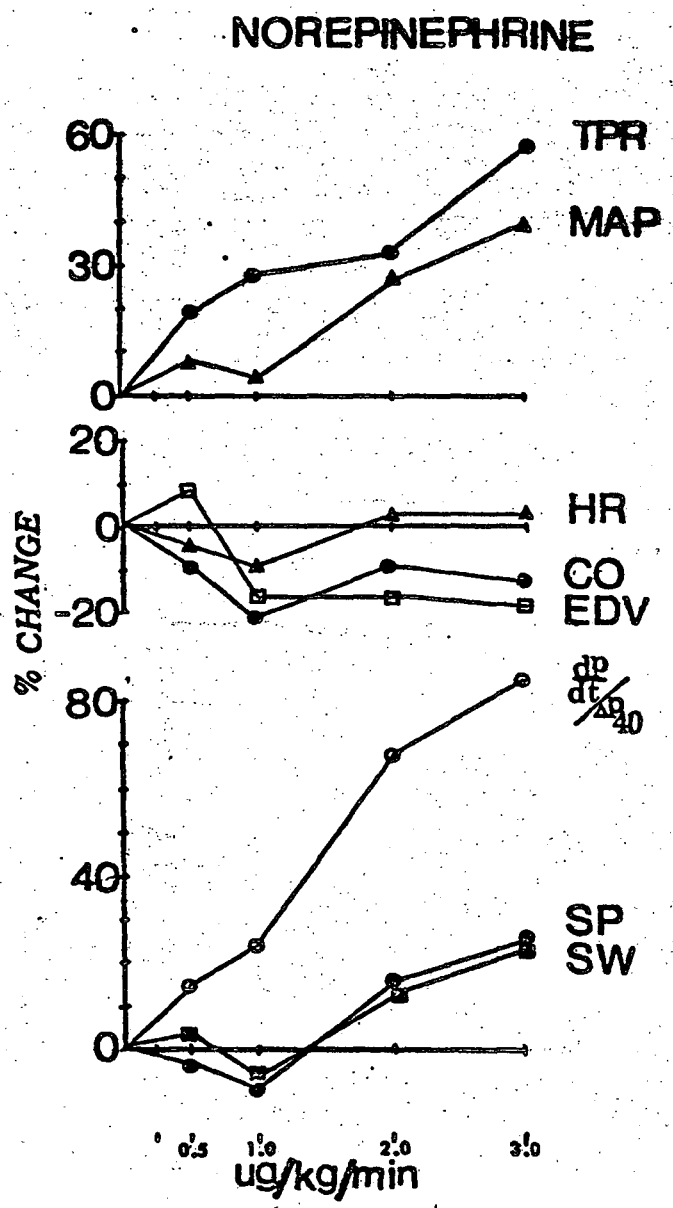
NOREPINEPHRINE
60
30
0
TPR
MAP
20
0
-20
HR
CO
EDV
% CHANGE
80
40
0
SP
SW
0
0.5
1.0
2.0
3.0
ug/kg/min

FIG. # 13

end-diastolic volume by 15 to 20% below control levels. This appears to be due mainly to a decrease in venous return to the heart and is primarily a result of veno constriction.

Little change is seen in heart rate, especially at infusion levels above 1.0 μgm/Kg/minute. Because of this, and since stroke volume (not shown) is slightly decreased, cardiac output is below control value with infusions of norepinephrine concentrations above 1.0μgm/Kg/minute.

The ability of the heart to maintain the elevated arterial pressure level in the presence of a significantly increased TPR while at the same time operate from a smaller end-diastolic volume is due primarily to the increased myocardial contractility. This view is supported not only by the significant increase in dP/dt/lvp (40) but as well by the increased stroke work and stroke power which the ventricle produces from smaller end-diastolic volumes at infusion rates of 2.0 and 3.0 μgms/Kg/minute.

Norepinephrine Infusions after Beta Receptor Blockade

The study of the effects of norepinephrine infusions on the heart and circulation is greatly enhanced by the use of selected blockade of alpha or beta receptors. We have used only beta receptor blockade in these studies. Figure 14 shows, in the same animal, the effects of constant infusion of norepinephrine at different dose levels after nearly complete beta receptor blockade. To accomplish the block propanolol was given in a dose of 0.5 milligrams per kilogram of body weight; which dose effectively blocked all effects of a single intravenous injection of

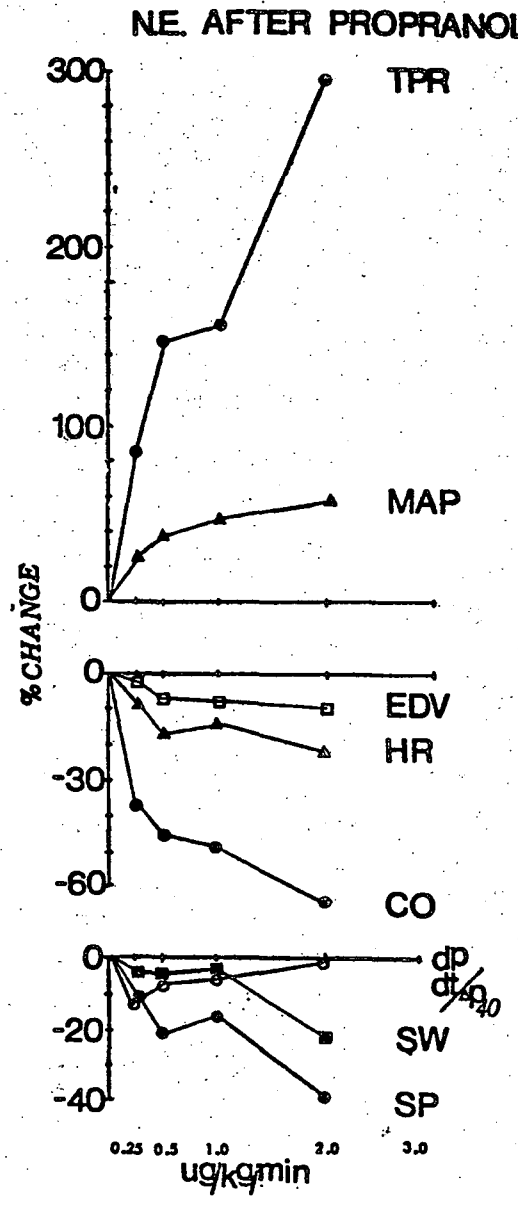
N.E. AFTER PROPRANOLOL
300
200
100
0
TPR
MAP
% CHANGE
0
-30
-60
EDV
HR
CO
0
-20
-40
dp/dt 40
SW
SP
0.25 0.5 1.0 2.0 3.0
ug/kg/min

FIG. # 14

isoproterenol (12 mgms/kg), the classic beta stimulating drug.

A comparison of the effects of infusions of norepinephrine after beta blockade (fig. 14) with those seen before (described above) will reveal that the effects produced by this drug are specifically a function of its beta receptor stimulating activity.

Effects on TPR

Total peripheral resistance is increased as much as 300% over control levels at norepinephrine rates of 2.0 ugms/Kg/minute after beta blockade (fig. 14). This is to be compared with an increase in TPR of only 35% before blockade (fig. 13). This ten fold difference is due mainly to the removal of the peripheral vasodilator effect of norepinephrine before beta receptor blockade. In other words in the normal "unblocked" animal norepinephrine causes selective arteriolar dilation in some vascular beds and constriction in others, consequently the net effect is a lesser change in total peripheral resistance after a given dose of norepinephrine than is the case when the same dose is given after beta blockade which removes the vasodilator effect.

Effects on Myocardial Contractility

An index of changes in myocardial contractility can be obtained by evaluating the shift in the ventricular function curve with various interventions. Typical ventricular function curves are shown in figure 15. This shows a plot of the relationship between left ventricular end-diastolic volume (LVED) in milliliters (ml) and stroke work (gm-m) in a conscious dog (dog #117). The open circles plot the stroke work-

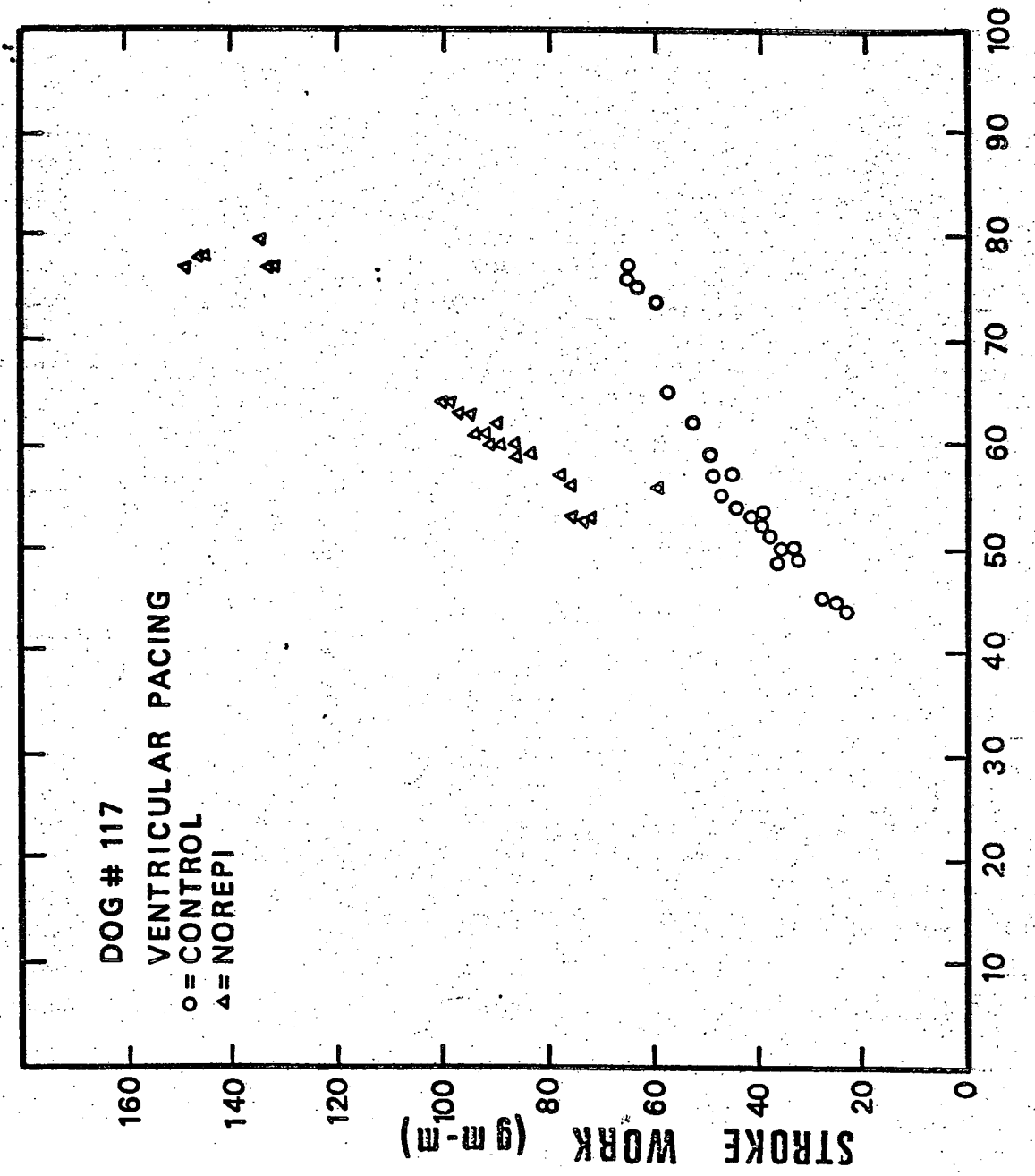
DOG # 117
VENTRICULAR PACING
o = CONTROL
Δ = NOREPI
STROKE WORK (g m-m)
LVEDV (ml)
0
20
40
60
80
100
120
140
160
10
20
30
40
50
60
70
80
90
100

FIG. # 15

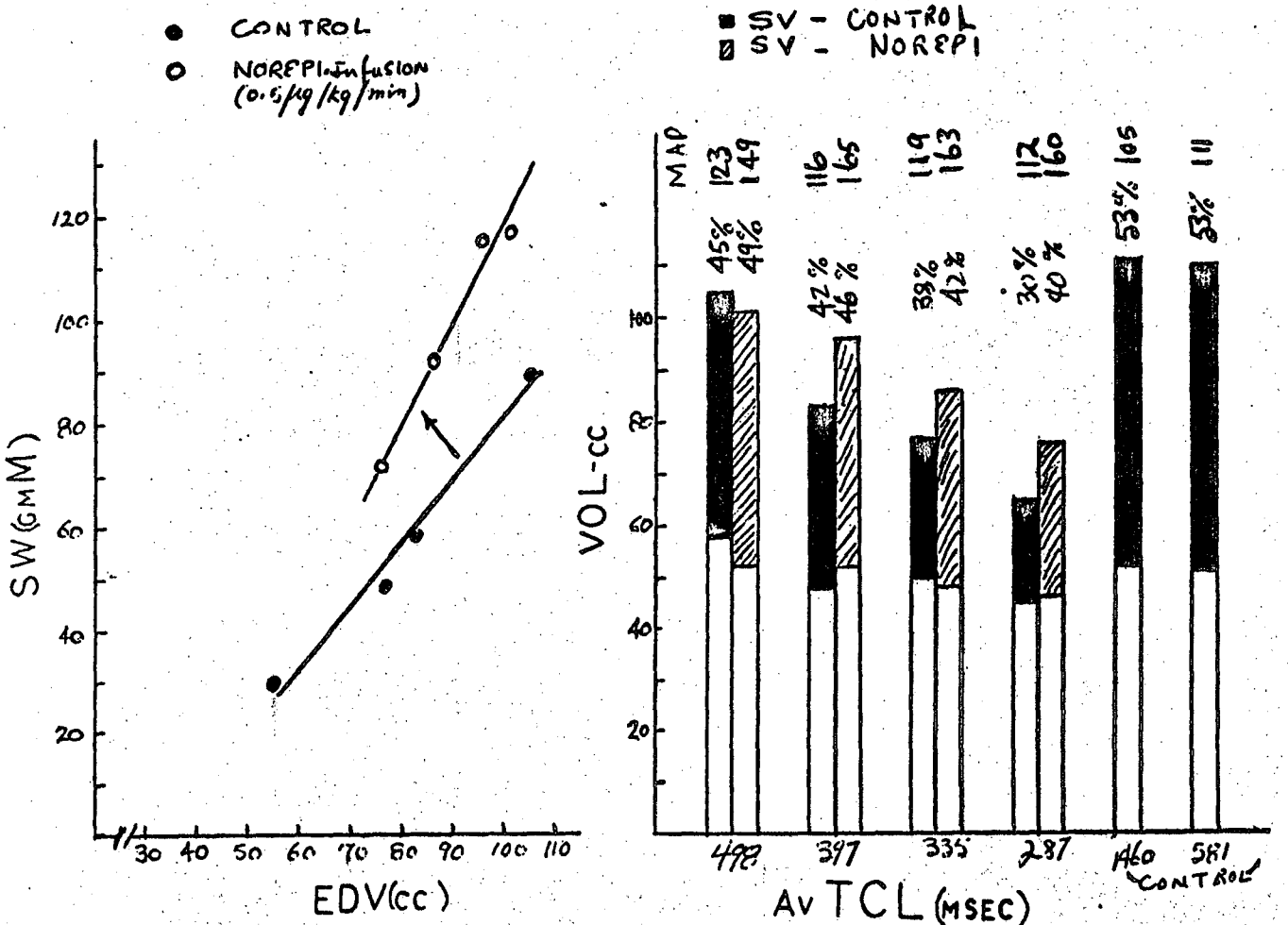
CONTROL
NOREPI. Infusion (0.5 µg/kg/min)
SW (GM M)
EDV (cc)
SV - CONTROL
SV - NOREPI
MAP
123 149
116 165
119 163
112 160
53% 105
53% 111
45% 49%
42% 46%
39% 42%
30% 40%
VOL-cc
Av TCL (MSEC)
CONTROL

FIG. # 16

ventricular end-diastolic volume relation for different end-diastolic volumes which were produced by "pacing" the ventricle at different rates during the control period where the dog was standing quietly in a modified Pavlov stand. It is seen that the larger the LVEDV the greater was the stroke work produced.

The triangles represent similarly acquired points except that the dog was under the influence of the effects of norepinephrine which was continuously infused intravenously at a constant rate of 0.5 micrograms/kilogram/minute. Note that during this period a much greater stroke work was produced from a given LVEDV than was the case during the control period. This "upward shift" in the "ventricular function curve" (the LVEDV/SW relationship) gives a clear indication that myocardial contractility was increased! That is, when the heart was under the influence of an increased myocardial norepinephrine concentration produced by infusing this catecholamine, a greater stroke work was produced when the heart contracted from any given end-diastolic volume than was present from that same end-diastolic volume during the control period.

A similar type of change would be seen if stroke power instead of stroke work had been plotted against end-diastolic volume.

There is one problem with using this type of shift in the ventricular function curve to identify the presence of a change in myocardial contractility; that is the fact that we have no knowledge about the levels of the aortic pressure during the periods studied. It is well known that an increase in the mean aortic pressure will have a depressant effect on the amount of stroke work the heart will perform from a

given end-diastolic volume. Thus other indices must be used in addition to the function curves to permit a more reliable evaluation of shifts in myocardial contractility. It appears that the use of $dP/dt/\Delta P$ (40) may be one such reasonably reliable indicator of change in myocardial contractility. That is the rate of rise of ventricular pressure up to some value of developed pressure in the left ventricle, which latter occurs clearly before the aortic valves open, is probably a reliable indicator of the velocity of contractile element shortening within the ventricular myocardium. Presumably the faster this velocity of contractile element shortening during periods of assumed isometric contraction of the ventricle, the greater is the myocardial contractility and vice versa.

Returning now to the effects on myocardial contractility produced by the norepinephrine infusions, a quick comparison between the changes produced before (fig. 13) and after beta blockade (fig. 14) reveals that beta receptor blockade completely prevented any increase in $dP/dt/\Delta P$, whereas this variable was increased as much as 75% above control values when 2.0 micrograms/Kg/min. of norepinephrine was infused before propranolol was given.

It can be observed also that stroke work and stroke power were decreased by the norepinephrine infusions after beta blockade while similar infusions of norepinephrine before propanolol increased stroke work and stroke power.

We learn from these observations first that norepinephrine increases myocardial contractility and second that it produces the effect primarily by its beta receptor stimulating effect, both of these observations are of course well known to you.

Summary

Norepinephrine infusions are informative to us in understanding how alpha and beta receptor stimulation affects cardiac performance. This drug increases total peripheral resistance without increasing cardiac output, produces sufficient stroke power to elevate the mean arterial pressure largely as a result of its ability to increase myocardial contractility and at the same time causes the heart to operate from a smaller end-diastolic volume. The latter is produced by norepinephrine decreasing venous return to the heart, which in turn is due to venoconstriction and vasodilation in the skeletal muscle vessels.

ISOPROTERENOL

Section II

Effect of Single Injection of Isoproterenol (0.4 μgms/kg)

The classical response to a single injection of this drug is shown in figure 17. The injection was made in the same conscious instrumented dog shown in figure 2 and into which the injection of norepinephrine was made that is shown in figure 10.

This record shows the increase in heart rate and peak dP/dt that regularly follows injections of isoproterenol. Simultaneous with these changes in heart rate and peak dP/dt both end diastolic and end systolic left ventricular internal diameter (LVID) decreased as did left ventricular end-diastolic pressure.

Figure 18 shows the changes that occurred in selected variables that were derived for every other cardiac cycle during the period of computer sampling (as indicated at the bottom of figure 17).

The chosen variables are the same as those followed during the single ejection of all the other drugs studied. The response to the injection of isoproterenol represents the effect of a practically pure beta adrenergic receptor stimulation. Here (fig. 18) an increase in myocardial contractility is indicated by the rise in dP/dt/P and the fall in ejection time (EJT), the rise in mean velocity of circumferential fiber shortening (mean V_{CF}).

Typically isoproterenol decreased markedly both end-diastolic and end-systolic ventricular volumes yet there was only a slight decrease in mean aortic pressure.

Effect of Constant Infusions of Isoproterenol

The cardiac and vascular response to constant infusions of isoproterenol at

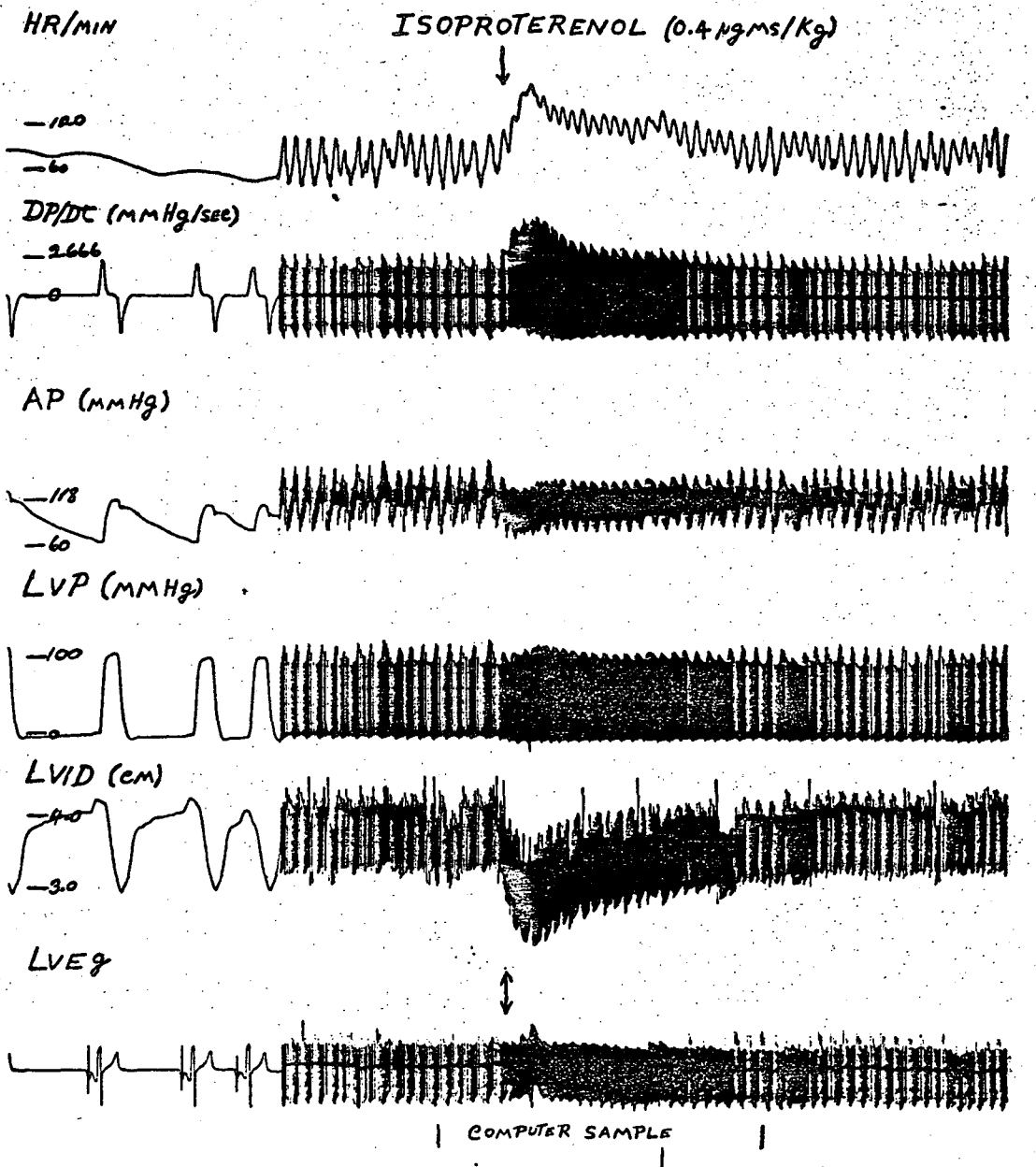
HR/MIN
ISOPROTERENOL (0.4 μgms/Kg)
180
60
DP/DT (mmHg/sec)
2666
0
AP (mmHg)
118
60
LVP (mmHg)
100
0
LVID (cm)
4.0
3.0
LVEg
COMPUTER SAMPLE

FIG. # 17

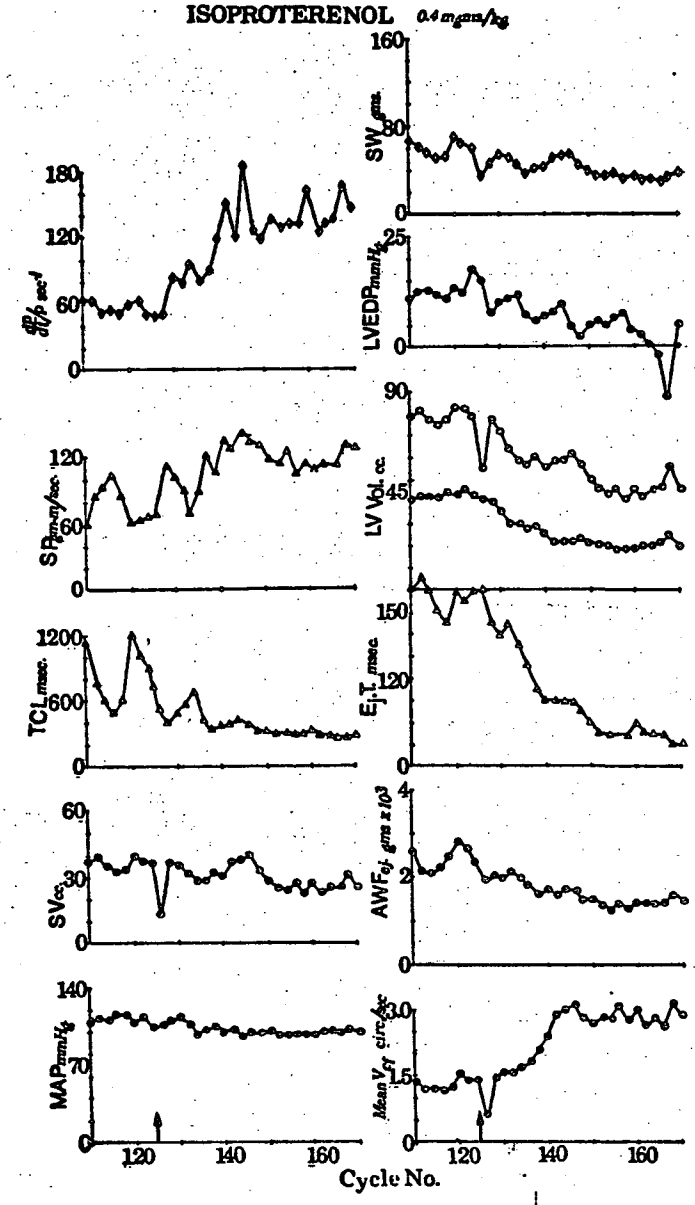
ISOPROTERENOL 0.4 mgms/kg
dP/dt sec⁻¹
SW gms.
LVEDP mmHg
SP mm-g/sec.
LV Vol. cc.
TCL msec.
Ej.T. msec.
SV cc.
AWF ejf gms x 10³
MAP mmHg
Mean V ejf circ/sec
Cycle No.

FIG. # 18

dose levels of 1.0, 2.0, 3.0 and 4.0 μgms/kg/min are shown in figure 19.

Isoproterenol has a powerful beta receptor stimulating action with almost no action on alpha receptors. As such, its main actions are on the heart where it increases myocardial contractility, on the skeletal muscle vasculature where it causes vasodilation, and on the smooth muscles of the bronchi and the gastro-intestinal tract which it relaxes.

It can be seen thru study of figure 19 that mean aortic pressure falls to about 20% below control levels at all dose levels infused. The most striking effects are those of increasing heart rate, cardiac output and $dP/dt/\Delta P$ (an index of increased myocardial contractility).

End-diastolic volume is decreased at all dose levels while at the same time stroke power is significantly elevated above control value. These observations indicate a shift of the relationship between left ventricular end-diastolic volume and stroke power such that the heart is producing more stroke power from a significantly decreased end-diastolic volume where it is under the influence of isoproterenol than was produced from the much larger end-diastolic volumes during the control periods.

It is of great interest that stroke work is reduced by the isoproterenol infusions. The major effect of isoproterenol is to cause the heart to effectively and significantly increase its cardiac output, and stroke power while operating from a smaller end-diastolic volume and at the same time reduce its stroke work. Thus a significant improvement in cardiac performance is achieved largely as the result of an increase in heart rate and myocardial contractility without a drastic drop in mean arterial pressure.

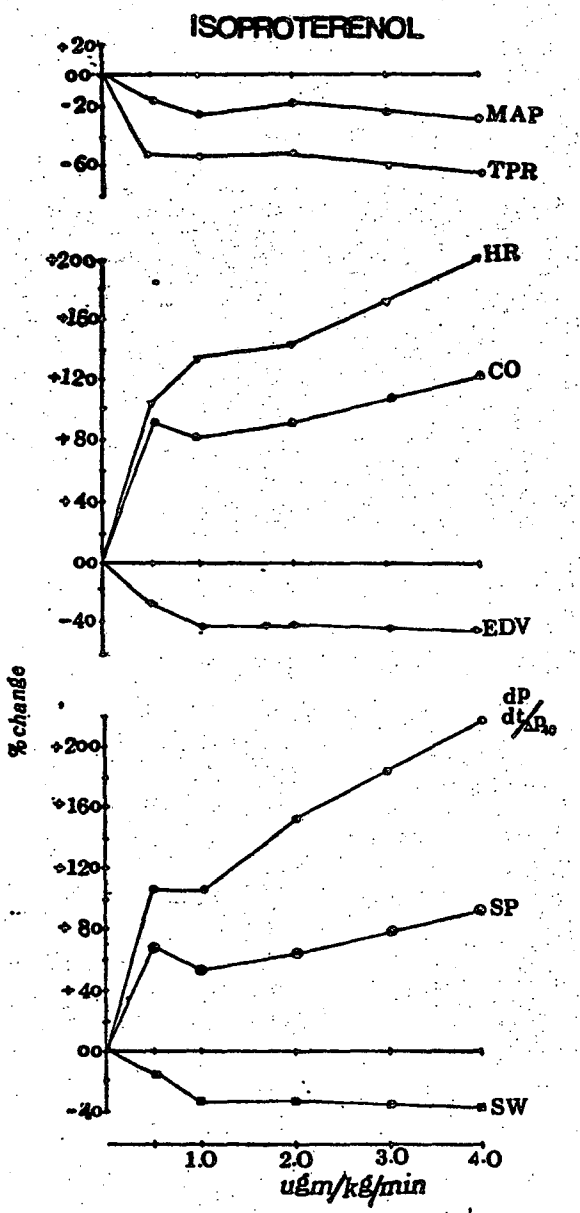
ISOPROTERENOL
+20
00
-20
-60
MAP
TPR
+200
+160
+120
+80
+40
00
-40
HR
CO
EDV
% change
dP/dt
+200
+160
+120
+80
+40
00
-40
SP
SW
1.0
2.0
3.0
4.0
ugm/kg/min

FIG. # 19

ANGIOTENSIN II

Section III

Effect of single injection of angiotensin II (0.12 μgms/Kg)

A typical analog recording of the changes occurring in aortic pressure (AP), left ventricular pressure (LVP), left ventricular internal diameter (LVID) and the left ventricular electrogram (LVEG) in response to a single intravenous injection of 0.12 μgm/kg into a conscious instrumented dog is shown in figure 20. Figure 21 shows the plot of the variables, the maximum rate of rise of left ventricular pressure at a developed ventricular pressure of 40 mm Hg ($dP/dt/\Delta P_{(40)}$), stroke power (SP), total cycle length (TCL), stroke volume (SV), mean aortic pressure (MAP), stroke work (SW), left ventricular end-diastolic pressure (LVEDP), left ventricular volume (LV Vol) where the open circles represent end-diastolic volume and the closed circles represent end-systolic volume, ejection time (EJT), average wall force during ejection (AWF), and mean velocity of circumferential fiber shortening (mean V_{CF}). Each point represents in sequence every other cardiac cycle starting with the 70th cardiac cycle analyzed by the digital computer. The sampling period is shown at the bottom of figure 15.

Thus figure 21 displays the variables listed above for every other cardiac cycle occurring in figure 20 during the period of the computer sampling.

The angiotensin II injection caused an increase in mean aortic pressure that was unaccompanied by a change in myocardial contractility since neither dP/dt/P nor stroke work nor left ventricular end-diastolic volume changed significantly.

Also ejection time was not reduced by the injection of angiotensin II.

Stroke power was increased suggesting that the left ventricle was able to generate more stroke power from a given end-diastolic volume as a result of the angiotensin injection.

It appears that this single injection of angiotensin II had its primary effect thru increasing total peripheral resistance with little or no effect on myocardial contractility.

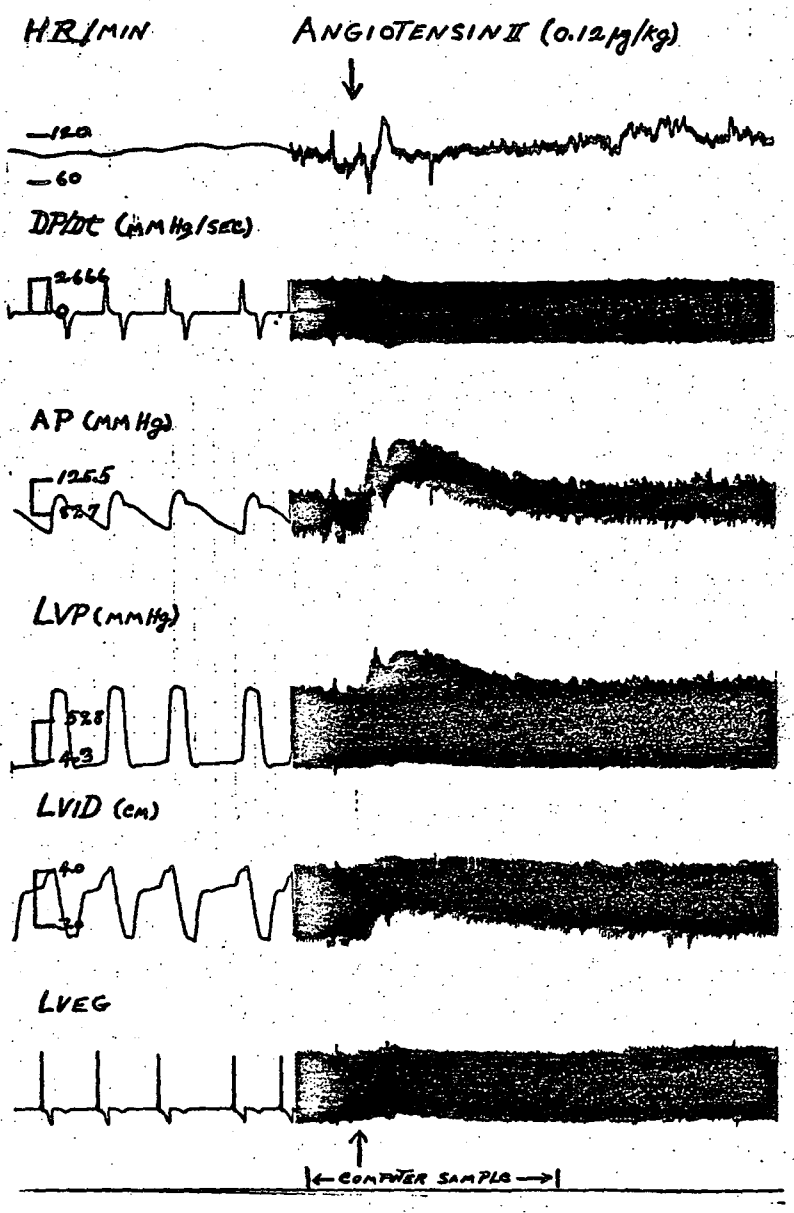
HR/MIN
ANGIOTENSIN II (0.12μg/kg)
120
60
DP/Dt (MM Hg/SEC)
2666
AP (MM Hg)
1255
LVP (MM Hg)
528
LVID (cm)
LVEG
← COMPUTER SAMPLE →

FIG. # 20

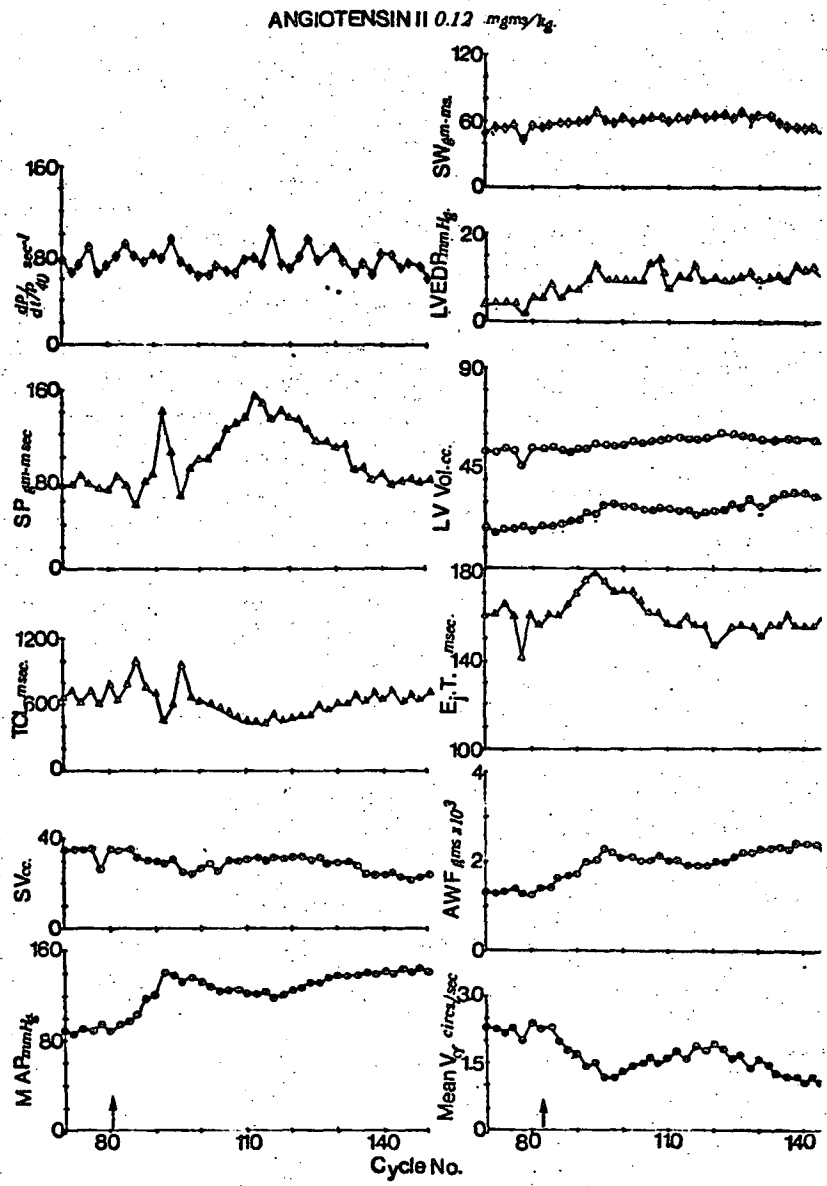
ANGIOTENSIN II 0.12 mgms/kg.
160
80
0
120
60
0
20
0
90
45
180
140
100
1200
300
4
2
40
160
80
80
110
140
Cycle No.

FIG. # 21

Effect of constant infusions of angiotensin II

The typical effect of constant infusion of angiotensin II on cardiac function when given to a conscious dog at dose levels of 0.2, 0.4, 0.6, and 0.8 μgms/kg/min. are shown in figure 22 where each increment in dose level angiotensin increased further total peripheral resistance and aortic pressure. Left ventricular end-diastolic volume was increased and as a result both stroke work and stroke power were also elevated; dP/dt/P was not changed indicating no change in myocardial contractility.

We may conclude from the observations that with angiotensin II infusion in conscious animals arterial pressure is elevated primarily by virtue of its effect in constricting the peripheral arterioles and thus increasing total peripheral resistance. The reduced cardiac output is produced primarily as a result of the decrease in heart rate which is reflexly produced as a consequence of the elevated arterial pressure activating the mechanoreceptors in the walls of the aortic arch and carotid sinuses. The increases in stroke work and stroke power apparently are brought about through the operation of Starling's Law since these increases parallel the increases in end-diastolic volume which accompanied each increase in dose level of angiotensin II that was infused.

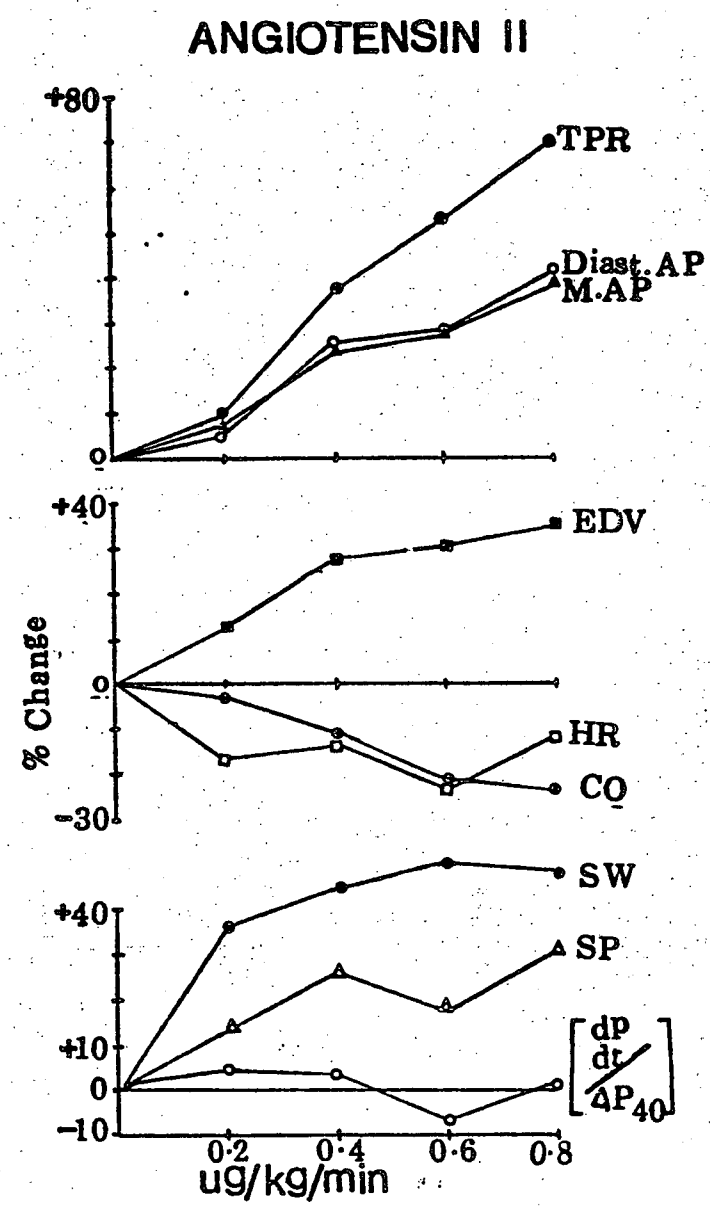
ANGIOTENSIN II
+80
0
TPR
Diast. AP
M.AP
+40
0
-30
% Change
EDV
HR
CO
SW
+40
+10
0
-10
SP
dP/dt/ΔP40
0·2
0·4
0·6
0·8
ug/kg/min

FIG. # 22

PHENYLEPHRINE

Section IV

Effect of Constant Infusions of Phenylephrine

The study of the effects of infusions of phenylephrine at different dose levels allow for the analysis of the cardiovascular response to a practically pure alpha receptor stimulating substance. and is to be contrasted to the effects of infusions of isoproterenol, a practically pure beta receptor stimulating substance. Again the chosen variables for study are the same as those discussed for all the previous dogs.

Figure 23 shows the response to infusions of 60, 80, and 100 μgms/kilogram/minute of phenylephrine, in terms of the percent change from the control level for each variable.

At the infusion rate of 100μgms/Kg/min a significant increase in total peripheral resistance (TPR) was produced and this is the expected effect of peripheral arteriolar constriction due to alpha receptor stimulation. Of particular importance is the observation that little or no change occurred in end-diastolic volume, stroke work, stroke power or dP/dt/P with infusions at any of the three dose levels. This shows that the rise in aortic pressure was primarily the result of arteriolar constriction and no change was produced by the drug in myocardial contractility. Heart rate was reduced at the highest dose level and as a result so was cardiac output. The reduction in heart rate was largely due to elevation in aortic pressure, which reflexly, via the aortic and carotid sinus mechano-receptor reflex mechanisms, caused an increase in vagal impulses to the heart.

This response of the heart and circulation to phenylephrine administration resembles quite closely the effect of norepinephrine administration in animals

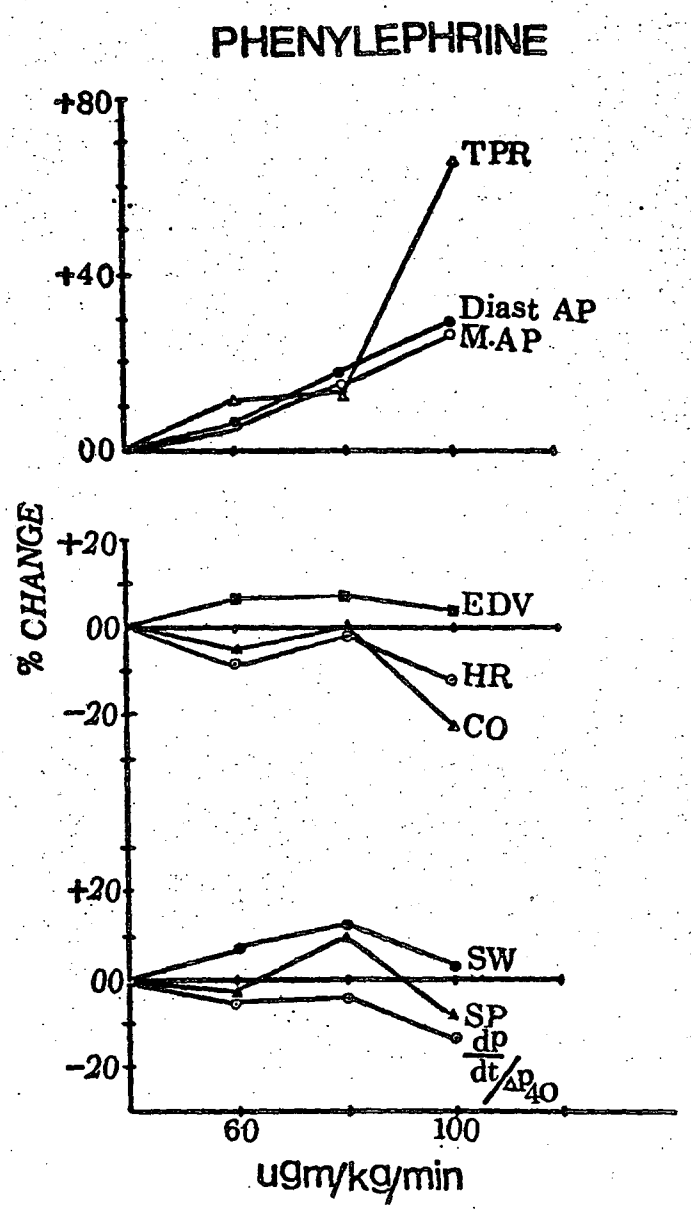
PHENYLEPHRINE
+80
+40
00
TPR
Diast AP
M.AP
% CHANGE
+20
00
-20
EDV
HR
CO
+20
00
-20
SW
SP
dp/dt/ΔP40
60
100
ugm/kg/min

FIG. # 23

who have their beta receptors blocked by use of propranolol or some other "beta blocking agent".

GLUCAGON

Section V

Glucagon: A potentially useful agent in cardiac therapy

Glucagon is a polypeptide hormone produced primarily by the alpha cells of the pancreas. It's primary physiologic role appears to be to promote hepatic glycogenolysis and increase blood glucose levels. These effects are just the opposite of the effects of insulin.

Glucagon has been shown to exert significant effects upon the cardiovascular system. These effects are mediated through glucagon's ability to increase cyclic adenosine monophosphate through activation of the enzyme adenyl cyclase. Some of these effects on the cardiovascular system are described below.

Experimental Observations

Table 1 shows the effect of glucagon on ventricular rate (VR), and cardiac output (CO), and mean arterial pressure (MAP) during sinus rhythm and during atrial fibrillation. In both conditions the heart rate and CO are clearly increased while the MAP is not significantly changed.

TABLE 1

Status	N	Vent Rate* (beats/min)	TCL (m sec)	CO (L/min)	MAP (mm Hg)
Sinus Rhythm	242	66 ± 17	995 ± 321	1.6	112 ± 10
Sinus Rhythm after Glucagon 50 microgram/kg	34	93 ± 22	680 ± 146	2.8	101 ± 6
Atrial Fibrillation (Spontaneous)**	280	88 ± 32	831 ± 450	1.9	105 ± 11
Atrial Fibrillation (Spontaneous) after Glucagon 50 microgram/kg	44	325 ± 31	187 ± 20	2.1	110 ± 10

* = Values are mean ± SD

** = After cessation of atrial pacing @ 20 Hz.

Dog # 132

The effects of glucagon on ventricular rate (VR), end-diastolic volume (EDV), stroke work (SW), tension time index (TTI); and ejection fraction is shown in table 2 both during sinus rhythm (SR), and atrial fibrillation (A. Fib,). It can be seen that glucagon(50 micrograms per kilogram) results in a significant increase in ventricular rate and stroke work without a significant change in EDV.

TABLE 2

Status	Vent. Rate* beats/min.	EDV (ml)	SW (gm-m)	TTI (per min)	Ejected fraction (%)
Sinus Rhythm	66 ± 17	52 ± 2	35 ± 3	1717	50 ± 1
Sinus Rhythm After Glucagon 50 microgm/Kg	93 ± 22	51 ± 2	44 ± 4	1632	57 ± 2
Atrial Fibrillation	88 ± 32	51 ± 3	31 ± 6	1971	51 ± 7
Atrial Fibrillation After Glucagon (50 microgm/Kg)	325 ± 31	25 ± 6	18 ± 11	2964	21 ± 23

* values are mean ± SD

The effect of glucagon in increasing myocardial contractility in the awake conscious dog is shown in table 3. The effect of an intravenous bolus injection of glucagon was manifest in 30 seconds and reached a maximum in 1 or 2 minutes and lasted for 10-15 minutes. An increase in dP/dt, dP/dt over developed pressure and mean velocity of circumferential fiber shortening was noted. This clearly indicates that myocardial contractility was increased.

TABLE 3

Status	Vent. Rate* (beats/min.)	Peak dp/dt (mm Hg/sec.)	$\frac{dp/dt}{LVP_{40} - LVEDP}$ (sec $^{-1}$)	Average Wall force (Gms.)	Mean Vcf** (Cm/sec)
Sinus Rhythm	66 ± 17	2531 ± 142	68.4 ± 9	1670	12.2 ± 0.5
Sinus Rhythm after Glucagon 50 microgm/kg	93 ± 22	3206 ± 67	94.8 ± 19	1631	21.9 ± 1.2
Atrial Fibrillation (Spontaneous)	88 ± 22	2545 ± 432	69.5 ± 17	1503	13.5 ± 2
Atrial Fibrillation (Spontaneous) after Glucagon 50 microgm/kg	325 ± 31	3646 ± 1139	109 ± 44	1271	10.8 ± 1

* = values are mean I S.D.

** = Endocardial Surface

Effect During Spontaneous Atrial Fibrillation

Table 4 shows the effect of various drugs on the ventricular response in atrial fibrillation compared to glucagon.

There is a slight slowing after ouabain and a slight increase in rate after nore-pinephrine. Cardiac sympathetic blockade with atropine and propanolol resulted in an increase in ventricular rate to 190 beats per minute from a control of 97. The administration of glucagon resulted in a dramatic rate increase to 340 beats per minute.

TABLE 4

Status	Aver. total cycle length (msec)	Aver. ventricular rate/min
Control	602	97
Ouabain 20 gm/kg	646	93
Nor-epinephrine 1.5 gms/kg/min	522	115
Atropine + Propanolol (2 mgms) (12 mgms)	316	190
Glucagon 50 gm/kg	176	340

Conclusion

Glucagon results in significant enhancement in ventricular performance. This has proved useful in the treatment of cardiac failure especially when induced by propanolol since glucagon effects are not blocked by propanolol. However, the data in dogs suggest that the administration of glucagon during atrial fibrillation may be hazardous.

Selected References

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8. Hawthorne, E. W. and Kraft-Hunter, F.: Current approaches to the study of the dynamic geometry of the left ventricle in conscious dogs. In: Hibernation-Hypothermia Perspectives and challenges, Amsterdam: Elsevier Publishing Co., 1972, p. 457-480.

IV. Further Development of Data Acquisition and Reduction Techniques with the Aid of a Small Dedicated Computer System.

The basic format and approaches we used in developing this system are described in our grant application in a section titled "A User Interactive Data Acquisition and Reduction System for the Study of Cardiac Dynamics". In addition we have published this information. (See publications section below).

Certain unique features of the system have been developed during the past year. These are:

A. Development of the capacity to take and analyze long samples (up to 4 minutes).

B. Development of programs to display plots of data.

C. Development of programs which permit plots of:

1. Histograms
2. Serial autocorrelograms
3. Spectral density plots
4. X-Y plots of any desired derived or primary variable against another

The capacity for analyzing up to four (4) minutes worth of data has been extremely helpful. This capability permits the investigator to request the A-D converter to sample simultaneously up to six (6) simultaneous recorded analog signals. Ordinarily we monitor dP/dt, aortic pressure, left ventricular pressure, left ventricular internal diameter, left ventricular length and the ventricular electrogram at either 2, 5, or 10 millisecond intervals for periods of from seven (7) seconds up to four (4) minutes if a five (5) msec. sampling rate is used. This program then will identify all the individual cardiac cycles in the sample and analyze each one producing a listing of all the desired information. In addition it will provide the means and standard deviations for each variable. Figure 24 shows a copy of one "printout" of this type. In this case it can be seen that the means and S.D.'s for a sample consisting of 307 consecutive cardiac cycles is provided. This sample was taken while monitoring the effects of LBNP (-40 mm Hg) on a conscious instrumented dog after beta blockade.

The remaining figures (25, 26, 27, 28) are samples of various computer generated plots.

DOG# 155 TAPEFILE# 1 #CYCLES 307 START OF EXPERIMENT 8/22/72

D155 8/22/72 LBNP AFTER PROPRANOLOL 0.5 MG/KG

AVERAGE HEART RATE/MIN=	85.8		SD=	26.4
PEAK DP/DT=	2104.0	MM HG/SEC	SD=	212.9
PEAK SYSTOLIC AP=	176.0	MM HG	SD=	14.1
DIASTOLIC AP=	118.3	MM HG	SD=	16.1
MEAN AORTIC PRESSURE=	147.5	MM HG	SD=	13.4
PULSE PRESSURE=	57.7	MM HG	SD=	12.5
GRADIENT=	7.9	MM HG	SD=	4.0
END DIASTOLIC VOLUME=	68.0	CC	SD=	5.6
END SYSTOLIC VOLUME=	33.0	CC	SD=	3.5
STROKE VOLUME=	35.0	CC	SD=	4.8
EJECTION FRACTION=	51.4	%	SD=	4.6
CARDIAC OUTPUT=	2.7	L/MIN		
END DIASTOLIC LVP=	-5.7	MM HG	SD=	4.4
PEAK LVP=	171.5	MM HG	SD=	16.0
LVP AT PEAK AP=	168.0	MM HG	SD=	15.5
END SYSTOLIC LVP=	137.4	MM HG	SD=	14.9
STROKE WORK=	77.0	GM METERS	SD=	13.8
STROKE POWER=	431.7	GM METERS/SEC	SD=	74.4
T.P.R.=	4505.0	DYNES-SEC/CM↑5		
TOTAL CYCLE LENGTH=	775.4	MSEC	SD=	255.9
EJECTION TIME=	178.3	MSEC	SD=	7.3
PERIOD OF IVC=	52.7	MSEC	SD=	5.5
MEAN VCF=	13.9		SD=	1.9
MEAN NVCF=	1.1		SD=	.1
AVERAGE LVP(EJ)=	155.9		SD=	13.1
END DIASTOLIC CIR.=	12.74		SD=	.46
END SYSTOLIC CIR.=	10.26		SD=	.37
END DIASTOLIC DIAM.=	4.05		SD=	.15
END SYSTOLIC DIAM.=	3.27		SD=	.12
EDWF=	-104.7		SD=	82.0
PSWF=	2755.1		SD=	327.6
AWFEJ=	2418.6		SD=	311.0
DP/DT /LVP-LVEDP(JUST<45)=	53.19	SEC↑-1	SD=	7.041
LVP-LVEDP(JUST<45)=	39.8	SEC↑-1	SD=	2.8

FIG. # 24

D#132 2/14/72 LAAP CONSTRICTION TO 20 MM HG PP TIME 7:50

N= 283
MTCL= 680.3
MVR= 88.2
SD= 82.5

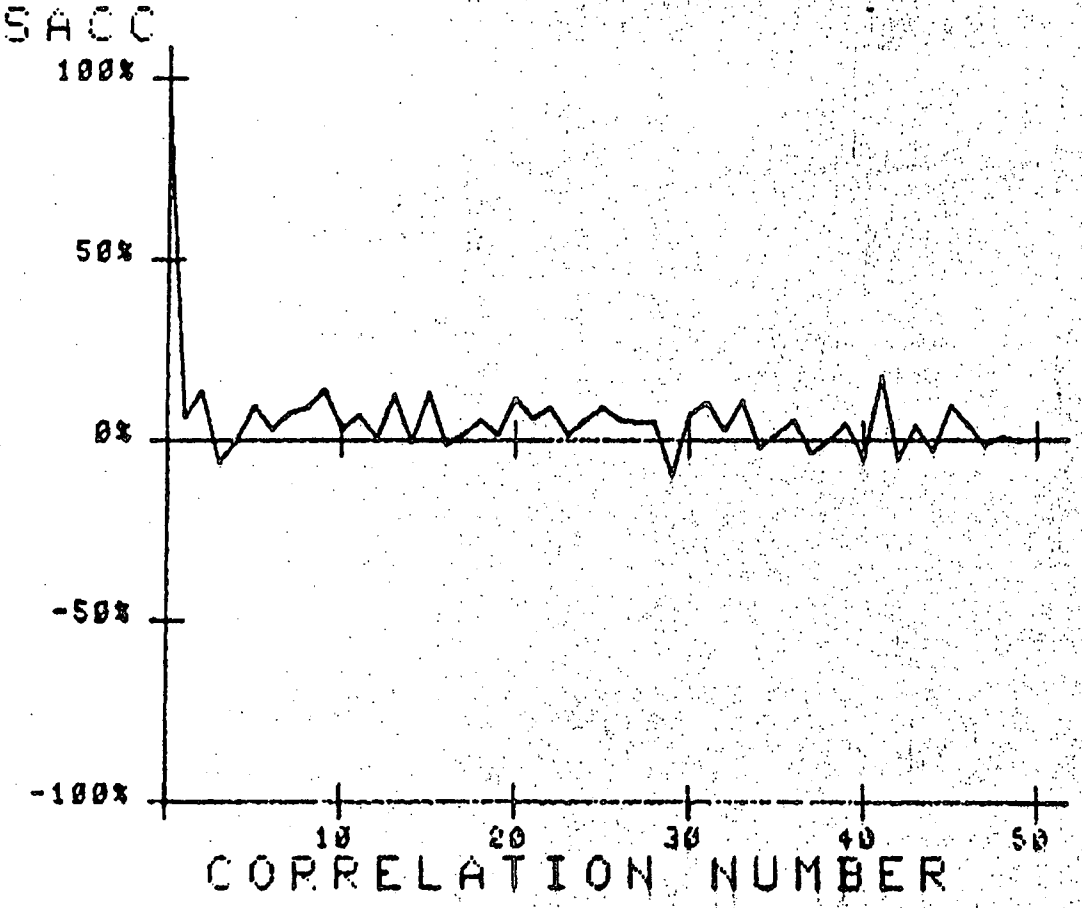

FIG. # 25

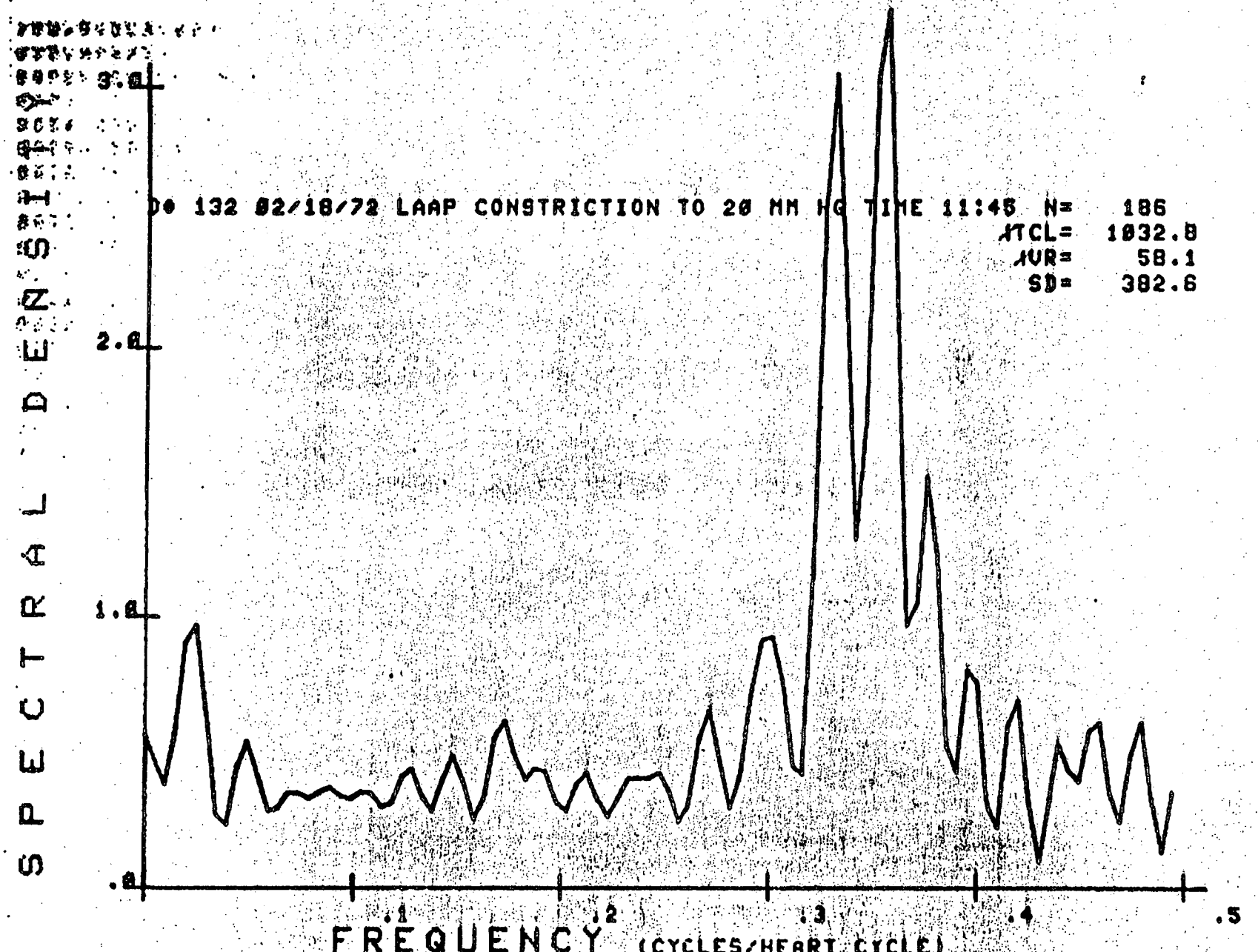
SPECTRAL DENSITY
3.0
2.0
1.0
.0
.1
.2
.3
.4
.5
FREQUENCY (CYCLES/HEART CYCLE)
0 132 02/18/72 LAAP CONSTRICTION TO 20 MM HG TIME 11:45
N= 186
MTCL= 1032.8
MVR= 58.1
SD= 382.6

FIG. # 26

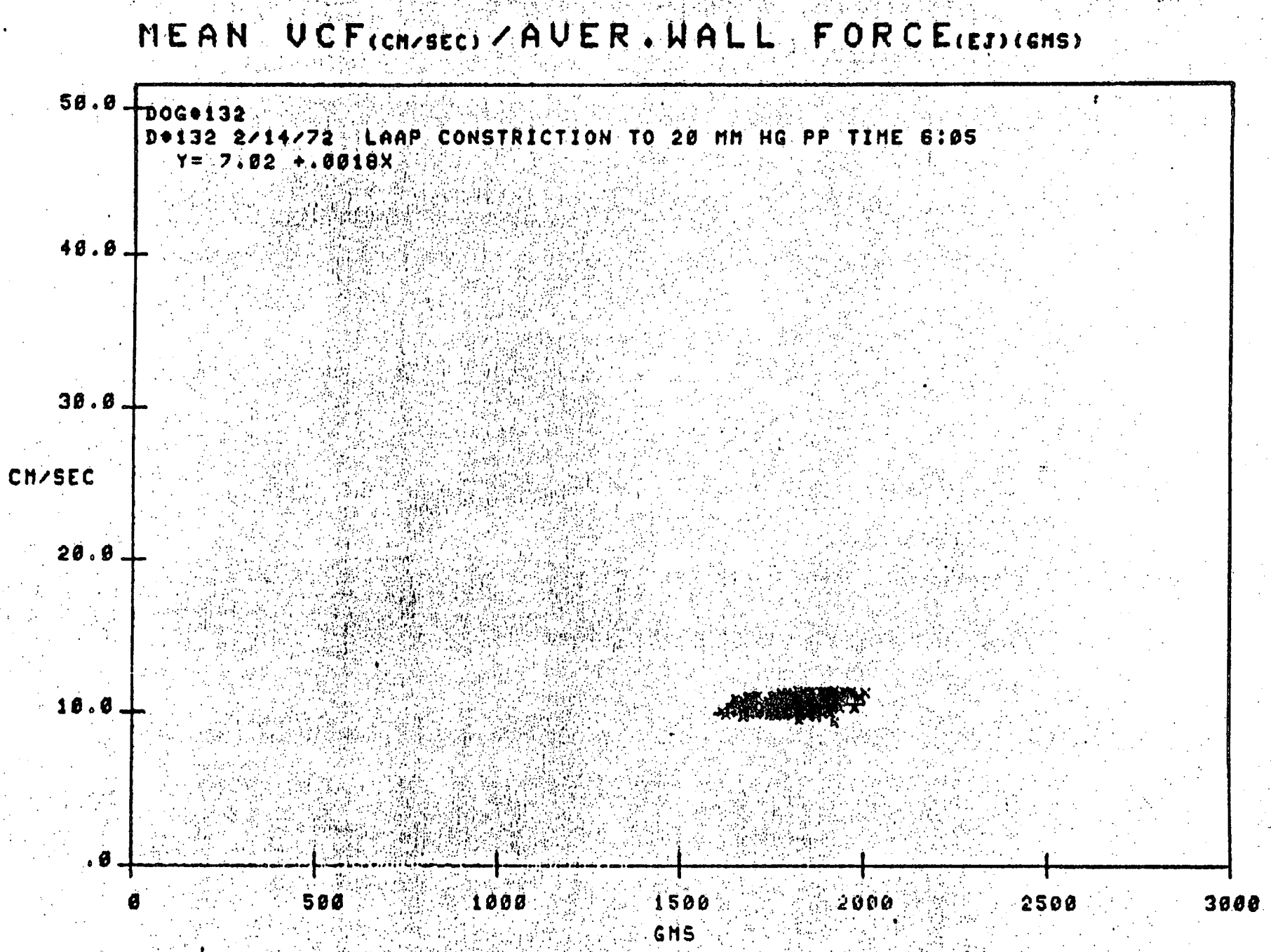
MEAN VCF(CM/SEC)/AVER.WALL FORCE(EJ)(GMS)
DOG#132
D#132 2/14/72 LAAP CONSTRICTION TO 20 MM HG PP TIME 6:05
Y= 7.02 +.0018X
50.0
40.0
30.0
20.0
10.0
.0
CM/SEC
0
500
1000
1500
2000
2500
3000
GMS

FIG. # 27

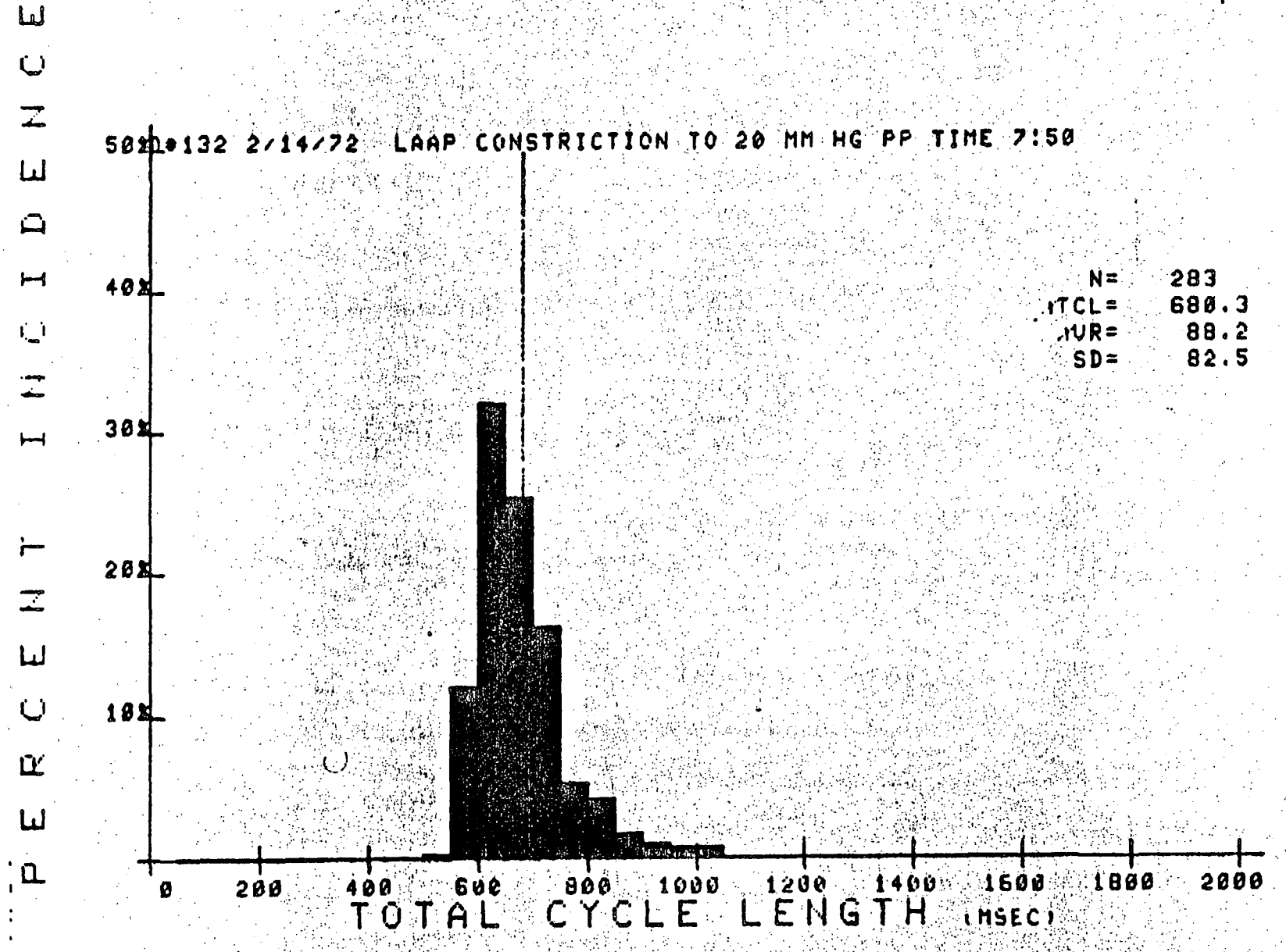
PERCENT INCIDENCE
50%
40%
30%
20%
10%
0
200
400
600
800
1000
1200
1400
1600
1800
2000
TOTAL CYCLE LENGTH (MSEC)
N= 283
MTCL= 680.3
MVR= 88.2
SD= 82.5

FIG. # 28

V. Development of a Totally Implantable Telemetry Package

Development of primary objectives in this area have proceeded through the joint efforts of Dr. Sandler and his group and our research group. A satisfactory design has been developed for these implantable biosensors and a contract has been made with Konigsberg Instrument Company to build these units for us. A recent manuscript published by Dr. Sandler (Sandler, H., Stone, H. L., Fryer, T. B. and Westbrook, R. M.: Use of Implantable Telemetry Systems for Study of Cardiovascular Phenomena. Circulation Research Suppl. II, 30-31: II-85, 1972) describes the basic system we hope to employ. Our system will have additionally an inductance micrometry channel to permit the recording of changes in left ventricular internal diameter. Test models of our telemetry units are still on the workbench, and receiving dates have been pushed back; we are hopeful that by late November they will have been received. Our intent is to test these systems in dogs in the late fall of this year and by early spring 1973 to implant and test these Biotelemetry Packs in chimpanzees.

Publications During the Past Year

1. Kraft-Hunter, F. and Hawthorne, E. W.: "Pacing" left ventricular function curves in conscious dogs. In the Paul D. White Symposium: Major Advances in Cardiovascular Therapy. The Williams and Wilkins Company. (In press)

2. Hawthorne, E. W., Walker, M. L., Hinds, J. E., Kraft-Hunter, with technical assistance from Adam Gordon: A user interactive data acquisition and reduction system for the study of cardiac dynamics. Advances in Chronically Implanted Cardiovascular Instrumentation, Academic Press. (In press).

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4. Perry, M. D., Hinds, J. E., and Hawthorne, E. W.: A linearized inductance micrometer for monitoring left ventricular internal diameter. J. Appl. Physiol. (In press)