The Action of Norepinephrine, Epinephrine and Isopropyl Norepinephrine on the Rhythmic Function of the Heart

By Morris H. Nathanson, M.D., and Harold Miller, M.D.

The actions of norepinephrine and isopropyl norepinephrine on the rhythmic property of the heart were studied and compared with that of epinephrine. Norepinephrine does not abolish cardiac standstill by carotid sinus stimulation, has no effect on the ventricular rate of heart block and induces a sinus bradycardia. Isopropyl norepinephrine acts similarly to epinephrine in that it abolishes the induced cardiac standstill, increases the ventricular rate of heart block and produces a sinus tachycardia. In the treatment of cardiac arrest, the isopropyl compound appears to possess optimum features as it is very potent in the prevention of cardiac standstill and does not predispose to ventricular fibrillation.

The property of rhythmicity or automaticity, the pacemaking function of the heart, is essential to normal cardiac activity. If a pacemaking mechanism is absent, cardiac or ventricular arrest follows in a heart which may be completely competent in its contractile function. In a previous report utilizing the cardiac standstill induced by stimulation of the carotid sinus in man, it was shown that epinephrine and related compounds were the only substances which increased cardiac rhythmicity. Recently two relatively new epinephrine-like compounds have received considerable attention. They are norepinephrine and isopropyl norepinephrine (Isuprel). Norepinephrine differs from epinephrine in the absence of a methyl group on the terminal nitrogen of the side chain and Isuprel has an isopropyl group substituted for the methyl group of epinephrine.

The recent studies on norepinephrine are an important development in the study of the chemistry and physiology of the sympathetic nervous system. It is now known that the adrenal medulla secretes considerable amounts of the nonmethylated compound. There is also considerable evidence that norepinephrine is an important chemical transmitter of sympathetic nerve impulses. Isopropyl norepinephrine (Isuprel) has recently been introduced as a substitute for epinephrine in the treatment of asthma. This compound differs from norepinephrine and epinephrine chiefly in its vascular effect, producing a vasodilatation and a depressor reaction. In the present study, the action of norepinephrine and isopropyl norepinephrine was observed in (a) patients in whom carotid sinus pressure induced cardiac standstill, (b) patients with complete heart block, and (c) patients with sinus rhythm. The effects of these sympathomimetic compounds were compared with those produced by epinephrine.

Action on Induced Cardiac Standstill

Norepinephrine was administered to six patients with a hyperactive carotid sinus cardio-inhibitory reflex. Levo-norepinephrine hydrochloride was used in all cases. The procedure was as follows: an electrocardiogram was first made to record the induced cardiac standstill. A blood pressure reading was also made at this time. Levo-norepinephrine hydrochloride, 0.03 mg., was then administered rapidly by intravenous injection and blood pressures recorded and electrocardiograms made with carotid sinus compression at one-minute intervals. Following the administration of the drug, there was an abrupt rise in blood pressure which ranged from an increase of 30 mm. systolic and 10...
mm. diastolic to 100 mm. systolic and 30 mm. diastolic. The duration of the pressor effect varied from five to eight minutes. Pressure on the carotid sinus consistently reproduced the standstill following the administration of the norepinephrine.

In a previous study, it was shown that Isuprel in doses of 0.14 to 0.2 mg. subcutaneously consistently abolished the cardiac standstill which could be induced by carotid sinus pressure. It was considerably more potent than epinephrine in this respect. In the present study, Isuprel was administered intravenously to six patients in whom cardiac standstill could be induced. The dose was 0.02 mg. After the administration of the drug, the standstill was prevented in each instance. Isuprel consistently produced a drop in diastolic pressure but systolic pressure was not significantly modified.

When compared with the action of epinephrine on the carotid sinus standstill as observed in previous studies Isuprel showed the following differences: (a) Isuprel did not produce a pressor effect, (b) Isuprel was more potent in its action, and (c) it prevented the standstill by restoring the activity of the sinus node or by initiating rhythmic foci in the auricles or high in the ventricles. Epinephrine more frequently abolished the standstill by stimulating lower ventricular foci.

**Action of Norepinephrine, Epinephrine and Isopropyl Norepinephrine on the Ventricular Rate of Heart Block**

**Effects of Intravenous Administration of the Three Substances**

The effect of an intravenous injection of the three compounds was studied in eight patients with complete heart block. Levo-norepinephrine and synthetic levo-epinephrine were administered in doses of 0.03 mg. by rapid injection and the dose of Isuprel was 0.02 mg. The smaller dose of Isuprel was used because, in an earlier study, the activity of Isuprel appeared to be greater than that of epinephrine. The procedure was as follows: A control electrocardiogram was made and the blood pressure recorded. The compound was then injected and a continuous electrocardiogram made. The blood pressure was recorded at 30 seconds and thereafter at one-minute intervals. The observations were followed for several minutes after the ventricular rate had returned to the preinjection level.

Following the administration of norepinephrine, there was only a slight and very transitory increase in the ventricular rate. There was a return to the preinjection rate usually within one minute. In contrast, there was a definite and sustained rise in the ventricular rate after the injection of epinephrine. Isuprel also induced a sustained increase in the ventricular rate, which, considering the smaller dose employed, was comparable to that produced by epinephrine. Typical responses of the blood pressure and ventricular rate to these compounds are shown in figure 1. In table 1 is shown the maximum increase in the ventricular rate following the administration of the three compounds. The superiority of epinephrine and Isuprel is considerably greater than is shown in this table, since, as has been mentioned, the ventricular stimulation following norepinephrine was of very brief duration.

In addition to the quantitative variations of ventricular rhythmicity, the drugs appeared to differ in the localization of their effects.
AN ACTION OF COMPOUNDS ON RHYTHMIC FUNCTION OF HEART

TABLE 1.—Maximum Increase in the Ventricular Rate (Beats per Minute) in Eight Patients with Complete Heart Block Following the Intravenous Administration of the Three Compounds

<table>
<thead>
<tr>
<th>Case</th>
<th>Norepinephrine</th>
<th>Epinephrine</th>
<th>Isopropyl Norepinephrine</th>
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<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>22</td>
<td>16</td>
</tr>
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</table>

Although norepinephrine showed only a slight and transient action on the basic ventricular pacemaker, it did cause transient excitation of lower ventricular foci resulting in multifocal ectopic beats (fig. 2). This effect was usually observed in the first minute after the administration of the drug. In contrast, the stimulating action of Isuprel was predominantly on the basic pacemaker. Epinephrine also induced ectopic ventricular beats in the early phase of its action. The following observations in a patient with complete heart block suggest that a drug which activates ectopic ventricular foci may produce the serious arrhythmia, ventricular fibrillation.

The patient was a woman, 84 years of age, who entered the hospital because of attacks of syncope and convulsions of two days duration. She was known to have had hypertension for many years and the blood pressure on admission was 240/90. The heart rate was noted to be 40 beats per minute and the electrocardiogram showed complete auriculoventricular block (fig. 3, strip 1). During the first minute after an intravenous administration of 0.03 mg. of epinephrine, many multifocal ventricular premature beats were present (fig. 3, strip 2). On another occasion, the patient received 0.03 mg. of norepinephrine intravenously. Within one minute the electrocardiogram showed a ventricular tachycardia (fig. 3, strip 3), and this passed into a definite ventricular fibrillation (fig. 3, strip 4). The duration of the arrhythmia was about four minutes, when the electrocardiogram again showed complete heart block. On the following day, the patient received 0.02 mg. of Isuprel by vein, which resulted in a definite increase in the ventricular rate arising from a single pacemaker high in the ventricles (fig. 3, strip 5). There was no indication of excitation of lower ventricular centers after the latter.

Effects of Subcutaneous Administration of Epinephrine and Isuprel

Since the usual mode of drug administration in heart block is by subcutaneous injection, the effect of Isuprel, given by this route, on the ventricular rate of five patients with heart

Fig. 2. The induction of multiple ectopic ventricular beats by norepinephrine in a patient with complete heart block.

Fig. 3. Strip 1 is the electrocardiogram of a patient with complete heart block, ventricular rate 40. Strip 2 shows multiple ectopic ventricular beats during the first minute after an intravenous injection of 0.03 mg. of epinephrine. Strips 3 and 4 show the development of transient ventricular fibrillation following an intravenous dose of 0.03 mg. of norepinephrine. Strip 5 shows a ventricular rhythm from a single focus, rate 60, after an intravenous injection of 0.02 mg. of Isuprel. Isuprel induced no ectopic beats.
block was studied. In three patients a comparison was made of the effects of epinephrine and Isuprel. Since our observations on carotid sinus standstill indicated that Isuprel was considerably more active than epinephrine, the dose of Isuprel used was 0.2 mg. and the response compared with that following the administration of 1 mg. of epinephrine. The procedure was as follows: after a control electrocardiogram was made, the drug was administered and electrocardiogram was then made at five-minute intervals for 15 minutes and thereafter at 15-minute intervals. Table 2 shows the results of these experiments. Following the subcutaneous injection of 0.2 mg. of Isuprel, there was a definite and sustained increase in the ventricular rate in each instance. In the three patients in whom both drugs were used, the smaller dose of Isuprel produced a greater effect than the larger dose of epinephrine.

Effect of the Sublingual Administration of Isuprel

The effect of the sublingual administration of Isuprel was observed in four patients with complete heart block. The drug was given to each patient in a 15 mg. dose on one occasion and in a 30 mg. dose at another time. After a control electrocardiogram was made and the drug administered, electrocardiograms were recorded at five-minute intervals for from one to two hours. In two patients, the response to both doses was slight but well sustained (table 3, patients 2 and 4). In two patients, there was a definite sustained increase in the ventricular rate (table 3, patients 1 and 3). The onset of the effect was from 15 to 30 minutes after the administration of the drug and the duration varied from 45 minutes to two hours. The 30 mg. dose produced only a slightly more intense action than did the smaller dose; however, the effect of the larger dose was more sustained. In three of the four patients, a comparison was made of the effects of intravenous and sublingual administration. In two patients, an intravenous dose of 0.02 mg. resulted in a more intense response than that induced by 30 mg. given sublingually. In one patient, the increase in ventricular rate resulting from 30 mg. sublingually was greater than that which followed an intravenous dose of 0.01 mg. The duration of the action following intravenous administration varied from 10 to 15 minutes while the effect lasted up to two hours after the sublingual application of the drug.

Table 2.—Effect of the Subcutaneous Administration of Epinephrine and Isuprel on the Ventricular Rate (Beats per Minute) in Complete Heart Block

<table>
<thead>
<tr>
<th>Patient</th>
<th>Epi. 1 mg.</th>
<th>Isup. 0.2 mg.</th>
<th>Epi. 1 mg.</th>
<th>Isup. 0.2 mg.</th>
<th>Epi. 1 mg.</th>
<th>Isup. 0.2 mg.</th>
<th>Epi. 1 mg.</th>
<th>Isup. 0.2 mg.</th>
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<tbody>
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<td>54</td>
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<td>50</td>
</tr>
</tbody>
</table>

Table 3.—The Effect of the Sublingual Administration of Isuprel on the Ventricular Rate (Beats per Minute) of Four Patients with Complete Heart Block

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose</th>
<th>Maximum Increase in Ventricular Rate</th>
<th>Duration of Increase in Ventricular Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15 mg.</td>
<td>32</td>
<td>45 min.</td>
</tr>
<tr>
<td>2</td>
<td>30 mg.</td>
<td>47</td>
<td>1½ hrs.</td>
</tr>
<tr>
<td>3</td>
<td>15 mg.</td>
<td>5</td>
<td>1 hr.</td>
</tr>
<tr>
<td>4</td>
<td>30 mg.</td>
<td>17</td>
<td>1½ hrs.</td>
</tr>
<tr>
<td>5</td>
<td>15 mg.</td>
<td>19</td>
<td>2 hrs.</td>
</tr>
<tr>
<td>6</td>
<td>30 mg.</td>
<td>3</td>
<td>1 hr.</td>
</tr>
<tr>
<td>7</td>
<td>30 mg.</td>
<td>4</td>
<td>1 hr.</td>
</tr>
</tbody>
</table>

Action of Norepinephrine, Epinephrine and Isopropyl Norepinephrine on Heart Rate in Normal Sinus Rhythm

The effect of the three compounds was studied in eight patients with sinus rhythm. After a control electrocardiogram was made and the blood pressure recorded, the drug was
administered intravenously and a continuous electrocardiogram was made. The dose of norepinephrine and epinephrine was 0.03 mg and that of Isuprel, 0.02 mg. Blood pressures were recorded at 30 seconds and thereafter at intervals of one minute. Following norepinephrine, there was a transient increase in rate of from 4 to 10 beats per minute, for a period of one minute or less. Following this reaction, there was either a drop in rate to the preinjection level or to a level 2 to 10 beats per minute below the preinjection rate. Following epinephrine, there was a moderate increase in rate of 8 and 16 beats per minute in two patients, the reaction subsiding in one minute. In six patients, epinephrine produced a greater increase in rate of from 26 to 67 beats per minute, the tachycardia subsiding usually within two minutes. However, in three patients a rise in rate of from 15 to 30 beats per minute persisted for 10 minutes. The increase in rate following Isuprel was comparable to that induced by epinephrine but was of longer duration. The maximum increase in rate varied from 25 to 62 beats per minute. The period of tachycardia was five minutes in two instances and the duration was 15 minutes or longer in six patients (fig. 4). The blood pressure responses were similar to those observed in the experiments in heart block.

**DISCUSSION**

The present studies show by several methods that norepinephrine does not have any sustained action on the rhythmic property of the human heart. Isopropyl norepinephrine, although a drug without pressor action, is very potent in its effect on cardiac rhythmicity and appears to act predominantly on higher centers and nodal tissues. Norepinephrine exhibits a transient activation of lower ventricular foci, while epinephrine stimulates both the higher and lower rhythmic centers. The recent studies of Greiner and Garb further indicate that Isuprel is less disposed to produce ectopic rhythms. These observers found that the three compounds increased irritability (lowered the irritability threshold) of heart muscle. Following the application of norepinephrine and epinephrine, automatic rhythm supervened at levels at which the increase in irritability was slight. Isuprel, while affecting a far greater lowering of the irritability threshold, did not produce a corresponding effect on automaticity.

The introduction of a new sympathomimetic compound requires an evaluation of its place in practical therapy and particularly an estimation of its activity as compared with that of epinephrine. In cardiac therapy, the application of the sympathomimetic compounds has been limited almost entirely to the therapy and prevention of cardiac arrest, especially that associated with heart block. The present studies show that norepinephrine has little or no action on the basic ventricular pacemaker and thus would be of no value in the prevention of cardiac standstill. From another standpoint, it is probable that there is a definite danger in the administration of this compound to patients who are susceptible to sudden cessation of cardiac activity. It has generally been supposed that the chief mechanism for the Adams-Stokes syndrome is ventricular standstill. However, it has become increasingly evident that varying degrees of ventricular acceleration and ventricular fibrillation are frequently the basis for this syndrome. Recently
Garb and Chenoweth produced ventricular fibrillation consistently in cats during hydrocarbon inhalation by the administration of norepinephrine and epinephrine while Isuprel did not induce this serious arrhythmia under the same conditions. It is frequently difficult to determine which mechanism, ventricular standstill or fibrillation, is the basis for a sudden cessation of effective cardiac action. If transient ventricular fibrillation is the mechanism, the administration of norepinephrine or epinephrine would tend to perpetuate this arrhythmia, with a possible fatal termination. It is of interest that in the patient described earlier, who was susceptible to the development of ectopic ventricular beats and ventricular fibrillation, Isuprel stimulated only a single rhythmic focus in the ventricles. It would appear that Isuprel possesses optimum features for the prevention and therapy of sudden cessation of cardiac function, in that it is potent in the treatment of cardiac standstill and yet does not dispose to ventricular fibrillation.

There appears to be a difference in the relative potencies of Isuprel and epinephrine, depending on the mode of administration. By the subcutaneous route, on the carotid sinus standstill and on the ventricular rate of heart block, Isuprel is about five times more active than epinephrine. By intravenous administration, Isuprel does not show this degree of superiority. In part, the greater effectiveness by the subcutaneous route may be due to the fact that Isuprel possesses a local vasodilating action in contrast to the vasoconstrictor effect of epinephrine, and thus a more favorable absorption of Isuprel is to be anticipated. For the prevention of cardiac standstill in heart block, drugs are usually administered by the subcutaneous route. The present studies indicate that a dose of from 0.14 mg. to 0.2 mg. of Isuprel will effectively increase the activity of the ventricular pacemaker and thus lessen the tendency to ventricular standstill.

The activity of Isuprel by the sublingual route is of interest in the therapy of conditions in which cardiac standstill may occur, the hyperactive carotid sinus reflex and complete heart block. When attacks are frequent, the patient is usually under observation in a hospital and the drug may be administered by the subcutaneous route. However, in the treatment of patients who are having infrequent attacks and who are ambulant, a drug which can be self administered is desirable. The orally active sympathomimetic compounds, Paredrine and ephedrine may be effective in such instances. The sublingual administration of Isuprel is an addition to the therapy of these conditions by self medication. Our studies indicate that the ventricular rate may be increased by a sublingual dose of 15 mg. of Isuprel. It is suggested that this dose be used three or four times a day or every two hours if indicated.

Conclusions

1. The effects of norepinephrine, epinephrine and isopropyl norepinephrine (Isuprel) on cardiac rhythmicity have been studied by the following methods, (a) the action on cardiac standstill induced by carotid sinus pressure, (b) the response of the ventricular rate of heart block, and (c) the effect on sinus rhythm.

2. As compared with epinephrine and Isuprel, norepinephrine, a potent pressor compound, shows little or no effect on cardiac rhythmicity.

3. Isuprel, having little or no pressor action, produces a potent and sustained increase in rhythmic function.

4. Norepinephrine is of no value in the therapy of cardiac arrest. There may be a definite hazard in the use of this drug in cardiac and vascular conditions because of its disposition to produce ventricular fibrillation.

5. Isuprel appears to possess optimum features for the prevention and therapy of sudden inactivity of the heart in that the drug is very effective in cardiac standstill and yet it does not seem to dispose to ventricular fibrillation.

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