Degeneration of the Cardiac Nerves in Chagas' Disease

Further Studies

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SUMMARY

The Valsalva maneuver was performed by a series of eight patients with chronic Chagas' heart disease who had no current evidence nor past history of heart failure. The fact that all the patients showed recovery of arterial pressure during the latter portion of the period of increased airway pressure and exhibited significant overshoot in pressure in the post-straining period of the Valsalva maneuver strongly suggests that reflex activity of arteriolar tone was present. However, slowing of the heart rate was not found in association with the blood pressure overshoot in half of the patients. This abnormal response was observed only in patients in whom atropine sulfate failed to cause an increase in heart rate. These results are interpreted as a further indication of degeneration of autonomic nervous system controlling heart rate in chronic Chagas' heart disease.

Additional Indexing Words:
Atropine sulfate Cardiac output
Right atrial pressure Heart rate
Valsalva maneuver Blood pressure

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From RESULTS of the earlier studies it has been inferred that the major derangements in Chagas' disease are caused by a wide involvement of the autonomic nervous system. In this regard, in some patients, the observed failure to increase heart rate following administration of atropine was interpreted as a functional disorder related to degeneration of the neuronal supply to the sino-atrial region of the heart. The importance of the autonomic nervous system in the circulatory alterations associated with the Valsalva maneuver are well known. Therefore, circulatory responses induced by the Valsalva maneuver in patients with chronic Chagas' heart disease have been studied in relation to responses observed in normal subjects.

Methods

All patients included in this study had a complement-fixation test positive for Chagas' disease. A complete history was taken and physical examination was done on each patient. Further evaluation by roentgenograms and electrocardiogram was included (table 1). At the time of these studies no clinical evidence of cardiac failure was present, and no clear evidence of cardiac failure in the past was obtained. Catheterization of the right atrium and percutaneous needle puncture of a systemic artery were done under local anesthesia, without prior sedation. Patients breathed room air in near basal conditions. The room temperature was kept at 24C. Pressures in the vascular system were measured by means of specially adapted Statham strain-gauge manometers. Intra-oral pressure was measured by a strain-gauge manometer and also by an aneroid manometer connected to a mouthpiece; the latter manometer was used for visual monitoring and for voluntary control of airway pressure by the patient during the strain.
Cardiac output was determined in the control situation by the indicator-dilution method using continuously recording dye concentration in arterial blood sampled through a Waters cuvette. Heart rate was continuously recorded using a cardiotachometer, coupled with a standard lead of the electrocardiogram. Blood pressure, intra-oral pressure, heart rate, the electrocardiogram, and blood flow were recorded by means of a photokymographic assembly.6

Prior to study, all patients were instructed and trained in the technic of the Valsalva maneuver. Cardiac output and heart rate were measured, and the levels of systemic arterial, right atrial, and oral pressure were determined just prior to the performance of the Valsalva maneuver. After these control measurements, the patients quickly raised oral pressure to nearly 40 mm Hg and maintained airway pressure at as constant a level as possible for approximately 30 seconds. Continuous recordings were obtained before, during, and for 60 seconds after the release of the increased airway pressure. The data reported in table 2 were derived from analysis of recordings in which a satisfactory rise in airway pressure was maintained during the maneuver.

**Table 1**

Summary of Clinical Findings for Patients with Chronic Chagas' Heart Disease

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Heart on chest x-rays</th>
<th>ECG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>34</td>
<td>Normal</td>
<td>Sinus rhythm, apical infarction</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>43</td>
<td>Biventricular enlargement (+)</td>
<td>Sinus rhythm, ventricular extrasystoles, incomplete RBBB</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>47</td>
<td>Left ventricular enlargement (+)</td>
<td>Sinus rhythm, ventricular extrasystoles, RBBB</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>40</td>
<td>Left ventricular enlargement (+)</td>
<td>Sinus rhythm, RBBB</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>35</td>
<td>Normal</td>
<td>Sinus rhythm, RBBB</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>34</td>
<td>Normal</td>
<td>Sinus rhythm, RBBB</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>35</td>
<td>Normal</td>
<td>Sinus rhythm, apical infarction</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>32</td>
<td>Normal</td>
<td>Sinus rhythm, ventricular extrasystoles, apical ischemia</td>
</tr>
</tbody>
</table>

Abbreviation: RBBB = Right bundle-branch block.

**Figure 1**

Effect on heart rate of continuous intravenous infusion of 2.0 mg of atropine sulfate over an 8-minute period. Individual values and mean (dashed line) in eight patients with chronic Chagas' heart disease.
Table 2

Effect of the Valsalva Maneuver on Heart Rate, Systemic Arterial Pressure, and Mean Right Atrial Pressure of Patients with Chronic Chagas' Heart Disease*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Phase of maneuver†</th>
<th>Group I patients*</th>
<th>Group II patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1    2  3  4</td>
<td>5    6  7  8</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>Control</td>
<td>3.4  4.2  4.2  3.2</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>77   75  90  58</td>
<td>76   112  70  100</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>84   72  100 63</td>
<td>86   115  75  100</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>97   72  110 75</td>
<td>91   130  77  103</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>116  102 130 86</td>
<td>100  125  97  118</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>116  100 125 86</td>
<td>100  130  100 118</td>
</tr>
<tr>
<td></td>
<td>Recovery</td>
<td>72   110 110 71</td>
<td>101  130  80  119</td>
</tr>
<tr>
<td></td>
<td>(20 sec)</td>
<td>53   65  75 48</td>
<td>88   118  75  113</td>
</tr>
<tr>
<td>Systemic arterial pressure</td>
<td>Control</td>
<td>108/58 140/80 140/80 150/78</td>
<td>125/70 120/80 115/55 121/75</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td>I</td>
<td>127/82 170/110 165/100 175/103</td>
<td>180/120 130/90 145/90 158/105</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>90/72 120/85 95/80 127/92</td>
<td>102/85 72/62 108/72 82/68</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>110/90 155/122 150/130 172/132</td>
<td>160/120 100/80 150/100 135/106</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>63/50 105/80 100/85 121/91</td>
<td>110/80 60/50 85/50 88/68</td>
</tr>
<tr>
<td></td>
<td>Recovery</td>
<td>158/72 200/110 240/130 213/110</td>
<td>218/132 180/105 150/75 202/118</td>
</tr>
<tr>
<td></td>
<td>(20 sec)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean right atrial pressure</td>
<td>Control</td>
<td>9     10  4</td>
<td>2    4   4</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td>I</td>
<td>41    34  31</td>
<td>38   40  36</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>42    47  35</td>
<td>36   43  42</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>49    50  38</td>
<td>35   47  44</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>11    20  7</td>
<td>12   5.5  7</td>
</tr>
<tr>
<td></td>
<td>Recovery</td>
<td>12    14  5</td>
<td>5    5   5</td>
</tr>
</tbody>
</table>

* Patients were divided in two groups according to their response to intravenous administration of 2.0 mg of atropine sulfate. In group I atropine caused an increase in cardiac rate; in group II it failed to increase the cardiac rate.
† Phases of maneuver: I = onset of straining; II = sustained straining; III = cessation of straining; IV = overshoot of the systemic arterial pressure.

Subsequently, continuous recordings of heart rate were made during the continuous intravenous infusion of a total dose of 2.0 mg of atropine sulfate over an 8-minute period.

**Results**

On the basis of heart rate response to atropine, the chagasic patients have been divided into two groups. In four patients, atropine caused the expected alteration in heart rate (group I), which increased from an average of 68 (range, 60 to 78) beats/min to an average of 100 (range, 83 to 118) beats/min. In the other four patients (group II), atropine failed to increase the cardiac rate, the control averaging 93 (range, 68 to 117) beats/min as compared with 90 (range, 67 to 110) beats/min at the end of administration. These results are shown in figure 1.

The circulatory responses to the Valsalva maneuver were analyzed in accordance to the phases proposed by Hamilton and associates. These results are shown in table 2.

In phase I (onset of straining), the systolic arterial pressure rose immediately in all the patients while the pulse pressure remained close to the control value (fig. 2). Mean right atrial pressure increased 24 to 36 mm Hg, an amount approaching the expected increase in the intrapleural pressure. In group I, the heart rate averaged 80 (range, 63 to 100) beats/min, an average increase of 5 (range, −3 to 10) beats/min, and in group II, it averaged 94 (range, 75 to 115) beats/min, an increase of 4 (range, 0 to 10) beats/min (fig. 3).

In phase II (sustained straining), there was an initial accentuated decline in systolic and pulse pressures reaching levels significantly below the control measurements. A secondary
rise in the systemic pressure was seen in all the patients, as the strain continued (phase II-r, table 2 and fig. 2). The mean right atrial pressure indicates that the strain was sustained at a fairly constant level through phase II. At the lowest value of blood pressure, the average heart rate in group I was 89 (range, 72 to 110) beats/min, and in group II, 100 (range, 77 to 130) beats/min. The increment was 14 (range, −3 to 20) beats/min in the former, but 10 (range, 3 to 18) in the latter. On the other hand, at the peak of recovery in blood pressure, heart rate averaged 109 (range, 86 to 130) beats/min in group I, as compared with 110 (range, 97 to 125) in group II. In the two groups, the change in relation to the control situation were respectively 34 (range, 27 to 40) and 20 (range, 13 to 27) beats/min.

In phase III (cessation of straining and sudden decrease in intrathoracic pressure), there was a uniform response of the systemic arterial circulation, the blood pressure falling abruptly to values below the control level. The pulse pressure usually remained as it was in the initial part of phase II. There was a small and inconstant further change in heart rate. In group I, it was 107 (range, 86 to 125) beats/min and in group II, it was 112 (range, 100 to 130). In comparison to the control situation the increments were 32 (range, 25 to 39) beats/min in the former and 22 (range, 18 to 30) in the latter.

The most striking difference between the two groups was observed in phase IV (recovery). A rebound occurred in both systolic and pulse pressures. In group I, the post-straining overshoot in systemic arterial blood pressure averaged 203 (range, 158 to 240) mm Hg systolic and 106 (range, 72 to

Figure 2

Continuous recording of the systemic arterial pressure (upper panels) and mean right atrial pressure (lower panels) during performance of the Valsalva maneuver by patients with chronic Chagas' heart disease. Group I, group II, and the phases are as indicated in table 2. Peak systolic pressure of each patient is shown by a continuous line and the pulse pressure by a dashed line. The systemic arterial pressure showed a secondary rise while the strain was sustained at a fairly constant level (IIr). In group II, arterial pressure returned slowly toward the control situation in the recovery period.
Changes of heart rate during performance of the Valsalva maneuver in patients with chronic Chagas' heart disease. Temporal relationships with the associated changes in mean right atrial pressure are indicated by the shaded areas (averaged for corresponding phase of the maneuver) for groups I and II, and phases as indicated in table 2. Continuous recordings were made prior to, during, and in the first 60 seconds (Recovery) after the completion of the maneuver. Although both groups exhibited a rebound in systemic arterial pressure at phase IV (fig. 2), the decrease in heart rate to control levels in group II was slow, in contrast to the changes seen in group I.

130) mm Hg diastolic. The pulse pressure increased by an average 36 (range, 30 to 50) mm Hg. In group II, these parameters averaged 188 (range, 150 to 218), 108 (range, 75 to 132), and 30 (range, 15 to 38) mm Hg. At the moment of greatest pressure change, the cardiac rate averaged 91 (range, 71 to 110) beats/min in group I, and 107 (range, 80 to 130) in group II. In the following 60 seconds, the blood pressure returned gradually to control levels. In group I, return of blood pressure toward control levels (fig. 2) was faster than it was in group II, while the heart rate (fig. 3) was moderately or markedly slowed, reaching values below those seen in the control situation. In group II on the other hand, the decrease in blood pressure was slow and was not associated with bradycardia.

Discussion

Several investigations of normal subjects have established a typical pattern of response of the systemic arterial pressure during the Valsalva maneuver, which can be divided into several descriptive stages. Attempts have been made to relate this response to the variables of flow and peripheral vasoconstrictor reflexes. It is also known that in patients with advanced organic heart disease the responses to the maneuver differ significantly from those of normal individuals. For the purpose of this study, therefore, we have
excluded all the patients with very enlarged hearts, all patients in congestive failure, and those patients suspected from the history of having cardiac failure in the past. In general, the control measurements made prior to the maneuver support the clinical trial.

Our observations of the circulatory responses to the Valsalva maneuver suggest that chronic chagasic cardiac patients may respond differently when compared with normal subjects. We were able to divide these patients in two groups, in accordance to their response to atropine. Of special interest are these observations: (1) In all the patients, following the sudden fall in systemic arterial pressure (phase II), recovery in blood pressure occurred while the increased intrathoracic pressure was maintained nearly constant. In association with the blood pressure recovery both groups showed an increase in heart rate, although this seemed more distinct in group I (atropine positive). Reflex sympathetic stimulation is believed to cause the secondary rise in pressure and increase in heart rate. (2) As the strain was released, an initial decrease in arterial pressure was immediately followed by an overshoot in the systemic arterial pressure. The blood pressure changes in both groups of patients were similar. (3) The major difference in response of the two groups occurred in the recovery stage, after the release of the elevated intrathoracic pressure. Although the overshoot in blood pressure was closely similar in the two groups, bradycardia did not occur in group II (atropine negative).

The sudden changes in blood pressure during the different stages of the Valsalva maneuver cause reflex changes in heart rate in the opposite direction. These effects may be eliminated by drugs. In normal subjects, (1) tetraethylammonium chloride abolishes the overshoot in arterial pressure and thus the stimulus for the reflexogenic bradycardia, and (2) atropine sulfate increases the magnitude and duration of the overshoot without the corresponding bradycardia. Absence of blood pressure overshoot following release of the raised intrathoracic pressure in patients with idiopathic orthostatic hypotension and in other conditions involving interruption of the autonomic nervous pathways has been interpreted as a failure of compensatory constriction of vascular beds. The failure of subjects with cardiac abnormalities to demonstrate the normal response (overshoot and bradycardia) to the Valsalva maneuver is believed to be due to the inability of the heart to respond to an increase in venous return with an increase in stroke volume, whether the limiting factor is primarily myocardial, pericardial, or valvular.

The mechanism for the absence of bradycardia in some of our patients cannot be related to the absence of overshoot in systemic blood pressure, as it is in the pathologic conditions mentioned above. Rather this response is comparable to that observed in healthy individuals following atropinization. The difference in response between our two groups of patients is in agreement with the failure to increase the heart rate after administration of atropine. Furthermore, it does not appear to correlate with the clinical situation.

Our own studies with chronic chagasic heart patients showed that on many occasions (1) administration of atropine sulfate during an acute elevation in systemic arterial blood pressure (induced by intravenous administration of metaraminol) was accompanied by minor or no alteration in heart rate and (2) a prompt decrease in systemic arterial blood pressure (induced by intramuscular administration of methacholine chloride) caused no impressive changes in heart rate. In both situations, comparisons were made with non-cardiac patients. Therefore, it appears that the abnormal responses to the Valsalva maneuver described herein are a further indication of neuronal degeneration in the sino-atrial region of the heart.

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