Influence of Syrosingopine on the Cardiovascular Response to Acute Hypoxemia and Exercise

By Charles A. Chidsey, M.D., Robert L. Frye, M.D., Richard L. Kahlert, M.D., and Eugene Braunwald, M.D.

Although the mechanism responsible for the increased cardiac output which occurs during acute hypoxemia has not been clearly defined, the participation of the sympatho-adrenal system has been repeatedly implicated. It is now well established that the rauwolfia alkaloids are capable of depleting the heart and blood vessels of their stores of norepinephrine. In this manner, they appear to produce a functional sympathetic denervation of these organs, as judged by inhibition of the responses of: (a) the arterial pressure to pharmacological stimulation of the sympathetic ganglia, and to electrical stimulation of the splanchnic nerve; (b) the pupil to electrical stimulation of the superior cervical ganglion; and (c) the heart rate to electrical stimulation of the accelerans nerve. The purpose of this investigation was to examine the effects of one of these agents on the cardiovascular response to acutely induced hypoxemia in intact human subjects. Since the circulatory effects of exercise have also been considered to be mediated largely by the autonomic nervous system, similar studies on the effects of syrosingopine upon the response to this stimulus were also carried out. In addition, this study was designed to determine the effect of the chronic administration of this agent on cardiac output and on left-ventricular work. The latter observations were considered of importance in view of the widespread clinical use of these drugs and the paucity of objective hemodynamic measurements in man.

Methods

The 10 subjects were normal volunteers ranging in age between 18 and 21 years, 6 male and 4 female. All studies were carried out in the basal postabsorptive state, without any premedication, after the subjects had been thoroughly familiarized with the laboratory, equipment, and procedure. Each subject was studied twice. After the initial control measurements were performed, syrosingopine was administered intramuscularly every six hours over a seven-day period. The amount, usually limited by postural hypotension or other symptoms related to the drug's administration, ranged from 1.5 to 6 mg./day and averaged 4.8 mg./day. The total dose varied between 0.3 and 0.9 mg./Kg. and averaged 0.6 mg./Kg. At the conclusion of the treatment period, the control study was undertaken first in all five subjects exposed to hypoxia. In two of the subjects in whom the response to exercise was studied, observations were first made while the subject was receiving syrosingopine and the control study was carried out three weeks after the drug had been discontinued.

In the studies involving hypoxemia, each of the subjects breathed through a mouthpiece continually for two periods of 15 minutes each. In one period, the gas mixture contained 21 per cent oxygen in nitrogen, in the other 12 per cent oxygen in nitrogen. In the different subjects, the order in which these were given was randomized. At 8 and 12 minutes in each breathing period, cardiac output and central blood volume were measured.

In the exercise studies, control measurements were first made with the subject's legs resting quietly on a bicycle ergometer, and then during exercise consisting of pedaling the ergometer at a rate of 55 r.p.m. for 10 minutes (1,500 foot pounds/min.). Measurements of heart rate, blood pressure, cardiac output, minute ventilation, and oxygen consumption were made prior to the initiation of exercise and, with the exception of oxygen consumption which was measured at six and nine minutes, at three-minute intervals during the exercise period.

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Cardiac output and central blood volume were measured by the indicator-dilution technique using indocyanine dye. Exactly 2 ml of dye solution were injected via a 50-cm, polyethylene catheter (PE 50, 0.58-mm I.D.) which was introduced percutaneously through an antecubital vein into the superior vena cava or right atrium. Blood was sampled from the brachial artery through an indwelling needle and was delivered to a cuvette densitometer. The details of this technique have been described previously.11 The cardiac output and central blood volume were calculated utilizing the formulas of Stewart and Hamilton12 after the recorded curves had been re-plotted on semilogarithmic paper. The standard deviation of the mean value; that for central blood volume was 65 ml, or 4 per cent of the mean value. Differences between 20 duplicate determinations of cardiac output, and these were analyzed for gas content using the manometric method of Van Slyke and Neill. The arterial blood pressure was measured, by means of a Statham pressure transducer, intermittently throughout each study and was recorded, together with the electrocardiogram, on an oscillographic recorder.

Platelet serotonin was assayed in three subjects by the method of Weissbach and Redfield. In brief, the platelets were isolated by differential centrifugation, washed, and lysed in a small volume of 0.1 N HCl. Serotonin was measured spectrophotofluorometrically in a deproteinized aliquot of the lysate. Protein concentration was also measured and blood serotonin was expressed as 

**Results**

**Clinical Observations**

Symptoms developed in every subject as a result of syrosingopine administration. These included: (1) light headedness, dizziness, and other symptoms secondary to postural hypotension; (2) lethargy and somnolence; (3) gastrointestinal disturbances including anorexia, nausea, diarrhea, and abdominal distress. The arterial pressure, as recorded by sphygmomanometry, declined in all subjects during the period of drug administration. When the subjects were in the erect position, the fall in pressure averaged 8/5 mm. Hg with a maximum fall of 21/19 mm. Hg; when they were in the recumbent position, the fall in blood pressure averaged 22/11 mm. Hg with a maximum fall of 32/18 mm. Hg. In several subjects, individual doses of syrosin-
Table 2

Group II: Hemodynamic Data Measured in Five Subjects at Rest and During Exercise Before and After Syrosingopine*

<table>
<thead>
<tr>
<th>Subject</th>
<th>Condition</th>
<th>$\text{VO}_2$</th>
<th>HR</th>
<th>CI</th>
<th>SV</th>
<th>BAP</th>
<th>MWLV</th>
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<tbody>
<tr>
<td>6</td>
<td>Rest</td>
<td>194 133</td>
<td>66</td>
<td>53</td>
<td>2.94 2.66</td>
<td>44 50</td>
<td>81 91</td>
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<tr>
<td>1.88</td>
<td>Ex3</td>
<td>— —</td>
<td>105</td>
<td>92</td>
<td>5.71 5.00</td>
<td>54 54</td>
<td>93 110</td>
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<tr>
<td>7</td>
<td>Ex9</td>
<td>622 650</td>
<td>108</td>
<td>96</td>
<td>6.12 5.15</td>
<td>57 54</td>
<td>91 105</td>
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<tr>
<td>1.56</td>
<td>Rest</td>
<td>86 112</td>
<td>78 68</td>
<td>2.42 2.82</td>
<td>31 42</td>
<td>92 77</td>
<td>5.9 5.8</td>
</tr>
<tr>
<td>8</td>
<td>Ex3</td>
<td>— —</td>
<td>120</td>
<td>112</td>
<td>3.97 5.34</td>
<td>33 48</td>
<td>98 95</td>
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<tr>
<td>1.59</td>
<td>Ex9</td>
<td>626 658</td>
<td>120</td>
<td>128</td>
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<td>96 87</td>
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<tr>
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<td>Rest</td>
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<td>87 86</td>
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<td>40 44</td>
<td>100 119</td>
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<td>140</td>
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<tr>
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<td>Ex9</td>
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<td>168</td>
<td>166</td>
<td>6.64 6.94</td>
<td>40 42</td>
<td>117 134</td>
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<tr>
<td>1.86</td>
<td>Rest</td>
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<td>76 73</td>
<td>2.64 3.14</td>
<td>35 44</td>
<td>69 92</td>
<td>4.1 6.5</td>
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<tr>
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<td>Ex3</td>
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<td>130</td>
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<td>49 43</td>
<td>85 114</td>
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<tr>
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<td>162</td>
<td>7.15 7.46</td>
<td>42 46</td>
<td>82 109</td>
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<tr>
<td>1.66</td>
<td>Rest</td>
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<td>75 54</td>
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<td>30 44</td>
<td>85 85</td>
<td>6.2 5.5</td>
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<td>— —</td>
<td>— —</td>
<td>— —</td>
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<tr>
<td>10</td>
<td>Ex9</td>
<td>531 600</td>
<td>128</td>
<td>98</td>
<td>5.39 5.65</td>
<td>42 52</td>
<td>102 95</td>
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Average

<table>
<thead>
<tr>
<th>Condition</th>
<th>$\text{VO}_2$</th>
<th>HR</th>
<th>CI</th>
<th>SV</th>
<th>BAP</th>
<th>MWLV</th>
</tr>
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<tbody>
<tr>
<td>Rest</td>
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<td>76 67</td>
<td>2.84 2.95</td>
<td>37 45</td>
<td>85 93</td>
<td>6.1 6.9</td>
</tr>
<tr>
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<td>5.46 5.29</td>
<td>43 46</td>
<td>97 115</td>
<td>12.7 14.9</td>
</tr>
<tr>
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<td>648 672</td>
<td>140 130</td>
<td>6.34 6.37</td>
<td>46 49</td>
<td>98 106</td>
<td>16.4 16.8</td>
</tr>
</tbody>
</table>

*Observations at six minutes of exercise were almost identical to those made at nine minutes and have not been included.

**Conditions**: $\text{VO}_2$, oxygen consumption (ml./min./M$^2$).

For other abbreviations see footnote to table 1.

Hemodynamic Response to Acute Hypoxemia (Group I)

During the control study, the inhalation of 12 per cent O$_2$ resulted in an increment in heart rate which ranged from 12 to 22 and averaged 18 beats/min., representing a 27 per cent increase. After syrosingopine, hypoxia again produced an increase in pulse rate, but ventricular minute work declined in two instances in group I, coincident with the large fall in cardiac output, while in group II an increase in this parameter occurred in two subjects (subjects 8 and 9). Since no deliberate attempt was made to control the position of the catheter tip from one study to the next, no comparisons were made of central blood volume measurements. There were no demonstrable effects upon any of the other measurements including frequency of ventilation, minute ventilation, oxygen consumption, respiratory quotient, and arterial oxygen saturation.
it tended to be of a smaller magnitude, ranging from 6 to 14, and averaging 10 beats/min., representing a 17 per cent increase. Thus, the average pulse rate during hypoxia after syrosingopine (69 beats/min.) was substantially lower than that observed during hypoxia without the drug (85 beats/min.).

When the cardiac index was related to the arterial oxygen saturation (fig. 1), it was apparent that the output response of the heart to any given hypoxicemic stimulus was generally comparable under both conditions. Both in the control period and after syrosingopine, the stroke volume demonstrated a small increase with hypoxia. In three of the five subjects, there was a small increment in arterial pressure during hypoxia, both in the control period and after syrosingopine. Left-ventricular minute work also increased in the same fashion. This increase, however, tended to be less after syrosingopine. The central blood volume rose substantially during hypoxia in two (subjects 3 and 5) of the four subjects studied during the control period; it rose in two (subjects 2 and 4) of the five subjects subjected to hypoxia during syrosingopine; the changes in the other studies were not considered to be greater than the error of the measurement. A comparable increase in minute ventilation and respiratory rate was observed in response to hypoxia both during the control period and after syrosingopine.

Physiological changes with exercise during a control study and after syrosingopine administration.

Hemodynamic Response to Exercise (Group II)

Nine minutes of muscular exercise resulted in an augmentation of the oxygen consumption to approximately five to seven times the resting level in both the control and syrosingopine periods. The average absolute increase in pulse rate was the same in both periods. The average increase in cardiac output was also essentially the same in both conditions at nine minutes. During the control period, the stroke volume increased in four of the five subjects, with no changes in the fifth, during exercise, and the average increase was 9 ml./M.2. There was a smaller increase during syrosingopine administration in four of the subjects and the average increase was 4 ml./M.2. The increase of arterial pressure in both periods was essentially the same. This was also true of left-ventricular minute work.

The rate at which these variables changed during exercise was essentially the same dur-
ing the control and syrosingopine periods. The response of subject 9 is depicted in figure 2 and is representative of the entire group (table 2).

Serotonin Measurements

The biochemical response to syrosingopine was estimated by measuring the platelet concentration of serotonin. The control observations, 0.19 to 0.60 μg./mg. of platelet protein, were within the normal range. The concentration of amine fell sharply after the first day of drug administration and thereafter remained below the level which can be detected by this method (less than 0.03 μg./mg. platelet protein) (table 3).

Discussion

Since this study was undertaken to examine the effects of norepinephrine depletion and its functional counterpart, sympathetic denervation, on the cardiac response to hypoxia and exercise, it is necessary first to determine if depletion occurred during the administration of the syrosingopine. Although the answer to this question must of necessity be indirect in man, certain observations suggest that a reduction in the norepinephrine content of the cardiovascular system did indeed occur. Syrosingopine, a semisynthetic rauwolfia alkaloid, has been shown to be effective in depleting norepinephrine from the heart. The total amount given in the studies reported herein, 0.3 to 0.9 mg./Kg. over a seven-day period, is in excess of the amount required in the dog and rabbit to achieve maximal depletion. In the rabbit, doses of syrosingopine (0.5 mg./Kg. in one injection) which were 20 times greater than that required to produce myocardial norepinephrine depletion resulted in only a moderate reduction of platelet serotonin; therefore, the pronounced depletion of platelet serotonin observed in the three subjects in whom this measurement was made suggests that reduction in heart norepinephrine occurred at this dose level.

All subjects exhibited sedation and increased somnolence during syrosingopine treatment. These findings have been shown to correlate with central nervous system depletion of amines in animals after reserpine. In addition, heart rate was reduced in all patients during the period of drug administration. These findings all suggest that syrosingopine, as given in this study, had the anticipated effect, and it would therefore seem reasonable to assume that a significant reduction in the norepinephrine content of the cardiovascular system occurred during syrosingopine administration.

The data obtained indicate that of all of the measurements carried out, only the heart rate appeared to be consistently reduced by syrosingopine. The brachial arterial pressure was reduced by syrosingopine in every subject in group I, but this was not observed in group II. In fact, in three of the five subjects, there was a substantial increase. Since in group I these measurements were made in the supine position with the legs level and in group II the legs were elevated on the bicycle ergometer, the observations are not entirely comparable; for this reason, the observations in the two groups of patients are presented separately.

The augmentation of cardiac output which occurred as a result of hypoxemia was not altered by the administration of syrosingopine in three of five subjects. While one subject (subject 5) was receiving syrosingopine, the arterial oxygen saturation was not reduced to the level to which it fell during the control period. However, in the other (subject 3), the hypoxemic stimulus was comparable, and the reason for the reduction of augmentation

Table 3

<table>
<thead>
<tr>
<th>Subject</th>
<th>Control</th>
<th>After one day syrosingopine</th>
<th>After three days syrosingopine</th>
<th>After eight days syrosingopine</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0.19</td>
<td>&lt;0.03</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>7</td>
<td>0.19</td>
<td>&lt;0.03</td>
<td>&lt;0.03</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>10</td>
<td>0.45</td>
<td>0.60</td>
<td>0.13</td>
<td>0.13</td>
</tr>
</tbody>
</table>

* (μg./mg. platelet protein)
of the cardiac output is not clear. The increase of the heart rate resulting from hypoxemia was less during the study carried out after syrosingopine administration than during the control study in four subjects. Muscular exercise also resulted in a comparable increase of cardiac output during the syrosingopine and control periods. However, the increase in stroke volume which exercise produced during the control period tended to be reduced during syrosingopine.

The primary implication of these observations is that the parenteral administration of relatively large doses of a rauwolfia alkaloid may not interfere with the overall ability of the heart to meet the demand for an increased blood flow to the tissues, although it may alter the manner in which the cardiac output is increased by interfering with the augmentation of the heart rate. Whether large amounts of this drug, which might produce more profound cardiac depletion of norepinephrine, would interfere with the ability of the cardiac output to increase upon demand is not known. Observations somewhat similar to those reported above have also been made by others with guanethidine, a drug the action of which may be similar to that of syrosingopine. The increased cardiac output which occurs during exercise was not altered by the administration of amounts of these drugs which were sufficient to lower systemic arterial pressure. It would therefore appear that, although the sympathetic nervous system may play a role in the response of the heart to acute hypoxemia and exercise, other factors such as release of catecholamines from the adrenal medulla and the operation of the Frank-Starling mechanism may be equally significant. It is of interest to note that earlier experiments had shown that the cardiovascular response to anoxia is not prevented by carotid-sinus denervation, although this is true of the respiratory response.

The clinical implication of the findings reported herein is clear. Since large doses of syrosingopine do not interfere with two basic adaptive responses of the cardiovascular system in the normal unanesthetized subjects, the therapeutic administration of these agents may be fraught with less danger than would be expected from the studies on experimental animal preparations. In the light of this experience, the clinical impression that there is a hazard in anesthetizing patients treated with reserpine should be subjected to more thorough investigation.

Summary

Large parenteral doses of a rauwolfia alkaloid, syrosingopine, administered to normal volunteers, although inducing a consistent reduction in pulse rate, did not interfere with the increase in cardiac output resulting from acute hypoxemia and exercise. The physiological and pharmacological implications of these observations are discussed.

References

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BOOK REVIEW

Diagnosis and Treatment of Diseases of the Trachea and Bronchi, Herman J. Moersch, M.D., and Howard A. Andersen, M.D. Springfield, Illinois, Charles C Thomas, 1960, vii + 108 pages, illustrated. $4.25.

This is a synopsis on the diagnosis and treatment of diseases such as bronchiectasis, tuberculosis, and bronchogenic carcinoma. Most of the 35 illustrations are roentgenographic plates. The diagnosis is emphasized more than the therapy, and a discussion of bronchodilators has been omitted under bronchial asthma.
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