Effects of Reserpine Therapy on Cardiac Output and Atrioventricular Conduction During Rest and Controlled Heart Rates in Patients with Essential Hypertension

By Stafford I. Cohen, M.D., Melvin W. Young, M.D., Sun H. Lau, M.D., Jacob I. Haft, M.D., and Anthony N. Damato, M.D.

SUMMARY
The effects of long-term reserpine therapy (1) on cardiac output during rest and induced atrial tachycardia and (2) on atrioventricular (A-V) conduction were examined in a group of eight men with previously untreated essential hypertension. The patients were studied before and after 20 to 205 days of reserpine therapy. All studies were performed in the cardiopulmonary laboratory with the patients supine. Heart rate was controlled with a transvenous pacing catheter and a battery-powered pacemaker. After therapy six of six patients had a fall in cardiac output with a statistically significant difference ($P < 0.001$) between the means of paired pre-reserpine and reserpine cardiac outputs during both rest and paced tachycardia. At comparable heart rates, atrioventricular conduction increased in six of eight patients following reserpine, and a significant difference ($P < 0.05$) was evident when the means of pooled paired pre- and post-reserpine A-V conduction were compared.

This study indicates that therapeutically administered reserpine in a hypertensive population (1) may significantly lower cardiac output at rest with no further decrease during induced atrial tachycardia, and (2) may increase A-V conduction and enhance second degree heart block during induced atrial tachycardia.

Additional Indexing Words:
Atrial pacing Second degree heart block Atrial tachycardia Catecholamines

For approximately 13 years, reserpine has been used as an effective agent in the management of hypertension.1 During this interval, few inquiries have been made into the hemodynamic and electrophysiological alterations resulting from therapeutically prescribed reserpine. This study was undertaken to assess some of the effects of long-term administration of reserpine on a group of men with newly diagnosed essential hypertension. Of particular interest were (1) the effects of reserpine on cardiac output during rest and induced atrial tachycardia and (2) the effects of reserpine on atrioventricular (A-V) conduction. This information was considered to be of practical importance in view of the extensive use of reserpine in the treatment of an illness which may, in its natural course, result in hypertensive or coronary heart disease2,3 with attendant compromise in hemodynamic and electrophysiological function.

Methods
The study group consisted of eight previously untreated male patients with newly diagnosed essential hypertension. Their average age was 51.5 years (range, 43 to 61 years). Appropriate studies had been performed to exclude secondary...
causes of hypertension. A diagnosis of established hypertension was made if average arm cuff blood pressure recordings were more than 150/90 during 2 weeks' observation. No patient had symptoms of arteriosclerotic heart disease or evidence of congestive heart failure. Resting electrocardiograms were abnormal in five patients, and exercise tolerance tests produced "ischemic RS-T segment depression." 5 of more than 1 mm in two additional subjects.

Seven patients were studied before and after an average of 31 days of reserpine therapy (range, 20 to 48 days); the reserpine was administered in daily oral doses of either 0.25 or 0.50 mg. The mean total dose was 11.61 mg (range, 7.5 to 16.5 mg). The remaining patient was followed for 205 days while he was receiving 0.50 mg of reserpine per day. If a greater reduction of blood pressure was required after daily doses of 0.50 mg of reserpine, the patient was re-studied prior to the addition of other antihypertensive medication. At least 24 hours prior to the first study, each patient was introduced to all participating personnel and was familiarized with the setting of the cardiopulmonary suite.

All studies were performed in the cardiopulmonary laboratory with the patient supine and in a non-sedated, post-absorptive state. Utilizing 1% procaine anesthesia, a no. 7 transvenous luminal pacing catheter* was introduced percutaneously into an antecubital vein. It was then positioned against the lateral wall of the right atrium with fluoroscopic and electrocardiographic guidance. A battery-powered pacemaker (Medtronic "R" wave pulse generator model 5837) was utilized as a power source. It delivered impulses of 2-msec duration at an amperage which was adjusted between 2 and 7 ma to ensure reliable atrial "capture." The atrium was paced for 2-min intervals at rates which were started at slightly faster than the sinus rate and which were raised to a maximal rate of 150 beats/min or to the point of second degree A-V block.

A no. 18 Cournand needle was then introduced into the radial or brachial artery of the opposite arm. Resting cardiac output was determined by the dye-dilution technique with 7.5 mg of indocyanine green being injected into the right atrium through the luminal catheter. Blood was sampled at a constant rate from the brachial artery through a Gilford densitometer. Heart rate was then adjusted by atrial pacing to a fixed tachycardia (range, 105 to 135 beats/min). Circumstances necessitated a paced heart rate of only 80 beats/min in one patient because of the appearance of second degree A-V block at slightly higher rates. After 5 min of fixed paced heart rate, cardiac output was again determined. The patients experienced no subjective changes during the induced tachycardia.

All recordings were made on an Electronics for Medicine photographic oscilloscopic recorder. Cardiac outputs were obtained in duplicate and were determined from the inscribed curves by use of the Stewart-Hamilton formula.

A-V conduction time was determined from simultaneous standard electrocardiographic leads at a recording speed of 100 mm/sec. Intra-atrial electrocardiograms were recorded when a tripolar pacing catheter was utilized. For the sake of uniformity, pacemaker stimulus to onset of R wave was assumed to correspond to A-V conduction time. This assumption was based on the fact that there was no apparent delay from stimulus artifact to the onset of P waves as recorded during this and other studies7 by standard electrocardiographic leads and intra-atrial electrocardiograms.

Blood pressures were recorded at the start and end of each study by the arm cuff method.

Careful attention was given to proper grounding of all equipment and to the avoidance of handling the terminal poles of the electrode catheter during fluoroscopy.

Results

The results are summarized in tables 1 and 2. Comparative A-V conduction times were obtained in eight patients, of whom six had comparative cardiac output determinations.

Cardiac Output

Dye curves were reproducible when done in duplicate. In this laboratory cardiac output (CO) determined by the dye-dilution technique is comparable to that determined by the Fick method. All patients served as their own control. After therapy six of six had a fall in cardiac output during both sinus rhythm and paced tachycardia. The average pre-reserpine resting CO was 7.07 ± 1.01 L/min as compared to 5.25 ± 1.33 L/min during reserpine administration. Cardiac index (CI) values for the respective states were 3.72 ± 0.34 L/min/m² and 2.75 ± 0.53 L/min/m². There was a statistically significant difference (P < 0.001) between the means of the paired resting control and the resting reserpine CO (fig. 1).

The average pre-reserpine CO during paced atrial tachycardia (one exception, rate 80

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Table 1

Studies on Eight Patients Before and During Treatment with Reserpine

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Age (yr)</th>
<th>ECG</th>
<th>X-rays</th>
<th>Reserpine</th>
<th>BP</th>
<th>Heart rate</th>
<th>CO (L/min)</th>
<th>CI (L/min/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Days</td>
<td>Total (mg)</td>
<td>Rest</td>
<td>Paced</td>
<td>Rest</td>
</tr>
<tr>
<td>W.</td>
<td>45</td>
<td>+ Ex. tol. test</td>
<td>N</td>
<td>20</td>
<td>7.5</td>
<td>C 190/110</td>
<td>76</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R 140/80</td>
<td>72</td>
<td>105</td>
</tr>
<tr>
<td>V.</td>
<td>43</td>
<td>LAD</td>
<td>LVH</td>
<td>30</td>
<td>11.25</td>
<td>C 200/108</td>
<td>45</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R 150/90</td>
<td>44</td>
<td>80</td>
</tr>
<tr>
<td>S.</td>
<td>54</td>
<td>LVH</td>
<td>N</td>
<td>27</td>
<td>13.5</td>
<td>C 209/108</td>
<td>95</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R 175/9</td>
<td>93</td>
<td>110</td>
</tr>
<tr>
<td>F.</td>
<td>61</td>
<td>+ Ex. tol. test</td>
<td>N</td>
<td>21</td>
<td>8.0</td>
<td>C 180/95</td>
<td>60</td>
<td>135</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R 160/70</td>
<td>63</td>
<td>135</td>
</tr>
<tr>
<td>H.</td>
<td>56</td>
<td>N</td>
<td>N</td>
<td>36</td>
<td>13.5</td>
<td>C 160/110</td>
<td>72</td>
<td>125</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R 140/85</td>
<td>60</td>
<td>125</td>
</tr>
<tr>
<td>L.</td>
<td>54</td>
<td>LVH</td>
<td>N</td>
<td>38</td>
<td>11.0</td>
<td>C 180/105</td>
<td>76</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R 170/90</td>
<td>78</td>
<td>120</td>
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<tr>
<td>C.</td>
<td>48</td>
<td>LVH</td>
<td>LVH</td>
<td>205</td>
<td>102.5</td>
<td>C 194/120</td>
<td>80</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>A.</td>
<td>51</td>
<td>LAD</td>
<td>nonspec. ST &amp; T</td>
<td>48</td>
<td>16.5</td>
<td>C 180/110</td>
<td>58</td>
<td>Mean</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>sd</td>
</tr>
</tbody>
</table>

Abbreviations: ECG = electrocardiogram; BP = blood pressure; CO = cardiac output; CI = cardiac index; + Ex. tol. test = positive exercise tolerance test; LAD = left axis deviation; nonspec. ST & T = nonspecific ST & T wave abnormality; LVH = left ventricular hypertrophy; N = normal; C = control; R = reserpine therapy; sd = standard deviation; m² = square meter.
A-V Conduction at Paced Rates

<table>
<thead>
<tr>
<th>Pt.</th>
<th>A-V conduction time (msec) at paced rates of</th>
<th>Pooled AVC (msec) at comparable rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>80/min</td>
<td>100/min</td>
</tr>
<tr>
<td>W.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>230</td>
<td>250</td>
</tr>
<tr>
<td>R</td>
<td>240</td>
<td>260</td>
</tr>
<tr>
<td>V.</td>
<td></td>
<td>200</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>298</td>
<td></td>
</tr>
<tr>
<td>S.</td>
<td></td>
<td></td>
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<tr>
<td>C</td>
<td>166</td>
<td>177</td>
</tr>
<tr>
<td>R</td>
<td>170</td>
<td>186</td>
</tr>
<tr>
<td>F.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>169</td>
<td>190</td>
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<tr>
<td>R</td>
<td>234</td>
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<tr>
<td>H.</td>
<td></td>
<td></td>
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<tr>
<td>C</td>
<td>200</td>
<td>216</td>
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<tr>
<td>R</td>
<td>200</td>
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<tr>
<td>L.</td>
<td></td>
<td></td>
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<tr>
<td>C</td>
<td>210</td>
<td>300</td>
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<tr>
<td>R</td>
<td>238</td>
<td>310</td>
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<tr>
<td>C.</td>
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<tr>
<td>C</td>
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<td>222</td>
</tr>
<tr>
<td>R</td>
<td>200</td>
<td>220</td>
</tr>
<tr>
<td>A.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>190</td>
<td>197</td>
</tr>
<tr>
<td>R</td>
<td>200</td>
<td>206</td>
</tr>
</tbody>
</table>

Abbreviations: AVC = atrioventricular conduction; C = control; R = reserpine therapy. For definition of pooled AVC at comparable rates, refer to text and figure 3.

Figure 1
Cardiac output during rest and paced atrial tachycardia during control and reserpine states. The paired data yield a statistically significant fall in cardiac output after reserpine.

beats/min) was 6.98 ± 1.12 L/min as compared to 5.32 ± 1.20 L/min during reserpine therapy. CI values for the respective states were 3.66 ± 0.39 L/min/m² and 2.76 ± 0.39 L/min/m². There was also a significant difference (P < 0.001) between the means of these paired cardiac outputs (fig. 1).

Atrioventricular Conduction
At comparable heart rates, A-V conduction time increased in six of eight patients during reserpine therapy (table 2, fig. 2). In one of
the two remaining patients (C), A-V conduction time inconsistently increased over a full range of heart rates. In the other patient (H) although the P-R interval was not increased at a paced heart rate of 100, a rate of 110 beats/min resulted in markedly prolonged A-V conduction. Second degree block occurred before the next comparable rate could be reached. A significant difference \( (P < 0.05) \) was found between the pooled control and pooled reserpine A-V conduction times at comparable rates* (fig. 3). The average pooled change for all patients was + 53 msec with a range of 0 to 164 msec.

Atrioventricular block occurred at slower paced heart rates after reserpine in five of the eight patients. The average decrease was 14 beats/min for the entire group (range, 0 to -40 beats/min).

Heart Rate

Resting heart rate fluctuated slightly \( (\pm 4 \text{ beats/min}) \) in six patients, with an equal incidence of increasing and decreasing rates. The two remaining patients had decreases of 12 and 17 beats/min, respectively.

Discussion

Reserpine is a drug widely used in the treatment of hypertension. This study indicates that therapeutically administered reserpine in a hypertensive population may (1) significantly lower CO at rest with no further decrease during induced atrial tachycardia, (2) increase A-V conduction, and (3) enhance second degree heart block during induced atrial tachycardia.

Cardiac Output

The consistent and significant reduction of cardiac output following reserpine therapy is not in full agreement with previous investigations. In nonanesthetized canines, Moyer and associates\(^8\) found variable alterations in cardiac output during the first hours following intravenous administration of reserpine. The cardiac outputs were determined by the pulse contour method of Remington and Hamilton.

The effects on cardiac output following intramuscular reserpine were investigated in two human studies. Chidsey and associates\(^9\) administered parenteral syrosingopine to 10 nonhypertensive subjects, eight of whom had small and inconsistent changes in cardiac output, while the remaining two had a fall in cardiac output of 33%. Smulyan and associates\(^10\) administered 2.5 mg of parenteral reserpine to 22 patients with labile hypertension who were

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*Pooled A-V conduction time at comparable rates refers to the sum of A-V conduction times obtained at the same heart rates in the control and reserpine states, that is, for patient W, pooled control A-V conduction time = 230 + 250 + 260 msec; pooled reserpine = 240 + 260 + 280 msec.

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Figure 3

A-V conduction time following reserpine. A statistically significant increase in pooled A-V conduction time at comparable heart rates is noted after reserpine therapy.

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free of evidence of arteriosclerotic heart disease. Cardiac output was determined by the indicator-dilution method before and 4 hours after drug administration. The only significant difference between the reserpine group and a control group was a fall in mean blood pressure. It should be emphasized that this population had labile hypertension and the selection criteria included absence of evidence arteriosclerotic heart disease. These authors qualify the study as not relating "to the changes that take place during chronic oral administration of reserpine."

The long-term effects of oral administration of reserpine (Serpasil) and Rauwolfia serpentina (Raudixin) were sought by Cotten and associates in 98 hypertensive patients, 79% of whom had "clinical, ECG, or x-ray evidence of heart disease." Fifty-eight of these patients had a reduction of cardiac output as determined by the Starr formula (stroke volume = 100 + 0.5 pulse pressure - 0.6 diastolic blood pressure - 0.61 age. CO = stroke volume x average pulse rate). These investigators stated that "the validity of the formula devised by Starr for determining cardiac output by blood pressure and age remains to be proven." This formula later was shown inaccurate in a heterogeneous group of hospital patients.

It can be appreciated from this brief review of previous investigations that the present study differs in design with respect to duration and route of reserpine therapy, nonexclusion of patients because of arteriosclerotic or hypertensive cardiovascular disease, and accepted methodology for determining cardiac output. We suggest that the consistent decline in cardiac output found in the present study was a result of these considerations.

Reserpine in clinical dosage may effectively deplete myocardial catecholamine content. Chidsey and associates found a striking lowering of atrial appendage norepinephrine stores in a group of nonhypertensive patients receiving oral doses of reserpine prior to open heart surgery. Myocardial catecholamines, which are essential to a functionally intact adrenergic nervous system, appear to be of little importance to the normal organism in the basal state. Adverse hemodynamic effects of catecholamine depletion in resting man have been reported in patients with congestive heart failure. After guanethidine administration, congestive heart failure was intensified in the more severe cases.

The patient free of congestive heart failure with hypertensive cardiovascular disease or arteriosclerotic heart disease may be more dependent than normal persons on catecholamine stores in order to maintain basal hemodynamics.

An alternate mechanism to explain the consistent fall in cardiac output noted in our study is the effectiveness of reserpine in decreasing peripheral venous resistance and in diminishing venous return.

Mean arterial pressure was not directly recorded in this study, therefore an accurate statement cannot be made regarding changes in total peripheral resistance following reserpine therapy.

**Tachycardia and Cardiac Output**

Acceleration of heart rate after several minutes of atrial pacing in normal subjects does not alter cardiac output. This finding was once again demonstrated in the present series of pre-reserpine control measurements (fig. 4).

The effect of induced tachycardia on cardiac output in the catecholamine-depleted heart was a question of great interest, for cardiac compensation had been noted in the experimental animal during rapid atrial pacing. Nakano induced atrial and ventricular tachycardia in reserpine poisoned canines at rates ranging from 200 to 240 beats/min. Catecholamine depleted dogs demonstrated a greater reduction in cardiac output and contractile force during tachycardia than nondepleted control animals. Whittington and Zaimis noted a decline in the force of contraction of the "chronically reserpinized" cat heart at rates of approximately 320 beats/min, whereas decompenation did not occur in control animals until rates of 400 beats/min were employed. No compromise in cardiac output was noted during the modest tachycardias induced in the
norepinephrine are capable of enhancing conduction across the atrioventricular node. 27-30 Norepinephrine is the predominant myocardial catecholamine, and there is direct evidence that myocardial tissue is depleted of norepinephrine following reserpine administration. Reserpin-induced norepinephrine loss in the human atrial appendage has been previously cited.13 In addition, Gaffney and associates31 reported reserpine-induced norepinephrine depletion from the area of the canine sino-atrial node. Slowed A-V conduction would be an expected result after effective loss of myocardial as well as adrenal stores of catecholamine. Several investigators have commented on apparent slowing of A-V conduction following administration of reserpine; however there is no agreement on the mechanism.

Innes and associates22 noted a prolongation of A-V conduction time and functional refractory period of atrioventricular transmission in the canine heart-lung preparation. This finding was attributed to a direct effect of reserpine rather than to depletion of norepinephrine.

Several reports have noted a decrease in the ventricular response during atrial fibrillation in patients who have received reserpine or guanethidine.15, 33, 34 After a detailed study of atrial rates and ventricular response during atrial fibrillation, Modell and Hussar23 concluded that “the only simple and reasonable explanation for the ventricular slowing is depression of A-V conduction by reserpine.” Gaffney and Braunwald15 concluded that the conductive properties of the A-V conduction system had been adversely affected by guanethidine. The mechanism was presumed to be an increase in the refractory period of the A-V conduction system following depletion of myocardial catecholamine stores as well as withdrawal of adrenergic stimuli.

The present study provides additional evidence that reserpine prolongs A-V conduction presumably by the same mechanism advanced by Gaffney and Braunwald. Increased A-V conduction time was noted in six of eight patients following reserpine administration during all comparable paced heart rates. In
addition, the total group demonstrated a significant difference between pooled pre-reserpine and reserpine A-V conduction times at comparable heart rates \((P < 0.05)\) (fig. 3).

Further evidence of the adverse effects of reserpine therapy on the functional integrity of A-V conduction was provided by the appearance of second degree A-V block at slower paced heart rates in five of the eight patients following treatment.

These changes in A-V conduction indicate that a potential source of clinical difficulty exists when reserpine is administered to a patient with a pre-existing A-V conduction disturbance or when reserpine is used in combination with other agents known to increase A-V conduction time. Existing reports pertaining to both animal and clinical observations have made reference to this danger.\(^{27, 85}\)

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References


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