Infra-stellate upper thoracic sympathectomy results in a relative bradycardia during exercise, irrespective of the operated side

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Abstract

Objective: Removal of accessory fibres coming from the sub-stellar thoracic chain to the heart during infra-stellate surgical upper thoracic sympathectomy (ISS) may be responsible for a decreased heart rate to workload relationship during exercise following surgery. We hypothesised that heart rate would decrease not only following right ISS. Methods: We performed repeated bicycle incremental exercise tests in 11 control subjects (26.9 ± 9.5 years, 61.4 ± 12.4 kg, 167 ± 10 cm), and 11 patients (29.8 ± 10 years, 59.3 ± 12.0 kg, 168 ± 7 cm) referred for bilateral ISS: results are mean ± standard deviation. Surgery was performed at two distinct times allowing to study the consequences of unilateral and bilateral sympathectomy to confirm whether a significant relative bradycardia was constant and dependent on the operated side. Results: For control subjects, test durations were 13.55 ± 3.29, 14.09 ± 4.01 and 13.00 ± 3.26 min and heart rates were 187 ± 7, 187 ± 8 and 186 ± 7 beats min⁻¹ at the first, second and third test, respectively. Although time to exhaustion was comparable to controls and unchanged between tests: 12.32 ± 2.87, 12.3 ± 2.90, 12.33 ± 3.76 min, heart rate at maximum exercise decreased significantly from 176 ± 16 to 164 ± 15, and 148 ± 15 beats min⁻¹, before, following unilateral and bilateral ISS, respectively. The operated side did not allow for the prediction of the effect of unilateral sympathectomy. Conclusions: Patients should be informed of the exercise bradycardia resulting from ISS, although clinical tolerance seems excellent in endurance exercise. Contrary to previous reports at rest, during exercise no right-sided dominance was observed. These findings are consistent with reports of random distribution of sub-stellate cardiac fibres from anatomical studies. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Sympathectomy; Collateral effects; Palmar hyperhidrosis; Complications; Exercise; Bicycle; Heart rate

1. Introduction

Sympathetic control of the microcirculation of the upper limb occurs via the sympathetic nerves from the first thoracic ganglia. Cardiac sympathetic neural control is generally assumed to be devoted to the cervical sympathetic fibres but accessory fibres from the sub-stellar thoracic chain to the heart have been described in some anatomical studies. Little is known about the prevalence and distribution of these fibres in the population [1–4].

Surgical thoracic sympathectomy is widely used in the surgical treatment of vascular disorders in the upper limb, such as primary palmar hyperhidrosis or severe Raynaud’s syndromes. Several studies have demonstrated successful treatment of these disorders with infra-stellate sympathectomy (ISS) with minimal complications or collateral effects [5–7]. In these reviews, the risk of Horner’s syndrome and other reported collateral effects (haemo-pneumothorax, pain, infection, pulmonary parenchymal injury, etc.), except for compensatory hyperhidrosis, is estimated to range from 4.3 to 14% of surgically treated patients [7,8]. Compared to these occasional (although sometimes debilitating) complications, a cardiac effect seems to be frequently observed although asymptomatic. Several reports also demonstrate significantly lower heart rate increases during exercise in subjects who have undergone bilateral ISS [9–12] compared to pre-surgical levels. In spite of this high occurrence, recent reviews on the usual collateral effects of thoracic sympathectomy still do not include these possible cardiac consequences [6].

Bilateral ISS is usually performed during a single surgical procedure. Therefore, the potential side effect of right or left unilateral sympathectomy cannot be evaluated. We performed a prospective study in subjects undergoing bilateral sympathectomy on two distinct surgical procedures allowing us to study the consequences of unilateral and,
subsequently, bilateral infra-stellate sympathectomy, in the same subjects.

The aim of the present prospective study was to confirm that a significant impairment of the heart rate to workload relationship was consistently observed following unilateral and/or bilateral surgery. We further hypothesised that the effect was proportional to the level of exercise, and that the magnitude of this effect was not dependent on the operated side.

2. Materials and methods

2.1. Inclusion

Over a one-and-a-half year period, all patients referred for bilateral infra-stellate thoracic sympathectomy for hyperhydrosis were proposed the present protocol if they fulfilled the inclusion criteria listed in Table 1. After complete explanation of the proposed protocol, the subjects were asked to give written informed consent to the study that had been approved by the local ethics committee.

2.2. Surgical procedure

Bilateral sympathectomy was performed in two distinct surgical procedures, usually separated by 3 months, (mean 79 days; range: 15–277). The first operated side was the dominant side of the patient defined as the hand used for writing. Minimal invasive video-assisted procedures with excluded lung by Carlens tube were performed under general anaesthesia. Three incisions performed on the fourth and fifth intercostal spaces allowed for the excision of the second to the fourth thoracic sympathetic ganglia using electrocoagulation. First thoracic sympathetic ganglion is connected to the last cervical one forming the stellate ganglia, in 80% of cases according to Ellison and Williams [13]. This first thoracic ganglion was always avoided to prevent the development of Horner’s syndrome. One chest drain was routinely left in place for about 48 h after surgery.

2.3. Protocol

Each subject was submitted to three different investigations. These included (1) interrogation searching for any cardiac complains and for the importance and localisation of hyperhidrosis; (2) clinical examination and (3) exercise tests. Each subject served as his or her own control for the investigations and particularly for the exercise tests that were performed: (1) pre-operatively in the week preceding the first sympathectomy, (2) inter-operatively at least 2 days before the second surgical procedure and at least 10 days after the first surgery and (3) post-operatively, 3 months following the second sympathectomy.

2.3.1. Interrogation

Attention was paid to any personal or familial history of cardiovascular or respiratory disease at rest or during exercise. Subjective evaluation of hyperhidrosis at the palmar or thoracic level was performed.

2.3.2. Clinical examination

Examination of the usual signs of Horner’s syndrome (ptosis, myosis, enophthalmia) was performed for both eyes. Routine examination focusing on the upper body skin, heart noise and respiratory murmur was performed. Weight and height were measured. Smokers were asked to avoid cigarette smoking 4 h before the tests, and all subjects were asked to fast for at least 2 h before the visit and exercise test.

2.3.3. Control group

A control group of 11 healthy volunteers matched for age, height and weight was included and submitted to three consecutive exercise tests separated by 1–3 months, to control the reproducibility of exercise measurements.

2.3.4. Exercise tests

Maximal incremental exercise tests were performed on a calibrated cycle-ergometer (PPG40 Hellige, Germany). The incremental exercise tests were performed in an air-conditioned room (23–26°C). For each subject the protocol was chosen at the first test between two different workload increments in order to attain maximal exercise in an estimated time of 7–15 min, either 10 W min^{-1} increments starting at 25 W or 15 W min^{-1} increments starting at 50 W. Choice of the protocol was made by calculating the theoretical exercise ability of the subjects according to estimated maximal workload calculated from the formulas proposed by Jones [14] and Wasserman et al. [15]. For each subject the exercise protocol chosen at the first visit was kept unchanged for the second and third exercise test.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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</thead>
<tbody>
<tr>
<td>Indication for bilateral ISS</td>
<td>Uncontrolled hypertension</td>
</tr>
<tr>
<td>Age &gt; 18 years</td>
<td>Lower limb pain at exercise</td>
</tr>
<tr>
<td>Written informed consent signed</td>
<td>Any history of cardiopathy</td>
</tr>
<tr>
<td>No change of usual treatment if any (e.g. oestro-progestatives), within 2 months</td>
<td>Infection within 8 days</td>
</tr>
<tr>
<td></td>
<td>Permanent cardiac arrhythmia</td>
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<tr>
<td></td>
<td>Atrio-ventricular block &gt; type 1</td>
</tr>
</tbody>
</table>
During exercise, a 12 lead electrocardiogram was continuously recorded (Max1, Marquette, Mountain view, CA, USA), and the detection of spikes was automatically performed by the program. For the analysis, heart rate was averaged every 30 s and transferred to a personal computer for future analysis. Systolic and diastolic blood pressures were determined manually before exercise in the sitting position, repeatedly during exercise and at maximal exercise when the patient signalled that he or she was close to exhaustion. Usual criteria for exercise termination were respected [16]. Exercises were symptom limited and not limited to the theoretical maximal heart rate or a fraction of it.

2.3.5. Blood samples
In patients, erythrocyte and haemoglobin concentrations, and haematocrit were determined pre-operatively and 8 days following the second surgery.

2.4. Analysis of results
For the exercise test, values reported are the average of the last 30 s of each level of exercise. Throughout the text the results are expressed as mean ± standard deviation. Comparison between pre-operative, inter-operative and post-operative results within each group and analysis of differences between patients and control subjects were performed using Kruskal–Wallis test and Wilcoxon signed rank test, respectively (Prism 2.01 Graphpad software, USA). For each test a two-tailed $P < 0.05$ is considered to indicate statistical significance.

3. Results
Eleven patients aged 29.8 ± 10 years (range: 19–48) were included in this study (seven females, four males). Two of the patients were left-handed and therefore had the left side operated first. Mean weight was 59.3 ± 12.0 kg and height was 168 ± 7 cm. Control subjects were six females and five males whose age, weight and height were 26.9 ± 9.5 years (range: 18–46), 61.4 ± 12.4 kg and 167 ± 10 cm, respectively.
No apparent complication was noted in any patient during or immediately following surgery; specifically, no Horner’s syndrome occurred. Symptoms of palmar hyperhidrosis disappeared completely immediately after the operation in all patients. A compensatory hyperhidrosis was noted in four of the subjects. Before and following surgery, patients reported no episode of dyspnea, no apparent decrease in exercise tolerance, no palpitation, orthostatic intolerance or syncope.

The exercise tests were performed until exhaustion during all three tests and were never limited by pain even in the patient in whom inter-operative measurements were performed 14 days following the first sympathectomy. Results for erythrocyte and haemoglobin concentrations, haematocrit of patients, as well as exercise duration, heart rate at rest and at maximal exercise in the patients and controls are reported in Table 2. In brief, no significant change occurred in red blood cell and haemoglobin concentrations. Heart rate at rest was significantly decreased compared to pre-surgical values only after bilateral sympathectomy. Maximal heart rate was significantly decreased after unilateral ISS compared to pre-operative values, whereas no change in the exercise duration and the workload performed was noted (Table 2). The decrease in maximal heart rate following the first (and unilateral surgery) was non-homogeneous among the population. Four of the 11 patients showed less than 6 beats min$^{-1}$ heart rate changes after the unilateral surgery, whereas maximal heart rate decrease of 20 or more beats min$^{-1}$ in four others. Results from the control group showed no significant change for maximal heart rate and time to maximum exercise. Maximal heart rate was consistently and significantly lower compared to pre-surgical values after bilateral ISS whereas duration of exercise to exhaustion remained unchanged. The mean decrease in maximal heart rate was $-15.8 ± 7.4\%$ of pre-surgical values, ranging from $-8$ to $-29\%$. No significant change of heart rate or exercise duration was noted in the control group. As shown in Fig. 1, the decrease in heart rate was proportional to exercise intensity.
As a result of sympathetic inhibition, systolic blood pressure was decreased compared to pre-surgical values at maximal exercise after both unilateral and bilateral surgeries.

| Table 2 | Exercise duration (mean ± SD, min) in operated patients and in the control group observed during the three tests |
|---------|---------------------------------|----------------|----------------|
|         | Test 1                          | Test 2         | Test 3         |
| Erythrocytes (10$^6$ ml$^{-1}$) |Patients                        | 4.4 ± 0.4      | 4.4 ± 0.6      | 4.3 ± 0.5 |
| Haemoglobin (g% ml$^{-1}$)     |Patients                        | 13.4 ± 1.2     | 13.4 ± 1.3     | 13.2 ± 1.0 |
| Haematocrit (%)                |Patients                        | 39.3 ± 3.5     | 39.3 ± 3.9     | 39.0 ± 3.6 |
| Exercise duration (min)        |Patients                        | 12.3 ± 2.9     | 12.3 ± 2.9     | 12.3 ± 3.8 |
|                                 |Control                         | 13.6 ± 3.3     | 14.1 ± 4.0     | 13.0 ± 3.3 |
| Heart rate at rest (beats min$^{-1}$) |Patients                        | 79 ± 4         | 72 ± 9         | 67 ± 9** |
|                                 |Control                         | 78 ± 14        | 71 ± 9         | 74 ± 9   |
| Heart rate at maximal exercise (beats min$^{-1}$) |Patients                        | 176 ± 16       | 164 ± 15**     | 148 ± 15** |
|                                 |Control                         | 187 ± 7        | 187 ± 8        | 186 ± 7  |

** $P < 0.05$ vs. test 1.
whereas no significant change was observed in control subjects as reported in Table 3.

Fig. 2 shows individual values for the percent decrease in maximal heart rate following the first and second sympathectomy surgeries. The effect of surgery on maximal heart rate was not homogeneous, with some patients showing comparable responses whereas others showed clear differences. Neither left/right handedness, nor the operated side allowed for the prediction of the effect of the surgery on the cardiac response to exercise.

4. Discussion

Sympathetic afferent fibres are involved in the neural control of the cardiovascular system at the level of the heart and peripheral vessels. At the level of the heart, sympathetic stimulation increases heart rate, contractility and conduction velocity. Thus, inhibition of cardiac sympathetic system is expected to decrease heart rate, and to modify the conductivity of the heart and repolarisation. In the limbs, sympathetic stimulation mainly induces piloerection, vasoconstriction and sweating [17]. Thus, sympathectomy of the upper extremity results in prolonged vasodilation and decrease of sweat production in the area of denervation. Due to these physiological effects of sympathetic fibres, surgical interruption of the cervico-thoracic sympathetic chain has been performed for years both in heart diseases (such as long QT syndromes, severe arrhythmia, angina pectoris) and vascular diseases (such as Raynaud’s syndrome) or palmar hyperhidrosis [18–20]. Nevertheless, those cervico-thoracic surgical procedures including the stellate ganglion were limited and progressively abandoned because of the frequent occurrence of Horner’s syndrome. Also, the improvement of chemical beta-blocker’s specificity and safety allowed for more effective pharmacologic treatment of some of these disorders [21]. Recently, with video-assisted approaches and with surgery limited to the infra-stellate fibres, the risk of complications, and particularly that of Horner’s syndrome has dramatically decreased. This has led to a renewed interest and development of surgical sympathectomy for the treat-

**Table 3**

Arterial blood pressure (mean ± SD, mmHg) before the end at maximal exercise in operated patients and in the control group

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time</th>
<th>Parameter</th>
<th>Test 1</th>
<th>Test 2</th>
<th>Test 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operated patients</td>
<td>Starting values</td>
<td>Systolic</td>
<td>126 ± 19</td>
<td>125 ± 12</td>
<td>116 ± 10**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diastolic</td>
<td>79 ± 10</td>
<td>79 ± 6</td>
<td>75 ± 7</td>
</tr>
<tr>
<td></td>
<td>Maximal exercise</td>
<td>Systolic</td>
<td>182 ± 31</td>
<td>170 ± 24**</td>
<td>158 ± 10**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diastolic</td>
<td>89 ± 18</td>
<td>86 ± 10</td>
<td>83 ± 10</td>
</tr>
<tr>
<td>Control subjects</td>
<td>Starting values</td>
<td>Systolic</td>
<td>126 ± 15</td>
<td>125 ± 19</td>
<td>123 ± 16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diastolic</td>
<td>70 ± 14</td>
<td>69 ± 15</td>
<td>74 ± 12</td>
</tr>
<tr>
<td></td>
<td>Maximal exercise</td>
<td>Systolic</td>
<td>175 ± 14</td>
<td>178 ± 20</td>
<td>176 ± 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diastolic</td>
<td>78 ± 12</td>
<td>80 ± 17</td>
<td>79 ± 7</td>
</tr>
</tbody>
</table>

** P < 0.05 vs. test 1.
ment of vascular diseases of the upper limb. Among the different complications or secondary effects of upper thoracic sympathectomy, recent reports of infra-stellate sympathectomy estimate the risk of Horner’s syndrome, haemo-pneumothorax and compensatory hyperhidrosis as 0.5–1%, 1–3.6% and 50–75%, respectively, in surgically treated patients [5,7,22]. Although a number of recent studies have focused on these complications of ISS, the effect on heart rate is rarely reported and, when estimated, the effect of unilateral surgery at exercise was not studied [9,10,23].

Consistent with these previous reports [9–12], we found a significant and consistent decrease of maximal heart rate in patients following bilateral ISS compared with pre-surgical values. The higher the workload performed during incremental exercise, the larger the absolute value of heart rate decrease. Percent decrease from pre-operative values was in the same range as that observed by Drott et al. [9] or Noppen et al. [11–12] and almost constant at both rest and different levels of exercise. The amplitude of relative heart rate decrease observed during exercise is in the same range as the values reported in the literature in patients treated with beta-blocking agents, but contrary to beta-blockers no significant decrease was seen in exercise tolerance in the present study [24].

Although heart rate is known to decrease following bilateral sympathectomy, little is known about the effects of unilateral treatment on heart rate. In case of unilateral left stellectomy for treatment of long QT syndromes Schwartz et al. [18] found no significant decrease in resting heart rate. Consistently, in the study of Papa et al. [10], intra-operative recording of resting heart rate in patients undergoing bilateral upper thoracic sympathectomy using the supra-clavicular approach shows no significant change following left sympathectomy (n = 5) whereas heart rate decreased from 87 ± 4 to 73 ± 3 in 10 min following right sympathectomy (n = 5). In this study, the heart rate decrease found after bilateral sympathectomy was in the same range in the ten subjects as in the five patients initially operated on the right side. According to Papa et al. [10], these results are supportive of a unilateral right side effect of sympathectomy on heart rate.

The results of the present study, however, do not confirm this laterisation of the effect on heart rate during exercise. On one hand, although only performed in two subjects unilateral left surgery led to an important decrease of maximal heart rate in one subject whereas right sympathectomy showed no further decrease in the same patient. On the other hand, if an exclusively right-sided effect (or at least dominant effect) exists, why should patients operated on the right side first experience a substantial decrease in heart rate following their second (left-sided) sympathectomy? Further, whereas individual responses were highly variable, the average response to unilateral than bilateral surgery are comparable. Also, Fig. 2 shows that neither right or left side, nor the dominant side (writing hand of the subject) showed an apparent relationship with the occurrence or magnitude of the heart rate decrease at maximal exercise.

It is likely that previous recordings at rest, particularly during anaesthesia, may have underestimated the effect of sympathectomy. First, parasympathetic control at rest may have masked the effect of sympathectomy. Second, anaesthetic drugs and environmental conditions of surgery (stress, pain, cold, etc.) may have interfered with the study of resting heart rate in those studies [10]. The probable absence of lateralisation of the effect of sympathectomy on heart rate suggested by the present work is consistent with the random distribution of infra-stellate sympathetic fibres reported in anatomic studies [3,4]. Whether or not the effect on heart rate is only observed after right sympathectomy is an important issue for clinical practice, since ISS has been proposed in severe ischaemic heart diseases [25–27] to reduce the sympathetic input to the heart and attain an effect similar to the beta-blockers on heart rate during exercise. If a right-sided exclusive effect existed, surgery could be limited to unilateral right sympathectomy in the most frail patients. This is probably not the case. Therefore, aiming to reduce the heart rate response to exercise, either a bilateral surgery should be systematically performed or the efficiency of a unilateral approach evaluated, and if not sufficient completed by contralateral surgery.

5. Conclusions

To the best of our knowledge, this is the first report on the effect of unilateral and bilateral ISS on heart rate response to exercise in the same patients. A significant decrease in the heart rate to workload relationship during exercise is constantly observed a few weeks after surgery, but does not seem to exclusively result from right-sided surgery as previously suggested. Patients are generally aware of severe but infrequent complications. They should also be informed of the relative exercise bradycardia resulting from this kind of surgery, although clinical tolerance for endurance exercise seems excellent.

Acknowledgements

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