Association of body mass with pulmonary function in the Childhood Asthma Management Program (CAMP)

K G Tantisira, A A Litonjua, S T Weiss, A L Fuhlbrigge, for the Childhood Asthma Management Program Research Group

Background: While increases in body mass index (BMI) have been associated with the incidence and prevalence of asthma, the mechanisms behind this association are unclear. We hypothesised that BMI would be independently associated with measures of asthma severity in a population of children with mild to moderate asthma enrolled in the Childhood Asthma Management Program (CAMP). A multivariable baseline cross sectional analysis of BMI with our outcomes of interest was performed.

Methods: We hypothesised that BMI would be independently associated with measures of asthma severity in a population of children with mild to moderate asthma enrolled in the Childhood Asthma Management Program (CAMP). A multivariable baseline cross sectional analysis of BMI with our outcomes of interest was performed.

Results: BMI was generally not associated with symptoms, nor was it associated with atopy. While BMI was positively associated with the methacholine concentration that causes a 20% fall in forced expiratory volume in 1 second (PC20FEV1), this association did not persist after adjustment for FEV1. Increasing BMI was associated with increasing FEV1 (β = 0.006 l, 95% CI (0.001 to 0.01)) and forced vital capacity (FVC) (β = 0.012 l, 95% CI (0.007 to 0.017)). However, decrements in the FEV1/FVC ratio were noted with increasing BMI (β = −0.242, 95% CI (−0.118 to −0.366)). Thus, an increase in BMI of 5 units was associated with a decrease in FEV1/FVC of over 1%.

Conclusions: Although the association of FEV1 and FVC with BMI did not support our initial hypothesis, the decrease noted in the FEV1/FVC ratio has potential relevance in the relationship between BMI and asthma severity.

Methods

Study population

The CAMP study is a randomised clinical trial comprising 1041 children with asthma. The trial design and methodology have been previously published. Inclusion criteria included: age 5–12, asthma for at least 6 months, mild to moderate asthma severity, and methacholine sensitivity with a provocative concentration (PC20) of no more than 12.5 mg/ml. Data on all subjects were collected at baseline and at least 28 days on salbutamol (albuterol) on an as needed basis.

Pulmonary function testing

Spirometric and methacholine testing were performed on a Collins Stead-Wells dry seal Survey III spirometer. At least three acceptable manoeuvres meeting American Thoracic Society (ATS) standards were required, with at least two reproducible forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) manoeuvres within 5% of best required for each test. Airway responsiveness was performed in a standardised fashion, at least 4 hours after use of short acting bronchodilators and 24 hours after use of long acting bronchodilators.
BMI and pulmonary function in CAMP

Effect of asthmatic status and environmental factors on childhood asthma severity

Measures
BMI was calculated from measured values of height and weight by the equation BMI = weight (kg)/height² (m²). Pulmonary function outcomes included pre- and post-bronchodilator FEV₁, FVC, FEV₁/FVC ratio, and peak flow, analysed as quantitative traits. Asthma symptom outcomes were dichotomised and considered relevant as follows: school absences (>5, since fewer than this might be expected from non-asthma factors), emergency department visits and hospital admissions (any), doctor visits (>6, since reasonable visits may be expected every other month for a healthy asthmatic), days on oral steroids (>7, since up to a week’s worth may be dispensed for mild asthma), physical education restriction (any reported), and cough/wheeze at rest or with exercise (>once/month over 6 months). Outcomes were based upon occurrences over past year, except steroid days (past 6 months) and cough/wheeze (monthly average over the past 6 months). Intermediate phenotypes of asthma and atopy included FEV₁ change with bronchodilator and log transformations of PC₂₀, serum IgE, and eosinophil count, evaluated in a quantitative fashion.

BMI was the primary predictor of interest. Potential confounders included clinic attended, age, race, sex, caregiver education, family income, familial asthma history, presence of environmental tobacco smoke, and participating Tanner stage. Tanner stage was defined by male genital and female breast development. BMI was modelled as a linear term, while the other potential confounders were either dichotomised or categorised into groups. Additional analyses using other surrogates of total body fat (waist circumference and waist to hip ratio) as predictors were also performed. Finally, analyses of the upper extremes of BMI were performed using age, ethnic, and sex specific BMI percentile cut offs of 85% for overweight and 95% for obese.

Statistical analysis
Univariate and multivariable regression analyses incorporating significant potential confounders were performed. Modelling using linear regression was performed for all of the pulmonary function and intermediate phenotype outcomes. Symptom outcomes were modelled using logistic regression techniques. Height adjustment was performed for models evaluating the FEV₁, FVC, and peak flows. Collinearity diagnostics were performed. Potential for effect modification of sex with BMI was evaluated by use of stratified analyses and interaction terms. The assumption of linearity within the BMI predictor was assessed by dividing BMI into quintiles and looking for threshold and non-linear effects. To further evaluate the potential for the age dependency of BMI, Box-Cox transformations of age on BMI were used to provide age adjusted estimates of the relationships. The results of these subsequent analyses paralleled our primary results (data not shown).

Relationship between BMI and respiratory symptoms
The relationship between BMI and reported measures of asthma severity are shown in table 2. In the multivariable analysis only cough/wheeze with exercise was related to BMI (OR 1.05, 95% CI 1.01 to 1.10 for more than one coughing/wheezing episode with exercise per month over the past 6 months).

RESULTS
Table 1 presents baseline descriptive data on the BMI of 1039 asthmatic children participating in the CAMP study. 123 of the children (11.8%) met the criteria for obesity and a further 181 (17.4%) for overweight. Overall, asthma was mild in these children, with a mean post-bronchodilator FEV₁ of 102% predicted. As expected, BMI was significantly associated with measures of growth and development such as age and Tanner stage. Other significant potential confounders associated with BMI in the univariate analysis included ethnicity, clinical centre, and presence of any parental smoking. Sex, parental income, caregiver education, and history of parental asthma were not significantly associated with BMI. Since age is closely correlated with BMI in children, we reassessed all analyses using a Box-Cox transformation of age on BMI to provide age adjusted estimates of the relationships. The results of these subsequent analyses paralleled our primary results (data not shown).

Table 1 Relation of BMI to selected confounders* of asthma severity in the Childhood Asthma Management Program (CAMP) population

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Median BMI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1039</td>
<td>17.09</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–6</td>
<td>263</td>
<td>15.96</td>
<td></td>
</tr>
<tr>
<td>7–8</td>
<td>319</td>
<td>16.56</td>
<td></td>
</tr>
<tr>
<td>9–10</td>
<td>272</td>
<td>17.93</td>
<td></td>
</tr>
<tr>
<td>11–12</td>
<td>185</td>
<td>19.60</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>White</td>
<td>709</td>
<td>16.96</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>138</td>
<td>17.63</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>98</td>
<td>18.77</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>94</td>
<td>16.55</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>621</td>
<td>17.04</td>
<td>0.52</td>
</tr>
<tr>
<td>Girls</td>
<td>418</td>
<td>17.19</td>
<td></td>
</tr>
<tr>
<td>Tanner stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>749</td>
<td>16.61</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>202</td>
<td>18.10</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>56</td>
<td>20.57</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>24</td>
<td>21.11</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>3</td>
<td>24.69</td>
<td></td>
</tr>
<tr>
<td>Parental smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neither</td>
<td>746</td>
<td>16.97</td>
<td>0.04</td>
</tr>
<tr>
<td>Mother only</td>
<td>89</td>
<td>17.30</td>
<td></td>
</tr>
<tr>
<td>Father only</td>
<td>96</td>
<td>17.26</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>100</td>
<td>17.32</td>
<td></td>
</tr>
</tbody>
</table>

*Not shown are CAMP centre (p = 0.0001), history of parental asthma, parental educational level, and parental income (all with p values <0.20).
†Baseline height not recorded for two children.
‡For within group comparisons of ranked BMI (Kruskal-Wallis test).

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Relationship between BMI and pulmonary function

Table 4 shows the post-bronchodilator multivariable relationship between BMI and pulmonary function outcomes. BMI was positively associated with spirometric measurements including FEV₁, FVC, and peak flow. Pre-bronchodilator trends were similar (data not shown). The strongest relationships were noted for FVC. Specifically, an increase in BMI of 5 units (as would occur between normal weight and obesity) was associated with a gain in FVC of slightly more than 60 ml. Increases in BMI were thus associated with increased spirometric pulmonary function. In contrast, significant decrements in the FEV₁/FVC ratio were noted in association with increasing BMI (p for trend for boys = 0.002; fig 1).

The strength of the BMI effects on pulmonary function seemed to vary when stratified by sex. Although the direction of the effect was the same for both sexes, the association with BMI was significant only in girls in relation to the FEV₁, change in FEV₁ with bronchodilator, and log PC_{20} (table 4). The relationship between BMI and both pre- and post-bronchodilator FVC was also stronger in girls than in boys. However, the FEV₁/FVC ratio decrements with increasing BMI were more substantial in boys. Univariate analysis of the relationship between sex and the potential confounders of pulmonary function was performed. There were no significant differences between boys and girls with regard to height, ethnicity, age, parental smoking, or clinic. The addition of interaction terms to models evaluating sex and BMI as predictors of pulmonary function outcomes did not show a significant interaction between sex and BMI in any of the multivariable models tested (data not shown).

BMI quintile analysis

Age adjusted BMI quintile analysis was performed (fig 2). For both boys and girls spirometric measures (FEV₁, FVC, and peak flow) increased in a linear fashion as the BMI quintile increased. No significant within group differences were noted for either bronchodilator response or PC_{20}. Overall, no overt threshold effects were noted. Modelling BMI as a linear predictor of pulmonary function therefore seems reasonable. Moreover, while the results of obesity specific analyses paralleled our other results, the lack of a threshold suggests that the extremes of weight did not have a unique association with our outcomes. No results of obesity specific analyses are therefore presented.

DISCUSSION

The overall magnitude and direction of the associations seen do not support the hypothesis that increasing BMI significantly contributes to overall asthma severity in a large cross sectional population of children with mild to moderate asthma. In general, increasing body mass was correlated with increasing spirometric values and was not associated with asthma symptoms. The notable exception to this was the association of increasing BMI with decrements in the FEV₁/FVC ratio. The relationship between BMI and the intermediate phenotypes of asthma evaluated, however, were less clear. While measures of atopy were not correlated with BMI, we did find a significant relationship between BMI and two common intermediate phenotypes of asthma—change in FEV₁ with bronchodilator and degree of methacholine sensitivity. However, no significant relationship between BMI and PC_{20} remained after adjustment for baseline FEV₁, suggesting that this effect may have been driven by underlying airways size. This is further supported by the lack of association between these measures of airway responsiveness and waist circumference and waist to hip ratio.

Previous population based studies of children have reported increases in spirometric measurements with increases in body weight and BMI. In calculating reference values for FEV₁ and FVC, however, early studies concluded that adjustment for weight was unnecessary because the

Table 3: Relationship between measures of body fat and markers of asthma and atopy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>BMI (kg/m²)</th>
<th>p value</th>
<th>Waist (cm)</th>
<th>p value</th>
<th>Waist to hip ratio</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log eosinophil</td>
<td>-0.017 (-0.036 to 0.001)</td>
<td>0.06</td>
<td>-0.011 (-0.017 to 0.005)</td>
<td>0.0009</td>
<td>-0.051 (-1.470 to 0.456)</td>
<td>0.30</td>
</tr>
<tr>
<td>Log IgE</td>
<td>-0.028 (-0.059 to 0.003)</td>
<td>0.07</td>
<td>-0.005 (-0.016 to 0.061)</td>
<td>0.38</td>
<td>-0.029 (-1.193 to 1.159)</td>
<td>0.73</td>
</tr>
<tr>
<td>BD change</td>
<td>-0.003 (-0.010 to -0.0004)</td>
<td>0.02</td>
<td>-0.0007 (-0.014 to 0)</td>
<td>0.06</td>
<td>0.047 (-0.064 to 0.158)</td>
<td>0.41</td>
</tr>
<tr>
<td>Log PC_{20}</td>
<td>0.034 (0.012 to 0.057)</td>
<td>0.003</td>
<td>0.0007 (0.002 to 0.015)</td>
<td>0.11</td>
<td>-0.037 (-0.933 to 0.859)</td>
<td>0.95</td>
</tr>
<tr>
<td>Log PC_{20} (FEV₁ adjusted)</td>
<td>0.006 (-0.017 to 0.028)</td>
<td>0.64</td>
<td>-0.005 (-0.014 to 0.003)</td>
<td>0.21</td>
<td>0.0004 (-1.195 to 1.195)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

*Adjusted for age, race, sex, clinic, Tanner stage, and parental smoking.
†Natural log
‡Bronchodilator (BD) change defined as change in FEV₁ with bronchodilator divided by initial FEV₁.
BMI and pulmonary function in CAMP 1039

Trend = 0.002). FVC ratio. This effect was more pronounced in boys (p for both sexes increases in BMI are associated with decrements in the FEV1/FVC ratio. In Figure 1 Median post-bronchodilator FEV1/FVC ratio across age adjusted BMI quintiles after Box-Cox transformation of age on BMI. In both sexes increases in BMI are associated with decrements in the FEV1/FVC ratio. This effect was more pronounced in boys (p for trend = 0.002).

Table 4  Relationship between BMI and spirometric parameters and airway responsiveness*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Overall</th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$ (95% CI)</td>
<td>p value</td>
<td>$\beta$ (95% CI)</td>
</tr>
<tr>
<td>Post-BD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 (l)</td>
<td>0.006 (0.001 to 0.010)</td>
<td>0.01</td>
<td>0.003 (-0.003 to 0.009)</td>
</tr>
<tr>
<td>FVC (l)</td>
<td>0.012 (0.007 to 0.017)</td>
<td>0.0001</td>
<td>0.009 (0.002 to 0.016)</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>-0.242 (-0.118 to -0.356)</td>
<td>0.0001</td>
<td>-0.297 (-0.127 to -0.467)</td>
</tr>
<tr>
<td>Peak flow (l/min)</td>
<td>0.230 (-0.674 to 1.14)</td>
<td>0.61</td>
<td>0.149 (-1.127 to 1.425)</td>
</tr>
<tr>
<td>BD change</td>
<td>0.003 (-0.001 to 0.004)</td>
<td>0.02</td>
<td>-0.001 (-0.004 to 0.002)</td>
</tr>
<tr>
<td>Log PC20</td>
<td>0.034 (0.012 to 0.057)</td>
<td>0.003</td>
<td>0.021 (-0.008 to 0.054)</td>
</tr>
</tbody>
</table>

*Adjusted for age, race, sex, clinic, Tanner stage, and parental smoking.
†Bronchodilator (BD) change defined as change in FEV1 with bronchodilator divided by initial FEV1.

Additional explained variance was small after adjustment for height, sex, and race. Lazarus et al reported a much larger positive association of weight with height adjusted FEV1 and FVC in a cross sectional study of normal school-children. However, they subsequently found decreases in height and weight adjusted spirometric measures with increasing skinfold thicknesses, concluding that an increased BMI in children may not adequately distinguish increased lean tissue mass from increased fat mass. Fung et al also noted increased spirometric flows correlating to increased BMI in a population of Chinese schoolchildren. Nevertheless, overweight children (>90% predicted) had decrements in these pulmonary measures in association with increasing BMI, supporting other studies which noted a classic restrictive ventilatory defect in obese children. In contrast, only one of our subjects had an age adjusted BMI in excess of 150% of predicted. Any expected decline in spirometric parameters due to large increases in fat mass would not therefore have been powered to be detected in our study. Overall, our data suggest that the small but significant increases in FEV1 and FVC seen in normal children in association with increases in BMI are also present in children with mild to moderate asthma (table 4, fig 2).

Although airway responsiveness (AHR) has recently been correlated with asthma severity in children, little is known about the relationship between BMI and intermediate phenotypes of asthma, including measures of atopy, AHR, and bronchodilator response. In a cross sectional population based study of teenagers in Taiwan, Huang et al noted a decreased prevalence of AHR in the lowest quintile of BMI in teenage girls and increased atopy in girls with the highest BMI. These findings were not seen in boys. While other studies have not noted any independent effect of BMI on methacholine sensitivity, the consistent association of obesity with exercise induced bronchospasm in children has suggested a relationship between increased AHR and BMI. Although our cohort of asthmatic children differed from the above, the initial finding of a positive association between PC20 and BMI was still somewhat puzzling. However, this effect was not found when the regression was adjusted for airway size, nor was it seen with other measures of body fat (table 3). Similarly, none of the other intermediate phenotypes were consistently associated with any of the proxies for body fat mass.

The exact reason why the relationship between BMI and pulmonary function would be stronger in one sex in our study population (table 4) is unknown. However, this prepubertal relationship can be most readily explained by differential airways size. Throughout childhood girls have larger airways in relation to lung size than boys, a phenomenon that begins to reverse in adolescence. While airway size can help to explain the differential spirometric values noted in our study, smaller airway calibre has also been used to explain the increased AHR in adult women. Similarly, the findings of decreased AHR and bronchodilator responsiveness in the girls relative to the boys in our study may be simply related to differential airway calibre.

We cannot exclude the possibility that differences in sample size between the boys and girls in our study could account for our finding that decrements in FEV1/FVC ratio noted with increasing BMI were more prominent in the CAMP boys (fig 1); however, differences in airway size between boys and girls may also play a role. The FEV1/FVC ratio is commonly used as a measure of the degree of airflow

Figure 1  Relationship between median post-bronchodilator FEV1 and FVC and age adjusted BMI quintiles. Spirometric measures increased linearly across the BMI quintiles in both boys and girls.

Figure 2  Relationship between median post-bronchodilator FEV1 and FVC ratio across age adjusted BMI quintiles after Box-Cox transformation of age on BMI. In both sexes increases in BMI are associated with decrements in the FEV1/FVC ratio. This effect was more pronounced in boys (p for trend = 0.002).
obstruction and severity of asthma. While ratio measures are described in few population based studies of paediatric lung function, in young children overall measures of airflow to FVC are decreased in boys compared with girls\(^5\)\(^6\) and in asthmatics compared with non-asthmatics.\(^7\) Increasing BMI correlated with decreasing FEV\(_1\)/FVC ratio in one other population based study of paediatric spirometry.\(^8\) This association was also greater in boys. While the presence of asthma in that study did not appear to affect the relationship between BMI and FEV\(_1\)/FVC ratio, only 7% of these children reported a diagnosis of asthma, probably resulting in insufficient power for detection. Whether these differences help to explain the increased incidence of asthmatic symptoms in prepubertal boys requires further study.

While we found that many of the effects noted were stronger in one sex, analyses failed to note a significant interaction between sex and BMI. It is likely, given the modest effects noted as well as the parallel direction of the effects within each sex, that a larger sample size or sicker patient population could have resulted in significant interaction terms. The overall direction and magnitude of the relationships between BMI and the outcomes of interest in this study do not support a significant detrimental association between increasing BMI and asthma severity in children. The potential reasons for this departure from our hypothesised relationships are several. Firstly, our source population, a cohort of children with pre-existing asthma, differs from the general population based cohorts used in the incidence\(^9\)\(^10\) and prevalence\(^9\)\(^11\) studies associating asthma and BMI. Moreover, comparisons of within group phenotypes are not comparable to studies evaluating differences between asthmatic and normal subjects. The strict entry criteria for this clinical trial\(^11\) may also not have provided enough variability in the outcomes of interest to detect differences in our predictor of interest. Previous studies of asthma symptoms have used primarily inner city subjects,\(^12\)\(^13\) a population which contrasts with that of the CAMP children.\(^3\)

Additionally, many of these previous studies focused on obesity and asthma. Only one of the children enrolled in CAMP had a baseline BMI in excess of 150% of predicted for age. Thus, any potential associations due to extremes of BMI would not have been adequately powered within our cohort. In this study, BMI was modelled as our primary surrogate of total body fat. The usefulness of this measure in children has been criticised.\(^14\) The best epidemiological measure of body fat in children and adolescents remains controversial,\(^35\) but may be one using skinfold measures which were not assessed in CAMP. Hence, BMI used as a primary predictor may not have adequately distinguished between large children and obese ones. Finally, in a previous study of incident asthma in children, asthma risk was inversely related to Tanner stage in boys (RR 0.3 for stage V compared with stage I) but positively related to Tanner stage in girls (RR 1.6 for stage V compared with stage I).\(^1\) If puberty is highly correlated with any of our outcomes of interest, our study may not have been powered to detect these associations. The report of a much stronger association between BMI and the prevalence of asthma in children over 10 years of age compared with younger children\(^15\) lends support to this possibility. Over 90% of our cohort were Tanner stages I or II, and less than 3% were stages IV or V at baseline assessment.

Our study also suffers from the limitations common to cross sectional studies. Certainly the association between BMI and pulmonary function cannot demonstrate causality or even the direction of the relationship. One could infer that children with higher FEV\(_1\) and FVC levels are more apt to eat more and therefore increase their BMI or, equally, that BMI levels directly alter levels of pulmonary function. Longitudinal studies within a cohort of asthmatic subjects are necessary to help clarify this relationship.

In conclusion, we have noted changes in spirometric pulmonary function related to BMI in a cohort of asthmatic children. BMI at baseline, however, was not prominently related to respiratory symptomatology or to any of four prominent intermediate phenotypes of asthma and atopy. Although these findings do not support our original hypothesis, the discovery of a decrement in the FEV\(_1)/FVC ratio in association with increasing BMI suggests that a significant relationship may yet exist. Further studies evaluating specific aspects of the BMI/asthma relationship are warranted. Such studies evaluating change in BMI over time, extremes of body mass effects, or sex specific pubertal changes on this relationship may provide further insights into the pathogenesis and treatment of childhood asthma.

**ACKNOWLEDGEMENT**

The Childhood Asthma Management Program is supported by contracts NO1-HR-16044, 16045, 16046, 16047, 16048, 16049, 16050, 16051, and 16052 with the National Heart, Lung, and Blood Institute and General Clinical Research Center grants MO1RR00051, MO1RR009978-14, M01RR02719-14, and RR00036 from the National Center for Research Resources.

Dr Tantisira is supported by NIH: 2T32 HL07427, Clinical Epidemiology of Lung Diseases, Dr Litonjua is supported by a Mentored Clinical Scientist Development Award: K08-HL03870, and Dr Fuhlbrigge is supported by a Mentored Clinical Scientist Development Award: K08 HL03919-01, from the National Heart, Lung, and Blood Institute.

Members of the CAMP Research Group are available on the Thorax website at www.thoraxjnl.com/supplemental.

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Funding: The Childhood Asthma Management Program is supported by contracts NO1-HR-16044, 16045, 16046, 16047, 16048, 16049, 16050, 16051, and 16052 with the National Heart, Lung, and Blood Institute and General Clinical Research Center grants MO1RR00051, MO1RR009978-14, M01RR02719-14, and RR00036 from the National Center for Research Resources.

**REFERENCES**


LUNG ALERT

Factors associated with physicians’ decisions to withdraw mechanical ventilation in anticipation of death

Eight hundred and fifty one consecutive patients mechanically ventilated for at least 72 hours in intensive care units in 15 different centres were prospectively followed. The relation between various factors and withdrawal of mechanical ventilation was assessed using Cox proportional hazards analysis.

Ventilation was withdrawn in 19.5% of the original cohort. Four factors were identified as being associated with withdrawal of ventilation: use of inotropes and vasopressors (hazard ratio 1.78, p = 0.004), physician’s prediction of a less than 10% chance of survival (hazard ratio 3.49, p = 0.002) and of severely impaired future cognitive function (hazard ratio 2.51, p = 0.04), and the physician’s perception that the patient did not want life support (hazard ratio 4.19, p<0.001).

Physicians’ perceptions and predictions formed the majority of factors in this study, which extends our understanding of the process of withdrawal of life support and questions the traditional biomedical model used (age and severity of illness or organ dysfunction were not factors). It is encouraging that one of the key factors was the wishes of the patients, but these might not be accurately reflected by relatives or physicians. Further research is required to clarify this issue.

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Thorax 2003 58: 1036-1041  
doi: 10.1136/thorax.58.12.1036

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