The Direct Effects of Norepinephrine, Epinephrine, and Methoxamine on Myocardial Contractile Force in Man

By Leon I. Goldberg, Ph.D., M.D., Robert D. Bloodwell, M.D., Eugene Braunwald, M.D., and Andrew G. Morrow, M.D.

Although the direct effects of sympathomimetic amines on myocardial contractile force have been well documented in the experimental animal, such data have not previously been obtained in man. The effects of these agents on the cardiac output and arterial pressure of man have frequently been measured. However, these two functions may be profoundly modified by numerous other hemodynamic and reflex influences. Accordingly, any conclusions concerning their direct effect on myocardial contractility, based on such measurements alone, must be viewed with caution. Indirect measurements in man have led to diverse and conflicting concepts of the myocardial actions of sympathomimetic amines and to speculations that these agents, particularly norepinephrine, may have different cardiac effects in man and in experimental animals. Aviado and Selzer and Rytand, in recent comprehensive reviews of the cardiovascular effects and therapeutic indications of sympathomimetic amines, concluded that more definitive studies of these agents in man were needed in order to permit their rational clinical use.

In the present study, the direct effects of norepinephrine, epinephrine, and methoxamine on human myocardial contractile force were studied by means of the Walton-Brodie strain-gage arch in patients undergoing thoracotomy. This instrument has been extensively utilized in the study of the effects of drugs on the heart in the dog and has been found useful in monitoring myocardial contractility during cardiac operations in man.

Methods

Sympathomimetic amines were administered during operation to 16 patients. They ranged in age from 4 to 40 years, and the average age was 25 years. Eleven of these patients had atrial septal defects, 3 had ventricular septal defects, and 2 had pulmonary stenosis. None had a history of heart failure or severely diminished cardiac reserve. Preanesthetic medications included meperidine (25 to 75 mg.), scopalamine (0.1 to 0.4 mg.) and promethazine (15 to 50 mg.). After intravenous thiopental induction, all patients were maintained under light general anesthesia with nitrous oxide, oxygen, and a muscle relaxant, either succinylcholine or d-tubocurarine. Thiopental and meperidine were administered in small doses to all patients for maintenance of anesthesia. Atropine was given intravenously in doses of 0.2 to 0.4 mg. to 3 patients prior to thoracotomy.

After a median sternotomy had been performed and the pericardium opened, the strain-gage arch was sutured to a convenient area on the right ventricle and the segment of myocardium between the 2 feet of the arch was stretched to about 50 per cent of its diastolic length. Arterial blood pressure was measured through a polyethylene catheter in the left radial artery by means of a Statham pressure transducer. Continuous recordings of blood pressure and myocardial contractile force were made simultaneously with a multichannel oscillograph.

L-Norepinephrine bitartrate (Levophed, Winthrop), I-epinephrine bitartrate (Suprarenin, Winthrop), and methoxamine hydrochloride (Vasoxyl, Burroughs-Wel come) were administered intravenously either by rapid injection or by infusion. Norepinephrine was administered at least once to all 16 patients. In 5 patients methoxamine was administered in a dose sufficient to approximate the diastolic pressure increment produced by norepinephrine. In 6 patients norepinephrine and epinephrine were injected in succession in equal doses. Metaraminol bitartrate (Aramine, Merek, Sharp and Dohme) and mephentermine sulfate (Wyamine, Wyeth) were also used in several patients. All amines, unless stated otherwise, were injected before institution of cardiopulmonary bypass or cannulation of the venae cavae, generally.
at a time when the femoral artery was being prepared for cannulation and the heart was not being manipulated. Contractile force and arterial pressure were recorded during a control period before each administration of an amine. The doses of the amines were calculated as the base except for methoxamine, which was calculated as the hydrochloride salt.

Results

The effects of norepinephrine, epinephrine, and methoxamine on right ventricular contractile force (CF), arterial pressure (BP), and heart rate (HR) are shown in Table 1. The amplitudes of the contractile force recordings, which are directly proportional to the force applied by the myocardium to the strain-gage arch, were measured in millimeters. Since the height of the contractile force recording depends upon such variables as the direction of placement of the strain-gage arch, the depth of the sutures and the degree of initial tension placed on it, no attempt was made to convert the deflections into grams of force. The amplitude of the oscillographic deflection during the control period was adjusted arbitrarily in each patient and these control values are not, therefore, comparable in the different patients. The percentage change, however, from the control value following the injection of a drug into an individual patient permits meaningful comparisons.

Norepinephrine

The intravenous administration of norepinephrine increased ventricular contractile force in all 15 patients in whom valid measurements were made (Figs. 1 and 2). The response was always transient, lasting about 5 minutes. In 1 additional patient (M.T.), no increase in contractile force was observed, but she developed atrial fibrillation during the norepinephrine injection, and the irregularity of the ventricular contractions made accurate measurements of contractile force impossible. This patient continued to have transient episodes of this arrhythmia during the operation, so that its development may not have been related to administration of the amine. As may be noted in Table 1, there was considerable variation in the contractile force, arterial pressure, and heart rate responses in the different patients. Similar variability of response to norepinephrine and other amines has been noted in anesthetized animals and probably depends upon such factors as the different responses of patients to the same dose per kilogram of body weight, variations in the depth of anesthesia, the level of circulating catecholamines, the amount of blood loss, and the activity of the sympathetic nervous system. Although there was some correlation between the contractile force and pressure increments produced by norepinephrine, this relationship also varied among patients (Fig. 3).

It is interesting that the 3 youngest patients, aged 4 to 8 years, had relatively small increases in contractile force per unit increase in arterial pressure, suggesting that in children the arteriolar bed is relatively more sensitive to sympathomimetic amines than the myocardium. The patient (A.C.) in whom the contractile force rose only 5 per cent in response to norepinephrine, apparently had an elevated contractile force level at the time it was administered, since the contractile force gradually decreased by 40 per cent during the subsequent period of observation. It is possible that this weak response to norepinephrine was related to a high endogenous level of circulating catecholamines, since a typical response to epinephrine was obtained at a later time when the initial contractile force value was lower. The changes in heart rate in the 14 patients with sinus rhythm ranged from an increase of 18 beats per minute to a decrease of 18 beats per minute. These changes in rate were undoubtedly influenced by the variable state of vagal block that resulted from the pre-anesthetic and anesthetic medications, because norepinephrine is known almost always to result in bradycardia in unanesthetized subjects.

Epinephrine

Epinephrine was administered in the same dose as norepinephrine in 6 patients. In 4 instances, myocardial contractile force increased to approximately the same extent as with the norepinephrine injections (Figs. 1 and 2). Systolic pressure also increased in

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Table 1

Cardiovascular Effects of Norepinephrine, Epinephrine, and Methoxamine

<table>
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<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Weight (Kg.)</th>
<th>Drug</th>
<th>Dose µg./Kg.</th>
<th>CF mm.</th>
<th>BP mm. Hg</th>
<th>HR beats/min.</th>
<th>CF mm.</th>
<th>BP mm. Hg</th>
<th>HR beats/min.</th>
<th>CF %</th>
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<th>HR beats/min.</th>
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<td>96</td>
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<td>140/90</td>
<td>114</td>
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P.S., pulmonary stenosis; VSD, ventricular septal defect; ASD, atrial septal defect, CF, cardiac force; BP, blood pressure; HR, heart rate.

*Infusion of solution containing 4 mg. of norepinephrine/500 ml.
5 of the patients, but the change in diastolic pressure was variable, ranging from a decline of 7 mm. Hg to an increase of 20 mm. Hg. This difference is apparent in figures 1 and 2; in one instance, the diastolic pressure fell approximately 5 mm. Hg in the presence of a contractile force increment of 38 per cent; in the other patient (fig. 2), however, after an unstable initial period the diastolic pressure rose 20 mm. Hg and the contractile force increased 50 per cent. The heart rate either increased up to 24 beats per minute or remained unchanged after epinephrine administration. The duration of the effects of this amine was similar to those produced by norepinephrine.

**Methoxamine**

This drug was administered to 7 patients (figs. 2 and 3). In 5 of these, contractile force either did not change significantly or decreased slightly (-6 to -9 per cent); in the remaining 2 patients, there were slight increases in contractile force (13 and 18 per cent). The heart rate fell by 4 to 18 beats per minute in 4 of the patients and the rate did not change or increased slightly (6 and 12 beats per minute) in the others. The duration of the pressor effect following a single injec-
tion of methoxamine was usually between 10 to 15 minutes. The pronounced differences between the effects of methoxamine and norepinephrine on contractile force are shown in figure 3. As shown in figure 2, 0.25 µg. per Kg. of norepinephrine increased myocardial contractile force 46 per cent and the arterial pressure rose by 40/25 mm. Hg. Methoxamine (in a dose of 2 mg.) in this same patient produced an identical increment in diastolic arterial pressure but contractile force increased only 13 per cent.

**Mephenetermine and Metaraminol**

Mephenetermine (5 mg.) was administered intravenously to patient L.H. and contractile force increased 71 per cent; the arterial blood pressure increased from 100/70 to 125/80 mm. Hg. This amine was also given in a dose of 15 mg. to an additional patient who had profound hypotension (65/25 mm. Hg) and who is not included in table 1. The blood pressure rose to 110/85 and contractile force increased 30 per cent. The duration of these effects of mephenetermine exceeded 15 minutes in each patient.

Metaraminol was administered to 2 patients prior to cardiopulmonary bypass. In patient D.A. a dose of 1 mg. increased contractile force by 75 per cent while the arterial pressure rose from 90/60 to 160/95 mm. Hg. In a second patient, not included in the table, the administration of 1 mg. of metaraminol resulted in a contractile force increment of 43 per cent with an increase in arterial pressure from 80/50 to 125/75 mm. Hg. This drug (0.5 mg.) was also administered to patient S.G. following the repair of an atrial septal defect when hypotension (50/30 mm. Hg) suddenly developed. Contractile force increased 90 per cent and the arterial pressure rose to 108/76 mm. Hg. The duration of the effects of this amine also exceeded 15 minutes.

**Discussion**

The results of the clinical studies described above demonstrate that epinephrine, norepinephrine, mephenetermine, and metaraminol substantially increase myocardial contractile force in man. Injections of norepinephrine and of epinephrine, in the same patients and in equal doses, resulted in almost identical increments in myocardial contractile force. Methoxamine, on the other hand, had virtually no effect on myocardial contractile force in doses that produced pronounced increases in arterial pressure. These results are similar to those previously reported in anesthetized and unanesthetized dogs and demonstrate that there are no qualitative differences in the effects of these amines on contractile force in man and the dog.

Previous studies in man have consistently demonstrated that epinephrine augments cardiac output and that norepinephrine either does not change or diminishes this function. These results have led to the erroneous conclusion that norepinephrine is an amine with a purely pressor action and with no effect on myocardial contractility,
but that epinephrine is a stimulant of myocardial contractility. It is apparent from the present investigations that the different effects of these agents on cardiac output are not the result of any dissimilarity in their actions on myocardial contractility, but are probably related to different effects on the peripheral vascular bed. The changes in cardiac output may be explained as follows; norepinephrine augments systemic vascular resistance,8 which in turn tends to result in reflex bradycardia and diminished cardiac output, despite the increased myocardial contractile force. Epinephrine, on the other hand, tends to diminish peripheral resistance,9 and its positive chronotropic effect is unopposed by a stimulation of baroreceptors. Cardiac output thus rises with increments of myocardial contractile force of a similar magnitude to those produced by norepinephrine. A similarity in the cardiac actions of these catecholamines in man had been previously suggested by the data obtained by Wilber and Brust,24 which showed that norepinephrine increased cardiac output after atropine or tetraethylammonium bromide had prevented reflex bradycardia.

Although the longer acting sympathomimetic amines, mephentermine and metaraminol, were administered on relatively few occasions in the present study, they always produced increments in contractile force of a magnitude similar to those following nonepinephrine, but of longer duration. It appears, therefore, that sympathomimetic amines that increase arterial blood pressure in man may be divided, as in the dog, into 3 classes:8 Class I amines, such as norepinephrine and epinephrine, increase myocardial contractility and have a short duration of action; Class II amines, such as methoxamine, have little or no effect on myocardial contractility and act longer; Class III amines, mephentermine and metaraminol, increase contractility and have an action of long duration. Additional studies are being conducted with other amines to ascertain whether these agents may be similarly classified.

The strain-gage arch, as a method for measuring myocardial contractile force, was found to be applicable in man as in the experimental animal. No complications arose from its use in the present investigation, and the presence of the arch did not interfere with the surgical procedure. It should be emphasized that in order for the strain-gage arch to measure the direct effects of drugs on the contractile force of the heart, the segment of myocardium between the 2 legs of the strain-gage must be stretched to approximately 50 per cent of its initial length. As Cotten and associates23, 25, 26 previously demonstrated in the dog, this procedure eliminates significant changes in contractility produced by extracardiac effects of drugs, such as alterations in peripheral resistance, which would modify the end-diastolic fiber length and consequently the force of contraction. Other possible effects of increased systemic vascular resistance on myocardial contractile force measurements were further minimized in this study, since the strain-gage arch was placed on the right ventricle. The augmentation in contractile force produced by norepinephrine and other sympathomimetic amines cannot, therefore, be attributed to increases in peripheral resistance. With the strain-gage arch the effects of at least 2 agents on myocardial contractile force should be compared in the same patient, since it has been demonstrated that considerable variability

Figure 3
Relationships between the changes in diastolic arterial blood pressure and myocardial contractile force that occurred after each administration of sympathomimetic amines in 16 patients.

CHANGES IN DIASTOLIC ARTERIAL PRESSURE (mm Hg)

CHANGES IN CONTRACTILE FORCE, CHANGE IN PERCENT

EPINEPHRINE
NOREPINEPHRINE
METHOXAMINE

GOLDBERG, BLOODWELL, BRAUNWALD, MORROW
exists in the magnitude of the contractile force increments produced by the same agent in different patients. If one agent is considered as the standard of reference, as norepinephrine was in this study, the effects of all other drugs may be compared with those of the standard and individual responses in various patients can be analyzed.

The results of the present study are important in any consideration of the therapeutic indications for the administration of amines. They emphasize that the cardiovascular actions of these drugs differ strikingly when equipressor doses are given. It is now apparent that although norepinephrine and methoxamine both elevate the blood pressure and diminish the heart rate, these 2 agents should not be considered to be interchangeable, as has previously been suggested.27, 28 For example, if a patient is hypotensive because of impaired myocardial contractility, as in shock that may accompany myocardial infarction, the administration of an amine with only a pressor effect, such as methoxamine, would appear to be contraindicated. The augmentation of peripheral resistance produced by this amine, in the absence of a direct cardiac action, could result in cardiac dilatation and in pulmonary venous hypertension. Amines such as norepinephrine and metaraminol increase both myocardial contractility and peripheral resistance and would appear to be more suitable in this clinical situation. On the other hand, if a patient is hypotensive primarily because of a fall in peripheral resistance but has no impairment of myocardial contractility, as may occur during spinal anesthesia, methoxamine may be more applicable. These concepts had been presented previously on the basis of extensive animal experimentation3, 5, 6 and a few preliminary clinical observations.6 Perhaps because of the mistaken impression that these amines do not have the same actions in animals and man, these principles have not been widely applied in clinical practice. It is hoped that a more rational basis for clinical use has been provided by the present comparative studies of the direct effects of these drugs on the contractility of the human heart.

Summary

The effects of 5 sympathomimetic amines on myocardial contractile force were determined with the Walton-Brodie strain-gage arch in 16 patients undergoing operations for congenital heart disease. Equal doses of norepinephrine and epinephrine produced almost identical increments in myocardial contractile force; equipressor doses of methoxamine resulted in little or no change in the force of contraction. Mephentermine and metaraminol produced increments in myocardial contractile force similar to those following norepinephrine administration but the duration of action was longer. The results of these studies indicate that there are no qualitative differences in the actions of these amines on cardiac contractile force of dog and man and provide a basis for the rational clinical use of these agents.

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Sommario in Interlingua

Le effectos de 5 aminas sympathomimetic super le fortia del contraeltitale myocardial eseva determinate per medio del arco de Walton-Brodie in 16 patientes subjicite a operationes pro congeniti morbo cardiac. Doses equal de norepinephrina e de epinephrina produceva quasi identic augmentos in le fortia de contraction del myocardio. Doses equipressori de methoxamina resultava in pauc o nulle alteration del fortia de contraction. Mephentermina e metaraminol produceva augmentos del fortia de contraeltilitale myocardial simile a illos occurrente post le administration de norepinephrina, sed le duration del effecto eseva plus longe. Le resutatos de iste studios indica que il existe nulle differentias qualitative in le action de iste aminas super le fortia de contraction cardiac in canes o in humanos. Illos provide le base pro le utilisation rational de iste agentes in le practica clinica.

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The Direct Effects of Norepinephrine, Epinephrine, and Methoxamine on Myocardial Contractile Force in Man
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