Annals of Oncology **8**: 1251–1255, 1997.
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Original article

Correlation between physical performance and fatigue in cancer patients

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Summary

Background: Fatigue and a reduction in physical ability are common and often severe problems of cancer patients regardless of disease stage and modality of treatment. However, while physical performance can be assessed objectively with laboratory tests, fatigue is a subjective phenomenon whose perception is influenced by past experience and expectations for the future.

Patients and methods: To evaluate the correlation between fatigue and physical impairment, we assessed maximal physical performance with a treadmill test, and mental state with two questionnaires, the Profile of Mood States (POMS) and the Symptom Check List (SCL-90-R), in a successive series of 78 cancer patients with solid tumors or hematological malignancies.

Results: A weak association between fatigue and maximal physical performance was found ($r = -0.30$; $P < 0.01$). However, intensity of fatigue showed a strong correlation with several indicators of psychological distress such as depression ($r = 0.68$), somatization ($r = 0.64$) and anxiety ($r = 0.63$; P for all < 0.001). Furthermore, patients with lower levels of physical performance had significantly higher scores for depression ($P = 0.005$), somatization ($P = 0.03$) and anxiety ($P = 0.08$), and significantly lower scores for vigor ($P = 0.05$) than their counterparts whose physical performance was higher.

Conclusions: We conclude that fatigue in cancer patients may be related to mood disturbance but appears to be independent of physical performance. Moreover, low physical performance can be viewed as an independent predictor of mental distress in cancer patients.

Key words: cancer fatigue, physical performance, psychological distress

Introduction

Fatigue figures among the most common problems of cancer patients. According to several studies, this symptom affects up to 70% of patients during chemo- and radiotherapy [1–3]. It has been reported that impairment of physical functioning may persist for years after cessation of therapy in up to 30% of cancer survivors [3–5]. For many cancer patients, fatigue is severe and imposes limitations on normal daily activities. Postulated etiological mechanisms for the development of fatigue include anemia, impaired nutritional status, sleep disturbances, biochemical changes secondary to disease and treatment, psychosocial factors, and a reduced level of activity [6]. However, the causes of the impairment of physical functioning in this setting are not yet fully understood.

In fact, fatigue represents only one aspect of the problem of physical impairment experienced by cancer patients. Cancer is usually accompanied by an 'asthenic syndrome' consisting of two components, one objective (loss of physical performance) and one subjective (fatigue). This difference considerably complicates the study of asthenia in cancer patients. Physical performance can be directly determinated by laboratory tests and expressed in units (maximal oxygen uptake in ml/kg/min, maximal workload in km/h or watts). Fatigue, on the other hand, has to be assessed indirectly by self-ratings.

Another factor complicating evaluation of fatigue in cancer patients is that – as with every subjective phenomenon – perception of fatigue strongly depends on past experience. Since cancer-related decreases in physical activity can persist for a long time, perception of fatigue can change as it becomes chronic. It has been suggested that cancer patients gradually become accustomed to their impaired physical condition and finally experience it as normal [7]. Furthermore, the subjective and objective evaluation of the limitation in physical performance can produce different results: a substantial discordance has been observed in estimations of functional ability with the Karnofsky index by patients and medical staff [8]. Nevertheless, in some clinical situations fatigue can exist independently of deterioration in physical performance; for example, fatigue is frequently a symptom in patients with depressive disorders whose physical performance is not necessarily impaired.

In light of these considerations, we investigated the relationship between fatigue and physical performance in cancer patients.

Table 1. Baseline data of patients in the study ($n = 78$).

Gender	48 women, 30 men	
Age	40 ± 11.3 (18–60)	
Body mass index	23.9 ± 3.7 (18–34)	

	Number of patients	Percentage
Disease		
Breast cancer	25	32%
Metastatic breast cancer	9	11%
Testicular cancer	11	14%
Sarcoma	3	4%
Small-cell lung carcinoma	1	1%
Multiple myeloma	2	2%
Hodgkin's disease	6	8%
Non-Hodgkin's disease	21	27%
Maximal physical performance		
Very poor (50% of maximum)	49	62%
Poor (50%–54% of maximum)	6	8%
Fair (55%–65% of maximum)	7	9%
Good (66%–69% of maximum)	6	8%
Excellent (70%–75% of maximum)	8	10%
Superior (> 75% of maximum)	2	3%

Maximal physical performance of the patients was classified in accordance with tables of normal values for aerobic power tests for healthy adults [13]. Values are shown as mean ± standard deviation; ranges are shown in brackets.

Patients and methods

A series of 89 successive cancer patients with solid tumors or hematological malignancies were enrolled in the study (Table 1). Inclusion criteria were: age between 18 and 60 years, active malignancy, an absence of associated psychiatric, muscular, cardiovascular or pulmonary disease, and the ability to understand written German. All patients were considered for a high-dose chemotherapy (HDC) with peripheral autologous blood stem cell transplantation. In the weeks preceding hospital admission for HDC, all of them received one to four chemotherapy cycles consisting of etoposide 500 mg/m^2, ifosfamide 4 g/m^2, and cisplatinum 50 mg/m^2, with or without epirubicin 50 mg/m^2 (VIP/VIP-E).

After giving their informed consent, all patients underwent a treadmill stress test for assessment of maximal physical performance. The test began with 3 km/h and 1.5% elevation; the speed was increased by 1 km/h every third minute, while the elevation remained unchanged. The test was carried out under continuous ECG monitoring. The heart rate was assessed at the end of every workload. Eleven patients (13%) discontinued the test because of pain or coordinatory problems and were excluded from the study. Altogether, data on 78 patients were included in the statistical analysis.

Following evaluation of their physical performance, all patients underwent an assessment of their psychological state by completing two questionnaires, the short version of the Profile of Mood Status (POMS) [9, 10] and the Symptom Check List (SCL-90-R) [11, 12]. These instruments consist of statements about subjective experiences and allow an assessment of affective states during the past week (the SCL-90-R) or on the current day (the POMS). The short version of the POMS yields a total mood disturbance score (TMD) and separate subscale scores for depression, fatigue, anger-hostility and vigor. Similarly, the SCL-90-R yields a global severity index (GSI) and separate subscales for somatization, obsessivity, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. Higher TMD and GSI scores indicate greater overall mood disturbance, while higher subscale scores indicate a greater intensity of disturbance in the examined areas. These instrument have been used in several clinical studies to evaluate affective states and mental symptomatology in different patient populations and have shown high reliability and validity.

Maximal oxygen consumption in ml O_2 per kg of body weight per minute was calculated according to the guidelines of the American College of Sports Medicine [13].

Statistical analysis

To evaluate the association between intensity of fatigue and physical performance, a partial correlation test, including age and gender as independent covariables, was carried out. Employing the Spearman rank correlation test, in a further analysis we calculated the correlation between fatigue and the remaining sub-scales of the POMS (vigor, anger, and depression), and between fatigue and the sub-scales of the SCL-90-R considered to be of relevance (somatization, depression, anxiety, hostility, and interpersonal sensitivity).

Maximal physical performance of the patients was compared with the values for aerobic power of healthy persons, obtained from standard tables [13]. In these tables, maximal physical performance can be assigned to one of six functional categories representing percentages of the maximal oxygen uptake (VO_2max) values recorded in healthy persons. The six categories are: very poor (VO_2max lower than 50% of the maximal observed value), poor (50%–54%), fair (55%–65%), good (66%–70%), excellent (71%–75%), and superior (higher than 76%). To evaluate the influence of physical performance on mental distress, the psychological scores of patients whose physical performance was in the lowest categories ('very poor' and 'poor') were compared with the remaining patients by the Mann–Whitney ranks test. To identify significant predictors of fatigue, a stepwise multiple regression analysis was carried out. It included all POMS subscales, the SCL-90-R subscales considered relevant (depression, somatization, and anxiety) and maximal physical performance as independent variables, and fatigue as a dependent variable. All statistical calculations were carried out using the Statistical Package for the Social Sciences (SPSS 6.1.2). A value of $P < 0.05$ was considered to show statistical significance, and a value of $r > 0.50$ to indicate relevant correlation.

Results

According to the guidelines of the American College of Sports Medicine, the physical performance of 55 of 78 patients in the study (70%) was classified as 'poor' or 'very poor' (Table 1). These patients had significantly more somatic complaints ($P = 0.03$), were more depressed ($P = 0.005$) and anxious ($P = 0.08$), had a higher insecurity in interpersonal contacts ($P = 0.09$) and significantly lower vigor ($P = 0.05$) than their counterparts with higher physical performance (Table 2). There was no difference in the extent of fatigue in the two groups ($P = 0.30$). Altogether, the global intensity of mental distress (GSI) in patients with reduced physical performance was more severe than for their counterparts with higher endurance ($P < 0.006$).

Statistical analysis showed a weak correlation between fatigue and maximal physical performance (Table 3). On the other hand, a strong correlation between fatigue and somatization, anxiety, and depression was observed. Multiple regression analysis showed depression, somatization and vigor/activity to be the only significant predictors of fatigue ($f\ (3,73) = 39{,}5$; $P < 0.0001$). These three parameters accounted for 61% of the variance in fatigue intensity.

Table 2. Differences of psychological distress between patients according to maximal physical performance.

	Patients in the lowest quartiles	Patients in the three highest quartiles	*P*-value
Number	56 (72%)	21 (28%)	
Maximal oxygen uptake (ml/kg/min)	21 ± 63	7 ± 3	< 0.001
POMS			
Depression	14.4 ± 2.0 (0–70)	11.3 ± 3.1 (0–63)	0.46
Fatigue	10.9 ± 1 (0–42)	7 ± 1.5 (0–25)	0.30
Vigor-activity	18.9 ± 1.1 (0–37)	22.6 ± 1.6 (1–34)	0.05
Anger-hostility	5.7 ± 1 (0–36)	5.2 ± 1.5 (0–24)	0.83
Total mood disturbance	12.1 ± 33 (−30–115)	1 ± 29 (−31–93)	0.16
SCL-90-R			
Somatization	5.5 ± 0.7 (0–23)	2.8 ± 0.6 (0–10)	0.03
Obsessive-compulsive	4.6 ± 0.6 (0–21)	3.4 ± 0.7 (0–11)	0.27
Interpersonal sensitivity	3.7 ± 0.5 (0–19)	2.2 ± 0.6 (0–11)	0.09
Depression	7.4 ± 0.9 (0–35)	4.1 ± 1.2 (0–22)	0.005
Anxiety	4.7 ± 0.8 (0–28)	2.3 ± 0.8 (0–16)	0.08
Hostility	2.0 ± 0.35 (0–11)	1.1 ± 0.3 (0–5)	0.20
Phobic anxiety	1.6 ± 0.33 (0–13)	1.1 ± 0.4 (0–6)	0.50
Global severity index	39.2 ± 4.6 (4–173)	22.0 ± 5 (1–34)	0.006

Abbreviations: POMS – Profile of Mood States; SCL-90-R – Revised Symptom Check List 90.
Data are shown as mean ± standard deviation; ranges are shown in brackets. Data were compared with the Mann–Whitney ranks test.

Discussion

Fatigue is a common and sometimes severe problem of cancer patients. The origin of fatigue in this setting is certainly multifactorial; however, psychological factors seem to play an important etiologic role. Fatigue in cancer patients has been related to depression, anxiety, distress, and global mood disturbance [1, 14–18]. Nerenz et al. found tiredness to be strongly associated with the emotional distress experienced during chemotherapy [15]. Depression in particular is considered to be a contributor to fatigue in cancer patients. Two reports found an association between fatigue and depression in a group of cancer patients undergoing radio- or chemotherapy [14, 19]. Furthermore, Fobair reported a strong correlation between energy loss and depression in lymphoma patients, evaluated several years after completion of treatment [20].

Table 3. Correlation between maximal physical performance and examined psychological domains.

	Correlation with fatigue	Significance of *P*
Maximal physical performance (VO_2max in ml/kg/min)	−0.30	< 0.01[a]
Depression (POMS)	0.61	< 0.001[b]
Vigor (POMS)	−0.52	< 0.001[b]
Anger (POMS)	0.52	< 0.001[b]
Depression (SCL-90)	0.68	< 0.001[b]
Somatization (SCL-90)	0.64	< 0.001[b]
Anxiety (SCL-90)	0.63	< 0.001[b]
Hostility (SCL-90)	0.53	< 0.001[b]
Interpersonal sensitivity (SCL-90)	0.47	< 0.001[b]
Global severity index (SCL-90)	0.68	< 0.001[b]

[a] Partial correlation including age and gender as covariates.
[b] Spearman rank-difference.

When considered from a teleological perspective, fatigue appears as a normal and necessary instrument of physiological self-regulation. Fatigue that appears after intense or prolonged activity protects the body from exaggerated or harmful effort. However, fatigue can also become pathological when it occurs during normal activity, persists for a long time, does not improve after rest, or becomes severe enough to force patients to reduce their level of activity [21]. The incidence of fatigue in healthy populations has been estimated to be between 21% and 47% [22–24]. Therefore, studies of the incidence and intensity of fatigue in cancer patients should include a comparison with sex- and age-matched healthy controls. Interestingly, when this methodology was used, mean fatigue levels in cancer patients were only slightly higher than those observed in controls [18, 25]. This is surprising, in view of the clinical observation that many cancer patients experience a severe diminution of their physical performance.

Our study suggests a possible explanation for this observation. Analyzing the subjective and objective data of our patients, we discovered a divergence between their objective life situation and their subjective perception of it. In fact, according to the standards of the American College of Sports Medicine, the physical performance of 70% of the patients in our study was 'poor' or 'very poor'; a similar percentage has been observed by other authors [3]. However, in our study, these patients did not experience more fatigue than their counterparts whose physical performance was higher. These data appear to be counterintuitive since many of these patients (especially those with a physical performance considered to be 'very poor') reported limitations in normal activities such as stair climbing or housekeeping. Thus, we wonder why patients do not feel fatigued despite impaired physical performance?

Breetvelt et al. [7] have proposed a theoretical explanation for this. Fatigue is a subjective experience. According to the North American Nursing Diagnosis Association, the major feature of chronic fatigue is verbalization or self-report of a sustained and significant lack of energy. However, since cancer fatigue can persist for a long time, the patient's subjective standards of measurement can change in the course of the disease. Therefore, patients affected by chronic loss of physical performance can gradually become accustomed to this impairment and finally experience it as normal.

The findings of the present study are clinically relevant, because our data show that evaluation of fatigue in cancer patients can be misleading, since many cancer patients deny feeling fatigued despite severe limitations in physical performance. To assess the actual degree of physical impairment, patients have to be explicitly asked about the objective limitations they experience in daily activities, such, for instance, as stair climbing or walking.

In our study, patients with impairment of physical performance had significantly higher scores of mental distress. Patients with the lowest performance level were significantly more depressed and anxious, had more severe obsessive-compulsive traits, were more insecure in social contacts, and had a higher intensity of somatic complaints than their counterparts with better physical performance. This association between impaired physical performance and increased psychological distress has been previously reported. In a study by Baker et al., the Karnofsky Index was the most significant predictor of satisfaction with quality of life, total mood disturbance and vigor [26].

Whether mood disturbance in these patients is a consequence or the cause of the impaired physical performance is difficult to determine; both possibilities seem plausible. Impaired physical performance can result in increased dependence, decreased self-esteem, reduction in social activities, limitations in family life, and a pessimistic mood. Furthermore, impaired physical performance can be interpreted by the patient as a sign of poor health and thereby increase his or her psychological distress. On the other hand, depressed and anxious patients are more likely to reduce their outdoor activity and revert to a passive lifestyle; this can result in muscular deconditioning and loss of physical performance. Clearly, the association between impaired physical performance and increased psychological distress in cancer patients can have therapeutical consequences. For example, an improvement of physical performance by a physical training program could reduce negative mood states in cancer patients; in fact, we have reported a substantial improvement of physical performance and emotional stability in cancer patients who participated in an aerobic training program [27–29].

To our knowledge, this report represents the first objective evaluation of impairment of physical performance and its relation to mood in cancer patients. All participants in our study were candidates for a high-dose chemotherapy with peripheral stem cell transplantation and had received treatment with identical doses of cytostatic drugs in the months preceding enrollment. Therefore, the sample evaluated in our study was homogeneous with regard to stage of disease, tumor burden and treatment modality.

Our study included a single evaluation of maximal physical performance and psychological status. This is a limitation of the study design, since cancer is a chronic disease and several factors (treatment, anemia, infection, recurrence, use of opioids or antihistaminic drugs) can modify physical performance and psychological distress during illness. Hence, the correlation between fatigue, physical performance and mood status can change in the course of disease. Moreover, as mentioned above, several studies have shown fatigue to be present for years after the conclusion of treatment. However, less is known about the limitations in physical performance suffered by these patients. Further research will be necessary to answer these important questions.

We conclude that cancer-related fatigue can be independent of the impairment of physical performance experienced by cancer patients; furthermore, low physical performance appears to be an independent predictor of mental distress in this group of patients.

Acknowledgements

This study was supported by the Nenad Keul Foundation, Freiburg, and Daimler-Benz AG, Stuttgart, Germany.

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Received 17 June 1997; accepted 4 September 1997.

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Bone Marrow Transplantation 1996; 18: 1557-1160

An aerobic exercise program for patients with haematological malignancies after bone marrow transplantation.

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Summary

We describe the effects of an aerobic exercise program designed to improve the physical performance of patients undergoing bone marrow transplantation. Twenty patients entered the rehabilitation program, consisting of walking on a treadmill and carried it out for six weeks. Patients started the training program 30 ± 6 days (range 18 to 42) post BMT. By the end of the program we observed a significant improvement of the patients' maximal physical performance and maximum walking distance, and a significant lowering of the heart rate with equivalent workloads (p for all significances <0.001). All participants of the program reached a peak performance (calculated in metabolic equivalents, METs) more than sufficient for carrying out all basic activities of daily living. These results contrast with literature reports indicating that spontaneous recovery of physical functioning after BMT can take many months and that about 30% of the patients experience a long-lasting impairment of physical performance. We conclude that fatigue and loss of physical performance in patients undergoing BMT can be corrected with adequate rehabilitative measures.

Keywords: Bone marrow transplantation, rehabilitation, fatigue, aerobic exercise.

Introduction

Bone marrow transplantation has become standard treatment for many haematological malignancies, improving relapse-free survival in a significant percentage of patients compared with conventional treatment modalities. However, BMT conditioning-therapies (high dose chemotherapy and/or total body irradiation) and immunosuppression following allogeneic BMT routinely cause significant morbidity. Reduced physical performance and fatigue thus are a universal problem after BMT. These symptoms can impose limitations in occupational and leisure activities, making resumption of daily activities after discharge difficult and adversely affecting the patient's quality of life after BMT (1,2).

Literature reports mention fatigue and loss of physical performance as common symptoms experienced by BMT long-term survivors. 40% of the patients need up to a year for full recovery of physical functioning and loss of stamina prevents about 30% of patients from going back to work during the first two years following BMT (3). In another report, two-thirds of BMT adult survivors, interviewed at least 6 months post-BMT, perceived their physical abilities to be unimpaired or slightly affected; however, one-third of the patients reported experiencing limited physical functioning, with a Karnofsky Score of 80 or less (4). Other authors documented a similar frequency of these problems post BMT (5,6,7,8). A multicentric study showed a high incidence of fatigue in BMT survivors; 200 adult patients were interviewed at least 12 months post BMT: 78% of them reported feeling tired, 42% feeling weak and 76% a compromised ability to engage in vigorous physical activities (9).

Aerobic exercise, as defined as the rhythmical contraction and relaxation of large muscle groups over a prolonged time, is a new method for rehabilitation of cancer patients affected by "energy loss" (10). A small number of observations indicate that aerobic exercise improves the physical performance of cancer patients: a randomized study including 45 women with breast cancer receiving adjuvant chemotherapy showed a significant improvement of maximal oxygen consumption of patients who participated in a 10-week training program (biking on a cycle ergometer, three times a week), when compared with non-training controls (11). An unstructured walking program was also shown to significantly improve the maximal walking distance and the mood state of nine breast cancer patients during adjuvant chemotherapy, when compared with five controls (12). Finally, one short report describes an aerobic training program for patients undergoing BMT: exercise consisting of biking on a cycle ergometer failed to improve physical performance and to alleviate depression in five leukemia patients (13). Interestingly, the low physical performance of the patients in the mentioned report prevented them from starting this kind of aerobic activity until four months after BMT.

We present the results of an aerobic training program intended to improve the physical performance of patients with haematological malignancies undergoing BMT.

Subjects and Methods

A consecutive series of twenty patients participated in the rehabilitation program. Characteristics of the patients are described in Table 1. Seventeen patients had undergone an allogeneic BMT as treatment of an haematological malignancy (AML, n=8; CML, n=5; ALL, n=4); three additional patients (Hodgkin's Disease, n= 1; Non Hodgkin's Lymphoma, n=2) underwent autologous BMT. Treatment before BMT-conditioning included chemotherapy (n=15), chemotherapy and radiation (n=3), and IFN-alpha followed by chemotherapy (n=2). Two patients had prior autologous (n=1) or allogeneic (n=1) BMT.

Conditioning regimens in the allogenic setting included Bu/CY (8), TBI/CY (7), TBI/VP16/CY (1) and VP16/Bu (1). Conditioning regimens in the autologous setting included BEAM, CBV and BEAC in one patient each.

Patients were enrolled in the study after fulfilling inclusion criteria of sustained platelet count of $20x10^9/l$ or more, ANC count of $1x10^9/l$ and stable clinical condition. Participation in the training program was offered to all eligible patients (n=22) as they fulfilled inclusion criteria. Two patients refused participation in the study. According to standard proceedings at the Freiburg University Medical Centre, patients remained in hospital eight weeks after allogeneic BMT for clincial monitoring and treatment of complications. Training was started 30±6 days (ranging from 18 to 42 days) post BMT**.**

Prior to the rehabilitation program, cardiovascular function was examined by ECG and echo-cardiogram. For assessment of physical performance a treadmill stress-test (beginning with 3 km/h and 1.5% elevation, acceleration of 1 km/h every third minute by unchanged elevation, continued until exhaustion) was carried out under continuous ECG-monitoring. Lactate concentration in capillary blood (Analyser 5060, Eppendorf, Germany) was determined at the end of every workload. No patient presented pathological changes of heart activity, function or dimensions by the mentioned tests.

The training program, consisting of walking on a treadmill according to an interval-training pattern, was carried out daily on weekdays for the following six weeks. Training was initiated during hospitalization and concluded while participants were outpatients. Daily duration of training sessions was 30 minutes. During the first week training consisted of five workloads of three minutes each per day; training intensity corresponded to the speed necessary to reach a lactate concentration of 3 ± 0.5 mmol/l in capillary blood (slightly below the anaerobic threshold, 14). This intensity was found to coincide with a heart rate of 80 ± 5% of the calculated maximal heart rate (220 minus age in years). Exercise duration was gradually increased to 4 x 5 minutes per day in the second week, 3 x 8 minutes in the third, 3 x 10 minutes in the fourth and 2 x 15 min in the fifth week; between workloads patients walked with half-speed for 3 minutes. Four patients who trained with a speed of 4 km/h or slower were not able to walk during the complete training session (thirty minutes) and were allowed to sit during the intervals. In the sixth week exercise was carried out daily without interruption for 30 minutes. Heart rate during training was controlled by a heart-rate monitor (Polar Sport Tester, Finland); lactate concentration was controlled every fifth training day. As lactate concentration sank below 2.5 mmol/l and exercise heart rate decreased as a result of training adaptation, treadmill speed was increased by 0.5 km/h to maintain training intensity. During training patients were continuously supervised by a physician.

Maximal performance in metabolical equivalents (METs, a unit corresponding to 3,5 ml O_2 per kg of body weight per minute) was calculated according to the standards of the American College of Sports Medicine (15). After controlling for variance homogeneity and normal distribution we compared parameters of physical performance before and after the rehabilitation program with a Student's t-test for paired groups. All statistics were carried out with the Statistical Package for Social Sciences (SPSS 4.0.1). Values are expressed as mean ± 1 SD.

Results

Fourteen patients completed the program's six weeks; two of these patients interrupted training for three weeks (one due to herpes zoster, the other due to haemorrhagic cystitis) and resumed it after improvement of the symptoms. Six patients (all after allogeneic BMT) had to abandon the program due to acute GvHD (2), hemorrhagic cystitis (2), streptococcal sepsis (1), and CMV-pneumonia (1). As shown by weekly increases in training distance and speed, physical performance in these six patients improved while they were participating in the program. However, due to the sudden interruption of training, a formal examination of physical performance prior to drop out was not possible. All reported findings are based on the fourteen patients who finished the study.

By the end of the training program, physical performance of all patients improved (see Table 2 and Figure 1). Training intensity was increased from 4.6 ± 1.1 km/h, in the program's first week to 6 ± 0.6 km/h in the sixth week ($p<0.001$). The distance walked per training session (30 minutes) improved from 1621 ± 572 m to 3257 ± 340 m ($p<0.001$). Patients' maximal performance was improved by the end of the program from 5.8 ± 1.2 km/h, equivalent to 4.7 ± 1.2 METs, to 8.1 ± 1 km/h, equivalent to 7.4 ± 2.5 METs ($p<0.001$, Figure 2). Heart rate and lactate concentration at an equivalent submaximal workload (5 km/h, the usual walking speed) decreased significantly from 149 ± 18 bpm to 120 ± 19 bpm ($p<0.001$), and from 3.6 ± 1.2 mmol/l to 1.7 ± 0.5 mmol/l ($p<0.001$). No cardiac, infectious or bleeding complications attributable to training were observed during the program.

Cardiovascular function of all patients was evaluated after the program with ECG in rest and exercise and echocardiogram. No patient presented pathological changes of cardiac activity, function and dimensions.

Discussion

The results presented in this report show that aerobic training can lead patients undergoing BMT to a substantial improvement of physical performance within weeks of discharge from the BMT unit, without increased morbidity.

Fatigue and impaired performance are a universal problem in patients after BMT. To diminish fatigue, these patients are often advised to rest and lower their level of activity. However, prolonged rest can cause further loss of muscle mass and thus further loss of performance (16,17). This explains the persistence of impaired performance in some patients for years after otherwise successful BMT. An aerobic training program, implemented early in the initial rehabilitation phase following BMT, can break this vicious circle of lack of exercise, impaired performance and easy fatigueability.

Since many factors (anemia, immunosuppressive agents, GVHD, infection) can impair the physical performance of patients after allogeneic BMT, the absence of a control group in this study makes an exact interpretation of results difficult. However, it is encouraging that all participants of the program reached a peak performance (calculated in METs) sufficient or more than sufficient for carrying out all basic activities of daily living (18). This contrasts with reports documenting impaired physical functioning by most of patients 90 days after allogeneic BMT (3). Moreover, physical activity can produce secondary benefits such as improved emotional stability. We repeatedly observed patients gaining self-confidence and improving their hitherto depressed mood as the training program led them to higher levels of physical independence. Although these findings were not quantified by questionairies, we feel that these emotional benefits represent an important effect of an aerobic training program in the setting early after BMT. Acceptance of the training program was high: 90% of the eligible patients decided to participate in the program. For most of them, this represented the first possibility in months to change their traditional patient roles: from passive objects of diagnostic procedures and treatment, to active participants in the rehabilitation process. Most patients were thrilled by this change.

The incidence of major complications in patients participating in this program (infection: 12%, haemorrhagic cystitis=12%, GvHDGrade 3/4=12%; all in patients after allogeneic BMT) was not statistically higher than the historical average at our Hospital for this patient population. Apart from the above mentioned benefits, our study demonstrates that aerobic physical activity can be carried early after BMT without detrimental effects.

As mentioned, one previous study also tested aerobic training in the rehabilitation of patients after BMT using a cycle ergometer. This form of physical activity is particularly inadequate after BMT, because of the severe muscular waste usually ocurring in these patients. We decided to carry out training on a treadmill based on the many advantages of this form of exercise as compared with eg. biking. Walking is a more natural form of exercise, it allows to reach a higher maximal oxygen uptake, produces less fatigue, requires less coordinative ability, and causes lower increments in blood pressure (19).

We feel that, in light of these positive findings, further studies are warranted to evaluate the short- and long-term beneficial effects of an aerobic training program on the physical performance and quality of life of patients after allogeneic and autologous BMT.

Acknowledgments: We are indebted to Monika H. Tilmann, MD and Brigitta G. Rumberger, MD for the many helpful suggestions, and Ian A. York, DVM, MSC, PhD for assisting in translation.

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Table 1: Characteristics of the patients (mean ± SD; ranges in brackets)

Age (years)	36 ± 8 (22-55)
Sex	11 male, 9 female
Weight (kg)	69,7 ± 13 (51-110)
Height (cm)	174 ± 8 (160 - 190)
Body-Mass-Index	22,8 ± 3,2 (18 - 32)

Table 2: Improvement of parameters of physical performance after 6 weeks training; data of the 14 patients who completed the program are included (mean ± SD; ranges in brackets).

	Pre	Post	Significance
Training speed (km/h)	4,6 ± 1,1 (3-6)	6 ± 0,6 (5-7)	<0,001
Maximal walked distance (m)	1621 ± 572 (670-2100)	3257 ± 340 (2800-4000)	<0,001
Maximal performance (km/h)	5,8 ± 1,2 (5-7)	8,1 ± 1 (7-10)	<0,001
Maximal performance (METs)	4,7 ± 1,2 (2,8-8,1)	7,4 ± 2,5 (5,2 ± 11,2)	<0,001
Heart rate by 5 km/h	149 ± 18 (125-180)	120 ± 19 (85-141)	<0,001
Lactate by 5 km/h	3,6 ± 1,2 (1,9-6,5)	1,7 ± 0,5 (1,1-3,1)	<0,001

Titles and legends to figures:

Figure 1: Increment of maximal training distance (in km) and intensity (speed in km/h) during the aerobic training program. Six patients abandoned the training program due to complications; number of patients remaining in the program is indicated for each week.

Figure 2: Maximal performance at the beginning begin (discharge from BMT unit) and at the end (six weeks later) of the training program.

Aerobic Exercise in the Rehabilitation of Cancer Patients after High Dose Chemotherapy and Autologous Peripheral Stem Cell Transplantation

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BACKGROUND. Fatigue and loss of physical performance are frequent problems of cancer patients. In a pilot study, the authors evaluated the feasibility and effects of aerobic training in the rehabilitation of cancer patients after completing high dose chemotherapy.

METHODS. Sixteen patients participated in a specially designed rehabilitation program for 6 weeks. The patients entered the program, which consisted of walking on a treadmill, shortly after completing treatment. Sixteen patients who did not train served as controls. Physical performance (maximum speed on the treadmill test), cardiac function, and hemoglobin concentration were compared at the time of discharge from the hospital and 7 weeks later. At the second examination, fatigue and limitations in daily activities due to impaired endurance were assessed during personal interviews.

RESULTS. At the time of discharge from the hospital, maximum physical performance (training group: 6.2 ± 1.1 km/hour; controls: 6.2 ± 1.3 km/hour) and hemoglobin concentration (training group: 10.1 ± 1.4 g/dL; controls: 10.1 ± 1.2 g/dL) were similar for both groups. After 7 weeks, improvement in maximum physical performance (training group: 8.3 ± 1.6 km/hour; controls 7.5 ± 1.3 km/hour) and hemoglobin concentration (training group: 13 ± 1 g/dL controls: 12 ± 1.4 g/dL) were significantly higher for the training group ($P < 0.05$). By the second examination, no patient in the training group but 4 controls (25%) reported fatigue and limitations in daily activities due to low physical performance.

CONCLUSIONS. Aerobic exercise improves the physical performance of cancer patients recovering from high dose chemotherapy. To reduce fatigue, this group of patients should be counseled to increase physical activity rather than rest after treatment. ***Cancer* 1997;79:1717–22.** *© 1997 American Cancer Society.*

KEYWORDS: cancer fatigue, high dose chemotherapy, peripheral stem cell transplantation, exercise, rehabilitation.

Supported by the Nenad Keul Foundation-Preventive Medicine, Freiburg i. Br., Germany.

The authors are indebted to Brigitta G. Rumberger, M.D. for helpful suggestions, and Ian A. York, D.V.M., M.Sc., Ph.D. for assisting in the translation.

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Received January 13, 1997; accepted January 24, 1997.

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Most cancer patients experience a loss of energy and an impairment of physical performance in the course of their illness. Studies report that this problem affects up to 70% of cancer patients during chemotherapy and radiotherapy or after surgery.[1–4] Furthermore, up to 30% of cancer survivors have been reported to experience a loss of energy for years after cessation of treatment.[4–6] This impairment in physical fitness is a significant contributor to decreased quality of life in cancer patients.[7,8] Fatigue has been linked to a number of factors, including nutritional status, sleep disturbances, biochemical changes secondary to disease and treatment, psychosocial factors, and level of activity.[9] However, the causes of this impairment of physical performance in this setting are not fully understood. Low physical performance has been postulated to be a substantial contributor to cancer fatigue.[9] Cardiorespiratory and musculoskeletal deconditioning can reduce work capacity; therefore, patients need a higher degree of effort to perform usual activities. The resulting increments in metabolic rate and energy consumption produce tiredness and fatigue even with normal daily activities. To reduce fatigue, patients are usually advised to avoid physical efforts and to down-regulate their level of activity.

Pharmacotherapy of fatigue and asthenia in cancer patients has not produced convincing results.[10] So far, exercise programs in oncologic rehabilitation have been mostly limited to physical therapies addressing specific impairments caused for example by amputation or surgery. Aerobic exercise, defined as the rhythmic contraction and relaxation of large muscle groups over a prolonged time, has been proposed as a new method for rehabilitation of cancer patients affected by the problem of ‘‘energy loss.’’[11] It is not as yet a fully accepted concept, because many cancer patients and physicians believe that vigorous exertion is potentially harmful, especially after recent exposure to cardiotoxic agents such as anthracyclines. The few available studies on aerobic exercise programs for cancer patients are limited by methodologic deficiencies (training duration or intensity not indicated or variable, small number of patients, or absence of a control group) making interpretation and comparison of results difficult.[12–14]

The authors present the results of a pilot rehabilitation program, comprised of aerobic training, designed to improve the physical performance of cancer patients after high dose chemotherapy followed by autologous peripheral blood stem cell transplantation.

PATIENTS AND METHODS

A consecutive series of 36 cancer patients with solid tumors (n = 22) or non-Hodgkin’s lymphoma (n = 14) participated in the study after high dose chemotherapy and autologous peripheral blood stem cell transplantation. Preceding high dose chemotherapy, all lymphoma patients and five patients with solid tumors had completed conventional chemotherapy; three lymphoma patients and two patients with solid tumors had also undergone local radiotherapy. In the weeks preceding high dose chemotherapy, all patients received 1 to 4 chemotherapy cycles of etoposide, 500 mg/m^2, ifosfamide, 4 g/m^2, cisplatin, 50 mg/m^2, and epirubicin, 50 mg/m^2, followed by the administration of colony-stimulating factors; in the days after these procedures, leukapheresis for collection of blood stem cells was performed.

High dose chemotherapy regimens in patients with solid tumors were comprised of cumulative doses of etoposide, 1500 mg/m^2, carboplatin, 750–1500 mg/m^2, and ifosfamide, 12 g/m^2 (VIC) (n = 18), or the same regimen plus epirubicin, 150 mg/m^2 (VIC-E) (n = 5). Non-Hodgkin’s lymphoma patients received carmustine, 300 mg/m^2, cytarabine, 200 mg/m^2, etoposide, 100 mg/m^2, and melphalan, 140 mg/m^2 (BEAM) (n = 9), or busulfan, 16 mg/kg and cyclophosphamide, 120 mg/kg (BU/CY) (n = 4) (Table 1). Chemotherapy was followed by autologous peripheral blood stem cell transplantation.

On the day of discharge, informed consent was obtained from all eligible participants (n = 40); four female patients (breast carcinoma patients, age range 41–57 years) refused to participate in the study. No patient showed signs of neurologic or muscular disease. Cardiovascular function of all participants was examined by electrocardiogram (ECG) and echocardiogram. No patient was found to have any abnormalities on these tests. For assessment of physical performance, a treadmill stress test (beginning with 3 km/hour and 1.5% elevation, with an acceleration of 1 km/hour every 3 minutes by unchanged elevation that was continued until exhaustion) under continuous ECG monitoring was performed. Lactate concentration in capillary blood (Analyser 5060, Eppendorf, Hamburg, Germany) was monitored at the end of every workload. To take part in the training program, patients had to travel to the hospital daily. Therefore, patients living within an area of 50 km from the hospital were included in the exercise group (n = 18); the remaining

TABLE 1
Characteristics of the Patients

	Training group (n = 16)	Control group (n = 16)
Age (yrs)	42 ± 9	39 ± 11
Body mass index	25.6 ± 5.2	24.5 ± 3.6
Female	10	11
Male	6	5
Diagnosis		
Breast carcinoma	8	9
Non-Hodgkin’s lymphoma	6	6
Nonsmall cell lung carcinoma	1	
Sarcoma	1	
Seminoma		1
Chemotherapy		
VIC	7	8
VIC-E	3	2
BEAM	5	3
Bu/Cy	1	3

VIC: etoposide, carboplatin, and ifosfamide; VIC-E: etoposide, carboplatin, ifosfamide, and epirubicin; BEAM: carmustine, cytarabine, etoposide, and melphalan; BU/Cy: busulfan and cyclophosphamide.

patients were assigned to the control group (n = 18). The number of days between stem cell reinfusion and discharge was similar in both groups (training group 20 ± 4 days, control group 18 ± 7 day, P = not significant). The training program was comprised of walking on a treadmill following an interval training pattern. The patients trained daily on weekdays for 6 weeks. During the first week, exercise duration was 5 × 3 minutes per day. Exercise duration was gradually increased to 4 × 5 minutes per day in the second week, 3 × 8 minutes in the third week, 3 × 10 minutes in the fourth week and 2 × 15 minutes in the fifth week; during the sixth week exercise was performed without interruption for 30 minutes. The training speed corresponded to a lactate concentration of 3 ± 0.5 mmol/L in capillary blood (slightly below the anaerobic threshold[15]); this intensity was found to correspond to 90 ± 5% of the maximal heart rate obtained by stress test and 80 ± 5% of the calculated maximum heart rate (220 minus age in years). Between workloads patients walked at half-speed for 3 minutes; one patient who walked 4 km/hour was allowed to sit during the intervals. Heart rate during training was controlled by a heart rate monitor (Polar Sport Tester; Gross Gerau, Germany); lactate concentration was controlled every fifth training day. As lactate concentration sank below 2.5 mmol/L and exercise heart rate decreased as a result of training adaptation, treadmill speed was increased by 0.5 km/hour to maintain training intensity. During training, patients were continuously supervised by a physician. Control patients performed normal daily activities but did not engage in an exercise program. ECG, echocardiogram, and stress test were repeated 7 weeks after dismissal from the hospital. At this time, patient's feelings of fatigue and limitations in daily activities (such as stair climbing, walking, or shopping) due to reduced physical performance were assessed in a personal interview. Three patients (two in the training group and one in the control group) abandoned the program due to disease progression. Another patient in the control group presented 3 weeks after discharge with chemotherapy-related cardiotoxicity, resulting in impairment of systolic function, and was excluded from the study. In the 3 months after discharge, two patients (one in each group) presented with recurrent malignancies; all other participants were in complete remission. All reported results are based on the 32 patients who completed the study.

Maximum performance in metabolic equivalents (METs) (a unit corresponding to 3.5 mL O_2 per kg of body weight per minute) was calculated according to the guidelines of the American College of Sports Medicine.[16] This method is a recognized procedure for estimation of physical fitness.[16,17] A maximum physical performance of 5 METs or more was considered sufficient to perform all basic activities of daily living.[17] Theoretical maximum heart rate was calculated as 220 minus age in years.[16] Statistical calculations were performed with the Statistical Package for the Social Sciences (SPSS 4.0.1). After evaluating data distribution, results of the two groups were compared with a Mann–Whitney U test. A value of $P < 0.05$ was considered to be statistically significant. Values are expressed as mean ± standard deviation.

RESULTS

Body mass index at discharge (a factor that influences physical performance) was similar in both groups (Table 1). The maximum performance of both groups was similar at the beginning of the study. Each patient in the exercise group performed better in the second test 7 weeks after discharge. The performance of 3 control patients (19%) did not improve in the 7 weeks after discharge (Fig. 1). Improvement of maximum performance was significantly higher for the exercise group than for the control group ($P = 0.042$). Maximum heart rates and percentage of expected maximum heart rates on the treadmill test of the two groups were similar at initial and final testing (Table 2). By the second examination 7 weeks after discharge, four patients in the control group (25%) but only one patient in the training group (6%) failed to reach a maximum performance (calculated in METs) sufficient to perform all basic activities of daily living. By the interviews 7 weeks after discharge, no patient in the training group but four patients in the control group (25%) reported feeling fatigue with usual daily activities; these patients also reported limitations in usual activities due to reduced endurance.

The hemoglobin concentration in the two groups was not different at the time of discharge (Table 2); after 7 weeks, it was significantly higher in the training group than in the control group ($P = 0.04$). ECG at rest and during the stress test showed no changes between initial and final examination. Similarly, cardiac function and dimensions remained unchanged as shown by echocardiography. No cardiac, infectious, or bleeding complications attributable to training were observed.

DISCUSSION

Easy fatigability and reduced endurance are severe problems of patients in the recovery phase immediately after high dose chemotherapy. For some patients, this impairment of physical performance imposes severe limitations in normal daily activities such as stair climbing, walking, or housekeeping. To avoid fatigue caused by physical effort, patients are often advised

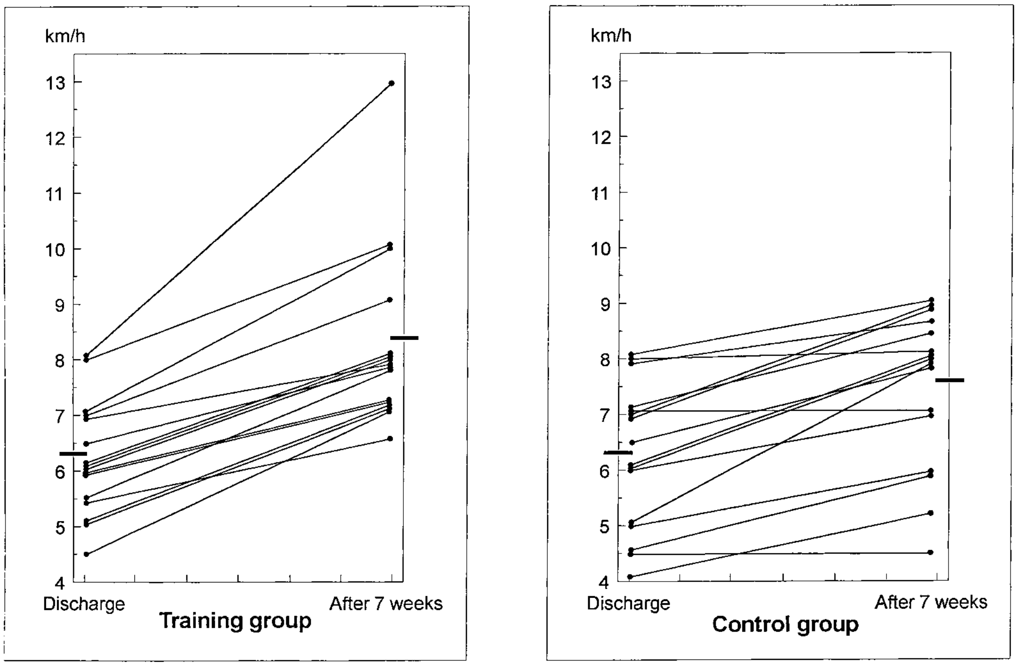

FIGURE 1. Improvement of maximum physical performance of patients in the 7 weeks after discharge from the hospital. Means are indicated as bars on the margins.

TABLE 2
Maximum Performance and Hematologic Indexes of Patients by Discharge and after 7 Weeks

	Training group (n = 16)	Control group (n = 16)
Maximum performance at discharge (km/hour)	6.27 ± 1.1	6.21 ± 1.3
Maximum performance after 7 weeks (km/hour)	8.28 ± 1.6	7.50 ± 1.3
Hemoglobin at discharge (d/dL)	10.0 ± 1.4	10.0 ± 1.2
Hemoglobin after 7 weeks (g/dL)	13.0 ± 1	12.0 ± 1.4
Maximum heart rate by the first examination (bpm)	165 ± 14	166 ± 14
Percentage of maximum expected heart rate	93 ± 8%	92 ± 8%
Maximum heart rate by the second examination (bpm)	169 ± 20	169 ± 16
Percentage of maximum expected heart rate	95 ± 10%	94 ± 6%

bpm: beats per minute.

to rest and to limit their daily activities. However, these well meaning recommendations can cause paradoxical results. Physical inactivity induces muscular wasting; therefore, prolonged rest can produce further loss of performance.[11,18,19] Lowering endurance thus creates a self-perpetuating condition: diminished activity leads to easy fatigability and vice versa. This mechanism could explain the persistence of this problem in some patients even years after completion of treatment. The patients gradually become accustomed to their impaired condition and finally experience it as normal.[20] An aerobic training program can break this vicious circle of lack of exercise, impaired performance, and easy fatigability.

In a previous report, the authors have shown aerobic exercise to significantly improve physical performance of cancer patients after allogeneic bone marrow transplantation.[21] However, the absence of a control group in the mentioned study made an exact interpretation of the findings difficult. The current study adds evidence to the mentioned results and underlines the benefits of an aerobic training program in the early rehabilitation of cancer patients after high dose chemotherapy and autologous blood stem cell transplantation.

The results of the current study also strongly indicate the need for physical rehabilitation in the mentioned group of patients; physical performance of 3 patients in the control group showed no improvement between the first and second examination 7 weeks later. By this time, no patient in the training group but 4 patients in the control group (25%) reported feeling fatigued by usual daily activities and experienced limitations in activities such as stair climbing or shopping due to reduced endurance. Furthermore, the percentage of patients experiencing severe impairment of physical performance (maximum performance lower than 5 METs) 7 weeks after discharge was substantially higher in the control group (4 of 16:25%) than in the training group (1 of 16: 6%). Nevertheless, the patient in the training group who failed to reach a maximum performance of 5 METs was severely obese (body mass index of 37); this factor clearly reduced her ability to reach a high physical performance.

Physical activity also can produce secondary benefits such as improved mood state. The authors repeatedly observed that patients gained self-confidence and improved their often depressed mood as the training program led them to higher levels of physical independence. Although this clinical observation was not objectively assessed with questionnaires, the authors believe that these emotional benefits represent an important outcome of aerobic training.

Intensive exercise may be contraindicated (e.g., during infections, fever, malnourishment, or for patients with bony metastases). Assessment of hematopoietic function is indispensable before starting an intensive aerobic training program. To diminish the risk of hemorrhages and infections, the patients in this study did not start training until their platelet counts surpassed 20×10^9/L and their leukocyte counts 1.5×10^9/L. These values are lower than suggested by other authors[11]; however, using these values as a baseline, no bleeding or infectious episodes were observed in the training group. Anemia was not a contraindication for inclusion in this rehabilitation program for two reasons. First, exercise has been shown to improve the physical performance[22–24] and hemoglobin concentration[23,24] in patients with anemia due to renal insufficiency; no complications were observed in these training programs. Second, because a substantial percentage of cancer patients suffer from anemia, defining this condition as a contraindication for a training program would exclude many patients from rehabilitation at a time when they might most benefit from it. Furthermore, the current study results suggest that exercise can induce a partial correction of anemia in cancer patients after myelotoxic chemotherapy. It should be taken into account that all patients in this study underwent autologous stem cell transplantation; what effect aerobic training has on bone marrow after chemotherapy without stem cell support remains to be determined.

A critical point of the current study was the comparability of the two groups. In selecting criteria for assignment of patients to the training or control group, two factors had to be considered: first, to take part in the training program, patients had to travel to the hospital daily; second, the assignment procedure had to be based on a random factor. Therefore, the geographic distance between place of residence and the study hospital was used as the assignment parameter. Although statistic comparison of baseline characteristics showed no differences between the training and control group assigned in this fashion, the influence of social or economic factors in the outcome of the study cannot be ignored. However, such differences (if at all present) are unlikely because of the homogeneity of most socioeconomic and demographic variables in this part of Germany.

Another critical point in the current study was the similitude of the training and control groups regarding motivation to reach maximum performance in the stress test. The authors assumed that less motivated patients would stop the stress test before reaching exhaustion. Therefore, the presence of a higher percentage of patients with lower motivation in one of the groups would lead to a systematic error in the evaluation of physical performance. To exclude this possible source of bias, the authors compared the percentage of maximum theoretic heart rate (220 minus age) reached by participants in the study in the stress tests. No differences were found between the training and control groups. These results indicate a comparable degree of effort in the two groups by all tests.

The most accurate indicator of physical fitness is maximum oxygen uptake (VO2max). However, after considering the poor physical condition of patients after high dose chemotherapy, the authors abstained from making a determination. By the time of the first examination, several patients were still recovering from chemotherapy-related mucositis and therefore could not tolerate a mouthpiece for direct assessment of VO2max. Instead, maximum physical performance was indirectly assessed by calculating the intensity of effort by the stress test in METs. This is a usual method for determining of maximum physical performance.[17] It also allows a cutoff point to be established for the requirements of normal daily activities (5 METs). It is assumed that patients not reaching this level of endurance experience limitations in daily activities due to low physical performance.

Echocardiography and resting and exercise ECG showed no pathologic changes in the training group at final testing. This indicates that patients who present with no signs of impaired cardiac function after high dose chemotherapy and autologous peripheral blood stem cell transplantation can participate in an aerobic training program without fear of cardiac complications, despite their recent exposure to potentially cardiotoxic agents.

The authors conclude that to avoid fatigue, cancer patients should be counseled to increase their level of exercise rather than the amount of rest in the recovery phase after high dose chemotherapy. Furthermore, aerobic exercise can be safely performed shortly after myelotoxic chemotherapy and autologous hematopoietic stem cell transplantation.

In light of these positive findings, a larger randomized study to evaluate the short and long term effects of an aerobic training program on the physical performance and quality of life of cancer patients after high dose chemotherapy and autologous peripheral stem cell transplantation is warranted.

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Effects of Aerobic Exercise on the Physical Performance and Incidence of Treatment-Related Complications After High-Dose Chemotherapy

By Fernando Dimeo, Sebastian Fetscher, Winand Lange, Roland Mertelsmann, and Joseph Keul

Loss of physical performance is a universal problem of cancer patients undergoing chemotherapy. We postulated that this impairment can be partially prevented by aerobic exercise. In a randomized study, 33 cancer patients receiving high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation (training group, T) performed an exercise program consisting of biking on an ergometer in the supine position after an interval-training pattern for 30 minutes daily during hospitalization. Patients in the control group (C, n = 37) did not train. Maximal physical performance was assessed with a treadmill test by admission and discharge. Physical performance of the two groups was not different on admission. The decrement in performance during hospitalization was 27% greater in the control group than in the training group (*P* = .05); this resulted in a significantly higher maximal physical performance at discharge in the trained patients (*P* = .04). Duration of neutropenia (*P* = .01) and thrombopenia (*P* = .06), severity of diarrhea (*P* = .04), severity of pain (*P* = .01), and duration of hospitalization (*P* = .03) were reduced in the training group. We conclude that aerobic exercise can be safely carried out immediately after high-dose chemotherapy and can partially prevent loss of physical performance. Based on the potential significance of the observed outcomes, further studies are warranted to confirm our results.

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FATIGUE AND IMPAIRMENT of physical performance are common, and sometimes serious, side effects of cancer treatment. It has been estimated that the problem affects up to 70% of cancer patients during chemotherapy or radiotherapy.[1-4] For many patients, particularly in the recovery phase immediately after treatment, low physical performance imposes limitations on basic daily activities. Postulated etiologic mechanisms for the development of this problem include impaired nutritional status, sleep disturbances, biochemical changes secondary to disease and treatment, psychosocial factors, and reduced level of activity.[5] However, the causes of impaired physical performance in this setting are not yet fully understood. One frequently underestimated factor contributing to loss of physical performance in cancer patients is the lack of muscular activity during in-hospital treatment. Inactivity inevitably results in muscular catabolism, producing rapid loss of performance. The deleterious effects of prolonged bedrest are well documented.[6-8]

Aerobic exercise (defined as the rhythmical contraction and relaxation of large muscle masses over an extended time) has been shown to improve physical performance and reduce fatigue in cancer patients.[9-12] However, this is not yet a widely accepted concept. Furthermore, some physicians fear that vigorous exertion may be harmful for cancer patients, although no literature reports support this notion.

We investigated the effects of aerobic exercise on the loss of physical performance and on the incidence and severity of complications in patients undergoing high-dose chemotherapy (HDC) followed by autologous peripheral blood stem cell transplantation (PBSCT).

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Submitted December 27, 1996; accepted July 7, 1997.

Supported by the Nenad Keul Foundation Preventive Medicine, Freiburg in Breisgau, Germany.

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0006-4971/97/9009-0036$3.00/0

MATERIALS AND METHODS

Eighty patients with solid tumors selected for treatment with HDC were considered for participation in the study. Inclusion criteria were the following: malignancy confirmed by biopsy; Eastern Cooperative Oncology Group (ECOG) performance score of 0-2; age between 18 and 60 years; no evidence of impairment of cardiac, pulmonary, renal, and hepatic function; absence of bony metastases in the lower extremities; and transplantation of at least 1×10^6 $CD34^+$ peripheral blood stem cells/kg body weight. The study was approved by the Ethics Committee of the University of Freiburg and informed consent was obtained from all patients. From the 80 potential participants, 72 (90%) fulfilled inclusion criteria and were enrolled in the study.

Before HDC, all patients received one to four chemotherapy cycles consisting of etoposide 500 mg/m^2, ifosfamide 4 g/m^2, cisplatinum 50 mg/m^2, with or without epirubicine 50 mg/m^2 (VIP/VIP-E), followed by administration of granulocyte colony-stimulating factor (G-CSF) at a dose of 5 μg/kg body weight/d. Ten days after the last cycle of chemotherapy, leukapheresis for collection of peripheral blood stem cells was performed. In the week before admission for HDC, all patients underwent a complete physical and cardiovascular examination (electrocardiogram [ECG] and echocardiogram). Two patients showed abnormalities on electrocardiography and were excluded from the study.

Overall, 70 patients fulfilled all requirements for participation (Table 1). On their first day of hospitalization, patients were assigned randomly to a training (T) or a control group (C). In the week preceding HDC, a treadmill stress-test under continuous ECG monitoring (starting at 3 km/h and 1.5% elevation, acceleration of 1 km/h every third minute by unchanged elevation and continued until exhaustion) was performed for assessment of physical performance. This stress-test is one of the standard protocols used in Germany for assessment of maximal physical performance of patients with reduced physical performance as sequel of chronic diseases and correlates highly with VO2max.[13,14] During the test patients were not allowed to hold handrails.

All patients underwent high-dose chemotherapy with cumulative doses of etoposide 1.5 g/m^2, ifosfamide 12 g/m^2, and carboplatin 750-1500 mg/m^2 (VIC, n = 57); 13 patients also received epirubicine, 150 mg/m^2 (VIC-E, n = 13). One patient in the training group refused to complete chemotherapy and received the full dose of etoposide and only 2/3 of the planed dose of ifosfamide and carboplatin. After chemotherapy all patients received autologous

Table 1. Baseline Characteristics of the Patients

	Training	Control	Significance of *P*
No.	33	37	
Age (yr)	39 ± 10	40 ± 11	.52
Gender	23 female, 10 male	28 female, 9 male	.75
Body-mass-index	25 ± 6	24 ± 4	.30
Diagnosis:			
Breast cancer	16	19	
Metastatic breast cancer	7	4	
Germ cell cancer	6	7	
Sarcoma	2	3	
Small cell lung carcinoma	—	1	
Non-small cell lung carcinoma	1	2	
Adenocarcinoma	1	—	
Neuroblastoma	—	1	
Chemotherapy:			
VIC	27 (81%)	30 (81%)	
VIC-E	6 (9%)	7 (9%)	
Mean no. of chemotherapy cycles preceding HDC	1.8 ± 0.4	1.8 ± 0.5	.65
Dose of carboplatin (mg)	429 ± 103	395 ± 100	.17
Retransfunded stem cells (10^6/kg body weight)	4.65 ± 3.5	3.90 ± 2.9	.34

Values are expressed as mean ± SD.

PBSCT and daily subcutaneous (sc) injections of G-CSF at the above-mentioned dose during neutropenia (absolute neutrophil count [ANC] $<0.5 \times 10^9$/L).

Patients in the training group performed a daily program of aerobic exercise, consisting of ''biking'' with a bed ergometer (Rotomed; Reck Machinenbau GmbH, Betzenweiler, Germany). This device allows one to simulate a biking motion without leaving bed. The patients ''biked'' for 1 minute with an intensity sufficient to reach a heart rate equivalent to at least 50% of the cardiac reserve, calculated as 220 minus age minus rest heart rate.[14] The procedure was repeated 15 times with pauses of 1 minute between bouts; therefore, training was carried out for a total of 30 minutes each day. Mean workload during the training program was 32 ± 5 W (range, 20 to 40 W). During training sessions patients were continuously supervised by instructed study personnel. Physical performance of patients changed during hospitalization as a result of variations in clinical parameters (eg, hemoglobin concentration, nutritional status, infections, etc). Therefore, pedaling speed was re-adjusted daily to achieve the aimed heart rate and then kept constant within single training sessions (15 bouts); the daily pedaling frequency varied between 30 and 50 cycles/min. To calculate the mean heart rate during a training session, heart rate was assessed at the end of each 1-minute workload and added; heart rate during pauses was not considered.

Patients with fever (>37.5°C) or platelet counts below 10×10^9/L were instructed to interrupt training. Patients with World Health Organization (WHO) grade I and II infections and no other complications restarted training after abatement of fever and performed the training until discharge, whereas patients with severe infections (WHO grade III) or multiple complications were instructed not to resume training. Two patients in the training group elected to abandon the study after the second training unit for personal reasons; these patients did not develop major complications during the rest of hospitalization.

Complete blood counts and serum chemistry (including evaluation of hepatic and renal function) were carried out daily between 6:00 and 8:00 AM, ie, after at least 12 hours without training. Criterion for blood transfusion was hemoglobin concentration of less than 8 g/dL; criteria for platelet transfusion were thrombopenia $< 20 \times 10^9$/L or bleeding. Discharge criteria were trilinear hematopoietic reconstitution, transfusion independency, an afebrile period of at least 2 days after discontinuing intravenous antibiotics, resolution of mucositis, ability to tolerate solid food, and absence of clinical signs of fluid overload or dehydration.

On day of discharge, a second cardiologic examination consisting of an ECG, echocardiogram, and stress-test was carried out. By this time most patients were still recovering from chemotherapy-related mucositis and could not tolerate a mouthpiece for direct assessment of VO2max. Therefore, this parameter was not assessed. Instead, maximal physical performance was defined as the maximal speed (in kilometers per hour) reached in the treadmill stress-test. Because VO2max is a function of maximal walking speed,[14] these two parameters are intimately correlated.

Four patients in the control group (three patients refusing participation, another patient presenting with atrial fibrillation) and two patients in the training group (refusal of participation) did not undergo a second stress-test. Severity of chemotherapy-related complications of these six patients was included in the statistical analysis; however, data of their physical performance were not considered.

Hematologic and nonhematologic toxicity were analyzed according to standard WHO criteria.[15] These assessments were made by an investigator who was blinded to the patients' assignments to control and treatment group. Duration of hospitalization was measured as number of days between blood stem cells reinfusion and discharge. Based on the characteristics of the study, we considered a blinding of the medical team difficult to warrant. Therefore, to avoid an intentional or unintentional manipulation of results, medical teams were not informed about the secondary endpoints of the study.

Statistical analysis. The study was performed following the ''intention-to-treat'' principle. Primary endpoint was the loss of maximal physical performance (defined as maximal speed in kilometers per hour on a treadmill test) during hospital stay; a difference in the loss of physical performance of at least 25% between the two groups was considered to be clinically relevant. To detect this difference with a probability of an α and β error of 5% and 10%, respectively, at least 30 patients in each group were required.

Nominal data were compared with the Fisher's exact test, normally distributed continuous data with the Student's *t*-test, and categorical and not normally distributed continuous data with the Mann-Whitney U test; all tests were two-tailed. To rule out the effect of confounding factors on the observed outcomes, we performed a post-hoc backward multiple regression analysis including secondary endpoints found to differ significantly between the groups as dependent variables, and age, body mass index, maximal physical performance (in kilometers per hour) by admission, total dose of carboplatin, number of peripheral blood stem cells retransfused, and training as independent variables. All calculations were performed with SPSS for Windows 6.1.2 (SPSS GmbH Software, Munich, Germany). A value of $P < .05$ was accepted as statistically significant. Data are expressed as mean ± standard deviation. Because many of the evaluated parameters considered in the statistical analysis were clearly related to a single event (hematopoietic reconstitution), Bonferroni corrections were not applied.

RESULTS

At the beginning of the study no differences in the baseline characteristics of the two groups were observed (Table 1).

Table 2. Physical Performance, Hematologic Values, and Secondary Effects of Chemotherapy in the Two Groups

	Training	Controls	Significance of P	95% CI
Hospital admission:				
Maximal performance (km/h)*	7.91 ± 1.2	7.51 ± 1.3	0.18	−0.18; 1.17
Maximal heart rate in the stress-test (bpm)	170 ± 18	168 ± 16	0.58	−6; 10
Percentage of estimated maximal heart rate (220 − age)	94 ± 7%	94 ± 8%	0.89	−3; 4
Hemoglobin concentration (g/dL)	10.5 ± 1.6	10.7 ± 1.3	0.50	−0.98; 0.48
Hematocrit	30 ± 4%	31 ± 4%	0.42	−2.96; 1.26
Discharge from hospital:				
Maximal performance (km/h)*	6.85 ± 1.1	6.08 ± 1.3	0.04 (1)	0.12; 1.41
Maximal heart rate in the stress-test (bpm)	166 ± 21	168 ± 19	0.84	−11; 9
Percentage of estimated maximal heart rate (220 − age)	92 ± 10%	93 ± 9%	0.69	−6; 4
Hemoglobin concentration (g/dL)	9.7 ± 0.9	9.5 ± 1.1	0.49	−0.31; 0.65
Hematocrit	27 ± 2%	27 ± 3%	0.71	−1.27; 1.72
Loss of physical performance during hospitalization (%)	14 ± 9%	19 ± 11%	0.05	−10.43; 0.20
Duration of neutropenia $<0.5 \times 10^9$/L (d)	6.6 ± 1.5	7.6 ± 1.6	0.01	−1.71; −0.16
Duration of thrombopenia $<50 \times 10^9$/L (d)	10.9 ± 3	12.4 ± 3.7	0.06	−3.14; 0.14
Blood transfusions (U)	3.3 ± 1.4	3.3 ± 2	0.92	−0.89; 0.82
Platelets transfusions (U)	19.5 ± 14.1	26.9 ± 19.5	0.06	−15.7; 0.8
In-hospital days	13.6 ± 2.2	15.2 ± 3.6	0.03	−3.07; −0.10
Severity of mucositis†	2.34 ± 0.8	2.43 ± 0.55	0.38	−0.42; 0.24
Severity of diarrhea†	1.90 ± 1	2.37 ± 0.86	0.04	−0.92; −0.01
Severity of infection†	2 ± 0.5	2.1 ± 0.39	0.33	−0.23; 0.47
Severity of pain†	1.87 ± 0.75	2.4 ± 0.49	0.01	−0.68; −0.56

* Data of 28 patients in the training and 32 patients in the control group who performed the stress-test before and after HDC; see text.
† According to the WHO scale. Values are expressed as mean ± SD and 95% confidence intervals for the difference between groups.

Patients in the training group performed the aerobic exercise program for 82% (±10%) of hospital days.

Physical performance. Maximum performance of both groups was not different at initiation of the study (see Table 2). Loss of performance during hospitalization was 27% higher in the control group than in the training group (absolute values: training group 14%, control group 19%, P = .05, resulting in a significant difference between the maximal performance of both groups at discharge (P = .04).

Hematological indexes. Hemoglobin concentration and hematocrit were not different between the groups at admission or discharge. The training group had a shorter duration of neutropenia (ANC $< 5 \times 10^9$/L, P = .01) and of thrombopenia (platelets $<50 \times 10^9$, P = .06, see Fig 1); the requirement for platelet transfusions was also lower in the training group (P = .06). Number of erythrocytes transfusions was not different for the two groups (P = .92).

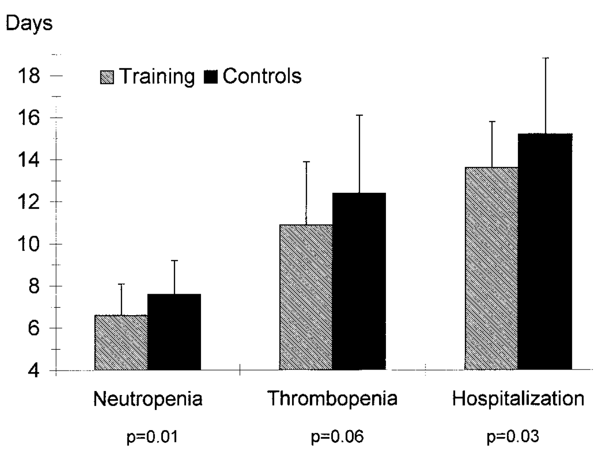

Fig 1. Duration of neutropenia (ANC < 0.5 × 10^9/L), thrombopenia (platelets <50 × 10^9/L), and hospitalization (calculated as days between stem cell reinfusion and discharge) for the training and control groups.

Cardiologic examinations. One patient in the control group developed atrial fibrillation shortly after HDC. For the remaining patients, ECG at rest and during stress-test, and echocardiographic assessment of cardiac dimensions and function (heart volume, HV and shortening fraction, SF) showed no changes between the two examinations (by admission: T: HV 733 ± 134 mL, SF 37% ± 4%, C: HV 733 ± 140 mL, SF 38% ± 5%; at discharge: T: HV 713 ± 128 mL, SF 36% ± 4%; C: HV 720 ± 143 mL, SF 37% ± 6%).

Toxicity of HDC. Fifteen patients (21%) developed significant complications: severe infection (4 patients in the training group, 5 controls), moderate infection combined with diarrhea (1 patient in each group), hepatic hemorrhage (1 patient in the training group), atrial fibrillation (1 patient in the control group), chemotherapy-related seizures (1 control), and moderate infection followed by allergic reaction after platelet transfusion (1 patient in the training group). Severity of mucositis was not different for the two groups (Fig 2). The incidence of diarrhea was lower in the training group (P = .04). Severity of pain was for patients in the training group lower than for control patients (P = .01). No patient in the training or control group developed signs of renal toxicity. One patient in the training group died of hepatic hemorrhage on the fourth day after PBSCT. Severe intraabdominal bleeding necessitated laparotomy, which showed liver necrosis. This complication is a well-known

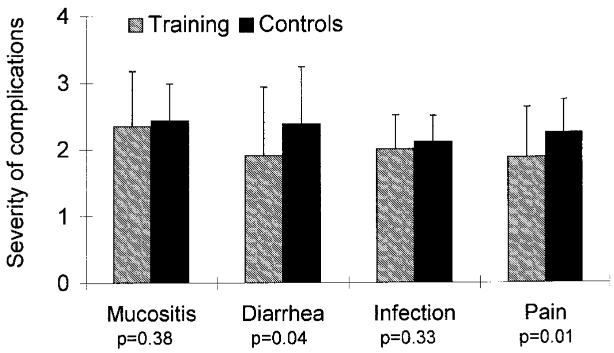

Fig 2. Intensity of complications after HDC according to WHO criteria.

serious side-effect of treatment with alkylating agents and has been described with high-dose cyclophosphamide, etoposide, and carboplatin. Bleeding began suddenly 8 hours after the end of the last workout; the patient was physically active without symptoms between conclusion of training and onset of bleeding. In light of these considerations, a causal relationship between this complication and training seems extremely unlikely. No other patient in the training or control group developed signs of hepatic toxicity.

Duration of hospitalization. Duration of hospitalization was shorter for patients in the training group than for patients in the control group ($P = .03$, Fig 1).

Multiple regression analysis showed aerobic training to be the most significant predictor of loss of physical performance, duration of neutropenia and thrombopenia, number of platelets transfusions, severity of pain and diarrhea, and duration of hospitalization (Table 3).

DISCUSSION

Loss of physical performance and fatigue are a universal phenomenon in cancer patients after myelotoxic chemotherapy. After discharge, most patients find it difficult to perform daily activities. Moreover, some patients may need weeks or months to regain their pretreatment level of fitness.[2] Our study shows that the severe loss of performance regularly observed after HDC can be at least partially prevented with adequate rehabilitative measures. Our results also indicate that starting rehabilitation immediately after completion of HDC is possible without increasing morbidity.

Moreover, several positive outcomes were observed in patients who performed aerobic training during hospitalization. Firstly, duration of neutropenia in the training group was significantly shorter than for controls. Because neutropenic infections represent one of the principal complications after HDC and PBSCT, the importance of this observation is obvious. Indeed, 4 patients in the training group (13%) but only 1 patient in the control group (3%) developed a light infection, whereas the remaining patients developed moderate to severe infections. Although many effects of physical activity on the immune system have been described,[16] the exact mechanism underlying these effects remains to be determined. Further investigation seems warranted to explain the interactions between physical activity and hematopoiesis indicated by our study. Whether accelerated intestinal epithelial cell reconstitution, in addition to improved immune function, may lead to the lower severity of diarrhea observed in the training group must also remain speculative at this time.

Another positive effect observed was the different need for analgesics for the two groups. Eight patients in the training group (25%) but only 1 patient in the control group (3%) did not need analgesics during hospitalization; moreover, a

Table 3. Multiple Regression Analysis of the Influence of Factors Affecting Duration of Myelosupression and Intensity of Complications After HDC

	Predictors											
Endpoints	Age		BMI		Carboplatin*		Physical Performance†		Stem Cells‡		Training§	
	β	P	β	P	β	P	β	P	β	P	β	P
Loss of physical performance‖	0.27	.05	0.13	.32	0.08	.52	0.26	.06	−0.04	.70	0.31	.01
Duration of neutropenia (d)	−0.28	.02	−0.03	.76	0.15	.20	−0.17	.18	−0.20	.08	0.29	.01
Duration of thrombopenia (d)	0.05	.44	0.04	.69	0.16	.13	−0.10	.24	0.21	.09	0.24	.07
No. of platelets transfusions	0.05	.70	0.05	.69	0.16	.19	−0.10	.43	0.01	.90	0.25	.05
Intensity of pain¶	−0.15	.23	−0.15	.24	−0.04	.72	−0.11	.42	0.16	.18	0.26	.03
Intensity of diarrhea¶	0.06	.60	−0.01	.95	0.17	.18	0.10	.46	0.16	.21	0.27	.02
Duration of hospitalization (d)	0.03	.80	0.16	.21	0.02	.81	−0.15	.24	−0.18	.13	0.24	.04

Table 3 shows the β coefficients and the significance of a multivariable linear regression analyzing the influence of several predictors to the intensity of complications following chemotherapy, duration of myelosupression, and duration of hospitalization. *P* values are for the comparison with 0 (the values obtained by the null hypothesis).

* Total dose of carboplatin.

† Maximal physical performance (in km/h) on treadmill test by admission.

‡ Number of reinfunded blood stem cells.

§ Coded as training group = 0 and control group = 1.

‖ Loss of physical performance during hospitalization (expressed as percentage of the physical performance on admission).

¶ According to the WHO scale.

substantially higher percentage of patients in the control group required treatment with opioid analgesics (training group 4 patients, 12%; control group 10 patients, 27%). Literature reports offer an explanation for this finding. In several studies, physical exercise has been shown to elevate pain threshold[17-19]; the mechanisms proposed to underlie this effect are an activation of central pain inhibitory systems and a higher production of endorphins.[20]

Average duration of hospitalization was shorter for the training group than for controls. Because the decision to discharge a patient is made by the medical team based on clinical considerations, we cannot exclude that subjective factors affected this outcome. However, several objective parameters that also influence duration of hospitalization showed differences between the training and control groups. Furthermore, the medical staff was not informed about the secondary endpoints of the study. Therefore, the shorter duration of hospitalization for the training group may not entirely be an artifact because of subjective decisions made by the medical staff.

A critical point in our study was the comparability of effort of patients in the training and control groups during both stress-tests. To analyze this point, we compared the percentage of maximal predicted heart rate (220 minus age) reached by participants in the study in the stress-tests. No differences were found between the training and control groups (Table 2). These results indicate a comparable degree of effort in the two groups by all tests. Moreover, mean heart rate in all tests was more than 90% of the maximal predicted heart rate, indicating that the tests were performed until exhaustion and were not prematurely interrupted due to factors like coordinatory problems or pain.[14]

Echocardiography, resting, and exercise ECG showed no pathological changes in the training group at final testing. Furthermore, no patient in the training group developed clinical signs of cardiotoxicity during the 2 months after chemotherapy. This indicates that patients with no signs of impaired cardiac function can perform aerobic exercise after HDC with the described protocol and autologous PBSCT without fear of cardiac complications.

In the present study we have furnished evidence that aerobic exercise may be useful in preventing the loss of physical performance in cancer patients after myelotoxic chemotherapy. Furthermore, these data, while limited, suggest that exercise can be performed safely after HDC and PBSCT. Likewise, our finding of reduced chemotherapy-related complications in trained subjects is provocative. Clearly, all of these findings require confirmation. A randomized prospective study including patients with hematologic malignancies undergoing autologous and allogeneic bone marrow transplantation has been initiated to address this question.

ACKNOWLEDGMENT

The authors thank the doctoral students Annette Hahn, Ulrike Augustin, Murad Ruf, and Christoph Janzen, who supervised the patients during the study; Dominik Grathwohl for his advice concerning statistics; and Monika Tilmann, MD, and Ralf Beneke, MD, for revision of the manuscript and many helpful suggestions.

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Effects of Physical Activity on the Fatigue and Psychologic Status of Cancer Patients during Chemotherapy

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BACKGROUND. Fatigue is a common and often severe problem in cancer patients undergoing chemotherapy. The authors postulated that physical activity training can reduce the intensity of fatigue in this group of patients.

METHODS. A group of cancer patients receiving high dose chemotherapy followed by autologous peripheral blood stem cell transplantation (training group; n = 27) followed an exercise program during hospitalization. The program was comprised of biking on an ergometer in the supine position following an interval training pattern for 30 minutes daily. Patients in the control group (n = 32) did not train. Psychologic distress was assessed at hospital admission and discharge with the Profile of Mood States and Symptom Check List 90.

RESULTS. By the time of hospital discharge, fatigue and somatic complaints had increased significantly in the control group (P for both < 0.01) but not in the training group. Furthermore, by the time of hospital discharge, the training group had a significant improvement in several scores of psychologic distress (obsessive-compulsive traits, fear, interpersonal sensitivity, and phobic anxiety) (P value for all scores < 0.05); this outcome was not observed in the control group.

CONCLUSIONS. The current study found that aerobic exercise can reduce fatigue and improve psychologic distress in cancer patients undergoing chemotherapy. ***Cancer*** **1999;85:2273–7.** *© 1999 American Cancer Society.*

KEYWORDS: exercise, fatigue, mood, high dose chemotherapy, peripheral blood stem cell transplantation.

Fatigue is one of the most frequent side effects of cancer treatment. According to several studies, this symptom affects up to 70% of patients during chemotherapy and radiotherapy.[1-3] For many cancer patients, treatment-related fatigue is severe and imposes limitations on normal daily activities. Furthermore, this symptom can affect the course of treatment; indeed, fatigue is a dose-limiting symptom for some cancer therapies (e.g., those with interferon or interleukin-2). Nonetheless, up to 30% of cancer survivors have been reported to experience a loss of stamina for years after the cessation of treatment.[4-6] The causes of this problem are not understood completely; however, the origin of chronic fatigue most likely is multifactorial and includes physiologic, psychologic, and social components.[7]

Impairment of physical performance figures among the most important etiologic factors of chemotherapy-related fatigue. Cardiorespiratory and muscular deconditioning and chemotherapy-induced anemia can reduce work capacity; therefore, patients require a higher degree of effort to perform their usual activities. The resulting increments in metabolic rate and energy consumption produce tiredness and fatigue even

Supported by the Nenad Keul Foundation, Freiburg, and Daimler-Benz AG, Stuttgart, Germany.

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Received August 5, 1998; revision received January 11, 1999; accepted January 11, 1999.

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with normal daily activities. To reduce fatigue, patients may avoid physical exertion and down-regulate their level of activity. The resulting physical inactivity induces muscular wasting and can produce further loss of performance. Lowering endurance thus creates a self-perpetuating condition: diminished activity leads to easy fatigability and vice versa.[7]

Aerobic exercise (defined as the rhythmic contraction and relaxation of large muscle masses over an extended time) has been shown to improve physical performance in cancer patients.[8-11] In recent studies we observed a reduction in the fatigue reported by cancer patients after participation in an aerobic training program designed to improve physical performance.[9,11,12] However, the lack of an objective assessment of fatigue made an exact interpretation of our observations difficult.

In view of these considerations, we investigated the effects of an exercise program on the psychologic distress of cancer patients undergoing high dose chemotherapy (HDC).

PATIENTS AND METHODS

A successive series of 63 cancer patients with solid tumors or lymphomas were enrolled for participation in the study. Inclusion criteria were: age 18–60 years; active malignancy confirmed histologically; absence of associated psychiatric, muscular, cardiovascular, or pulmonary disease; and ability to understand written German. All patients had been selected for HDC followed by peripheral stem cell transplantation. The study was approved by the Ethical Commission of the University of Freiburg and informed consent was obtained from all participants.

In the week preceding HDC, all patients underwent a cardiologic examination (electrocardiogram [ECG], stress ECG, and echocardiogram). One patient showed abnormalities on the ECG and was excluded from the study. Overall, 62 patients fulfilled all requirements for participation in the study. Prior to the initiation of chemotherapy, patients were assigned to a training group (n = 29) or a control group (n = 33) according to the datum of hospitalization (patients recruited in odd weeks were included in the training group and patients recruited in the even weeks were included in the control group).

Psychologic status was assessed with two questionnaires, the short version of the Profile of Mood Status (POMS) [13,14] and the Symptom Check List (SCL-90-R).[15,16] These instruments are comprised of statements regarding subjective experiences and allow an assessment of affective states during the last week (in the case of the SCL-90-R) or the present day (in the case of the POMS). The short version of the POMS yields separate subscale scores for depression, fatigue, anger/hostility, and vigor. Similarly, the SCL-90-R yields a global severity index (positive symptoms distress index [PSD]) and separate subscales for somatization, obsessive-compulsive traits, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. Higher PSD scores indicate greater overall mood disturbance; lower vigor scores and higher scores for the remaining subscales indicate a higher intensity of disturbance in the examined areas. These instruments have been used in several clinical studies to evaluate affective states and mental symptomatology in different patient populations and have shown high reliability and validity.

Patients with solid tumors underwent HDC with cumulative doses of etoposide, 1.5 g/m^2; ifosfamide, 12 g/m^2; and carboplatin, 750–1500 mg/m^2 (n = 40); 5 patients also received epirubicin, 150 mg/m^2. Therapy for 1 patient in the control group was comprised of thiotepa, 500 mg/m^2; cyclophosphamide, 6 g/m^2; and carboplatin, 800 mg/m^2. One patient in the training group refused to complete chemotherapy and received the full dose of etoposide and only 67% of the planned doses of ifosfamide and carboplatin. Patients with lymphoma received cumulative doses of busulfan, 14 mg/m^2, plus cyclophosphamide, 60 mg/m^2 (n = 10) or carmustine, 300 mg/m^2; cytosine arabinoside, 1600 mg/m^2; etoposide, 800 mg/m^2; and melphalan, 140 mg/m^2 (n = 6). After chemotherapy all patients received peripheral autologous stem cell transplantation and daily subcutaneous injections of granulocyte-colony stimulating factor at a dose of 5 μg/kg body weight/day during neutropenia (absolute neutrophil count$< 0.5 \times 10^9$/L).

Patients in the training group performed a daily program of aerobic exercise comprised of "biking" with a bed ergometer (Rotomed; Reck Machinenbau GmbH, Betzenweiler, Germany). This device allows the simulation of biking motion without the patient leaving the bed. The patients "biked" for 1 minute with an intensity sufficient to reach a heart rate equivalent to at least 50% of the cardiac reserve, calculated as 220 − age − resting heart rate.[17] The procedure was repeated 15 times with pauses of 1 minute between bouts; therefore, training was performed for a total of 30 minutes each day. The mean workload during the training program was 30 ± 5 watts (range, 20–40 watts). During training sessions patients were supervised continuously by instructed study personnel. The physical performance of patients changed during hospitalization as result of variations in clinical parameters (e.g., hemoglobin concentration, nutritional status, infections, etc.). Therefore, the pedaling speed was readjusted daily to achieve the goal heart rate and then kept constant within single training sessions (15 bouts). The daily pedaling frequency varied between 30–50 cycles/minute. To calculate the mean heart rate during a training session, the heart rate was assessed at the end of each 1-minute workload and added; heart rate during pauses was not considered.

Patients who were febrile (> 37.5 °C) or who had platelet counts $< 20 \times 10^9$/L were instructed to interrupt training. Patients with World Health Organization (WHO) Grade 1 and 2 infections and no other complications restarted training after the abatement of fever and continued until discharge, whereas patients with severe infections (WHO Grade 3) or multiple complications did not resume training. Two patients in the training group elected to abandon the study after the second training day for personal reasons. Nine patients (three in the training group and six in the control group) developed significant complications during hospitalization: severe infection (one patient in the training group and three in the control group), moderate infection combined with gastrointestinal toxicity (one patient in the control group), moderate infection followed by allergic reaction after platelet transfusion (one patient in the training group), and nephrotoxicity combined with infection (two patients in the control group and one patient in the training group).

On the day of discharge, a second evaluation of the patient's psychologic status was performed. One patient in the control group refused to complete the questionnaire and was excluded from the study.

Statistical Analysis

The study was performed following the "intention-to-treat" principle. Baseline data were compared with the Student *t* test. To evaluate the changes in psychologic distress during hospitalization, we compared data from the two groups at the time of hospital admission and at discharge with the two-tailed Wilcoxon matched pairs test. Statistical calculations were performed using Graph Pad Prism 3.0 for Windows, Graph Pad Software, San Diego, CA. A $P < 0.05$ was considered to show statistical significance. Data are shown as the mean ± the standard deviation and range (in brackets).

RESULTS

At the beginning of the study no differences in the baseline characteristics or psychologic stress between the two groups were observed (Table 1) (Fig. 1). Patients in the training group performed the exercise program for 82% ± 16% of the hospitalization days.

During hospitalization, patients in the training group showed significant improvement in the obsessive-compulsive traits ($P = 0.005$), anxiety ($P = 0.01$), interpersonal sensitivity ($P = 0.0004$), and phobic anxiety ($P = 0.02$) domains (Table 2). These changes resulted in a reduction in the global psychologic distress in the SCL-90-R ($P = 0.03$). No significant increment in fatigue was observed during hospitalization ($P = 0.28$). Patients in the control group showed significant increments in the fatigue and somatization scores ($P < 0.02$ and $P < 0.001$, respectively) and a reduction in vigor ($P = 0.05$) during hospitalization; no significant changes in the remaining scores were observed (Table 2).

TABLE 1
Baseline Characteristics of Patients Completing the Study

	Training group	Control group	*P* value
No. of patients	27	32	
Age (yrs) (range)	40 ± 11 (21–59)	40 ± 10 (20–56)	0.47
Gender	9 male, 18 female	13 male, 19 female	
Body mass index (range)	24.5 ± 3.8 (18–32)	23.6 ± 2.9 (19–32)	0.78
Retransfused stem cells			
10^6/kg body weight (range)	4.6 ± 3.7 (1.3–12)	4.1 ± 2.7 (1.1–14.5)	0.61
Diagnosis			
Breast carcinoma	13	12	
Metastatic breast carcinoma	3	3	
Seminoma	3	3	
Sarcoma/adenocarcinoma	2		
Small cell lung carcinoma		4	
Hodgkin disease	2	5	
Non-Hodgkin lymphoma	4	5	
Chemotherapy			
VIC/CCT	20	19	
VIC-E	1	3	
BEAM	4	2	
Bu/Cy	2	8	

VIC/CCT: etoposide, ifosfamide, and carboplatin/thiotepa, cyclophosphamide, and carboplatin; VIC-E: etoposide, ifosfamide, carboplatin, and epirubicin; BEAM: carmustine, cytosine arabinoside, etoposide, and melphalan; Bu/Cy: busulfan and cyclophosphamide.

DISCUSSION

Loss of physical performance and fatigue are frequent problems of cancer patients undergoing chemotherapy. After discharge from the hospital, the majority of patients find it difficult to perform daily activities. Moreover, some patients may require weeks to months to regain their pretreatment level of fitness. This impairment in physical fitness is a substantial contributor to reduced quality of life in cancer patients.

We previously have observed improvements in emotional stability in cancer patients participating in a training program.[9,11] However, the lack of a systematic and objective evaluation of psychologic distress made an exact interpretation of this observation difficult. We believe the current study adds additional evidence of the beneficial effects of physical activity on the mental status of cancer patients undergoing chemotherapy.

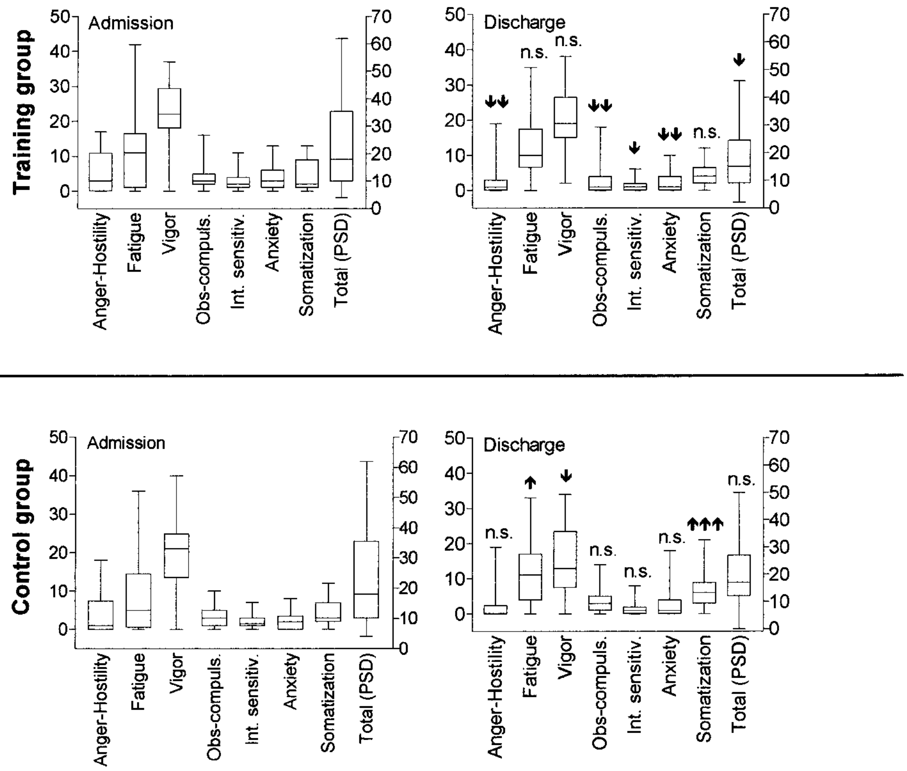

FIGURE 1. Scores in the Profile of Mood States (POMS) and the Symptoms Check List-90 (SCL-90-R) at hospital admission and at discharge. Scores were compared with the two-tailed Wilcoxon matched pairs test. Only domains showing differences between admission and discharge scores are shown. Obs-Compuls: obsessive-compulsive traits; Int. sensitiv: interpersonal sensitivity; ns: not significant ($P > 0.05$); ↑: increment; ↓: reduction; ↑, ↓: $P < 0.05$; ↑ ↑, ↓ ↓: $P < 0.01$; ↑ ↑ ↑, ↓ ↓ ↓: $P < 0.001$. The global severity index (positive symptoms distress index [PSD]) is shown on the right axis and all remnant scores are shown on the left axis.

Indeed, by the end of hospitalization, psychologic distress scores in several areas were reduced significantly in the training group whereas patients in the control group showed no improvement in mood state. Furthermore, the control group showed a significant increment in fatigue and somatization scores by the time of hospital discharge, an outcome not observed in the training group.

Several mechanisms may explain these results. Physical activity has been observed to improve symptoms of psychologic distress, particularly anxiety and depression, in patients with chronic diseases such as renal insufficiency,[18] ischemic heart disease,[19] and acquired immunodeficiency syndrome.[20] However, to our knowledge, the exact mechanisms underlying these observations have not been determined. Certainly the effects of physical activity are not limited to better cardiovascular or muscular function. Indeed, the improvement in physical performance can increase the feelings of control, independence, and self-esteem of patients; this improved self-confidence can result in better social interaction and a reduction in anxiety and fear. These mechanisms may explain the observed improvement in several indicators of psychologic distress (depression, anger/hostility, obsessive-compulsive traits, fear, interpersonal sensitivity, and phobic anxiety) observed in the training group. However, in our study, patients in the control group were not included in a structured program involving activities other than exertion; therefore, we cannot rule out possible nonspecific effects of attention or human contact on mood elevation. Further studies including placebo nonexercise activities for the control group are warranted to clarify this important question.

Conversely, the significant increment of fatigue during hospitalization observed in the control group suggests an organic etiology for this symptom in this setting. As mentioned earlier, the combined effects of chemotherapy and prolonged bed rest induce a substantial loss of physical performance. As result of the reduced work capacity, patients require a greater degree of effort to perform usual activities; the resulting increments in metabolic rate and energy consumption therefore produce tiredness and fatigue, even from normal activities. In a recent report we showed that aerobic training reduces the loss of physical performance in cancer patients undergoing HDC.[12] Consequently, these patients require a lower degree of effort to perform normal activities compared with their nontraining counterparts. As shown in the current study, this improvement in physical condition results in a reduction of fatigue during hospitalization.

Our results indicate that physical activity has beneficial effects on the mental status of cancer patients during chemotherapy. However, the current study included a small number of patients undergoing a particular treatment (HDC). Therefore, further studies are nec-

TABLE 2
Psychologic Status at Hospital Admission and at Hospital Discharge[a]

Training group	At admission	At discharge	*P* value
POMS			
Depression	12.8 ± 10.5 (0–35)	6.9 ± 10 (0–33)	0.11
Fatigue	9.6 ± 10.0 (0–42)	11.7 ± 8.9 (0–35)	0.28
Vigor	22.5 ± 8 (0–37)	19.6 ± 9 (2–38)	0.10
Anger/hostility	4.8 ± 5.7 (0–17)	2.7 ± 4.8 (0–19)	0.005
SCL-90-R			
Somatization	4.2 ± 4.1 (0–13)	4.3 ± 3 (0–12)	0.97
Obsessive-compulsive traits	3.8 ± 3.4 (0–16)	2.7 ± 3.8 (0–18)	0.005
Interpersonal sensitivity	2.7 ± 2.7 (0–11)	1.3 ± 1.5 (0–6)	0.004
Depression	5.5 ± 4.9 (0–21)	4.9 ± 4.6 (0–17)	0.51
Anxiety	3.4 ± 3.5 (0–13)	2 ± 2.5 (0–10)	0.01
Hostility	1.2 ± 1.5 (0–5)	0.9 ± 1.2 (0–5)	0.24
Phobic anxiety	1.7 ± 2.8 (0–13)	0.8 ± 1.3 (0–4)	0.02
Global psychologic distress	22.7 ± 14.9 (4–62)	17.7 ± 12.4 (2–46)	0.03
Control group	**At admission**	**At discharge**	***P* value**
POMS			
Depression	9.9 ± 9.6 (0–40)	6.2 ± 7.8 (0–34)	0.22
Fatigue	9.2 ± 10.2 (0–36)	11.5 ± 8.6 (0–33)	0.02
Vigor	19.9 ± 9.2 (0–40)	15.5 ± 9.8 (0–34)	0.05
Anger/hostility	3.7 ± 5.1 (0–18)	2.4 ± 4.7 (0–19)	0.21
SCL-90-R			
Somatization	4.1 ± 3.0 (0–12)	6.6 ± 5 (0–21)	0.001
Obsessive-compulsive traits	3.6 ± 2.9 (0–10)	3.7 ± 3.2 (0–14)	0.54
Interpersonal sensitivity	2.0 ± 1.7 (0–7)	1.5 ± 1.9 (0–8)	0.18
Depression	5.3 ± 3.7 (0–14)	6 ± 3.8 (0–14)	0.56
Anxiety	2.2 ± 2.3 (0–8)	3.0 ± 4.3 (0–18)	0.56
Hostility	1.3 ± 1.4 (0–6)	1.4 ± 2.3 (0–13)	0.60
Phobic anxiety	0.5 ± 1 (0–4)	0.6 ± 1.3 (0–5)	0.67
Global psychologic distress	19.6 ± 10.7 (3–43)	20.7 ± 11.4 (0–50)	0.68

POMS: Profile of Mood States; SCL-90-R: Revised Symptom Check List 90.

[a] Data are shown as mean ± the standard deviation with ranges in parentheses. Differences between scores at admission and discharge were compared with the Wilcoxon matched pairs test. Lower vigor score and higher scores in the remaining subscales indicate a higher intensity of disturbance in the examined areas.

essary to evaluate the effects of different programs of physical activity, including aerobic training and other forms of exercise, in patients with solid tumors and hematologic malignancies receiving conventional and intensified treatments. We have initiated further randomized studies addressing these important questions.

Aerobic training reduces treatment-related fatigue and improves the psychologic state of cancer patients receiving HDC.

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Aerobic exercise as therapy for cancer fatigue

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ABSTRACT

DIMEO, F., B. G. RUMBERGER, and J. KEUL. Aerobic exercise as therapy for cancer fatigue. *Med. Sci. Sports Exerc.*, Vol. 30, No. 4, pp. 475–478, 1998. **Purpose:** Fatigue and impairment of physical performance are common and severe problems of cancer patients. We describe the effect of an aerobic exercise program designed for cancer patients suffering from these symptoms. **Methods:** Five cancer patients (4 female, 1 male, age 18 to 55), participated in the training program. Fatigue had been present for a time ranging between 5 wk and 18 months and hindered the patients from carrying out normal daily activities. The training program consisted of walking daily on a treadmill with an intensity corresponding to a lactate concentration of 3 ± 0.5 mmol·L^{-1} and was carried out for 6 wk. **Results:** By the end of the exercise program we observed an improvement in maximal physical performance (from 6.4 ± 0.4 km·h^{-1} to 7.5 ± 0.9 km·h^{-1}, $P < 0.05$) and maximal walked distance (from 1640 ± 724 m to 3300 ± 953 m, $P < 0.05$). Heart rate and lactate concentration by an equivalent submaximal workload (5 km·h^{-1}) were significant reduced (from 138 ± 21 beats·min^{-1} to 113 ± 20 beats·min^{-1}, $P < 0.05$, and from 2.6 ± 1.4 mmol·L^{-1} to 1.3 ± 0.6 mmol·L^{-1}, $P < 0.05$); all patients experienced a clear reduction of fatigue and could carry out normal daily activities again without substantial limitations. **Conclusion:** We conclude that an aerobic exercise program of precisely defined intensity, duration, and frequency can be prescribed as therapy for primary fatigue in cancer patients. **Key Words:** AEROBIC EXERCISE, CANCER, REHABILITATION, CANCER FATIGUE

Most cancer patients experience a loss of energy and an impairment of physical performance. Some authors estimate that this problem affects up to 70% of cancer patients during chemo- and radiotherapy or after surgery (3,8,9,12,13,15). Furthermore, up to 30% of cancer survivors have been reported to experience a loss of energy for years after cessation of treatment (2–4). For many patients, fatigue is a severe and activity-limiting symptom. This impairment in physical fitness is a significant contributor to decreased quality of life (4,9). In response to fatigue, patients are often advised to rest and to downregulate their level of daily activities. But since inactivity induces muscular catabolism, prolonged rest can actually help perpetuate fatigue.

Aerobic exercise (defined as the rhythmical contraction and relaxation of large muscle groups over a prolonged time) has been suggested for rehabilitation of cancer patients affected by the problem of "energy loss" (14). However, it is not yet a fully accepted concept. Many cancer patients and physicians believe that vigorous exertion is potentially harmful, although no evidence in the literature supports this notion. Nevertheless, a growing body of evidence shows that exercise improves the physical performance of cancer patients (5–7,11,16).

We describe the effects of an aerobic training program on the performance of cancer patients suffering from fatigue.

PATIENTS AND METHODS

Five cancer patients suffering fatigue consulted in our department. Patient 1, an 18-yr-old girl with a medulloblastoma of the cerebellum, had been operated on and undergone chemotherapy 18 months before consultation; since then she had received no further medication. Patient 2, a 32-yr-old woman with non-Hodgkin's lymphoma, had undergone a bone marrow transplantation 9 months before consultation and developed a chronical graft-versus-host disease. By the time of consultation she was receiving corticoids (deflazacort, 42 mg·d^{-1}) and a calcium antagonist (nifedipine, 20 mg·d^{-1}). Patient 3, a 23-yr-old woman with Hodgkin's lymphoma, had started chemotherapy (adriamicin 25 mg/m^2, vinblastine 6 mg/m^2, dacarbazine 375 mg/m^2 every third week)

0195-9131/98/3004-0475$3.00/0
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Submitted for publication August 1996.
Accepted for publication August 1997.

2 months before consultation and received the same treatment for the following 3 months. Patient 4, a 55-yr-old man with a disseminated nonsmall cell bronchial carcinoma, had undergone a pneumectomy 3 months before consultation. The operation was followed by two cycles of chemotherapy (etoposide 500 mg/m^2, cisplatinum 50 mg/m^2, ifosfamide 4 g/m^2). He had received no medication in the month before consultation; one week after consulting he began treatment with a cytostatic (paclitaxel, 175 mg/m^2) every third week. Finally, patient 5, a 33-yr-old woman with breast carcinoma, had undergone a high dose chemotherapy followed by a peripheral stem cell transplantation 8 wk before consultation. Four weeks before consultation she had started an adjuvant radiotherapy that was carried out for a total duration of 6 wk.

Patients were selected for participation in the study on the basis of suffering from severe fatigue. In two cases this symptom was overwhelming: one patient had to quite school; another was unable to carry on her university studies. For the other three patients, fatigue imposed severe limitations in normal daily activities like stair climbing or housekeeping. All patients experienced fatigue first after undergoing chemotherapy; the symptom had been present for a time ranging between 5 wk and 18 months. A cardiac examination (ECG in rest and exercise and echocardiogram) showed no pathological changes. Hemoglobin concentration was in all cases within normal range. No patient showed signs of associated disease or psychiatric disorder.

For assessment of physical performance a treadmill stress test beginning with 3 km·h^{-1} and 1.5% elevation, acceleration of 1 km·h^{-1} every third minute by unchanged elevation was carried out until exhaustion. Continuous ECG monitoring was recorded. Lactate concentration in capillary blood was monitored every third minute.

Training program. After obtaining informed consent, the patients carried out an aerobic training program consisting of walking on a treadmill on weekdays for 6 wk. Training was carried out by a speed corresponding to a lactate concentration of 3 ± 0.5 mmol·L^{-1} in capillary blood (slightly below the anaerobic threshold, 10); this intensity coincided with a heart rate of 80 ± 5% of the maximum reached during stress test. Heart rate during training was controlled continuously; lactate concentration was controlled every fifth training day. As lactate concentration sank below 2.5 mmol·L^{-1} and exercise heart rate decreased as a result of training adaptation, treadmill speed was increased by 0.5 km·h^{-1} to maintain training intensity constant. During the first week, each patient walked five times for 3 min at the above mentioned speed; between these training bouts, patients walked with half-speed for 3 min to recover. One patient who trained at a speed of 3 km·h^{-1} was allowed to sit during the intervals. Exercise duration was increased weekly and the number of training bouts reduced (a 5-min bout four times in the second week, an 8-min bout three times in the third, a 10-min bout three times in the fourth, a 15-min bout two times in the fifth, and 30 to 35 min without interruption in the sixth week). In the week after concluding the training program, a second assessment of cardiac function (with ECG and echocardiogram) and of maximal physical performance (with a treadmill test) was carried out.

TABLE 1. Improvement of physical performance during the training program.

	Before	After	Significance
Training speed (km·h^{-1})	4.8 ± 1.5	5.9 ± 1.1	$P = 0.06$
Training distance (m)	1640 ± 724	3300 ± 953	$P < 0.05$
Maximal performance (km·h^{-1})	6.4 ± 0.4	7.5 ± 0.9	$P < 0.05$
Maximal performance (MET)	4.9 ± 0.3	5.5 ± 0.5	$P < 0.05$
Heart rate (beats·min^{-1}) (*)	138 ± 21	113 ± 20	$P < 0.05$
Lactate concentration (mmol·L^{-1}) (*)	2.6 ± 1.3	1.3 ± 0.5	$P < 0.05$

* by a submaximal workload of 5 km · h, corresponding to the usual walking speed.

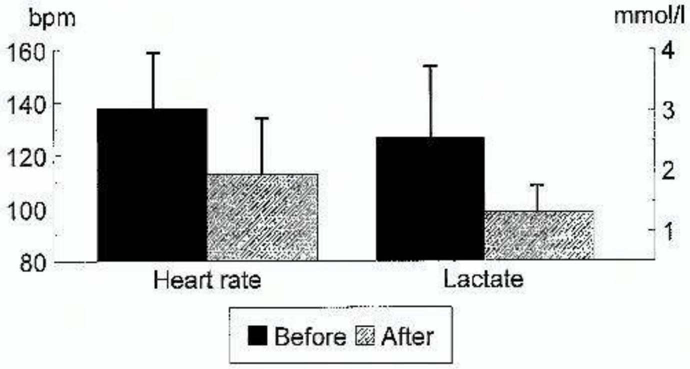

Figure 1—Reduction of heart rate (beats·min^{-1}) and lactate concentration (mmol·L^{-1}) by a submaximal workload of 5 km·h^{-1} (corresponding to the usual speed by walking) before and after the training program.

Statistical analysis. Data from patients before and after the program were compared with the Wilcoxon test; a value of $P < 0.05$ was considered to be statistically significant. Values are expressed as mean ± SD. Maximal performance in metabolical equivalents (METs, an indicator of intensity of physical effort corresponding to 3.5 mL O_2 per kilogram of body weight per minute) was calculated according to the American College of Sports Medicine (1).

RESULTS

By the end of the training program, all parameters of physical performance were substantially improved (see Table 1 and Figs. 1 and 2). Distance walked per training session improved significantly from 1640 ± 724 m to 3300 ± 953 m ($P < 0.05$). Patients maximal performance improved from 6.4 ± 0.4 km·h^{-1} to 7.5 ± 0.9 km·h^{-1} ($P < 0.05$); in METs: from 4.9 ± 0.3 to 5.5 ± 0.5 ($P <$ 0.05). Heart rate at equivalent submaximal workload (5 km·h^{-1}) decreased from 138 ± 21 beats·min^{-1} to 113 ± 20 beats·min^{-1} ($P < 0.05$); lactate concentration by the same workload decreased from 2.6 ± 1.3 mmol·L^{-1} to 1.3 ± 0.5 mmol·L^{-1} ($P < 0.05$). The feeling of fatigue improved clearly: two patients could resume their studies, the other three patients experienced no more fatigue with normal daily activities. Three patients started jogging regularly after the training program. The cardiovascular examination (ECG in rest and exercise and echocardiogram) showed no pathological changes of heart activity, function, and dimensions after the training program.

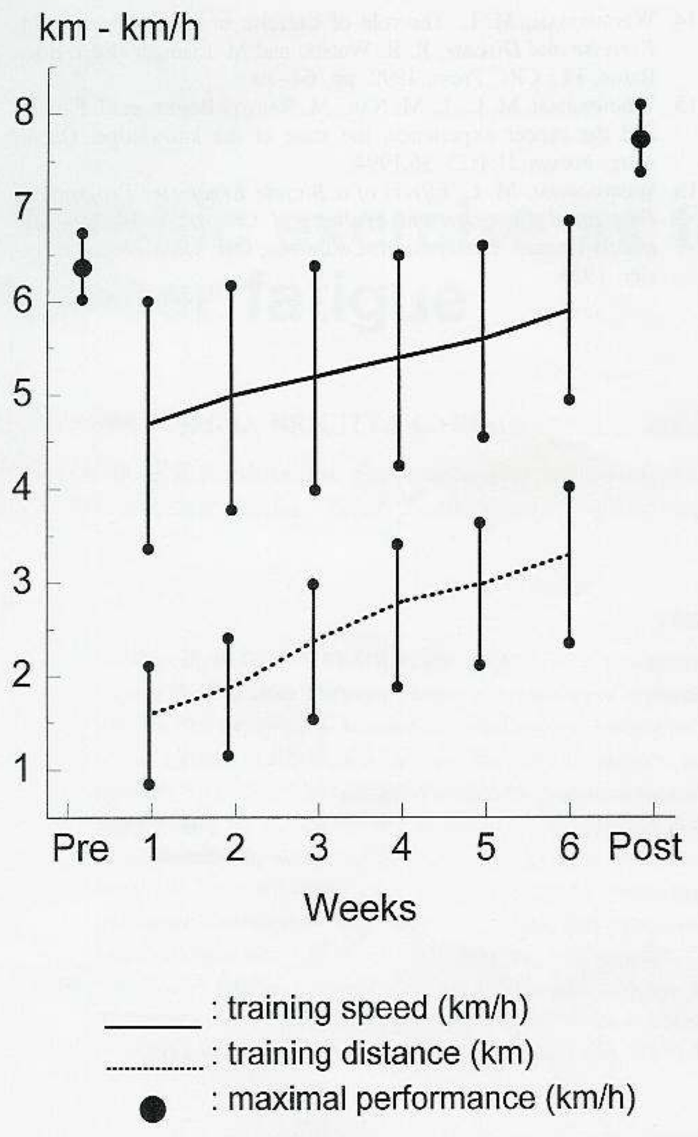

Figure 2—Improvement of maximal physical performance (pre- and post-program) and of training speed and daily walked distance during the 6 wk of the program.

DISCUSSION

The participants in this report presented a summary of the problems faced by cancer patients during and after treatment: organic deficiencies as sequel of surgical interventions, chronic graft-versus-host disease following bone marrow transplantation, loss of energy during and after radio- and chemotherapy. Since this symptom had been present for a long time (patients 1 and 2) or patients were receiving treatments that are known to cause fatigue (patients 3, 4, and 5), spontaneous remission of this symptom seems unlikely.

The loss of energy of these patients originated in extreme muscular deconditioning related to illness and treatment. To avoid fatigue they had been advised to seek periods of rest and to reduce their level of activity. However, these well-meaning recommendations had worked paradoxically: since inactivity induces muscular catabolism, prolonged rest can cause a further loss of performance. Therefore the patients needed a higher degree of effort to carry out normal daily activities, creating a self-perpetuating condition of diminished activity caused by easy fatigability and *vice versa*. This explains the persistence of fatigue for many weeks and even months after completion of treatment. An aerobic training program can break this circle of lack of exercise, impaired performance, and easy fatigability. Moreover, physical activity can produce secondary benefits such as improved emotional stability. As the training program led the patients to higher levels of physical fitness, we observed that they gained self-confidence and independence. They were no longer inactive objects of diagnostic and therapeutic measures but active participants in the rehabilitation process.

We conclude that, for some patients, cancer fatigue can originate in the diminished level of physical activity related to disease and to many treatment modalities. Therefore, cancer patients suffering from primary fatigue should not be advised to increase the amount of daily rest. Rather, they should be counseled to carry out aerobic exercise; counseling should include a precise definition of duration, intensity, and frequency of training. Further research is needed to determinate the feasibility and effects of aerobic training for cancer patients receiving diverse treatment modalities.

We are indebted to Ian A. York, DVM, MSC, Ph.D., for assisting in translation. This study was supported by the Nenad Keul Foundation Preventive Medicine, Freiburg i.Br, Germany.

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