HEART FORCE RESPONSES TO PRESSOR AMINES DURING HYPOTENSION PRODUCED BY HEXAMETHONIUM * †

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THE use of sympathomimetic (pressor) amines in the treatment of certain hypotensive states has received considerable attention within recent years. Most of this attention has been focused on the peripheral vascular actions of these drugs, often neglecting the fact that a substantial cardiac action of many of these drugs contributed to the total clinical effectiveness. Furthermore, recent experiments have demonstrated that various degrees of cardiac depression may accompany or may contribute to a specific cardiovascular crisis (1) and that this can be antagonized to some extent by amines which increase the force of myocardial contraction.

The present investigation was designed to study the effects of moderate hypotension produced by hexamethonium on the contractile force of the heart and to evaluate the effects of five pressor amines on the heart force and the blood pressure during this state of hypotension.

METHOD

The method employed to measure the force of myocardial contraction with strain gauge arches in intact dogs which had previously undergone operations has been described (2, 3, 4). A study of the various circulatory factors that influence the interpretation of such data has shown that associated influences are minimal or can readily be evaluated and discounted (5). The mechanical features of these metal enclosed strain gauge arches have been reported in detail (6).

Six dogs were employed during the course of these experiments and were surgically prepared in the following manner. Each was subjected to thoracotomy under pentobarbital anesthesia and a strain gauge arch was sutured directly to the anterior aspect of the right ventricle of the heart; polyethylene tubings were inserted under direct vision into the right femoral artery and vein through an incision in the leg. At the termination of the operation, the lead wires to the strain

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gauge arch were placed in a small metal can firmly attached to the chest wall by sutures and adhesive tape; the indwelling polyethylene catheters were flushed with heparinized Ringer-Locke solution (20 units per cubic centimeter), and the free ends were ligated and placed in a similar metal can over the femoral canal. All animals received penicillin, a high protein diet and special daily care by which they were maintained in good health.

In the resting, conscious animal and during the course of each experiment under anesthesia, measurements of heart force were made

TABLE 1

No. of Observations	Average Arterial Pressure Before Hexamethonium, mm.	Average Arterial Pressure Before Amine, mm.	Average Arterial Pressure After Amine, mm.	Average Increase in Heart Force, per cent	Average Change in Heart Rate, per minute	Average Duration of Action, minutes	Dose Range, per kilogram
1-Arterenol bitartrate (Levophed)							
23	134/96	89/57	138/108	81	+10	2	0.25 to 0.5γ
Methamphetamine HCl (Methedrine)							
10	134/96	101/72	144/118	36	+20	6	0.05 to 0.1 mg.
Ephedrine SO_4							
6	134/96	105/70	141/107	40	+23	4	0.15 to 0.2 mg.
Phenylephrine HCl (Neosynephrine)							
13	134/96	89/57	149/119	11	+ 7	5	10–15γ
Methoxamine HCl (Vasoxyl)							
9	134/96	95/64	148/120	21	− 3	8	0.07 to 0.1 mg.

with a Brush strain analyzer (Bl-320) and recorded simultaneously on a double channel oscillograph (Bl-202) with femoral arterial pressures measured with a Statham transducer and separate strain analyzer (Bl-320).

On the first or second postoperative day and on each subsequent day following an initial recording of arterial pressure and heart force, the animals were anesthetized and maintained throughout the experiment in plane 1 of surgical anesthesia with a slow intravenous drip of 0.4 or 0.6 per cent pentothal® sodium. Following a stable control

interval, these animals were given hexamethonium (hexameton® chloride) in doses of 2 to 7.5 mg. per kilogram (expressed as the ion). After suitable hypotension had developed, five sympathomimetic amines were administered by rapid intravenous injection in the following sequences: l-arterenol (levophed®), phenylephrine (neosynephrine®) or methoxamine (vasoxyl®) and ephedrine or methamphetamine (methedrine®). In one experiment, methamphetamine was administered after l-arterenol. The doses of the amines employed are given in table 1 and are expressed in terms of their salts. All animals rapidly recovered from the pentothal anesthesia after each experiment and were able to walk within three to four hours.

Results

The administration of hexamethonium to 2 fully conscious dogs in preliminary experiments demonstrated that it was not possible to

Figures 1 and 2.

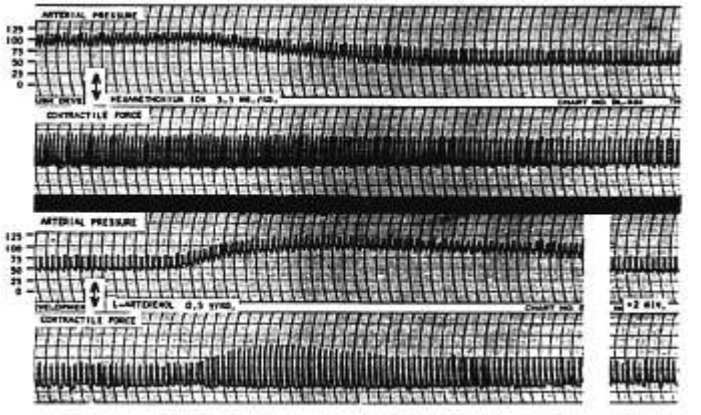

Fig. 1. Upper pair of synchronous tracings represents femoral arterial pressure and heart contractile force from a previously operated dog anesthetized with pentothal sodium. Cardiac contractile force was recorded with a strain gauge arch sutured directly to the right ventricle at an operation two days previously. Contractile force of the heart is directly proportional to the amplitude of the oscillograph recording. Arterial pressure was measured with a Statham transducer connected to an indwelling polyethylene catheter in the femoral artery. Hexamethonium (hexameton chloride®) was administered intravenously in the femoral vein through an indwelling catheter. Administration of hexamethonium resulted in a reduction of the contractile force and rate of the heart and of blood pressure. The interval between vertical lines equals one second.

Fig. 2. Lower pair of synchronous tracings. Continuation of the same experiment shown in figure 1. Same conditions are present. Administration of l-arterenol produced substantial increases in cardiac force and blood pressure which were of relatively short duration.

produce stable hypotension in a conscious animal; in these animals, the arterial pressures rapidly returned to control levels. All data included in this study were obtained, therefore, in animals under light surgical anesthesia with pentothal.

The intravenous administration of hexamethonium in fifteen experiments with 4 dogs produced a prompt average fall in arterial pressure of from 134 to 94 mm. systolic and from 96 to 57 mm. diastolic (fig. 1). Each of these experiments was performed on a different day. The hypotensive effects lasted about thirty minutes. The contractile force of

FIGURES 3 AND 4

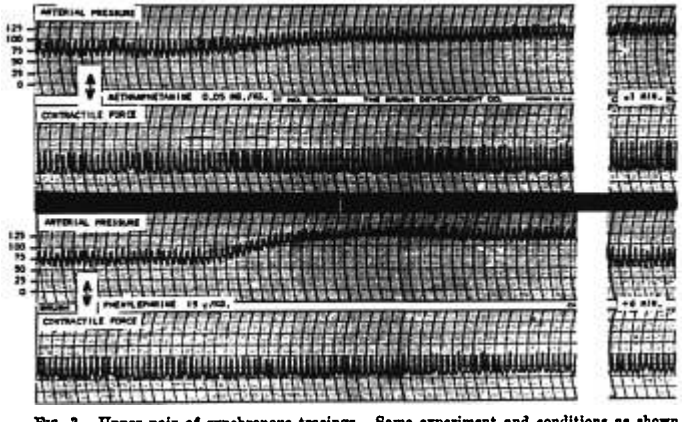

FIG. 3. Upper pair of synchronous tracings. Same experiment and conditions as shown in figures 1 and 2. Administration of methamphetamine produced a moderate increase in cardiac force with a substantial rise in blood pressure. These responses required about one minute to reach a maximum.

FIG. 4. Lower pair of synchronous tracings. Same experiment and conditions as shown in previous figures. Administration of phenylephrine produced only a very minimal increase in cardiac force but a substantial rise in blood pressure.

the heart was decreased an average of 27 per cent and heart rate was decreased an average of 22 beats per minute following the injection of hexamethonium. Marked dilation of the pupils occurred promptly and usually persisted throughout the period of action of the hexamethonium.

The results of sixty-one administrations of five sympathomimetic (pressor) amines to 4 dogs in fifteen experiments are summarized in table 1. All calculations of duration of action (blood pressure, force and rate changes) were based on a return to within 20 per cent of the immediately preceding control. In each of these experiments, moder-

ate, stable hypotension was produced by previous injection of hexamethonium. A single injection of l-arterenol produced substantial increments in heart force which lasted about one and one half minutes; increments in arterial pressure usually lasted about two minutes. A typical response to l-arterenol is shown in figure 2.

Methamphetamine and ephedrine produced moderate increments in heart force which were about one half those produced by l-arterenol although increases in blood pressure were about the same (fig. 3). Increments in cardiac contractile force and in arterial pressure with these drugs were more prolonged than those produced by l-arterenol.

Increases in heart force following administration of phenylephrine and methoxamine were relatively minimal as compared with l-arterenol, methamphetamine or ephedrine. Increments in arterial pressure, however, were similar to those produced by these last mentioned amines (fig. 4). The durations of actions of phenylephrine and methoxamine were comparable to those of methamphetamine and ephedrine (table 1).

In 2 other dogs, following injection of hexamethonium, sudden respiratory arrest was associated with a severe and relatively sharp fall in arterial pressure and heart force to shock levels. These animals apparently were exceptionally susceptible to the ensuing asphyxia. This cardiovascular-respiratory collapse was rapidly fatal; immediate intubation and artificial respiration were unsuccessful in resuscitating the animals. Intravenous or intracardiac injection of l-arterenol within thirty seconds following onset of respiratory arrest was ineffective in restoring blood pressure and heart activity.

Discussion

A substantial increase in arterial pressure resulted from the administration of each of five pressor amines to dogs with drug-induced hypotension. Similar results following the use of hexamethonium have been reported for l-arterenol (7, 8), for methoxamine (9) and for ephedrine (10). Simultaneously, the contractile force of the heart was substantially increased by l-arterenol and moderately increased by ephedrine and methamphetamine. Phenylephrine and methoxamine produced only minimal increase in heart force.

The small increases in heart force seen with phenylephrine and methoxamine are considered to have been the result of cardiac dilation secondary to hypertension and not a direct action of these drugs on the myocardium. Such dilation has been observed clinically by Keys and Violante with phenylephrine (11) and in "open-chest" dogs by Goldberg *et al.* with phenylephrine and methoxamine (12). Experiments with strain gauge arches in "open-chest" dogs have demonstrated that a 10 per cent dilation of the heart associated with saline infusions will increase heart force approximately 15 per cent (5). These latter results support the conclusion that phenylephrine and methoxamine do

not produce a direct increase in heart force. Melville and Lu (13) have shown that small doses of phenylephrine and methoxamine have no effect on the amplitude of contraction of the isolated rabbit heart. Likewise, Alexander (14) concluded that methoxamine had no effect on heart force from studies of aortic pulse pressure contours, and Opdyke (15) reported an absence of myocardial stimulation with phenylephrine in a clinical study of patients in hemorrhagic shock. Others have reported the failure of phenylephrine or methoxamine to precipitate arrhythmias in the cyclopropane-sensitized heart (16, 17).

l-Arterenol, methamphetamine and ephedrine produced significant increments in heart force following their administration. Luduena *et al.* (18) have shown that l-arterenol increased the amplitude of contraction of the dog heart and Garb (19) reported an increase in contractile force with l-arterenol using the cat papillary muscle technique. Chen and Schmidt (20) noted substantial increments in the amplitude of contraction of the dog heart with ephedrine, and Krop (21), using the papillary muscle technique, reported that small doses of ephedrine produced an increase in the force of contraction while large doses resulted in depression. Dilation of the heart has not been recognized with l-arterenol, methamphetamine or ephedrine and the recorded increases in heart force in the present experiments are considered to be the result of drug-induced changes in myocardial contractility.

Previous work in this laboratory employing equipressor doses of the sympathomimetic amines (12) showed that ephedrine and methamphetamine produced increases in heart force which were approximately equal to those obtained with l-arterenol. Furthermore, the clinical responses obtained with most of these amines are of much longer duration than those obtained in the present study. These apparent discrepancies with the present results, in which ephedrine and methamphetamine produced approximately 50 per cent of the heart force responses obtained with l-arterenol, and all durations of actions were much shorter than anticipated, may be attributed to the use of small dosages, the intravenous route of administration and the presence of an initial hypotension.

The decrease in heart force which occurred with the development of hypotension following hexamethonium is considered to be attributable largely to the fall in arterial pressure. Other experiments have shown that heart force is usually decreased by a fall in arterial pressure and may promptly be restored by a return of arterial pressure to control levels (22). Other factors, however, such as decreased cardiac autonomic activity or direct action of hexamethonium on the myocardium, may also have played a part in the present experiments, particularly with regard to the decreased heart rate.

The rapid cardiovascular-respiratory collapse which occurred with 2 dogs following administration of hexamethonium and short periods of asphyxia was particularly dramatic in contrast to the usual experience

in which animals have been exposed to considerable intervals of asphyxia with subsequent recovery. Typically, there occurs an interval of generalized discharge of the sympatho-adrenal system before the usual terminal events occur, and blockade of this emergency protective mechanism by hexamethonium apparently was responsible for the decreased tolerance to asphyxia. The disappearance or marked reduction of such sympatho-adrenal discharge following administration of hexamethonium has been reported by Paton and Zaimis (23).

Clinical use of a sympathomimetic amine to combat hypotension should be accompanied by a clear understanding of its cardiac effects as well as its peripheral vascular actions. In patients who have a previous history of heart disease, care should be taken to prevent cardiac embarrassment produced by a sudden increase in arterial pressure. Rapid intravenous administration of large doses of phenylephrine or methoxamine might be attended by acute cardiac dilation and subsequent failure. Slow intravenous infusion of dilute solutions of l-arterenol, methamphetamine or ephedrine would be indicated because of their action in increasing heart force simultaneously with arterial pressure. The usual caution should be maintained, however, against employing these latter agents during cyclopropane anesthesia because of their tendency to produce serious arrhythmias or even ventricular fibrillation.

SUMMARY

The adminstration of hexamethonium to lightly anesthetized, normotensive dogs produced a substantial fall in blood pressure, and in cardiac contractile force and rate.

Rapid intravenous administration of l-arterenol following hexamethonium produced substantial increments in heart force and blood pressure. Using doses which were equipressor with l-arterenol, the administration of methamphetamine and ephedrine produced moderate increments in the contractile force of the heart, while phenylephrine and methoxamine produced only minimal increments in heart force.

The increments in heart force produced by l-arterenol, ephedrine and methamphetamine are considered to represent actual drug-produced increases in heart force. The small increments in heart force produced by phenylephrine and methoxamine are considered to be largely or entirely responses to hypertension and not the result of direct stimulation of the myocardium.

Brief intervals of asphyxia produced rapid cardiovascular collapse and death in 2 dogs. This was considered to be the result of a blockade of the sympatho-adrenal system by hexamethonium.

The selection of a pressor amine to combat hypotension should be based on knowledge of its cardiac activity as well as its peripheral vascular actions. In conditions of hypotension associated with a weakened myocardium, pressor amines such as l-arterenol, methamphet-

amine or ephedrine are indicated as they produce increases in heart force as well as pressor responses.

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