The Effects of Hexamethonium on Certain Manifestations of Congestive Heart Failure

By Robert T. Kelley, M.D., Edward D. Freis, M.D., and Thomas F. Higgins, M.D.

Hypotensive doses of hexamethonium were administered intravenously to 19 patients with various types of heart disease in congestive failure. Clinical improvement as judged by the usual methods was seen in most cases. Intracardiac or pulmonary artery pressures paralleled the fall of arterial pressures following hexamethonium in four patients with hypertensive heart disease in congestive failure. It is suggested that hexamethonium, by reducing the total peripheral resistance and by a redistribution of blood volume, may interrupt the vicious cycle of heart failure.

Failure of the circulation is associated with a number of interrelated factors tending to aggravate it and perpetuate its existence. It is generally accepted that low output failure leads to an increase in peripheral resistance due to reflex vasoconstriction. The increased peripheral resistance in turn adds to the work of the failing heart, thereby further decreasing its output.

In addition, diminished cardiac output mechanically induces a redistribution of total blood volume toward the larger veins of the circulation. There is some evidence that constriction of smaller postarteriolar vessels may contribute to the venous engorgement. The failing right heart is then subjected to excessive filling pressures, producing a further decrease in output. Thus, a vicious cycle is established. Diminished cardiac output induces increased peripheral resistance and central venous congestion, both of which add further loads to the failing heart (fig. 1).

The therapeutic measures thus far available to interrupt this cycle have been directed at improving the function of the heart itself with digitalis, increasing the excretion of salt and water by use of mercurial diuretics, and direct reduction of venous engorgement by venesection or venous tourniquets. At the present time there are no recognized methods of lowering the peripheral resistance, thereby reducing the work of the failing heart, or of redistributing the total blood volume. This study was undertaken with a view toward decreasing the peripheral vascular resistance and central engorgement, using hexamethonium, a ganglionic blocking agent.

Materials and Methods

Nineteen patients with different types of heart disease in various degrees of congestive failure were studied at the Veterans Administration and Georgetown University Hospitals, Washington, D. C.

Peripheral venous pressure was measured in the antecubital vein with a saline manometer. The zero point was placed on a plane 10 cm. above the skin of the patient’s back. In seven cases a polyethylene catheter was inserted into the antecubital vein and advanced to the level of the subclavian. Decholin was the indicator used in measuring the arm-to-tongue circulation time. The vital capacity was determined by means of a McKesson-Scott Vital Capacity Apparatus. The blood pressure was measured by the auscultatory method. These procedures were employed immediately before the slow intravenous administration of hexamethonium and immediately after a satisfactory hypotensive response to the drug was observed.
HEXAMETHONIUM AND CONGESTIVE HEART FAILURE

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\left(\frac{\text{systolic} + 2 \times \text{diastolic}}{3}\right) \text{ arterial pressure was 35 mm. Hg. In all cases with an elevated venous pressure there was a significant reduction following hexamethonium (table 1), the range being from 40 to 133 mm. water and the mean 82 mm. water. Patients with normal levels of venous pressure initially exhibited less significant and consistent reduction. The most striking results were seen in cases with hypertensive heart disease and aortic valvular disease.}

Of 12 patients with an initial arm-to-tongue circulation time in excess of 20 seconds, eight

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\begin{array}{|c|c|c|c|c|c|c|c|}
\hline
\text{Patient} & \text{Age} & \text{Sex} & \text{Type of Heart Disease} & \text{Degree of Orthop.} & \text{Vital Capacity in Liters} & \text{Venous Pressure mm. Hg} & \text{Circulation Time in Seconds} & \text{Heart Rate per Min.} & \text{Blood Pressure mm. Hg} & \text{Amount of Hexamethonium mg.} \\
\hline
\text{Bre} & \text{Before} & 50 & M & \text{Hypertensive} & \text{None} & 1.9 & 168 & 20.5 & 88 & 240/150 & 65 \\
 & \text{After} & & & & & 2.2 & 35 & 19.5 & 74 & 168/120 & \\
\text{Rol} & \text{Before} & 49 & M & \text{Hypertensive} & 0 & 2.6 & 174 & 22 & 102 & 230/130 & 50 \\
 & \text{After} & & & & & 0 & 3.2 & 180 & 32 & 93 & 105/71 & \\
\text{Has} & \text{Before} & 53 & F & \text{Hypertensive} & +++ & & 385 & 45 & 80 & 200/130 & 17.6 \\
 & \text{After} & & & & & +++ & 290 & 27 & 80 & 105/70 & 25 \\
\text{Che} & \text{Before} & 44 & F & \text{Hypertensive} & \text{None} & & 175 & 25 & 79 & 230/140 & \\
 & \text{After} & & & & & & 100 & 12 & 71 & 170/105 & \\
\text{Bro} & \text{Before} & 59 & M & \text{Hypertensive} & \text{None} & 2.0 & 132 & 27 & 107 & 230/140 & 25 \\
 & \text{After} & & & & & 2.2 & 115 & 20 & 95 & 145/90 & \\
\text{Ups} & \text{Before} & 79 & M & \text{ASHD} & ++ & 1.6 & 180 & 44 & 70 & 150/100 & 45 \\
 & \text{After} & & & & & ++ & 1.6 & 130 & 20 & 74 & 106/70 & \\
\text{Sim} & \text{Before} & 57 & M & \text{RHD with AS} & +++ & 2.8 & 175 & 25 & 98 & 105/65 & 20 \\
 & \text{After} & & & & & ++ & 3.0 & 60 & 16 & 79 & 80/50 & \\
\text{Tay} & \text{Before} & 24 & M & \text{Myocarditis} & \text{None} & 2.8 & 90 & 25 & 107 & 112/75 & 75 \\
 & \text{After} & & & & & 2.75 & 50 & 17 & 107 & 90/60 & \\
\text{Fre} & \text{Before} & 57 & M & \text{Hypertension} & +++ & 1.0 & 170 & 47 & 115 & 190/140 & 25 \\
 & \text{After} & & & & & + & 1.0 & 90 & 45 & 110 & 120/90 & \\
\text{Ste} & \text{Before} & 56 & M & \text{Hypertension} & ++ & 2.6 & 184 & 40 & 90 & 160/130 & 30 \\
 & \text{After} & & & & & 2.95 & 115 & 29 & 71 & 120/80 & \\
\text{Shi} & \text{Before} & 54 & M & \text{ASHD} & + & & 250 & 45 & 115 & 120/80 & 17.5 \\
 & \text{After} & & & & & + & 140 & 25 & 110 & 94/68 & \\
\text{Rol} & \text{Before} & 64 & M & \text{Syphilitic} & ++ & 0.8 & 170 & 107 & 165/85 & 15 \\
 & \text{After} & & & & & + & 1.1 & 85 & 115 & 140/60 & \\
\text{Har} & \text{Before} & 37 & M & \text{RHD with MS} & \text{None} & 1.8 & 140 & 23 & 75 & 118/80 & 15 \\
 & \text{After} & & & & & 1.8 & 140 & 23 & 120 & 90/65 & \\
\text{Whi} & \text{Before} & 59 & M & \text{Hypertension} & ++ & 1.55 & 110 & 16 & 100 & 180/110 & 10 \\
 & \text{After} & & & & & 0 & 2.1 & 70 & 16 & 100 & 145/85 & \\
\text{Tro} & \text{Before} & 51 & M & \text{ASHD} & \text{None} & 140 & 19 & 80 & 120/75 & 8 \\
 & \text{After} & & & & & 130 & 19 & 75 & 80/50 & \\
\hline
\end{array}
\]

**Results**

The average dose of hexamethonium was 30 mg. and the average fall of "mean" manifested a reduction ranging from 26 to 54 per cent (mean 42 per cent). Of the other four cases, three showed little or no change and one
exhibited an increased circulation time. In the two patients whose circulation time was less than 20 seconds during the control period no further reduction occurred.

The heart rate slowed in 12 of 19 cases studied. The range of deceleration was 5 to 24 beats per minute with an average slowing of 12 beats per minute. There was no change in heart rate in four and an increase in three cases. However, despite the lack of slowing, the majority of these cases exhibited evidences of improvement in their circulatory status as judged by venous pressure and/or circulation time measurements. Two of the three patients who manifested an increase in heart rate had auricular fibrillation. The first, who had arteriosclerotic heart disease, showed a slight increase in rate. The second patient, who had mitral stenosis in the compensated phase, exhibited an increased ventricular rate from 75 to 120 beats per minute when the blood pressure fell. In this patient, in contrast to the others, there were no significant changes in the other functions studied.

The vital capacity improved in 5 of 11 patients in whom determinations were made. The remainder showed no significant change. Twelve cases manifested various degrees of orthopnea. In eight such individuals there was improvement in their respiratory embarrassment which was so marked and rapid that in several instances the patients commented on their relief during the test procedures without having the question presented to them. Cheyne-Stokes respirations cleared in the single patient who exhibited this type of breathing.

Aside from the general tendency towards slowing of the heart rate in the presence of normal sinus rhythm, the electrocardiographic tracings disclosed slight prolongation of the

Table 2.—Changes in Right Heart and Pulmonary Arterial Pressures in Patients with Hypertensive Heart Disease in Failure Treated with Hexamethonium

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Amount of Hexamethonium (mg.)</th>
<th>Systemic Arterial Pressure (mm. Hg)</th>
<th>Heart Rate per Min.</th>
<th>Right Heart Pressures (mm. Hg)</th>
<th>Degree of Orthopnea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dew</td>
<td>52</td>
<td>M</td>
<td>150</td>
<td>215/140</td>
<td>116</td>
<td>50 (PAP)</td>
<td>++++</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>165/115</td>
<td>92</td>
<td>40 (RAP)</td>
<td>+</td>
</tr>
<tr>
<td>Lum</td>
<td>40</td>
<td>F</td>
<td>37</td>
<td>210/140</td>
<td>100</td>
<td>30 (RAP)</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>164/100</td>
<td>92</td>
<td>23 (RAP)</td>
<td>+</td>
</tr>
<tr>
<td>Ash</td>
<td>59</td>
<td>M</td>
<td>31</td>
<td>160/120</td>
<td>80</td>
<td>30 (RAP)</td>
<td>++++</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>120/90</td>
<td>65</td>
<td>20 (RAP)</td>
<td>++</td>
</tr>
<tr>
<td>Cle</td>
<td>53</td>
<td>M</td>
<td>8</td>
<td>225/125</td>
<td>91</td>
<td>115/25 (RVP)</td>
<td>++++</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>175/87</td>
<td>91</td>
<td>85/15 (RVP)</td>
<td>±</td>
</tr>
</tbody>
</table>

(PAP) indicates pulmonary arterial pressure, (RAP) right auricular pressure, and (RVP) right ventricular pressure.

![Chart showing an increase in cardiac output and decrease in right ventricular and systemic arterial pressures after, as compared to before, the intravenous administration of 8 mg. of hexamethonium ion to Cle, a white male, age 53, with hypertensive heart disease in congestive failure.](http://circ.ahajournals.org/)

![Chart showing an increase in cardiac output and decrease in right ventricular and systemic arterial pressures after, as compared to before, the intravenous administration of 8 mg. of hexamethonium ion to Cle, a white male, age 53, with hypertensive heart disease in congestive failure.](http://circ.ahajournals.org/)
Cardiac catheterization studies were carried out in four patients with hypertensive heart disease in severe congestive failure (table 2). In each instance there was a decrease in intracardiac or pulmonary arterial pressures which paralleled the fall in arterial pressure. Cardiac output, as determined by the direct Fick method, was performed in one case with heart failure (fig. 2). Following hexamethonium there was an increase in cardiac output, a fall in total peripheral resistance and a decrease in right ventricular pressure. In all instances there was dramatic symptomatic improvement in breathing.

**DISCUSSION**

It is a common observation that venesection or the application of venous tourniquets may produce immediate relief of symptoms in low output types of heart failure. When this procedure is performed, the venous pressure decreases but the arm-to-tongue circulation time remains essentially unchanged. According to McMichael and associates, following venesection the blood pressure almost always falls in the presence of an increased cardiac output, indicating a decreased peripheral resistance.

Several workers have observed that aminophylline similarly reduces elevated venous pressure. Howarth, McMichael and Sharpey-Schafer observed that the fall in right auricular pressure after aminophylline was comparable to that following the pooling of blood in the lower extremities using tourniquets, but there was a greater increase in cardiac output which was attributed to aminophylline's direct action on the myocardium. The effects were most readily observed in hypertensive heart failure.

During the hypotensive response to veratrum viride an increase in cardiac output and a decrease in pulmonary arterial pressure were observed to occur in hypertensive heart failure. Others, using tetraethylammonium, which blocks transmission of impulses through peripheral autonomic ganglia, demonstrated a fall in venous and arterial pressures both in hypertensive and nonhypertensive heart failure. There were no consistent changes in arm-to-tongue circulation time. Hayward as well as Lyons noted decrease in dyspnea but this was not observed by Relman and Epstein.

Priscoline, an adrenolytic and sympatholytic drug, also produced a decreased venous pressure in patients with congestive heart failure. However, the heart rate fell only in cases of cor pulmonale. Dresdale and his associates also observed in patients with primary pulmonary hypertension a more marked decrease in pulmonary vascular resistance following Priscoline than after tetraethylammonium. Perhaps Priscoline has some special effect in patients with heart failure associated with primary pulmonary hypertension.

It seems apparent that a variety of agents and procedures will produce a definite fall in venous pressure, right auricular and pulmonary arterial pressures when there is elevation initially. However, in contrast to results from venesection and with tetraethylammonium, the circulation time following hexamethonium improved. This is in keeping with a more complete return toward compensation in a failing heart.

Clinically in the long term therapy of severe hypertension using hexamethonium it has been observed that congestive heart failure when present is easier to control, and in occasional cases it has been possible to discontinue digitalis and mercurial diuretics.

It is suggested that hexamethonium may interrupt the congestive failure cycle at two points: (1) by decreasing the total peripheral resistance the work demand on the left ventricle is lessened and (2) by reducing the filling pressure of the right heart the overloaded right ventricle is able to contract more effectively. The mechanism by which the right heart pressures diminish cannot be definitely established at present. It seems probable, however, that several factors may act conjointly. First, the increased output of the left ventricle resulting from the decreased peripheral resistance produces an unloading of the congested right heart and central veins. Second, blockade of vasoconstrictor reflexes may increase the vascular capacity as a
consequence of peripheral vasodilatation, particularly of the postarteriolar vessels, thus producing a redistribution of the total blood volume.

These data supply additional suggestive evidence that the degree of constriction of the peripheral vessels may have an important influence on the function of the failing heart as originally suggested by McMichael.14 In addition, the beneficial effects of hexamethonium suggest that the adverse vasoconstriction which occurs in heart failure may be under neurogenic control.

Since the conclusion of our study there has appeared a series of papers by Brod and Fejfar in which the authors observed the effects of the adrenergic blocking agent Dibenamine on heart failure.15,16 Their findings were similar to ours in that there was a decrease in peripheral resistance with the reduction of blood pressure and a transient increase in cardiac output. They concluded that in heart failure neurogenic reflexes increase the arteriolar and venous tone, and are the cause of numerous secondary effects. Halmágyi and his associates also have recently recorded similar observations and conclusions.17

**Summary**

1. The immediate effects of hypotensive doses of hexamethonium given to 19 patients with various types of heart disease in congestive failure were a fall in venous pressure in all patients exhibiting initial elevations; shortening of the circulation time and a decrease in heart rate in most cases; and frequent symptomatic improvement in the degree of dyspnea and orthopnea.

2. Right auricular, right ventricular and pulmonary arterial pressures also were reduced following hexamethonium in patients with congestive heart failure. An increase in cardiac output with a marked decrease in total peripheral resistance was observed in one cardiac patient in which such determinations were carried out.

3. It is suggested that hexamethonium, by reducing the total peripheral resistance and diverting blood volume to the peripheral vasculature, may interrupt the vicious cycle associated with congestive heart failure by, first, decreasing the work demand of the left ventricle and, second, reducing venous overloading of the right heart.

**SUMARIO ESPAÑOL**

Dosis hipotenias de hexamethonium fueron administradas intravenosamente a 19 pacientes con varias clases de enfermedades del corazón en decompensación. Mejoramiento clínico juzgado por los métodos usuales se observó en la mayoría de los casos. Las presiones intracardíacas y de la arteria pulmonar decrecieron paralelamente a la presión arterial, luego de la administración de hexamethonium en cuatro pacientes con enfermedad hipertensiva del corazón con decompensación cardíaca. Se sugiere que el hexamethonium, mediante reducción de la resistencia periférica y mediante una redistribución del volumen de sangre puede interrumpir el ciclo vicioso de la decompensación cardíaca.

**REFERENCES**


The Effects of Hexamethonium on Certain Manifestations of Congestive Heart Failure
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