# THE CARDIO-CIRCULATORY EFFECTS IN MAN OF SYNEPHRIN TARTRATE

(dl-α-hydroxy-β-methylamino-4-hydroxy-ethylbenzene hydrochloride) [1]

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Synephrin tartrate [2] differs from epinephrine in the absence of the OH group in the meta position on the benzene ring, and therefore has the same general formula as that of neo-synephrin.

The reports on the pharmacological action of synephrin tartrate in animals stress the qualitative similarity to epinephrine (1, 3, 4, 6, 7). Kuschinsky found, in anesthetized animals, that the cardiac augmentor effect of synephrin tartrate is relatively greater than the vasoconstrictor action and that the lethal dose/therapeutic dose ratio was relatively greater compared to epinephrine. The same author showed that synephrin tartrate dilates the coronary vessels markedly. Synephrin tartrate is used to some extent in Germany instead of epinephrine for clinical purposes but it has not been adopted elsewhere, chiefly because of its low potency and the paucity of information as to its effect in man.

## MATERIALS AND METHODS

The present paper is a report on results obtained with 22 normal subjects, from 18 to 40 years of age, all of whom were studied at several different dosage levels and were also tested with epinephrine and with neo-synephrin. The methods were identical with those used in our study of neo-synephrin (5). As in the previous study, the same requirements for basal state and controlled environmental conditions were maintained.

### *Threshold for subcutaneous injection*

The concentration of the drug in solution was 10 per cent; with all dosages larger than 100 mgm., the dosage was divided and administered in several injections in widely separated locations, so that the volume of a single injection never exceeded 1 cc.

Under the basal conditions the threshold effect of synephrin tartrate was a rise of 5 to 10 mm. in systolic blood pressure with no significant change in diastolic pressure or in pulse rate. In different normal adults of average body size this threshold effect was obtained with a dosage of 90 to 115 mgm. given subcutaneously, corresponding to from 55 to 70 mgm. per square meter of body surface or from 1.4 to 1.8 mgm. per kgm. body weight. The maximum effect is obtained in from 10 to 30 minutes after subcutaneous injection.

### *Blood pressure and pulse rate*

In all our subjects the subcutaneous injection of more than 100 mgm. of synephrin tartrate always resulted in well-marked effects on systolic blood pressure, with small and somewhat variable effects on diastolic pressure and pulse rate. In 6 experiments with 200 mgm. given subcutaneously, the average blood pressure changed from 103/67 to 126/62, while the average pulse rate fell from 69.7 to 64.7; in 14 experiments with 400 mgm., the average blood pressure changed from 111/64 to 147/63, while the average pulse rate fell from 67.1 to 64.4.

The effect of subcutaneous injection of synephrin tartrate is relatively prolonged, considerably more so than with epinephrine. A well-marked effect is maintained for close to an hour and a slight effect may persist for 2 hours. A typical example is given in Figure 1.

### *Intravenous administration*

Intravenous injection of 20 mgm. synephrin tartrate in the space of 30 seconds always produces a sharp rise in systolic pressure followed by a fall in pulse rate. The typical result of more prolonged intravenous injection of larger amounts of syneph-

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[2] Also known as "sympatol," "para" or "*p*-sympatol" and as para synephrin.

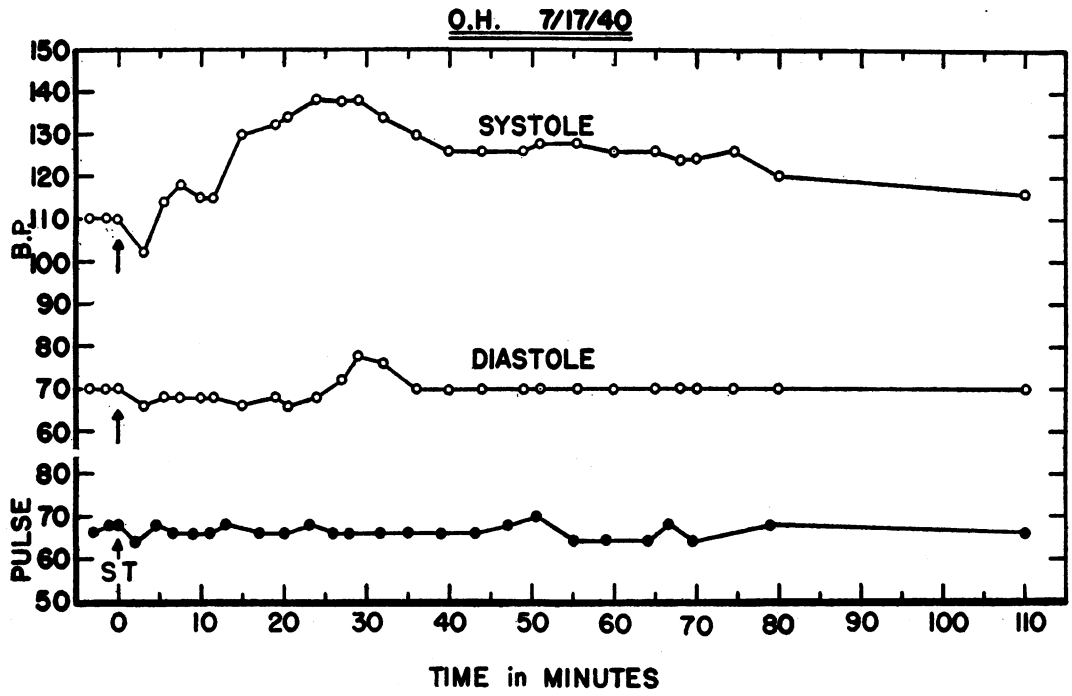


FIG. 1. BLOOD PRESSURE AND PULSE RATE FOLLOWING SUBCUTANEOUS INJECTION OF 400 MGM. SYNEPHRIN TARTRATE IN 4 CC. (TWO SITES)
O. H., normal young man.

rin tartrate is shown in Figure 2. The irregularities and marked bradycardia are in sharp contrast with the results of subcutaneous injection.

### *The electrocardiogram*

In general, synephrin tartrate in dosages up to 400 mgm. subcutaneously has no effect whatever on the electrocardiogram. In 2 instances, inversion of $P_2$ was produced with 400 mgm. An example of this is shown in Figure 3. In this subject, $P_3$ was also very slightly inverted. In contrast with epinephrine, ectopic and premature beats do not appear. Orth, *et al.* (8) noted that in dogs under cyclopropane anesthesia epinephrine produces multifocal ventricular tachycardia but that synephrin tartrate does not have such an effect in comparable (pressor) doses.

### *Circulation time*

The circulation time (arm-to-tongue) is almost invariably shortened by synephrin tartrate in dosages of 200 to 400 mgm. given subcutaneously. The greatest reduction in circulation time tends to appear somewhat later than the maximum pressor response. Typical results are given in Table I.

### *Heart size and output*

The results of measurements of heart size and output by the roentgenkymographic method are shown in Table II. The stroke output of the heart is generally increased, sometimes very markedly, and the net effect of slight reduction in pulse rate and this increase in stroke is usually to produce an augmentation of the minute volume of the heart.

Measurements of the stroke output and minute volume of the heart by the acetylene method are in general agreement with the roentgenkymographic measurements but the increases produced by synephrin tartrate tend to be larger in the acetylene experiments. The explanation for this apparent quantitative discrepancy is to be found in the effect of posture (*cf.* the preceding paper). The effects of synephrin tartrate in the semi-recumbent position are illustrated in Table III.

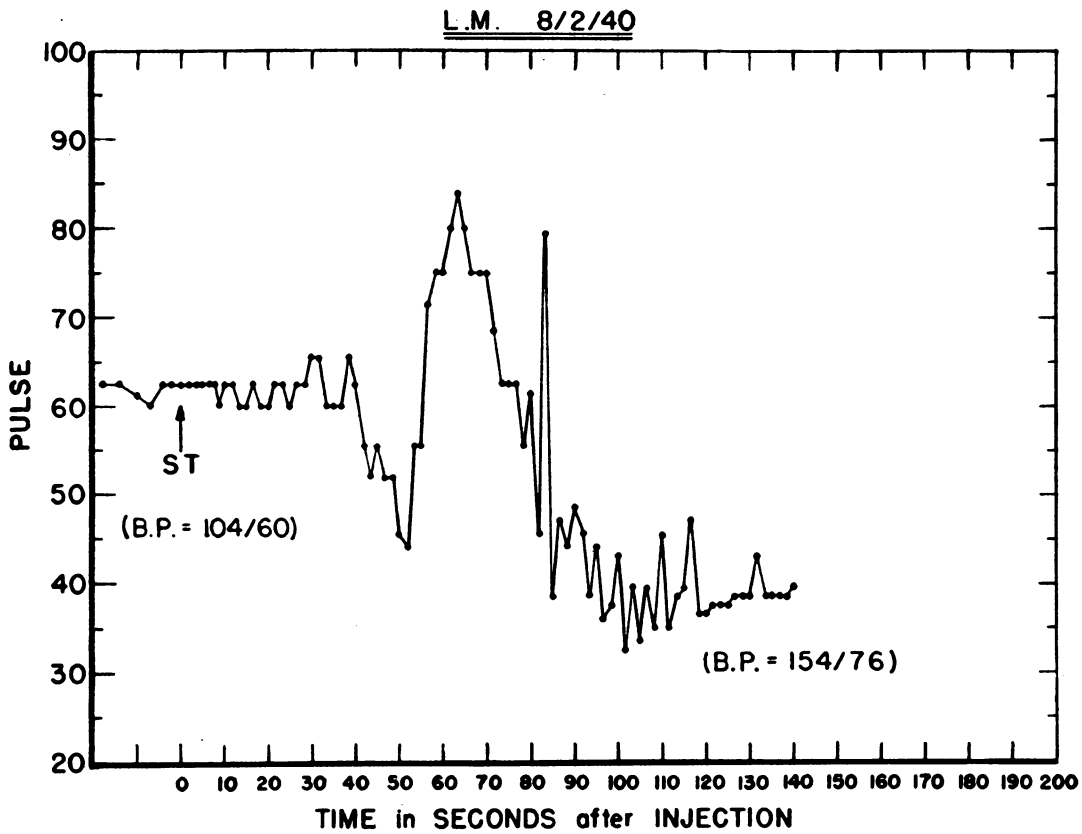


FIG. 2. INTRAVENOUS ADMINISTRATION OF 100 MGM. OF SYNEPHRIN TARTRATE IN 5 CC. SALINE SOLUTION OVER A PERIOD OF 60 SECONDS

L. M., normal young man. Pulse rates measured by continuous E.C.G.

*Effects in the atropinized subject*

Synephrin tartrate injections were made in normal persons after atropine injection. Atropine dosages of 0.65 to 1.3 mgm. ($\frac{1}{100}$ to $\frac{1}{50}$ grain) were used subcutaneously; all the subjects were also separately tested with atropine and with synephrin tartrate alone. The results on pulse rate and blood pressure in a typical experiment are given in Figure 4.

In all cases the parasympathetic paralysis produced by atropine resulted in an intensification of the pressor effect of synephrin tartrate but the most marked result was on the pulse rate. After atropine, even in small doses ($\frac{1}{100}$ grain), the pulse rate was always accelerated by synephrin tartrate and the responses were qualitatively identical with those produced with epinephrine.

*Subjective sensations*

Like neo-synephrin, synephrin tartrate fails to produce the familiar anxiety which results when epinephrine is given. The subjective sensations produced by synephrin tartrate, both alone and after atropine, are indistinguishable from those of neo-synephrin and, in general, are conspicuously absent with therapeutic dosages.

## DISCUSSION

It is clear that both neo-synephrin and synephrin tartrate have some well-marked parasympatheticomimetic effects. From experiments with epinephrine in atropinized subjects, and in vagotomized as well as atropinized animals, a similar but smaller action on the parasympathetic system was demonstrated. Synephrin tartrate occupies an intermediate position between epinephrine and neo-synephrin with regard to the vagus-like effect on the heart rate at a given pressor dose level.

Youmans, Haney and Aumann (9) estimated the cardiac-accelerator potency of these drugs in the denervated dog heart and found epinephrine to be about 25 times as powerful as synephrin

TABLE I

*Effect of subcutaneous injection of synephrin tartrate on arm-to-tongue circulation time in normal persons as measured with sodium dehydrocholate*

"Time decholin" indicates the time, in minutes and seconds, after the synephrin tartrate injection when the second injection of sodium dehydrocholate was made.

| Subject | Dose | Before | | | Time decholin | After | | |
|---|---|---|---|---|---|---|---|---|
| | | Heart rate before circulation time | Blood pressure arm | Circulation time | | Heart rate before circulation time | Blood pressure arm | Circulation time |
| | *mgm.* | | | *seconds* | | | | *seconds* |
| O.H. July 3 | 200 | 66 | 114/74 | 19 | 30′<br>44 | 64<br>62 | 130/64<br>130/68 | 16<br>16 |
| R.E. July 9 | 200 | 70 | 110/60 | 16 | 29<br>58 | 62<br>62 | 128/50<br>128/58 | 15<br>14 |
| L.M. July 11 | 250 | 72 | 110/62 | 19 | 27<br>37 | 64<br>74 | 120/62<br>122/70 | 18<br>19 |
| O.H. July 17 | 400 | 78 | 110/70 | 18 | 25 | 70 | 142/74 | 15 |
| B.E. July 16 | 400 | 58 | 114/58 | 20 | 33<br>48 | 60<br>60 | 142/60<br>136/50 | 16<br>15 |
| O.H. July 17 | 400 | 66 | 110/70 | 22 | 30<br>53<br>133 | 66<br>70<br>64 | 138/78<br>128/70<br>112/70 | 14<br>14<br>21 |
| L.M. July 18 | 400 | 66 | 110/64 | 20 | 23<br>45 | 60<br>62 | 150/66<br>126/64 | 22<br>22 |
| O.H. July 18 | 400 | 78 | 110/70 | 18 | 25 | 70 | 142/74 | 15 |
| Averages (maximum effect) | | 69 | 111/66 | 18.9 | | 66 | 132/67 | 16.8 |

tartrate in this respect. We find the same order of difference in the fully atropinized human subject.

The early publications (*op. cit.*) on synephrin tartrate stressed the long duration of action of this drug as compared with epinephrine. We do not find any significant difference between synephrin tartrate and neo-synephrin in this respect. The low pressor potency of synephrin tartrate has mitigated against its useful application as a pressor substance. However, the toxicity of the drug is relatively very low, so that the therapeutic index—toxic dose/pressor dose—is very favorable. Cranston and Bieter (2) studied the utility of a number of pressor drugs in the prevention of the hypotension of spinal anesthesia in the rabbit. They found synephrin tartrate to be much superior to the other drugs tested in respect to the margin of safety between pressor and toxic dosage. If we consider that cardiac irregularities and "nervousness" indicate beginning toxic action, then our results in man are in full agreement that synephrin tartrate has a higher therapeutic (pressor) index than epinephrine or ephedrine.

The synephrin tartrate used by us is a racemic mixture and this is the only form at present

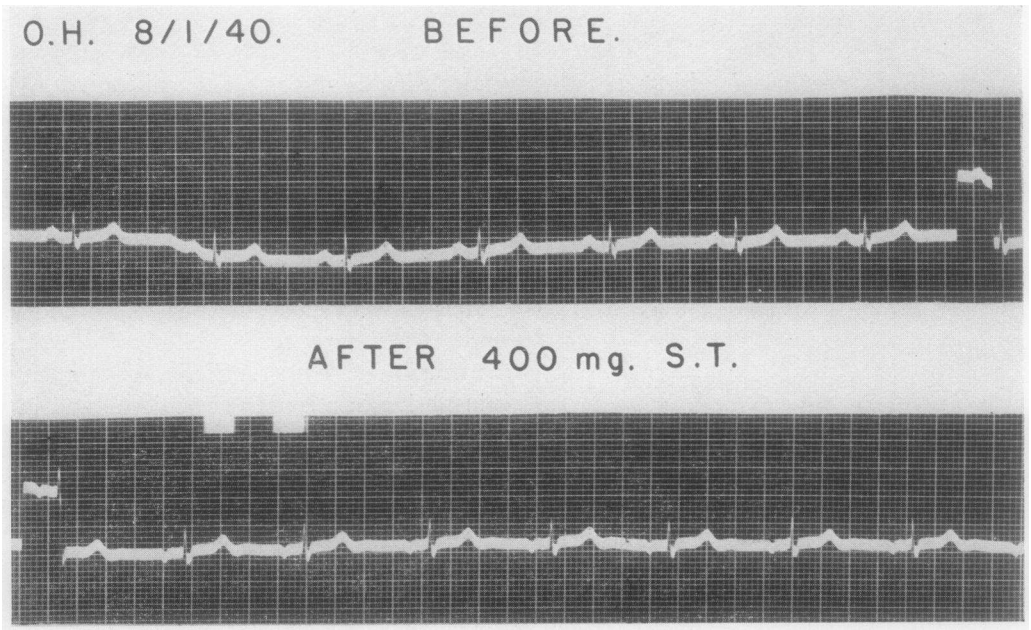


FIG. 3. INVERSION OF $P_2$ RESULTING FROM SUBCUTANEOUS INJECTION OF 400 MGM. SYNEPHRIN TARTRATE

O. H., normal young man.

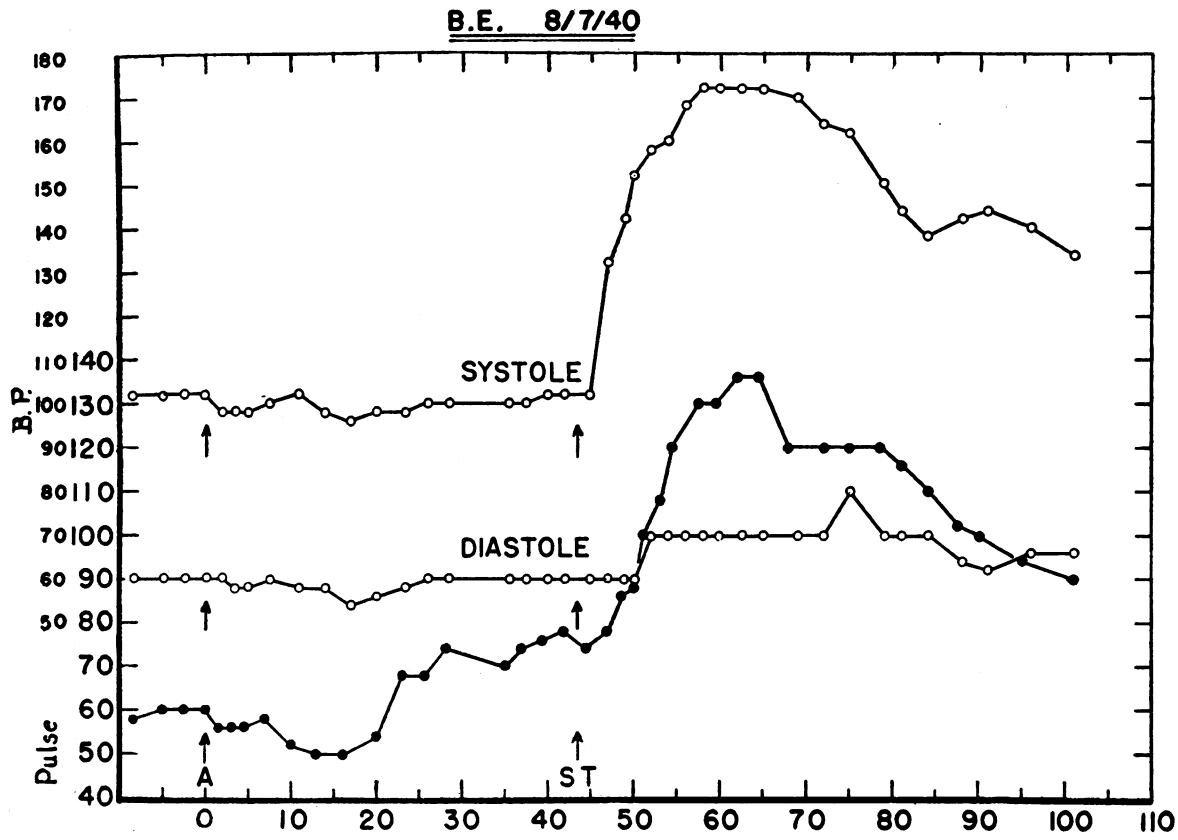


FIG. 4. EFFECT OF ATROPINE (1/50 GRAIN SUBCUTANEOUSLY) ON THE BLOOD PRESSURE AND PULSE RATE FOLLOWING SUBCUTANEOUS INJECTION OF 300 MGM. SYNEPHRIN TARTRATE IN A NORMAL YOUNG MAN

TABLE II

*The effect of subcutaneous injection of synephrin tartrate on the stroke output and systolic volume of the heart of normal resting young adults in the upright seated position*

Each value for heart size and output is the average from measurements made on 2 roentgenkymograms. Heart volumes and stroke outputs are in cc., minute volumes in liters.

| Subject | Dose | Before | | | | | Time after injection | After | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Heart rate | Blood pressure | Heart volume | Stroke volume | Minute volume | | Heart rate | Blood pressure | Heart volume | Stroke volume | Minute volume |
| | *mgm.* | | | | | | | | | | | |
| RR 25 A | 200 | 77 | 110/70 | 489 | 57 | 4.42 | 35′ | 68 | 132/70 | 453 | 53 | 3.65 |
| DW 26 A | 200 | 78 | 90/70 | 476 | 46 | 3.61 | 34′ | 71 | 107/70 | 440 | 68 | 4.77 |
| PW 38 A | 250 | 76 | 114/78 | 403 | 84 | 6.38 | 26′ | 64 | 130/74 | 392 | 90 | 5.69 |
| LM 27 A | 250 | 87 | 109/62 | 453 | 40 | 3.50 | 31′ | 74 | 122/70 | 449 | 56 | 4.14 |
| OH 28 A | 400 | 80 | 110/70 | 673 | 44 | 3.53 | 30′ | 73 | 136/74 | 633 | 66 | 4.78 |
| BE 29 A | 400 | 80 | 109/60 | 495 | 64 | 5.11 | 30′ | 75 | 146/58 | 492 | 70 | 5.23 |
| RR 3/21 | 400 | 64 | 110/70 | 507 | 73 | 4.70 | 32′ | 60 | 149/74 | 514 | 86 | 5.18 |
| Averages | | 77 | 107/68 | 499 | 58 | 4.46 | 31′ | 69 | 132/70 | 482 | 70 | 4.78 |

available. Since, like other related drugs, the dextro isomer is almost inert physiologically, we might predict that levo-synephrin tartrate would be a very useful drug if it could be made available. In almost all respects, except total potency, synephrin tartrate appears to warrant the claims of the German workers that it is one of the most satisfactory pressor agents yet developed.

TABLE III

*The effect of subcutaneous injection of 400 mgm. of synephrin tartrate on the output of the heart of normal resting young adults in the semi-recumbent position*

Measurements by the acetylene method. Values for stroke output in cc., minute volumes in liters.

| Subject | Before | | | | After | | | |
|---|---|---|---|---|---|---|---|---|
| | Heart rate | Blood pressure | Stroke volume | Minute volume | Heart rate | Blood pressure | Stroke volume | Minute volume |
| O.H. August 1 | 63 | 108/70 | 74.6 | 4.70 | 67 | 132/68 | 110.3 | 7.39 |
| F.M. August 2 | 73 | 120/60 | 56.3 | 4.11 | 73 | 150/57 | 155.5 | 11.35 |
| B.E. August 6 | 59 | 102/60 | 78.0 | 4.60 | 56 | 142/50 | 106.0 | 5.94 |
| H.Mc. August 8 | 73 | 124/70 | 76.0 | 5.55 | 74 | 162/80 | 118.5 | 8.77 |
| Averages | 67 | 113/65 | 71.2 | 4.74 | 67.5 | 147/64 | 122.6 | 8.36 |

## SUMMARY

A study has been made, under controlled environmental and physiological conditions, of the

cardio-circulatory effects in man of racemic synephrin tartrate.

The threshold subcutaneous dosage is about 100 mgm. and the indicated therapeutic dosage for pressor action is about 400 mgm. given subcutaneously.

In normal man synephrin tartrate produces a marked rise in systolic blood pressure, a slight rise in diastolic blood pressure and a slight fall in pulse rate. With subcutaneous administration these effects are at a maximum in 10 to 30 minutes after injection and the effects persist in diminishing degree for more than an hour.

Synephrin tartrate produces a well-marked rise in stroke output of the heart and an increase in the minute volume. The arm-to-tongue circulation time is shortened.

The systolic heart size is slightly diminished with therapeutic doses of synephrin tartrate. The electrocardiogram is generally unaltered but occasionally *P* may be depressed. No irregularities in heart action have been seen in any of our studies.

It is believed that synephrin tartrate is intermediate between epinephrine and neo-synephrin in its relative sympathetico-parasympathetico-mimetic action.

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