ORIGINAL ARTICLES

Relationship between cardiopulmonary response to exercise and adiposity in survivors of childhood malignancy

J T Warner, W Bell, D K H Webb, J W Gregory

Abstract

Many long term sequelae result from previous treatment for malignancy in childhood. However, little information exists on cardiopulmonary response and energy expenditure during exercise and their possible associations with excess body fat. Measurements of body composition and exercise capacity both at low intensity and maximal aerobic capacity were made on 56 long term survivors of childhood malignancy (35 survivors of acute lymphoblastic leukaemia (ALL) and 21 survivors of other malignancies) and 32 siblings acting as controls. Female survivors of ALL had significantly greater mean (SD) body fat than survivors of other malignancies and siblings (32.5 (6.4)% v 24.3 (4.4)% and 26.3 (8.5)% respectively, $p < 0.005$). Energy expenditure at low intensity exercise was reduced in survivors of ALL, and negatively correlated with body fat after controlling for weight (partial r range -0.21 to -0.47 , $p < 0.05$). Stroke volume, measured indirectly, was reduced and heart rate raised in ALL survivors at submaximal exercise levels. Peak oxygen consumption was significantly reduced in girls and boys treated for ALL compared with siblings (30.5 v 41.3 ml/kg/min for girls, $p < 0.05$ and 39.9 v 47.6 ml/kg/min for boys, $p < 0.05$ respectively). Reduced exercise capacity may account in part for the excess adiposity observed in long term survivors of ALL.

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Keywords: exercise capacity; childhood malignancy; body composition

Many adverse late sequelae are recognised to result from previous treatment for childhood malignancy. The nature and extent of these effects are dependent upon the type and quantity of treatment received. Abnormalities of growth and puberty¹ and psychological development^{2,3} are recognised after cranial irradiation, and asymptomatic cardiomyopathy as a result of anthracycline toxicity has been reported.^{4,5} More recently several authors have reported obesity as a late effect in survivors of

acute lymphoblastic leukaemia (ALL).⁶⁻¹⁰ The mechanism underlying this problem is unknown but may involve an imbalance between energy intake and energy expenditure. In children, energy expenditure from exercise is a substantial proportion of the total daily energy expenditure. In one study of 7-15 year old children, in excess of 40% of the waking day was spent in physical activity, and around 40% of the total daily energy expenditure came from energy expended above basal metabolic rate.¹¹ Therefore impaired exercise capacity may predispose to the increased incidence of obesity.

Exercise testing as a means of identifying functional limits and of detecting cardiorespiratory disease is a non-invasive procedure and provides a valuable medical evaluation of the cardiopulmonary system in children from the preschool to adolescent age group.¹² Exercise testing places the body under physical stress and allows evaluation of functional limits, abnormalities of which may not be evident in the resting state. In long term survivors of childhood malignancy, adverse effects on exercise capacity may theoretically result from physical factors such as myocardial damage and dysfunction (as a consequence of chemotherapy) or from psychological effects on behaviour or endocrinopathy (as a result of irradiation of the brain). Previous research has shown that 43% of patients who had received anthracycline therapy for ALL have abnormalities on exercise testing which limit their stamina.⁵ Two further studies have demonstrated reduced maximal exercise capacity in girls treated for a variety of malignancies,¹³ and in both boys and girls treated for ALL.¹⁴ In both these studies the limitations on exercise were postulated to result from a combination of chemotherapy and cranial irradiation or from limited participation in sporting activity. Calzolari *et al*, using psychological testing, found that children previously treated for leukaemia perceive their exercise capacity as limited and therefore fail to participate in sporting activity.¹⁵

The aim of this study therefore was to measure the physiological responses to both low intensity and maximal exercise in survivors of childhood malignancy compared with a group of healthy sibling controls. We hypothesised that abnormalities in exercise capacity and

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Table 1 Diagnoses and treatment protocols for the survivors of ALL and other malignancies

Diagnosis	Protocol	No	Anthracycline dose (mg/m ²)	No receiving cranial irradiation dose:	
				24 Gy	≤18 Gy
ALL					
ALL	UKALL X	24	90–270	3	21
	UKALL VIII	8	0–90	—	8
	UKALL VI	2	0	2	—
NHL	UKCCSG NHL	1	330	—	1
Other malignancies					
AML	AML 10	4	300	—	—
	AML 9	2	450	—	—
	AML 8	1	450	—	—
NHL	CHOP	1	200	—	—
	NHL 904	1	270	—	—
Wilms' tumour	UKWM 1	3	—	—	—
	UKWM 2	3	—	—	—
Neuroblastoma	OPEC	2	—	—	—
Yolk sac	JEB/BEP	2	—	—	—
Rhabdomyosarcoma	MMT 89	1	—	—	—
Hodgkin's lymphoma	CLVPP	1	—	—	—

AML=acute myeloid leukaemia; NHL=non-Hodgkin's lymphoma.

energy expended during exercise may influence body composition, and in particular lead to excess adiposity.

Subjects and methods

Anthropometric measurements, dual energy *x* ray absorptiometry (DXA) scanning, lung function, and cardiopulmonary fitness testing were all performed on the same day for each child. Pubertal staging according to Tanner criteria was determined by a single trained observer in each child.¹⁶ Ethical approval was granted by the South Glamorgan ethics committee and parental consent obtained for each child.

SUBJECTS

Measurements were performed on a total of 88 children of whom 56 were long term survivors of childhood malignancy, at least 1.5 years from treatment and aged between 7 and 19 years. Thirty five children (14 boys) had received treatment for ALL including chemotherapy and prophylactic cranial irradiation and 21 children (11 boys) were a heterogeneous group of children who had received chemotherapy for a variety of tumours but had not received radiotherapy. One child in the ALL group had received treatment for non-Hodgkin's lymphoma but was included in this group since he had received cranial irradiation.

Children with ALL had been treated according to the Medical Research Council, United Kingdom ALL (UKALL) protocols VI, VIII¹⁷ or X¹⁸ (table 1). Essentially the treatment consisted of a period of induction to induce remission followed by cranial irradiation at a dose of 24 or 18 Gy. Intensification therapy was included in the later protocols with maintenance chemotherapy continuing for two or three years.

The diagnoses and treatment protocols for the children treated for other malignancies are detailed in table 1. The major differences in therapy between the two groups include cranial irradiation and the more prolonged continuous nature of chemotherapy in the ALL group compared with no radiotherapy and the shorter and more pulsed nature of chemotherapy for children treated for the other malignancies.

The cumulative dose of the individual chemotherapeutic agents was recorded from retrospective case note analysis. For intrathecal methotrexate and prednisolone, the number of injections and days on therapy respectively were recorded. All the children were in continuous first remission except one child in the ALL group, who had suffered a haematological relapse but received no further radiotherapy.

The remaining 32 (18 male) children were siblings of the survivors, who were invited to participate in the study to act as healthy controls. Where there was a choice of more than one sibling within the appropriate age range, the one closest in age to the index case was chosen.

METHODS

Anthropometry and body composition

Height and weight to the nearest 0.1 cm and 0.1 kg respectively were measured by a single trained observer using a wall mounted Harpenden stadiometer (Holtain Ltd, Crymych, Dyfed) and Avery beam balance (Avery Ltd, Birmingham). Body mass index (BMI) was calculated from the formula, weight (kg)/height²(m²). SD scores for the anthropometric data were calculated from the 1990 British reference data.^{19 20}

Fat free mass (FFM) and fat mass (FM) were measured by DXA using the Hologic QDR 1000/W (Hologic Inc, Waltham, MA, USA). Briefly, DXA involves the differential attenuation of collimated *x* rays, the mean energy of which is rapidly alternated by switching the *x* ray tube voltage between 70 and 140 kVp. The attenuation data are converted into FFM and FM by comparison with a step phantom of differing densities which is scanned simultaneously. The technique is non-invasive, requires minimal cooperation, and exposes the child to very small amounts of radiation (6 µSv, equivalent to one day's background radiation).^{21 22} For three children, one from each study group, body composition was not assessed by DXA, two because of lack of parental consent and one because of equipment failure. For these individuals body composition was assessed by skinfold measurements and the use of appropriate equations²³ and adjusted for the differences between skinfold and DXA measurements of body composition observed within our department.

Submaximal exercise testing

Submaximal cardiopulmonary exercise testing was performed in the afternoon, at least 90 minutes after lunch using a motorised treadmill (PK Morgan) and an incremental discontinuous protocol. Belt speed was commenced at 2 km/h and raised by 1 km/h until a heart rate (HR) approaching 190 beats per minute (beats/min) was reached. Each three minute exercise period was separated by a rest period of one minute. Children walked at speeds of 2 and 3 km/h and were encouraged to jog and run from speeds of 4 km/h and upwards. A warm up period was allowed between the walking and running period in order to accustom the children to running on the treadmill.

Table 2 Mean (SD) auxological and body composition measurements of the study patients

	Boys			Girls		
	ALL (n=14)	Other malignancies (n=11)	Control (n=18)	ALL (n=21)	Other malignancies (n=10)	Controls (n=14)
Age (years)	12.4 (3.4)	10.8 (4.4)	12.8 (2.7)	11.8 (3.7)	11.6 (3.4)	12.2 (2.8)
Height (cm)	150.4 (18.7)	142.7 (23.9)	155.2 (16.1)	142.2 (17.2)	144.9 (13.7)	147.5 (11.2)
Height SD score	-0.21 (0.62)	0.18 (0.74)	0.17 (0.88)	-0.48 (1.14)	0.06 (0.93)	-0.07 (0.90)
Weight (kg)	50.9 (29.1)	38.6 (15.3)	51.0 (16.3)	49.0 (20.6)	41.2 (12.8)	45.5 (23.9)
Weight SD score	0.59 (1.48)	0.37 (1.07)	0.77 (0.92)	1.01 (1.17)	0.34 (0.84)	0.26 (1.45)
BMI (kg/m ²)	21.3 (8.2)	18.3 (3.4)	20.7 (3.6)	23.0 (5.4)	19.2 (3.2)	20.0 (6.9)
BMI SD score	0.79 (1.39)	0.36 (1.47)	0.89 (1.04)	1.48 (1.02)*	0.43 (0.89)	0.30 (1.24)
Body fat (%)	23.1 (7.8)	20.7 (6.4)	21.0 (7.1)	32.5 (6.4)*	24.3 (4.4)	26.3 (8.5)

*ANOVA $p < 0.005$, Tukey's post hoc multiple comparison test $p < 0.05$ for the ALL compared with the other malignancies and control groups.

Expired gases were collected by means of a two way non-rebreathing valve (Salford) and monitored continuously using an on line breath by breath analysis system (Medgraphics, Salford). This measured oxygen consumption ($\dot{V}O_2$, litres/min) by means of a paramagnetic oxygen sensor, carbon dioxide production ($\dot{V}CO_2$, l/min) by infrared absorptiometry, ventilation ($\dot{V}_E$, l/min) and respiratory rate (f_R /min) by means of a flow sensor and pneumotachograph. Energy expenditure at each exercise level was calculated using the equation of Weir²⁴ (energy expenditure (kJ/min) = $(16.3 \times \dot{V}O_2) + (4.6 \times \dot{V}CO_2)$). Heart rate was recorded by telemetry using the Polar Sport Tester PE4000 (Polar Electro, Oy, Finland) recording at 15 second intervals. The third minute of each exercise period was used for analysis after steady state conditions had been achieved.

Maximal exercise capacity

Immediately after submaximal exercise testing in which the subject attained a heart rate approaching 190 beats/min, peak oxygen consumption (peak $\dot{V}O_2$) was determined by increasing the treadmill slope by increments of 2° every two minutes while maintaining the same belt speed. The test was terminated when the point of voluntary exhaustion was reached, when despite strong verbal encouragement the child was unable to continue. If a plateau in increments of ≤ 2 ml/kg/min of $\dot{V}O_2$ was not achieved during the final stages of the test, the highest $\dot{V}O_2$ achieved was accepted as peak $\dot{V}O_2$ in the presence of signs of extreme fatigue such as unsteady gait, hyperpnoea, facial flushing, a HR = 200 ($\pm 5\%$) beats/min and/or a respiratory exchange ratio (RER, $\dot{V}CO_2/\dot{V}O_2$) ≥ 1.00 . Peak $\dot{V}O_2$ was expressed per kilogram of total body weight or FFM, or adjusted for FFM using the technique of Toth *et al.*²⁵ Three children, two from the ALL group and one from the other malignancies group, failed to reach these criteria for peak $\dot{V}O_2$. For these children an estimated peak $\dot{V}O_2$ was calculated from the individual regression equation for $\dot{V}O_2$ on HR obtained from the submaximal response, using an age predicted maximal HR (maximal HR = 220 - age).

Respiratory function testing

Respiratory function at rest was determined using the Microlab 3000 spirometer (Micro Medical Ltd). Measurements of forced expired volume in one second (FEV₁), peak expiratory

flow rate (PEFR), and forced vital capacity (FVC) were made at body temperature and pressure saturated with water vapour (BTPS). Each child inhaled maximally, placed their mouth tightly around the mouthpiece, and exhaled as fast and for as long as possible. Measurements were repeated until there were no further positive increments and the best reading was recorded.

STATISTICAL ANALYSES

Mean (SD) values are given unless otherwise stated. Comparison of means between the three groups was made by one way analysis of variance (ANOVA). Where the F ratio was significant ($p < 0.05$), Tukey's post hoc multiple comparison test was applied to compare individual groups with each other. Pearson correlation and backward multiple regression were used to examine the inter-relationships between variables and their associations with therapy. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) for windows, version 6.0.

Results

Patient details including auxology and body composition for each study group are shown in table 2. There were no significant differences in age, height, or weight between groups. ALL girls had increased BMI SD scores and body fat when compared with both other malignancies and controls ($p < 0.05$). There was no difference in the mean age at diagnosis (3.2 (1.4) and 3.9 (3.2) years), or mean length of time off treatment (6.6 (3.3) and 6.7 (2.8) years), between those treated for ALL and those treated for other malignancies respectively. There were no significant differences in the puberty ratings between the three groups.

CARDIOPULMONARY RESPONSE TO SUBMAXIMAL EXERCISE

The mean HR, $\dot{V}O_2$ /kg total body weight (ml/kg/min), and energy expenditure for the different subject groups at each belt speed (2–8 km/h) are summarised in table 3. HR was significantly raised in survivors of ALL compared with controls at all speeds ($p < 0.05$). $\dot{V}O_2$ /kg and energy expenditure were significantly reduced in the ALL group compared with the controls at 4 and 5 km/h. After combining all groups $\dot{V}O_2$ and energy expenditure were correlated with body fat after controlling for body weight at each speed (partial r ranging

Table 3 Mean (SD) cardiorespiratory responses to submaximal exercise

Speed (km/h)	Group	Heart rate (beats/min)	$\dot{V}O_2$ /kg (ml/kg/min)	Energy expenditure (kJ/kg/h)
2	ALL (n=33)	119 (14)*	9.3 (1.8)	11.3 (2.2)
	OM (n=20)	112 (12)	11.0 (4.1)	13.3 (4.8)
	C (n=32)	106 (15)	10.7 (3.4)	12.9 (4.6)
3	ALL (n=34)	125 (17)*	10.7 (2.3)	13.1 (2.7)
	OM (n=21)	116 (10)	12.5 (3.6)	15.2 (4.3)
	C (n=32)	109 (14)	11.8 (4.3)	14.3 (5.1)
4	ALL (n=33)	153 (18)*	17.7 (4.2)*	22.2 (5.3)*
	OM (n=17)	142 (8)	20.3 (5.6)	24.9 (6.7)
	C (n=31)	138 (19)	21.1 (5.3)	26.0 (6.3)
5	ALL (n=35)	165 (17)*	20.6 (4.3)*	25.9 (5.5)*
	OM (n=21)	155 (11)	22.4 (5.6)	27.7 (6.7)
	C (n=32)	150 (19)	23.7 (5.2)	29.4 (6.2)
6	ALL (n=34)	178 (14)**	24.3 (4.0)	30.7 (5.0)
	OM (n=21)	167 (11)	25.9 (5.1)	32.1 (6.2)
	C (n=32)	162 (19)	26.4 (5.3)	33.0 (6.5)
7	ALL (n=28)	183 (13)*	27.3 (3.7)	34.6 (4.6)
	OM (n=20)	179 (12)	28.6 (5.0)	35.8 (5.9)
	C (n=32)	172 (19)	29.4 (4.8)	36.9 (5.7)
8	ALL (n=13)	188 (13)*	30.6 (4.9)	38.9 (6.2)
	OM (n=17)	186 (10)*	32.4 (5.5)	40.6 (6.7)
	C (n=24)	175 (16)	34.0 (4.3)	42.6 (5.1)

OM=other malignancies; C=controls.

* $p < 0.05$ compared with controls; ** $p < 0.05$ compared with other malignancies and controls.

from -0.23 to -0.46 for $\dot{V}O_2$ and from -0.21 to -0.47 for energy expenditure; $p < 0.05$ at all speeds). At speeds of 2–6 km/h both asparaginase and prednisolone were associated with a significant reduction in energy expenditure ($p < 0.005$ and $p < 0.05$ respectively). Intrathecal methotrexate and daunorubicin were associated with a significant reduction in energy expenditure at 7 and 8 km/h ($p < 0.005$ and $p < 0.05$ respectively).

A greater proportion of children from the other malignancies and control groups achieved speeds of 9 km/h (20% of the ALL group, 38% of the other malignancies group, and 56% of the control group) and 10 km/h (6% of the ALL group, 14% of the other malignancies group, and 38% of the control group) before reaching the criteria for progression on to a maximal exercise test.

During submaximal exercise testing, $\dot{V}O_2$ and HR for each individual were significantly correlated (mean $r = 0.98$ (0.04), $p < 0.0001$ for the ALL group, 0.98 (0.02), $p < 0.0001$ for the other malignancies and 0.99 (0.01), $p < 0.0001$ for the controls) with no difference between groups. The mean slope of the individually derived regression line for $\dot{V}O_2$ on HR (fig 1) after correction for body weight (ml/kg/beat) was significantly reduced in the ALL group compared with controls (0.26 (0.06) and 0.30 (0.07); $p < 0.05$ respectively) but not for other malignancies (0.28 (0.07)). There were no dif-

Figure 1 Mean slope of regression lines $\dot{V}O_2$ /kg against heart rate. ALL, mean (SD) slope = 0.26 (0.06) ml/kg/beat, compared with controls; other malignancies, mean (SD) slope = 0.28 (0.07) ml/kg/beat; and controls, mean (SD) slope = 0.30 (0.07) ml/kg/beat.

ferences in the intercepts (-22.2 (8.7), -20.2 (8.9), and -21.3 (8.9) for the ALL, other malignancies, and controls respectively, $p = 0.72$). The partial correlation for the slope of the individual regression lines and body fat after controlling for body weight for the groups combined was significant, $r = -0.58$, $p < 0.001$. Intrathecal methotrexate was the only significant independent variable which led to a reduction in the slope of $\dot{V}O_2$ on HR after allowing for body weight ($p < 0.05$).

CARDIOPULMONARY RESPONSE TO MAXIMAL EXERCISE

There were no differences in the HR, RER, $\dot{V}E$, or respiratory rate between groups for either sex at peak $\dot{V}O_2$ (table 4). The ventilatory equivalent for oxygen ($\dot{V}E/\dot{V}O_2$), which provides a measure of cardiorespiratory efficiency, was significantly higher—that is, less efficient—for boys in the other malignancies group than for controls. After correction, for either total body weight or FFM, both boys and girls who had survived ALL had significantly reduced peak $\dot{V}O_2$ compared with controls. Boys from the other malignancies group also had significantly reduced peak $\dot{V}O_2$ compared with controls. Peak $\dot{V}O_2$ was significantly correlated with percentage fat after controlling for either body weight (partial $r = -0.71$, $p < 0.001$) or FFM (partial $r = -0.41$, $p < 0.001$) for all groups combined (fig 2). Prednisolone ($p < 0.0001$), daunorubicin ($p = 0.0001$), cyclophosphamide ($p = 0.0004$), epirubicin ($p < 0.05$), mitozantrone ($p = 0.0009$), and bleomycin ($p < 0.005$) were all significantly associated with a reduction in peak $\dot{V}O_2$.

Table 4 Mean (SD) cardiorespiratory response to maximal exercise capacity

	Male			Female		
	ALL	Other malignancies	Controls	ALL	Other malignancies	Controls
Heart rate (beats/min)	203 (7)	201 (10)	201 (6)	203 (9)	209 (4)	205 (11)
RER	1.16 (0.11)	1.09 (0.08)	1.16 (0.14)	1.14 (0.11)	1.14 (0.11)	1.15 (0.08)
$\dot{V}E$ (litres/min)	79.8 (38.0)	64.3 (24.9)	86.5 (26.9)	65.5 (22.7)	72.4 (24.2)	69.6 (20.1)
$\dot{V}E/\dot{V}O_2$	41.0 (5.2)	42.7 (7.0)*	36.7 (5.1)	44.7 (6.9)	44.8 (6.1)	40.0 (5.4)
RR (f_b /min)	61 (15)	67 (14)	60 (12)	66 (11)	68 (13)	58 (15)
$\dot{V}O_2$ (l)	1.99 (1.01)	1.54 (0.64)*	2.40 (0.84)	1.49 (0.66)	1.63 (0.56)	1.76 (0.55)
$\dot{V}O_2$ /kg total body weight (ml/kg/min)	39.9 (8.5)*	40.4 (5.7)	47.6 (8.4)	30.5 (6.1)**	39.5 (8.0)	41.3 (9.2)
$\dot{V}O_2$ /kg FFM (ml/kg/min)	53.1 (9.1)*	52.2 (6.1)*	61.5 (7.9)	46.4 (9.0)*	53.3 (10.3)	57.3 (9.7)
Adjusted $\dot{V}O_2$ (l)	1.79 (0.36)*	1.75 (0.25)*	2.09 (0.33)	1.60 (0.23)*	1.81 (0.27)	1.91 (0.28)

*Significantly different from controls ($p < 0.05$); **significantly different from other malignancies and controls ($p < 0.05$).

Figure 2 Correlation between peak $\dot{V}O_2$ /kg and percentage body fat.

PULMONARY FUNCTION TESTING

Using regression modelling, FEV₁, PEFR, and FVC were correlated with height, age, and gender. The results are therefore expressed as a percentage of a predicted value derived from the model based on the combined data for the three groups. There were no significant differences in the mean FEV₁ (101 (20)%, 103 (17)%, and 99 (12)%), PEFR (102 (19)%, 103 (17)%, and 98 (13)%), or FVC (102 (25)%, 104 (19)%, and 100 (14)%) between the ALL, other malignancies, and control groups respectively.

Discussion

The importance of the late effects of therapy for childhood malignancy increases as the number of long term survivors increases. This report describes a reduction in both submaximal and maximal response to exercise, which is associated with increasing levels of adiposity. This finding is particularly significant as the selection of healthy siblings to act as controls in this study has the advantage of controlling for familial factors which may also influence exercise capacity and body composition.

Obesity after treatment for ALL is now recognised, although the mechanism is as yet undefined. Obesity is a poorly defined term for excess body fat or adiposity and is associated with increased morbidity and mortality. To date, obesity in survivors of ALL has been reported using indirect measures of body fat such as BMI.^{7-9,10} Odame *et al* have demonstrated that there is an increased prevalence of obesity in female survivors of ALL with 57% having a BMI SD score greater than +2 at four year follow up compared with 21% of boys.⁷ In this study a more direct measure of body composition was made using DXA. This has been shown to have a precision of approximately 2%²⁶ and an accuracy of approximately 4.5%²⁷ for the assessment of total body composition in paediatric subjects. Girls who had survived ALL were significantly fatter than both survivors of other malignancies and healthy controls. Boys who survived ALL were not significantly fatter than controls (as assessed by DXA, table 2) although the latter were significantly overweight compared with the British reference population^{19,20} as demonstrated by a mean (95% confidence interval) weight SD score of 0.77 (0.31 to 1.22) and BMI SD score of 0.89 (0.38 to 1.41). Hence, our control population of boys are likely to be fatter than the general population.

Excess body fat is the stored energy that accumulates as a consequence of an imbalance between energy intake and expenditure. This may occur when energy intake is excessive or energy expenditure impaired. No attempt was made to measure energy intake in this study as this is inaccurate, particularly in obese individuals.²⁸ However, the use of siblings as a control group may partially control for genetic differences in energy intake. Reductions in energy expenditure for ALL survivors were found at all submaximal work loads and were statistically significant at 4 and 5 km/h. This represents a fairly low level of exercise intensity such as a fast walk. Furthermore, energy expenditure was significantly negatively correlated with body fat after controlling for body weight at all the submaximal exercise levels. Taken together, these findings suggest that increased adiposity is associated with less energy expenditure during exercise.

Peak $\dot{V}O_2$ was significantly reduced in both male and female survivors of ALL compared with controls either expressed per kg body weight or FFM, or adjusted for FFM. The control values for peak $\dot{V}O_2$ in the present study were similar to those for other healthy randomly selected British children.²⁹ The mean peak $\dot{V}O_2$ for control girls and boys in this study was 41.3 ml/kg/min and 47.6 ml/kg/min respectively compared with 37–43 ml/kg/min and 48–50 ml/kg/min for British girls and boys respectively, aged 11 to 16 years.²⁹

Two previous studies have found a reduction in peak $\dot{V}O_2$ in both a heterogeneous group of childhood malignancy survivors,¹³ and in children treated for ALL.¹⁴ In both these studies children were exercised on bicycle ergometers and no attempt was made to correlate exercise parameters with body composition.

Limitations in aerobic exercise capacity may be accounted for by abnormalities in the oxygen transport chain, which conveys oxygen from inspired air to the mitochondria in the active muscle. The stages in this chain comprise the ventilation and diffusion of oxygen at the lungs, circulation of oxyhaemoglobin, diffusion of oxygen across the capillary muscle membrane and within the muscle, and incorporation of oxygen into the mitochondria. A similar transport chain conveys carbon dioxide in the opposite direction.³⁰

The results from this study did not show any differences in pulmonary function at rest, in contrast with other studies.¹⁴ This would suggest, in our study population, that any inadequacy in the oxygen transport chain does not occur at the level of the lung. The adequate transport and circulation of oxyhaemoglobin requires normal cardiac output and function. Children who have received anthracycline therapy have been shown to have reduced shortening fraction (SF) on resting echocardiography,^{4,5} and an inappropriate increase in SF in response to stress³¹ and exercise.³² Cardiac output is a function of both stroke volume and heart rate. Direct assessment of cardiac output during exercise is difficult and complex. Peak $\dot{V}O_2$ is an indirect measure of maximal cardiac output.³³ The

reduction in peak $\dot{V}O_2$ in children treated for ALL would imply a reduced maximal cardiac output. Furthermore, $\dot{V}O_2/HR$ (the oxygen pulse; a measure of the $\dot{V}O_2$ per heart beat, and an indirect measure of stroke volume)³⁴ was significantly reduced in survivors of ALL during submaximal exercise, suggesting that the reduction in cardiac output results from a reduced stroke volume. Reduction in stroke volume, possibly as a result of anthracycline toxicity, could account for the raised HR rate seen in ALL survivors in response to exercise in order to maintain adequate cardiac output.

Identification of individual factors used in the treatment of childhood malignancy that may account for the reductions in exercise capacity is difficult because of interactions between these variables and the fact that most treatment is rarely administered in isolation. Multiple regression analysis has demonstrated that the cumulative dose of asparaginase and the number of days on prednisolone are both associated with a reduction in energy expenditure at lower levels of exercise, whereas at higher exercise levels both intrathecal methotrexate and daunorubicin had significant contributory effects. At peak $\dot{V}O_2$, prednisolone and daunorubicin continued to have a negative influence with the addition of cyclophosphamide, epirubicin, mitozantrone, and bleomycin, although few children received these drugs. Both cyclophosphamide³⁵ and bleomycin³⁶ have been previously shown to cause reduction in pulmonary function as a result of fibrosis, while epirubicin and mitozantrone are both anthracyclines and have similar cardiotoxic effects to daunorubicin. The apparent inconsistency of some of the variables that impair exercise capacity needs further evaluation.

In conclusion, children treated for ALL have increased body fat and reduced exercise capacity compared with children treated for other malignancies and healthy controls, the effect being more pronounced in girls. The two effects are significantly correlated although further research is required to evaluate whether obesity is caused by impaired exercise capacity as a consequence of chemotherapy induced cardiorespiratory impairment.

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