ORIGINAL ARTICLE

# Role of a mixed type, moderate intensity exercise programme after peripheral blood stem cell transplantation

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**Objectives:** To evaluate the effect of peripheral blood stem cell transplantation on functional capacity, and to determine the role of a mixed type, moderate intensity exercise programme in the recovery of patients after intensive cancer treatment.

**Methods:** Peak aerobic capacity and muscular strength (upper body, lower body, and handgrip strength) measures were assessed before (PI) and after (PII) transplant and after a 12 week intervention period (PIII). After PII, 12 patients aged 16–64 years were allotted in equal numbers to a control group or exercise intervention group.

**Results:** Mean peak aerobic capacity and muscular strength were reduced after the transplant, with significant ($p<0.05$) decreases for upper body strength. No change was found in aerobic capacity and muscular strength between PII and PIII for the control group. In contrast, participation in the exercise programme led to significant improvements in peak aerobic capacity ($p<0.05$) and upper and lower body strength ($p<0.01$). In addition, values recorded after the three month intervention period were significantly higher than before treatment for peak aerobic capacity (litres/min ($p<0.05$) and ml/kg/min ($p<0.01$)) and lower body strength ($p<0.01$).

**Conclusion:** Intensive treatment for cancer can adversely affect aerobic capacity and muscular strength. A mixed type, moderate intensity exercise programme can help patients to regain fitness and strength within three months. No exercise can exacerbate physical losses resulting from treatment.

As medical technology has advanced, outcomes have improved for many malignancies, and, in turn, survival rates (defined as a relative combined five year statistic) for those diagnosed with cancer are progressively increasing each year. Overall for all cancer sites, the survival rate is now estimated at 59%.[1] Facilitating recovery after treatment and improving quality of life are essential as survival rates continue to rise.

In association with the adverse side effects of the disease itself are the ramifications of having cancer treatment, which usually includes surgery, chemotherapy, radiation therapy, or a combination of the three.[2] Furthermore, cancer and its treatment have been associated with reduced levels of physical activity. As early as 1978, it was estimated that at least one third of the functional decline observed in cancer patients can be attributed to hypokinetic conditions that develop as a result of prolonged inactivity.[3] The adverse physical condition includes diminished cardiovascular function, reduced lean body tissue and muscular strength, and impaired pulmonary function.[4]

These detrimental changes lead to a reduction in work capacity, and, in turn, greater effort is required to perform any given task. It is therefore not surprising that tiredness and fatigue are associated with performing normal daily activities[5] after cancer treatment. To avoid fatigue, patients may downregulate their level of activity and thereby further induce muscular and cardiorespiratory losses. Unfortunately, the creation of a self perpetuating condition of ''diminished activity which leads to easy fatigability and vice versa'', is common.[5] Previous research has highlighted the potential benefits of a structured aerobic exercise based, physical activity programme. Patients with breast cancer who exercise have shown improved work capacities, lower heart rate (HR) at a given power, increased maximum workload, increased peak aerobic capacity ($VO_2PEAK$), and lengthened time to achieve $VO_2PEAK$ compared with non-exercising patient controls.[6–10] Improvements in functional capacity after participation in a walking programme have also been observed in patients undergoing bone marrow transplantation.[11 12]

In summary, it has been shown that cancer, cancer treatment, and the resulting reduction in physical activity may have adverse effects on functional capacity. However, limited data exist on the functional capacity of patients before intensive cancer treatment, such as a peripheral blood stem cell transplant (PBST), and hence meaningful comparisons with measures after have not occurred. Therefore, it was a purpose of this study to investigate changes in aerobic capacity and muscular strength after PBST. Although there is evidence for a role for exercise in facilitating recovery after treatment for cancer, most work has assessed patients with breast cancer and the type of programme implemented has been limited to the prescription of aerobic exercise. Therefore this study also investigated the effect of a three month, mixed type, moderate intensity exercise programme on the recovery of aerobic capacity and muscular strength after a PBST.

## METHODS

### Subjects

After ethical approval from the Wesley Hospital ethics committee and the Queensland University of Technology human research ethical committee, 12 patients receiving high dose chemotherapy followed by an autologous PBST at the Wesley Hospital provided written informed consent to participate in this investigation. After the treatment, patients were allocated in equal numbers to an experimental or a control group. Initially, patient allocation was to be random, with age stratification, as they presented to the study.

**Abbreviations:** HR, heart rate; FFM, fat free mass; PBST, peripheral blood stem cell transplantation; RER, respiratory exchange ratio; RM, repetition maximum; $VO_2PEAK$, peak aerobic capacity

Unfortunately, a slow recruitment rate and hence low subject numbers meant randomisation was difficult and could pose more problems during the statistical analysis than if patients were ''allocated'' to a group. Therefore the two groups were matched as closely as possible, by taking into account factors that had the potential to influence the level of change in an intervention project, notably those outlined in table 1.

### Treatment

Table 2 outlines the timing of medical events and testing phases. Although three testing phases were scheduled (before (PI) and after (PII) transplant and after the exercise intervention (PIII)), because of variations in the time patients were informed of, and recruited into, the study, only seven patients were assessed during the first testing phase (PI) which was scheduled before the transplant. All 12 subjects were assessed during the second testing phase (PII). Treatment cessation was classified as the day of stem cell infusion. For those on a three transplant treatment regimen, this reflects the day of stem cell infusion of the last transplant. One patient in the control group relapsed before PIII, and therefore only 11 patients were assessed during the final testing session (PIII).

### Exercise intervention

During PI and PII, the effect of the transplant was being assessed and all patients were considered to be in the same group. Immediately after PII, patients were allocated to either the control/stretching group or the exercise intervention group. Subjects in the control group were required to participate in a supervised three month stretching programme, three times a week. During each session, stretches were performed for all major muscle groups, with each stretch being performed twice and taken to the point of discomfort, not pain. To ensure that the same contact time was spent with the control group as with the exercise group, the number of stretches performed across the three months progressed from 20 to 30 and the duration of each stretch was increased from 15 to 30 seconds. Although participation in the stretching programme could lead to mobility improvements, it was unlikely that it would result in improvements in other physiological variables.

The exercising subjects participated in a supervised three month moderate intensity and mixed type exercise programme, consisting of aerobic exercise (combination of treadmill walking and stationary cycling, three times a week, for 20–40 minutes, at an intensity of 70–90% maximum heart rate) and resistance exercise (three to six machine and free weight exercises, twice a week, with the weight set to induce failure at 8–20 repetitions). Progression was ensured throughout the three month programme by gradually increasing exercise intensity and duration. The initial resistance training programme consisted of a ''seated bench press'', ''lat pulldown'', and ''leg press'' exercise using machine weights. In the fifth to sixth week of the programme, an additional exercise (''upright row'' using a Smith machine) was introduced. By the final week of the programme, patients were also performing ''a seated shoulder press'' and ''lunges'' using free weights. All exercises were performed until the participant was unable to successfully complete one more repetition—that is, to failure. The weight was set so that failure occurred at 15–20 repetitions within the first six weeks of the programme. To focus more on achieving strength gains, this repetition range was decreased to 8–12 repetitions for the second half of the programme.

### Functional capacity

A patient specific maximal graded treadmill exercise test was performed to assess peak oxygen consumption ($\dot{V}O_{2PEAK}$), peak heart rate, the respiratory exchange ratio (RER), and exercising blood pressure, using a Quinton treadmill (Q65 Series 90), electrocardiogram (ECG-Q4500), and gas analysis machine (Q-Plex 1). All testing sessions were medically supervised, and electrocardiographic monitoring was performed throughout the testing protocol. The treadmill speed began at a slower than normal or comfortable pace for each subject, with the initial workload set at a speed of 1–4 km/h and a grade of 0%. Workload was increased every 1–2 minutes through the use of speed and/or grade. Standard criteria outlined elsewhere[13] were used to determine test

**Table 1** Group characteristics

| Variable | Control group | Exercise group |
|---|---|---|
| Age (years) | Mean = 54.5<br>Median = 54<br>Range = 46–64 | Mean = 39.5<br>Median = 40.5<br>Range = 16–64 |
| Sex | 4 males<br>2 females | 3 males<br>3 females |
| Marriage status | Married/significant relationship = all 6 patients | Married/significant relationship = 5 out of 6<br>Single = 1 out of 6 |
| Previous exercise history* | 1 = 1 patient<br>2 = 3 patients<br>3 = 1 patient<br>4 = 1 patient | 1 = 1 patient<br>2 = 3 patients<br>3 = 1 patient<br>4 = 1 patient |
| Weight after transplant | Mean = 71.82 kg<br>SD = 23.71 kg<br>Range = 50.4–113.3 kg | Mean = 87.35 kg<br>SD = 26.09 kg<br>Range = 52.9–121.7 kg |
| Living distance from the centre | Mean = 80 km<br>Range = 10–150 km | Mean = 33 km<br>Range = 5–100 km |
| Diagnosis | 1 acute myeloid leukaemia<br>1 high risk stage II breast cancer<br>2 multiple myeloma<br>1 non-Hodgkin's lymphoma<br>1 stage IV breast cancer | 1 lymphoblastic lymphoma/leukaemia<br>1 high risk stage II breast cancer<br>1 rhabdomyosarcoma<br>3 non-Hodgkin's lymphoma |
| Number of transplants | 1 transplant = 4 patients<br>3 transplants = 2 patients | 1 transplant = 5 patients<br>3 transplants = 1 patient |
| High dose chemotherapy | ''Lighter'' programme = 2 patients<br>''Heavy'' programme = 4 patients | ''Lighter'' programme = 1 patient<br>''Heavy'' programme = 5 patients |

*1, No regular exercise; 2, limited and sporadic exercise; 3, regular exercise before diagnosis; 4, regular exercise at diagnosis and up until transplant.

**Table 2** Timing of medical events and testing phases

| Medical events and testing phases | Mean | SD | CV | Range |
|---|---|---|---|---|
| PI (no of days before the start of high dose chemotherapy) | −8 | −1 | 11.6% | −7 to −10 |
| High dose chemotherapy duration (no of days) | 5 | 1 | 16.7% | 3 to 5 |
| Day of stem cell infusion | 0 | 0 | | 0 |
| Day of hospital discharge (no of days from stem cell infusion) | 1 | 1 | 60% | 0 to 2 |
| PII (no of days from stem cell infusion) | 17 | 3 | 15.5% | +14 to +21 |
| PIII (no of days from PII) | 85 | 2 | 2.7% | 82 to 89 |

CV, Coefficient of variation; PI, before transplant; PII, after transplant; PIII, after exercise programme.

cessation and $\dot{V}O_2$PEAK. On presentation of any of these criteria, treadmill speed was reduced to a comfortable speed, as judged by the patient, at a 0% grade. HR, blood pressure, and electrocardiographic traces were continually recorded until HR was below 100 beats/min.

Muscular strength was assessed by an isometric handgrip strength test, a 15 repetition maximum (RM) bench press, and 15RM leg press test. Maximal handgrip strength was evaluated through the use of a hand dynamometer (Smedley's Dynamo Meter TTM) and was performed three times for each hand. The maximal score attained for each side was recorded. Both the bench press and leg press test were assessed using Calgym machine weights. Subjects were given verbal and practical instructions on the correct performance of the test. The test was implemented only when the subject felt comfortable and was able to display the correct technique when performing the exercise. The weight that could be lifted 15 times was initially estimated, and, according to the number of repetitions reached, it was either increased or decreased until an accurate 15RM was attained. Subjects were allowed to rest between each set to ensure that fatigue did not influence the results. Although the patients essentially controlled the length of the rest intervals, a minimum of three minutes elapsed for all subjects between each set. Strength measures were adjusted for changes in fat free mass (FFM), and thus are expressed as a ratio of strength values (units or kg) and FFM (kg) (units/kg or kg/kg). FFM was calculated from the measurement of total body water using the deuterium dilution technique.[14]

### Statistical analysis

Calculations of sample size were based on the changes in aerobic capacity and muscular strength observed in the first two subjects recruited in this investigation. It was determined that 12 subjects, six in each group, were required to detect a 1 standard deviation difference, with power and significance set at 80% and 5% (two tailed) respectively. A two way analysis of variance, with repeated measures on one factor (phase), was used to determine the main effects of phase and group and the group by phase interaction for all dependent variables. Where significant interactions or main effects were observed, post hoc analysis (model based contrasts performed within the model) was performed to determine the loci of the variance. *t* tests were also used to detect differences in the change measured for peak aerobic capacity and muscular strength between PII and PIII, for the two groups. Statistical procedures were applied either on normally distributed original or log transformed data using the statistical package SPSS 10.0 for Windows.

## RESULTS

Factors that had the potential to confound the results of this investigation were evaluated and are outlined in table 1. Few differences exist between the control and intervention group for these factors, except for age. Although subject numbers in the age categories were too limited for statistical analysis, examination of the raw data by comparison of the youngest and oldest subject provided some understanding of the effect of age on the results. No consistent relation was identified between age and aerobic capacity and muscular strength.

Although seven subjects were recruited at PI, equipment problems during one patient's testing session reduced the accuracy of the aerobic capacity data collected and the data were therefore not included in the analysis. As shown in table 3, mean values for peak aerobic capacity and muscular strength were reduced after the transplant, with significant ($p<0.05$) declines for upper body strength.

No changes were found in peak aerobic capacity and muscular strength between PII and PIII for the control group (table 4). Peak HR was similar for the control group at all testing phases (PI = 158, PII = 155, PIII = 157), as was peak RER (PI = 1.05, PII = 1.10, PIII = 1.15). Table 4 shows that participation in the exercise programme led to significant improvements in peak aerobic capacity ($p<0.05$) and upper and lower body strength ($p<0.01$). In addition, results recorded after the three month intervention period were significantly higher than before treatment for peak aerobic capacity (litres/min, $p<0.05$ and ml/kg/min, $p<0.01$) and lower body strength ($p<0.01$) (table 5). Peak HR and RER did not alter throughout the testing phases for the exercise group (PI = 172, PII = 173, PIII = 174 and PI = 1.12, PII = 1.10, PIII = 1.15 respectively).

Figures 1 and 2 show individual changes in aerobic capacity (ml/kg/min) and lower body strength across the

**Table 3** Aerobic capacity and strength measures before (PI) and after (PII) transplant for the study group

| | PI | | | PII | | | |
|---|---|---|---|---|---|---|---|
| Variable | Mean | SE | No | Mean | SE | No | p Value |
| $\dot{V}O_2$PEAK (litres/min) | 1.9 | 0.1 | 6 | 1.7 | 0.1 | 12 | 0.135 |
| $\dot{V}O_2$PEAK (ml/kg/min) | 23.71 | 1.25 | 6 | 21.76 | 0.79 | 12 | 0.211 |
| Hand grip strength (units/kg) | 0.81 | 0.07 | 7 | 0.76 | 0.05 | 12 | 0.470 |
| Upper body strength (log(kg/kg)) | −0.46 | 0.06 | 7 | −0.61 | 0.04 | 12 | 0.049 |
| Lower body strength (kg/kg) | 1.17 | 0.08 | 7 | 1.06 | 0.06 | 12 | 0.450 |

**Table 4** Aerobic capacity and strength measures after the transplant (PII) and after the exercise programme (PIII) for the exercise and control group

| | Exercise group | | | | | Control group | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | PII (n = 6) | | PIII (n = 6) | | | PII (n = 6) | | PIII (n = 5) | | |
| Variable | Mean | SE | Mean | SE | p Value | Mean | SE | Mean | SE | p Value |
| Body weight (kg) | 87.4 | 1.4 | 89.7 | 1.4 | 0.315 | 71.8 | 1.4 | 72.8 | 1.6 | 0.573 |
| $VO_{2PEAK}$ | | | | | | | | | | |
| litres/min | 2.0 | 0.2 | 2.9 | 0.2 | 0.004 | 1.4 | 0.2 | 1.6 | 0.1 | 0.290 |
| ml/kg/min | 23.38 | 1.11 | 32.55 | 1.11 | 0.001 | 20.13 | 1.11 | 21.53 | 1.28 | 0.359 |
| Muscular strength | | | | | | | | | | |
| HGS (units/kg) | 0.72 | 0.05 | 0.76 | 0.05 | 0.450 | 0.79 | 0.05 | 0.72 | 0.06 | 0.442 |
| UBS (log(kg/kg)) | −0.61 | 0.06 | −0.32 | 0.06 | 0.003 | −0.61 | 0.06 | −0.59 | 0.06 | 0.882 |
| LBS (kg/kg) | 1.10 | 0.10 | 1.81 | 0.10 | 0.001 | 1.03 | 0.10 | 0.98 | 0.12 | 0.812 |

HGS, Hand grip strength; UBS, upper body strength; LBS, lower body strength.

testing phases for subjects in the control and exercise group. The pattern and magnitude of change in these measures was similar for all subjects except one between PI and PII. By three months after transplant, greater gains in aerobic capacity and muscular strength were evident in all six patients participating in the exercise intervention programme than in the five subjects in the control group. In addition, all exercising subjects showed improvements, whereas control subjects displayed gains, no change, or losses in these measures.

The magnitude of change between PII and PIII for peak VE, $VO_{2PEAK}$ (litres/min and ml/kg/min), and upper and lower body strength was significantly larger ($p<0.05$) for the exercising group (27 litres/min, 0.88 litres/min, 9.17 ml/kg/min, 0.29 kg/FFM(kg), 0.71 kg/FFM(kg) respectively) than for the controls (−2.24 litres/min, 0.12 litres/min, 1.4 ml/kg/min, 0.02 kg/FFM(kg), −0.05 kg/FFM(kg) respectively).

## DISCUSSION

This investigation shows that PBST was associated with mean declines in aerobic capacity and muscular strength. Except for upper body strength, these changes were not significant. However, comparisons with normative data show their clinical significance. Eleven out of 12 of the study group assessed at PII recorded fitness values below the 25th centile for normative age and sex matched data, and would require at least 50% of their peak aerobic capacity to undertake normal daily tasks, which often have calculated MET values of 2.5–4.5.[15] In addition, between PI and PII, the study group lost 4%, 28%, and 19% of handgrip, upper body, and lower body strength respectively. These changes indicate that more strength was lost in the muscles of the thigh and trunk than in those of the hand. During the treatment period, patients spent most of their time in bed and were performing few movements that required upper and/or lower body strength. Any movement performed while in bed, such as eating, reading, and writing, would have predominantly required hand strength, which probably minimised losses in handgrip strength. Moreover, the decline observed by PII in strength measures highlights that both isometric and isodynamic strength are affected.

Participation in the moderate intensity, mixed type exercise programme for three months after the transplant led to significant improvements in peak aerobic capacity and upper and lower body strength. Exercising patients also attained higher aerobic capacity and lower body strength scores by PIII than before transplant. Although the non-exercising patients also showed mean improvements in certain variables after the intervention period, the magnitude of change between PII and PIII was significantly less for peak aerobic capacity and upper and lower body strength compared with the exercising patients. Of particular importance is whether the improvements shown by the exercising patients were of sufficient magnitude to allow participation in normal daily activities without undue fatigue. A maximal MET value of 5 (≈17.5 ml/kg/min) is regarded as sufficient to perform daily tasks.[11] Whereas all exercising patients exceeded this level (range 21–51 ml/kg/min), 40% of the control group failed to reach the minimum requirement (range 11.8–32.2 ml/kg/min).

It is possible that the greater familiarisation of the exercise group with treadmill walking than the control group contributed to their improvements in peak aerobic capacity. However, peak HR was within 10% of the age predicted maximum, and peak RER was 1.1 or greater during each of the graded exercise treadmill tests for all subjects, and did

**Table 5** Aerobic capacity and strength measures before transplant (PI) and after exercise programme (PIII) for the exercise and control group

| | Exercise group | | | | | Control group | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | PI (n = 4) | | PIII (n = 6) | | | PI (n = 3) | | PIII (n = 5) | | |
| Variable | Mean | SE | Mean | SE | p Value | Mean | SE | Mean | SE | p Value |
| Body weight (kg) | 96.7 | 1.8 | 89.7 | 1.4 | 0.028 | 78.6 | 2.2 | 72.8 | 1.6 | 0.041 |
| $VO_{2PEAK}$ | | | | | | | | | | |
| litres/min | 2.0 | 0.2 | 2.9 | 0.2 | 0.034 | 1.8 | 0.2 | 1.6 | 0.1 | 0.182 |
| ml/kg/min | 23.73 | 1.11 | 32.55 | 1.11 | 0.007 | 23.16 | 1.79 | 21.53 | 1.28 | 0.304 |
| Muscular strength | | | | | | | | | | |
| HGS (units/kg) | 0.75 | 0.07 | 0.76 | 0.05 | 0.875 | 0.86 | 0.08 | 0.72 | 0.06 | 0.319 |
| UBS (log(kg/kg)) | −0.49 | 0.17 | −0.32 | 0.06 | 0.068 | −0.43 | 0.09 | −0.59 | 0.06 | 0.245 |
| LBS (kg/kg) | 1.12 | 0.13 | 1.81 | 0.10 | 0.001 | 1.21 | 0.16 | 0.98 | 0.12 | 0.401 |

HGS, Hand grip strength; UBS, upper body strength; LBS, lower body strength.

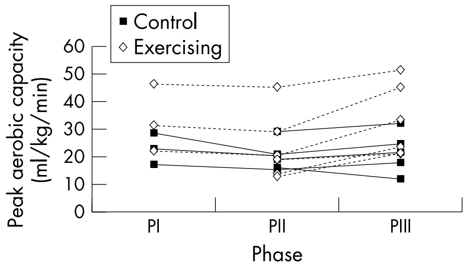


**Figure 1** Individual changes in peak aerobic capacity of the control and exercising subjects across the testing phases: before transplant (PI); after transplant (PII); after exercise programme (PIII).

not change between testing phases. These data provide credence to the results observed. Furthermore, the results of this investigation support previous findings of gains in aerobic capacity of 20.7–57% after aerobic-only exercise programmes by patients with breast cancer and those who had received bone marrow transplantation.[7 8 11] The wide range in gains may reflect factors such as the type of cancer, the treatment regimen, the initial fitness of the participants, the length of the intervention period, and the type of intervention programme.

Differences were detected in the changes in strength across the phases between the exercising and control patients, with the former showing improvements and the latter showing no change. Continued losses of strength or an inability to regain lost strength after the transplant will affect the patient's ability to perform daily tasks. Although not significant, the negative magnitude of change experienced in hand grip and lower body strength observed in the control group emphasises the risk of continued strength losses with failure to participate in physical activity after treatment. The inability to regain strength without the implementation of a structured intervention has also been shown in 36 long term acute lymphoblastic leukaemia survivors.[16] Reduced muscle strength was identified when results for the children under investigation were matched with results for school peers.

About 40% of patients who have a bone marrow transplantation require a full year to regain previous fitness levels, and about 30% are unable to return to work during the first two years after the transplantation.[17] Other work has shown that, although cardiovascular impairment after a bone marrow transplantation is not progressive, it is persistent up to 16 years after treatment.[18 19] However, the results of this investigation show that adverse changes associated with a transplant are potentially reversible. The patients who participated in the mixed type, moderate intensity exercise programme were able to attain higher aerobic capacity and strength levels within three months than those recorded before the transplant. This shows that the inability to regain

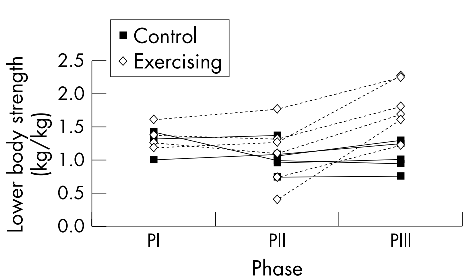


**Figure 2** Individual changes in lower body strength of the control and exercising subjects across the testing phases: before transplant (PI); after transplant (PII); after exercise programme (PIII).

### Take home message

Although preliminary, the findings indicate that participation in an exercise programme can bridge the gap between cancer treatment cessation and return to a ''normal'' lifestyle.

fitness and strength may be the consequence of lack of aerobic and/or strength exercise rather than adverse treatment effects.

The number of subjects in this investigation reflects the recruitment difficulties faced when dealing with patients with cancer. In addition, the small sample size adversely influences the generalisability of the findings. Nevertheless, although preliminary, the positive findings highlight the need for further research in this area that both replicates and extends previous studies. A unique aspect of this investigation was the inclusion of resistance training in the intervention as well as the assessment of $Vo_2$PEAK, by a maximal exercise test, and strength, by a 15RM test. However, it was not possible to determine the contribution of the strength or aerobic programme to the results. Future research needs to consider and clearly document the types of exercise programmes implemented and investigated, as well as the effects. Furthermore, it should consider testing the limits of current exercise prescription guidelines available for patients with cancer, before, during and after treatment.

In summary, PBST leads to clinically significant decrements in aerobic capacity and muscular strength. However, through participation in a three month, moderate intensity, mixed type exercise programme, patients can attain higher levels of aerobic capacity and muscular strength than before treatment. Furthermore, failure to participate in an exercise programme after treatment may exacerbate any losses in physical function resulting from the treatment.

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## COMMENTARY

This study shows that for PBST patients, muscular strength as well as aerobic capacity can be significantly increased in as little as three months. Where this study differs from similar previous investigations is inclusion of resistance training in the rehabilitation of the patients. Muscular strength (or lack of) can have a profound effect on quality of life. This study emphasises the importance of resistance training for those recovering from PBST and, indeed, serious illness in general.

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