Cardiopulmonary Response to Exercise in Patients with Different Degrees of Lung Toxicity after Radio-chemotherapy for Hodgkin’s Disease

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Abstract. The combination of mediastinal radiotherapy (RT) and polychemotherapy (CT) regimens can produce late toxic pulmonary and cardiac effects which often remain at the subclinical level. The aim of the present study was to investigate the cardiopulmonary response to exercise in this kind of patient. Therefore, 126 patients suffering from Hodgkin’s disease were investigated after a follow-up of at least 5 years from the completion of the combined treatment. Sixty-two patients had been submitted to ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine)-RT, 40 to ABVD-MOPP (mechloretamine, vincristine, procarbazine, prednisone)-RT and 24 to VEBEP (vincristine, epidoxorubicin, bleomycin, cyclophosphamide, etoposide, prednisone)-RT. The patients were divided into three groups on the basis of respiratory function: group 1 (67 patients), normal spirometry and lung transfer function for carbon monoxide (DLCO); group 2 (52 patients), normal spirometry and DLCO less than 80% of predicted; and group 3 (7 patients), total lung capacity and DLCO less than 80% of predicted. The patients were submitted to respiratory function evaluation and 2D-echocardiography before exercise, and to the determination of cardiac output by the acetylene rebreathing method before and during symptom-limited exercise on a cycloergometer using an incremental protocol. The patients of group 3 and to a lesser extent the patients of group 2 showed, in comparison to patients of group 1, a lower tolerance to exercise, a lower oxygen consumption, a higher respiratory rate, a lower O2 pulse and a lower cardiac output per oxygen uptake. These data indicated an abnormal exercise physiology in the patients with persistent pulmonary impairment, especially when the reduction of DLCO was associated with a decrease of total lung capacity. The lower exercise capacity seems to be due to a combination of decreased cardiac performance and an impairment of gas diffusion capacity.

At the present time, the majority of patients diagnosed with Hodgkin’s disease can be cured with an appropriate combination of active chemotherapeutic agents and radiotherapy (1).

Considerable interest exists over the late cardiopulmonary toxic effects of the combined chemo-radiotherapy regimens for Hodgkin’s disease because of the effectiveness of these treatments (2-8). Mediastinal irradiation has been associated with both cardiac and pulmonary toxic effects, the incidence and severity of which depend on the irradiation techniques employed, the volume of lung irradiates and the daily dose of radiotherapy, and which can develop months to years after completion of the therapy. Complications include pericarditis, coronary artery fibrosis, cardiac valve sclerosis, myocardial infarction, decreased ventricular function, electrocardiographic abnormalities and radiation pneumonitis and fibrosis (2, 6, 9-19). The incidence and severity of these toxic effects can be potentiated by the chemotherapeutic agents delivered in combination with the radiotherapy (7, 20-22). It is well known that bleomycin and anthracyclines, and to a lesser extent, other antineoplastic drugs (such as cyclophosphamide and etoposide), all of which are frequently used in chemo-therapeutic regimens, can cause dose-related pulmonary and cardiac toxicity (23-30). The more common signs of pulmonary toxicity are represented by abnormal radiological findings, the occurrence of restrictive lung syndrome and in particular by the decrease of lung transfer function for carbon monoxide, CO (8, 21, 22). The risk of chronic dose-related cardiomyopathy limits the use of cardiotoxic agents such as anthracyclines in long-term treatment (23-25).

It is difficult to separate the effects of radiotherapy and chemotherapy in patients who receive both.
Moreover the majority of studies have been directed to the evaluation of cardiopulmonary function at rest using conventional procedures (spirometry, determination of the lung transfer factor for CO, echocardiography) and very often have screened cancer survivors with a limited number of testing modalities.

In addition only minimal research has been directed to evaluating cardiopulmonary function and reserve during exercise (31-34).

Therefore, the aim of the present investigation was to evaluate the cardiopulmonary toxicity in a population of Hodgkin’s patients submitted to different chemotherapeutic regimens followed by mediastinal irradiation after a follow-up of more than 5 years from the completion of the combined treatments, an interval long enough for pulmonary and cardiac damage to be considered irreversible. In particular, cardiopulmonary function was evaluated by means of spirometry, determination of the lung transfer factor for CO, chest X-ray, 2D-echocardiography and by exercise test in order to obtain a comprehensive evaluation of the full range of cardiopulmonary abnormalities.

**Patients and Methods**

The study was conducted on 126 patients suffering from Hodgkin’s disease submitted to chemotherapy and radiotherapy with follow-up from completion of treatment of more than 5 years. Twenty-four patients had been treated with the polychemotherapy regimen VEBEP, 62 with the ABVD regimen and 40 with the MOPP-ABVD regimen.

The VEBEP schedule consisted of the administration of etoposide (VP16) 120 mg/m² i.v. and epidoxorubicin 40 mg/m² i.v. on day 1 and 2, bleomycin 10 mg/m² on day 1 only, cyclophosphamide 300 mg/m² i.v. on day 1 and 2, with prednisone 50 mg/total dose given by oral route on day 1 to 7. The cycles were repeated every 21 days and 2, bleomycin 10 mg/m² on day 1 only, cyclophosphamide 500 mg/m² by oral route on day 1 and 15 with each cycle repeated every 28 days.

The ABVD treatment schedule included doxorubicin 25 mg/m², bleomycin 10 mg/m², vinblastine 6 mg/m² and dacarbazine 375 mg/m². All the drugs were delivered by the i.v. route on day 1 and 15 with each cycle repeated every 28 days.

The MOPP-ABVD regimen included mechloretamine 6 mg/m² i.v. and vincristine 1.4 mg/m² i.v. on days 1-8, procarbazine 40 mg/m² by oral route and prednisone 40 mg/m² by oral route on days 1-14 as well as the ABVD agents. The treatment was repeated every 28 days. In the alternating protocol, the ABVD regimen was monthly alternated with the MOPP regimen, while hybrid protocol patients received a monthly half cycle of ABVD alternated with a half cycle of MOPP. The number of patients was 19 in the MOPP-ABVD alternated and 21 in the MOPP-ABVD hybrid protocol.

**Radiotherapy. VEBEP protocol.** In the patients achieving partial remission or complete remission after chemotherapy, the involved lymphonodal regions were irradiated. The total dose to complete remission sites was 36 Gy.

**ABVD protocol.** The patients were randomly assigned to involved fields or subtotal nodal irradiation (STNI). The total dose to previously involved lymphonodal regions ranged from 36 Gy (in patients with confirmed complete remission) to 40 Gy (in patients with unconfirmed complete remission or partial remission). In the patients allocated to receive STNI, the planned dose to uninvolved sites was 30 Gy.

**Alternating or hybrid MOPP-ABVD protocol.** Radiation treatment was planned to treat the initial bulky lymphonodal regions achieving complete remission or maximal tumor shrinkage after chemotherapy. Radiation treatment encompassed the sites of bulky disease in the majority of patients and the contiguous involved and uninvolved sites in a majority of cases. The median total dose was 30 Gy.

RT started four weeks after chemotherapy completion, after complete restaging. All the involved lymphonodal regions were mapped before chemotherapy started, but target volumes were defined on the basis of post-chemotherapy radiological examinations and delineation was obtained on standard X-rays during conventional simulation. CT simulation or computerized treatment plans were performed. Daily fractionation was 90+90 cGy for 5 days per week, and was given through antero-posterior and postero-anterior equally weighted portals, usually using a 6-MV linear accelerator for supradiaphragmatic irradiation and a 6- or 18-MV linear accelerator, depending on the thickness of the area, for the infradiaphragmatic treatments. In order to give the scheduled total dose, physicists prepared a dose-distribution map for each patient. After set-up was planned, customized shields were produced for all the patients with more than one site to be treated. Lung shields were not modified during the treatment and no subcarinal block was added; the spinal cord was shielded in the postero-anterior field at 30 Gy. Portal films were obtained on day 1 and repeated every week.

**Evaluation of pulmonary function.** Standard spirometric parameters were determined using a model Pulmonary Function Test Horizon Systems Spirometer (Sensor Medics, Yorbalinda, California). Spirometry was performed at least three times in each patient during each examination and as a measure of reproducibility at least two of the tests had to be within 5% of each other.

The pulmonary function test data were described as a percentage of predicted values. The lung transfer factor for CO (DLCO) was measured with the single breath technique of Blakemore et al. (35) as modified by Cotes (36). DLCO values measured while breathing room air were corrected for hemoglobin concentration using the method of Dinakara et al. (37) in order to obtain a DLCO value under standard conditions. The two components of DLCO, the diffusing capacity of the alveolar capillary membrane (Dm) and the pulmonary capillary blood volume (Vc) were determined from measurements of DLCO at high (60%) and low (40%) inspiratory oxygen concentrations. The calculation followed the equation originally used by Roughton and Foster (38).

**Radiographic evaluation of lung damage.** Radiographic evidence of pulmonary toxicity was defined as the presence of pulmonary fibrosis on chest X-ray during or following radio-chemotherapy in the absence of infection. Parenchymal lung damage was graded as: grade 0, no evidence of lesions; grade 1, interstitial retracting sclerosis without paramediastinal retraction; grade 2, interstitial retracting sclerosis with cranial retraction of pulmonary hila and verticalization of cardiovascular structure; and grade 3, interstitial and alveolar retracting sclerosis with mediastinal traction and dislocation.

**Cardiac function evaluation.** All the patients underwent a cardiological examination based on resting ECG, clinical evaluation and 2D-echocardiography (ATL Ultramark 9 device with >3.5 MHz
phased array transducer). The echocardiographic examination consisted of a complete two-dimensional and Doppler study with the patient placed in a supine position.

The left ventricular dimensions were obtained in M-Mode by the conventional parasternal long axis view and the ejection fraction was the result of two different evaluations based on the Teicholz formula.

**Determination of hemodynamic parameters.** Cardiac output was determined by the non-invasive acetylene rebreathing technique using a commercially available mass spectrometer (Amis 2000; Innovision, Odense, Denmark). The precision and reliability of this system have been validated in animals and humans (38-42). The patients were instructed to breathe through the mouthpiece of the apparatus. The nostrils were occluded with a nose clip. The rebreathing bag was filled with a gas mixture of 50% oxygen, 0.3% acetylene, 5% sulfur hexafluoride and the balance N₂ to a total volume corresponding to 40% of the patient’s vital capacity. Rebreathing started at normal end-tidal level with the patient completely emptying the bag and was performed for 30 s. Thereafter the cardiac output was calculated by an integrated computer from the disappearance curve of acetylene in the bag (38-42). The test was performed at rest and twice during incremental bicycle exercise (30 W/3 min).

In all the patients, the simultaneous measurement of oxygen consumption and cardiac output was performed which allowed the relationship between O₂ consumption and cardiac output to be calculated in each patient.

**Results**

The patients who entered the study were arbitrarily divided into three groups according to respiratory function results: in particular, 67 were found to have normal spirometry and lung transfer function for CO (DLCO) (group 1), 52 had normal spirometry and DLCO less than 80% of predicted (group 2), and finally 7 had total lung capacity and DLCO less than 80% of predicted (group 3). The clinical characteristics of the patients are listed in Table I.

Fifty-five out of the 126 patients were male (43.65%) and 71 were female (53.35%). Most of the patients were under 40 years of age. The mean age was lower in group 3 in comparison to the other groups.

Nodular sclerosis accounted for 55% of the cases and stage I and II accounted for more than 80% of the cases. Bulky mediastinal involvement was present in 27.7% of patients.

As shown in Table II, no statistically significant differences were found in the cumulative doses of anthracyclines, cyclophosphamide and radiotherapy to the mediastinal area. The cumulative dose of bleomycin was found to be significantly lower in group 3 with respect to group 1 and 2, and significantly higher in group 2 with respect to group 1.

The measurements of the different components of DLCO, allowed the identification of Dm as the component involved in the reduction of DLCO and therefore in the development of late lung toxicity (Table III).

<table>
<thead>
<tr>
<th>No.</th>
<th>M/F</th>
<th>Age (years)</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>I</td>
</tr>
<tr>
<td>67</td>
<td>32/35</td>
<td>39.2±1.2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(23-64)</td>
<td>6.0%</td>
</tr>
<tr>
<td>52</td>
<td>20/32</td>
<td>38.2±1.3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(25-65)</td>
<td>7.7%</td>
</tr>
<tr>
<td>7</td>
<td>3/4</td>
<td>31.6±1.9**</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(25-38)</td>
<td></td>
</tr>
</tbody>
</table>

N: Number of patients, *p<0.05 vs. Group 1, ^p<0.05 vs. Group 2.

Chest X-ray review showed that most of the patients of group 1 did not have important parenchymal lung damage, but damage of grade 3 was present in 4/67 of the patients of group 1 (6%), 10/52 of group 2 (19.2%) and 4/7 of group 3 (57.1%) (Table IV). A good correlation was found between the increase of radiological toxicity and DLCO reduction (data not shown).

Minimal ECG changes, represented by flattening of T waves, and isolated atrial premature beats were recorded in a few patients. No statistically significant differences were observed at rest between the three groups in relation to heart rate, left ventricular systolic and diastolic dimensions, ejection fraction or minor axis shortening. Blood pressure at rest was significantly lower in group 2 (Table V).

The cause of cessation of exercise test was mainly given as muscular exhaustion (76.1% in group 1, 67.3% in group 2 and 71% in group 3). Dyspnea was a relevant cause of cessation only in group 3 (27% versus 9.6% in group 2 and 4.5% in group 1). The exercise capacity to incremental exercise testing is reported in Table VI and was apparently lower than expected in healthy individuals, and progressively decreased from group 1 to group 3. No statistically significant differences were found in heart rate after exercise. Diastolic blood pressure after exercise was significantly reduced in group 2 and systolic blood pressure was significantly reduced in group 3 respect group 1 (Table VI).

Oxygen consumption at peak (VO₂ max) and O₂ consumption at the anaerobic threshold were found to be significantly reduced in group 3. The oxygen pulse was progressively reduced from group 1 to group 3, in particular the difference between group 1 and group 3 was statistically significant. No significant differences were observed in minute ventilation between the three groups suggesting that oxygen extraction was slightly but significantly attenuated from group 1 to group 3. The slight progressive increase of minute
Table II. Mean cumulative dose of bleomycin, anthracyclines (doxorubicin (DXR) and 4’-epidoxorubicin), cyclophosphamide and radiotherapy.

<table>
<thead>
<tr>
<th>No.</th>
<th>DXR (range)</th>
<th>4’-EpiDXR (range)</th>
<th>Cumulative dose</th>
<th>Cumulative dose</th>
<th>Cumulative dose</th>
<th>Median mediastinal RT dose</th>
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</thead>
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<tr>
<td></td>
<td>(mg/m²) (range)</td>
<td>(mg/m²) (range)</td>
<td>(mg/m²) (range)</td>
<td>(mg/m²) (range)</td>
<td>(Gy) (range)</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>334.6±30.7 (230.2-626.5)</td>
<td>7474.5±208.2 (5567.0-8292.7)</td>
<td>33.8±0.5 (23.0-43.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>72.4±1.2 (50.6-95.5)</td>
<td>54</td>
<td>175.8±4.4 (103.4-287.6)</td>
<td>33.8±0.5 (23.0-43.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>269.6±21.1 (119.3-324.3)</td>
<td>7337.1±314.4 (4810.1-8108.1)</td>
<td>35.4±0.5 (25.2-45.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>76.8±1.6* (38.9-112.4)</td>
<td>42</td>
<td>185.6±5.6 (81.1-261.9)</td>
<td>35.4±0.5 (25.2-45.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>297.7</td>
<td>7441.9</td>
<td>35.7±1.7 (30.6-44.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>55.3±9.6*^ (17.7-81.7)</td>
<td>6</td>
<td>134.2±27.7 (44.8-202.2)</td>
<td>35.7±1.7 (30.6-44.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No.: Number of patients, *p<0.05 vs. Group 1, ^p<0.05 vs. Group 2.

Table III. DLCO and its components, capillary volume (Vc) and diffusing capacity of the alveolar capillary membrane (Dm).

| DLCO corr. (% of predicted) | Vc (ml) | Dm (ml/mmHg/min⁻¹) | Group 1 | 93.7±2.1 | 94.5±5.4 | 50.5±3.2 |
| Group 2 | 70.8±0.8* | 98.4±12.2 | 36.3±2.9* |
| Group 3 | 68.3±3.2* | 97.3±17.3 | 32.8±2.5* |

DLCO corr.: DLCO corrected for hemoglobin concentration. *p<0.05 vs. Group 1.

Table IV. Radiological evaluation of pulmonary toxicity.

<table>
<thead>
<tr>
<th>Grade</th>
<th>No. of patients</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Group 1</td>
<td>67</td>
<td>12</td>
<td>17.9</td>
<td>35</td>
<td>52.2</td>
</tr>
<tr>
<td>Group 2</td>
<td>52</td>
<td>6</td>
<td>11.5</td>
<td>20</td>
<td>38.5</td>
</tr>
<tr>
<td>Group 3</td>
<td>7</td>
<td>2</td>
<td>28.6</td>
<td>1</td>
<td>14.3</td>
</tr>
</tbody>
</table>

Table V. Cardiac parameters at rest.

<table>
<thead>
<tr>
<th>Blood pressure Max (mmHg)</th>
<th>Blood pressure Min (mmHg)</th>
<th>Heart rate (beat/min) (% of predicted)</th>
<th>Left ventricular diastolic dimension (cm)</th>
<th>Left ventricular systolic dimension (cm)</th>
<th>Ejection fraction (%)</th>
<th>Minor axis shortening (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>127.5±1.8</td>
<td>85.7±1.2</td>
<td>92.7±1.6</td>
<td>4.7±0.1</td>
<td>3.0±0.04</td>
<td>64.5±0.6</td>
</tr>
<tr>
<td>Group 2</td>
<td>120.2±1.8*</td>
<td>82.0±1.4*</td>
<td>94.2±2.2</td>
<td>4.6±0.1</td>
<td>3.1±0.1</td>
<td>63.2±0.9</td>
</tr>
<tr>
<td>Group 3</td>
<td>118.6±4.6</td>
<td>85.7±3.8</td>
<td>96.3±5.1</td>
<td>4.4±0.2</td>
<td>2.8±0.1</td>
<td>62.7±1.9</td>
</tr>
</tbody>
</table>

*p<0.05 vs. Group 1.

Table VI. Functional parameters recorded during exercise test.

<table>
<thead>
<tr>
<th>Blood pressure Max (mmHg)</th>
<th>Blood pressure Min (mmHg)</th>
<th>Heart rate (beat/min) (% of predicted)</th>
<th>VO₂ Max (ml/kg/min)</th>
<th>VO₂ at anaerobic threshold (% of predicted)</th>
<th>Watts % predicted</th>
<th>VE (L/min)</th>
<th>VE/VT (%)</th>
<th>O₂ pulse Max (ml/beat)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>190.2±3.2</td>
<td>101.4±2.0</td>
<td>96.8±1.0</td>
<td>63.2±1.7</td>
<td>92.5±1.6</td>
<td>72.2±2.1</td>
<td>53.8±2.2</td>
<td>15.6±1.0</td>
</tr>
<tr>
<td>Group 2</td>
<td>183.0±3.9</td>
<td>94.6±2.0*</td>
<td>95.6±1.1</td>
<td>60.1±2.5</td>
<td>94.3±2.8</td>
<td>67.8±2.1</td>
<td>54.2±2.2</td>
<td>14.5±1.2</td>
</tr>
<tr>
<td>Group 3</td>
<td>167.1±10.6*</td>
<td>91.4±5.1</td>
<td>96.8±2.8</td>
<td>56.0±2.7*</td>
<td>81.1±7.1*</td>
<td>64.2±5.4*</td>
<td>62.3±7.1</td>
<td>18.7±2.0</td>
</tr>
</tbody>
</table>

VO₂: Oxygen consumption, VE: ventilation, VE/VT: dead space volume/tidal volume. *p<0.05 vs. Group 1.
ventilation from group 1 to group 3 (Table VI) was associated with a higher breathing frequency and lower tidal volume as shown in Figure 1. The correlation between the cardiac index (l/min/m²) and oxygen consumption, simultaneously recorded at rest and during exercise, is illustrated in Figure 2 and showed a progressive displacement of the curves from left to right with increasing pulmonary disability.

Discussion

The present results confirmed that the three chemo-radiotherapeutic regimens were able to produce subclinical pulmonary toxicity as evidenced in some patients by radiological findings, decrease of DLCO sometimes associated, in the more severe cases, with a decrease of total lung capacity (TLC) and by significant modifications of ventilation dynamics. In particular, the decrease of DLCO was due only to a reduction of Dm, which is considered to be the physical component of resistance to diffusion, therefore its reduction could be the expression of remodelling of the interstitium.

A progressive increase of ventilation was demonstrated from group 1 to group 3, which was found to be associated with a higher breathing frequency and lower tidal volume. This observation was consistent with an alteration of mechanical properties of the lung probably in relation to subclinical radio-chemotherapy induced lung fibrosis in agreement with the radiological and DLCO findings as previously described (30). The lower tidal volume may also have compromised gas exchange by increasing the ratio between the physiological dead space and the tidal volume (Table VI).

A relatively large number of retrospective studies have reported cardiac function impairment induced by chemotherapy associated with radiotherapy. In the present study, no significant modifications of left ventricular dimensions, ejection fraction or minor axis shortening were observed at rest in the three groups. In contrast, the exercise test demonstrated significant differences between the three groups. In particular, a progressive and significant (in group 3) decrease of maximum workload attained, oxygen pulse and oxygen consumption was observed from group 1 to group 3. Oxygen uptake at peak exercise (maximal oxygen uptake) is usually reduced in patients suffering from interstitial lung disease (43-44). In cardiac disease or deconditioning, similar decreases result from inadequate
oxygen delivery to, or utilization by, the exercising muscles, while in interstitial lung disease these usually result from exercise terminating at a lower load because of ventilatory limitation. The present data suggested that in group 3, exercise was limited not only by ventilation factors as previously described, but also by exercise-associated cardiac dysfunction.

In healthy individuals exercise is accompanied by the recruitment of small pulmonary vessels arterioles and capillaries that allow cardiac output to increase without significantly altering pulmonary vascular resistance or pulmonary artery pressure. Moreover, $O_2$ pulse increases during exercise principally because of a widening difference between arterial and mixed venous oxygen concentrations. One possible explanation of the reduced performance during exercise in group 3 is that in this group exercise could have been associated with an increase of pulmonary vascular resistance and pulmonary artery pressure which could have reduced the volume of blood flowing from the right to left ventricles (reduced left ventricular preload). In addition, as the right ventricle becomes overloaded, the intraventricular septum shifts, altering the geometry of the left ventricle and further restricting left ventricular filling. On the other hand, the occurrence of masked ventricular dysfunction, detectable only during exercise stress, could not be excluded among the factors able to reduce exercise performance.

It must be noted that all the patients were treated with anthracyclines which can cause cardiac toxicity and were submitted to mediastinal irradiation which has been associated with late cardiac and pulmonary toxic effects.

In conclusion, abnormal exercise physiology is seen in patients treated for Hodgkin’s disease with persistent lung function impairment, especially when the reduction of DLCO is associated with a decrease of TLC. The lower exercise capacity seems to be due to a combination of a decrease in heart performance and an impairment of gas diffusion capacity.

References


