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EFFECTS OF ANGIOTENSIN II AND NOREPINEPHRINE ON VENTRICULAR PERFORMANCE DURING OLIGEMIC SHOCK**

The administration of single large doses of angiotensin II has been shown to elicit positive chronotropic and inotropic effects in isolated heart preparations.[1,2] Continuous infusions of this hormone in normotensive animals, however, in amounts sufficient to produce marked vasoconstrictor responses, elicit only infrequent and transient increases of contractility.[3] Occasionally, negative inotropic transients associated with reduced coronary flow may occur.[3] The effects of angiotensin II upon ventricular function early and late in the course of oligemic hypotension has not been systematically examined. The data presented here indicate that animals in which ventricular function deteriorates after prolonged oligemic shock have large, sustained, positive inotropic responses to continuous infusions of angiotensin II.

METHODS

Cats weighing 3 to 5 kg. were anesthetized with 30 mg/kg of pentobarbital and prepared for measurement of left ventricular performance as described previously.[3] Cardiac output was measured with a Shipley-Wilson rotameter[4] and controlled by means of a pump-operated arteriovenous shunt that permitted blood to be pumped from the aortic flow meter circuit to the superior vena cava at controlled flow rates. Arterial pressure was controlled when desired by means of an adjustable constant-pressure reservoir. Temperature was maintained with a warm-water bath heat exchanger at 36±1°C. Heart rate was maintained constant by bipolar electrical pacing of the right atrium. Aortic pressure was measured by passing a polyethylene catheter into the aortic arch via the branchiocephalic artery. Left ventricular pressure was measured by passing a #13-gage blunt needle through the apical dimple into the left ventricular chamber. The first derivative of the left ventricular pressure (dP/dt) was recorded, utilizing a differentiating circuit.[5] Pressures were measured with Sanborn transducers and recorded, along with left ventricular output (minus coronary flow), on a Sanborn 964 direct-writing oscillograph.

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Ventricular function curves[6,7] derived from the foregoing measurements relate stroke volume to left ventricular end-diastolic pressure (LVEDP) at constant mean aortic pressure and heart rate. The inotropic state (contractility) of the left ventricle was expressed as stroke volume at a given left ventricular end-diastolic pressure as follows:

$$\frac{\text{stroke volume (milliliters)}}{\text{left ventricular end-diastolic pressure (mm Hg)}} \times 100,$$

with units of ml/100 mm Hg. The value for a given ventricular function curve was obtained by averaging the values for each point on the ascending portion of the curve. This ratio is similar to that used by Peserico[8] and permits measurement of the contractile state of the myocardium in relative terms. The time from the onset of ventricular contraction to the development of peak pressure in the left ventricle (peak pressure time, PPT) has been shown for this preparation to be relatively unaltered by stroke volume or aortic pressure, but changed by inotropic agents or heart rate.[9] This measurement was used as further evidence for an inotropic change in the ventricle. Angiotensin II, 0.1-2.5 ug/kg/min., was infused with a Harvard constant-infusion pump and compared with the effects of norepinephrine administered at the same rate. Response to these hormones was studied in normotensive preparations, in those with aortic pressures reduced to 35-50 mm Hg for about one hour, and in those with aortic pressures maintained at 35-47 mm Hg for several hours.

RESULTS

Data are presented from 11 technically successful preparations. In addition, 30 cats were employed as donor animals for priming blood. One hundred and twenty-one left ventricular function curves were obtained relating stroke volume to left ventricular end-diastolic pressure at constant mean aortic pressure. Data showing the speed of ventricular contraction are also presented (PPT).

Normotensive preparations

Continuous infusion of angiotensin II (0.1 to 2.5 ug/kg/min) in normotensive preparations failed to produce a sustained increase of ventrciular contractility. This was in contrast to the effects of norepinephrine, which consistently produced a large and sustained improvement in ventricular performance. As illustrated in Figure 1, right panel, a large increase of stroke volume for a given LVEDP occurred in the presence of continuous norepinephrine infusion (2.5 ug/kg/min). No shift of the curve took place after infusion of angiotensin at the same rate (Fig. 1, left panel).

The time from the onset of ventricular contraction to the peak pressure developed in the ventricle (PPT) represents a complex function of the rate of isometric pressure development and the velocity of isotonic shortening. Continuous infusion of norepinephrine (2.5 ug/kg/min)

consistently produced a large reduction of PPT (Fig. 1, right panel) in normotensive preparations while infusion of angiotensin II at the same rate resulted in no significant reduction of PPT (Fig. 1, left panel). As shown in Figure 1, the PPT fell from an average value of 124 (±2.4 S.E.) milliseconds to 104 (±1.3 S.E.) milliseconds during norepinephrine infusion. During angiotensin II infusion, however, the average of 114 (±1.1 S.E.) milliseconds was essentially the same as that for the control curve, 116 (±2.5 S.E.) milliseconds.

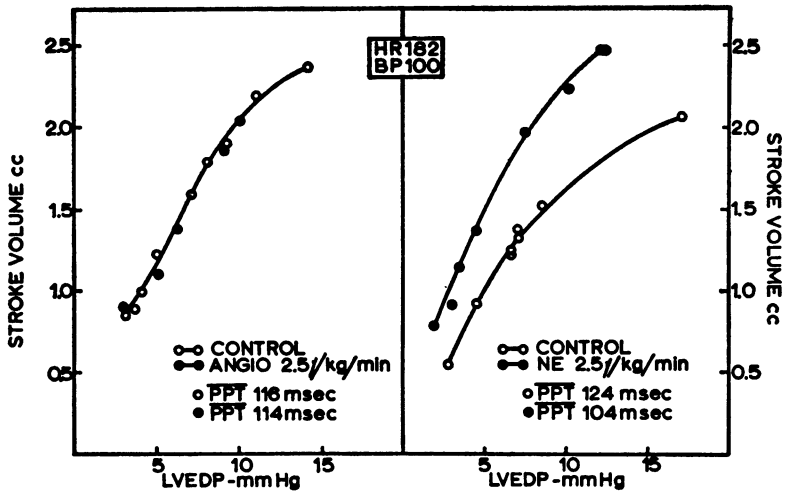

FIG. 1. Effects of angiotensin II (angio), left panel, and of norepinephrine (NE), right panel, upon the relation between stroke volume and left ventricular end-diastolic pressure (LVEDP) in the normotensive preparation. PPT = mean peak pressure time in milliseconds. HR = heart rate electrically paced at 182 per min. BP = mean aortic pressure in mm Hg.

Hypotensive preparations

Reduction of mean aortic pressure to 35-45 mm Hg for periods of one hour or less was associated with minimal evidence of depressed myocardial performance. The responses of these preparations to angiotensin II and to norepinephrine were comparable to those seen in the normotensive preparations. Mean aortic pressure had been maintained at 38±2 mm Hg for about one hour and was maintained at that value throughout the ventricular function curves (Fig. 2). Continuous infusion of angiotensin failed to produce a demonstrable sustained improvement of left ventricular performance in these preparations (Fig. 2, left panel). The continuous infusion of norepinephrine, on the other hand (right panel), resulted in

a stroke volume for a given LVEDP of 35.5 ml/100 mm Hg, a large increase over the mean control value of 19 ml/100 mm Hg. Furthermore, the mean PPT fell from 123 to 93 milliseconds.

Peak pressure time responses to angiotensin and norepinephrine in those animals in which mean aortic pressure was maintained at 35-45 mm

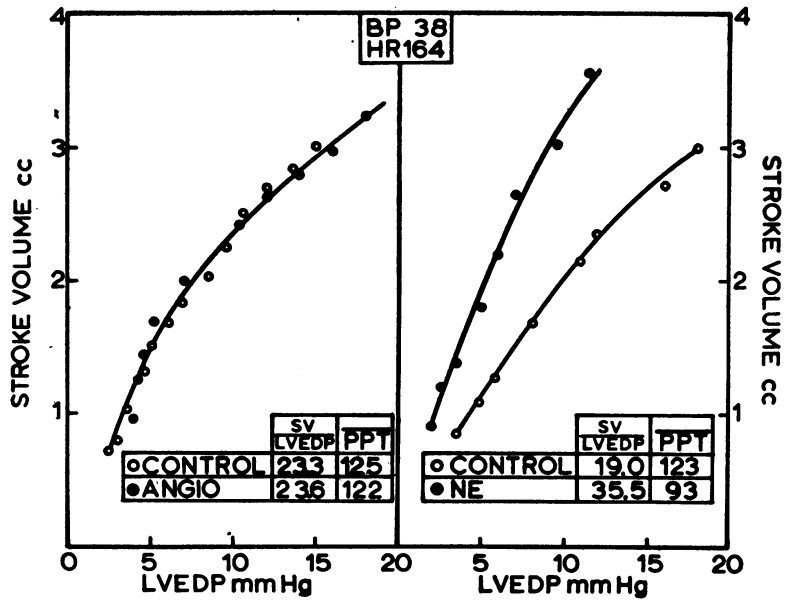

FIG. 2. Effects of infusions of 1.1 ug/kg/min angiotensin II (angio), left panel, and of norepinephrine (NE), right panel, upon the relation between stroke volume and left ventricular end-diastolic pressure (LVEDP) in the short term hypotensive preparation. The angiotensin curve was obtained approximately 55 minutes after reducing the arterial pressure to an average mean value of 38 mm Hg. Values for the stroke volume to LVEDP ratio in ml. per 100 mm Hg are shown, as well as mean peak pressure time (PPT) for each curve. There is evidence for an inotropic response to angiotensin, but the same preparation is highly responsive to norepinephrine.

Hg for two hours or less are shown in Tables 1 and 2. Corresponding to those changes seen in the normotensive preparation, continuous infusion of norepinephrine (Table 2) resulted in a considerable reduction of PPT. Average control values for the group were 111 (±5.8 S.E.) milliseconds and during norepinephrine infusion, 91 (±3.3 S.E.) milliseconds. No significant change in PPT occurred after continuous infusion of angiotensin at the same rate. Average control values were 108 (±4.6 S.E.) milliseconds, and 102 (±5.7 S.E.) milliseconds during angiotensin infusion.

TABLE 1. INOTROPIC RESPONSES TO ANGIOTENSIN II EARLY AND LATE IN THE COURSE OF OLIGEMIC HYPOTENSION

	Control				Angiotensin II				Change	
Cat no.	No. of observations	Mean aortic pressure (mm Hg)	SV x 100* LVEDP	PPT** (milliseconds)	No. of observations	Mean aortic pressure (mm Hg)	SV x 100 LVEDP	PPT (milliseconds)	SV x 100 LVEDP	PPT (milliseconds)
				Early (<100 min. of hypotension)						
2	5	50	11.8	104	..	..	...	..	—0.7	—1
	5	54	9.5	102	5	53	11.1	103	+1.6	+1
6	8	45	21.8	100	7	41	20.2	88	—1.6	—12
	7	44	15.1	102	7	44	17.9	94	+2.8	—8
7	6	47	17.1	90	5	41	15.1	82	2.0	—8
8	5	46	36.9	129	4	43	34.1	128	—2.8	—1
9	14	35	23.3	125	10	39	23.6	122	+0.3	—3
10	16	37	11.5	109	6	43	12.9	99	+1.4	—10
Totals	66				44					
Means	8.3	44.8	18.4 ±3.2S.E.	108 ±4.6S.E.	6.3	43.3	19.3 ±3.0S.E.	102 ±5.7S.E.	+0.9	—6
				Late (>100 min. of hypotension)						
2	9	47	10.4	102	6	53	12.2	97	+1.8	—5
5	6	37	11.2	119	7	38	18.1	109	+6.9	—10
6	7	45	9.7	104	6	45	17.6	87	*7.9	—17
	8	42	7.6	91	5	44	12.5	85	+4.9	—6
8	5	35	13.2	126						
9	8	35	19.1	123	11	40	30.1	124	+11.0	+1
	7	38	9.4	130	8	36	19.8	96	+10.4	—34
	6	35	8.2	129	7	38	13.6	102	+5.4	—27
10	4	39	13.8	120	4	41	28.0	86	+14.2	—34
					4	41	21.9	88	+8.1	—32
11	4	33	9.3	105	5	33	11.1	96	+1.8	—9
Totals	64				63					
Means	6.4	38.6	11.2 ±1.0S.E.	115 ±4.3S.E.	6.3	40.9	18.5 ±2.0S.E.	97 ±3.9S.E.	+7.3	—18

* Stroke volume/left ventricular end-diastolic pressure, ml/100 mm Hg.

** Peak pressure time, left ventricle.

TABLE 2. INOTROPIC RESPONSES TO NOREPINEPHRINE DURING OLIGEMIC HYPOTENSION

	Control				*Norepinephrine*				*Change*	
Cat no.	*No. of observations*	*Mean aortic pressure (mm Hg)*	*SV x 100* LVEDP*	*PPT** (milliseconds)*	*No. of observations*	*Mean aortic pressure (mm Hg)*	*SV x 100 LVEDP*	*PPT (milliseconds)*	*SV x 100 LVEDP*	*PPT (milliseconds)*
2	9	47	10.4	102	8	57	13.4	93	+3.0	—9
5	7	43	25.4	93	8	54	37.4	81	+12.0	—12
6	8	42	7.6	91	9	46	12.3	76	+4.7	—15
8	5	42	18.2	134	9	45	40.6	106	+22.4	—28
9	8	34	19.1	123	6	45	35.5	93	+16.4	—30
	7	38	9.4	130	8	40	31.4	91	+22.0	—29
11	4	37	10.7	119	5	37	11.5	99	+0.8	—20
	4	33	9.3	100	4	35	15.1	91	+5.8	—9
Totals	52				57					
Means	6.5	39.3	13.8 ±2.2S.E.	111 ±5.8S.E.	7.1	44.9	24.7 ±4.5S.E.	91 ±3.3S.E.	+10.9	—20

* Stroke volume/left ventricular end-diastolic pressure, ml/100 mm Hg.

** Peak pressure time, left ventricle.

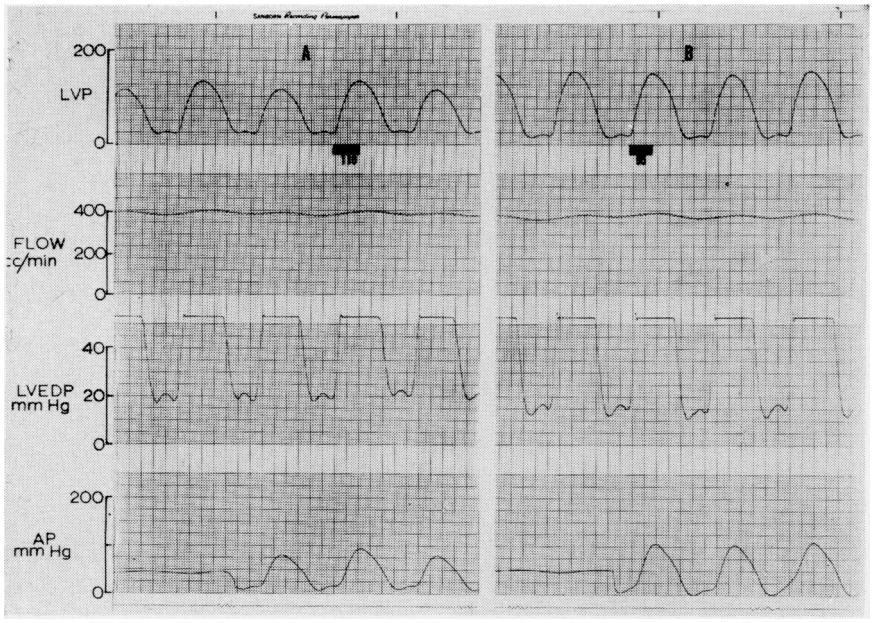

FIG. 3A. Left ventricular contractility response to angiotensin II (1 ug/kg/min) in prolonged hypotensive preparation. LVP = left ventricular pressure. FLOW = left ventricular output (minus coronary flow). LVEDP = left ventricular end-diastolic pressure (i.e. lower portion of high gain left ventricular pressure). AP = aortic pressure. Black bars indicate onset and duration of peak pressure time (PPT) in milliseconds. Panel A, control. PPT 110 msec. Pulsus alternans present. Panel B, during infusion of angiotensin II. PPT 95 msec. Pulsus alternans cured.

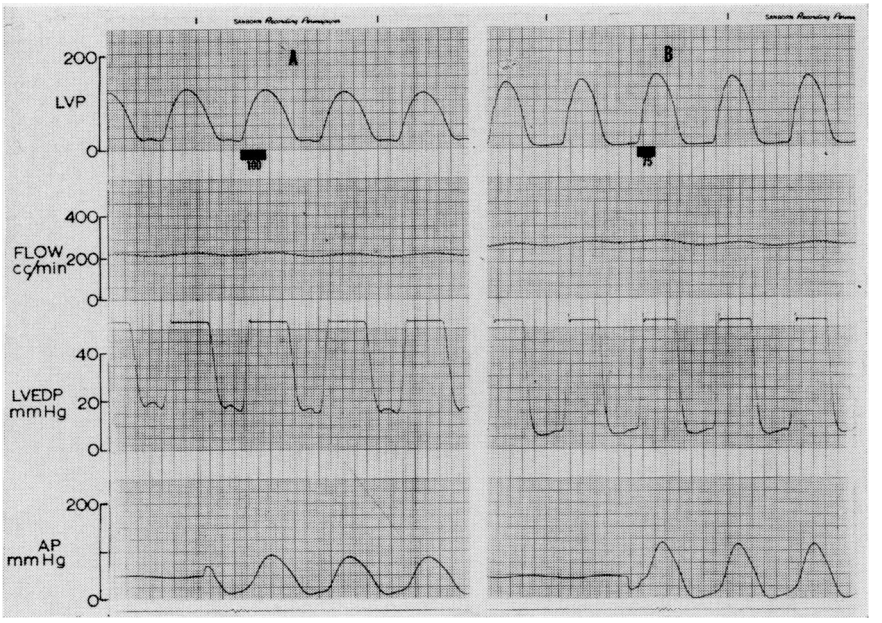

FIG. 3B. Left ventricular contractility response to norepinephrine (1 ug/kg/min) in same preparation. Panel A, control. PPT 100 msec. Panel B, during infusion of norepinephrine. PPT 75 msec. Chart speed 100 mm/sec.

The maximal rate of development of isometric tension in the left ventricle (dP/dt, max.) in the hypotensive preparations was greatly increased at a given LVEDP in response to norepinephrine infusion, but did not change after angiotensin II infusion.

Prolonged hypotensive preparations

Left ventricular performance declined progressively in animals maintained continuously with aortic pressure of 35-40 mm Hg for longer than 90 minutes. Two out of nine such preparations developed conduction disturbances before significant depression of the contractile elements, which precluded further performance measurements and resulted in ventricular fibrillation. In the remaining seven preparations, myocardial performance declined significantly (Table 1).

The continuous administration of angiotensin II in all of these hypotensive preparations resulted in a considerable improvement of left ventricular performance (Table 1), in sharp contrast to the effect on hearts in good condition. Figure 3A shows tracings demonstrating the positive inotropic response to angiotensin after two hours of hypotension. Left ventricular performance improved substantially as the LVEDP fell from 19 (panel A) to 14 (panel B) mm Hg at the same heart rate, cardiac output, and stroke volume. Furthermore, peak pressure time (black bars) dropped from 110 (panel A) to 95 (panel B) milliseconds. Pulsus alternans, present in panel A, disappeared during the angiotensin infusion (panel B). The response to norepinephrine was considerably greater (Fig. 3B); the LVEDP was reduced from 16 (panel A) to 7.5 (panel B) mm Hg in the presence of a somewhat greater stroke volume (panel B). The PPT fell from 100 milliseconds in panel A to 75 milliseconds in panel B.

Ventricular function curves, measured after 1½ and 3 hours of hypotension, showed a progressively greater response to angiotensin as ventricular performance diminished. Thus, after 1½ hours of hypotension (BP 45) the administration of angiotensin (0.5 ug/kg/min) produced a small increase of stroke volume for a given LVEDP (Fig. 4, left panel). The ratio of stroke volume to LVEDP for this curve increased from 15.1 to 17.9 ml/100 mm Hg. A small but detectable decrease of mean PPT (102 to 94 milliseconds) was also observed. After three hours of hypotension, left ventricular performance declined further. The continuous administration of angiotensin II at the same rate now produced a greater improvement of left ventricular performance as indicated by a greater increase of stroke

volume from a given left ventricular end-diastolic pressure (Fig. 4, right panel). The SV to LVEDP ratio increased from 9.7 to 17.6 ml/100 mm Hg. A greater reduction in PPT (104 to 87 milliseconds) also occurred. Sustained, positive inotropic responses to administration of angiotensin were observed only in those preparations that remained hypotensive long enough to show reduced myocardial contractility. In these, substantial improvement of left ventricular performance was demonstrable.

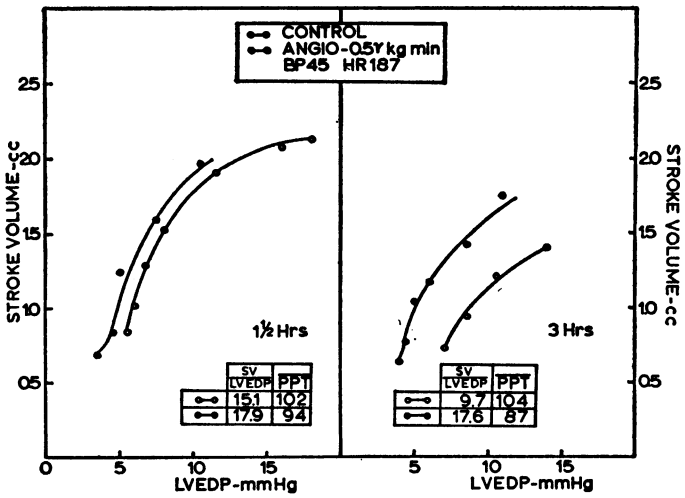

FIG. 4. Left panel. Left ventricular contractility responses to angiotensin II after 1½ hours of oligemic hypotension. BP = mean aortic pressure. HR = heart rate/min. SV/LVEDP = mean stroke volume to left ventricular end-diastolic pressure ratio, ml/100 mm Hg. PPT = mean peak pressure time in msec. Right panel, responses after three hours of continuous hypotension.

The contractility of the left ventricle during continuous oligemic hypotension is illustrated in Figure 5. Each point represents the mean value of eight to 14 points of a complete ventricular function curve. It is evident from the control points (closed circles) that the contractility of the left ventricle is diminishing progressively with continuation of shock, from a value of 25.3 ml/100 mm Hg at 17 minutes to a value of 8.2 ml/100 mm Hg at 180 minutes (Fig. 5, upper panel). Infusions of angiotensin (1 ug/kg/min) at 56 minutes and again at 78 minutes (closed squares) produced no significant alteration of contractility. However, after 100 minutes of shock, a positive inotropic response occurred to an angiotensin infusion at the same rate. This response was reproduced at 162 and 190

minutes and was still evident at the time of sacrifice of the animal about one hour later. None of these responses was as great as that to equivalent amounts of norepinephrine, although equal responses have occasionally been observed.

Figure 5, lower panel, illustrates the mean PPT values corresponding to the points in the upper panel. With the notable exception of the first

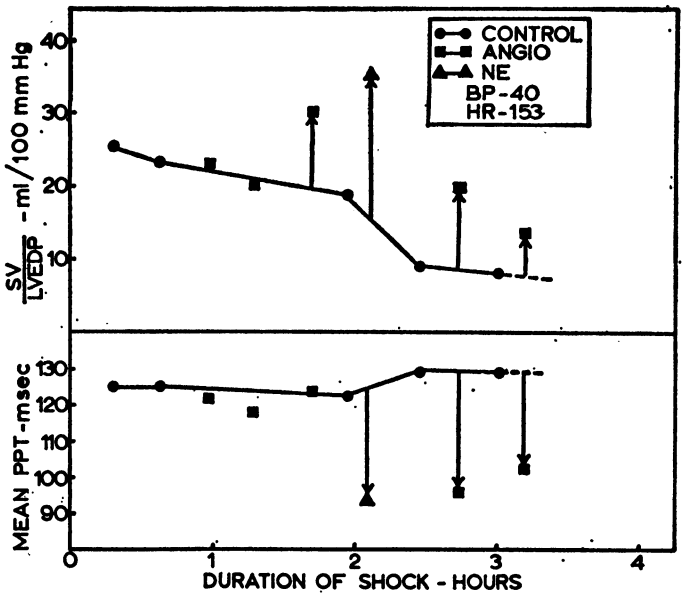

FIG. 5. Left ventricular performance characterized by a force parameter (above) and a speed parameter (below) during continued arterial pressure at shock level. SV/LVEDP = average ratio of stroke volume to left ventricular end-diastolic pressure in ml/100 mm Hg. Mean PPT = mean peak pressure time for each complete ventricular function curve, corresponding to points directly above. Control values connected by solid lines. Vertical arrows indicate responses to hormone infusions. ANGIO = values during angiotensin II infusion (1 ug/kg/min). NE = values during norepinephrine infusion (1 ug/kg/min). BP = mean aortic pressure in mm Hg. HR = heart rate/min.

angiotensin point, all increases of contractility were associated with a reduction of PPT, indicating a faster ventricular contraction. In contrast with the control points above, the PPT control points are minimally altered by progressive deterioration of the myocardium.

Figure 6 summarizes 346 observations on seven animals subjected to oligemic shock. It is evident that the contractility of the heart was greatly

reduced in the group under prolonged hypotension. The stroke volume to LVEDP ratio was reduced from 18.4 (±3.2 S.E.) to 11.2 (±1.0 S.E.) ml/100 mm Hg. The early response (<100 minutes of hypotension) to angiotensin II was very small, within the standard error of the mean values. In the prolonged hypotensive group, on the other hand, the SV to identical with the original short term hypotensive control value (18.4 ±

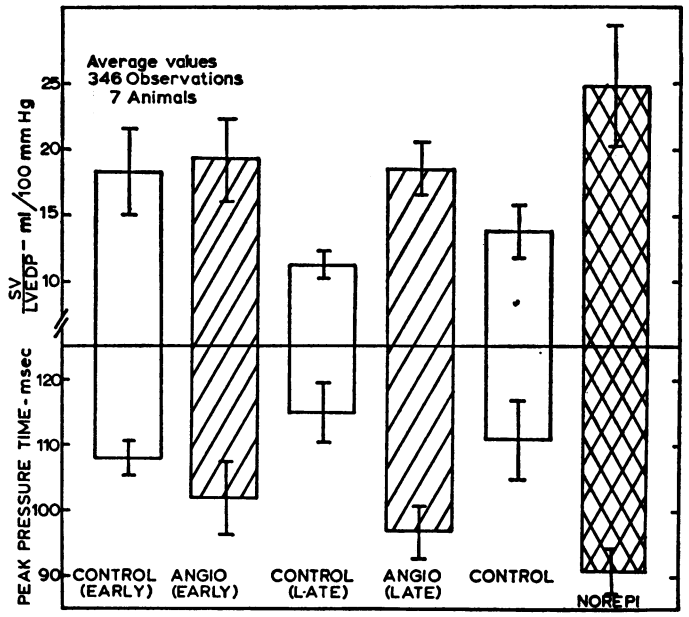

FIG. 6. Left ventricular contractility characterized by force (above) and speed (below) parameters during oligemic hypotension. EARLY = less than 100 minutes of hypotension. LATE = greater than 100 minutes of hypotension. ANGIO = angiotension II infusions. NOREPI = norepinephrine infusions. Norepinephrine and its control are not separated into early and late groups because little difference in respose was observed. SV/LVEDP = stroke volume to left ventricular end-diastolic pressure ratio.

LVEDP ratio increased in response to angiotensin II infusion by 7.3 ml/100 mm Hg (from 11.2 to 18.5 ml/100 mm Hg) to a value essentially 3.2 S.E.). Furthermore, the speed of ventricular contraction was significantly increased as the PPT fell by 18 milliseconds (from 115 ± 4.3 S.E. to 97 ± 3.9 S.E.).

The average responses to the norepinephrine infusions and the respective values of the controls are also shown in Figure 6. No difference in the response to norepinephrine was evident between the group subjected to

less than 100 minutes of hypotension and the group subjected to a longer period of hypotension. It is evident that norepinephrine possesses a marked positive inotropic action upon the ventricle in shock since the SV to LVEDP ratio increased by 10.9 ml/100 mm Hg (from 13.8 ± 2.2 S.E. to 24.7 ± 4.5 S.E.), and the PPT was reduced by 20 milliseconds (from 111 ± 5.8 to 91 ± 3.3 S.E.).

DISCUSSION

Administration of angiotensin II produces no sustained, positive inotropic effect in normotensive animals.[8] This study indicates that angiotensin has no effect on the myocardium despite systemic arterial hypotension per se, with assumed attendant reduction of coronary perfusion, as well as reduced perfusion of the tissues of the remainder of the body.

On the other hand, continuation of oligemic hypotension in these preparations for two to three hours at levels of 35-50 mm Hg mean aortic pressure is associated with a progressive reduction of myocardial performance (Fig. 5). As myocardial depression progresses with continuation of arterial pressure at shock level, the inotropic response to angiotensin II becomes progressively more pronounced. The stroke volume for a given LVEDP may be increased by more than 100 per cent, and the PPT reduced as much as 26 per cent. These findings are in contrast with those associated with infusion of norepinephrine. This hormone enhances the performance of hearts that appear to be in good condition[3, 7, 10] as well as those with reduced contractility.

It has been concluded from previous work[11] that angiotensin II possesses positive inotropic properties in normal dogs and humans. This conclusion, however, was reached from calculations of stroke work. It is now clear that calculated stroke work for a given LVEDP is dependent upon existing arterial pressure.[10,12] The administration of a non-inotropic drug which raises the arterial pressure may increase calculated stroke work for a given end-diastolic pressure simply by altering the afterloading of the heart.[10]

Continuous angiotensin infusion in normotensive preparations occasionally produces acute depression of ventricular contractility, associated with a simultaneous reduction of coronary blood flow.[8] That angiotensin produces coronary constriction has been amply demonstrated,[9, 13-15] although constriction is generally considered to be slight. When contrasted with norepinephrine, which produces a reduction in coronary vascular resistance, however, the differences are more pronounced.[8] In the hypotensive prepara-

tions transient negative inotropic responses have not been observed. If the assumption is correct that negative inotropic transients are a result of coronary constriction, it must then follow that angiotensin is capable of little if any important constrictor effect upon the coronary vessels in the preparations in shock, although still capable of increasing peripheral vascular resistance.

Of considerable interest is the reported capacity of angiotensin II to stimulate sympathetic elements within the central nervous system, thereby causing a reflex rise of arterial pressure[16] or tachycardia.[17] That this mechanism could contribute to an observed positive inotropic effect upon the heart would seem unlikely, however, since no increase of sympathetic outflow to the heart could be detected with direct electroneurographic techniques after its infusion.[18] Furthermore, in the preparation employed in the present experiments the arterial blood supply to the brain and upper spinal cord was largely eliminated by ligation, preventing the function of the higher reflex centers of the CNS. In addition, the very low arterial pressures used in this study would further militate against the continuing viability of those sympathetic elements not excluded by the ligation procedure.

It is concluded from this study that whereas the continuous infusion of angiotensin II elicits no sustained, positive inotropic effect on the well-compensated heart, this hormone brings about a clear, positive inotropic effect on the depressed ventricle. Further, this positive inotropic response is characterized by an increase of both force and velocity functions. From these findings, and the absence of the transitory myocardial depression that has been observed occasionally in normotensive preparations, it would appear that angiotensin II might be a useful agent in the clinical treatment of certain hypotensive states.

SUMMARY

Ventricular performance during oligemic hypotension was characterized by a force parameter, expressed as stroke volume for a given ventricular end-diastolic pressure (SV/LVEDP), and a speed parameter, expressed as peak ventricular pressure time (PPT). With continuation of arterial pressure at shock level the SV/LVEDP ratio progressively decreased while the PPT became somewhat prolonged. Continuous administration of angiotensin II at 0.1-2.5 ug/kg/min elicited no significant inotropic effect in normotensive preparations o. preparations subjected to less than 90 minutes of hypotension. Animals in which ventricular performance had deteriorated

after longer periods of hypotension showed large, positive inotropic responses to infusion of angiotensin II. Both force and speed parameters were significantly increased over control values. The administration of equal amounts of norepinephrine brought about pronounced positive inotropic responses in normotensive preparations as well as in the short-term and prolonged hypotensive preparations. The inotropic response to angiotensin II in the prolonged hypotensive preparations was usually less than the response to norepinephrine. Transient negative inotropic responses to angiotensin II, occasionally observed in normotensive preparations, were not observed in the hypotensive animals. The mechanism whereby angiotensin II, which has no sustained inotropic effect in the well-compensated heart, elicits a pronounced increase of ventricular force and speed in a depressed myocardium remains uncertain.

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