Influence of L-Norepinephrine Upon Cardiac Output in Anesthetized Dogs

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It was the purpose of this investigation to test again the general conclusion that norepinephrine augments cardiac output during experimental hemorrhagic hypotension but has no such effect on normal animals or man. Results are presented which fail to support this differential action in normal and hypotensive dogs and an explanation is offered for failure of the drug to increase cardiac output in human subjects.

Numerous studies of the influence of norepinephrine upon the human circulation have failed to reveal any augmentation of cardiac output.1-7 In the intact dog, similar results have been reported,8,11 although cardiac output was assessed by indirect techniques in most of these experiments. When the circulation was depressed by hemorrhagic hypotension11,12 or by ether,13 however, norepinephrine was found to have a pronounced facilitatory influence. The present series of experiments was designed to test the hypothesis that norepinephrine improves cardiac output in the dog with a depressed circulatory system, but not in the more normal animal.

Methods

Nineteen experiments were conducted upon mongrel dogs varying in weight between 7.5 and 19.5 Kg. Each animal received a subcutaneous injection of morphine sulfate, 1.0 mg./Kg. body weight, followed in 30 min. by an intravenous injection of sodium pentobarbital, 180 mg./Kg. Mean arterial pressure was registered continually from a femoral artery by means of a damped mercury manometer. Cardiac output was estimated by means of the direct Fick technique. Mixed venous blood samples were obtained from the pulmonary artery through a cardiac catheter inserted under fluoroscopic guidance. The position of the catheter tip was verified at the termination of each experiment. The oxygen content of arterial and venous blood samples was determined by the method of Roughton and Schonander. The rate of oxygen consumption was measured with a Benedict-Roth spirometer which was connected directly to a tracheal cannula. Immediately after each arterial blood sample was drawn for analysis of the oxygen content, an additional sample was collected for the determination of the hematocrit ratio.

Two series of experiments were performed: (a), the effects of norepinephrine infusions during hemorrhage, and (b), the effects of such infusions in intact dogs.

Infusions during Hemorrhage

In eleven experiments, after all surgical preparations had been completed, heparin* was administered and samples were drawn, usually in duplicate, for the estimation of the control cardiac output. Hemorrhage was then begun from a peripheral artery and continued over a 20 min. period, during which a total quantity of 35 ml. blood/Kg. body weight was removed at a fairly uniform rate. This blood was then stored in the refrigerator. The animal was maintained in this state for a total of 1 hour after the termination of bleeding and samples for the estimation of cardiac output were withdrawn, usually in duplicate, halfway through this period. At the end of this interval, an additional 10 ml. blood/Kg. was removed over a 20 minute period, and added to the blood stored in the refrigerator. Thirty minutes later, another cardiac output measurement was made. Exactly 45 min. after cessation of the second hemorrhage, the blood, which had been rewarmed to body temperature, was reinfused rapidly by way of a peripheral vein. Thirty minutes after completion of the reinfusion, a final, recovery estimation of cardiac output was made.

In 6 of these 11 experiments, the animals were treated with an infusion of norepinephrine during the hemorrhage periods; in the remaining 5 experiments, which were conducted in an alternating sequence, no treatment was instituted during the

* Heparin supplied through the courtesy of Dr. W. R. Kirtley, The Lilly Research Laboratories.
periods of hypovolemia. The norepinephrine infusion was composed of 8 mg. L-norepinephrine bitartrate monohydrate (4 mg. L-norepinephrine base) dissolved in 1 L. of 5 percent glucose solution. A graduated cylinder served as the infusion flask, and was connected to a peripheral vein by means of rubber tubing. A special screw-type clamp was applied to this tubing so that the rate of flow could be adjusted very delicately. In those animals treated with norepinephrine, the control blood pressure of each animal served as the guide for the rate of infusion for that particular experiment. During the first hemorrhage period, as soon as mean arterial pressure commenced to fall, the clamp was released slightly and the infusion begun. Thereafter, the rate was adjusted at frequent intervals in order to maintain the blood pressure as close as possible to the control level throughout both hemorrhage periods. The volume of infusion remaining in the cylinder was recorded frequently in order to permit calculation of the rate of administration throughout each experiment. The infusion was terminated at the end of the second period, just prior to reinfusion of the blood.

**Infusions in Intact Dogs**

In eight experiments, dogs were anesthetized and prepared surgically as above. During a control period, mean arterial pressure and cardiac output were measured in exactly the same manner as in the preceding series. After the control data had been collected, an infusion of norepinephrine was begun in order to elevate the arterial pressure an arbitrary 50 mm. Hg above the control level for each experiment as rapidly as possible. The rate of infusion was then reduced and continued at a rate just sufficient to maintain this degree of hypertension. Between 10 and 15 min. after pressure had been stabilized at this level, samples were taken for the estimation of cardiac output. The rate of infusion was then accelerated again, until a level 100 mm. Hg above control was attained. The rate was then re-adjusted to maintain this degree of hypertension. After the arterial pressure had been stabilized at this new level for from 10 to 15 min., cardiac output was again measured. The norepinephrine infusion was then discontinued, and a final determination of output was made one-half hour later. Electrocardiograms were recorded periodically throughout all but 1 experiment.

**Results**

**Infusions During Hemorrhage**

Figure 1 portrays the mean data from the 11 experiments in this series. In the untreated animals (solid circles), the control mean arterial pressure (M.A.P.) averaged 103 mm. Hg and cardiac output (C.O.), 3.38 ± 0.75 (mean ± S.D.) L./min./M.² body surface. After withdrawal of 35 ml. blood/Kg., the pressure decreased to 85 mm. Hg, while cardiac output declined to 1.28 ± 0.30. Removal of an additional 10 ml./Kg. elicited a further drop in pressure to 70 mm. Hg, while output fell to 0.90 ± 0.43. One-half hour after reinfusion of the blood, the pressure had climbed to 116 mm. Hg, while the output had risen to 2.78 ± 0.26. The calculated total peripheral resistance (T.P.R.) increased markedly during the periods of hemorrhagic hypotension, and returned toward the control value after reinfusion of the blood.

The average control data for the series which were subsequently treated with norepinephrine (open circles) were virtually identical with those from the untreated group. The success with which blood pressure was maintained at close to control values by the norepinephrine

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1 The L-norepinephrine was generously supplied by the Sterling-Winthrop Research Institute in the form of 4 ml. ampuls of Levophed.
infusion during the hemorrhage periods is attested to by the fact that the mean pressure averaged only 3 mm. Hg above control during the first hemorrhage period, and 5 mm. Hg above control during the second stage. To maintain these pressure levels, a mean infusion rate of 2.5 (range, 1.1 to 3.2) µg. norepinephrine base/min./Kg. was administered during the first hemorrhage period, while a mean rate of 3.3 (range 0.65 to 6.2) µg./min./Kg. was necessary during the second period.

It is evident from figure 1 that cardiac output remained relatively unchanged when this degree of hemorrhage was combatted with norepinephrine infusions. From a control value of 3.41 ± 0.82 L./min./M.², the output was held at 3.33 ± 1.22 during the first stage of hemorrhage and fell slightly to 2.99 ± 0.88 during the second stage. Thirty minutes after cessation of norepinephrine and reinfusion of blood, the output of the heart was 3.04 ± 0.44, which is virtually identical with the preceding value.

The cardiac output data in this series are presented in more detail in figure 2, where the open and closed circles have the same significance as in the preceding illustration, but each circle represents an individual experiment. Fortuitously, the control data are virtually identical for the two groups of animals (p > 0.9). In each hemorrhage period, however, the treated and untreated animals fall into two distinct groups, and there can be no question that, for an equivalent degree of bleeding, the cardiac output is markedly greater in those animals treated with norepinephrine than in the untreated group (p < 0.01 in each stage). No significant difference is apparent between the two groups during the recovery period (0.3 < p < 0.4).

Since it appeared evident that norepinephrine was capable of maintaining cardiac output at approximately normal levels during periods of hemorrhage, it was considered worthwhile to determine the influence of infusions of norepinephrine upon cardiac output in the absence of hypovolemia.

**Infusion in Intact Dogs**

In this series of experiments, the mean value for the control blood pressure was 115 mm. Hg. During the first period of hypertension, the average arterial pressure was 165 mm. Hg, indicating the success of the attempt to stabilize blood pressure at 50 mm. Hg above the control level in each experiment. An average infusion rate of 1.4 (range, 0.6 to 2.8) µg. norepinephrine base/min./Kg. was necessary to accomplish this. The initial, accelerated rate of infusion employed to elicit the sudden rise in pressure at the beginning of this period was not included in computing this average infusion rate. During the second stage of hypertension, mean arterial pressure averaged 214 mm. Hg (99 mm. Hg above control) and this was accomplished by a mean infusion rate of 8.0 (range, 3.6 to 9.6) µg./min./Kg. During this period, cardiac arrhythmias (premature ventricular systoles and paroxysmal ventricular tachycardia) were especially prominent and one animal died in ventricular fibrillation before cardiac output could be measured. The arterial pressure fell below control levels after cessation of infusion and averaged 101 mm. Hg during the recovery period.
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Figure 3. Cardiac output, L./min./M.$^2$ (ordinate), in intact dogs during a control period, C; first phase of hypertension, 50; second phase of hypertension, 100; and recovery, R.

Figure 3 reveals the changes in cardiac output brought about by these infusions of norepinephrine. The control value in this series was $2.72 \pm 0.72$ L./min./M.$^2$. With sufficient norepinephrine to maintain mean pressure at a level 50 mm. Hg above control, the output was found to increase to $3.62 \pm 1.15$. When each value during this period was referred to its own control value, the increase in output in response to this rate of norepinephrine infusion was found to be statistically significant ($p = 0.05$). During the second stage of hypertension, in which mean pressure was elevated by approximately 100 mm. Hg, cardiac output increased still further to a value of $4.81 \pm 1.26$, which also is significantly above control ($p < 0.01$). The recovery value of output was $2.68 \pm 0.96$, which is virtually identical with the control level ($p > 0.9$).

In this series of experiments, the changes in cardiac output paralleled almost exactly the alterations in pressure. Thus T.P.R., which is simply the ratio of arterial pressure to cardiac output, remained virtually constant throughout each experiment. The average T.P.R., in mm. Hg/ml./min./M.$^2$ was 0.046, 0.051, 0.048 and 0.043 for the control period, +50 mm. Hg stage, +100 mm. Hg stage, and recovery period, respectively.

Discussion

The facilitatory influence of L-norepinephrine upon cardiac output in the intact animal as well as during hemorrhagic hypotension may be attributed to the pronounced effects of this agent upon myocardial contractility and venous return. It has been demonstrated that norepinephrine enhances the contractility of the isolated rabbit atrium$^{11}$ and the cat papillary muscle.$^{15,16}$ In the isolated perfused heart of the frog, rabbit, guinea pig, cat and dog, it improves the force and amplitude of ventricular contractions.$^{14,17,19}$ Racemic norepinephrine increases cardiac output by 12 to 27 per cent in the heart-lung preparation of the cat.$^{20}$ In addition, myocardiographic tracings reveal that norepinephrine increases the amplitude of ventricular contractions, despite an accompanying tachycardia, in the intact circulatory system of the dog under barbital anesthesia.$^{21}$ In addition to its influence upon the myocardium, norepinephrine also results in a shift of blood from the peripheral venous bed$^{22,23}$ and the spleen$^{24,25}$ toward the heart. It also reduces the mechanical impedance of the ventricular wall, thus facilitating ventricular filling.$^{26}$

The discrepancy between the effects upon cardiac output in the present study and those upon unanesthetized humans may be attributable to species differences or to the influence of anesthesia. However, it should be recognized that norepinephrine results in a more profound reflex bradycardia in conscious human subjects$^{1,2}$ than in dogs anesthetized with pentobarbital. It is plausible, therefore, that norepinephrine may tend to enhance cardiac output in man also, but that it is counteracted by the reflex bradycardia. In one experiment reported by Bayer, Blumberger and Effert,$^{3}$ norepinephrine diminished cardiac output under control conditions; after atropine, however, it had the reverse effect upon the minute volume of the heart.

The second major discrepancy between the present study and those upon human subjects
is the absence of any significant change in T.P.R. during infusions of norepinephrine in the dog, while pronounced increases are observed in man. These findings do not imply, however, that this humoral agent does not possess vasomotor activity in the dog. Indeed, studies too numerous to cite have demonstrated unequivocally that norepinephrine does increase vasomotor tone appreciably in a large variety of vascular beds in this species.

In the experiments depicted in figure 3, the increases in cardiac output were accompanied by proportionate changes in pressure with the consequence that T.P.R. remained virtually constant. In a previous study, it was demonstrated that, at arterial pressures above hypotensive levels, large changes in output occasioned only slight alterations in mean pressure when the moderator reflexes were intact. Therefore, in the present study, the enhancement of output induced by norepinephrine would undoubtedly have resulted in an appreciable reduction of T.P.R. if this agent had been devoid of vasomotor activity.

Finally, it must be emphasized that, although intravenous infusions do not alter the total systemic resistance appreciably, they may elicit profound modifications in the distribution of flow. The recent study by Frank and co-workers reveals clearly that, in hemorrhagic hypotension and shock, infusions of norepinephrine diminish flow through certain regions and improve it through other areas. It is vital to know, therefore, the alterations in distribution of flow, as well as the changes in total flow, in appraising the virtues of any compound acting upon the circulatory system.

Summary

In the intact dog anesthetized with sodium barbital, continuous infusions of norepinephrine, sufficient to elevate mean arterial pressure to levels of 50 and 100 mm Hg above control, produce proportionate changes in cardiac output. Under these conditions, no significant changes in total peripheral resistance are observed. If during severe hemorrhage mean arterial pressure is maintained at control levels by means of norepinephrine, then cardiac output does not decline appreciably. Under these conditions, only slight elevations of total peripheral resistance are obtained. Apparently, in the anesthetized dog, norepinephrine exerts a much more potent effect upon the output of the heart and a much more feeble influence upon calculated vascular resistance than it does in man.

Summario in Interlingua

In canes intacte, anesthesiate con natrium barbital, continue infusiones de norepinephrina—de grados sufficiente a elevar le pression arterial medie a nivellos de 50 a 50 mm Hg supra le valores de controlo—resulta in alteraciones proportional del rendimento cardiac. Sub iste conditions, nulle significative alteraciones del total resistentia peripheric es observate. Si durante sever hemorrhagias nor-epinephrina es usate pro mantenier le pression arterial medie al nivello de controlo, le rendimento cardiac non experientia un reduction appreciable. Sub iste conditions, solmente leve augmentos del total resistentia peripheric es obtenite. Il pare que in canes anesthesiate norepinephrina exerce un multo plus potente influentia super le rendimento cardiac e un multo minus potente influentia super le calculare resistentia vascular que in humanos.

REFERENCES

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