# THE USE OF NOR-EPINEPHRINE(L-ARTERENOL) AS A PRESSOR DRUG WITH SPECIAL REFERENCE TO THORACO-LUMBAR SYMPATHECTOMY*

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THE FREQUENT EMPLOYMENT during the past decade of thoracolumbar sympathectomy in the treatment of essential hypertension has made surgeons and anesthetists aware of the value of a dependable pressor drug in addition to blood replacement during and after operation. While it is true that depressions of blood pressure during the first stage of sympathectomy may be so minor as to require no artificial support, the fluctuations in pressure observed during the second stage are often profound despite the administration of whole blood during the procedure. It is generally agreed by American surgeons that the maintenance of a constant mean level somewhat above normotensive levels during and for some hours after this operation contributes significantly to the safety of the patient and his smooth recovery. Although it is uncertain whether protection against myocardial infarction or even cerebrovascular accident during the period of surgical management can be assured, the occurrence of postoperative vasomotor collapse and occasional severe psychosis which may follow a period of hypotension can be avoided. As serious a sequela to postoperative hypotension as transverse myelitis is said to have occurred several times in the experience even of outstanding surgeons in this field. One cannot over-emphasize the desirability of sustaining arterial pressure above a mean of 80 mm. of mercury in order to maintain adequate renal, coronary and cerebral blood flow as well as to protect certain other vital functions, especially if a marked hypotension exists for a period greater than one hour.

In any discussion of pressor drugs in the surgical field it is important to emphasize that no drugs should be used to supplant or make unnecessary blood replacement. It appears, however, that in extensive sympathectomy, besides the factors of anesthesia and blood loss, the sudden augmentation of the vascular beds in the lower extremities and splanchnic areas contributes to a period of hypotension. Although the body can compensate in time by physiologic mechanisms such as the development of intrinsic vascular tone in the denervated areas, the intervening period of hypotension is one of potential danger.

Some surgeons in their distrust of pressor drugs rely on large quantities of whole blood for such support, even after operative blood loss has been replaced. Too often this extravagant method has fallen short, however. In addition, we have observed a number of patients with hypotension on the basis of bleeding peptic ulcer or traumatic hemorrhage. In some of these, vigorous and continued administration of blood has failed to allow maintenance of a safe mean blood pressure. The supplementary administration of nor-epinephrine in an infusion has served to add the necessary increment.[1]

The desirable qualities of a pressor drug to be employed during thoracolumbar sympathectomy and other hypotensive states are as follows:

1. Immediate action.
2. Short duration of action.

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3. Ease of administration and control.
4. Low toxicity.
5. Elevation of both systolic and diastolic pressures, without significant change in cardiac output.
6. Absence of coronary constriction.
7. Action arising from and mediated by normal physiologic mechanisms.

Some of the drugs employed at the Presbyterian Hospital have been Neosynephrine, Drinalfa and ephedrine. This paper is concerned with the characteristics and performance of a pressor agent called variously, nor-epinephrine, noradrenalin and levo-arterenol. It is now available for investigational use under the name "Levophen" (Winthrop).

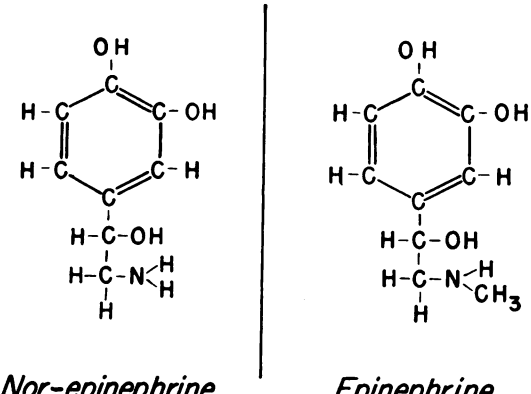


FIG. 1.—Chemical formulas for nor-epinephrine and epinephrine. (Reprinted from Am. J. Med., 5: 792, 1948.)

Nor-epinephrine is a primary amine identical in chemical formula to epinephrine except for the absence of a methyl group on the N atom (Fig. 1).[2] This drug was first synthesized by Stolz[3] in 1904, and has been found to be a normally occurring substance in the mammalian body. Nor-epinephrine has been extracted from post-ganglionic adrenergic nerves, the adrenal medulla and from pheochromocytomas of man.[4-6]

It is now believed that this substance is a possible precursor of epinephrine *in vivo*, since methylation occurs readily in the body. Although both epinephrine and nor-epinephrine are similar in structure and exist in the body, the action of the two drugs are quite different in regard to the cardiovascular system of man (Table I). From extensive studies, including cardiac catheterization on a number of normal and hypertensive patients receiving infusions containing epinephrine or nor-epinephrine, specific data has been reported to show that this difference in action is indeed significant (Table II).[7] From these data it is apparent that nor-epinephrine produces a slowing of the pulse, a rise in systolic and diastolic pressure, and a total increase of peripheral resistance without any significant effect on cardiac output in marked contradistinction to the effect of epinephrine. The use of pure samples of each drug as well as aliquot mixtures of the two consistently demonstrated these differences in action.

An interesting investigation by Goldenberg and co-workers[6] revealed by chromatography that varying but significant amounts of nor-epinephrine are present in standard commercial samples of extracted epinephrine as well as in human pheochromocytomas. The actual content of nor-epinephrine in the adrenal medulla appears to vary under different physiologic conditions. This substance is a transmitter of sympathetic nervous impulses and appears to be identical with sympathin E. The effect on the heart and metabolism is much less pronounced in man than that of epinephrine. It is important here to indicate that the difference in action of the two drugs varies according to the tissue studied and more important, according to the species of mammal studied. This variability made it difficult for some of the earlier investigators to recognize from work done on dogs and lower animals the true cardiovascular effects observed in man. A study in dogs of the effect of nor-epinephrine on blood flow in the coronary arteries by Dr. Rene Wegria revealed a significant and

prolonged increase to follow administration of a single small injection of nor-epinephrine.[8]

METHOD OF STUDY

It should be emphasized here that single injections of nor-epinephrine should never be used in the attempted control of arterial pressure. The duration of such administration lasts but a very few minutes and the resultant marked elevation of pressure which follows the single administration results only in a sharp spike of no distinct benefit. Indeed, we have observed the same thing to occur with single intermittent doses of neosynephrine, as will be demonstrated later.

The most suitable method of administration, consequently, is in a continuous infusion of normal saline or dextrose in water. The dosage can be adjusted instantly by regulating the number of drops per minute, and can similarly be controlled by the anesthetist during operation. We have found a dosage of from 2 to 4 mg. of nor-epinephrine in one liter of solution to be very suitable. It was found in titration experiments on normal and hypertensive unanesthetized resting patients of average weight, that a dose of from 0.1 to 0.3 micrograms per kilogram per minute resulted in an average rise of systolic pressure of from 22 to 40 mm. of mercury.[7] This is the same dosage which was found to be most useful during operation and appeared to produce a pressor effect of about the same magnitude. In the operating room the use of 2 mg. per liter permits greater control and flexibility of action.

Nor-epinephrine has been employed in a continuous infusion during 36 stages of thoracolumbar sympathectomy. These were performed in an unselected group of 21 patients. Nineteen of the operations were second stage sympathectomies. The sex incidence of this group was about equal, with all but one patient being in the fourth to sixth decade of life. The majority of the group had resection of the sympathetic chain as high as T-5 to T-7 with L-2 as the lower limit; in addition, all had complete splanchnicectomy.

The primary anesthetic agent was ether-oxygen in 30 of the operations, with Pentothal and nitrous oxide-oxygen employed in six. Induction was carried out with nitrous oxide-oxygen, Pentothal or cyclopropane. The latter anesthetic has not been used as the primary agent during operation because of the desire to avoid any possible type of cardiac arrhythmia or dysfunction observed[9-11] experimentally in dogs and cats under cyclopropane anesthesia and given single large intravenous doses of epinephrine and nor-epinephrine. However, since nor-epinephrine has a weaker effect on the

TABLE I.

*Changes of Certain Cardiovascular Functions During the Infusion of Epinephrine and Nor-Epinephrine* *

| Substance | Cardiac Output | Systemic Blood Pressure: Systolic | Systemic Blood Pressure: Diastolic | Systemic Blood Pressure: Mean | Total Peripheral Resistance | Pulse Rate | Mean Pulmonary Pressure |
|---|---|---|---|---|---|---|---|
| Epinephrine | +++ | +++ | ⊕ | + | −− | + | ++ |
| Nor-Epinephrine | ÷ | +++ | ++ | ++ | +++ | − | ++ |

* ⊕ is no change or slight increase; ÷ is no change or slight decrease.
Table I is reprinted from the Journal of the American Medical Association, 140: 776, 1949.

TABLE II

Case 1 J.S. Normal male 26 years b.s. 1.81 $m^2$

| Time in minutes | 0 | 14 | 34 | 55 | 76 | 93 |
|---|---|---|---|---|---|---|
| State and drug | Rest | Rest | Epinephrine | Rest | Nor-epinephrine | Epinephrine and Nor-epinephrine |
| Dose of drug mg/kg/min. | | | 0.15 | | 0.15 | 0.15 + 0.15 |
| Pulse rate/min. | 64 | 60 | 78 | 60 | 48 | 58 |
| Ventilation lits/min/$m^2$ | 2.9 | 3.1 | 4.1 | 2.7 | 3.0 | 3.6 |
| Oxygen consumption cc/min/$m^2$ | 144 | 145 | 176 | 142 | 143 | 168 |
| Oxygen arterio-venous difference cc/lit. | ·35 | 39 | 24 | 41 | 50 | 33 |
| Cardiac output lits/min. | 7.46 | 6.72 | 13.30 | 6.24 | 5.18 | 9.22 |
| Systemic blood pressure mm. Hg. | | | | | | |
| Systolic | 120 | 121 | 147 | 133 | 162 | 174 |
| Diastolic | 68 | 70 | 72 | 76 | 91 | 83 |
| Mean | 86 | 88 | 96 | 94 | 115 | 111 |
| Total peripheral resistance dynes cm -5 sec | 922 | 1030 | 577 | 1205 | 1785 | 960 |
| Mean pulmonary arterial pressure mm. Hg. | 14 | 14 | 22 | 14 | 19 | 25 |

TABLE II.—*Hemodynamic Changes Observed During the Successive Infusion of Epinephrine, Nor-epinephrine and a Combination of the two Substances. (Reprinted by permission from the American Journal of Medicine,* **5**: *792, 1948.)*

FIG. 2.—Effects of continuous infusion of nor-epinephrine on systemic blood pressure.

FIG. 3.—Effects of single doses of neosynephrine on systemic blood pressure.

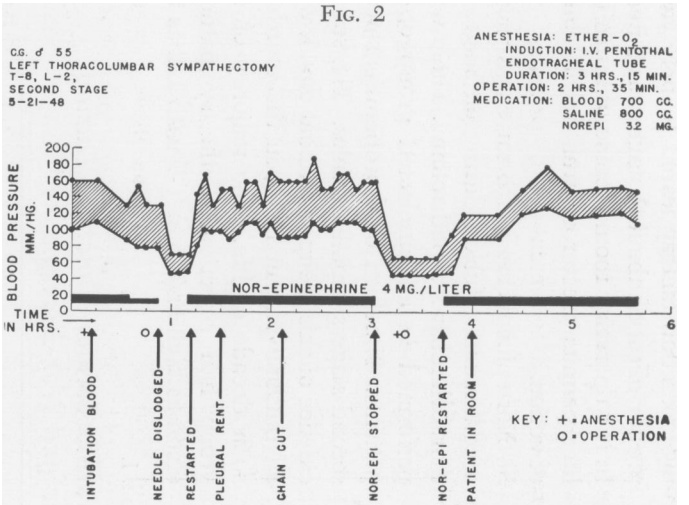


FIG. 2

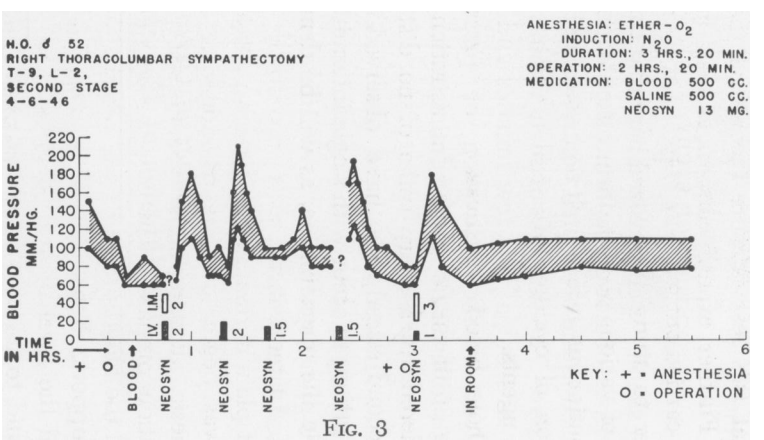


FIG. 3

heart in man than epinephrine and is used clinically by infusion in small doses, it may be that this fear is more theoretical than real. Further experiments on animals are being carried out with the help of Dr. E. M. Papper to study the effects of increasing doses of various pressor drugs administered by continuous infusion during the administration of cyclopropane and other anesthetic agents.

Whole blood transfusions were given during 30 of the 36 operations; it was not considered necessary in four first stage, and two second stage procedures. Ideally, administration of blood should be started early in the operation, especially in second stages. In most instances a separate infusion of plain normal saline or dextrose solution was begun at time of induction of anesthesia, allowing an immediate shift to a solution prepared with nor-epinephrine, should the blood pressure level require further support. It has thus been possible to control the level of arterial pressure carefully and to insure a stable cardiovascular status for the patient.

## RESULTS

The average dose employed in the first stage operations was 2.27 mg. with a range of 0.6 to 7.0 mg. being used. The average dosage employed in the second stage operations was 2.77 mg. with a range of 0.5 to 8.0 mg. The differential in dosage per stage per patient is not indicated adequately by these figures, as frequently two to three times the dosage employed during the first stage were needed in the second stage. The duration of the operation appeared to have no significant influence on the amount of drug required at any one time.

Since these patients were all severely hypertensive it was important to maintain their pressure after operation slightly above normotensive levels. At the end of operation, the nor-epinephrine infusion was stopped or interrupted in order to determine whether the blood pressure would stabilize at a satisfactory level. In only two patients following the first stage, was it necessary to continue the nor-epinephrine infusion postoperatively for seven to 24 hours respectively to maintain a pressure of 140/90 mm. of mercury. In eleven patients nor-epinephrine infusion was continued in the postoperative period following the second stage operation for from 11 to 96 hours, with an average of about 40 hours. These patients received whole blood as well. Stopping the nor-epinephrine during the early part of the postoperative period led to a dramatic fall in pressure to hypotensive levels. Later, when no significant change occurred from slowing the infusion, the administration of nor-epinephrine was stopped. Blood pressure was well controlled in all instances during and following operation, except one.

This failure was due to the sudden death of a severely hypertensive 32-year-old male near the completion of a second stage operation. Despite anesthetic difficulties, especially during the induction phase, pressure had been well maintained by whole blood and a slow administration of nor-epinephrine when he had an irreversible cardiac arrest. Cardiac massage, intracardiac procaine-epinephrine and intra-arterial transfusion were employed to no avail. No autopsy was performed, so we cannot be certain of the cause of death.

A minor complication followed displacement of an infusion needle from an ankle vein of a patient who required prolonged postoperative infusion of 4 mg. nor-epinephrine per liter in dextrose and water. A small ulcer of the skin developed near the area of extravasation. Since it is assumed that the nor-epinephrine might have contributed to this ulceration, one must guard against extravasation when employing large doses.

## DISCUSSION

It was of interest to us to attempt an

evaluation of this agent with the other pressor drugs employed during and following thoracolumbar sympathectomies. A review of 81 consecutive cases in which 156 operations were performed revealed the following facts. Of 81 first stage procedures, 40 per cent, or 33 operations, were performed without a pressor drug being used. Blood was given in 12 of these cases and albumin in one, however. Neosynephrine was used in 25 cases, nor-epinephrine in 17, ephedrine in three, Drinalfa in one, and a combination of agents in two. Of 75 second stage procedures, only 5 per cent, or four operations, were performed without a pressor drug being used. Neosynephrine was used in 42 cases, nor-epinephrine in 19, ephedrine in four, Drinalfa in four and a combination of agents in two.

A study of the response of blood pressure to administration of these drugs revealed them all to be satisfactory agents, with neosynephrine and nor-epinephrine being best insofar as over-all cardiovascular effects were concerned. The maintenance of a slow pulse rate and of a full pulse pressure with elevation of the diastolic pressure are outstanding features of both agents. Investigation of the additional effects on the cardiovascular system by neosynephrine have been reported and appear to correspond to those of nor-epinephrine.[12]

Analysis of cases in which intermittent single dosage was employed showed that neosynephrine and the other agents employed in this manner showed almost invariably a spiking type of blood pressure record. The smooth chart obtained with well-controlled continuous administration certainly is more desirable than the fluctuating chart seen frequently with the intermittent single dosage (Figs. 2 and 3). When the drugs were properly given as a continuous infusion there appeared to be no significant clinical difference between the pressor effects of neosynephrine and nor-epinephrine. The latter, however, is one of the naturally-occurring substances in the body and might exert its effect through more physiologic means.

The analysis presented here demonstrated to us that there appears to be a distinct place for suitable pressor drugs during and following thoracolumbar sympathectomy. It is most deplorable that too little has been written of the dangers of prolonged hypotension and of the other complications of thoracolumbar sympathectomy. Even the staunch advocates of this procedure must agree that adequate postoperative protection of these patients is necessary for this operation to enjoy any favor.

There are distinct times during administration of anesthesia and the performance of the operation when a patient may have a sudden drop in blood pressure. Among these the actual induction, intubation of the trachea, and placing of the patient in a lateral decubitus position are the danger points before the operation begins. It appeared that the use of sodium Pentothal or curare in this period produced hypotension more consistently. During the operative procedure, scraping the periosteum, tearing the pleura and manipulation and division of the splanchnic nerves and sympathetic chain may cause rather profound depressions of blood pressure. Since such drops are not observed consistently at any one single point, it is most important for there to be a close rapport between the surgeon and anesthetist during the operation. Smooth anesthetic management, adequate blood replacement and the proper use of pressor drugs appear to be desirable safeguards in the surgical management of a high-risk patient. The clinical use of nor-epinephrine during and following 36 stages of thoracolumbar sympathectomy has indicated it to be a very satisfactory pressor drug when employed in a continuous infusion.

SUMMARY

1. Proper use of a suitable pressor drug during and following thoracolumbar sympathectomy is urged to avoid the infrequent, but at times, serious sequelae of prolonged hypotension.

2. Such a drug, used as an adjunct to adequate blood replacement, should have ease of administration with rapid nontoxic action on the cardio-vascular system. A satisfactory agent should not constrict the coronary arteries or increase cardiac output, yet give a rise in both systolic and diastolic pressures.

3. Nor-epinephrine (Arterenol), a substance related in chemical structure to epinephrine, occurs naturally in the mammalian body as Sympathin E, and has an effect on the cardiovascular system of man quite different from epinephrine.

4. Employed during and following 36 stages of thoracolumbar sympathectomy in a continuous intravenous infusion with a dosage of from 0.1 to 0.3 micrograms per kilogram body weight per minute, nor-epinephrine exhibited all the actions of a very satisfactory pressor drug.

5. Cyclopropane has been avoided because of the possibility of cardiac arrhythmia occurring when used with nor-epinephrine. Experimental studies are being continued to clarify this further.

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