Comparison of the Circulatory Effects of Epinephrine and Norepinephrine

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A comparison was made of the circulatory effects of l-epinephrine and l-norepinephrine when various doses were given either intravenously or intra-arterially into anesthetized animals. No significant difference was found between the effects of identical doses of the two drugs on the arterial blood pressure, heart rate and blood flow. The intensity and duration of effect of either drug varied roughly with the dose given.

The literature on the circulatory effects of epinephrine and of norepinephrine reveals a variety of findings. In the presence of so many varied explanations concerning the circulatory effects of epinephrine and of norepinephrine, we decided to make a study of the influence of various concentrations of each of the two drugs on the heart rate and on the blood flow in the femoral arteries and veins and on the blood flow and blood pressure in the carotid artery of the anesthetized animal. In order to be able to separate as much as possible local effects from cardiac and systemic effects, the drugs were administered both intravenously and intra-arterially and the data on blood flow were correlated with those on the heart rate and arterial blood pressure.

Mertens and Kahlson, 1 Rein, 2 and Mertens and Rein 3 reported a decrease in the blood flow through the hind limb or resting muscle of anesthetized dogs upon intravenous administration of epinephrine, but Issekutz 4 obtained an increase. In anesthetized dogs, Rein and associates 5 observed a constrictor action of epinephrine and of "sympathetic impulses," if the muscle was at rest; but in the contracted or hyperemic muscle the injection of epinephrine or stimulation of the sympathetic nerves either was ineffective or brought about a dilator effect. Mertens and associates 6 and Rein and Schneider 7 demonstrated that epinephrine does not counteract the vasodilatation, and may even augment the already increased blood flow in active muscles.

In his plethysmographic studies on the skinned hind limbs of cats anesthetized with chloralose, McDowall 8 reported that the vessels of the muscles are tonically constricted by stimulation of fibers of the lumbar sympathetic nerves, in spite of the fact that they may be caused to dilate by injections of epinephrine or norepinephrine. By use of the venous occlusion plethysmograph, Allen and associates 9 obtained a fourfold to fivefold increase in blood flow in the human forearm during the first two minutes, when epinephrine was infused intravenously at the rate of 10 gammas per minute for 10 minutes. The changes in blood flow were much less conspicuous in the hand than in the forearm, indicating that the changes took place in the skeletal muscles. Konzett 10 found that in the dog isopropyl norepinephrine dilates the vessels of the limbs. Barcroft and Konzett 11 noted that infusions of norepinephrine at the rate of 3 gammas per minute caused a decrease in blood flow in the calf of the leg. Unlike epinephrine, norepinephrine has no transient vasodilator action in human skeletal muscle. In another communication, 12 they reported that norepinephrine infused intra-arterially caused vasoconstriction in the forearm and calf and reduced the blood flow, but intravenously there was no reduction in blood flow, while epinephrine caused a marked transitory vasodilatation, whether it was given intra-arterially or intravenously. They concluded that epinephrine caused transient vasodilatation in skeletal

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muscles while norepinephrine caused constriction of the vessels in skeletal muscle. Allen13 noted that epinephrine in doses of 1 mg, given intramuscularly induced active dilatation of the blood vessels of skeletal muscle in the human forearm. Grant and Pearson14 obtained an increase in limb volume and blood flow in the human forearm and leg. They reported that small doses of epinephrine regularly caused vasodilatation in human muscle. On the basis of intravenous administration of small doses in man, they concluded that epinephrine is a true vasodilator for muscle. However, Holling15 found that when epinephrine was infused intravenously the vasodilatation was only transient and passed off in a few minutes, although the infusion continued. Graham16 reported that in doses of 5 gammas per Kg. of body weight given intravenously, epinephrine produced a sharp vasoconstriction of the vessels of the cat's limb after slight passive dilatation.

By use of the cardiac catheterization technic in normotensive and hypertensive persons, Goldberg and associates17 found that epinephrine, by intravenous infusion in doses sufficient to cause significant hypertension, acted as an over-all vasodilator as well as a powerful cardiac stimulant. The primary action of norepinephrine was intense vasoconstriction. They noted that norepinephrine slows the human heart, diminishes the cardiac output and increases the peripheral resistance; its action in each case was opposite to that of epinephrine. Binet and Burstein18 reported that the reflex vasodilator effect of epinephrine on the peripheral vessels is associated with inhibition of the tone of the vasoconstrictors and augmentation of that of the vasodilators. Ranges and Bradley19 stated that the effect of epinephrine upon the vascular beds throughout the body varies from site to site; for instance, dilatation of the vessels of skeletal muscle and constriction of the arterioles of the skin and kidney.

In their plethysmographic studies of the effects of epinephrine on blood flow in the upper extremities of persons under basal conditions, Harpuder and associates20 reported that injection of epinephrine in doses of 1 to 2 gammas into the brachial artery produced vasoconstriction. Intra-arterial doses of 0.5 to 0.1 gamma apparently are ineffective. Doses of 0.05 to 0.0002 gamma introduced intra-arterially caused vasodilatation, sometimes followed by vasoconstriction. In their studies on the hind legs of anesthetized cats, Griffith and associates21-23 reported that the average effect of epinephrine injected intravenously at the rate of 0.004 mg. per Kg. of body weight per minute for five minutes was a 3 per cent increase in the blood flow, but either an increase or a decrease might occur. They stated that, as the rate of administration of epinephrine was increased, a balance between increasing degrees of local vasoconstriction and elevation of arterial pressure would explain the observed progressive decline in the augmentation of blood flow. When epinephrine was administered intra-arterially at the rate of 0.000,005 to 0.001 mg. per Kg. of body weight per minute for five minute periods, the changes in blood flow induced by the drug were explained on the basis of the prevailing evidence that minimally effective concentrations are: vasodilating and higher concentrations, constricting. Only the highest rates of injection invariably produced constriction. Puccinelli24 reported that upon injection of epinephrine into the femoral artery of the dog in minimal effective doses of 0.1 to 0.2 × 10^-6 Gm., there was reduction in blood flow from the muscles; however, Clark25 obtained dilatation followed by constriction of the vessels in the muscles of the cat when epinephrine was given intra-arterially in doses of about 0.05 × 10^-6 Gm. He considered the capillaries as the site of such action of epinephrine. In their studies on skinned and intact hind limbs of cats under chloralose-urethane anesthesia, Folkow and associates26 noted that in doses of 0.1, 1 and 2 gammas, epinephrine elicited a vasodilator response; higher doses, 3 and 5 gammas, caused predominantly vasoconstriction. Norepinephrine caused constriction of the blood vessels of both skin and muscle. They concluded that epinephrine in low concentrations dilates, whereas in high concentrations it constricts, the muscle vessels of the cat. In cats under chloralose anesthesia, Clark27 recorded venous outflow from muscle, skin or intestine. In some cases the leg was skinned to prevent all chances of anastomosis.
between skin and muscle. He obtained a two-fold response of muscle vessels to a single intrarterial injection of minute amounts of epinephrine; first, dilatation and then constriction, although at times only constriction resulted. By the use of a modified Ludwig stromuhr, Roome39 noted that the local effect of epinephrine upon the muscle blood vessels is, in all doses, dilatation of the capillaries and constriction of the arterioles, rather than a reversal of the capillary effect with increased concentrations.

By use of the Läwen-Trendelenburg perfusion method of assaying epinephrine, Trendelenburg29 obtained evidence that this drug in all dilutions causes vasoconstriction in the legs of the frog. Upon administration of epinephrine intravenously, Woods and associates39 obtained dilatation in the hind leg of the dog. They stated that epinephrine dilates muscle vessels. In their work on the perfused hind leg, Bulbring and Burn41 reported that epinephrine causes vasodilatation in the muscles of the dog, but the dilator fibers were cholinergic. They noted42 that in the dog's hind leg perfused with defibrinated blood, epinephrine caused vasoconstriction and this action was potentiated by prostigmine. From observations made by direct illumination of the sartorius muscle of the living cat, under the high-power objective of the microscope, Hartman and associates39 reported that epinephrine intravenously administered produced precapillary constriction and dilatation of the muscle capillaries. Direct application of epinephrine, in concentrations that could not be tolerated systemically, produced constriction of the capillaries. Erlanger and Gasser34 doubted the possibility of producing vasodilatation in skeletal muscles by epinephrine, and concluded that vasoconstriction of somatic and splanchnic areas is the main if not the only effect of continuous injection of epinephrine. They used extremely large doses, 6 to 11 cc. of a 1:1000 solution.

Gunning48 reported diminished circulation and vasoconstriction in the vessels of skeletal muscles upon administration of large doses of epinephrine. The preliminary increase in outflow, he stated, is due to the forcing out of blood present in the vascular spaces into the veins by vasoconstriction. He suggested that fatigue of the vascular musculature led to a maintained secondary dilatation. Gruber48 showed that, as in anesthetized animals, small doses of epinephrine injected intravenously into unanesthetized cats caused dilatation in the vessels of voluntary muscles as judged by increased venous outflow. He stated that vasodilatation is as much a characteristic action of epinephrine in weak solutions as vasoconstriction is in large doses. In their observations on the effects of epinephrine in the skinned limb, Hoskins and associates77 reported that under all conditions of dosage, duration of administration, and resultant effects on blood pressure epinephrine caused expansion of the skinned leg. They found that the volume of the leg with intact skin contracted, but when the skin was removed it expanded, under the influence of epinephrine. They concluded that the contraction of the intact leg is due to vasoconstriction in the skin, while the expansion in the skinned leg indicates that epinephrine causes vasodilatation in the muscle. Duncanson and associates48 injected norepinephrine intravenously at a rate of 2, 5, and 10 gammas per minute for five minutes in each instance. There was no change in blood flow of the forearm when a rate of 2 gammas per minute was used, but when the rate was 5 and 10 gammas per minute there was a slight reduction in flow when both systolic and diastolic pressures were raised.

Methods

Dogs weighing between 15 and 25 Kg. were used in this study. In order to determine if there is species difference in the reaction to epinephrine and norepinephrine, a number of observations were made on one monkey and one cat. Most of the animals were anesthetized with pentobarbital sodium given intravenously (25 mg. per Kg. of body weight), but a few were anesthetized with ether given by inhalation. To maintain an even level of anesthesia when pentobarbital sodium was used, a certain quantity of the drug was dissolved in the solution of heparin and was administered along with the heparin drip throughout the experiment. The blood pressure was recorded from the carotid artery by means of a mercury manometer writing on a kymograph. The heart rate was recorded electrocardiographically, and the blood flow by use of our modification of the Dumke and Schmidt39 bubble flowmeter. Both fem-
oral arteries were isolated; after heparinization of the animal, a bubble flowmeter was connected to each femoral artery. In some cases a bubble flowmeter also was connected to the femoral vein and another one to the carotid artery.

Heparinization was achieved in the following manner. Initially, 2 or 3 cc. of heparin sodium containing 1000 units per cc. was injected intravenously, and this was followed by the intravenous drip administration of 1 per cent heparin in saline solution throughout the experiment. With continuous heparinization and a maintained steady level of anesthesia, the blood flow and the blood pressure were maintained in a steady status and returned to control levels after every procedure throughout the period of study, which lasted as long as seven hours. The flowmeters were calibrated before they were connected to the blood vessels, and the volumes of flow were determined by the time required for a bubble of air to travel between two fixed points on the meter.

In some experiments, the effect of electric stimulation of the muscles of the extremity was investigated. For that purpose, special units containing the electrodes for stimulation were placed at the base of the thigh on both the femoral and the sciatic nerves of each leg.

The effects of varying doses of l-epinephrine bitartrate and of l-norepinephrine bitartrate on the peripheral circulation were studied after control blood flow, heart rate and blood pressure were established before each intra-arterial or intravenous injection. The dose varied from 0.01 to 10 gammas per Kg. of body weight.

To separate (1) the reaction to epinephrine and to norepinephrine of the blood vessels of the skin from (2) the reaction of the vessels of the muscles and to be able to determine to what extent the skin took part in the effect of these drugs, in a large number of experiments one limb was kept intact while the contralateral limb was skinned. The extremity was skinned by making a circular incision through the skin at the junction of the thigh with the trunk. The skin was carefully separated from the subcutaneous tissues of the whole extremity down to the insertion of the Achilles tendon. After the bleeding vessels had been carefully ligated, the skin was pulled back to its original position over the extremity. The distal edges of the skin were sutured in place to proximal edges along the circular incision. This procedure provided natural protection for the muscles and yet completely separated the skin from the rest of the tissues of the limb. In a number of instances a tourniquet was applied over the distal end of the tibia at the point where the skin was separated from underlying tissues. To eliminate the influence of vagal reflex effects on the heart rate and blood pressure, a number of experiments were performed in which epinephrine and norepinephrine were administered before and after bilateral cervical vagotomy.

**Results**

The intravenous administration of epinephrine or norepinephrine produced an immediate increase in blood flow concomitant with the increase in blood pressure. After this increase, the flow gradually returned, within four minutes, to the rate that had obtained before injection. Detailed data on the blood pressure or blood flow or both are presented in figures 1, 2, and 3. When either epinephrine or norepinephrine was injected intravenously in equivalent doses, the changes in blood pressure and in blood flow were practically indistinguishable. The repeatedly observed findings support the statement that intravenously administered epinephrine or norepinephrine in the dog produces a similar transient marked increase in blood flow accompanying the increase in blood pressure. Within four minutes, the values for blood flow returned to control levels. Sometimes, after the marked transient increase, there was a slight reduction in blood flow. The magnitude of these changes varied roughly according to dose, but the effects of epinephrine and of norepinephrine on the blood flow and blood pressure were so much alike that, for all practical purposes, they can be considered identical for exactly equal doses. The influence on the blood flow in the skinned limb of the dog was the same as that on the blood flow of the limb with intact skin. The contour of the blood flow curves for the skinned limb was similar to that of the curves for the intact limb, even though control values were not identical.

Accompanying the rise in blood pressure and the increase in blood flow was a reduction in heart rate after intravenous administration of either epinephrine or norepinephrine. The effects on the heart rate are presented graphically in figures 4 and 5. Immediately after intravenous injection in the intact animal, the arterial blood pressure increased (fig. 2) and was followed by reflex bradycardia (figs. 4 and 5). The magnitude of the increase in blood pressure was roughly proportional to the intravenous dose, no matter whether epinephrine or norepinephrine was injected. Occa-
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sionally, there was a slight initial increase in heart rate before the reflex bradycardia oc-
was used than when norepinephrine was used. These findings support the concept that the

curred, concomitant with the increase in arterial blood pressure. This initial transient tachycar-
dia occurred more frequently when epinephrine
marked increase in arterial blood pressure upon the intravenous injection of epinephrine or nor-
epinephrine, in the presence of intact vagus
nerves, reflexly brings about a slowing of the heart through the nervous mechanisms of the carotid sinus and aortic arch. In the absence of this reflex, consequent to severance of the vagus nerves, even though the increase in blood pressure is greater upon the intravenous injection of epinephrine or of norepinephrine, the direct action of either of these drugs on the heart is stimulatory.

After both vagus nerves were cut in the neck, the reflex bradycardia, after injection of either epinephrine or norepinephrine in doses of 2 or 5 gammas per Kg. of body weight, was replaced by tachycardia (figs. 4 and 5) even though the increase in blood pressure not only persisted but became slightly greater in magnitude than before vagotomy. However, 1 gamma of either drug per Kg. of body weight often produced slight bradycardia, even after vagotomy, in the anesthetized animal. This confirms the report of Tuohy and one of us (Essex) who found that even after vagotomy the heart showed evidence of vagus-like slowing when epinephrine was given intravenously. Occasionally in this group the injection of norepinephrine before and also after vagotomy produced a slightly greater pressor effect than did epinephrine. On the average, there was more often slightly greater tachycardia when norepinephrine was used after vagotomy and sometimes slightly greater bradycardia before vagotomy.

In a group of trained dogs the heart rate was recorded electrocardiographically immediately before and for 90 seconds after the intravenous injection of equivalent doses of epinephrine or norepinephrine (1 gamma per Kg. of body weight). In five of the 10 dogs the initial injection was epinephrine; to the other five, norepinephrine was given first. Both epinephrine and norepinephrine produced marked bradycardia in the trained animal. Figure 5 shows the control heart rates and the changes in heart rate produced 15, 30, 45, 60, 75 and 90 seconds respectively after injection of each drug. Bradycardia of varying magnitude under the influence of either drug is demonstrated. On the average norepinephrine produced a slightly greater degree of bradycardia than epinephrine, but both slowed the heart. These data demonstrate that both drugs produced bradycardia reflexly when given intravenously in the presence of intact vagus nerves. The bradycardia in the trained animal was much greater than when the animal was anesthetized. This is probably due to the depressive effect that barbiturate anesthesia has on the reflex mechanisms involved.

The intra-arterial administration of either epinephrine or norepinephrine (fig. 1) brought about either reduction or complete cessation of blood flow in the artery used for the injection, depending upon the magnitude of the dose. Very small doses usually produced transient slight reduction, but larger doses (fig. 1) produced complete cessation of blood flow in the artery for several minutes. Whenever the intra-arterial injection of either of the two drugs caused reduction but not complete cessation of blood flow in the injected artery, this was followed immediately by an increase in flow and in blood pressure as a result of the cardiac effect of the drug when it was carried back to the heart by the venous blood returning from the extremity used for the injection. Often, upon recovery of the circulation in the area supplied by the artery following the prolonged cessation of blood flow in that artery, there was a transient increase in the blood flow before the gradual return to preinjection levels. This

![Graph showing that simultaneous injection of 5 gammas of epinephrine per Kg. of body weight into both carotid and femoral arteries produced complete cessation of flow in the femoral artery for six minutes but only a reduction of flow in the carotid artery.](image-url)
FIGS. 4 and 5. The influence of intravenous epinephrine and norepinephrine on the heart rate before and after vagotomy. One may note the more marked bradycardia in the trained intact animal. One might be attributable to the metabolites which accumulated in the area during complete cessation of blood flow and which were washed out upon recovery of the ramifications of that artery from the vasoconstrictor effect of the drugs. This was confirmed by the increase in
blood flow which occurred upon release of the clamp from the artery which was mechanically occluded for a period equal in duration to that of cessation of flow induced by intra-arterial injection of either epinephrine or norepinephrine. From the data obtained on blood flow and their correlation with blood pressure, we find no indication of a vasodilator effect of either drug by any of the doses administered in this study.

The control blood flow in the electrically stimulated extremity was greater than that of the contralateral unstimulated limb. The administration of epinephrine or norepinephrine intra-arterially caused reduction or complete cessation of the blood flow but the duration of the cessation of flow was much shorter during stimulation of the extremity (fig. 6). Furthermore, recovery from vasoconstriction caused by epinephrine was hastened upon stimulation of the limb (fig. 6).

The findings obtained from the intravenous and intra-arterial injection of epinephrine or norepinephrine to one cat and one monkey were very similar to those herein reported on dogs.

In some experiments a bubble flowmeter was connected to the corresponding femoral vein in addition to the one on the femoral artery. Even during complete cessation of blood flow in the artery as a result of administration of epinephrine or norepinephrine intra-arterially, the flow in the vein was much reduced but was not completely arrested. This was attributed to the tributaries supplying blood to the vein outside the area of distribution of the artery under observation. This idea was substantiated by the fact that complete occlusion of the artery by a clamp did not produce complete cessation of blood flow in the vein but occlusion of the tributaries to the vein led to complete cessation of flow in the femoral vein.

A number of experiments were performed in which the blood flow was measured in the carotid artery. The administration into the carotid artery of the same dose of either epinephrine or norepinephrine which produced complete cessation of flow in the femoral artery would only produce moderate reduction in carotid blood flow when injected into the carotid artery (fig. 3). The mechanism of this phenomenon is under investigation.

A phenomenon which was repeatedly observed deserves comment. In most experiments, no matter whether the very first injection was epinephrine or norepinephrine its effect on the heart rate, blood pressure and blood flow was often slightly greater than the second and other consecutive injections even though the doses were identical. For instance, if epinephrine was given first, and, after its apparent effect had disappeared, an injection of norepinephrine in identical dose was given, the effect of epinephrine would be slightly greater even though the dose was identical to the norepinephrine which followed it. When this order was reversed, namely, if the first injection was norepinephrine, its effect would be slightly greater. One wonders whether this could be in part the basis for the reports that norepinephrine is slightly less effective than epinephrine in certain aspects, and epinephrine in other aspects. This observation suggested the advisability of alternating the injections of the various doses of either drug. One day the initial injection was made with epinephrine and on the second day the order was reversed starting with norepinephrine.

**Summary**

The circulatory effects of \( l \)-epinephrine bitartrate and of \( l \)-norepinephrine bitartrate were
studied in the heparinized dog under pentobarbital sodium or ether anesthesia. The former drugs were administered either intravenously or intra-arterially. The dose varied from 0.01 to 10 gamma per Kg. of body weight. The heart rate was recorded electrocardiographically; the blood pressure, by use of a mercury manometer connected to the carotid artery. The blood flow in the two femoral arteries and in addition sometimes in one femoral vein and one carotid artery was measured by use of bubble flowmeters. The simultaneous changes in blood pressure and blood flow produced by l-epinephrine were practically indistinguishable from those produced by l-norepinephrine. Administered intravenously, either of the drugs in equivalent doses produced an immediate increase in blood pressure of practically the same magnitude, and the occasionally resulting tachycardia was consistently followed by reflex bradycardia in the presence of intact vagus nerves during the peak of increased blood pressure. After bilateral cervical vagotomy there was a direct stimulatory effect on the heart of effective doses of either drug which resulted in an increase in heart rate. Immediately before the maximal increase in arterial blood pressure following the intravenous injection of either l-epinephrine or l-norepinephrine, there was a transient increase of several hundred per cent in blood flow accompanying the augmentation in the force of cardiac action and in cardiac output. This was attributed to the direct cardiac stimulatory effect of the drugs. Often, a moderate or very slight reduction in blood flow occurred before the return to the pre-injection level within about four minutes. Intra-arterial injection of l-epinephrine or l-norepinephrine brought about an immediate vasconstriction in the supplied area with reduction or cessation of blood flow in the skinned, as well as in the intact, limb. The degree and duration of the reduction or cessation of blood flow depended upon the dose. Very small intra-arterial doses caused slight and transient reduction in blood flow without significant effect on heart rate or arterial blood pressure. Larger doses caused a great reduction or complete cessation in blood flow in the arteries used for the injection. This was independent of the effects on the heart rate or arterial blood pressure.

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