Effect of Digitalis in Patients Receiving Reserpine

By Bernard Lown, M.D., Lee Ehrlich, M.D., Bernard Lipschultz, M.D., and John Blake, M.D.

Recently, we encountered an unusual response to digitalis. A patient with rheumatic valvular disease, congestive heart failure, and atrial fibrillation exhibited simultaneously evidence regarded by some as due to underdigitalization and by others as the result of overdigitalization. During mild exertion, the ventricular rate accelerated from 70 to 140 beats per minute with development of a pulse deficit suggesting inadequate digitalization. At the same time, however, this patient developed ventricular bigeminy with multi-form complexes suggesting digitalis intoxication (fig. 1). In order to clarify this anomalous situation, a digitalis tolerance test was performed with acetyl strophanthin.1 The first small increment of acetyl strophanthin provoked ventricular bigeminal rhythm (fig. 2), a response consistent with digitalis overdosage. Mild exercise immediately following the test, however, again accelerated the rate to 140, a response compatible with underdigitalization. Thus the paradox of apparent co-existing evidence suggesting both overdigitalization as well as underdigitalization remained unsolved.

This patient was receiving many medications. With the exception of reserpine, which was being administered in a daily oral dose of 1.0 mg., none of the other drugs appeared likely to alter the response to digitalis. A search of the literature did not reveal significant information concerning the effects of reserpine upon the digitalized state. The present study was therefore undertaken to determine (1) whether reserpine alters the toxic action of digitalis upon atrium, atrioventricular conduction system, and ventricle; (2) whether the carotid sinuses are unduly sensitized by the combined use of these two drugs; and (3) whether reserpine can control the ventricular rate in the partially digitalized patient with atrial fibrillation.

Material and Methods

The sensitivity of the myocardium to digitalis was tested with acetyl strophanthin both immediately before and during the administration of reserpine. Acetyl strophanthin is a synthetic aglycone of strophanthin. When it is given intravenously, a cardiac effect occurs within 3 minutes. Peak action develops in 12 minutes, and dissipation is complete within 2 hours.

Fifteen patients in congestive heart failure were studied. All were receiving maintenance doses of one of the long-acting digitalis preparations. Six were in normal sinus rhythm and nine had atrial fibrillation. Two of the patients with normal sinus rhythm had coronary artery disease, one rheumatic valvular disease, two cor pulmonale, and one idiopathic myocarditis. Of the patients with atrial fibrillation eight had rheumatic valvular and one had coronary artery disease.

The same experimental design was employed in each of the 15 patients. Two digitalizations were carried out in identical manner: 0.15 mg. of acetyl strophanthin in 2.5 ml. of diluent was injected intravenously every 5 minutes until development of the earliest evidence of intoxification or the administration of a total dose of 1.2 mg. Nausea, vomiting, and a change in rhythm or in conduction constituted the toxic end-point. This schedule represents a slight modification in the use of acetyl strophanthin from that proposed initially.1 The reduction in the size of the incremental dose has enhanced the safety of such ultra-rapid digitalizations.

Immediately following the first digitalization 1 mg. of reserpine was given intramuscularly. This was continued daily for 3 days. On the third day, a second digitalization with acetyl strophanthin was repeated. Prior to and immediately following each of the two digitalizations, the sensitivity of the heart to right carotid sinus massage was tested. This maneuver was employed to assess the cardiac...

From the Department of Nutrition, Harvard School of Public Health, the Medical Clinics of the Peter Bent Brigham Hospital, Boston, Massachusetts; and the Arizona State University Cardiac Laboratory at the Good Samaritan Hospital and the Veterans Administration Hospital, Phoenix, Arizona.

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response to vagus nerve stimulation when reserpine and digitalis were combined. Throughout this study there was no change in the maintenance dose of the long-acting digitalis preparations that these patients were receiving.

In addition, three of the patients with atrial fibrillation were subjected to mild exercise consisting of 10 sit-ups, accomplished before and after each of the two digitalizations.

Results

Patients with Atrial Fibrillation

Reserpine increased the toxic action of digitalis. This was clearly demonstrated in patients with atrial fibrillation. In the digitalization following reserpine, the tolerated dose of acetyl strophanthidin was reduced, the incidence or arrhythmias was increased, and the heart was more markedly slowed (table 1A).

In five of the nine patients with atrial fibrillation, after reserpine, the tolerated dose of acetyl strophanthidin was reduced. In these five patients, the mean tolerated dose of acetyl strophanthidin was 1.1 mg. in the first and 0.5 mg. in the second digitalization. The electrocardiogram in one of these five patients is illustrated (fig. 3). In the initial digitalization only one patient developed an arrhythmia before receiving the full dose of 1.2 mg. In the second digitalization, however, eight of the nine subjects exhibited toxicity consisting of complete heart block in one, nodal rhythm in three, and ventricular ectopic beats in five. In four of the five, the ventricular extrasystoles were either bigeminal or multiform. Another example of increased cardiac reactivity to acetyl strophanthidin is shown in figure 4. In this patient during the control digitalization, 1.2 mg. of acetyl strophanthidin merely slowed the ventricular rate; following reserpine, however, an identical dose of acetyl strophanthidin induced nodal rhythm with 3:2 antegrade block below a complete atrioventricular block with periodic ventricular escape beats. This same patient illustrates the remarkable slowing in heart rate that results from the combined action of reserpine and digitalis. In the entire group of nine patients with atrial fibrillation, the mean ventricular rate was reduced from 75 to 61 in the first and from 55 to 42 beats per minute in the second digitalization.

Patients with Normal Sinus Rhythm

In patients with normal sinus rhythm reserpine did not appear to alter the response
to digitalization (table 1B). Five of the six patients with normal sinus rhythm were digitalized twice. In none of the five was there a change in the dose of acetyl strophanthidin or in the incidence of toxic reactions following reserpine.

In order to determine whether reserpine increased the sensitivity of the heart to vagal stimulation in digitalized patients, with either sinus rhythm or atrial fibrillation, the carotid sinus on the right side was massaged on four different occasions, i.e., before and after each of the two digitalizations. Both acetyl strophanthidin and reserpine increased the cardiac response to this vagal maneuver. The most marked effect was noted when the two drugs were used together (table 2). Abnormal reactions exclusive of heart rate slowing were observed in three of the 15 patients before the first digitalization. Two of these three patients were unable to tolerate the full dose of 1.2 mg. of acetyl strophanthidin. When the carotid sinus was stimulated immediately after the first digitalization, abnormal reactions occurred in seven of the 15 patients. Carotid sinus stimulation after reserpine administration but before the second digitalization induced an abnormal response in nine of the 15 subjects. In one of these patients the vagal maneuver provoked ventricular bigeminal rhythm. The carotid sinus was tested in only 11 of the patients who were digitalized after reserpine, the four remaining patients showed advanced toxic reactions from acetyl strophanthidin and were therefore not considered to be suitable candidates for this maneuver. Of the 11 patients tested, nine reacted abnormally, two exhibiting bigeminal rhythm. Since the four patients in whom carotid sinus massage was not repeated had reacted adversely to vagal stimulation before the second digitalization, it is likely that following the digitalization with acetyl strophanthidin a similar but more marked response would have occurred. Thus 13 out of the 15 patients might have shown enhanced responsiveness to the carotid maneuver after both drugs.

In the digitalized patient, reserpine promotes bradycardia. To determine whether the slowing is maintained after exertion, three patients with atrial fibrillation were made to exercise before and after the two digitalizations. Though reserpine slowed the mean ventricular rate from 90 to 70 beats per minute

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**Figure 2**

*Same patient as in figure 1. A single increment of 0.15 mg. of acetyl strophanthidin induced multiform ventricular bigeminal rhythm.*
Table 1A

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose AS (mg.)</th>
<th>Heart rate</th>
<th>Toxic* reaction</th>
<th>Dose AS (mg.)</th>
<th>Heart rate</th>
<th>Toxic* reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before reserpine</td>
<td></td>
<td></td>
<td></td>
<td>After reserpine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Initial</td>
<td>Final</td>
<td></td>
<td>Initial</td>
<td>Final</td>
<td></td>
</tr>
<tr>
<td>1. R.M.A.</td>
<td>1.2</td>
<td>60</td>
<td>40</td>
<td>None</td>
<td>1.2</td>
<td>40</td>
</tr>
<tr>
<td>2. M.K.</td>
<td>1.2</td>
<td>70</td>
<td>68</td>
<td>None</td>
<td>1.2</td>
<td>55</td>
</tr>
<tr>
<td>3. R.N.</td>
<td>1.2</td>
<td>79</td>
<td>58</td>
<td>None</td>
<td>1.2</td>
<td>56</td>
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<tr>
<td>4. J.W.</td>
<td>1.2</td>
<td>60</td>
<td>42</td>
<td>None</td>
<td>1.2</td>
<td>52</td>
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<tr>
<td>5. B.R.</td>
<td>1.2</td>
<td>92</td>
<td>70</td>
<td>None</td>
<td>0.6</td>
<td>68</td>
</tr>
<tr>
<td>6. A.S.</td>
<td>1.2</td>
<td>80</td>
<td>68</td>
<td>None</td>
<td>0.75</td>
<td>64</td>
</tr>
<tr>
<td>7. G.C.</td>
<td>0.9</td>
<td>80</td>
<td>64</td>
<td>Occasional VPB</td>
<td>0.45</td>
<td>60</td>
</tr>
<tr>
<td>8. F.M.</td>
<td>1.2</td>
<td>80</td>
<td>35</td>
<td>None</td>
<td>0.6</td>
<td>55</td>
</tr>
<tr>
<td>9. E.M.N.</td>
<td>1.2</td>
<td>70</td>
<td>50</td>
<td>None</td>
<td>0.3</td>
<td>45</td>
</tr>
</tbody>
</table>

*Exclusive of nausea.

AS = Acetyl strophanthidin.

VPB = Ventricular premature beats.

Table 1B

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose AS (mg.)</th>
<th>Heart rate</th>
<th>Toxic* reaction</th>
<th>Dose AS (mg.)</th>
<th>Heart rate</th>
<th>Toxic* reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before reserpine</td>
<td></td>
<td></td>
<td></td>
<td>After reserpine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Initial</td>
<td>Final</td>
<td></td>
<td>Initial</td>
<td>Final</td>
<td></td>
</tr>
<tr>
<td>1. A.N.</td>
<td>1.2</td>
<td>100</td>
<td>88</td>
<td>None</td>
<td>1.2</td>
<td>84</td>
</tr>
<tr>
<td>Sinus pauses with nodal escape</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. W.C.</td>
<td>1.2</td>
<td>100</td>
<td>94</td>
<td>None</td>
<td>1.2</td>
<td>105</td>
</tr>
<tr>
<td>3. B.J.</td>
<td>0.6</td>
<td>87</td>
<td>75</td>
<td>Ventricular bigeminy</td>
<td>0.75</td>
<td>72</td>
</tr>
<tr>
<td>VPB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. M.S.L.</td>
<td>1.2</td>
<td>98</td>
<td>77</td>
<td>None</td>
<td>1.2</td>
<td>90</td>
</tr>
<tr>
<td>5. M.H.</td>
<td>1.2</td>
<td>105</td>
<td>100</td>
<td>None</td>
<td>1.2</td>
<td>108</td>
</tr>
<tr>
<td>6. J.M.S.</td>
<td>0.9</td>
<td>82</td>
<td>80</td>
<td>Ventricular bigeminy</td>
<td>Heart block after reserpine, not retested with A.S.</td>
<td></td>
</tr>
</tbody>
</table>

*Exclusive of nausea.

at rest, it did not prevent cardiac acceleration (table 3). Exercise raised the heart rate to the same level whether or not reserpine was given. Only digitalization controlled the ventricular rate during and after exercise.

Discussion

This investigation was undertaken to explain the occurrence of ventricular bigeminy in a patient having rapid heart rate and atrial fibrillation. The results of the present study afford an explanation for this phenomenon. When a digitalized patient who is receiving reserpine exhibits bradycardia and ventricular premature beats, the maintenance dose of digitalis is reduced. Since the rauwolfia alkaloids do not increase cardiac contractility, they cannot be substituted for the cardiac glycosides. Though the heart rate may continue to be slow at rest, with inadequate digitalis maintenance therapy cardiac decompensation might nevertheless recur. In the patient with atrial fibrillation, the earliest evidence of heart failure would consist of excessive
ventricular acceleration during exercise. The findings also indicate that reserpine sensitizes the myocardium to the induction of ectopic beats by digitalis. Since myocardial aerobic metabolism is seriously compromised during tachycardia, it seems likely that ventricular extrasystoles would be more readily produced by such drug interaction when the heart rate is rapid. In the patient with atrial fibrillation the end result may be bigeminal rhythm and a rapid ventricular rate.

Reserpine increases central parasympathetic outflow thereby augmenting vagal tone. In the present study this was demonstrated by response to carotid sinus stimulation before and after administration of reserpine. Of 15 patients tested only three had abnormal reactions to carotid sinus massage initially as contrasted to nine such reactions after pre-treatment with reserpine.

It is well established that digitalization also sensitizes the heart to vagal discharge. Carotid sinus stimulation may be employed to detect overdigitalization before it becomes otherwise evident. The emergence in the digitalized patient of heart block, nodal rhythm, or ectopic beats during this vagal maneuver suggests incipient intoxication. It is of interest that two of the patients who developed untoward reactions during the initial carotid sinus test were unable to tolerate the full dose of acetyl strophanthidin. These two were also the only patients to develop ventricular bigeminal rhythm during the control digitalization. In

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Effect of Carotid Sinus Stimulation in 15 Patients Receiving Acetyl Strophanthidin and Reserpine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reserpine</td>
<td>Acetyl strophanthidin</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*In four of the 15 patients severe toxic reaction precluded the carotid sinus maneuver.

†B = Ventricular bigeminy provoked by carotid sinus stimulation.

the patient receiving reserpine, therefore, an adverse response to carotid sinus stimulation does not constitute evidence of overdigitalization.

The vagal action of reserpine has been employed to control various atrial arrhythmias. In an occasional patient reserpine has proved effective in preventing supraventricular arrhythmias. Reserpine materially reduces the immediate mortality from ventricular fibrillation in dogs subjected to acute coronary artery ligation. Less well known is the finding that rauwolfia alkaloids may precipitate ventricular premature beats. Wilson and Wimberley described four patients in whom Ranidixin in a dose of 100 to 200 mg. per day produced numerous ventricular extrasystoles and bigeminy. Only one of the patients was receiving digitalis. Schreader and Etzl noted an increased incidence of ventricular ectopic beats in patients receiving both rauwolfia alkaloids and digitalis. Thus of 15 patients receiving both drugs, seven showed ventricular extrasystoles as contrasted with three of 15 patients who were receiving only rauwolfia alkaloids.

The mechanism by which reserpine predisposes to ventricular ectopic beats is unknown. Scherf and Schott have demonstrated that stimulating the vagus nerve in dogs receiving a cardiac irritant such as aconitine, induces ventricular extrasystoles and other ventricular arrhythmias. The enhanced ventricular automaticity shown in the present study may be due to such a vagal effect. An alternative mechanism may be suggested. Reserpine lib-
A dose of 0.9 mg of acetyl strophanthidin produced but a rare ventricular premature beat. After the administration of reserpine for 3 days, only half the control dose of acetyl strophanthidin was tolerated and resulted in the development of ventricular bigeminal rhythm.

Acetyl strophanthidin slowed ventricular rate from 79 to 58 without altering underlying mechanism of atrial fibrillation. After reserpine same dose of acetyl strophanthidin induced nodal rhythm with 3:2 antegrade block and occasional ventricular escape beats.

erates catechol amines from peripheral stores. Small intravenous doses deplete cardiac norepinephrine. The absence of neurohumoral transmitter inhibits the peripheral adrenergic system. The marked potentiation of epinephrine action by reserpine may be due to such a loss of norepinephrine from nerve endings thereby resulting in a functional sympathetic "denervation." Adrenal medullary innervation is cholinergic. If, in the reserpine-treated subject, digitalis enhances the action of acetylcholine at this site, it may then predispose to increase catecholamine release during exercise or excitement and favor the development of ventricular arrhythmias. It is of interest that reserpine potentiation
of digitalis action was observed only in patients with atrial fibrillation. Gold and Otto first called attention to the fact that digitalis-provoked bigeminal rhythm was more likely to occur in patients with atrial fibrillation as compared to those having sinus rhythm. Thus among 240 patients with atrial fibrillation 17 per cent exhibited digitalis bigeminy, whereas among 615 cardiac patients with normal sinus rhythm only 2.8 per cent had such an arrhythmia. It is not clear why the presence of atrial fibrillation should favor the occurrence of digitalis-induced ventricular ectopic beats. There is much evidence indicating that atrial fibrillation reduces the cardiac output and compromises cardiac efficiency. Presumably deterioration in cardiac function may be the necessary background for exhibition of the reserpine digitalis interaction.

The clinical implication of the findings here reported is that the commonly used indices of overdigitalization may prove deceptive in patients with serious heart disease who are receiving reserpine. Thus marked bradycardia, ventricular ectopic beats, and even bigeminal rhythm as well as abnormal responses to carotid sinus stimulation may not denote overdigitalization. These manifestations may indeed occur in patients who are inadequately digitalized.

Summary and Conclusions

Reserpine enhanced the toxic action of the digitalis-like drug, acetyl strophanthidin, upon the atria, atroventricular conduction system, and ventricles. This potentiation was demonstrated only in patients with atrial fibrillation. While eight of nine patients in atrial fibrillation who were receiving reserpine developed advanced toxic rhythms during acute digitalization, only one patient responded in this fashion when reserpine was not given. Patients receiving reserpine were unable to tolerate full doses of acetyl strophanthidin.

Reserpine increased cardiac sensitivity to carotid sinus stimulation. This was true irrespective of heart rhythm, and was most marked when the patient received digitalis as well.

Reserpine did not prevent significant acceleration in the ventricular rate following exercise.

References

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BERNARD LOWN, LEE EHRLICH, BERNARD LIPSCHULTZ and JOHN BLAKE

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