Heart Force Effects of Sympathomimetic Amines as a Basis for Their Use in Shock Accompanying Myocardial Infarction

By Peter C. Gazes, M.D., Leon I. Goldberg, Ph.D., and Thomas D. Darby, B.S.

The treatment of 14 patients in severe shock accompanying myocardial infarction with l-norepinephrine (Levophed) in some cases and phenylephrine (Neo-Synephrine) in others demonstrated a significantly higher recovery rate with l-norepinephrine. Twelve of the patients were in congestive heart failure. Using strain-gage technics in fully conscious, trained dogs, l-norepinephrine was shown to produce substantial increments in heart contractile force in addition to its recognized pressor effects. Approximately equipressor doses of Neo-Synephrine under the same conditions had little effect on contractile force. These pronounced differences in heart force effects are presented as a basis for the difference in clinical results.

SYMPATHOMIMETIC (pressor) amines are being widely used for the treatment of shock accompanying myocardial infarction.1-7 Most investigators advocating the use of such therapy have based its effectiveness on the peripheral vasconstrictor action of the amines. The present report presents clinical and laboratory evidence that the success of sympathomimetic amine therapy may additionally be based on its effects on heart contractile force. The clinical studies are based on 14 consecutively treated patients in severe shock accompanying myocardial infarction. Approximately half of this group were treated with intravenous infusions of phenylephrine (Neo-Synephrine). The other half received intravenous infusions of l-norepinephrine (Levophed). The laboratory studies, designed to measure relative contractile force and arterial pressure changes in unanesthetized dogs, include such determinations following 51 intravenous injections of l-epinephrine, l-norepinephrine and Neo-Synephrine in three previously operated dogs. These experiments were in essential confirmation of a larger series conducted with vagotomized, open-chest dogs under anesthesia.8

1. Clinical Studies

Methods

The 14 patients with myocardial infarction and shock described in this study were the total number of such patients observed by one of us (P. C. G.) during the period June 1950 to April 1953. These patients represented about 10 per cent of all cases of myocardial infarction treated during this period. Diagnosis was made in each case by studies which included serial electrocardiograms. Before therapy was instituted, all patients were in shock for at least one hour, with low blood pressure, ashen color, anxiety, periods of stupor, and cold, moist skin. Blood pressure measurements were obtained by sphygmomanometer at 10 to 30 minute intervals. The systolic pressure was below 80 mm. Hg in each case except one, a known hypertensive, who presented the typical picture of shock but had a blood pressure of 134/90. This patient's preinfarction pressure ranged from 210/100 to 250/150. The shock state of each patient in this study was of such an extent that survival would have been doubtful without treatment. Previous experience with this type of patient indicated about a 50 per cent mortality rate.

Six of the 14 patients were treated with l-norepinephrine, seven with Neo-Synephrine and one with both drugs. l-Norepinephrine was administered by intravenous drip in a solution containing 4 mg. l-norepinephrine and 5 per cent glucose in each liter of distilled water. Neo-Synephrine was administered in the same manner in a concentration of 10 mg. per liter in two cases and 20 mg. per liter in the others. The rate of infusion flow was determined by the level of systolic blood pressure, which was maintained below 120 mm. Hg in each case except the hypertensive patient noted above. The rate of infu-
### Table 1.—Results of Treatment with L-Norepinephrine and/or Neo-Synephrine of 14 Patients with Severe Shock Accompanying Myocardial Infarction

<table>
<thead>
<tr>
<th>Name, Age, Diagnosis</th>
<th>No. of Days after Infarction Shock Developed</th>
<th>Hours in Shock before Treatment</th>
<th>Congestive Heart Failure</th>
<th>B.P. before Amine Administration</th>
<th>B.P. response to Amine Administration</th>
<th>Total Amount of Amine and 5% Glucose Solution Administered</th>
<th>Total Hours Treatment of Shock</th>
<th>Arrhythmias Developing During Therapy</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. B. C., w. m., 43; Post. infarct</td>
<td>1</td>
<td>3</td>
<td>+</td>
<td>B.P. imperceptible</td>
<td>100/43</td>
<td>Neo-Synephrine 10 mg. 1000 cc.</td>
<td>24</td>
<td>None</td>
<td>Died 48 hrs. after infusion discontinued</td>
</tr>
<tr>
<td>B. T. B., w. m., 70; Post. infarct</td>
<td>4</td>
<td>1½</td>
<td>-</td>
<td>B.P. imperceptible</td>
<td>100/47</td>
<td>Neo-Synephrine 10 mg. 1000 cc.</td>
<td>30</td>
<td>None</td>
<td>Died during infusion</td>
</tr>
<tr>
<td>J. D., w. m., 64; Post. infarct</td>
<td>3</td>
<td>2</td>
<td>+</td>
<td>B.P. imperceptible</td>
<td>70/49</td>
<td>Neo-Synephrine 40 mg. 2000 cc.</td>
<td>24</td>
<td>Vent. premature contractions</td>
<td>Died during infusion</td>
</tr>
<tr>
<td>H. K., w. m., 84; Ant. infarct</td>
<td>1</td>
<td>1</td>
<td>+</td>
<td>60/?</td>
<td>80/46</td>
<td>Neo-Synephrine 40 mg. 2000 cc.</td>
<td>24</td>
<td>None</td>
<td>Died during infusion</td>
</tr>
<tr>
<td>J. K., w. m., 50; Post. infarct</td>
<td>1</td>
<td>2</td>
<td>+</td>
<td>70/?</td>
<td>100/70</td>
<td>Neo-Synephrine 40 mg. 2000 cc.</td>
<td>26</td>
<td>None</td>
<td>Died during infusion</td>
</tr>
<tr>
<td>J. F. V., w. f., 39; Post. infarct</td>
<td>1</td>
<td>2</td>
<td>-</td>
<td>B.P. imperceptible</td>
<td>130/100</td>
<td>Neo-Synephrine 40 mg. 2000 cc.</td>
<td>36</td>
<td>None</td>
<td>Recovered</td>
</tr>
<tr>
<td>C. W. P., w. m., 54; Ant. &amp; post. infarct</td>
<td>1½</td>
<td>½</td>
<td>+</td>
<td>B.P. imperceptible</td>
<td>90/70</td>
<td>Neo-Synephrine 20 mg. 1000 cc.</td>
<td>10</td>
<td>None</td>
<td>Died 18 hrs. after infusions discontinued</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>½</td>
<td>B.P. imperceptible</td>
<td>100/70</td>
<td>2</td>
<td>Aur. fibrillation</td>
<td>8</td>
<td>Aur. fibrillation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2¼</td>
<td>½</td>
<td>110/70</td>
<td>100/70</td>
<td>2</td>
<td>Aur. fibrillation</td>
<td>72</td>
<td>Aur. premature contractions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7½</td>
<td>½</td>
<td>B.P. imperceptible</td>
<td>108/70</td>
<td>16</td>
<td>None</td>
<td>4</td>
<td>Aur. premature contractions</td>
<td></td>
</tr>
<tr>
<td>Patient ID</td>
<td>Age</td>
<td>Duration</td>
<td>Blood Pressure</td>
<td>Treatment</td>
<td>Dosage</td>
<td>Ventricular Manifestations</td>
<td>Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
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<td>--------------------------</td>
<td>---------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>J. F., w. m., 69; Post. infarct</td>
<td>1</td>
<td>1</td>
<td>+</td>
<td>70/?</td>
<td>110/85</td>
<td>Neo-Synephrine 40 mg, 2000 cc.</td>
<td>30</td>
<td>Vent. &amp; aur. premature contractions Died during infusion</td>
<td></td>
</tr>
<tr>
<td>J. H., w. m., 46; Post. infarct</td>
<td>2 1/2</td>
<td>12</td>
<td>+</td>
<td>70/?</td>
<td>120/90</td>
<td>L-Norepinephrine 8 mg, 2000 cc.</td>
<td>18</td>
<td>Aur. premature contractions Recovered</td>
<td></td>
</tr>
<tr>
<td>J. M., w. m., 51; Post. infarct</td>
<td>1</td>
<td>1</td>
<td>+</td>
<td>B.P. imperceptible</td>
<td>120/90</td>
<td>L-Norepinephrine 8 mg, 2000 cc.</td>
<td>32</td>
<td>None Recovered</td>
<td></td>
</tr>
<tr>
<td>H. B., w. m., 53; Post. infarct</td>
<td>1</td>
<td>1 1/2</td>
<td>+</td>
<td>B.P. imperceptible</td>
<td>120/90</td>
<td>L-Norepinephrine 12 mg, 3000 cc.</td>
<td>48</td>
<td>Aur. premature contractions Recovered</td>
<td></td>
</tr>
<tr>
<td>J. A., w. m., 48; Post. infarct</td>
<td>1</td>
<td>1</td>
<td>+</td>
<td>B.P. imperceptible</td>
<td>120/80</td>
<td>L-Norepinephrine 16 mg, 4000 cc.</td>
<td>54</td>
<td>None Recovered</td>
<td></td>
</tr>
<tr>
<td>E. T., w. m., 48; Post. infarct</td>
<td>2</td>
<td>1</td>
<td>+</td>
<td>134/90</td>
<td>175/110</td>
<td>L-Norepinephrine 4 mg, 1000 cc.</td>
<td>16</td>
<td>None Recovered</td>
<td></td>
</tr>
<tr>
<td>H. L. H.,* w. m., 53; Post. infarct</td>
<td>3</td>
<td>1</td>
<td>+</td>
<td>60/?</td>
<td>140/90</td>
<td>L-Norepinephrine 32 mg, 8000 cc.</td>
<td>120</td>
<td>None Recovered</td>
<td></td>
</tr>
</tbody>
</table>

* These cases reported in detail in Case Abstracts.
flow ranged from 5 to 100 drops per minute. If the blood pressure remained stable with the slower flow rate, the pressor amine administration was discontinued. If shock recurred, the infusion was restarted.

Oxygen, sedation (morphine or Demerol), anti-arrhythmic drugs (quinidine or Pronestyl) and papaverine were used as indicated. Dicumarol was administered to all patients.

Results

The data in table 1 and the representative Case Abstracts summarize the clinical findings. The cases in table 1 are listed in chronologic order. The relatively recent introduction of l-norepinephrine for the therapy of shock accompanying myocardial infarction accounts for the exclusive use of Neo-Synephrine in the earlier cases.

Six of the seven patients treated with l-norepinephrine had a satisfactory recovery. Immediately after the start of l-norepinephrine administration the blood pressure rose and intensity of heart tones increased markedly. The pulse pressure was typically within normal limits. Approximately 1 liter of 5 per cent glucose solution containing 4 mg. of l-norepinephrine was infused over a 12 to 18 hour period. The initial infusion rates were 50 to 100 drops per minute and the final rates were usually 5 to 10 drops per minute. It was necessary to maintain the infusion rate for from 10 hours to 5 days in the various patients, before the blood pressure stabilized. Tachyphylaxis was not observed. The patient (C. W. P., see Case Abstracts) who succumbed after l-norepinephrine therapy had been initially unsuccessfully treated with Neo-Synephrine. l-Norepinephrine successfully raised and maintained the blood pressure in this patient for 48 hours, at which time it appeared stable and the infusion was discontinued. The patient died 18 hours later, apparently from extension of the infarction. In all patients treated with l-norepinephrine, congestive heart failure was present at the time of shock, as was evidenced by basilar rales and/or neck and peripheral vein distension. Antecubital venous pressure determinations in one case (H. L. H., see Case Abstracts) revealed a pressure of 232 mm. of blood before the l-norepinephrine infusion was begun. One hour after the start of the infusion the venous pressure had dropped to 180 mm. and there was a clearing of basilar rales. Decreasing or stopping the rate of l-norepinephrine flow in this patient caused an immediate rise in venous pressure; increasing the flow again lowered the venous pressure. On the third day, after the start of the infusion, the venous pressure of this patient had dropped to 67 mm. and has remained at normal levels.

Only two of the seven patients treated with Neo-Synephrine emerged from shock. These patients (B. T. B. and J. F. V.) were in shock typical of peripheral vascular collapse with no evidence of congestive heart failure. B. T. B. responded to Neo-Synephrine administration with an immediate blood pressure rise from imperceptible levels to a systolic level of 100 mm. Hg; the diastolic level could not be determined. The pressure later stabilized at 120/110 and the Neo-Synephrine infusion was discontinued. The patient succumbed 48 hours after discontinuance of therapy, apparently from extension of the infarction. J. F. V. (see Case Abstracts) responded to Neo-Synephrine therapy and recovered without complications. The other patients treated with Neo-Synephrine were in congestive heart failure. An immediate pressor response was observed in each of these cases, but the pressure failed to stabilize and the patients succumbed despite continuous Neo-Synephrine infusion (typified by case J. K.; see Case Abstracts). Unlike the response to l-norepinephrine, the pressor response to Neo-Synephrine was usually characterized by a small pulse pressure.

Case Abstracts

C. W. P. was a 54 year old white male admitted because of severe substernal pain of 30 minutes duration. On admission his blood pressure was 98/72, and his pulse was regular at 56 per minute. The electrocardiogram revealed an acute posterior infarction. Two hours later the patient was asymptomatic and blood pressure was 128/90. Thirty-four hours after admission, the patient complained of severe substernal pain, vomited and went into shock. The blood pressure was unobtainable for 60 minutes, and respiration was maintained by artificial means on several occasions during this period. Neck and peripheral veins were markedly distended and basilar rales were present. Intravenous infusion of
Neo-Synephrine, 20 mg. per liter of 5 per cent glucose solution, produced an immediate blood pressure response to levels of 90/70. An electrocardiogram taken at this time revealed that the infarction had spread to involve the anterior surface. Despite continuous Neo-Synephrine therapy, the blood pressure gradually declined and was again unobtainable 10 hours after the start of the infusion. Basilar rales did not diminish with Neo-Synephrine therapy and, in fact, became more prominent. When the blood pressure became unobtainable, intravenous infusion of l-norepinephrine, 4 mg. per liter of 5 per cent glucose solution, was begun with an immediate response of blood pressure to 100/70 and an increase in intensity of heart tones. Eight hours later, auricular fibrillation developed. Quinidine dosage was increased. Because of possible implication of l-norepinephrine in the production of this arrhythmia, its administration was discontinued and Neo-Synephrine was substituted. The blood pressure dropped to a systolic level of 70 mm. Hg, and l-norepinephrine infusion was again started with an immediate pressor response to 110/70, in spite of the auricular fibrillation. The arrhythmia reverted to normal sinus rhythm with many premature auricular contractions persisting during the infusion period. The infusion was continued until the third day when the blood pressure was 100/70. For the following two days, the blood pressure remained stable at about 100/70 when suddenly the patient became dyspneic and the blood pressure again became unobtainable. l-Norepinephrine infusion was restarted and the blood pressure rose to 108/70. The infusion was discontinued after 16 hours when the blood pressure appeared stable at 104/70. For the next 18 hours, the blood pressure remained at about this level. At the end of this period, the patient attempted to leave the bed, became cyanotic and died.

H. L. H., a 53 year old white male, was admitted to the hospital because of severe substernal pain with nausea and vomiting. On admission he appeared pale and his skin was cool. The blood pressure was 120/80 and the cardiac rhythm was regular. An electrocardiogram showed an acute posterior infarction. The blood pressure gradually dropped during the following 72 hours to a systolic level of 60 mm. Hg, at which time shock was apparent. Basilar rales were present and the venous pressure was 232 mm. of blood. An infusion of l-norepinephrine was begun and the arterial pressure rose immediately to 140/90. Heart tones improved and signs of congestive failure cleared. Venous pressure at this time was 180 mm. of blood. When the infusion rate of the solution was decreased, the venous pressure rose and dropped immediately when the rate was increased. Blood pressure was maintained between 95/60 and 110/70 during the following five days. Each attempt to discontinue the infusion resulted in a drop in systolic arterial pressure to levels below 70 mm. Hg, until the fifth day, when the blood pressure appeared stable at a level of 95/70. Venous pressure at this time was 67 mm., color was good, heart tones were regular and clear, and there was no evidence of congestive heart failure. An inflammatory reaction observed at the site of the venipuncture was possibly related to infiltration of l-norepinephrine. It completely healed in three days with use of warm packs and penicillin. This patient was discharged after having been asymptomatic for five weeks.

J. F. V., a 39 year old white female, was admitted to the hospital for the third attack of acute myocardial infarction during the past three years. Prior to admission, she developed severe substernal pain and convulsions, and collapsed. At home and on admission, her skin was cold and clammy, pulse was not present and blood pressure was unobtainable. Heart tones were not audible and only faint breath sounds were present. The patient was unresponsive. There was no evidence of congestive heart failure. An electrocardiogram showed right bundle branch block with an old anterior and a fresh posterior infarction. Infusion of Neo-Synephrine, 20 mg. per liter of 5 per cent glucose solution, produced an immediate rise of blood pressure to 130/100. The heart tones became faintly audible. In three hours the blood pressure appeared stable at levels of approximately 110/78. Ten hours later, the blood pressure dropped to 90/52 and the infusion rate was increased to 50 drops per minute with a pressor response to 116/76. The infusion was completed in 18 hours and another such 1000 cc. infusion was completed during the next 18 hours. At the completion of the second infusion, the blood pressure was 100/68 and remained at similar levels for the next 30 days without further Neo-Synephrine infusions, and the patient was discharged.

J. K., a 50 year old white male, was admitted to the hospital because of severe substernal pain radiating down both arms. His skin was cold and clammy, and he appeared very pale. Heart tones were faint. An electrocardiogram showed an acute posterior infarction with a few premature ventricular contractions. Initially, the blood pressure was 100/60, but 24 hours later it had dropped to a systolic level of 70 mm. Hg, and the patient was in shock with signs of congestive heart failure. An infusion of Neo-Synephrine was begun resulting in an immediate rise of blood pressure to 100/80. Blood pressure remained at this level for several hours. The patient, however, became dyspneic and had more basilar congestion. Ventricular premature contractions were controlled by Pronestyl. Twenty-four hours later, in spite of the Neo-Synephrine infusion, his blood pressure had gradually dropped to 60/50 with reappearance of shock. During the next 30 minutes, the pressure became unobtainable; the patient became cyanotic and expired.
2. Laboratory Studies

Methods

Three trained, mongrel dogs weighing between 10 and 15 Kg, were used in these studies. A metal encased strain gage arch was sutured to the anterior aspect of the right ventricle of each dog for the measurement of heart contractile force. The operation was performed with aseptic technic under pentobarbital anesthesia and with positive pressure respiration using room air. Description of the strain gage arch and the physiologic factors governing its use have been reported in detail. Clinical implications of studies conducted with the strain gage arch have been presented. While the animals were under anesthesia, polyethylene tubes (inside diameter 0.047 inch) were inserted and tied into an exposed femoral artery and vein for pressure measurements and drug injections. The tubings were filled with Ringer-Locke solution containing heparin (10 U.S.P. units per cubic centimeter) and were sealed by twisting and tying with thread. The incisions were closed and the tubings were placed in metal cans sutured to the skin and heavily taped to prevent interference by the animals. The animals recovered from the anesthesia within six hours and were ambulatory in about 12 hours.

The first experiments were conducted 18 to 24 hours after the operation. The unanesthetized animals were placed on dog boards, gently restrained and petted continuously. Heart contractile force was recorded through a Brush Universal Analyzer (B1-320). Diastolic and systolic femoral pressures were recorded through a Statham Transducer and another Brush Analyzer. The output from both analyzers was recorded synchronously by a two channel Brush ink-writing oscillograph (B1-202). A syringe filled with heparinized Ringer-Locke solution and provided with a two-way stopcock was attached to the venous tubing. All drug injections were made through this tubing, thus eliminating excitement of the animal resulting from venepuncture. Placebo injections of Ringer-Locke solution in approximate volume of the administered drugs were made in each experiment.

Before drug administration, a 15 minute control period with steady contractile force, diastolic and systolic pressure readings was obtained. The sympathomimetic amines were injected rapidly intravenously in the following order and in the following doses: l-epinephrine (as the bitartrate), 0.001 mg. per kilogram, l-norepinephrine (as the bitartrate) 0.001 mg. per kilogram and Neo-Synephrine hydrochloride, 0.015 mg. per kilogram. Mephentermine (Wyamine), 1.00 mg. per kilogram, and Vasoxyl, 0.10 mg. per kilogram, were also included in some of the experiments. Each amine was administered in a dose calculated to produce an approximately equivalent diastolic pressure increment. In one dog, on the third postoperative day, l-norepinephrine was infused intravenously by use of a special constant rate infusion pump at rates of 0.010 mg. per kilogram and 0.012 mg. per kilogram per minute. Neo-Synephrine was infused similarly into the same dog on the following day at the rate of 0.20 mg. per kilogram per minute.

Results

Results of the rapid intravenous injections of the amines are summarized in table 2.

After each of the 17 administrations of l-norepinephrine, there was a pronounced increment in heart contractile force. This increment averaged 151 per cent of control values. This stimulant response was very similar to that produced by l-epinephrine. Neo-Synephrine, however, produced an average increment of only 15 per cent in 14 administrations. This marked difference between the effects of l-norepinephrine and l-epinephrine on contractile force and the effects of Neo-Synephrine are typically illustrated in figure 1. The results are very similar to those observed in the previous study with open-chest, vagotomized dogs, except that the contractile force increments caused by Neo-Synephrine were relatively

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose mg./kg.</th>
<th>Number of Dogs</th>
<th>Number of Injections</th>
<th>Postoperative Days Drug Administered</th>
<th>Av. Increment in Contractile Force % of control values</th>
<th>Av. Diastolic B.P. Increment mm. Hg</th>
<th>Av. Systolic B.P. Increment mm. Hg</th>
<th>Av. Heart Rate Change beats/min.</th>
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</thead>
<tbody>
<tr>
<td>l-Epinephrine</td>
<td>.001</td>
<td>3</td>
<td>20</td>
<td>1st to 8th</td>
<td>128</td>
<td>47</td>
<td>65</td>
<td>−3</td>
</tr>
<tr>
<td>l-Norepinephrine</td>
<td>.001</td>
<td>3</td>
<td>17</td>
<td>1st to 8th</td>
<td>151</td>
<td>53</td>
<td>67</td>
<td>−38</td>
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<tr>
<td>Neo-Synephrine</td>
<td>.015</td>
<td>2</td>
<td>14</td>
<td>1st to 8th</td>
<td>15</td>
<td>63</td>
<td>58</td>
<td>−19</td>
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<tr>
<td>Vasoxyl</td>
<td>.000</td>
<td>1</td>
<td>2</td>
<td>4th &amp; 5th</td>
<td>10</td>
<td>50</td>
<td>60</td>
<td>−40</td>
</tr>
<tr>
<td>Wyamine</td>
<td>1.000</td>
<td>1</td>
<td>4</td>
<td>4th, 5th, 7th, 8th &amp; 8th</td>
<td>107</td>
<td>78</td>
<td>97</td>
<td>+25</td>
</tr>
</tbody>
</table>
smaller in the present series with unanesthetized animals.

L-Norepinephrine reduced the heart rate considerably more than did L-epinephrine, in the present investigation. In the previous cause of a greater diastolic than systolic pressure increment. The effects produced by l-norepinephrine and L-epinephrine on contractile force and heart rate lasted from about two to four minutes; the hypertensive effect

study with open-chest, vagotomized dogs, both amines produced approximately equivalent degrees of tachycardia.

Pressor effects with L-norepinephrine and L-epinephrine were closely similar, both amines usually producing an increase in pulse pressure, due to a greater systolic than diastolic pressure increment. Neo-Synephrine administration usually resulted in a decreased pulse pressure, be-

Fig. 1. Effects of L-epinephrine, L-norepinephrine and Neo-Synephrine on heart contractile force and femoral arterial pressure of an unanesthetized, trained dog. Ventricular contractile force was recorded from a strain gage coil cemented to a metal arch, which had been sutured to the anterior aspect of the right ventricle three days previously. Femoral arterial pressure was recorded by a Statham Transducer attached to polyethylene tubing previously inserted into the artery. The contractile force (upper curves) is directly proportional to the oscillograph lever stroke amplitude. Scales to the left of the arterial pressure tracings (lower curves) indicate millimeters of mercury. Injections were made rapidly through polyethylene tubing previously inserted in the femoral vein.

generally persisted for about one minute longer than the contractile force or heart rate effects. The blood pressure and heart rate effects produced by Neo-Synephrine usually persisted for 10 to 15 minutes. The duration of the slight contractile force increment produced by Neo-Synephrine was usually two to three minutes less than that of the heart rate and blood pressure effects.
In the experiment in which l-norepinephrine was administered by continuous intravenous infusion at a rate of 0.010 mg. per kilogram per minute, the contractile force and the diastolic and systolic pressures began increasing within two minutes after the infusion was begun. The heart rate began to drop during the same period. At the end of 10 minutes, the contractile force had increased to levels approximately 95 per cent above control values, the diastolic pressure about 20 mm. and the systolic pressure about 50 mm. above control values. The rate had decreased to a level 50 beats per minute below control. These levels remained approximately constant for the final five minutes of the infusion. About five minutes after the infusion was discontinued, contractile force and pressure values had returned to control levels. The heart rate, however, was still 30 beats per minute below control. The infusion was then started again and maintained at a slightly faster rate, 0.012 mg. per kilogram per minute. The response was similar to that of the first infusion, contractile force stabilizing in 10 minutes at levels about 100 per cent above control values, diastolic pressure 30 mm. above control and systolic pressure 65 mm. above control. The rate dropped 10 beats per minute slower than in the previous infusion. These levels were again maintained for five minutes before the infusion was discontinued. All values again returned to control levels in about five minutes, except heart rate which remained 40 beats per minute below control values.

On the following day, Neo-Synephrine was similarly infused into this same dog. The concentration of Neo-Synephrine solution was 0.020 mg. per kilogram per cubic centimeter, and the rate of infusion was 1 cc. per minute. Within two minutes, the diastolic pressure rose 70 mm., the systolic pressure 50 mm.; the contractile force decreased about 25 per cent. In 10 minutes, the diastolic and systolic pressures were at approximately the same high levels and the contractile force had risen to control levels. The infusion was discontinued 15 minutes after it was started. Systolic and diastolic pressures returned to control levels in approximately 15 minutes. There was no further change in contractile force. There was little change of rate during this experiment.

The four administrations of Wyamine and the two administrations of Vasoxyl indicated that the effects produced by these amines on the contractile force in unanesthetized dogs were similar to those reported for the open-chest series. Wyamine produced a pronounced increment in contractile force, averaging 107 per cent of control values and lasting for approximately 15 minutes. Vasoxyl produced little effect on heart contractile force.

DISCUSSION

The problem of shock accompanying myocardial infarction has been comprehensively studied and reviewed by several investigators in recent years. The conclusion of these investigators has been that the shock is the result of one or a combination of the following factors: (1) failure of the heart as a pump and (2) peripheral vascular collapse with a resultant further decrease in coronary flow. Digitalis has been advocated for shock primarily of the first type, and pressor amines, intra-arterial, and intravenous infusions for the second type. Recently, Fink, d'Angio and Biloon have differentiated these two types of shock on the basis of determinations of forearm venous pressure.

Results of the present investigation demonstrate that although l-norepinephrine is generally classified clinically as predominantly a pressor amine, it also has a powerful augmenting action on the contractile force of the heart and may thus be beneficially used in shock of either of the above types. Effects considered to be due to increase of contractile force were observed clinically in seven patients described in this report, in whom there were evidences of congestive heart failure in addition to shock. In these patients, there was an almost immediate clearing of pulmonary congestion, increase in intensity of heart tones, increase in pulse pressure and decrease of distension of the veins of the arms and neck. In one of these patients (H. L. H.) direct measurements revealed a drop in venous pressure to normal values during therapy. Kurland and Malach have also noted the clearing of existing pulmonary edema during l-norepinephrine ther-
therapy. Digitalis therapy may have been beneficial in the above patients, but digitalis does not exert a pressor effect and has a greater tendency to produce cardiac arrhythmias. Additionally, because of the longer period of action of digitalis, its effects cannot be as readily controlled.

The ability of norepinephrine to increase contractile force has been demonstrated by several investigators in a variety of isolated heart preparations14-17 and anesthetized animals. The present study confirms these results by use of unanesthetized dogs and further demonstrates that the effect on contractile force is maintained as long as the amine is infused.

The clinical impression that l-norepinephrine is predominantly a pressor amine, with little or no cardiac action, appears to have been based mainly on studies in normal and hypertensive individuals in whom l-norepinephrine administration either decreased or did not affect cardiac output. More recent studies with anesthetized dogs have shown definite increase in cardiac output with l-norepinephrine administration. It should be noted that cardiac output is a resultant of several factors, such as force of the heart, peripheral resistance, and heart rate. As l-norepinephrine affects each of these factors in varying degrees, administration of this amine may increase contractile force but may decrease or may not change cardiac output.

Neo-Synephrine appears to fulfill the usual definition of a pressor amine, in that its action is largely peripheral. Although amines of this type may be beneficial in those cases of shock accompanying myocardial infarction with peripheral vascular collapse as the major finding (type 2), they may be actually contraindicated in a major proportion of these patients, that is, in those with shock and congestive heart failure (type 1). This observation is supported by the therapeutic failure of Neo-Synephrine in all patients with congestive heart failure described in the present report. Similar views concerning Neo-Synephrine therapy have been expressed by Fink, d'Angio and Biloon.

The work of Hellerstein, Brofman and Caskey has demonstrated that Wyamine is of value in shock following myocardial infarction. From the previous pharmacologic study and the experiments presented here, it appears that Wyamine has a distinct augmenting effect on contractile force, and the success of this amine may also be related to such action. Vasoxy1, however, has been found to be very similar to Neo-Synephrine and should probably be used only with similar restrictions.

As additional sympathomimetic amines are recommended for use in shock accompanying myocardial infarction, it is apparent that all should not be considered as having similar pharmacologic actions and thus be used interchangeably. A thorough knowledge of both pressor effects and effects on heart contractile force should be obtained before therapy with sympathomimetic amines is attempted.

**SUMMARY**

1. The treatment of 14 cases of severe shock accompanying myocardial infarction by intravenous infusions of l-norepinephrine and/or Neo-Synephrine is described. Twelve of the patients were in congestive heart failure. Six patients in congestive heart failure treated with l-norepinephrine recovered. Five patients in congestive heart failure treated with Neo-Synephrine responded with an immediate blood pressure rise, but the pressure failed to stabilize and the patients succumbed despite continuous Neo-Synephrine infusions. Two patients, with no evidence of congestive heart failure, were brought out of shock by Neo-Synephrine. One of these patients recovered, the other died 48 hours after the Neo-Synephrine infusion was discontinued. One patient, treated with both amines, failed to respond to Neo-Synephrine and was later brought out of shock by l-norepinephrine. This patient died 18 hours after discontinuance of l-norepinephrine therapy.

2. l-Norepinephrine was found to produce pronounced increments in heart contractile force, in addition to pressor effects, in unanesthetized, trained dogs. The contractile force increments were of similar magnitude to those produced by l-epinephrine. Neo-Synephrine was found to be more predominantly a pressor amine, producing only minimal changes in heart contractile force.

3. The effect on contractile force of the
heart of l-norepinefrina is presented as a basis for the high recovery rate observed with this amine in the treatment of shock accompanying myocardial infarction, particularly in those cases with associated congestive heart failure.

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SUMARIO ESPAÑOL
El tratamiento de 14 pacientes en estado de choque severo como complicación de infarto del miocardio con l-norepinefrina (Levophed) en algunos casos y fenilefrina (Neo-Synephrine) en otros, demostró un promedio de recobro significativamente más alto con l-norepinefrina. Doce de los pacientes presentaban decompensación cardíaca. Usando la técnica de medida de esfuerzo en perros conscientes y amaestrados, la l-norepinefrina mostró producir incrementos substanciales en la fuerza de contracción cardíaca en adición a sus efectos vasopresores. Dosis aproximadamente equipresoras de Neo-Synephrine bajo las mismas condiciones tuvieron poco efecto en la fuerza de contracción. Estas pronunciadas diferencias en la contracción cardíaca se presentan como una base para la diferencia en resultados clínicos.

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Heart Force Effects of Sympathomimetic Amines as a Basis for Their Use in Shock Accompanying Myocardial Infarction
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