A COMPARISON OF RESPIRATORY (J) SENSATIONS INDUCED BY INTRAVENOUS LOBELINE INJECTION AND PRODUCED BY EXERCISE IN SUBJECTS WITH CORONARY ARTERY DISEASE

Gholam-Abbas Dehghani PhD*, Mohammad-Bagher Sharif-Kazemi MD**, Mohammad-Reza Parvizi MSc*, Ashima Anand PhD***, Athar S. Paintal MD FRCP****

Background: A small dose of intravenous bolus injection of lobeline (LB) gives rise to a range of sensations in the upper respiratory tract (named J sensations) including dryness, swelling, burning, suffocation in the upper respiratory tract, and dry cough. We were interested in investigating: a) whether people with coronary artery disease (CAD) feel the same kind of sensations with LB as those of healthy subjects, b) we also attempted to compare these sensations with those felt when they were exercising moderately, and c) finally, a similar comparison, undertaken in healthy subjects, allowed us to examine the origin of exercise-related sensations experienced by subjects with CAD.

Methods: J sensations were evoked by threshold doses of LB in 10 CAD patients and 10 healthy subjects as control. These sensations were then experienced in treadmill exercise tolerance testing (Bruce Protocol) and compared.

Results: Diversity and incidence of J sensations felt with the above protocol were significantly higher amongst CAD patients than the control subjects. CAD patients usually reported experiencing more than one kind of J sensations, when exercising. It is worth mentioning that dry cough was present in 30% of CAD patients while exercising, but was absent in the healthy subjects.

Conclusion: The notable similarity between J sensations evoked by threshold doses of LB and those felt while exercising, as reported by CAD patients, points to the common origin of these sensations in the two conditions. The foreseeable conclusion is that the similarity of J sensations encountered while exercising with those of the LB-induced ones in CAD patients points to the fact that the origin of these exercise-induced sensations is the stimulation of juxta-pulmonary capillary (J) receptors by transient increment in interstitial volume and/or increase in pulmonary blood flow.

Keywords: Coronary artery disease • dry cough • exercise • lobeline • respiratory sensations

Introduction

An intravenous bolus injection of lobeline (LB) has shown to stimulate juxta-pulmonary capillary receptors (J receptors) in human subjects and to produce respiratory discomfort, referred to the throat and upper chest. Using LB in awake healthy subjects has suggested that there is no evoked reflex motoneuronal inhibition. Instead, the noxious respiratory sensations followed by breathlessness generated by pulmonary C fibers may be crucial in deciding the stoppage of exercise. The absence of these sensations in subjects with bilateral lung transplantation, indicated that they are mediated by receptors in the lung.

Raising pulmonary capillary pressure or increasing its permeability leads to pulmonary interstitial edema, and markedly stimulates J
receptors. Increasing blood flow through the lobes of the cat’s lung has also shown to increase the activity of these receptors to the same extent as stimulating them with low doses of phenyl-diguanide.8 Stimulating J receptors in healthy subjects by injecting small doses of LB (7 – 20 µg/kg) has also shown to produce specific sensations such as choking, pressure, or fumes in the throat and upper chest (J sensations), and in a few cases accompanied with substernal pain.1, 4, 9 Moreover, the absence of these sensations in one year bilateral lung transplant recipients has excluded the contribution of carotid chemoreceptors or other mechanoreceptors.4 In addition, it is well documented that other stretch receptors of the lung do not contribute to these sensations.9 These cardio-pulmonary effects are also typically seen in animals, when their J receptors are exclusively stimulated chemically or naturally.6, 7 Hence, the origin of these sensations, most likely, are J receptors that are stimulated by chemical agents or while exercising.1, 2, 4, 9, 10 Recent studies have shown that normal subjects in response to higher doses of LB (10 – 52 µg kg⁻¹, known as cough threshold dose) reported a dry cough,5 – 7 analogous to those reported in earlier studies.10 – 12 Similar sensations (i.e. burning pain in the chest and dry cough) were also reported in healthy young male soldiers who developed pulmonary edema within hours of being airlifted to an altitude as high as 3,200 meters are thus assumed to have arisen by stimulation of their J receptors by interstitial edema.13 Sensations of inability to breathe, shortness of breath, suffocation etc, have also been reported in patients with chronic heart failure in response to exercise.5 In view of these findings, we were interested in studying the range of respiratory sensations produced in healthy subjects, when their J receptors are stimulated naturally by an increase in pulmonary blood flow/cardiac output while exercising,14 followed by comparison of these sensations with those produced by small doses of LB at rest, as was previously done by Raj and his colleagues.9 We also tried to investigate, for the first time, the nature and incidence of J sensations, which would occur in patients with coronary artery disease (CAD), while exercising, and to compare them with sensations that these patients experienced when their J receptors were stimulated by threshold doses of LB at rest. Finally, we compared respiratory sensations evoked by injecting LB into healthy and CAD subjects at rest, with those sensations experienced by both groups while exercising.

**Patients and Methods**

The details of this study were approved by the Ethical Committee of Shiraz University of Medical Sciences and conformed to the Helsinki Declaration.

**Selection of subjects**

Ten subjects (6 males and 4 females; with a mean age of 48 ± 3 yr) were selected from amongst confirmed cases of coronary artery disease (CAD) determined by angiography, under care of Motahari Polyclinic of Nemazi Hospital affiliated to Shiraz University of Medical Sciences. Eight subjects of this group had experienced a myocardial infarction (MI) about 6 – 12 months earlier and the angiography findings of 7 of them showed a 2 – 3 coronary artery blockade and 3 had distinct ECG changes. They were classified as having functional New York Heart Association (NYHA) class III symptoms (Table 1) and were on a stable medical regimen of drugs such as diltiazem, nitroglycerine, isosorbide dinitrate (Isordil), glibenclamide, aspirin, atenolol, inderal, etc. Their mean percentage of left ventricular ejection fraction (EF%) was 50.5 ± 1.9% (Table 1). Ten age-matched healthy subjects (3 males and 7 females; mean age 49.1 ± 4 yr) who came to this clinic with complaints of epigastric or chest pains, but had normal angiograms, served as control healthy subjects. These subjects had neither any medical history nor took any drugs and their EF% was 61 ± 1.0% (Table 1). Their mean body weight was 71.4 ± 3 kg, almost comparable to that of CAD patients, 73.6 ± 4.4 kg (Table 1). About 30% of the CAD patients (2 male cigarette smokers and one female hookah smoker), and 20% of the control subjects (2 female hookah smokers) had been smokers in the past. The final selection of the subjects was determined by their enthusiasm to take part in the study after the details had been explained to them and signed the consent form. All subjects were studied in isolation from each other, so as not to influence their individual reactions.

**Injection set-up (lobeline and saline)**

An indwelling catheter with a side-port was inserted into the left antecubital vein and connected to a saline drip via tubing that was...
Lobeline (Sigma) solution was prepared in normal saline at a concentration of 4 mg/mL (25 mL) and sterilized by a 0.45 disposable Millipore filter and intravenous bolus injections used as reported by Raj et al.9

Protocols

Sensations of lobeline IV at rest

Lobeline was (intravenous bolus injection [IV]) injected in increasing doses and interspersed with similar volumes of saline injections, which served as placebos. The purpose of injecting it in increasing doses was to find the threshold dose and familiarize the subjects with the intensity of the sensations felt. Only a minimal dose, in which the subject stated to produce a unique sensation (threshold dose) was used as the ‘test dose’ for that individual in the subsequent protocols (Table 2).

Subjects were asked to raise a hand as soon as they experienced certain sensations or odd feelings in their upper respiratory tract. Latency of these sensations was measured as the time difference between LB injection when the investigator pressed a stopwatch and the instance when the subject raised his/her hand on experiencing some thing unusual, when the watch was stopped (Table 2). After this, each subject described the nature of his/her sensation(s) and its location(s) in detail to the investigator, who wrote them down verbatim in Farsi and later translated it into English (Table 3). Subjects also reported, whether the sensations could be considered intense or just mildly irritating. A continues ECG tracing used to observe the heart condition and to obtain the heart rate. Arterial diastolic and systolic blood pressures were measured with a sphygmonanometer, at rest.
Deemed it fit for them to terminate. The latter was for as long as they could or till the investigator exercise on a treadmill according to Bruce Protocol. Exercise capability and sensations perceived (before LB and saline injection, at the start of exercise) and also during exercise at the end of each step of Bruce Protocol.

**Exercise capability and sensations perceived**

At first, all twenty subjects were made to exercise on a treadmill according to Bruce Protocol for as long as they could or till the investigator deemed it fit for them to terminate. The latter was determined by either reaching the target heart rate or in case any changes observed in the ECG traces (such as a shift in the S-T segment) by the physician in charge, or obvious breathlessness and fatigue. During the recovery stage, subjects were asked to describe the sensations that they had experienced while exercising and reasons for terminating exercise if they stopped on their own will. As a last question, on the completion of the study protocol, all subjects were asked if sensations they had felt during exercise were similar, or not, to those felt LB Protocol.

**Analysis of sensations/quantification**

Both LB and exercise protocols gave rise to a wide range of sensations related to respiratory areas in all subjects (Tables 2 and 3). Beside these sensations, a dry cough, chest pain, and a feeling of fatigue were also experienced by CAD patients (Table 2). These descriptors were divided into six categories as presented in Table 3. Each subsequent category indicated an increasing level of discomfort as depicted below.

I. Feeling of dryness/bitter taste in mouth/cool or hot air/smoke/tickling sensation in throat.
II. Burning/soreness/pressure/tightness/suffocating sensation in throat and in upper chest.
III. Shortness of breath or inability to breathe.
IV. Dry cough.

### Table 2. Threshold doses of lobeline (LB), Latency responses at rest, duration of exercise, and similarity of sensations evoked by LB and exercise in CAD patients and healthy control subjects.

<table>
<thead>
<tr>
<th>CAD patients</th>
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<th>6</th>
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<tr>
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<td>18</td>
<td>18</td>
<td>22</td>
<td>22</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>30</td>
<td>20.8 ± 0.6*</td>
</tr>
<tr>
<td>Latency response at rest (sec)</td>
<td>12</td>
<td>20</td>
<td>18</td>
<td>12</td>
<td>17</td>
<td>15</td>
<td>13</td>
<td>13</td>
<td>17</td>
<td>20</td>
<td>15.7 ± 2.0</td>
</tr>
<tr>
<td>Duration of exercise (min)</td>
<td>5.1</td>
<td>6.0</td>
<td>8.0</td>
<td>4.3</td>
<td>9.0</td>
<td>5.3</td>
<td>6.0</td>
<td>11.0</td>
<td>10.2</td>
<td>8.0</td>
<td>7.3 ± 0.7*</td>
</tr>
</tbody>
</table>

### Sensation descriptor

| II — | — | — | — | — | — | — | — | — | — | — |
| III — | — | — | — | — | — | — | — | — | — | — |
| IV — | — | — | — | — | — | — | — | — | — | — |
| V — | — | — | — | — | — | — | — | — | — | — |

**Control subjects**

<table>
<thead>
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<th>16</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>20</th>
<th>Mean ± SEM</th>
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<tr>
<td>Threshold dose of LB (µg/kg)</td>
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<td>15</td>
<td>15</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>20</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Latency response at rest (sec)</td>
<td>13</td>
<td>20</td>
<td>21</td>
<td>22</td>
<td>23</td>
<td>10</td>
<td>20</td>
<td>15</td>
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<td>13</td>
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<td>Duration of exercise (min)</td>
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<td>11.0</td>
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<td>8.5</td>
<td>10.0</td>
<td>11.0</td>
<td>7.5</td>
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</table>

| I — | — | — | — | — | — | — | — | — | — | — |
| II — | — | — | — | — | — | — | — | — | — | — |
| III — | — | — | — | — | — | — | — | — | — | — |
| IV — | — | — | — | — | — | — | — | — | — | — |
| V — | — | — | — | — | — | — | — | — | — | — |

Nature of sensations evoked by threshold doses of lobeline IV and exercise in CAD patients (1 – 10) and control subjects (11 – 20). ▲ = sensations (I-V) in response to LB; ■ = to exercise, — = response see Table 3 and text. The individual threshold doses of LB, latency of responses to LB (second) and the duration that each subject could exercise (min) are also presented. The number of the descriptor also represents an intensified response in comparison to the one lower to it. Note the occurrence of more than one respiratory sensation seen in most CAD patients as compared to those of control subjects in both protocols; * = mean data is significantly different from that of controls at P < 0.05.
V. Pain in the chest. Unrelated to respiratory system.

Statistical analysis
Values are presented as the mean ± standard error. Student’s unpaired t-test was used for assessing whether the mean threshold doses of lobeline, duration of exercise, and the latencies of sensations of both groups of CAD patients and control subjects were significantly different from each other or not. One-tailed Fisher’s exact test was used to compare the number of subjects in the two groups who reported three or more lobeline-induced sensations and two or more sensations with exercise. It was also used for finding the significance of prevalence of the respiratory sensations in the two groups. A P value of less than 0.05 (P < 0.05) over the control group was considered as being significantly different statistically.

Results
Lobeline (IV)-induced sensations at rest
The individual threshold doses of lobeline that produced sensations are presented in Table 2 and the verbatim descriptors of all sensations mentioned by each subject in Farsi (translated to English by the investigator) are presented in Table 3. The mean threshold doses of lobeline that produced distinct sensations at rest in CAD patients were 20.8 ± 0.1 µg/kg and was significantly higher (P < 0.03) than that of control subjects (17.5 ± 1.3 µg/kg; Table 2 and Figure 1). In about 90% of CAD patients and 55% of control subjects this threshold dose produced sensations of categories I and II (Table 2, Figure 3). Another notable difference was that, in response to injecting threshold doses of lobeline, CAD patients reported more than one kind of sensations in more than one

<table>
<thead>
<tr>
<th>Classification</th>
<th>Verbatim in Farsi</th>
<th>English translation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Talkhie zaban va galoo</td>
<td>Feeling bitter taste on tongue and throat</td>
</tr>
<tr>
<td>I</td>
<td>Dood dar galoo</td>
<td>Feeling smoke in throat</td>
</tr>
<tr>
<td>I</td>
<td>Boye bad dar dahan</td>
<td>Bad odor in the mouth</td>
</tr>
<tr>
<td>I</td>
<td>Khoshkie galoo</td>
<td>Feeling dryness in throat</td>
</tr>
<tr>
<td>I</td>
<td>Khonaki dar galoo</td>
<td>Feeling cool air in throat</td>
</tr>
<tr>
<td>I</td>
<td>Kharesh dar galoo</td>
<td>Feeling tickling in the throat</td>
</tr>
<tr>
<td>I</td>
<td>Bokhar dar galoo</td>
<td>Feeling burning fume in throat</td>
</tr>
<tr>
<td>I</td>
<td>Atash dar galoo</td>
<td>Feeling fire in throat</td>
</tr>
<tr>
<td>I</td>
<td>Khoshkie labha</td>
<td>Dry lips</td>
</tr>
<tr>
<td>I</td>
<td>Khoshkie dahane</td>
<td>Dry mouth</td>
</tr>
<tr>
<td>I</td>
<td>Adame tavan balae</td>
<td>Can not swallow</td>
</tr>
<tr>
<td>I</td>
<td>Ehsase balafadan</td>
<td>Swallowing sensation</td>
</tr>
<tr>
<td>II</td>
<td>Soozesh galoo</td>
<td>Feeling sour throat</td>
</tr>
<tr>
<td>II</td>
<td>Gerofagie galoo</td>
<td>Pressure in throat</td>
</tr>
<tr>
<td>II</td>
<td>Tir kashidan dar galoo</td>
<td>Smart feeling in throat</td>
</tr>
<tr>
<td>II</td>
<td>Ehsase feshar dar galoo</td>
<td>Pressure in throat</td>
</tr>
<tr>
<td>III</td>
<td>Tangie nafas</td>
<td>Shortness of breath</td>
</tr>
<tr>
<td>III</td>
<td>Ghatae tanafos</td>
<td>Apnea</td>
</tr>
<tr>
<td>IV</td>
<td>Sorfe khoshk</td>
<td>Dry cough</td>
</tr>
<tr>
<td>V</td>
<td>Dard dar seine</td>
<td>Chest pain</td>
</tr>
<tr>
<td>V</td>
<td>Khastegi</td>
<td>Feeling fatigued</td>
</tr>
<tr>
<td>Unrelated</td>
<td>Akhme shadid</td>
<td>Strong scowl</td>
</tr>
<tr>
<td>Unrelated</td>
<td>Ehsase sargije</td>
<td>Feeling dizziness</td>
</tr>
<tr>
<td>Unrelated</td>
<td>Ehsase tahavoa</td>
<td>Feeling vomiting</td>
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</table>

Sensations mentioned verbally by an individual with the threshold dose of LB at rest and while exercising with or without LB.

![Figure 1. Threshold doses of lobeline used in CAD patients and control subjects to induce respiratory sensations described in Table 3. * = values are significantly different from control at P < 0.05.](image)
location as compared to control subjects (Table 2, Figure 3). The latency of the onset of these sensations of each individual is also presented in Table 2. The mean latencies of these sensations in CAD patients and control subjects were 15.7 ± 2.0 and 17.0 ± 1.5 seconds respectively, which were not significantly different from each other.

Hemodynamics

Heart rate (HR), arterial diastolic (Pd), and systolic (Ps) blood pressures of individual subjects at rest (before starting exercise) and during exercise (at the last stage of Bruce Protocol) are shown in Table 4. The mean values of HR, Pd, and Ps of CAD patients were: 69 ± 5 beats/min, 80 ± 2, and 122 ± 5 mmHg, respectively. As was expected, these values increased to 129 ± 11 beats/min, 86 ± 2, and 163 ± 9 mmHg during exercise, respectively, indicating that the heart of CAD patients responded well to the body demands during exercise. In the control subjects, these values were 76 ± 3 beats/min, 67 ± 3, and 146 ± 6 mmHg at rest, and with exercise increased to 134 ± 6 beats/min, 94 ± 3, and 186 ± 6 mmHg, respectively.

Sensations of exercise versus lobeline IV

The replies of all subjects to a question about a similarity of sensations arising from injecting LB and during exercise are presented in Table 5. The majority of subjects with CAD (8 out of 10) reported that from the 2 to 3 different sensations evoked by LB, at least one was similar to that felt while exercising; one reported that the sensations generated by exercise were similar but stronger than those felt with LB.

Table 4. Cardiovascular hemodynamics at rest and during exercise.

<table>
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<tr>
<th>Number</th>
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<th>Ps</th>
<th>Pd</th>
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Control subjects

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<th>Ps</th>
<th>Pd</th>
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Similarity of sensations (SS) of injecting LB and of exercise. Each individual replied to a question whether the sensations he/she felt with LB were similar to those felt while exercising (Y = yes, they were similar; N = no, they were different). Also provided is the similarity of descriptors as judged from their verbatim responses presented in Table 2. Note that the percentage of similarity of sensations in response to LB and while exercising was 80 – 90% in CAD patients and 30% in control subjects. Pd = diastolic pressure; Ps = systolic pressure; HR = heart rate.

Sensations of exercise versus lobeline IV

The replies of all subjects to a question about a similarity of sensations arising from injecting LB and during exercise are presented in Table 5. The majority of subjects with CAD (8 out of 10) reported that from the 2 to 3 different sensations evoked by LB, at least one was similar to that felt while exercising; one reported that the sensations generated by exercise were similar but stronger than those felt with LB.

Table 5. Similarity of sensations of injecting LB and during exercise reported directly by the subject and judged from descriptors.

<table>
<thead>
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<td>Y</td>
<td>Y</td>
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<td>Y</td>
<td>Y</td>
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<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>100*</td>
<td></td>
</tr>
</tbody>
</table>

Control

<table>
<thead>
<tr>
<th>Control</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>20</th>
<th>SS % total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported directly</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>30</td>
</tr>
<tr>
<td>Judged from descriptors</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>30</td>
</tr>
</tbody>
</table>

Similarity of sensations (SS) induced by LB or experienced during exercise. Each individual replied to a question whether the sensations he/she felt with LB were similar to those felt while exercising (Y = yes they were similar; N = no, they were different). Also provided is the similarity of descriptors as judged from their verbatim responses presented in Table 3. Note that the patients percentage of similarity of sensations reported by CAD patients in response to LB and while exercising was 90% (and judged from descriptors100%) and 30% in control subjects.

* = mean data is significantly different from that of control at P < 0.0001.
than those of LB; and one subject did not answer in the affirmative way, yet an examination of his verbatim report yielded a similarity amongst the two. In comparison, only 3 out of 10 control subjects found any similarity, if at all (Table 5).

Sensations reported while exercising

The treadmill exercise tolerance test (ETT) of each subject, as stated by Bruce Protocol (in metabolic equivalent task [METs]) is presented in Table 1. The mean duration of exercise in CAD patients was significantly lower (7.3 ± 0.7 min; a little beyond stage II) than that of the control subjects (9.3 ± 0.6 min; a little beyond stage III (Table 2 and Figure 2).

All categories of sensations felt by both groups are illustrated in Table 3, and Figures 3 and 4. Though, 30% of CAD patients had 1 – 4 dry coughs while exercising; this was absent in the control subjects (Table 2, Figure 4). Almost, all of the subjects with CAD felt more than one sensation (dryness of mouth and throat or swallowing in throat, difficulty in breathing, and dry cough), whereas 30% of control subjects felt only one kind of these sensations while exercising.

Table 6. Reasons for discontinuing exercise in 10 CAD patients and 10 control subjects.

<table>
<thead>
<tr>
<th></th>
<th>CAD (%)</th>
<th>Control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortness of breath</td>
<td>3 (30)</td>
<td>—</td>
</tr>
<tr>
<td>Chest pain</td>
<td>2 (20)</td>
<td>1 + S-T Depression 10%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (20)</td>
<td>—</td>
</tr>
<tr>
<td>Target HR</td>
<td>2 (20)</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>S-T Deviation</td>
<td>1 (10)</td>
<td>—</td>
</tr>
<tr>
<td>Others</td>
<td>—</td>
<td>1* (10%)</td>
</tr>
</tbody>
</table>

* Exercise terminated because of dizziness + hypotension.

Discussion

The present study indicated that injecting small doses (threshold doses) of lobeline in subjects with evidence of coronary artery disease induced more kinds of sensation in the mouth, throat, and upper chest areas, which was significantly higher than the healthy subjects. These sensations were predominantly due to dryness, tickling, smoke, hot or cold air, choking, suffocation, etc, in these areas. The other known sensations of injecting LB were an inability to breathe/shortness of breath, dry coughs, and feeling of fatigue. In this context it is quite revealing to note that young soldiers with high altitude pulmonary edema, who were otherwise healthy and nonfebrile, had also complained of cough, breathlessness, and chest discomfort consisting of choking and pressure. The variety of sensations felt by healthy subjects in this study were the same as those seen amongst CAD patients (above) and were in conformity with those reported for healthy individuals in all earlier studies, but their incidence was notably less.

The mean threshold dose of lobeline of subjects with CAD was significantly higher than that of the age- and weight- matched healthy subjects.
Assuming that cardiac output (CO) of the CAD patients is lower than those of healthy subjects at rest (EF = 50.4%), this value should have been less than that of the latter (EF = 61%). Bhargava et al demonstrated that decreasing CO in healthy subjects by changing their position from supine to upright, reduces their lobeline threshold dose. Based on this report, there is a relationship between CO and threshold doses of lobeline for sensations, however, no explanation is forthcoming from the scope of the present study.

In normal conditions J receptors are silent, and the extent of their stimulation, by small doses of lobeline, is not substantial as judged from short-lasting and weak respiratory reflexes. However, from the effectiveness of small doses of lobeline in almost all CAD patients in the present study, one may suggest that their J receptors were continuously exposed to subthreshold stimulation by transient increases in pulmonary interstitial volume, that is why, the threshold doses of lobeline stimulate their J receptors more intensely.

A similar explanation follows with exercise. All CAD patients reported that they were experiencing these throat/chest-related sensations with moderate exercise before being stopped (without having reached their target heart rate) or giving it up for more severe reasons such as chest pain and fatigue (Table 2). Since exercise increases pulmonary blood flow by increasing cardiac output, the resultant stimulation of J receptors is likely to be far in excess of that being present at rest in CAD patients, due to increasing congestion in the pulmonary capillaries with exercise. Dry cough was noted in 30% of CAD patients, while exercising, but not in any of the healthy subjects. Dry cough needs larger doses of lobeline, hence only occurs at a higher intensity of J receptor stimulation in healthy subjects. It is also worth mentioning that a difference in the incidence of these sensations amongst the two groups cannot be explained on the basis of one group being predominantly of smokers, since an almost equal number of individuals in both groups had been smokers in the past. The most notable observation in this study was that the majority of CAD patients reported (90% reported directly and 100% judged from descriptors) a similarity between lobeline-induced sensations and those experienced while exercising (Table 5). This is an important observation, since in healthy individuals exercise neither evoked noteworthy sensations (only 30%) nor did they find these sensations to be alike when confronted (Table 5). Thus, the similarity of lobeline-induced sensations with those felt during exercise by almost all CAD patients, especially of soreness/dryness of throat, tightness of chest (Tables 2 and Figure 3), and cough strongly points to a common origin. Hence, it is noteworthy mentioning that the origin of throat/chest-related sensations felt by CAD patients during mild/moderate exercise, arises from the stimulation of their J receptors by transient increases in pulmonary interstitial volume, possibly owing to cardiac congestion.

Recent reports have indicated that exercise in healthy subjects with chronic heart failure is limited by dyspnea, chest pain, and muscle fatigue. Hence, the significantly shorter duration of exercise performed by CAD patients than by healthy subjects was not surprising. Nor it was surprising that 50% of these patients stopped to exercise because of tiredness (shortness of breath and fatigue; Table 6), as is documented in normal subjects. Hence, these noxious sensations in conjunction with dry cough, with the origin of J receptors stimulations, might be crucial in preventing the heart from further damage by abruptly reducing its work load.

In essence, the significance of this study lies in a close evaluation of these sensations in relation to exercise. It is important to keep in mind that healthy individuals reported experiencing sensations like dryness, swelling, or tightness in their throat/chest, or had a dry cough with exercise, as moderate as climbing stairs or running short distances as for catching a bus, should be diagnosed for possible heart diseases. In addition, it would also be useful to reveal to those patients of latent/early heart disease not to ignore sensations of dryness of the throat or a feeling of suffocation or dry cough when having to run unexpectedly in certain situations.

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