Dopamine, a biochemical precursor of levarterenol and epinephrine, has been shown in previous studies in intact animals to be pressor in the cat, depressor in the rabbit and guinea pig, and to have a variable, but predominantly pressor effect in the intact dog. Dopamine has been shown by Fowler, Shabetai, and Holmes to produce contraction of the rabbit aortic strip in amounts above 4 \( \mu \text{g} \). It has been reported by Horwitz, Goldberg, and Sjoerdsma that the effects of intravenous infusions of dopamine in man were significantly different from those of levarterenol, for dopamine increased chiefly systolic blood pressure, whereas levarterenol increased both systolic and diastolic pressure. Such results suggest that dopamine produces an elevation in blood pressure by increasing the cardiac output rather than by causing peripheral vasoconstriction.

It seemed desirable to study the cardiac effects of dopamine in such a way that changes in peripheral resistance, heart rate, and venous return could be avoided. Changes in blood pressure resulting from alterations in peripheral resistance could affect myocardial contractility. Such studies may be performed with the Langendorff preparation, ventricular muscle strips, isolated papillary muscle, or heart-lung preparation. The dog heart-lung preparation was chosen for the present study. A strain-gauge arch was used to measure changes in the force of ventricular contraction. Changes in ventricular diastolic pressure may alter the contractile force of the heart as recorded with this instrument, but such alterations are usually small.

Methods

Dogs were anesthetized with intravenous sodium pentobarbital (22 mg./Kg.). Twenty heart-lung preparations were prepared from mongrel dogs of either sex, weighing from 16 to 23 Kg. The Starling resistance was set at 85 mm. Hg; the blood entering the right atrium was kept at 37 to 39 C. The volume of blood in the preparation at the beginning of each experiment was approximately 800 ml. Each animal was given 50 mg. of heparin intravenously. All experiments lasted less than one hour. The height of the blood in the venous reservoir was maintained at 16 cm. above the level of the right atrium, except when it was necessary to raise the height in order to maintain baseline cardiac output above 300 ml./min. Direct measurements of systemic output were made in duplicate with maintenance of baseline venous level with donor blood during period of measurement. A strain-gauge arch (120 ohms) was sutured to the surface of the right ventricle. The right ventricle was chosen because of its greater accessibility and because its lower pressure minimized bleeding. Previous reports have indicated that similar results are obtained from either ventricle. The placement and tension adjustments were as recommended by Cotton, and the tension was recorded by a Sanborn multichannel oscillograph. In all experiments, heart rates were determined from the strain-gauge record. Systemic blood pressure and atrial pressures were recorded by means of Statham transducers.

All drugs were injected through the venous inflow cannula of the heart-lung preparation in a volume of less than 10 ml. for each injection. Both dopamine as the hydrochloride and levarterenol base were given to all preparations in amounts of 25 to 500 \( \mu \)g. and 1 to 5 \( \mu \)g., respectively. If drug effects were striking at the lower dosages, the higher amounts were not given. Successive doses were injected only after steady state had been attained. All doses are expressed as micrograms per heart-lung preparation. In 12 of the 20 experiments, the heart rate was kept constant at a rate of 200 to 282 per minute by driving the heart through the right atrial appendage using a Grass-rectangular-wave stimulator.
CARDIAC EFFECTS OF DOPAMINE

This was done to eliminate the effects of changes in rate upon contractile force.

Results

During control observations, the peak systolic tension recorded by the strain-gauge arch did not vary more than 2 mm. (out of 10 to 15 mm. response) in each experiment. After the injection of the drug, increases or decreases of 1 mm., or more beyond this limit, were interpreted as positive or negative inotropic effects, respectively.

In each of eight uncontrolled rate preparations, dopamine (0.5 to 1.0 mg.) had a positive inotropic effect, increasing the contractile force an average of 86 per cent. In these same preparations, the average rate increase was 18 per cent and average cardiac output increase was 32 per cent. A significant decrease in both right and left atrial pressures occurred in each of these animals.

Figure 1 shows the effects of dopamine and levarterenol on cardiac output in 12 heart-lung preparations with the heart rate held constant by the Grass stimulator. Cardiac output was increased 2 to 53 per cent in 5 of the 10 preparations receiving 25 to 50 μg. of dopamine. With 100 to 500 μg. of dopamine, each of 12 preparations showed an increase in cardiac output; the range of increase was 3 to 121 per cent (fig. 1). Dopamine (25 to 50 μg.) increased above control levels the ventricular force (7 to 12 per cent) in only 3 of the 10 preparations; however, 100 to 500 μg. increased the contractile force in all preparations 6 to 150 per cent.

Dopamine (25 to 50 μg.) increased the blood pressure in 5 of 10 preparations 1.5 to 12 per cent, whereas 100 to 500 μg. increased blood pressure in all 12 animals by 2 to 36 per cent.

Levarterenol (1 to 5 μg.) given after dopamine to 9 of the 12 preparations increased the ventricular force 12 to 157 per cent, cardiac output 6 to 169.8 per cent, and the blood pressure 4 to 40 per cent.

In the majority of the preparations, dopamine (100 to 500 μg.) produced a prompt decrease in right atrial pressures (3.5 to 57 per cent) and in left atrial pressures (4 to 60 per cent). With small doses (25 to 50 μg.) of dopamine, only 4 of 10 animals showed a decrease in atrial pressures. Levarterenol (1 to 5 μg.) produced a 6 to 49 per cent decrease in right atrial pressures.
FIGURE 3
(Upper) Record showing the changes in left atrial pressure, ventricular force, right atrial pressure, and systemic blood pressure following injection of 250 μg of dopamine into venous inflow cannula of dog heart-lung preparation with controlled cardiac rate. Time intervals 5 mm. = 1 second. (Lower) Record showing the changes in left atrial pressure, ventricular force, right atrial pressure, and systemic blood pressure following injection of 5 μg of levarterenol into venous inflow cannula of dog heart-lung preparation with controlled cardiac rate. Time intervals 5 mm. = 1 second.

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and a 5 to 64 per cent decrease in left atrial pressures. Reversal of the order of administration of these two drugs in three preparations showed similar results.

Figure 2 shows that successive doses of dopamine or levarterenol in the same animals produced no significant cumulative effects in either cardiac output, ventricular force, or blood pressure.

It was shown consistently in these experiments that the onset of effect of dopamine was later than that of levarterenol, but that the duration of effect of dopamine exceeded that of levarterenol. Following the maximum effect of levarterenol, there was a decline of cardiac output which was not observed with dopamine. Figure 3 (upper and lower) shows a representative record of changes in ventricular force, blood pressure, and atrial pressures produced by dopamine and levarterenol. Figure 3 (upper) demonstrates the decrease in atrial pressures and increase of blood pressure, cardiac output, and right ventricular contractile force after 250 μg. of dopamine. Figure 3 (lower) demonstrates similar changes after 5 μg. of levarterenol. It may be observed that the effect of dopamine upon blood pressure, cardiac output, and ventricular contractile force lasts longer than that of levarterenol.

Discussion

The pathway for the biosynthesis of epinephrine in the human and dog is now considered to proceed from tyrosine through dopa, dopamine, norepinephrine (arterenol), and epinephrine. Although this metabolic sequence was first postulated in 1939 by Blaschko, convincing evidence could not be obtained even in experimental animals until the advent of isotopic tracer techniques and chromatographic methods for separating the three amines, 3, 4 dihydroxyphenylethylamine (dopamine), levarterenol, and epinephrine. It has now been shown in animals that phenylalanine-C¹⁴ (which gives rise to tyrosine), tyrosine-C¹⁴, 3, 4 dihydroxyphenylalanine-C¹⁴ (dopa), and dopamine-C¹⁴, are precursors of adrenal levarterenol and epinephrine. It is usually assumed that the formation of levarterenol precedes that of epinephrine.

Horwitz, Fox, and Goldberg recently reported the effects of intravenous infusions of dopamine (5 to 11 μg./Kg./min.) on arterial pressure and cardiac output (by the dye-dilution technique) determined in five normal human volunteers. Cardiac output was significantly increased in each subject (average = +33 per cent), with increased stroke volume as the major factor. Heart rate changes were slight and variable.

From the present studies it is apparent that dopamine has a significant positive inotropic and chronotropic cardiac effect in the dog over the dosage range studied. In the dog heart-lung preparations considerably larger dosage of dopamine than of levarterenol was required to produce these positive inotropic and chronotropic effects. It is possible that dopamine may have useful clinical application; however, additional studies of the effects of dopamine on the peripheral circulation and the circulation of isolated organs, such as the kidney and lung, are indicated to evaluate further the possible clinical applications of this drug. Although the rate of dissipation of these two sympathomimetic amines may be different in the intact animal, the present studies suggest that the duration of effect of dopamine is significantly longer than levarterenol and that the rebound fall of cardiac output seen with levarterenol was not present with dopamine.

Summary

The cardiac effects of dopamine, an epinephrine precursor, were studied in 20 dog heart-lung preparations. In 8 uncontrolled rate preparations, dopamine, 0.5 to 1 mg., increased the heart rate an average of 18 per cent. In controlled rate preparations, dopamine, 100 to 500 μg., consistently increased ventricular contractile force, cardiac output and blood pressure; there was a consistent decrease of right and left atrial pressure. Comparable hemodynamic effects were produced by 1 to 5 μg. of levarterenol.
except that the effects of dopamine tended to be of longer duration and were less likely to be followed by cardiac depression. It is concluded that dopamine has significant positive inotropic and chronotropic effects in the dog heart-lung preparation.

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