AN INVESTIGATION INTO ASPECTS OF ENERGY BALANCE AND NUTRITIONAL STATUS OF PATIENTS WITH CHRONIC LUNG DISEASE

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DEDICATION

To my parents

SUMMARY

Weight loss is a common complaint amongst patients with chronic obstructive lung disease (COPD). Irrespective of the severity of airflow obstruction, COPD patients who lose weight suffer a greater mortality and morbidity than their weight stable peers. Whilst the poor prognostic implication of weight loss is well recognised, the exact cause for its occurrence in these patients is unknown.

The main aim of the investigations that comprise this thesis was to study the contributions of the energy cost of breathing, beta agonist therapy and acute infective exacerbations to the energy balance of patients suffering from chronic respiratory disease. A subsidiary aim was to study methods of improving the nutritional status of malnourished patients with COPD.

In all the studies resting energy expenditure (REE) was measured by indirect calorimetry using a non-invasive ventilated hood system for expired gas collection. The hood system was used following a study of patients with severe respiratory impairment which revealed that the more widely used mouth-piece system, probably due to its invasive nature, resulted in an over estimation of REE.

Patient with deformities of the chest wall due to scoliosis and thoracoplasty are known to suffer from a mechanical inefficiency of the thoracic cage which results in an increased work of breathing. In order to detect whether increased work of breathing always results in an elevation of REE, REE was estimated in twenty patients with chest wall disease

and ten controls. This study showed that despite a major impairment of lung function, and by implication an increase in the work of breathing, REE was not elevated in patients with chest wall disease.

The next study involved the measurement of the oxygen cost of breathing in patients with respiratory impairment due to chest wall disease and COPD. The oxygen cost of breathing was estimated by a previously described method involving the addition of a dead space to the breathing circuit. REE, oxygen cost of breathing and nutritional status were measured in six patients with scoliosis, six patients with thoracoplasty, six patients with COPD and six controls. It was found that whilst the oxygen cost of breathing was inversely related to lung function, there was no relation between oxygen cost of breathing and REE or nutritional status. It was concluded that the oxygen cost of breathing could not be the sole or major cause of weight loss in COPD patients.

Beta adrenergic drugs, including salbutamol, are known to cause a dose dependent increase in energy expenditure. The thermogenic and heart rate response to an 800 µgm inhaled dose of salbutamol was measured in twelve COPD patients and twelve controls. The thermogenic and heart rate response to salbutamol was blunted in patients compared with controls, leading to the conclusion that the thermogenic effect of beta agonist drug therapy does not result in a state of negative energy balance in patients with chronic lung disease.

The effect of an acute exacerbation of disease on the energy balance of COPD patients was the focus of a further study. REE and

calorific intake were estimated in twenty patients hospitalised with an acute infective exacerbation of COPD. All patients exhibited an increase in REE at the time of admission and even at the time of discharge they were in a state of considerable energy deficit.

Two studies were conducted to assess the efficacy of nutritional programmes for malnourished COPD patients. The first study, employing a standard outpatient approach of dietary advice and supplement provision, did not improve the nutritional status or respiratory function . A second study involving the use of Clenbuterol, a beta agonist with muscle performance enhancing properties, showed that nutritional supplementation plus Clenbuterol in a conventional dose of 20 μ gms twice daily, did not improve nutritional status, respiratory muscle strength or lung function.

In conclusion, the studies comprising this thesis have shown that:

(1) In patients with severe respiratory impairment resting energy expenditure is better measured by a hood than a mouth piece system of indirect calorimetry;

(2) The oxygen cost of breathing is not in itself an important cause of poor nutritional status in patients with lung disease;

(3) The thermogenic effect of beta agonist drugs is blunted in patients with COPD who are long term users of the drug; beta agonist therapy is unlikely to be an important cause of negative energy balance in these patients;

(4) Patients with COPD suffer a state of considerable negative energy balance during an acute infective exacerbation which could contribute to cachexia in COPD;

(5) Outpatient based nutritional supplementation programmes on their own or in conjunction with Clenbuterol at a dose of 20 μ gms twice daily do not improve nutritional status or lung function in malnourished patients with COPD.

PROLOGUE

Factors related to nutrition are being increasingly implicated in the pathogenesis of a wide variety of diseases. Most attention has focused on the now well established link between diet, energy imbalance (obesity) and cardiovascular disease, particularly coronary artery disease (WHO Expert Committee, 1982). The critical role of nutrition has also been recognised with regard to chronic disease states of the other organ systems, for e.g., the primacy of dietary measures in the management of metabolic disorders like diabetes (Lean et al, 1991); the relation between poor nutritional status and failure of the immune system (Chandra, 1990); the value of nutritional support and dietary modification in renal and liver failure (Lee, 1980); and the importance of special diets in the management of disorders of the gastrointestinal system (Cummings, 1993). The part played by nutrition in the pathogenesis of cancer has also been the subject of extensive research in recent years (Doll and Peto, 1981).

In striking contrast to the situation pertaining to the other organ systems, the relation between nutrition and diseases of the respiratory system has received little attention. Major texts of nutrition often mention the lungs only in passing, or not at all (James and Garrow, 1993). Some of the reasons for this relative neglect can, however, be postulated. Firstly, asthma excluded, the most common respiratory diseases of the present day, chronic obstructive lung disease and lung cancer, are principally caused by smoking (Doll and Peto, 1976). The

link between cigarette smoking and these diseases is so strong and obvious that other factors like nutrition have been subjected to less scrutiny than would otherwise have been the case. Secondly, even in those respiratory diseases like cystic fibrosis and emphysema, where nutrition plays a significant role, the relationship between nutrition and disease state is not directly causal, depending on modification of immune and metabolic mechanisms, rendering assessment of the role of nutrition in the pathological process difficult.

As will become apparent as this thesis unfolds, the link between nutrition, energy balance and respiratory function is well worth studying, not only for the obvious clinical implications it has in the management of patients with respiratory dysfunction, but also for the interesting insights it provides into the complex relation between our breathing and bodily habitus.

Definitions and abbreviations

In view of the common use of abbreviations, in particular in the fields of calorimetry and respiratory function testing, this brief introduction defines some of the key abbreviations and terms used in this thesis.

REE - Resting energy expenditure; in practice, the minimum energy expenditure of an awake individual in a restful supine or semi-supine posture after an overnight fast.

$\dot{V}O_2$ - Oxygen consumption; expressed usually in ml / min.

$\dot{V}CO_2$ - Carbon dioxide production; expressed in ml / min.

RER - Respiratory exchange ratio; ratio between carbon dioxide production and oxygen consumption; usually refers to expired gas; does not assume steady state.

RQ - Respiratory Quotient; ratio between carbon dioxide production and oxygen consumption; usually refers to tissues; assumes steady state.

FEV_1 - Forced expired volume in 1 second; defined as the maximal volume of gas that can be expired from the lungs in the first second of a forced expiration from a position of full inspiration.

VC - Vital capacity; in this study refers to forced vital capacity which is defined as the maximal volume of gas that can be expired from the lungs during a forced expiration from a position of full inspiration.

BMI - Body mass index or the Quetlet Index; weight in kilograms divided by (height in metres) ^{2}. [Wt in kg / {ht} ^{2}].

% IBW - Percentage of ideal body weight as predicted from the Metropolitan Life Assurance Co., tables.

TSF - Triceps skinfold thickness

MAC - Mid upper arm circumference.

MAMC - Mid arm muscle circumference.

CHAPTER 1: Literature review and background

While clinical interest in the relation between nutrition and respiratory dysfunction in patients with emphysema and cystic fibrosis is a recent phenomenon, remarkably comprehensive information on the effects of malnutrition on ventilatory function has been available since the early part of this century. This chapter seeks to provide a historical background to the investigations in the field of nutrition and lung disease and summarises the current state of knowledge in this area, setting the scene for the various studies that form the basis of this thesis.

1.1 Effects of starvation on lung structure and function - results of the Carnegie, Minnesota and Warsaw camp studies

In 1919 Benedict and others published the results of their starvation experiments on human volunteers (Benedict et al, 1919). Thirty- four subjects from the Young Men's Christian Association College in Springfield, Mass. were placed on a diet which provided about 60% of recommended energy requirements for a period of three months. Various physiologic changes which accompanied the weight loss (about 10% of initial body weight) on this diet were measured. It was noted that after weight loss the overall basal heat production or, as it is now known, resting energy expenditure (REE), fell by 20% and oxygen consumption by 18%. Minute ventilation was recorded to have fallen from an average of 5.09 litres per minute to 4.49 litres per minute, although there was no

accompanying change in the alveolar carbon dioxide tensions. The essentially negative effect of nutritional deprivation on ventilatory function was confirmed by the Minnesota experiments (Keys et al, 1950). The mean weight loss achieved in this study after a starvation period of 24 weeks was 24% of initial body weight. This was accompanied by a fall in basal metabolic rate of 25 - 40%. Vital capacity fell by an average of 390 millilitres while minute ventilation fell from an average of 4.82 litres to 3.35 litres. Most interestingly, respiratory efficiency, which was arbitrarily defined as the amount of oxygen removed (in millilitres) per litre of expired air, decreased by 16% during aerobic work and 11% during anaerobic work. While the vital capacity returned to baseline values after 12 weeks of refeeding, measures of respiratory efficiency took a longer time (20 weeks) to return to normal. Although no measure of respiratory muscle strength was made, the conclusion was that the deleterious effect of starvation on ventilation resulted from weakness of the respiratory muscles.

While the Carnegie experiments and the Minnesota studies provide useful information on the effect of nutritional depletion on ventilatory function, the most striking observations on the effect of starvation on respiratory morbidity come from the studies of the Jewish physicians in the Warsaw ghettos in the early 1940s (Winick, 1979). Under the leadership of Dr. Israel Milejowski a group of investigators studied and described in remarkable detail the clinical and pathological consequences of food deprivation (Dmochowski and Moore, 1975). It was noted that in severe malnutrition minute ventilation decreased to half

of normal values and there was an increased tendency to pulmonary infection , including tuberculosis (*'death from starvation is death from pneumonia'*). Most interestingly, starvation was described as causing a condition of 'atony of the lungs' which was thus described : "*However, in the few cases where X-rays were available we could demonstrate radiolucency of the lungs, free costophrenic angles, lowering of the lower lung borders, and decreased pulmonary mobility in the absence of tubercular signs. This new syndrome of atony of the lungs , never described before in hunger disease, was characteristic and consistent in the lungs of our patients*". These features would now be readily recognised as characteristic signs of emphysema. Stein and Fenigstein, who carried out the autopsies, reported that findings of emphysema were present in 50 of the 370 cases. In 26 of those cases the individuals were less than 40 years of age, and the authors drew particular attention to the singular appearance of 'senile emphysema' in so young a population (Stein and Fenigstein, 1946). Even allowing for the fact that the authors did not define precisely their criteria for making a diagnosis of emphysema, these remarkable observations were the first to describe in any detail the link between nutritional depletion and emphysema, a subject which was to command the attention of investigators once again almost half a century later (Wilson et al, 1985).

1.2 Malnutrition and lung disease - prevalence and the clinical link

The fact that weight loss heralded a state of terminal decline in patients with chronic airways disease was known even in the late 19 th. century (Fowler and Godlee, 1898). Although the association between weight loss and mortality from lung disease was thus recognised, it was not until the 1960 s that attempts were made to investigate this relation. A number of studies of this period, especially longitudinal studies aimed at predicting the prognosis of patients with of airways disease, clearly demonstrated that a significant proportion of these patients suffered from malnutrition (Simpson, 1958; Carroll, 1960; Lopes,1962; Wilson et al, 1964). Sukmalchantra and Williams, for example, followed up a group of 44 patients with airways disease between 1959 and 1964, performing annual tests of pulmonary function, arterial CO_2 estimation and diffusing capacity measurements (Sukmalchantra and Williams, 1965). They observed that 37% of these patients lost greater than 10% of their initial weight during this 5 year period. Not only did the group that lost weight show a more rapid decline in lung function and exercise tolerance, they were also more likely to die from their illness in comparison with their weight stable counterparts (Mortality rate: 32% in weight losing group and 16% in weight stable group). The Veterans Co-operative study of pulmonary function confirmed the prevalence of malnutrition in patients with COPD and also presented evidence to suggest that there might be an inverse relation between body weight and lung function (Renzetti et al, 1966).

The mean weight of patients with a forced expired volume in 1 second (FEV_1) of less than 0.5 litres was 124 lb. and the mean height 68 inches whilst the same measures in patients with an FEV_1 of greater than 1.5 litres were 152 lb. and 70 inches respectively. Vandenberg and colleagues (Vandenberg et al, 1966) in a study of the prognostic significance of weight loss showed that mortality was 30% three years after the onset of weight loss and 49% five years after. Only a fifth of the patients died without exhibiting weight loss. Investigators, following on a clinical impression well laid out by Dornhurst (1955), began to express the opinion that changes in weight and body habitus were of more than just prognostic significance and that these changes had pathophysiological connotations. The concept that patients with COPD could be distinctly divided into two groups - the 'pink puffers' and the 'blue bloaters' thus arose (Figures 1.1 and 1.2). Clinicopathological studies in London and Chicago of patients with COPD showed that the 'pink puffer' patient suffered predominantly from emphysema whilst the 'blue bloater' suffered mainly from a bronchial disease (Burrows et al, 1966). Filley and his colleagues (1966) , much of whose work forms the bulk of evidence in favour of this hypothesis, drew up the different characteristics of the two distinct groups of COPD patients (Table 1.1). They observed that the pink puffer, who had a lesser weight for a given body surface area, also had a lower oxygen consumption, even when expressed per unit body surface area. On the basis of cardiac catheterisation studies and measurements of arterial- mixed venous O_2

difference they showed that this type of patient had a low resting cardiac output and also failed to augment his cardiac output on exercise compared with the blue bloater. They postulated that this inability to augment oxygen delivery and cardiac output could, in a situation comparable to cardiac cachexia (Pittman and Cohen, 1964), account for the poor nutritional status of these patients. Subsequent investigations (Thurlbeck WM, 1975; Nocturnal oxygen therapy trial group, 1980), however proved that the division of patients into two clear-cut groups was rather simplistic although more recent studies do not really show up this classification to be entirely without merit (Jamal et al, 1990). Filley et al's observations on COPD patients with and without weight loss remain a vital piece of information in this field and will be alluded to in subsequent discussions.

Not much interest was evinced toward the link between malnutrition and lung disease subsequently until the last decade when workers, mainly in the United States, pointed out once more the high prevalence and significant clinical import of malnutrition in patients with COPD. In contrast to the investigations of the 60s, the studies of the 80s and 90s that have followed the observations of these workers have largely been preoccupied with the clinical rather than the pathophysiological significance of nutritional depletion. Hunter and her colleagues measured nutritional status, dietary intake and immunological responses in 38 patients with COPD and found 27 showed evidence of weight loss although their mean recommended intake for 9 vital nutrients (and by implication their overall diet) was above the recommended daily

allowances (Hunter et al, 1981). Skinfold measurements revealed a depletion of both lean body mass and fat stores although visceral protein stores as estimated by serum albumin and transferrin were normal. Nine of the 32 patients who underwent immunologic testing (intradermal injections of PPD and Candida antigens) showed anergy. The workers concluded that malnutrition of the marasmic type (Blackburn and Bistrian, 1974) was widely prevalent in patients with COPD. This was followed by a report from Openbrier et al (1983) who, in a survey of 77 emphysematous and 30 bronchitic patients, made the important observation that only one bronchitic patient was <90% ideal body weight (IBW), while 43% of the emphysematous patients were below 90% IBW. (Bronchitis was defined as FEV $_1$/ FVC < 70%, diffusing capacity > 80%; emphysema as FEV $_1$ / FVC < 70% , diffusing capacity <60%). In the 4 bronchitic and 14 emphysematous patients who underwent anthropometry there was a significant difference in the mid arm muscle circumference and triceps skinfold thickness between the two groups, with the emphysema group exhibiting significantly lower values. In the emphysema group there were significant correlations between nutritional measures and lung function. For the first time measures of respiratory muscle function were made (Peak inspiratory and expiratory pressures, P I max. and P E max.) and these showed that inspiratory muscle weakness was evident in 9 of the emphysema patients but none of the bronchitics, even after allowing for the mechanical disadvantage caused by hyperinflation in the emphysema group (Table 1.2).The authors proposed

that the impairment of lung function in COPD may be in part due to the effects of nutritional depletion on respiratory muscle mass and activity, a theory which was to attract much attention in subsequent years. A few other subsequent studies confirmed the prevalence of malnutrition in COPD patients, with one particular study examining the incidence of malnutrition in an outpatient population to avoid the confounding effect of acute illnesses that hospitalised COPD patients may exhibit (Braun et al, 1984). This study too confirmed that a significant proportion of patients with COPD who were not acutely unwell were malnourished (weight loss in 27%; TSF < 60% in 33%). Wilson , Rogers and Hoffman in an extensive review of the link between nutrition and chronic lung disease (1985) summarised these and various other studies and concluded "malnutrition is a common problem with patients COPD, so that nutritional assessment including anthropometric measures as well as inspiratory and expiratory pressures, should be included in the evaluation of patient with suspected nutritional impairment ".

Perhaps the most comprehensive and informative study linking nutritional status and the course of COPD was a retrospective analysis of the National Institutes of Health Intermittent Positive Pressure Breathing Trial (Wilson et al, 1989). Data collected from a three year clinical trial assessing the effect of intermittent positive pressure ventilation (Intermittent Positive Pressure Breathing Trial Group, 1983) was used to detect the relation between body weight, pulmonary function and mortality in 779 men (women were not analysed as they were fewer in number and had a different distribution of weight

from the men). The population was divided into cohorts on the basis of degree of airflow obstruction (mild, moderate, severe) and percentage ideal body weight based on the Life Insurance Company Standards (New York, Metropolitan Life, 1983). Mortality over the three year period was influenced by body weight in all three groups of airflow obstruction (Figure 1.3). In patients with FEV_1 <35%, mortality increased with decreasing body weight (p =0.093). In patients with FEV_1 35-47% the relation was stronger (p = 0.048), while in patients with FEV_1 > 47% it was even stronger (p = 0.007).In other words, the relation between low body weight and mortality was strongest in those patients who did not particularly suffer from severe airflow obstruction. Another important finding of the study was that body weight was a powerful predictor of diffusing capacity in patients with same FEV_1 (p=0.0001). After adjustment for FEV_1 body weight correlated positively with exercise capacity (p = 0.0001). The study, its retrospective nature notwithstanding, was an authoritative confirmation, if one was required, of the importance of the link between nutritional status and morbidity and mortality from lung disease.

Another significant study highlighting the problem of nutritional depletion in COPD patients came from the Dutch group (Wouters and Schols, 1993). These investigators assessed the body composition of a group of 255 patients with moderate COPD (mean FEV_1 35% predicted) who were part of a pulmonary rehabilitation programme . Arguing that body weight is not a sensitive measure of nutritional status or body composition, they estimated fat free mass

(FFM) in these patients using the bioimpedence technique (Lukaski, 1987). Classification of patients on the basis of body weight and fat free mass revealed that not only did underweight patients show evidence of depletion of FFM but that a significant proportion of normal body weight patients too were depleted of FFM (Figure 1.4). These normal weight patients with low FFM exhibited greater physical impairment than underweight patients with preserved FFM. It appears from this recent and important study that malnutrition may be more widespread a problem than hitherto believed.

1.3 Pathogenesis of malnutrition in patients with COPD

Although malnutrition has been recognised as a significant problem in patients with COPD, attempts to elucidate the underlying pathophysiology of this phenomenon have been few. While a large number of centres have been involved in providing nutritional support to these patients, only a handful have adopted a scientific approach to the problem. This is particularly unfortunate as considerable effort and resources are being deployed on supplementary feeding programmes which have, as we shall see, bestowed very little benefit. This was highlighted by Koretz (1985), who observed with regard to nutritional therapy," The enthusiastic embracement of this therapy is based largely on the notion that patients must do better when they are fed than when they are not, an attitude that does my grand mother's chicken soup philosophy proud".

The following section summarises the various theories that have been proposed to explain the occurrence of malnutrition in COPD patients.

1.3.1. Decreased intake

The earlier investigators of the relation between malnutrition and COPD were of the belief that weight loss resulted from persistent anorexia, a common complaint amongst patients with COPD (Browning and Olsen, 1961; Wilson et al 1964). Vandenberg et al in their oft cited paper on mortality rates in different subpopulations of COPD, stated that weight loss probably resulted from diminished caloric intake. In their study there was indeed a difference in the caloric intake between patients with and without weight loss (Vandenberg et al, 1967). It must be pointed out that most of these studies employed methods of random recall and other methods of dietary assessment that would be considered inaccurate in the present day (Bingham et al, 1994). Moreover even in the patients studied there was a wide range of dietary intakes with some patients in the weight losing group apparently consuming more than those in the weight stable group. In any case, subsequent studies have not confirmed the conclusions of these investigators. In a study comparing the food intake of hypercapnoeic, overweight patients and malnourished, normocapnoeic patients, Semple at al found no difference in dietary intake between the two groups (Semple et al, 1979). Braun et al (1984), in their study of 60 outpatients with COPD, assessed the diet of the patients by written records and

concluded that caloric intake was adequate at 156% predicted basal energy expenditure, although it was speculated that this intake might not allow for increased activity and might thus, conceivably result in weight loss. Schols and her colleagues measured dietary intake by dietary history (validated in this patient group by a previous study, Schols et al, 1990) in 80 patients with stable COPD who were divided into a weight losing and a weight stable group. Absolute dietary intake was lower in the weight losing patients while absolute resting energy expenditure was comparable in the two groups. When subgroup analysis was based on severity of disease it was found that in the less compromised group , a moderate proportion of the patients had an increased REE but this was matched by an increased intake such that there was no weight loss. With increasing airflow obstruction there was a greater elevation of REE but dietary intake did not always increase, resulting more frequently in weight loss in this group. In the most compromised group not only was REE much elevated, but dietary intake had also dropped, resulting in pronounced negative balance and weight loss. In an attempt to explain these findings the same investigators measured transcutaneous oxygen saturation and carbon dioxide tensions during meals and concluded that breathlessness caused by the effort of eating does not explain weight loss in normoxemic COPD patients but may contribute to limited intake in patients who were already hypoxemic (Pa O_2 < 7.3 kPa), echoing the findings of a previous study (Brown et al, 1983). The conclusion that emerges from these studies is that the more severely compromised the

COPD patient, the greater his/ her weight loss and the less his dietary intake. This, of course, does not imply that weight loss is the consequence solely of a decreased dietary intake. It appears likely that decreased dietary intake, whilst contributing to weight loss once the process has started in association with severe disease, is not the initial cause of weight loss.

Other theories postulating decreased dietary intake, for example as a result of increased incidence of peptic ulcer disease in emphysema patients (Latts EM et al, 1956; Zasly et al, 1960), have not been substantiated.

1.3.2. Variations in hormonal response to hypoxia.

Investigations exploring the hormonal response to COPD were prompted by the observations of Pugh (1962) and Campbell (1975) that hypoxia inhibited adrenal and gonadal function and could cause weight loss. Marmorston et al (1966) drew attention to the abnormal urinary hormonal profile of patients with emphysema and cancer. These results were followed up by Semple et al who compared the steroid hormone profile of sixteen patients with two distinct types of COPD, the 'pink puffer'(PP) and 'blue bloater'(BB) alluded to in previous discussions (Semple et al, 1979). The 'blue bloaters' were all hypercapnoeic whilst the 'pink puffers' group were normocapnoeic. They found that whilst seven of the eight BB group were overweight, seven of the eight PP group were underweight. The hypercapnoeic BB

group showed significantly depressed testosterone levels and the authors speculated whether the increased weight in the BB group was the result of low testosterone levels. However there was no convincing explanation for the occurrence of weight loss in the normocapnoeic PP group and the theory invoking a hormonal basis for weight loss in COPD remains unproved.

1.3.3. Weight loss as the result of tissue hypoxia

As previously mentioned, Filley and his colleagues studied the physiologic differences between two distinct subtypes of COPD patients (Filley et al, 1968) and showed that the poorly nourished emphysematous patient was characterised by a low resting cardiac output, near normal arterial oxygen saturation (Sa O_2), a high ventilation to cardiac output ratio in contrast to the bronchitic type of patient who exhibited a normal cardiac output, a low Sa O_2 and a low ventilation to cardiac output ratio. Whilst resting oxygen arterial tensions were higher in the thin, emphysematous patient, tissue oxygenation, as estimated by the ratio of oxygen delivered (cardiac output x arterial oxygen content) to the oxygen consumed (arterial - mixed venous oxygen content) was better in the plethoric, bronchitic patient. They hypothesised that the muscle wasting of the emphysematous patient was really the result of tissue hypoxia, secondary to low cardiac output and that a high cardiac output, in the presence of a destroyed pulmonary vascular bed (the underlying pathology of emphysema) would in fact not only increase the load of the right ventricle but would also reduce the time which the

blood spends in the capillaries. They speculated that with a restricted cardiac output the emphysematous patient was increasing the pulmonary transit time, thus avoiding dangerous hypoxemia. They asked, " Is not the low cardiac output and high ventilation the only way a PP patient has available to supply adequate oxygen to his tissues ?". It is surprising that this entirely plausible explanation based on painstaking experimental data has not been the subject of further research.

1.3.4. Increased energy cost of breathing

Under normal circumstances the energy cost of ventilation (i.e. the oxygen consumption of the respiratory muscles) is very low, amounting to no more than 5% of the body's total oxygen consumption (Millic- Emili and Petit, 1960). Whilst it was widely believed that this oxygen cost of breathing (OCB) would be increased in patients with COPD due to increased airways resistance, it was Cherniack who first demonstrated this to be the case (Cherniack, 1959). Measuring OCB by adding dead spaces to the breathing circuit he showed that whilst the cost of increasing ventilation by a litre in normal subjects was 1 - 2 mls of O_2 / min, in COPD patients this value was 6 - 11 mls of O_2 / min. These observations have since been confirmed by other investigators (Levison and Cherniack, 1968; Field et al , 1982; Donahoe 1989). Wilson, Rogers and Hoffmann (1985) proposed the theory that this increased oxygen cost of breathing resulted in a state of increased resting energy expenditure and, this in the face of normal or decreased nutritional intake, led to weight loss. In keeping with this theory was the

finding of many investigators that resting energy expenditure was indeed elevated in patients with emphysema (Goldstein et al, 1987, 1988; Wilson et al, 1990; Schols et al 1991). To account for the fact that weight loss was not a feature of patients with bronchitis who had similar degree of airflow obstruction, and by implication a similar increase in work load, the proponents of this theory put forward two complementary explanations: (1) Although patients with emphysema and bronchitis have equal levels of airflow obstruction, patients with emphysema show a greater tendency to hyperinflation (greater ratio of residual volume to total lung capacity) and that this results in flattening of the diaphragm, and therefore a loss of efficiency of the muscle due to a shift to the less efficient portion of the force- length relationship (Roussos and Macklem, 1977). This loss of efficiency leads to increased energy consumption by the respiratory muscles and raised REE and weight loss. (2) In contrast to bronchitic patients, emphysematous patients showed evidence of respiratory muscle weakness (Openbrier et al, 1983). It was postulated that the increased work of breathing caused respiratory muscle fatigue which in turn rendered the muscles even more inefficient , setting up a vicious circle of worsening efficiency and increasing oxygen consumption ultimately resulting in weight loss (Figure 1.5).

Donahoe et al (1989) in a study of emphysematous patients with and without weight loss noted that the OCB was significantly elevated in patients with weight loss compared to those without and that there was a significant correlation between OCB and REE. This was

shown as evidence to support that raised OCB was the reason for weight loss and malnutrition in patients with emphysematous COPD. The Dutch workers also provided evidence from a larger study to show that emphysematous COPD patients with weight loss have an elevated REE and that this results in a state of negative energy balance and weight loss (Schols et al, 1991). It is in this regard a recent paper from another group of workers is interesting. Ryan and co-workers (1993) measured caloric intake, REE and the thermogenic effect of food in 10 malnourished COPD patients (< 85% IBW) in a clinically stable state. In contrast to the other previous workers they found that REE was 94 ± 16.5% of values predicted by the Harris-Benedict equation (Harris and Benedict, 1919). Refeeding caused a large increase in energy expenditure (24 ± 18 %). They concluded from their study that stable COPD patients were in fact not hyper metabolic and consumed enough calories to meet average requirements, but that the thermogenic effect of a meal was considerable, as noted by previous investigators (Goldstein et al, 1987). In an attempt to explain the variance of their findings from those of previous investigators, the authors suggested that methodological differences (use of a non-invasive canopy system rather than an invasive mouth- piece plus nose clip system to measure REE) may have been responsible for the lower values for REE (Askanazi et al, 1980). This, however is not an entirely satisfactory explanation, as other workers (Schols et al, 1991) also used a non-invasive canopy system to estimate REE and have demonstrated elevated values.

Ryan and co-workers are not the only investigators to show that hyper metabolism is not a consistent feature of emphysematous COPD patients. Green and Muers (1992) measured REE by indirect calorimetry using a ventilated canopy in six emphysematous patients, eight chronic asthmatic patients, nine non-smoking related COPD patients and six controls. All controls, four out of six emphysema patients, five of nine hypercapnoeic COPD patients and three of eight asthmatics had REE within 10% of the predicted values (Harris-Benedict equation). The study also showed that a given patient's metabolic state could not be predicted from lung function tests or arterial blood gas analysis.

It is noteworthy that although the increased energy cost of breathing is postulated to result in a state of hyper metabolism and weight loss, very few attempts have been made to study the energy balance of patients with lung diseases other than emphysema to detect whether or not the increased work of breathing in the context of other lung diseases can influence energy balance adversely. Fitting et al (1990) studied a heterogeneous group of 12 patients with interstitial lung disease due to a variety of causes ranging from sarcoidosis to silicosis and found that REE was elevated by 17 - 21% above predicted values. Their contention that this elevation was the result of increased work of breathing did not however explain the reason for the lack of relation between lung function and elevation in REE and the authors admit that other mechanisms, including ongoing inflammation could account for the elevated REE. There have been no studies of patients with other types of

respiratory impairment without accompanying inflammatory phenomena, for example those with disease of the chest wall like scoliosis, who have a marked increase in the work of breathing (Kafer, 1975; Jones et al 1981). This issue is the focus of detailed attention in a later chapter of this thesis.

1.3.5. Thermogenic effect of food

Total energy expenditure is the sum of REE, the energy cost of physical activity and the thermogenic effect of nutrients (diet induced thermogenesis). There is some evidence to suggest that diet induced thermogenesis (DIT) is elevated in patients with emphysematous COPD (Goldstein et al, 1987; Ryan et al, 1993; Green and Muers, 1993), although more recent studies show evidence to the contrary (Hugli et al, 1993). Even if DIT is increased in COPD there is no evidence to suggest that this increase in DIT is any different from that following refeeding in other states of malnutrition (Piers et al, 1992) or that this state of elevated DIT precedes and is responsible for weight loss.

1.3.6. Influence of concurrent illnesses.

Bates (1973), in an interesting lecture brought together the various clinical and pathophysiological observations pertaining to patients with COPD and attempted to provide an explanation for weight loss in these patients. He suggested that in patients with COPD, episodes of lower respiratory tract infection or any other intercurrent illness

results not only in an increase in the energy needs of the individual but also a decrease in food intake, thus causing net negative energy balance and weight loss (Figure 1.6). The theory however fails to provide an explanation as to why patients with chronic bronchitic type of COPD, who have as many or more episodes of infection, do not show a tendency to lose weight, whilst emphysematous COPD patients do.

1.3.7 Drug therapy

Air flow obstruction in COPD is treated with inhaled beta-adrenergic agents like salbutamol and terbutaline. Although these drugs are prescribed to be used on an as required basis, most COPD patients use these drugs regularly. It is known that adrenergic drugs cause a dose dependent increase in energy expenditure (Fellows et al, 1985). More recently, studies have demonstrated that inhaled salbutamol, even in small doses, cause an appreciable increase in REE (Amoroso et al, 1993). Given that COPD patients use a considerable amount of beta agonists for symptom relief it is possible that the thermogenic effect of these drugs may have an adverse influence on the energy balance of these patients and leads to weight loss.

1.4 Malnutrition and cystic fibrosis

Any account of the link between malnutrition and lung disease would be incomplete without a reference to cystic fibrosis. Cystic fibrosis (CF) is an autosomal recessive genetic disease of the exocrine

glands that predominantly affects the lungs and the pancreas. The genetic abnormality leads to failure of synthesis of a protein vital to the transport of electrolytes across the cell membrane, resulting in the production of viscid secretions that obstruct the ducts of the glands. The first manifestation of the disease is often meconium ileus, i.e., obstruction of the intestine by thick, inspissated stool. Chronic pulmonary sepsis, pancreatic insufficiency and focal biliary cirrhosis occur gradually leading to respiratory failure, malabsorption and malnutrition. The pathogenesis of malnutrition that is associated with CF is distinctly different from that associated with COPD in that it is the result, not primarily of a pulmonary pathology, but of the pancreatic abnormality associated with the disease leading to malabsorption. Nevertheless some of the nutritional aspects of CF are worthy of note.

(1) Although the prognosis of CF is primarily related to pulmonary function, poor nutritional status (as measured by anthropometry) is associated with a worse prognosis (Kraemar et al, 1978).

(2) Resting energy expenditure is elevated in CF, and falling REE has been shown to be a more sensitive indicator of clinical improvement from an acute exacerbation of the disease than pulmonary function tests and chest radiographs (Naon et al, 1993).

(3) Parenteral nutritional support may improve pulmonary function (Levy et al, 1985), although this is not always the case (Shepherd et al, 1988).

Whilst the pathogenesis of the nutritional abnormalities in CF is different from that in COPD, the significant influence of nutrition

on the course of CF underscores the importance of the relation between nutritional status and lung function in patients with chronic lung disease.

1.5 Diet composition and respiratory function

The previous sections of this review have been concerned primarily with the effect of respiratory dysfunction on the nutritional status of a patient. There is however another aspect of the relation between nutrition and respiratory dysfunction that merits attention. This is the effect of dietary composition on gas exchange and respiratory function.

Energy for the sustenance of vital functions of the body is obtained by the combustion of proteins, carbohydrates and fats in the diet. In this process of combustion, oxygen is consumed and carbon dioxide produced. The ratio of carbon dioxide produced to oxygen consumed is termed the Respiratory Quotient or RQ. The RQ of the three sources of energy are : fat : 0.7, carbohydrate : 1.0 and protein 0.8. The implication of the different Respiratory Quotients is that during the metabolic process more carbon dioxide is produced per amount of oxygen consumed if the metabolic fuel is carbohydrate than if the fuel is fat. In healthy individuals the ingestion of a large carbohydrate load results in increased CO_2 production but increase in minute ventilation ensures that this increased CO_2 is expired and that arterial tensions of CO_2 do not rise (Saltzman and Salzano, 1971). The situation is however different in patients who have a limited respiratory reserve and cannot

increase their ventilation. Attention was first drawn to this as a clinical problem in the intensive care setting where acutely unwell patients were reported to have developed respiratory failure following parenteral feeding with high glucose loads (Askanazi et al, 1980 ii). The possible negative impact of high carbohydrate diets on patients with limited respiratory reserve had been studied earlier by Giesckc at al (1977) who fed 13 patients with airflow obstruction a high carbohydrate diet and monitored its ventilatory effects. As expected there was an increase in minute ventilation, CO_2 production and O_2 consumption. However there was no increase in arterial CO_2 tension in patients who were normocapnoeic and a small, statistically insignificant increase in CO_2 tensions in hypercapnoeic patients. The authors concluded that an increased carbohydrate load was generally well tolerated by patients with chronic airways disease. These findings were refuted by Angelillo et al (1985) in their study of 14 ambulatory patients with COPD. In this study, patients were given three diets: low carbohydrate, high fat (28% carbohydrate, 55% fat), a moderate carbohydrate, moderate fat (53% carbohydrate, 30% fat), high carbohydrate, low fat (74% carbohydrate, 9.4% fat). Each diet was administered as a liquid in a randomised double blind manner for 5 days. Daily measurements of O_2 consumption, CO_2 production , arterial P O_2, arterial P CO_2, tidal volume, respiratory frequency and minute volume were made. FEV_1 and FVC were also determined at the beginning and end of each 5 day period. The investigators found that whilst O_2 consumption did not vary between the

diets CO_2 production and arterial CO_2 tensions were lower on the low and moderate carbohydrate diets. (A significant and unexplained finding of the study was that, despite a caloric intake greater than estimated requirements there was a statistically significant weight loss in the group as a whole!). The study thus suggested that a diet restricted in carbohydrate content may be beneficial to patients with chronic airways disease. Brown et al (1985) extended this line of investigation further and studied the effects of a carbohydrate load on the exercise capacity of patients with chronic airways disease. Compared with a placebo drink, a carbohydrate drink (480 ml grape juice + 150 g sucrose; 980 kcal) resulted in a decrease in maximal power output during exercise although maximal ventilation at exhaustion was nearly identical. At equivalent power outputs the carbohydrate drink resulted in a significant increase in minute ventilation and CO_2 output. However there were no changes in arterial CO_2 tensions although Pa O_2 during exercise was higher after carbohydrate loading. Subsequent studies of the influence of diet on exercise tolerance in patients with COPD have compared carbohydrate and fat based diets on exercise capacity and have concluded that carbohydrate rich diets not only decrease exercise capacity but also increase the sensation of breathlessness (Efthimiou et al, 1992; Kuo et al, 1993).

In conclusion, carbohydrate rich diets appear to have an adverse effect on ventilation and exercise capacity in patients with limited respiratory reserve due to chronic airflow obstruction. Whether dietary manipulation by increasing the proportion of calories obtained from fat

will improve morbidity and mortality in patients with chronic respiratory impairment remains unknown. This thesis will not address further this issue of diet composition and respiratory function.

1.6 Clinical implications of malnutrition - refeeding studies

The logical consequence of identifying malnutrition as an adverse prognostic factor in COPD patients was the attempt to improve prognosis by improving the nutritional status of these patients. With nutritional depletion being clearly associated with poorer lung and respiratory muscle function, it appeared entirely appropriate to reverse the negative trend by nutritional repletion. However, the results of such refeeding studies have been, at best, equivocal and at worst extremely disappointing. Wilson and his colleagues , whose significant work in this field has already been alluded to (Wilson et al, 1985), were the first to report the results of a study of nutritional supplementation in patients with COPD. In an uncontrolled study involving six patients with a mean body weight which was 75% of values predicted (75% IBW), they demonstrated an increase in weight, anthropometric measures (TSF, mid-arm muscle circumference(MAMC)) and peak inspiratory and expiratory pressures after 2 weeks with a dietary intake of 1.5 times BMR (Wilson et al, 1986). Likewise, in a controlled study, Goldstein and co-workers showed a 10% improvement in peak inspiratory and expiratory (P I and PE max) pressure values over a two week period on a diet providing calories to the amount of 1.7 times measured REE (Goldstein et al,

1988). Similar findings were also reported by Whittaker et al (1990) in a study of nutritional supplementation (nasoenteric feeding) in 10 malnourished patients with COPD. Whilst the aforementioned studies were all performed in the surroundings of a clinical research unit, Efthimiou and colleagues extended the investigations to the outpatient setting in their study of a nutritional support programme in 14 malnourished and 7 well nourished COPD patients (Efthimiou et al, 1988). Subjects were studied over a nine month period. After a 3 month baseline period the malnourished COPD patients were randomised to receive nutritional supplementation or continue their regular diet for 3 months. At the end of the 3 months the supplementation group returned to their usual dietary habits. The well nourished COPD group were on their usual intake for the entire nine month period. Tests of respiratory muscle function (including sternomastoid fatiguability), spirometry, 6 min walking distances, quality of life assessments and anthropometric measurements were performed at 3 monthly intervals. During the entire study dietary supervision was close and intensive, with an increase in the caloric intake of the supplementation group amounting to 48% over their original intake. In the group which received nutritional supplementation the weight gain over the 3 month period of supplementation was 4.2 kg (range 0.7 - 8.2 kg). Weight gain was associated with significant improvements in sternomastoid and handgrip strength, 6 min walking distances, well being scores and decreased sternomastoid fatiguability. Interestingly all these measures tended to return to the original abnormal

levels on return to the usual diet. The conclusion was that a well supervised outpatient nutritional support programme was capable of producing an improvement in the clinical condition of malnourished COPD patients.

However, these encouraging findings have not been confirmed by other observers. Lewis et al (1987), in a randomised study of 21 malnourished COPD patients showed that there was no significant improvement in weight, anthropometric measures, respiratory muscle strength or endurance after 8 weeks of nutritional supplementation. The investigators made the important observation that subjects limited their caloric intake from the usual dietary sources whilst on supplements and for this reason their overall caloric intake whilst on supplements rose only by 15%. These findings were essentially confirmed by Knowles et al (1988) who performed a randomised, crossover study in 25 COPD patients. Caloric intake which increased by a mean value of 28% over baseline values after 4 weeks of supplementation, was only 18% above baseline intake at the end of 8 weeks. Weight gain and improvements in respiratory muscle strength were noticeable only in those subjects who had increased their intake by more than 30%. The impression that nutritional supplementation *per se* was of limited value was reinforced by a well designed , placebo controlled, randomised, double blind study conducted by a group of Danish investigators (Otte et al, 1989). Only 13 of a group of 28 patients who were given supplements for 13 weeks increased their weight by mean of 1.5 kg weight whilst the control group gained 0.16 kg. No differences were observed in the pulmonary function

or immunologic status (T-helper/suppressor ratio, mitogen reaction of T lymphocytes to phytohaemagglutin).

Perhaps the most comprehensive of the refeeding studies is the more recent investigation of Rogers and his colleagues (1992), in which 15 malnourished COPD patients and 12 controls well matched for nutritional status and lung function were studied. Intervention comprised of a nutritional supplementation programme providing calories 1.7 times REE with approximately 1.5 g / kg of protein daily for a period of 3 weeks. The intervention group was admitted to a clinical research unit for this purpose. Anthropometry, lung function tests (spirometry, diffusing capacity, respiratory muscle strength), 12 min walking tests, handgrip strength and biochemical tests were performed at weekly intervals for the 3 weeks prior to randomisation and again 1 and 4 months post randomisation. The intervention group showed a significant weight gain (+2.4 kg *vs* - 0.5 for control), improved hand grip strength, expiratory muscle strength and walking distance after the 4 month period. It was noted that the weight gain achieved in the intervention group during their initial 4 week stay in the research unit could not be sustained in the outpatient environment despite the provision of full and intensive nutritional support. The authors concluded that whilst under controlled conditions refeeding resulted in significant improvements in some measures of respiratory function, nutritional therapy was 'costly, time - intensive and of limited therapeutic magnitude'.

In summary (Table 1.3), nutritional repletion by intensive refeeding techniques, whilst logical and attractive, appears to of limited

value in the management of malnourished patients with COPD. Significant weight gain is clearly associated with some improvement in respiratory muscle function, exercise capacity and general well being; however achieving a weight gain in this group of patients requires intensive and expensive techniques which are clearly not sustainable in the long term. At the time of writing of this review no study has addressed the issue of whether long term nutritional supplementation has an effect on mortality and morbidity in malnourished COPD patients.

1.7 Conclusions

1. Weight loss is a frequent complication of end stage chronic obstructive pulmonary disease.

2. The presence of signs of nutritional depletion is associated with a greater morbidity and mortality from the disease.

3. Malnutrition is a feature of emphysematous but not chronic bronchitic type of COPD; malnutrition appears to be more closely related to the pathophysiological correlates of emphysema (abnormal gas exchange) rather than airflow obstruction *per se* .

4. Poor nutritional status has a negative impact on respiratory muscle function and this issue may be crucial in the overall relation between malnutrition and lung function and clinical outcome.

5. The cause of malnutrition in patients with emphysema remains unclear. The theory that has attracted most attention suggests that weight loss results from a state of negative energy balance following from the higher energy requirements of the fatigued respiratory muscles (increased work of breathing) in the face of normal or reduced nutrient intake. Other possible explanations, not mutually exclusive, include:

(a) a state of stepped decline in body weight and lung function occasioned by hypermetabolism and anorexia during intercurrent illnesses like lower respiratory tract infections ultimately leading to malnutrition;

(b) destruction of the pulmonary vascular bed due to emphysema results in an inability of the cardiopulmonary system to provide the nutritional and oxygen demands of the tissue resulting in nutritional depletion;

(c) drug (beta-adrenergic agents) induced thermogenesis contributing to a state of hyper metabolism and negative energy balance.

6. Attempts at improving the nutritional status of malnourished COPD patients, even by intensive hospital based nutritional supplementation programmes, have achieved only limited success.

1.8 Aims of the thesis

The main aim of the investigations that comprise this thesis was to illuminate some of the aspects of the relation between lung function, energy balance and nutritional status of patients with respiratory impairment. This was achieved by a series of studies which addressed the following hypotheses and specific questions :

1. *Severe respiratory dysfunction and by implication, increased work of breathing, increases resting energy expenditure in patients with lung disease.*

Do all patients with an increase in the work of breathing due to lung disease exhibit an elevation of resting energy expenditure? For example, is resting energy expenditure elevated in patients (not previously studied) with chest wall deformities due to scoliosis and thoracoplasty which are characterised by a mechanical inefficiency of the thoracic cage?

2. *Increased resting energy expenditure in patients with lung disease is related to an increase in the oxygen cost of breathing and leads to increased resting energy expenditure, negative energy balance and poor nutritional status.*

What is the relation between the energy or oxygen cost of breathing, lung function, resting energy expenditure and nutritional status in patients with chest wall disease and in patients with emphysema? Is there a direct relation between poor lung function, increased oxygen cost of breathing and elevated resting energy expenditure and poor nutritional status?

3. *The recognised thermogenic effect of beta agonists contributes to the state of negative energy balance and weight loss in patients with lung disease.*

What is the effect of inhaled beta agonist drug therapy on resting energy expenditure in respiratory patients who are long term users of the drug? Is it possible that the thermogenic effect of beta adrenergic agents documented previously in normal healthy subjects, contributes to a state of negative energy balance and weight loss in COPD patients?

4. *Negative energy balance suffered during an acute infective exacerbation of chronic lung disease contributes to a state of malnutrition in patients with COPD.*

What is the exact energy cost of an acute infective exacerbation in patients with COPD? Do nutritionally depleted and well nourished COPD patients differ with respect to their thermogenic response to infection?

A subsidiary aim of the research project was to assess the efficacy of routine and novel methods of therapy in improving the nutritional status of malnourished patients with COPD. One study addressed the question whether the relative success achieved by intensive

supplementation programmes in improving the nutritional status of COPD patients could be matched by routine outpatient dietary programmes provided as a clinical service. A further pilot study explored the use of Clenbuterol (a beta agonist drug with muscle performance enhancing properties) in conjunction with nutritional supplementation in improving nutritional status and muscle mass in underweight COPD patients.

1.9 Layout of the thesis

The literature in the field of nutrition and lung disease with particular reference to the links between energy balance, nutritional depletion and lung function, is summarised in **Chapter 1**. The chapter ends with a section on the aims of the thesis.

The various methods of measurement employed in the study, particularly of nutritional status and energy expenditure (calorimetry) are outlined in **Chapter 2**. The chapter also presents the results of a study comparing a ventilated hood system with a mouth piece and nose clip system to measure resting energy expenditure in patients with severe lung disease.

The investigations exploring the relation between resting energy expenditure and respiratory impairment begin in **Chapter 3**, which reports the results of a study of resting energy expenditure in a group of patients with chest wall deformities, a condition known to be associated with an increase in the energy cost of breathing.

Chapter 4 extends the studies of the previous chapter to make direct measurements of the oxygen cost of breathing and compares the oxygen cost of breathing and its relation to lung function, nutritional status and resting energy expenditure in patient groups with respiratory impairment due to scoliosis, thoracoplasty and emphysema.

A study assessing the impact of inhaled beta agonist therapy (salbutamol) on the resting energy expenditure of patients who are long term users of the drug constitutes **Chapter 5.**

Chapter 6 quantifies the energy deficit suffered by patients with COPD during an acute exacerbation of the disease; results are presented of a study in which resting energy expenditure and dietary calorific intake were measured on admission and at the time of discharge in patients hospitalised with an acute lower respiratory tract infection.

Chapter 7 presents the experience of the investigator in clinical studies aimed at improving the nutritional status of patients with chronic lung disease. A section is devoted to a pilot study of Clenbuterol, a beta adrenergic agonist which has, in addition to bronchodilator properties, an ability to alter body composition and muscle strength favourably.

Chapter 8 brings together the results of the various studies and reviews other studies in the field that have been published during the time when the investigations that comprise this thesis were in progress. A section of this chapter attempts to provide a unified view of the link between energy balance, nutrition and respiration; the concluding section highlights areas of research for future studies in this field.

PINK PUFFER	BLUE BLOATER
Thin in appearance; frequent history of loss of weight.	No history of weight loss except terminally.
Narrow cardiac shadow on chest radiograph	Significant cardiac enlargement.
No history of congestive heart failure until terminally	Frequent episodes of heart failure which respond to treatment.
Hearnatocrit less than 55%	Haematocrit greater than 60%
Low $\dot{V}O_2$ per square metre body surface area	High $\dot{V}O_2$ per square metre body surface area
High resting ventilation	Low resting ventilation
Low cardiac output; inability to augment cardiac output during exercise	Normal cardiac output
High Sa O_2	Low Sa O_2
Bronchial mucosal gland hyperplasia not prominent (2/ 10 patients)	Bronchial gland hyperplasia prominent (7 / 10 patients)
Emphysema in all 10 patients	Emphysema in 8/ 10 patients

Table 1.1 : The differences in the clinical and pathophysiological features of the two different subtypes of patients with COPD . From Filley et al, 1968.

	Chronic Bronchitis (n=4)	Emphysema (n=14)
Age	62 ± 4.2	57 ± 5.1
Forced vital capacity*	98 ± 29.5	82 ± 21.9
FEV_1 *	57 ± 17.3	35 ± 16.6 **
FEV_1 / FVC *	47 ± 11.5	33 ± 10.2 **
Total lung capacity *	102 ± 17.4	106 ± 12.7
Diffusing capacity *	135 ± 19.1	32 ± 16.4 **
Peak inspiratory pressure	> 60 cms in all patients	< 60 cms in 10 / 14 patients
Peak expiratory pressure	> 60 cms in all patients	< 60 cms in 6 / 14 patients
% Ideal body weight	124 ± 13.2	88 ± 15.1 **
Arm muscle circumference *	125 ± .37	91 ± .09 **
Triceps skin fold thickness *	168 ± .69	85 ± .45 **
Creatinine height index	112 ± 32.2	80 ± 29.8

All values as mean ± standard deviation.

* Values as % predicted.

** $p < 0.05$

Table 1.2 : Anthropometric measures and lung function in patients with chronic bronchitis and emphysema highlighting the nutritionally depleted state of emphysematous patients. From Openbrier et al, 1983.

Table 1. 3 : Studies of refeeding in COPD

Authors	Study Design	Number of subjects	Setting	Duration	Dietary intervention	Weight gain	Outcome
Wilson et al (1986)	Non-randomised, non-controlled.	6	Inpatient	3 weeks	Caloric intake of 50 % over predicted energy requirements	3.1 kg (significant)	Improved hand grip strength, maximal inspiratory strength and transdiaphragmatic pressures.
Knowles et al (1988)	Randomised, controlled, cross-over	25 patients	Outpatient	8 weeks	Caloric intake aimed to be improved by 50% over baseline.	1.1 kg (not significant)	No change in respiratory function or muscle strength.
Goldstein et al (1988)	Non-randomised, non-controlled	10 patients 6 controls	Inpatient	2 weeks	Caloric intake increased by 1.7 times REE by an enteral or parenteral infusion of a carbohydrate or fat based diet.	2.0 kg (significant)	Improvement in quadriceps, respiratory muscle strength and endurance.

Efthimiou et al (1988)	Randomised, controlled	14 patients 7 controls	Outpatient	3 months	Caloric intake 2500 kcal in men and 2300 kcal in women (25 - 50% greater than recommended intake)	4.2 kg (significant)	Improvement in respiratory muscle strength, hand grip strength, sternomastoid fatiguability, well being, six minute walking distance and breathlessness scores.
Lewis et al (1989)	Randomised, controlled	21 patients 10 controls	Outpatient	8 weeks	Improvement of intake by 15% only on ad-libitum supplements	1.1 kg (not significant)	No change respiratory muscle strength, endurance or handgrip strength.
Otte et al (1989)	Randomised, double blind, placebo controlled	28 patients	Outpatient	13 weeks	Supplementary feed resulting in 15% increase in caloric intake	1.5 kg (not significant)	No change in pulmonary function or immunologic status

Whittaker et al (1990)	Randomised, controlled	10 patients (Supplementary feeding in 6)	Inpatient	16 days	Calories to 1.7 times REE by nasoenteric feeding	2.4 kg (significant)	Improvement in maximal expiratory and sustained inspiratory pressure. No change in adductor pollicis function
Rogers et al (1992)	Randomised, controlled	15 patients 12 controls	3 weeks inpatient; 3 months outpatient	3 week inpatient and 3 month outpatient supplementation	1.7 times REE	2.4 kg (significant)	Improvement in hand grip strength, expiratory muscle strength and walking distance.

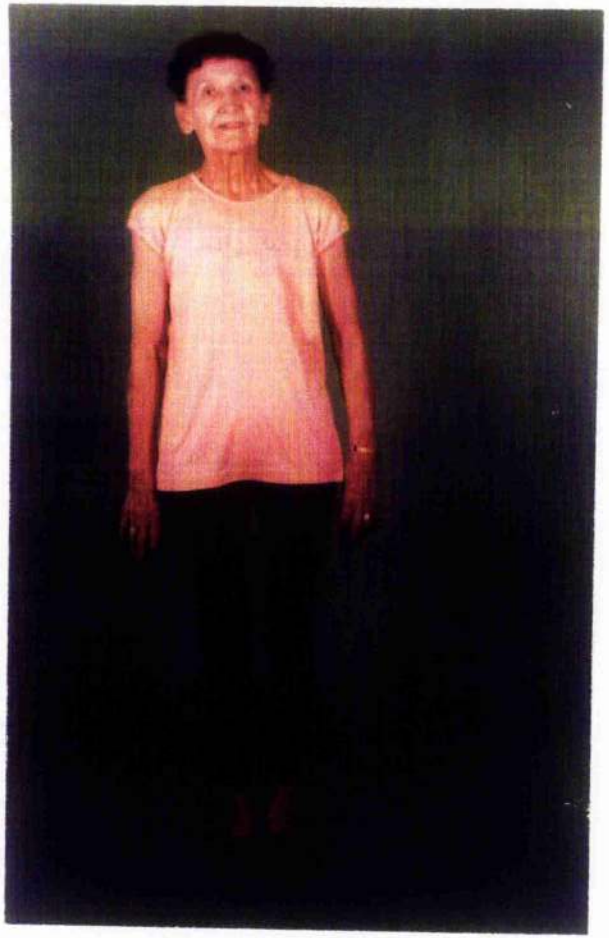


Figure 1.1 : Typical bodily habitus of an emphysematous patient ('Pink Puffer)

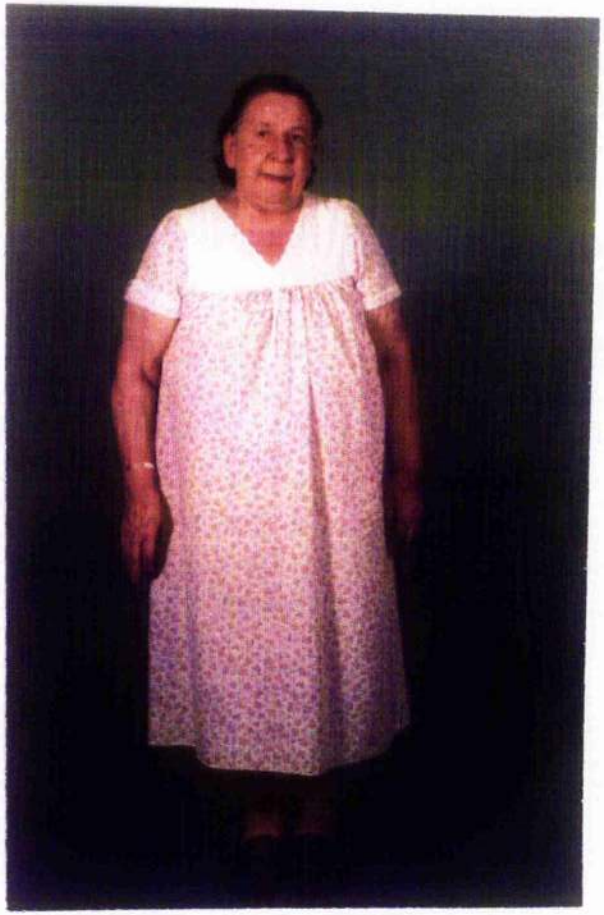


Figure 1.2: Typical patient with chronic bronchitis ('Blue Bloater')

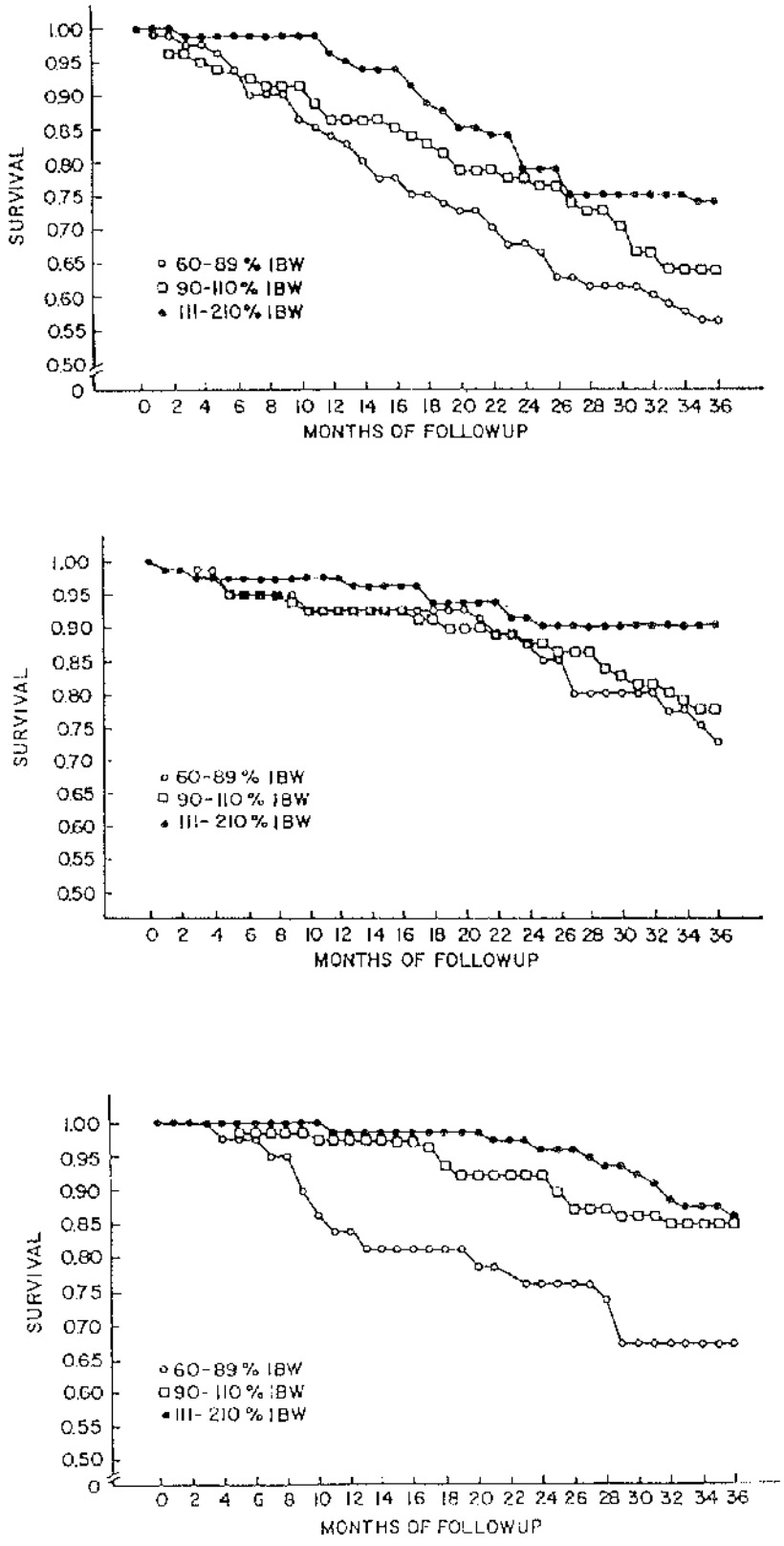


Figure 1.3 : Survival data from the NIH trial of COPD patients showing increased impact of low body weight on mortality in patients with less (lower panel) compared with patients with moderate (middle panel) and very severe (upper panel) airflow obstruction (Reproduced with permission).

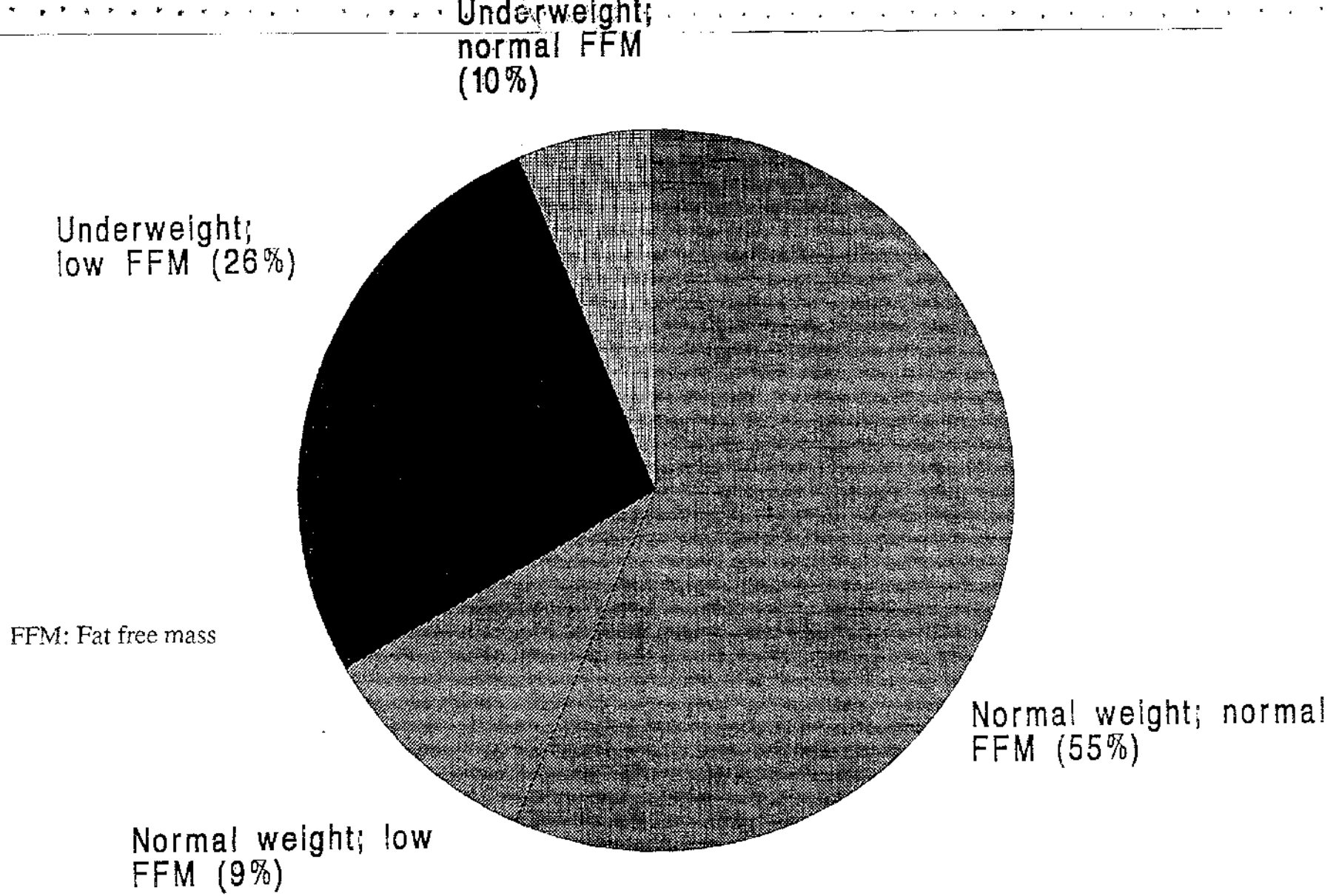


Figure 1.4 Prevalence of nutritional depletion in a Dutch COPD population. The use of fat free mass as an indicator of nutritional status uncovers greater prevelance of nutritional depletion than the routine index of body weight.

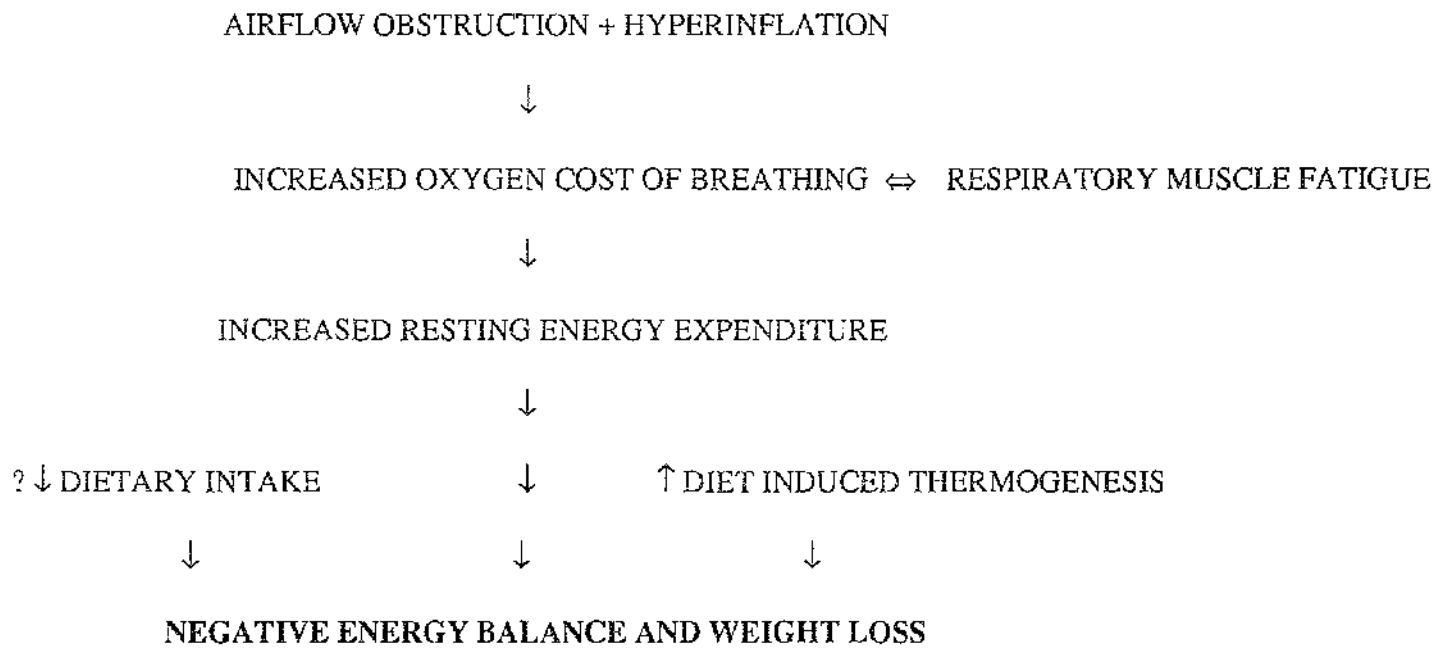
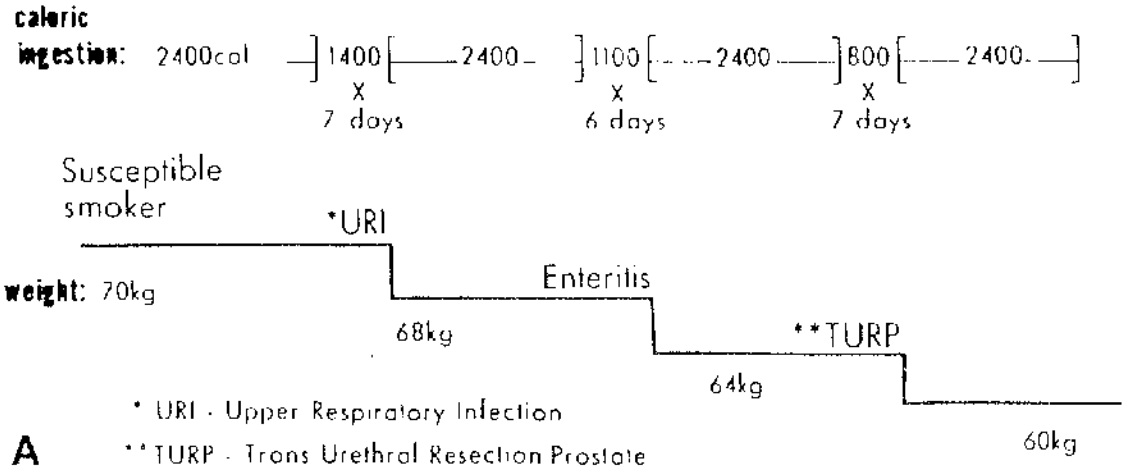


Figure 1.5: Model of pathogenesis of weight loss in emphysema (suggested by Wilson, Rogers and Hoffman, 1985).



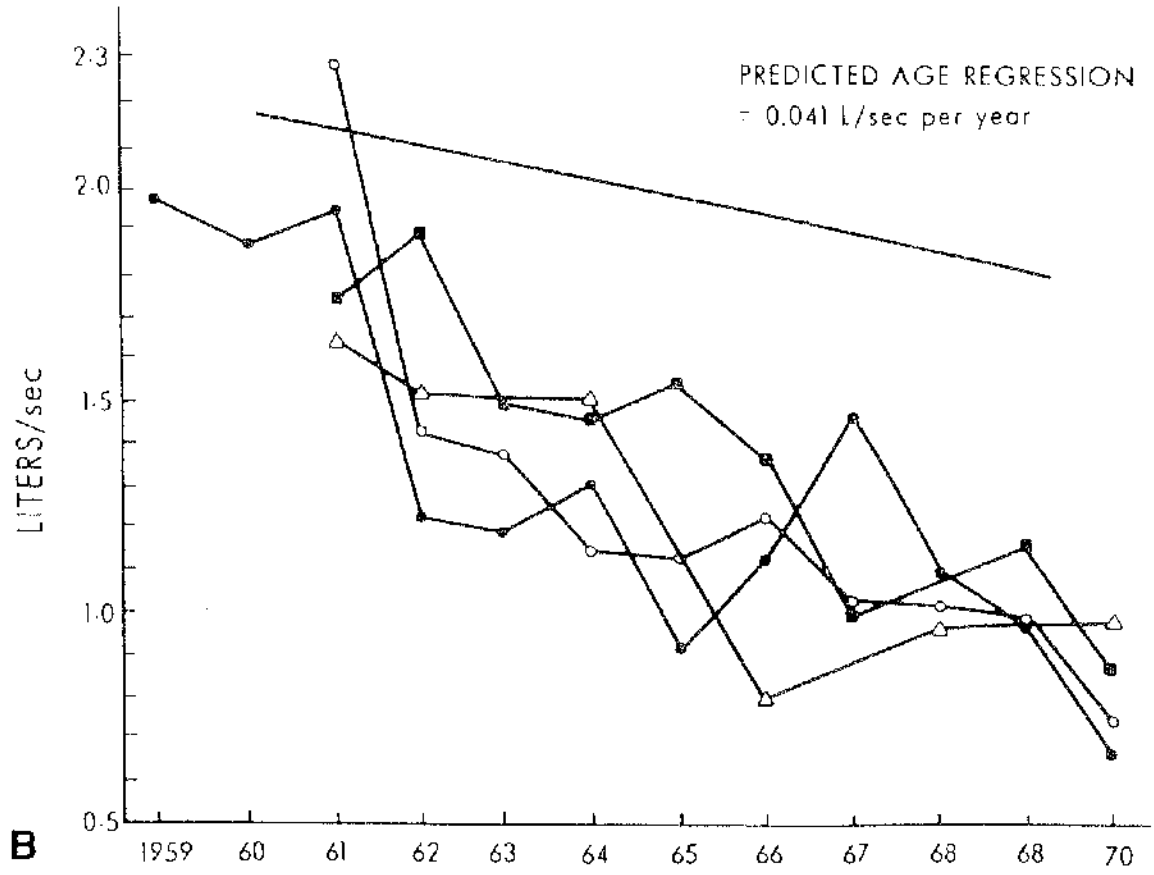


Figure 1.6 : Influence of concurrent illnesses on weight loss and lung function in COPD (after Bates; reproduced with permission from the original). Each intervening illness is associated with decreased food intake and weight loss. Lower panel shows actual stepped decline in lung function of same subject compared to the predicted age related loss, which is linear.

CHAPTER 2: Methods

2.1 Introduction

This chapter provides a description of the various methods of measurement used in the studies that comprise this thesis. The methods of measuring resting energy expenditure and the oxygen cost of breathing are described in greater detail than the standard and relatively well established techniques used to assess nutritional status and lung function.

2.2 Measurement of resting energy expenditure

2. 2.1 Principles and practice

The energy spent by a person in the course of a day is the sum total of the basal metabolic rate or BMR, the energy cost of arousal and physical activity and the thermogenic effect of food (Figure 2.1, Ravussin and Bogardus, 1986). Since true basal conditions are difficult to define and seldom achieved, sleeping metabolic rate is accepted as a close approximation. For practical purposes resting energy expenditure (REE) is defined as the minimum rate of energy expended in an awake, relaxed, comfortable state in the supine or semi-supine posture after an overnight fast and is estimated to be about 8% greater than the sleeping metabolic rate. REE normally constitutes 70- 80% of the total

energy expenditure in sedentary persons. Of the REE, 90% is consumed by the various osmotic pumps which maintain a difference in electrolyte concentrations between intracellular and extra cellular fluids and by the processes involved in the synthesis of vital proteins and macromolecules. At rest, less than 10% of the REE is required for breathing, cardiac contraction and the other mechanical processes that sustain life.

Calorimetry is the science of energy measurement. It is based on two fundamental principles. First, the law of thermodynamics which states that energy can neither be created nor destroyed and therefore, by implication, the energy in a closed system is a constant. Second, the measurable form of energy expenditure is heat output. Almost 200 years ago, Lavoisier, Priestly and Black demonstrated that combustion or energy generation was an oxygen consuming and heat generating process. Lavoisier and Laplace carried out experiments in which a guinea pig was placed in a small chamber covered with ice, and showed that the rate at which the ice melted over a ten hour period was related to the amount of CO_2 produced by the animal (Guggenheim, 1981). At the end of a century which witnessed intense research activity in this field, Atwater and Rosa (Atwater and Benedict, 1899) succeeded in designing a chamber in which the heat produced by a human could be measured with an accuracy of

0.1%. This technique whereby energy expenditure is estimated by the direct measurement of heat produced is called direct calorimetry. In practice this is achieved by the measurement of heat changes within a chamber confining the subject or by using a heat exchanging body suit (Murgatroyd et al, 1993). The methods employed by Atwater and co- workers to estimate energy expenditure and the measures of energy expenditure made by their equipment still remain the gold standard in the field of calorimetry. In addition to measuring energy expenditure, the Atwater and Rosa chamber also enabled confirmation of two important hypotheses that form the basis of calorimetry : (1) The total energy expenditure as measured by the heat produced was equal to the net energy from the food ingested (total chemical energy in food minus energy lost in faeces and urine), i.e. the first law of thermodynamics was true and (2) the total energy expenditure was related quantitatively to the amount of oxygen consumed. It is the latter observation that forms the basis of indirect calorimetry.

2.2.2 Indirect Calorimetry

Indirect calorimetry is based on the principle that energy generation is an oxygen consuming phenomenon and therefore measurement of the amount of oxygen consumed provides a reliable indication of energy expended.

Under conditions of equilibrium, estimates of energy expenditure obtained from measurement of gas exchange i.e., oxygen consumption and carbon dioxide production have been shown to compare very favourably with values obtained by the elaborate techniques of direct calorimetry (Kinney, 1988). This method of determining energy expenditure by gas exchange measurements has achieved much popularity mainly due to the availability of a number of simple devices with inbuilt computerised data processing equipment (metabolic carts) that measure oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$) and calculate energy expenditure from expired gas analysis (Kemper, 1989). There are a number of different types of such equipment, but in essence all of them measure the difference in oxygen and carbon dioxide content between inspired and expired gas, and where necessary, minute ventilation, to calculate $\dot{V}O_2$ and $\dot{V}CO_2$ and hence REE (Figure 2.2). Expired gas is usually collected through a mouth piece after application of a nose clip ('Closed system' of indirect calorimetry). Expired gas may also be performed on a sample of air drawn from a chamber, usually a hood, which encloses the subject's head or upper body ('Open system of calorimetry).

2.2.3. Factors influencing REE measurements .

Measurements of REE need to be performed under strictly controlled conditions in order to be reliable. REE is usually measured after an overnight fast, in a relaxed, supine or semi-supine posture. The importance of maintaining a thermoneutral environment whilst calorimetry is being performed, particularly in the very young and the elderly, is well recognised. Buskirk et al (1960) provided evidence to show that previous nutrition, sleep patterns and body temperature are three of the other variables that influence REE. Methodological factors may also be of relevance, in particular, whether, during indirect calorimetry, expired gas is collected by a mouthpiece and nose clip system, face mask or a non-invasive ventilated hood (Kinney, 1988).

2.3. Prediction equations for REE used in the study

Although indirect calorimetry is a reliable method of estimating a person's energy expenditure, the equipment and the expertise required to carry out the procedure are not readily available. In situations where calorimetry is not available, REE is usually calculated from one of many prediction equations that have been published (Harris and Benedict, 1919; Schofield, 1985; Quebbeman and Ausman,

1982; Wilmore, 1977; Hansell et al, 1987). These equations were derived from calorimetry performed in normal subjects and are used not only to predict REE when calorimetry is not available, but also as standards against which measured REE values are compared. The most commonly used equations are:

(a) Harris- Benedict equations (1919): These are the most widely used and were derived from a population of 239 healthy adults. There are separate equations for males and females; age, height and sex are the measured variables. The equations are as follows:

REE in kcalories / 24 hours

Male : 66.473 + 13.751 (weight in kg) + 5.03 (height in cm) - 6.755 (age in years)

Female : 655.5095+ 9.463 (weight) + 1.8496 (height) - 4.675 (age)

(b) Schofield (1985) : These equations are increasingly used as they involve the measurement of only one variable, weight. The equations were derived from data pooled from 114 separate studies involving over 7000 subjects of a wide range of body composition and ethnicity.

REE in MJ / 24 hours

Male : 31-60 yr. : 0.048 (weight in kg) + 3.653 ;

Over 60 yr.: 0.049 (weight) + 2.459;

Female: 31-60 yr.: 0.034 (weight) + 3.538;

Over 60 yr.: 0.038 (weight) +2.755;

(c) Quebbeman - Hausmann (1982): Though not widely applicable to the general population, this equation has been used as a reference for a hospitalised or ill patient group (Moore and Angelillo, 1988). The equations were derived from patients receiving parenteral nutrition for various reasons.

REE in kcal/ day

Males: 12.3 (weight in kg) + 754;

Females : 6.9 (weight) + 874

Based on body surface area (BSA):

Male : 789 (BSA) + 137

Female : 544 (BSA) + 414

Although it involves measurement of more variables (height and weight) than the Schofield equation (weight), the equation that has been used widely in studies of energy balance in patients with lung disease is the HB equation (Goldstein et al 1987; Donahoe et al 1989; Wilson et al 1990; Schols et al 1991; Green and Muers, 1992). It is was felt that in order to conform to standard practice, REE obtained by the HB equation would be taken as the value against which comparison of measured values would be made. In patients with scoliosis and thoracoplasty in whom

body height could not be considered a reliable indicator of body dimension, arm span was used in place of height in the HB equation (Harper et al, 1965). In these patients the Schofield equation was also applied and the results thus obtained are also quoted if they were different from those obtained from the HB equation.

2.4 Indirect calorimetry in patients with lung disease - comparison of hood and mouthpiece plus noseclip systems

2.4.1 Introduction

The measurement of resting energy expenditure by calorimetry is influenced by a number of biological and environmental factors (Buskirk et al, 1960; *vide supra*). In the case of indirect calorimetry, in addition to the biological and environmental variables, certain methodological factors also come into play (Kinney, 1988). As discussed previously, indirect calorimetry involves the collection for expired gases for analysis of oxygen and carbon dioxide content. Some investigators have shown that in normal individuals the method of expired gas collection, whether by relatively invasive mouth piece and nose clip system, face mask or by non-invasive systems like a ventilated canopy, has no bearing on REE measurements (Segal, 1987; Soares et al, 1989). However other workers have found that the use of invasive

respiratory apparatus in the form of a mouth piece and nose clip increases the inspiratory flow and tidal volume (Askanazi et al, 1980). If this were the case in subjects undergoing calorimetry the use of such apparatus will influence the results of indirect calorimetry. Furthermore, as the ventilatory capacity of the population under investigation (patients with lung disease) is restricted it would also be possible that the documented effect of respiratory apparatus may have an even more pronounced influence on minute ventilation and therefore gas exchange measurements. It seemed appropriate, therefore, to assess the two systems, mouthpiece plus nose clip ("invasive") and a ventilated hood ("non-invasive"), in the study population before adopting one of them as the standard for all the studies of energy expenditure. Hence a study comparing an invasive (mouth piece plus nose clip) and a non-invasive (ventilated canopy) system of indirect calorimetry was undertaken.

2.4.2 Subjects and methods

Twelve patients with severe lung disease recruited from Respiratory outpatient clinics of the Glasgow Royal Infirmary and eight healthy were studied (Table 2.1). Six patients suffered from COPD, four from COPD and respiratory dysfunction due to previous chest wall surgery for tuberculosis (thoracoplasty). Two patients had respiratory

failure secondary to scoliosis. The controls were healthy adults (current or past staff of the Respiratory Department and Department of Human Nutrition, Glasgow Royal Infirmary and their relatives) who were naive to the techniques employed in the study.

The study was approved by the local Ethics committee and all subjects gave informed consent.

Study protocol

The subjects were studied on two consecutive mornings in the fasting state. Indirect calorimetry was performed in a dedicated energy and exercise laboratory. Patients who were being treated with inhaled beta agonist therapy were studied at least two hours after the last dose of the drug. After a 30 minute rest period during which a detailed explanation of the techniques was given, indirect calorimetry was performed first with a ventilated hood system. This was followed by a ten minute rest period after which REE was estimated by a mouth piece plus nose clip system. This order was followed in view of previous investigations in the field suggesting an 'order effect' in the measurements with the REE remining elevated for a considerably longer period of time following measurement with a mouth piece and nose-clip system than with a non-invasive system (McAnena et al, 1986). Calorimetry by both

techniques was conducted at a room temperature of 20°C, with the subjects fully clothed in the semi-recumbent posture. The same procedure was repeated on the second day. Lung function tests were carried out after calorimetry on the second day in all except one subject who was studied two days after calorimetry. At the end of the study, subjects were asked as to rate the two systems of calorimetry.

After the initial study, in order to assess the effect of respiratory apparatus on REE and RER, calorimetry was performed in eight subjects (controls) with the subjects breathing unimpeded within the hood and subsequently through a mouth piece plus nose clip system whilst within the hood. Experience in patients with lung disease indicated that such a procedure caused unacceptable respiratory distress and this part of the study was not carried out in these patients.

Calorimetry

Hood system: (Figure 2.3): Indirect calorimetry with the hood system was performed with the Deltatrac Metabolic Monitor ™ (Datex instrumentarium corporation, Helsinki) (Appendix 1). In this system the subject's head is enclosed in a transparent plastic hood and ventilated with a constant flow of about 40 liters/min of room air. Infra-red and differential paramagnetic sensors measure the differences in carbon dioxide (CO_2) and oxygen (O_2) concentrations between

inspired and expired air. Oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$) and respiratory exchange ratio (RER) were estimated every minute for a period of 20 minutes. The data obtained in the first five minutes were discarded and data obtained in the last 15 minutes were used to estimate REE if there was less than 5% minute to minute variation in the RER and $\dot{V}O_2$ (Appendix 2). REE was calculated using Weir's formula (Weir, 1949). Artifacts produced by coughing were automatically eliminated in the final calculations.

Arterial oxygen saturation was monitored (Radiometer Ltd., Copenhagen) during the study to ensure that patients did not desaturate whilst inside the hood. Gas calibration was performed before each measurement with a standard high purity gas mixture provided by the manufacturer. The system was checked by a methanol burning test every week during the study period and the average RER values for the last 15 minutes of a 30 minute methanol burning run were confirmed to be within 0.64 and 0.69. Flow calibration was also performed by calculating the total amount of CO_2 produced during the methanol burning test and the flow constant adjusted if the actual CO_2 production differed from the expected values.

The theoretical basis of the methodology and the data supporting the time course of the measurements are given in Appendix 1.

Mouth piece system: (Figure 2.4) The mouth piece system (PK Morgan Ltd., Rainham, United Kingdom) involved subjects breathing through a low resistance, low dead space (150 ml) valve box. The valve box incorporates a turbine ventilometer in the expired limb for the measurement of ventilation. Expired gas was analysed for O_2 and CO_2 concentrations by para-magnetic and infra-red analysers respectively. $\dot{V}O_2$, $\dot{V}CO_2$ and RER were averaged over a minute and measured for 15 minutes. Data obtained in the first five minutes were discarded and REE was calculated from the remaining data. Gas analysers were calibrated as previously mentioned.

All subjects underwent lung function tests. Forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC) were measured using a whole body plethysmograph (PK Morgan Ltd) and expressed as percentage of predicted values (Grimby and Soderholm, 1963).

Statistics

Day to day and between method differences in REE were compared by paired 't' tests and Wilcoxon test, using a standard computer programme (MINITAB Release 9.2, State

College, PA, USA). Mean difference between methods, 95% confidence intervals and 'p' values were calculated. Significance was assessed at the 5% level. REE estimated by the hood and mouth piece techniques were also compared for limits of agreement by the method of Bland and Altman (1986). Pearson product moment correlation coefficient was used to assess correlation between variables.

2.4.3 Results

Day to day variation

There was no significant day to day variation in the REE measured by either method in patients and in controls (Figure 2.5). In controls mean difference between Day 2 and Day 1 with the hood was 11 kcal / 24h (95% Confidence Intervals: -22, 43; p = 0.4); mouth piece: -68 kcal/ h; CI : -188, 13 kcal/ 24h; p = 0.16). In patients mean difference between Day 2 and- Day 1 with the hood technique was - 11 kcal/ 24h (95% confidence intervals (CI): - 69, 48 kcal/ 24h; p =0.62); with the mouth piece system the value was: 23 kcal/ 24h (CI : -76, 136; p = 0.64).

Between method variation

There was a significant difference between the methods in patients but not in controls (Figure 2.5). In controls the mean difference was 19 kcal/ 24h (95% CI: - 65, 92 kcal/ 24h; p = 0.57). In patients the mean difference in

REE between the methods was 186 kcal/ 24h (95% CI: 55, 278 kcal/ 24h; p = 0.01).

The mouth piece technique gave higher values than the hood system in 10 out of 12 patients and in 5 out of 8 controls. As estimated by the method of Bland and Altman, the limits of agreement (mean difference ± 2 standard deviation) between the methods was much greater in patients than in controls (Figure 2.6); the range of difference between the two methods was also much higher in patients than in controls (-156 to + 467 kcal / 24h in patients vs - 126 to 120 kcal/ 24h in controls).

Respiratory exchange ratio

In patients, but not in controls, respiratory exchange ratio (RER) was significantly higher when breathing through the MP system (Figure 2.7). In patients, mean difference in RER between the method, RER in MP being higher, was 0.08 (CI: 0.03, 0.13; p = 0.002). In controls the mean difference was 0.01 (CI: -0.01, 0.03; p = 0.21).

Mouth piece in hood

There was some evidence (p <0.06) to suggest that REE and RER were higher when controls breathed through a mouth piece within the hood compared with breathing unimpeded in eight control subjects (Table 2.2). The mean difference in REE between breathing with the MP and

breathing unimpeded was 71 kcal/ 24h (CI : -10, 151 kJ/ 24h; p = 0.06) The difference in RER was 0.03 (CI: 0.00, 0.07; p = 0.06).

There was a correlation between RER on the mouth piece and the difference between the two methods of estimating REE ($r = 0.59$; $P < 0.05$), but there was no correlation between lung function and the difference between the methods ($r = -0.30$). There was no correlation between the mean REE measured by the two methods and the difference between the methods.

Ten out of twelve patients expressed a preference for the hood method; one preferred the mouth piece system as she had felt claustrophobic in the hood; the remaining patient did not express a preference for either system. Four of the controls preferred the hood, one the mouth piece; the other three did not express a preference for either system.

2.4.4 Discussion

The WHO Expert Consultation Report on protein and energy requirements drew attention to the importance of measuring rather than predicting energy expenditure in the estimation of energy requirements of individuals (FAO/WHO/UNU Report, WHO technical report series, 724, 1985). Studies in healthy adults have shown that

the methods employed to collect expired gas for measuring REE do not affect the results, and in routine circumstances use of a hood, mask or mouth piece systems for indirect calorimetry give similar results (Segal, 1987). However, others have suggested that a ventilated hood system is preferable to other systems of data collection as it is non-invasive and does not affect the subject's breathing pattern (Kinney, 1980).

Most measurements of REE are brief and it is well recognised that the RER measured in a non-steady ventilatory state does not represent the respiratory quotient (RQ) of the tissues (Kinney, 1980). Increased ventilation leads to a washout of CO_2 from the lungs and therefore an elevation in the REE calculated from $\dot{V}\,CO_2$ values measured at the mouth. In a study of healthy volunteers Askanazi et al (1980) demonstrated that the use of respiratory apparatus (mouth piece plus nose clip) resulted in a stimulation of ventilation and caused a significant increase in inspiratory flow . It is most likely that this effect, in the presence of compromised lung function leads to more pronounced alterations in breathing pattern and work of breathing, resulting in elevated RER and REE. This would account for the tendency of the mouth piece method to give higher values for REE (and RER) and the clearly wider difference in REE estimated by the hood and mouth piece methods in patients compared with healthy

subjects. It is noteworthy that Segal's study of healthy volunteers also documented an elevated, albeit statistically non-significant, RER in subjects using the mouth piece . Lending support to the view that the mouth piece and nose clip system causes an increase in RER and REE is the observation that these measures are elevated when subjects were made to breathe through a mouthpiece and nose clip within the hood compared with breathing unhindered inside the hood (Table 2.2).

The results of this study are of particular relevance to the investigation of the energy balance of patients with chronic lung disease. The apparently contradictory results of studies in this field may well be the result of methodological differences, as the study employing a non-invasive hood system found REE in malnourished COPD patients to be low (Ryan et al, 1993) whilst a study using a mouth piece system gave the opposite results (Donahoe et al, 1989). It is important that studies in the field adopt appropriate standard techniques and on the basis of the results of this study it seems appropriate that in patients with breathing difficulties more reliable estimates of REE are obtained from a non-invasive ventilated hood system. The other advantage of the ventilated hood system in patients with lung disease is that it does not inhibit coughing, which is a common problem in this patient group. Not uncommonly measurements employing a mouth

piece and nose clip are interrupted by bouts of coughing, rendering the achievement of a steady state difficult.

It is however possible that in some patients (one out of twelve in this group) a feeling of claustrophobia may render the hood technique unattractive, and others have drawn attention to the effect of interaction between subjects and the hood system in those unaccustomed to the apparatus (Soares et al, 1989). In such cases a mouth piece may be used to collect expired gases, bearing in mind that this apparatus may stimulate ventilation and thus cause a spurious elevation in REE. In these situations monitoring minute ventilation, oxygen saturation and RER may enable detection of hyper ventilation, alerting the investigator to the possibility of a methodological cause for an elevated REE.

2.4.5 Conclusion

In conclusion, this study has shown that the method of data collection has a greater influence on the results of indirect calorimetry in patients with breathing difficulties compared to healthy individuals. In these patients use of a mouth piece may stimulate ventilation and result in an over estimation of REE. Unless claustrophobic feelings preclude their use, non-invasive hood systems are preferable in this patient population. On the basis of this study all measurements

of REE performed in the investigations of this thesis were made with a ventilated hood system.

2.5 Oxygen cost of breathing

2.5.1 Principles and practice of measurement

The bulk of the work of breathing is directed at overcoming the resistance of the airways, pulmonary tissue and the chest wall. In the healthy adult only about 20% of the total resistance is tissue resistance, the remaining 80% being airway resistance (Bartlett, 1979). Although it was acknowledged that the work of breathing was increased in patients suffering from chronic obstructive lung disease, it was not until the late 1950s that consistent attempts were made to quantify this work in terms of oxygen consumption. Partly, the interest in measurement of the oxygen cost of breathing (OCB) arose from attempts to verify the theoretically attractive but unproved, and technically difficult to prove, hypothesis proposed by Otis (1954) that in patients with lung disease there was a point of "critical gain" at which the oxygen gain associated with increased ventilation was less than the oxygen cost of ventilation i.e. the oxygen consumption of the respiratory muscles and that this was the cause of effort limitation in these patients. The most commonly used method of estimating the oxygen cost of breathing was the added dead space technique originally

described by Liljestrand (1918). Other techniques have since been used by various investigators (Campbell and Westlake, 1959; Thung et al 1963). The principles underlying the various techniques are described below.

1. Closed circuit, added dead space technique (Liljestrand, 1918) : The oxygen consumption ($\dot{V}O_2$. R) and minute ventilation ($\dot{V}_E$. R) at rest are measured in the usual fashion. After adequate data collection in a stable state a suitable dead space is added to the breathing circuit to cause an increase in ventilation and oxygen consumption. After a steady state has once again been reached the oxygen consumption ($\dot{V}O_2$ +) at the level of augmented ventilation ($\dot{V}_E$ +) is estimated. The oxygen cost of breathing is calculated as the increase in oxygen consumption between dead space and resting intervals relative to the increase in minute ventilation.

$$\text{Oxygen cost of breathing (ml } O_2 \text{ / litre ventilation)} = \frac{(\dot{V}O_2 +) - (\dot{V}O_2.R)}{(\dot{V}_E +) - (\dot{V}_E.R)}$$

2. Carbon dioxide induced ventilation (Levison and Cherniack, 1968): Here ventilation is augmented, not by the addition of a dead space but by increasing the fraction of carbon dioxide in the inspired air to 5%.

3. Estimating OCB during mechanical ventilation (Thung et al, 1963) :

In patients undergoing mechanical ventilation the work of 0breathing is performed by the ventilator. The difference between the oxygen consumption during spontaneous ventilation and that with the patient relaxed during artificial ventilation is taken as the oxygen cost of breathing.

2.5.2 Values for the oxygen cost of breathing

The actual values for the oxygen cost of breathing vary considerably depending on the technique and the levels of ventilation at which OCB was estimated. In general, in normal subjects, the oxygen cost of breathing is 1-2 ml O_2 / litre of ventilation over a minute ventilation range of 6-15 litres/ min. Assuming a resting oxygen consumption of about 250 ml / minute the oxygen cost of breathing is thus less than 5% of the total (1-2x 6 = 6-12 ml O_2 / min). However at higher levels of ventilation, for example during exercise, the OCB increases such that at a minute ventilation of a greater than 50 l/min OCB is 8 - 10 ml /L, constituting a greater proportion of the total oxygen consumption. Table 2.3 summarises the various studies in the field of measurement of OCB.

2.5.3 Description of technique used to measure OCB in study

OCB was measured by the method based on the technique described by Lijestrand (1918) and Cherniack (1958). Expired gas was collected via a mouthpiece attached to a low dead space valve and passed through to a metabolic measurement cart (Benchmark system, PK Morgan Ltd, England). The cart measures ventilation by a flexible membrane flow meter. Oxygen and carbon dioxide tensions are measured with a zirconia crystal and a rapid infra-red analyser respectively. At the beginning and end of each measurement the gas analysers were calibrated using a high purity gas mixture (BOC Ltd). The flow meter was calibrated using a 5 litre syringe at various flow rates and accuracy of the flow measurements were confirmed to be within 2% over a wide range of flow rates. Resting $\dot{V}O_2$, $\dot{V}CO_2$ and minute ventilation (V_E) were measured first for 15 minutes using the metabolic cart and the data obtained during a 5 minute period of stable ventilation (minute to minute variation in ventilation < 1 litre) was used in the calculations (Figure 2.8). Following this a 15 minute rest period of breathing without the mouthpiece was allowed. Then the subject was again attached to the mouthpiece, now with a dead space tubing added to the breathing circuit (Figure 2.9). The volume of the

dead space added was variable and aimed to increase the subject's minute ventilation by 5 to 10 litres. Once the subjects achieved a stable level of ventilation with the dead space, $\dot{V}O_2$, $\dot{V}CO_2$ and V_E were estimated again over a stable 5 minute period. Oxygen cost (in ml O_2/ L ventilation) was defined as the ratio of the increase in the oxygen consumption between the dead space and resting ventilation relative to the increase in minute ventilation.

2.6 Measures of nutritional status

The nutritional measures that were made during the study were: body weight, skin-fold thickness at four standard sites and mid-upper arm circumference. Mid-arm muscle circumference was calculated as noted below. Body height and arm span were also measured as indices of stature.

2.6.1 Body weight

Body weight was measured to the nearest 0.1 kg by a beam balance (Weylux Model 424, England). Subjects were weighed standing barefoot in light indoor clothing. In studies involving serial measurements, weighing was done at the same time of the day. The beam balance was calibrated at monthly intervals with known weights over the measurement range (30 - 100 kg).

2.6.2 Body height and arm span

Body height was measured to the nearest centimetre using a stadiometer attached to the weighing scales, with the subjects head in the Frankfurt plane (lower border of the orbital margin and upper border of the external auditory meatus in the same horizontal line).

Arm span was measured the distance between the tips of the middle fingers with the arms abducted to right angles. In patients with musculoskeletal deformities arm span was used as a measure of body dimension in lieu of height (Harper et al 1965).

2.6.3 Skin fold thickness

Skin fold thickness was measured at four standard sites (triceps, biceps, subscapular and suprailiac) with the Holtain calipers (Dyfed, United Kingdom) (Durnin and Womersley, 1974). The calipers were calibrated at regular intervals using a calibration block. In patients with chest wall deformities subscapular and suprailiac skinfolds were grossly distorted and therefore these were not measured.

Triceps skin fold thickness (TSF): With the elbow flexed to a right angle, the mid-point between the acromion and the olecranon processes was marked and the skin-fold at this point picked between the thumb and forefinger of the left hand (Figure 2.10). The calipers were applied and the reading on the dial taken as soon as the phase of rapid compression

was over. Three measurements were made and averaged. If the first three readings were not within 2 mm of each other, the measurements were repeated until three consecutive readings agreed to 2 mm.

Biceps skinfold: This was measured as the thickness of the vertical fold on the front of the left arm, directly above the cubital fossa, at the same level as the triceps skin fold (Weiner and Lourie, 1969).

Subscapular skinfold: Measured below and lateral to the angle of the left shoulder blade, with the shoulder and arm relaxed. The skin fold was raised at the same angle as the inner border of the scapula (medially upward and laterally downward) (Lohman et al, 1968).

Suprailiac skinfold: This skinfold was measured in the mid-axillary line immediately superior to the iliac crest (Lohman et al, 1968).

Mid upper arm circumference (MAC) and Mid-arm muscle circumference (MAMC)

Mid upper arm circumference was measured with a steel tape (Holtain Ltd, Dyfed), at the same level as the triceps and biceps skinfolds (Figure 2.11).

Mid arm muscle circumference (MAMC) was calculated by the formula :

MAMC (in cm) = MAC (in cm) - π TSF.

2.6.4 Body composition

A number of techniques are available for the determination of body composition, most based on the two compartment model which considers the body to be made of two chemically distinct compartments - fat and fat-free, the latter also referred to as lean body mass (Lukaski, 1986). The method that was employed in a study in this investigation was total body potassium measurement. This technique is based on the principle that potassium (K +) is an intracellular cation that is not present in fat and that all the measurable K+ content of the body comes from the fat free mass (Forbes et al, 1961). Total body potassium (TBK; the isotope K+ 40) is measured by a specially constructed counter; the potassium content of fat-free mass being known from factors derived from cadaver analysis (2.46 g/ kg FFM for men and 2.28 g/ kg FFM for women, Behnke, 1974), FFM is derived from the measured TBK value.

2.7 Pulmonary function tests

2.7.1 Lung volumes and spirometry

Vital capacity (VC) and forced expiratory volume in the first second (FEV_1) were measured as indices of pulmonary function. The tests were performed using a body plethysmograph system (PK Morgan Ltd, Kent). Procedures were performed in accordance with formal guidelines which have since been recommended by the British Thoracic Society and the Association of Respiratory Technicians and physiologists (Guidelines for the measurement of respiratory function, 1994). Results of at least three technically satisfactory manoeuvres were inspected and the best value was chosen for analysis. Measured pulmonary function was compared with reference ranges and expressed as a percentage of predicted values (Grimby and Soderholm, 1963).

2.7.2 Exercise capacity

Bicycle ergometry: Symptom limited exercise tests were carried out initially using an electrically braked bicycle ergometer (Siemens Ltd) with the patient breathing through a low dead space low resistance valvebox. The valve box incorporated a turbine ventilometer on the inspired limb for the measurement of ventilation. Expired gas was analysed for oxygen (O_2) and carbon dioxide (CO_2) by an infra-red spectrometer and para magnetic analyser respectively (P.K.Morgan Ltd, England). After a 2 minute rest period

while seated on the bicycle the patients were instructed to cycle with no additional load for 2 minutes. Thereafter the load was increased by 25 watts every 2 minutes until symptoms limited exercise. Two trial tests were performed on separate occasions before the first exercise test to familiarise the patients with the equipment and avoid confounding of the results by a training effect. The maximum value for oxygen consumption attained ($\dot{V}O_2$ max) was taken as an indicator of peak exercise capacity.

Six minute walking test: After the initial investigation using bicycle ergometry was completed, some of the patients taking part in the investigations noted that, despite familiarisation with bicycle ergometry, a measure of exercise capacity which was more in keeping with activities of day to day living would be preferable and therefore, for the subsequent study of nutritional supplementation and Clenbuterol a six-minute walking test was used. In this test subjects were asked to walk as far as they could in six minutes, with a standard encouragement (Butland et al, 1982). Familiarisation with the test was achieved by two practice tests (Guyatt et al, 1984).

2.7.3 Respiratory muscle strength

Maximal inspiratory and expiratory pressures (P I and P E max) were measured at the mouth indicators of respiratory muscle strength. The apparatus was based on that described by Black and Hyatt (1969). P I max was measured from functional residual capacity (FRC) and PE max from total lung capacity (TLC), in accordance with standard

practice. The highest of three technically satisfactory measurements was taken as the value for analysis in each case.

2.8 Peripheral muscle strength assessment

Peripheral muscle strength was measured by hand grip dynamometry, using commercially available equipment (Grip dynamometer, Model 1201; Takei & Company, Tokyo, Japan). Subjects were instructed on the use of the equipment and the best of three grips with the dominant hand was taken as an indicator of peripheral muscle strength (Values expressed in kg-W).

	Controls (n = 8)	**Patients (n = 12)**
Age (yr.)	53 ± 14.5	61.9 ± 10.4
Sex	4 male; 4 female	6 male; 6 female
Weight (kgs)	60.3 ± 6.2	59.8 ± 7.1
Height (cms)	163.7 ± 7.9	162.7 ± 11.3
FEV 1 (% predicted)	95.6 ± 9.1	34.9 ± 9.6

Table 2.1

Characteristics of study population for the study comparing hood and mouthpiece systems of indirect calorimetry .
Values as Mean ± SD.
Key to abbreviation : FEV 1 - Forced expiratory volume in first second.

Subject no:	REE. Hood	REE. Hood + MP	RER. Hood	RER. Hood + MP
1	1340	1453	0.81	0.85
2	1218	1367	0.79	0.82
3*	1980	2207	0.94	1.06
4	1134	1209	0.82	0.84
5	1768	1744	0.84	0.86
6	1464	1511	0.87	0.88
7	1244	1223	0.77	0.77
8	1166	1169	0.80	0.79

Table 2.2: REE (kcal / 24h) and RER in eight healthy subjects estimated during unrestricted breathing within the hood (Hood) and while breathing through a mouth piece plus nose clip within the hood (Hood + MP). * Subject in post-absorptive state.

Authors	Study population	Method used	OCB in ml O_2 / litre ventilation
Cherniack, 1959	16 normal; 22 emphysema	Closed circuit (dead space addition)	Normals: Mean 1.16 (range : 0.45-1.87) Emphysema: 5.96 (1.68 - 18.5)
Campbell et al, 1959	3 normal	Closed circuit	2. 4 (1.2 - 4.5)
Levison and Cherniack, 1968	11 normal; 17 emphysema	5% carbon dioxide	Normals: 1.96 at rest; 4.2 during exercise Emphysema: 6.3 at rest; 9.3 during exercise
Field et al, 1983	13 patients with cadiorespiratory disease requiring ventilation	Mechanical ventilation technique	Mean 8.8 (0.7 - 11.7)
Katsardis et al, 1986	3 normals; 3 cystic fibrosis		

Table 2.3 : Studies on measurement of the oxygen cost of breathing

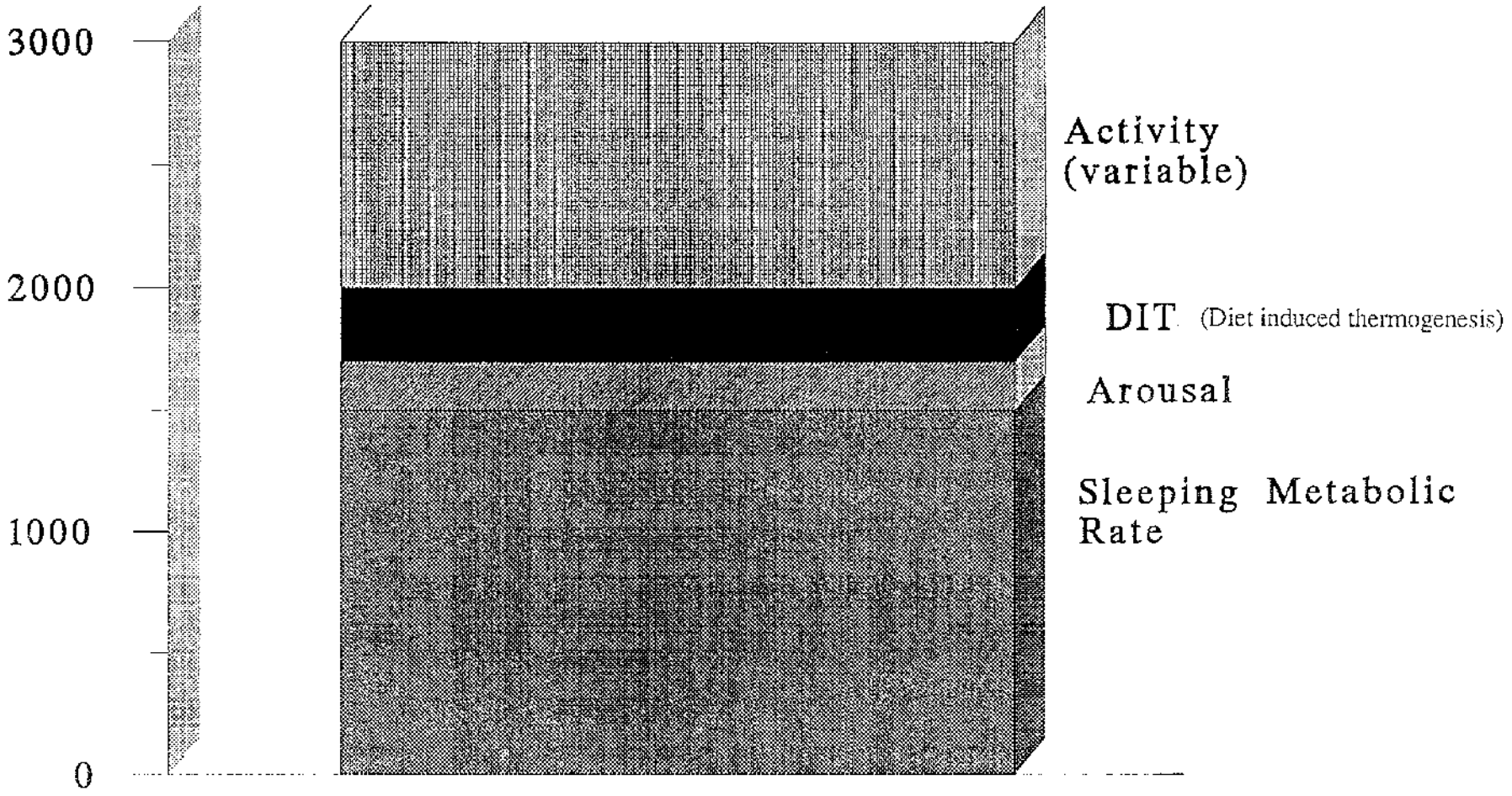


Figure 2.1: Components of 24 hour energy expenditure in an average (70 kg) man.

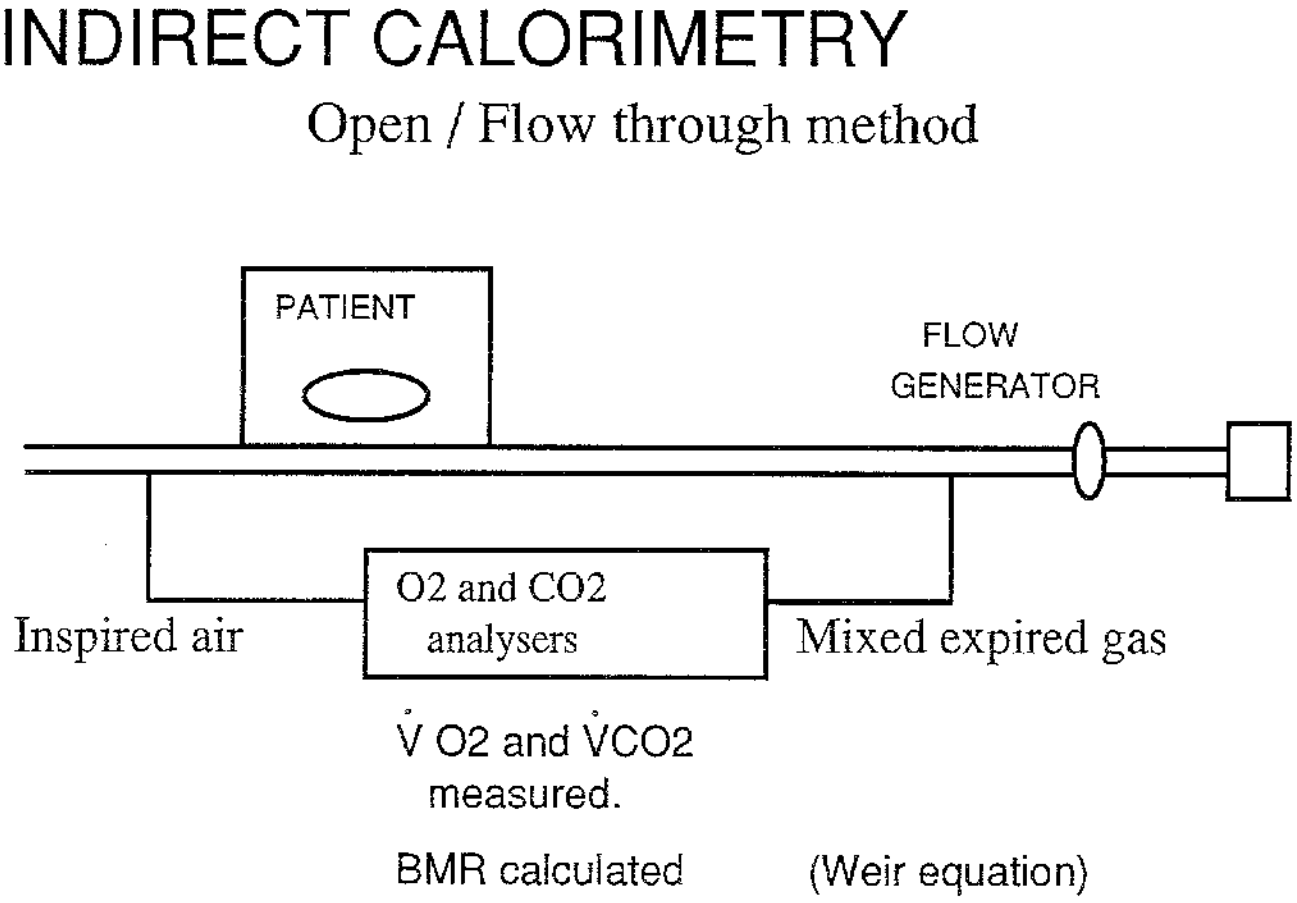


Figure 2.2 : Indirect calorimetry by gas exchange measurements. Standard model of technique.

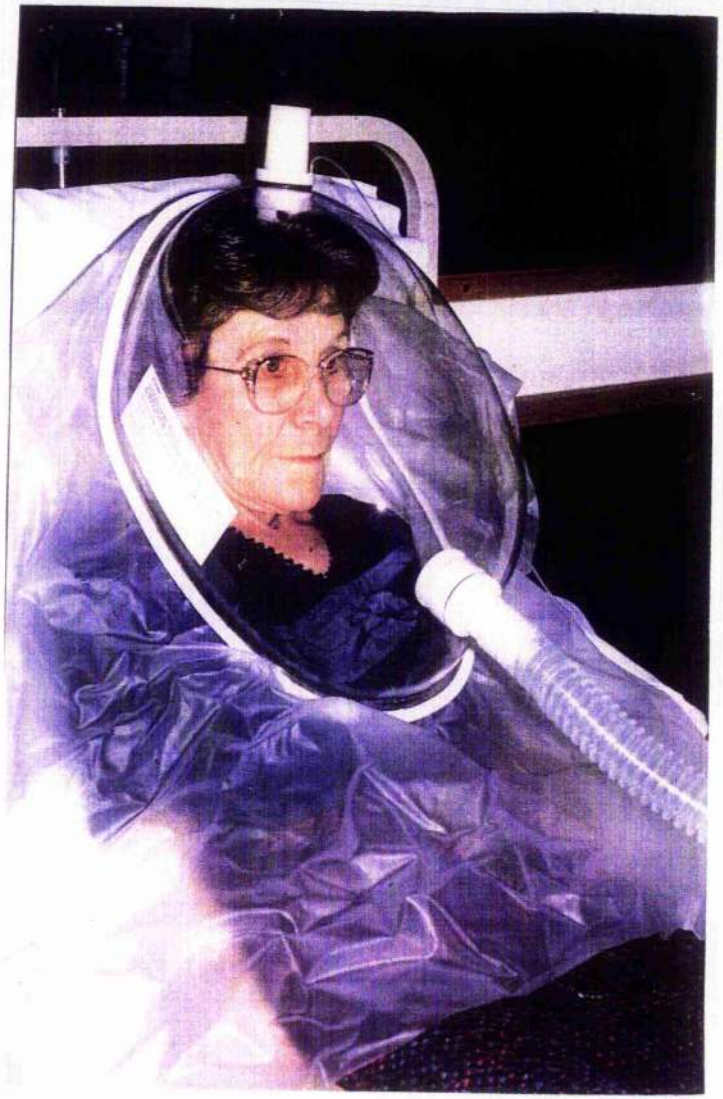


Figure 2.3: Patient in a ventilated hood during indirect calorimetry with a non-invasive system.

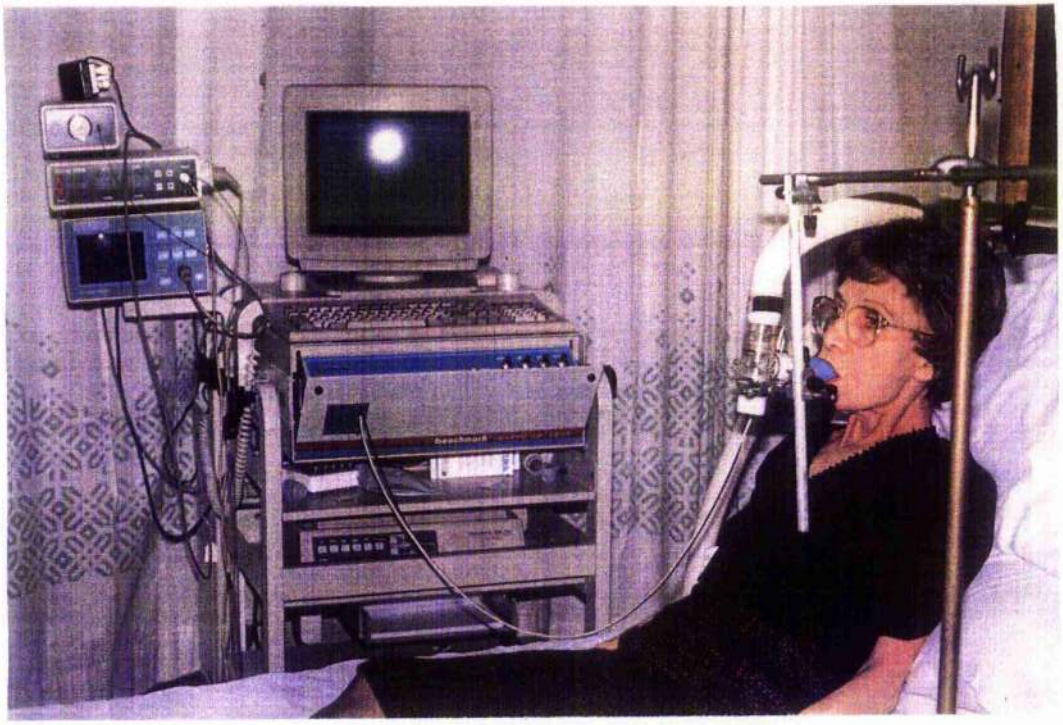
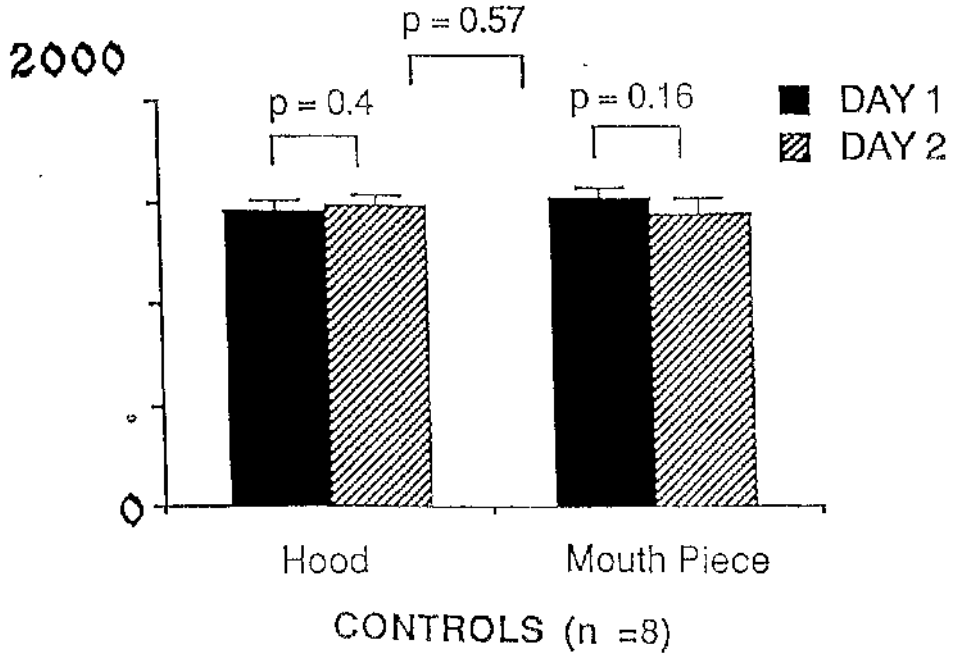


Figure 2.4: Indirect calorimetry using an invasive mouth piece and nose-clip system for expired gas collection.



REE

All values in kcal

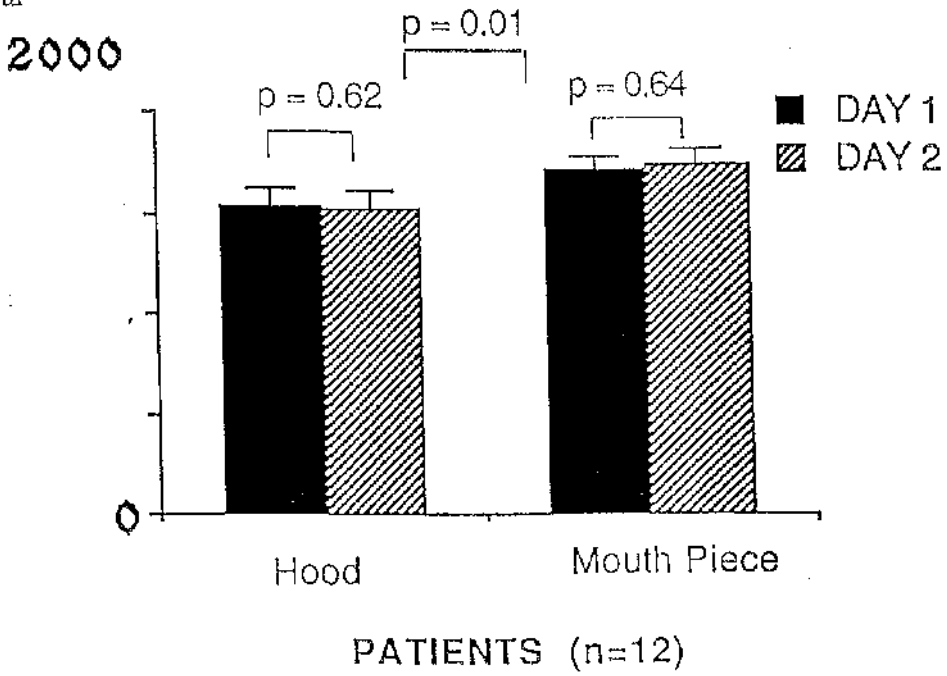


Figure 2.5: REE in patients and controls estimated by the two systems on two days. Note the absence of day to day variation in both systems but a significant difference between the systems in patients but not controls.

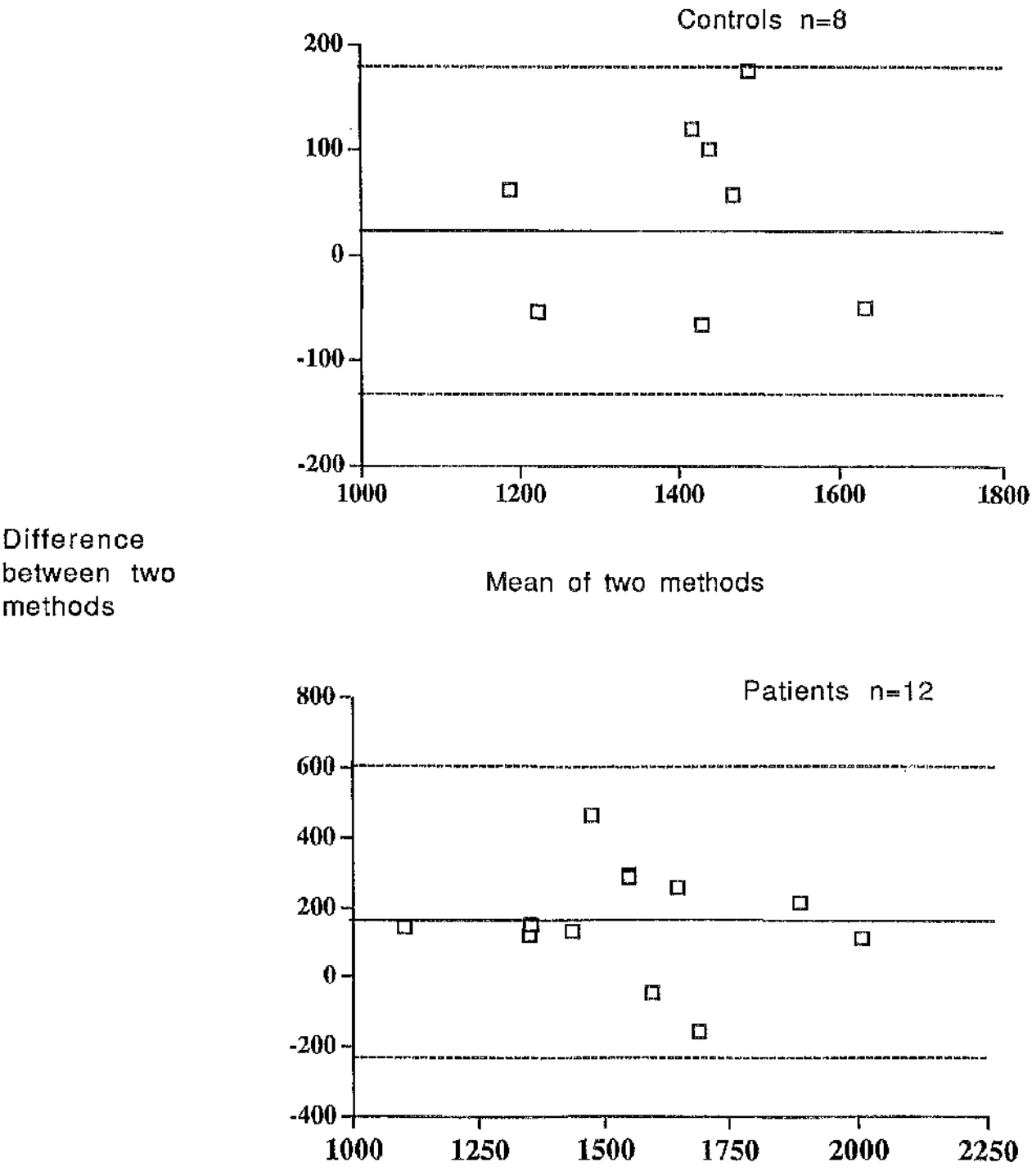


Figure 2.6: Bland and Altman plots showing a greater mean difference between the methods in patients but not in controls (all values in kcal). The limits of agreement between the methods for patients are 606 and -233 kcal/24h, whilst for controls it is only 19 and -158 kcal/24h.

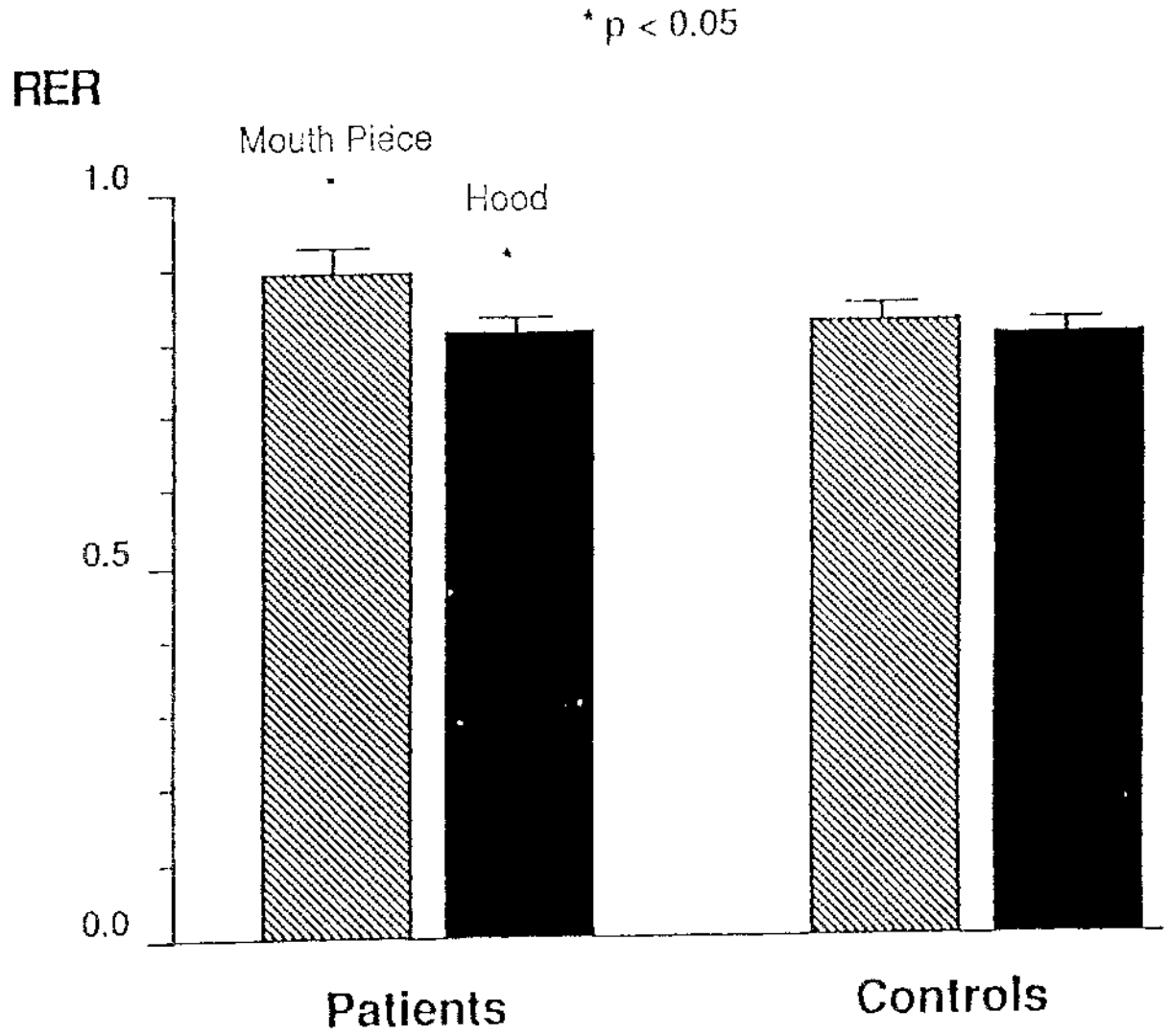
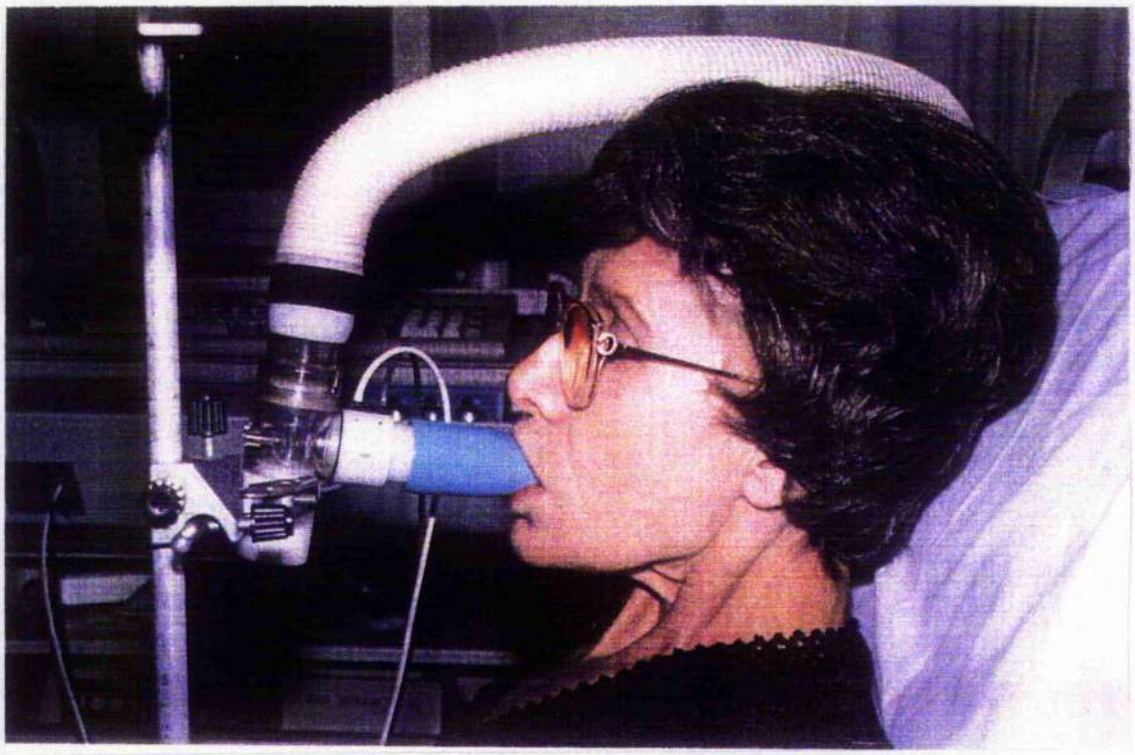
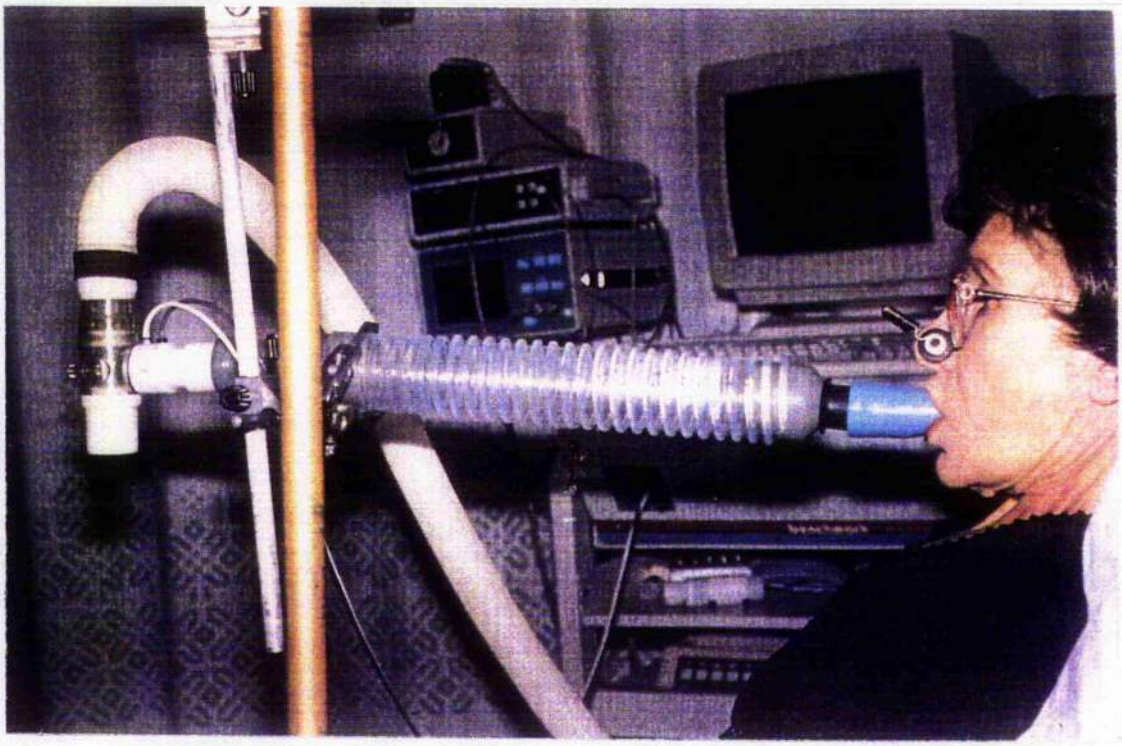
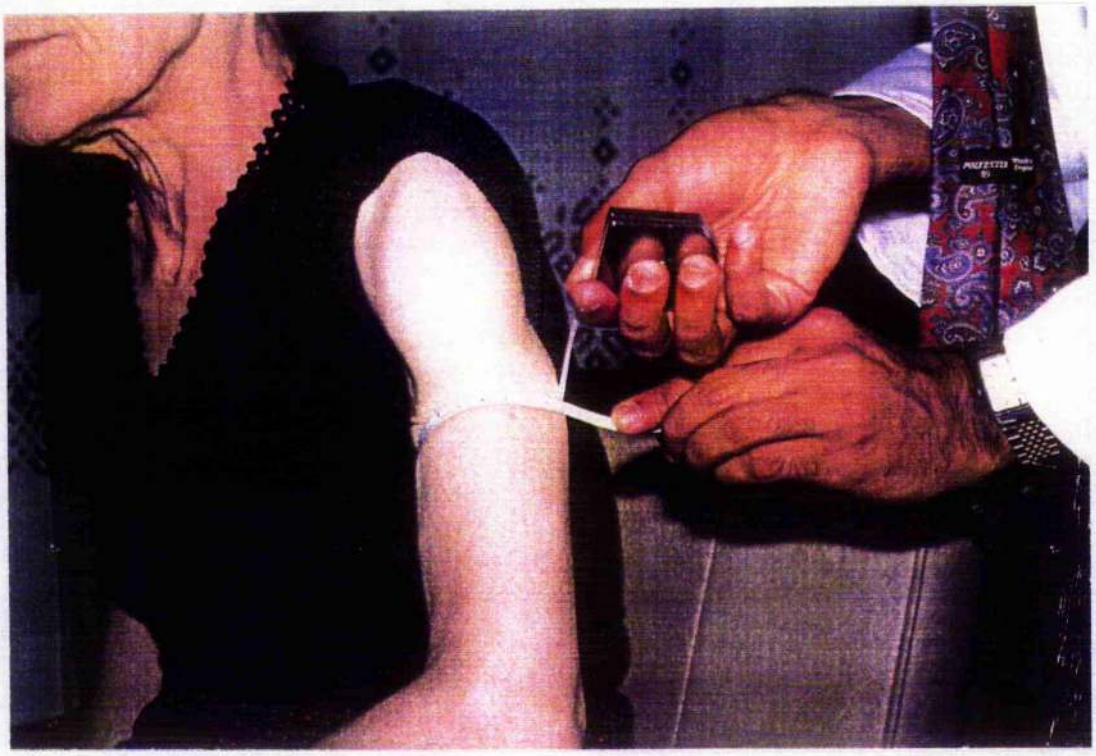


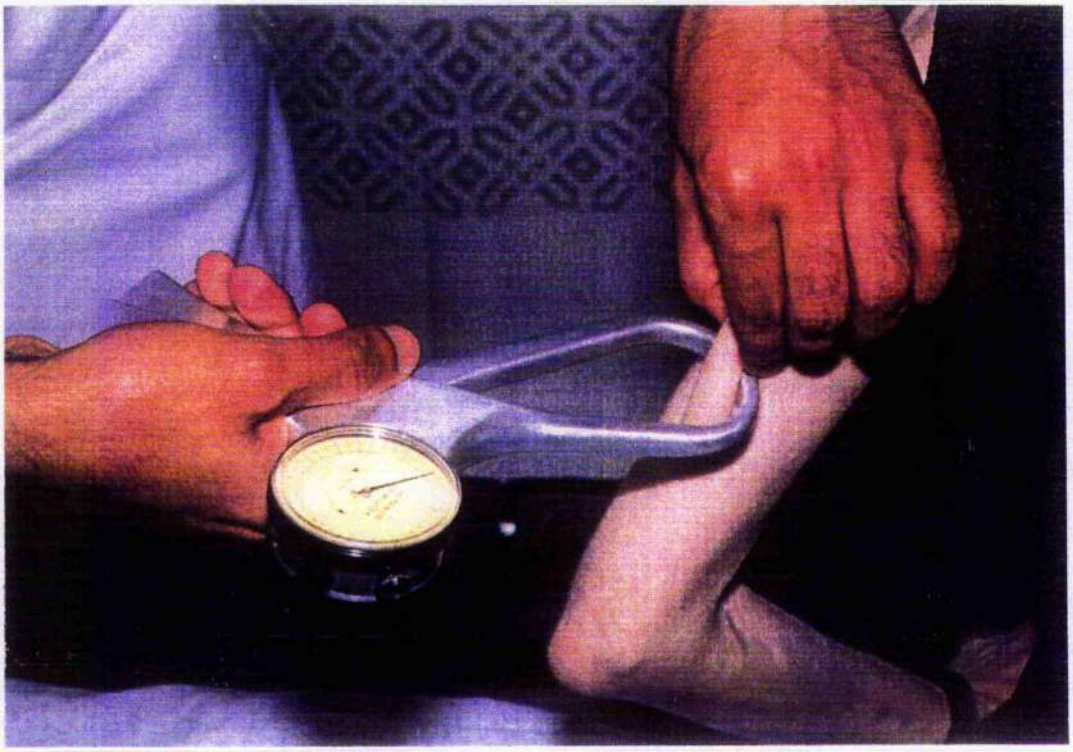
Figure 2.7: Respiratory exchange ratio in patients and controls with the invasive and non-invasive systems.





Figures 2.8 and 2.9 : Measurement of oxygen cost of breathing. Upper figure shows normal breathing; lower figure shows breathing through added dead space.





Figures 2.10 and 2.11: Measurement of mid-arm circumference and triceps skin fold thickness.

CHAPTER 3: Resting energy expenditure and lung function in patients with chest wall disease

3.1 Introduction

One of the theories put forward to explain the weight loss in patients with emphysematous COPD is that airflow obstruction results in an increase in the work of breathing, which causes an elevation of REE and this, in the face of normal or reduced calorific intake results in net negative energy balance and weight loss (Donahoe et al, 1989) (Figure 1.5). A study of patients with respiratory insufficiency and (by implication) increased work of breathing due to interstitial lung disease, revealed that these patients too had higher than predicted resting metabolic rates (Fitting et al, 1990), lending support to the view that the increased work of breathing causes of an elevated REE in patients with respiratory impairment. However, more recent studies have shown that this is not always the case and that malnourished COPD patients and other patients with chronic airflow obstruction, including asthmatics, are not always hyper metabolic (Green and Muers, 1992; Ryan et al, 1993).

Scoliosis is a condition characterised by an abnormal curvature of the spine and an associated deformity of the thoracic cage (Figure 3.1). Respiratory function abnormalities are quite common in patients with scoliosis (Bergofsky, 1979), and cardiorespiratory failure is a well recognised complication (Branthwaite, 1986). The respiratory dysfunction in scoliosis results from a number of distinct but related mechanisms (Kafer, 1975). Most important amongst these are (a) the abnormal elastic and mechanical properties of the respiratory system consequent upon the vertebral and rib cage deformity and (b) impaired respiratory muscle function (Lisboa et al, 1985). It is well accepted that the abnormal thoracic cage architecture imposes a considerably greater load than normal on the chest bellows mechanism (Figure 3.2), with the result that the work of breathing is considerably increased (Bergofsky, 1979; Jones, 1985). A similar problem exists in patients with thoracoplasty, a condition in which ribs which form a part of the bony thoracic cage are removed surgically, usually as treatment for tuberculosis (Figure 3.3).

Given that it has been suggested that severe respiratory dysfunction and by implication, increased work of breathing, increases resting energy expenditure in patients with lung disease, and that patients with chest wall deformities suffer from an increase in the work of breathing, it was felt that

studying their lung function and resting energy expenditure (REE) would provide a useful insight into the relation between the work of breathing and REE in patients with chronic respiratory insufficiency in general. In the case of patients with COPD and pulmonary fibrosis, the two groups with lung disease in whom REE has been reported to be elevated it is possible that in addition to the increased work of breathing coexistent subclinical inflammatory phenomena (infection in COPD, alveolitis in pulmonary fibrosis) may have influenced resting energy expenditure. In comparison in patients with chest wall deformities the only known major abnormality that could have a bearing on resting energy expenditure is the work of breathing. Hence in order to study more clearly the impact of the work of breathing on resting energy expenditure, a study investigating the resting energy expenditure of patients with chest wall deformities was conducted.

3.2 Subjects and methods

Twenty patients with chest wall disease and ten age and sex matched controls were studied (Table 3.1). All the patients were recruited from a specialist clinic to which they had been referred for assessment for domiciliary ventilation. All the patients were stable at the time of investigation with

no evidence of intercurrent respiratory tract infection. Thyroid function tests were not performed but there were no symptoms or signs in any of the patients to suggest thyroid disease. None of the patients suffered from an active gastrointestinal disorder or cancer. The controls were healthy volunteers who were employees or relatives of employees of the Glasgow Royal Infirmary.

The study was approved by the local Ethics committee and all subjects gave their informed consent.

3.2.1 Indirect calorimetry

REE was estimated by indirect calorimetry using a ventilated hood system as described in detail in the previous chapter.

Oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$) and respiratory exchange ratio (RER) were estimated every minute for a period of 20 minutes. The data obtained in the first five minutes were discarded and data obtained in the last 15 minutes were used to estimate REE if there was less than 5% minute to minute variation in the RER and $\dot{V}O_2$. REE was calculated using Weir's formula (Weir, 1941). Arterial oxygen saturation was monitored by a pulse oximeter (Radiometer Ltd., Copenhagen) during the study to ensure that patients did not desaturate whilst inside the hood.

Gas calibration was performed before each measurement with a standard high purity gas mixture as described earlier.

The values for REE obtained by indirect calorimetry were compared with values predicted by the Harris-Benedict equation, using height, weight and sex (Harris and Benedict, 1919) and the Schofield equation (1985). As height is an unreliable anthropometric measure in patients with chest wall deformities, arm span was used instead of height in the HB equation and other calculations (Harper et al, 1965). As confirmation, the Schofield equation, which involves the use of weight as the only measured variable and does not include height, was also used to predict REE.

3.2.2 Lung function

Vital capacity and forced expiratory volume in first second were measured using a body plethysmograph system (PK Morgan Ltd, Rainham, England) and expressed as a percentage of predicted values (Grimby and Soderheim, 1963).

3.2.3 Anthropometry

Body weight was measured to the nearest 0.1 kg by a beam scale (Weylux Model 424, England) with the subjects standing barefoot and expressed as a percentage of ideal body

weight (IBW) (Metropolitan Life Insurance Company Weight Standards for men and women, New York: Metropolitan Life, 1983). Height and arm span (distance between the tips of middle fingers of the two hands with the arms abducted to right angles) were measured to the nearest centimetre. Triceps skin fold thickness (TSF) was measured to the nearest 0.2 mm by skin fold calipers (Holtain Ltd, Dyfed, United Kingdom) using the standard technique (Durnin and Womersley, 1976). Mid-arm circumference was measured and mid-arm muscle circumference was calculated as previously discussed.

3.2.4 Statistical analysis

REE of patients and controls, measured and predicted REE were compared by paired 't' tests. Stepwise regression analysis was performed with measured REE as the dependent variable, weight, MAMC and percentage predicted VC as explanatory variables (MINTAB, Clecom Ltd, Birmingham, England). Correlation between % REE and % VC, between % IBW and % VC were also calculated by Pearson product moment correlation.

3.3 Results

3.3.1 Anthropometry and pulmonary function tests

Results are summarised in Table 3.2. TSF and MAMC data were not available in two patients. There was no significant difference in the mean body weight of patients and controls, although seven subjects in the patient group were less than 90% ideal body weight whilst only two in the control group were so. Significant differences were evident in MAMC and indices of pulmonary function.

3.3.2 Indirect calorimetry

There was no significant difference between measured REE and REE predicted by the HB or Schofield equation (Figure 3.4). There was also no difference in the measured REE of patients and controls (Figure 3.5). Five patients had REE greater than 110% predicted by the HB equation (four if the Schofield equation was used) while only one control had an REE of greater than 110% predicted. The patients with an REE of greater than 110% predicted were not exclusively on any drug (two on theophylline, two on protriptyline)

3.3.3 Relation between REE and other variables

On step wise regression analysis 71.8% of the variation in REE was explained by body weight, 74.4% by body weight plus MAMC, 78.8% by weight, MAMC and % predicted VC. There was no relation between % VC and indices of nutritional status (% IBW or MAMC) (Figure 3.6). There was also no relation between % predicted REE and % VC (Figure 3.7).

The expression of REE in terms of units per kilogram body weight did not alter the results.

3.4 Discussion

Malnourished patients with COPD have been shown to be hyper metabolic (REE > 110% predicted) and this state of hypermetabolism, in the face of normal or reduced food intake, is believed to be the cause of weight loss in these patients. One study which measured the oxygen cost of breathing and energy expenditure of emphysematous patients showed that malnourished patients were characterised by an elevated oxygen cost of breathing and REE, suggesting that the increased work of breathing might account for the hyper metabolic state (Donahoe, 1989). A study of patients with interstitial lung disease appeared to confirm this view, with

indirect calorimetry in a group of twelve patients with ILD of different aetiologies showing REE to be elevated by around 18% - 21% above predicted values (Fitting et al, 1990). The latter study also revealed a relationship between % IBW of patients and % predicted VC, raising the possibility that in patients with lung disease there was direct relation between body weight and lung function. However more recent studies have shown that malnourished patients with COPD (Ryan, 1993) and indeed other patients with increased work of breathing due to asthma (Green and Muers, 1992) are not always hyper metabolic, and that the work of breathing does not always elevate REE. The new work of this thesis in hitherto unstudied patients with respiratory impairment due to chest wall disease supports the latter view. Of the twenty patients with chest wall deformity and respiratory distress severe enough to warrant referral for consideration of domiciliary ventilation, only five patients had an REE of greater than 110% predicted. Also these hyper metabolic patients were not necessarily the ones with most severe respiratory impairment or decreased body weight, as demonstrated by the poor correlation between %IBW and %VC and between % predicted REE and %VC.

The significant difference in MAMC between patients and the control group in the presence of comparable

IBW merits comment. One possible explanation is that this reflects a depletion of muscle mass, total body weight being preserved due to fluid retention. However none of the patients was oedematous at the time of investigation and it is therefore unlikely that fluid retention is the cause of normal body weights. It seems likely that the normal %IBW in patients represents normal body cell mass and the reason for the decreased MAMC is the relative wasting of the upper arm musculature which is seen in most patients with musculoskeletal deformities. Unfortunately reliable data on the total lean body mass of the patients with chest wall deformities is not available. Skin fold anthropometry was clearly inappropriate in patients with deformed thoracic cages due to anatomical abnormalities of the subscapular and suprailiac skin folds. Thoracic cage deformities also prevented body composition estimation by whole body potassium counting as patients were unable to pass through a counting chamber of narrow dimensions in the supine posture. Under water weighing was available as a method of estimating body composition (Lukaski, 1987) but most patients were unwilling to undergo the investigation. The view that the decreased MAMC and normal %IBW in patients represents a relative wasting of upper limb musculature and not total lean body mass is thus conjectural.

3.5 Conclusion

In conclusion, REE is not elevated in patients with severe respiratory impairment due to chest wall disease. There is no relation between lung function, resting energy expenditure and nutritional status in these patients. These finding raise the possibility that the work of breathing may not be a major determinant of energy imbalance and poor nutritional status in patients with chronic lung disease.

	Patients with chest wall disease (n=20)	Controls (n=10)
Sex	15 females; 5 males	7 females; 3 males
Age (years)	59.6 ± 2.0	59.6 ± 8.6
Diagnosis	11 post-TB thoracoplasty; 9 scoliosis (8 congenital/ idiopathic; 1 post-poliomyelitis)	Healthy volunteers from amongst the staff of Glasgow Royal Infirmary
Drug therapy	6 patients on inhaled β agonists; 8 on diuretics; three on oral theophylline; 4 on protriptyline.	
Smoking history	11 ex-smokers; no current smokers	

Table 3.1: Characteristics of population studied . Values as mean ± SEM

	Patients (n = 20)	Controls (n = 10)	P value
Weight (kg)	56.1 ± 3.8	53.6 ± 3.2	0.62
Height (cm)	154.1 ± 12.1	159.9 ± 12.9	0.32
Arm span (cm)	162.0 ± 11.1	159.7 ± 12.7	0.61
% IBW*	91.8 ± 4.4	92.4 ± 2.3	0.77
MAMC (cm)*	19.5 ± 0.5	22.3 ± 0.7	0.01
VC (% predicted)	42.5 ± 2.4	93.6 ± 2.2	<0.0001
FEV 1 (% predicted)	35.2 ± 2.4	94.4 ± 1.2	<0.0001

Table 3.2 : Anthropometric and pulmonary function data of patients and controls. P values of paired 't' tests are given in the last column.

* Key to abbreviations : IBW - Ideal body weight ; MAMC - Mid arm muscle circumference

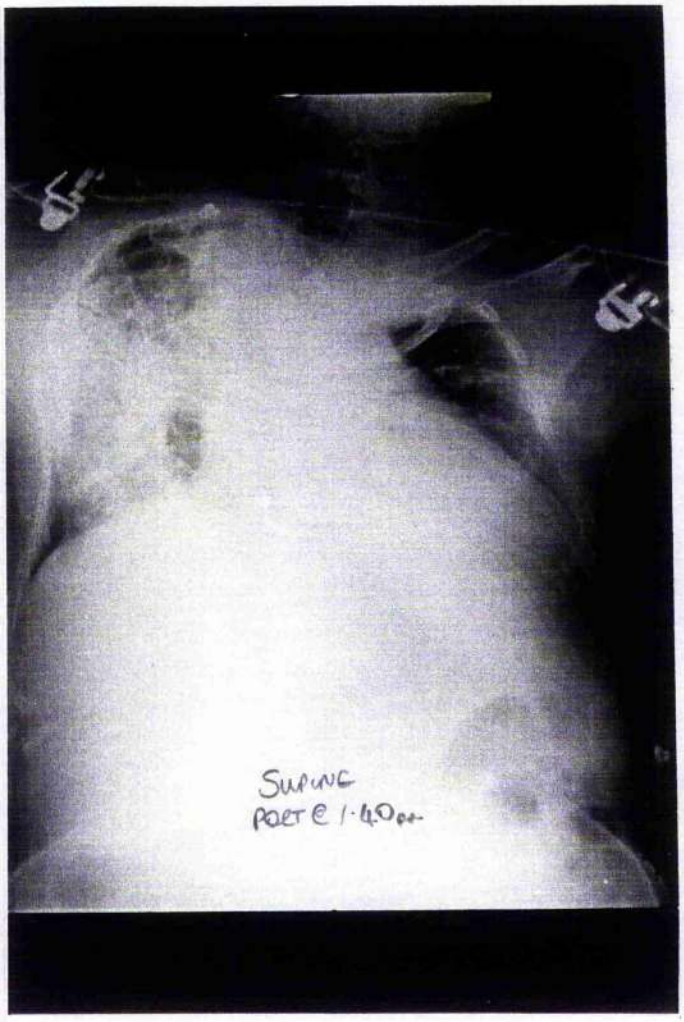


Figure 3.1: Chest radiograph of patient with chest wall disease due to congenital scoliosis, detailing the severe mechanical deformity of the thoracic cage.

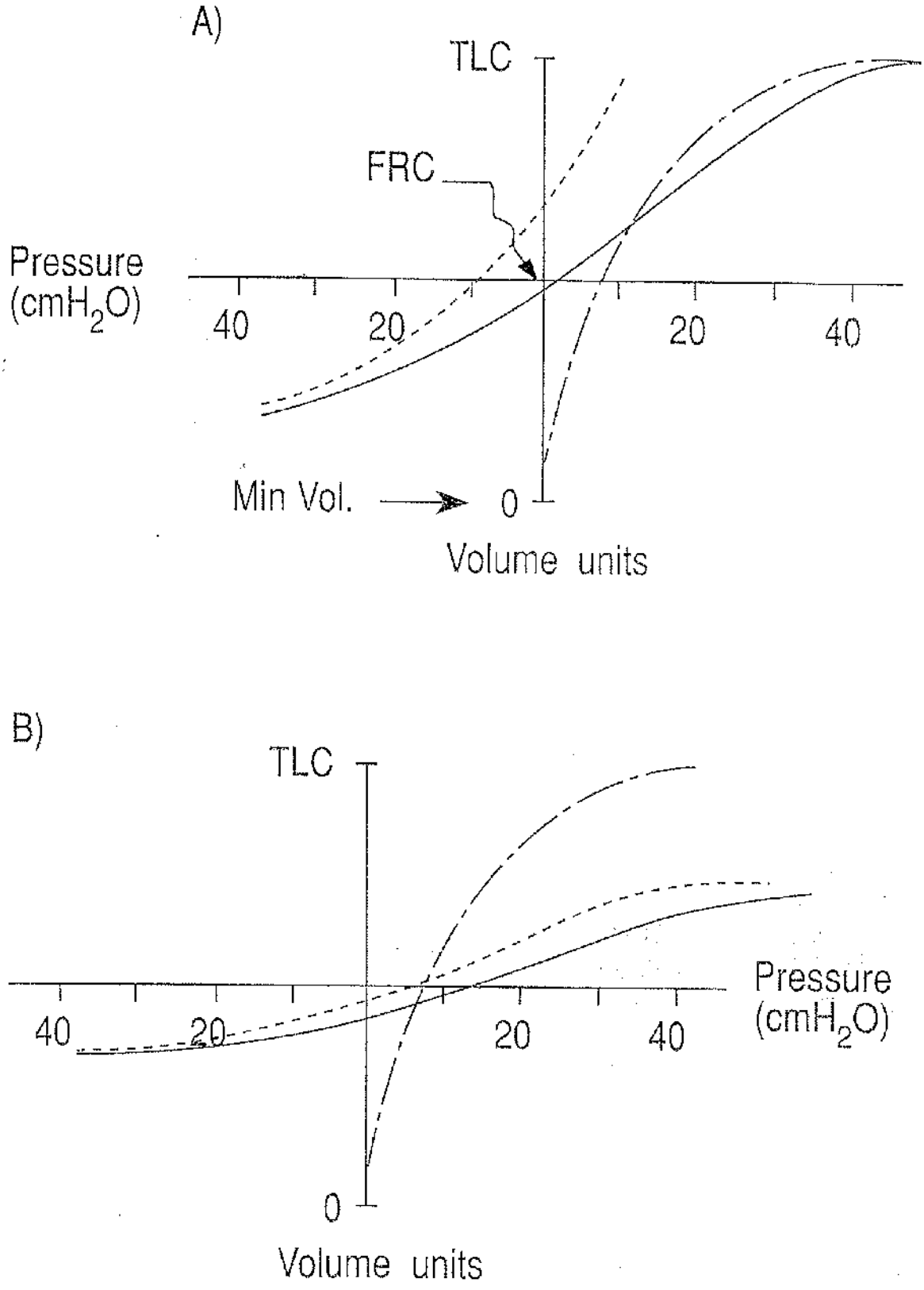


Figure 3.2 : Pressure volume relationship in a normal individual and a patient with chest wall disease. The curve is much flatter in chest wall disease indicating that to effect similar changes in lung volume, the patient with chest wall disease has to generate greater pressures, resulting in an increase in the work of breathing.

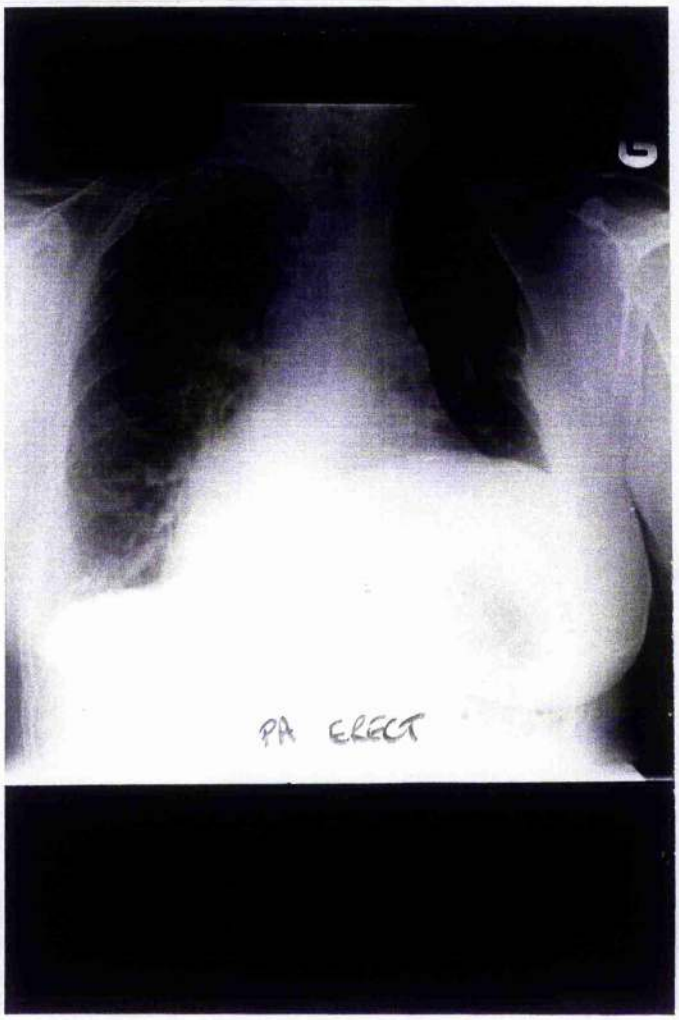


Figure 3.3: Chest radiograph of patient with a thoracoplasty. Note absence of ribs and flattening of the thoracic cage on the left (apex).

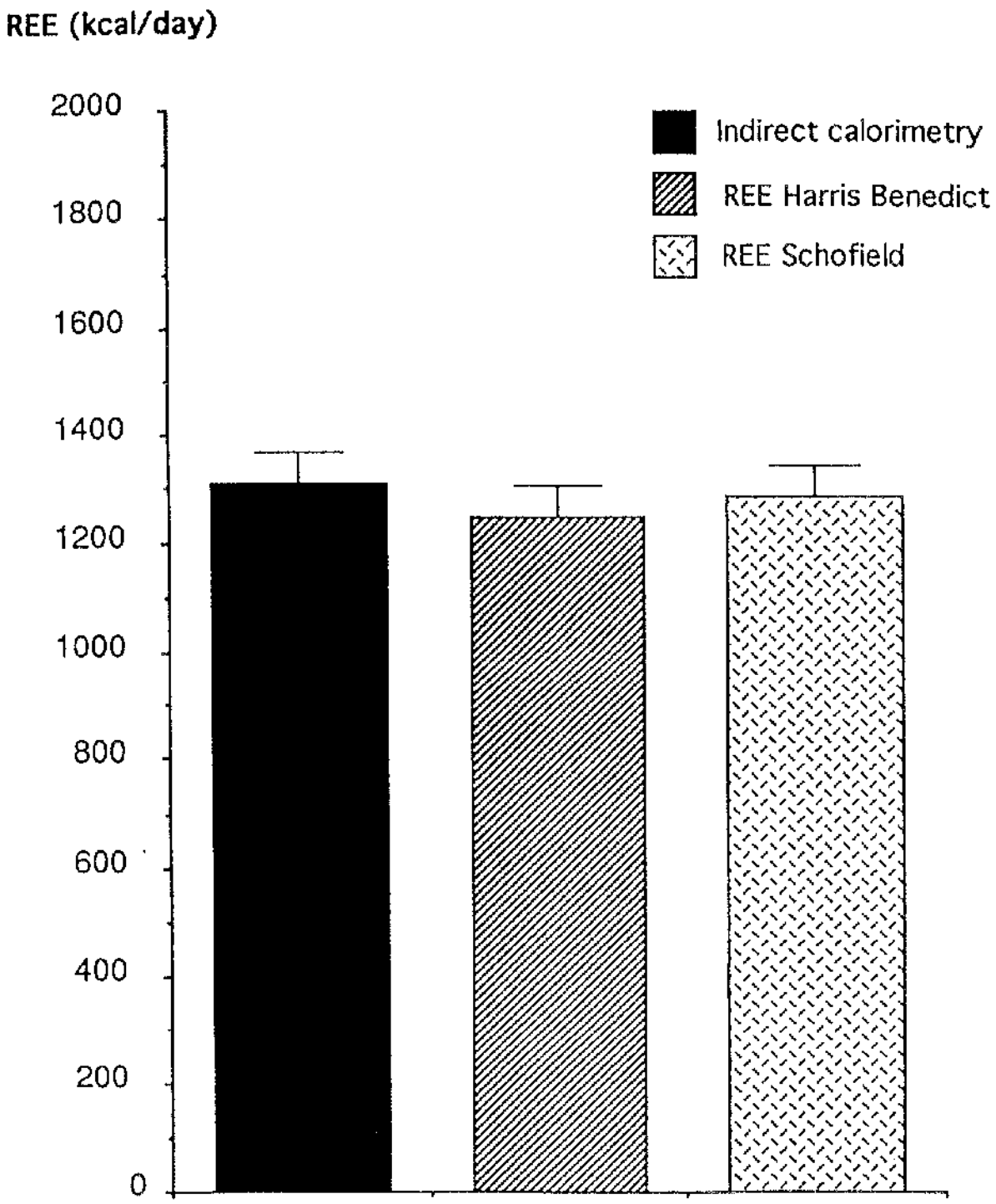


Figure 3.4: REE of patients compared with values predicted by Harris-Benedict and Schofield equations.

(Values as mean (SE)).

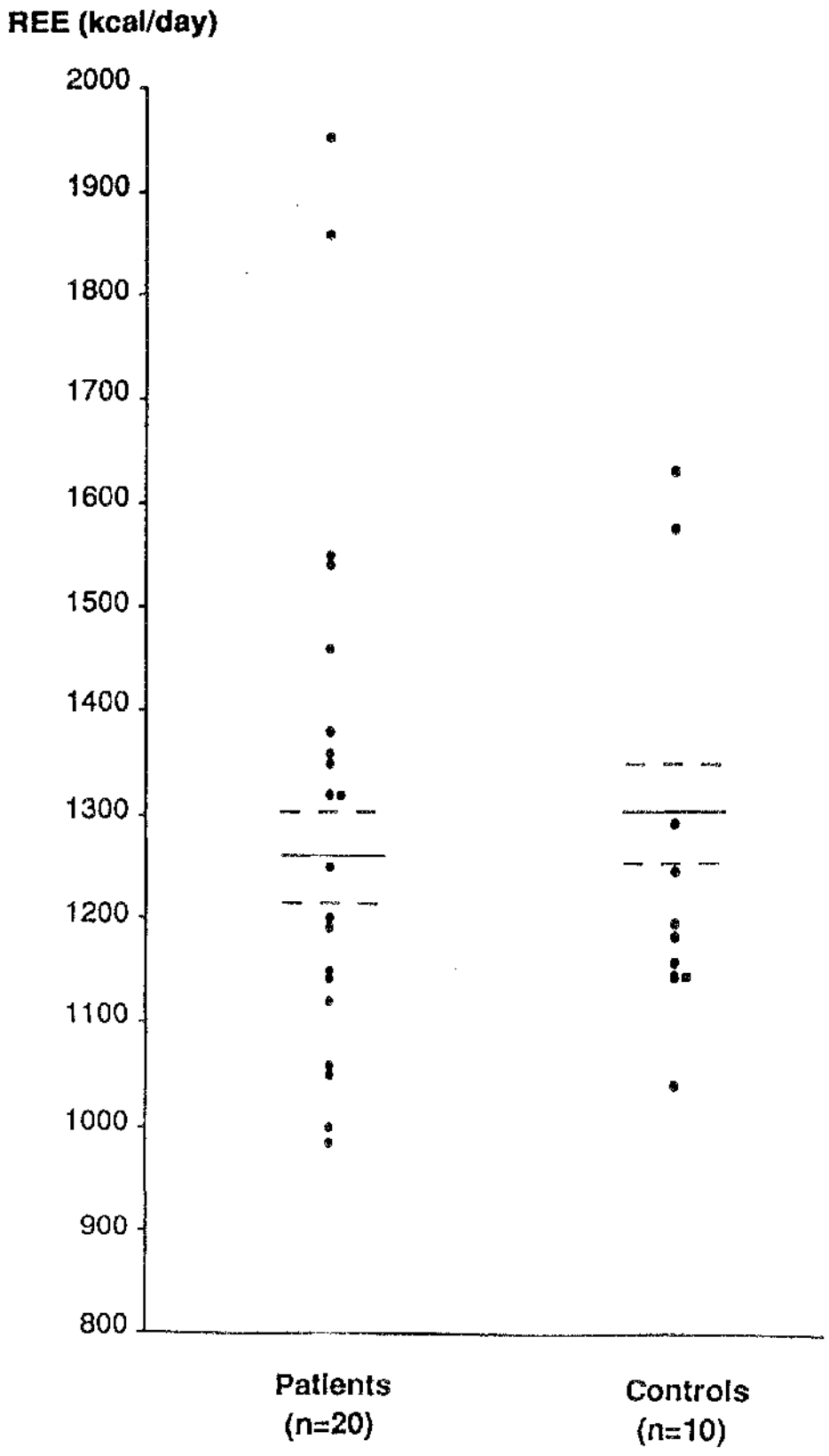


Figure 3.5 REE in patients with chest wall disease and in controls (Values given in absolute terms; scatter and results essentially unchanged if values are expressed as % predicted).

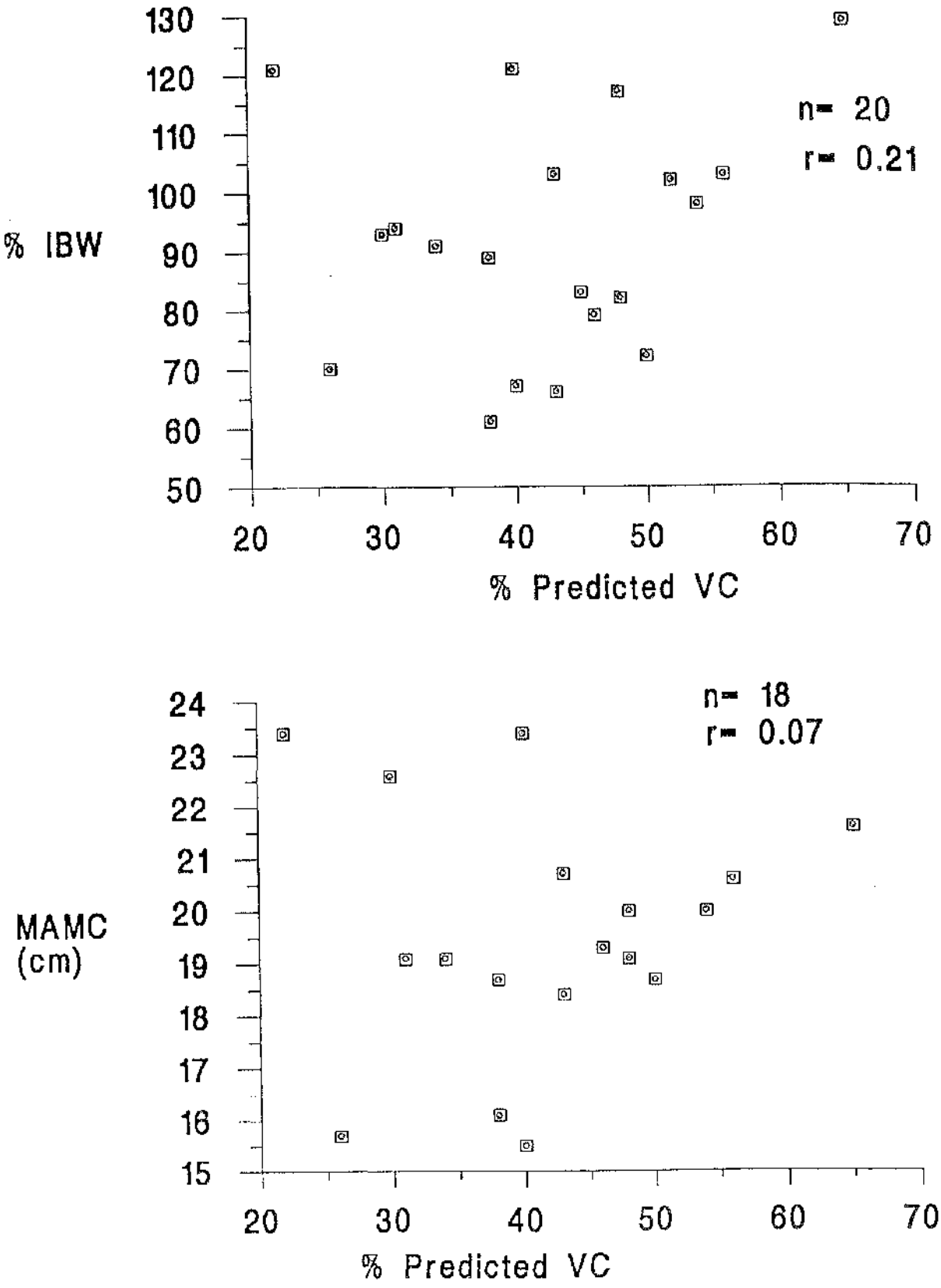


Figure 3.6: Regression analysis between indices of nutritional status and indices of lung function.
Abbreviations: VC - Vital capacity; MAMC - Mid-arm muscle circumference; IBW- Ideal body weight.

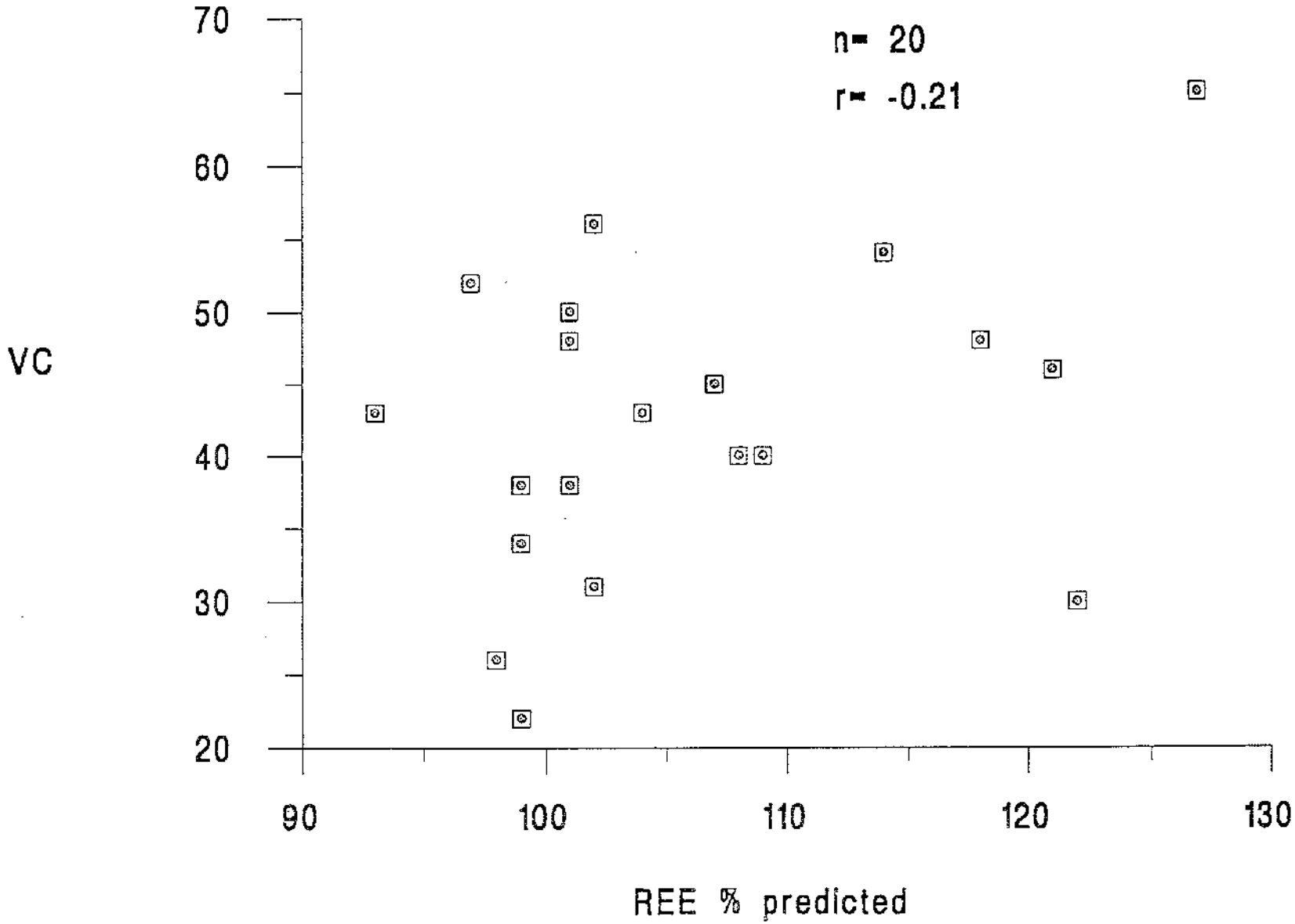


Figure 3.7: Regression analysis between REE and indices of lung function (% predicted Vital capacity).

CHAPTER 4: Relation between REE, oxygen cost of breathing and nutritional status in patient groups with different types of chronic lung disease (emphysema, scoliosis and thoracoplasty)

4.1 Introduction

The study that constituted the previous chapter showed that REE was not significantly elevated in patients who are known to have an increased work of breathing due to chest wall disease. It was concluded that respiratory impairment presumed to result in an increase in the work of breathing is, in itself, probably not enough to produce a significant elevation in REE. However, no measurement, direct or indirect, was made of the actual work of breathing. In order to determine whether an increased work or oxygen cost of breathing (OCB) is associated with an elevated REE and malnutrition and to explore further the relation between REE, OCB, lung function and nutritional status, these parameters were measured in patients with respiratory impairment due COPD and in some of the patients with scoliosis and thoracoplasty who participated in the previous study .

4.2 Patients and methods

4.2.1 Patient characteristics

Six COPD (3M 3F; mean age 67.0 yr. (SD 3.0)), six scoliosis (3M 3F; 51.0 yr. (7.2)), six thoracoplasty (2M 4F; 61.7 yr. (5.7)) patients were studied. All the patients were in a clinically stable state, free from overt oedema and signs of respiratory tract infection. All the COPD patients and five of the thoracoplasty patients were on inhaled beta-agonists. There had been no changes in the drug therapy of any of the patients in the three months prior to the study. All patients were current non-smokers; all the COPD patients, four thoracoplasty patients and two scoliotic patients were ex-smokers. Six non-smoking healthy volunteers (2M 4F; 45.5 yr. (9.9)) were also studied in order to assess the reliability of the various techniques used in the study.

4.2.2 Nutritional measures, calorimetry and lung function

These were made according to techniques previously described in detail (Chapter 2). TSF and MAMC were measured and also compared with normal values and expressed as percentage predicted (Bishop et al, 1981).

4.2.3 Oxygen cost of breathing

OCB was measured by the method described in detail in Chapter 2. (Section 2.4; Figures 2.8 and 2.9). At the beginning and end of each measurement the gas analysers were calibrated using a high purity gas mixture (BOC Ltd). Accuracy of the flow measurements were confirmed to be within 2% over a range of flow rates. The coefficient of variation for $\dot{V}O_2$ measurements with added dead space, based on a study of ten patients on separate occasions, was between 6 - 11%. It was felt that given the relative unpredictability of a patient's response to dead space breathing this was an acceptable level of variability and could not be improved upon any further by refinements of this particular technique.

4.2.4 Statistical methods

Data was analysed using the MINITAB statistical programme (Clecom, Birmingham, UK). Comparison between the patient groups was by analysis of variance. Correlation between variables was determined in each group by Pearson product moment correlation coefficient. Linear regression equations were developed using stepwise regression analysis. REE was used as the dependent, response variable, body

weight, lung function, and OCB as independent, explanatory variables. Significance was assessed at the 5% level.

The study was approved by the local Ethics committee and the patients gave their informed consent to the investigations.

4.3 Results

4.3.1 Anthropometric measures and pulmonary function (Table 4.1)

All patients in the COPD group, 4 in the scoliosis and 3 in the thoracoplasty group were less than 90% ideal body weight. Comparison between the three patient groups by analysis of variance showed no significant difference in any of the measures except vital capacity.

4.3.2 Resting energy expenditure (Figure 4.1)

REE was greater than 10% of predicted values (Harris-Benedict equation) in 1 COPD , 2 scoliotic and 2 thoracoplasty patients. All controls had REE within 10% of the predicted values. There was no significant difference in the fasting RQ of the various groups. The hyper metabolic patients were not different either in terms of drug therapy or smoking status from the patients whose REE was within the normal range.

4.3.3 Oxygen cost of breathing (Table 4.2)

OCB was 3 or 4 times higher in patient groups compared with controls. Analysis of variance showed no significant difference between patient groups.

4.3.4 Oxygen cost and lung function (Figure 4.2 and 4.3)

There was a negative relation between OCB and FEV 1 and between OCB and VC in all patient groups. The correlation was significant at the 5% level in the COPD group.

Oxygen cost and REE : There was no relation between OCB and REE (r values for OCB vs REE : COPD = 0.15; Thoracoplasty : - 0.62; Scoliotics: 0.41; controls : 0.56).

There was no correlation between REE and indicators of nutritional status (TSF or MAMC) in any of the groups.

On multiple regression body weight alone accounted for over 80% (r^2 =83.6) of the variation in measured REE .

4.4. Discussion

The relation between REE, lung function, oxygen cost of breathing and malnutrition in patients with lung disease, particularly COPD and cystic fibrosis, has been the focus of much attention in recent years (Donahoe et al, 1989; Schols et al, 1991; Naon et al, 1993). While some studies have shown that both well nourished (Lanigan et al, 1990) and malnourished patients are hyper metabolic (Goldstein et al, 1987), others have concluded that hyper metabolism is not a universal feature of these patients (Green and Muers, 1992; Ryan et al, 1993). In the present study of the thesis only five of eighteen patients with different types of respiratory impairment (COPD, chest wall disease) exhibited an elevated REE. Oxygen cost of breathing was elevated in line with deteriorating lung function but was not always associated with an elevation in REE . Moreover, there was no consistent relationship between REE, OCB and indicators of nutritional status. This study thus adds support to the view that the increased work of breathing is not always accompanied by an elevated REE and that a high OCB *per se* is unlikely to account for the poor nutritional status of patients with lung disease.

One possible reason for the results of this study differing from that of Goldstein (1987) and Donahoe (1989) is

methodological. Firstly, this study used a non invasive system to measure REE in order to circumvent the effect of respiratory apparatus on the breathing pattern (Askanazi et al, 1980). As already demonstrated in the study described in detail in Chapter 2, in patients with severe respiratory impairment there is a significant difference in the REE estimated by the ventilated canopy and mouthpiece plus nose clip systems, with the latter consistently tending to overestimate the REE . Secondly patients were all studied in the fasting state early in the morning in this study, unlike those of other workers whose patients were studied at various times of the day whilst on an intravenous infusion of nutrients (Goldstein et al, 1987).

Although it is known that the work of breathing is increased in patients with chest wall disease (Bergofsky, 1979), there are no data in the literature regarding their actual oxygen cost of breathing. Since the values for OCB in patients with COPD obtained in this study (6.5 (1.3) ml O_2/ L) match well with studies by Cherniack (5.96 ml O_2/ L) and Levinson and Cherniack (6.3 ml O_2/ L), it would appear that the methods applied in this study were reliable and compare with those of previous investigators. This study of the OCB of patients with chest wall disease and COPD leads to the conclusion that in both these patient groups OCB is elevated in line with their respiratory dysfunction. It must however be

noted that the cause for an increase in the work of breathing in either group is very different: in patients with COPD it is due to an increase in airways resistance while that in patients with chest wall deformities it essentially the result of alterations in chest wall compliance characteristics (Cherniack, 1959; Kafer, 1975).

Whilst the techniques and methodology seem reliable, as demonstrated by the results of studies on controls, this study as a whole suffers from some limitations. Like other studies in this field (Goldstein et al ,1987; Donahoe et al, 1989; Ryan et al, 1993), this study is small and this obviously limits its power. For example, whilst the correlation between OCB and lung function for the study population as a whole (n=24) is strikingly significant (OCB vs FEV 1, r = 0.87), because of the small numbers in each group (n=6), correlations in each group, while showing a consistent negative trend, do not reach significance except in the COPD group. Also, in this group of eighteen severely disabled patients only five were found to be hypermetabolic. A greater number of such patients would have allowed a valuable comparison of patients with normal and elevated resting energy expenditure, irrespective of underlying disease. It is also arguable as to whether the cost of augmenting ventilation (i.e., ventilation at a higher minute ventilation) can be taken to

be the cost of resting ventilation, especially in patients who may find it difficult to augment their ventilation. It is certainly possible that the oxygen cost of resting ventilation is not particularly different in patient groups and that the OCB rises at different rates with increasing ventilation. Thus the differences in the oxygen cost of augmenting ventilation need not represent a difference in the oxygen cost of resting ventilation. Similar criticism of methodology would, however apply to the other studies in this field.

The unreliability of various anthropometric measures in patients with chest wall deformities (scoliosis and thoracoplasty) was discussed in the previous chapter and merits re-emphasise. The Harris-Benedict equation uses a subject's age, sex, height and weight to calculate REE. In patients with skeletal deformities height could not be used as a measure of body dimension and armspan was used instead. Using the Schofield equation, which is based on weight, age and sex, did not alter the results. The presence of thoracic cage deformities rendered measurement of subscapular and suprailiac skinfold thickness unreliable, making anthropometric estimation of body composition difficult. As noted in the previous chapter it was proposed that body composition be measured by under water weighing, but this technique did not find favour with the patients and was not pursued. Therefore potentially useful data on the body

composition of the various patient groups and its relation to their REE are not available. It is however worth emphasising that this does not in any way detract from the conclusions of the study, as normalising REE values for body composition without reference to a larger population is not, in itself, particularly satisfactory (Ravussin and Bogardus, 1989); also, as has been pointed out, normalisation to lean body mass, particularly in malnourished, weight losing individuals is a far from satisfactory method of standardising REE (Shetty, 1993).

4.5 Conclusions

In conclusion, this study has shown that in clinically stable patients with respiratory disease the increased oxygen cost of breathing is inversely related to lung function. There is no consistent relation between oxygen cost of breathing, resting energy expenditure and nutritional status in these patients. It is unlikely that the increased oxygen cost of breathing is the sole or major cause of negative energy balance and malnutrition in patients with lung disease.

	COPD	Scoliosis	Thoracoplasty	Controls)	ANOVA
	(n = 6)	(n = 6)	(n = 6)	(n = 6)	(p value)
% IBW	77.1 (7.8)	94.5 (26.6)	91.0 (21.1)	106.2 (3.5)	0.32
TSF (% pred)	37.7 (20.8)	70.0 (31.7)	81.3 (38.9)	94.8 (8.0)	0.17
MAMC (cm)	18.7 (2.1)	19.3 (3.1)	19.9 (2.0)	23.0 (3.8)	0.72
MAMC (% pred.)	74.8 (2.6)	77.8 (6.6)	77.5 (10.5)	93.9 (7.1)	0.74
FEV 1 (% pred)	34.3 (8.8)	29.8 (12.4)	35.6 (12.4)	95.6 (6.2)	0.65
VC (% pred)	66.1 (15.2)	30.2 (12.4)	42.3 (6.6)	100.2 (4.3)	< 0.01

Table 4.1 : **Anthropometric and pulmonary function data** (Values as Mean (SD))

Key to abbreviations : IBW- Ideal body weight; TSF - Triceps skinfold thickness; MAMC - Mid-arm muscle circumference; FEV 1 - Forced expiratory volume in 1 second; VC - Vital capacity; ANOVA- analysis of variance (P values)

	Controls	COPD	Scoliosis	Thoracoplasty
	(n = 6)	(n = 6)	(n = 6)	(n = 6)
Resting V_E	6.7 (1.7)	7.9 (1.3)	6.5(1.6)	6.5 (1.4)
(Litres / min)				
Resting f R	10.7 (1.8)	12.3 (2.0)	13.5 (1.4)	12.8 (1.9)
(breaths / min)				
OCB	**1.9 (2.0)**	**6.5 (1.3)**	**7.6 (1.1)**	**7.0 (2.0)**
(ml O_2 / L ventilation)				

Table 4.2 : Oxygen cost of breathing data

Key to abbreviations: V_E - minute ventilation; f R- respiratory frequency; OCB- Oxygen cost of breathing

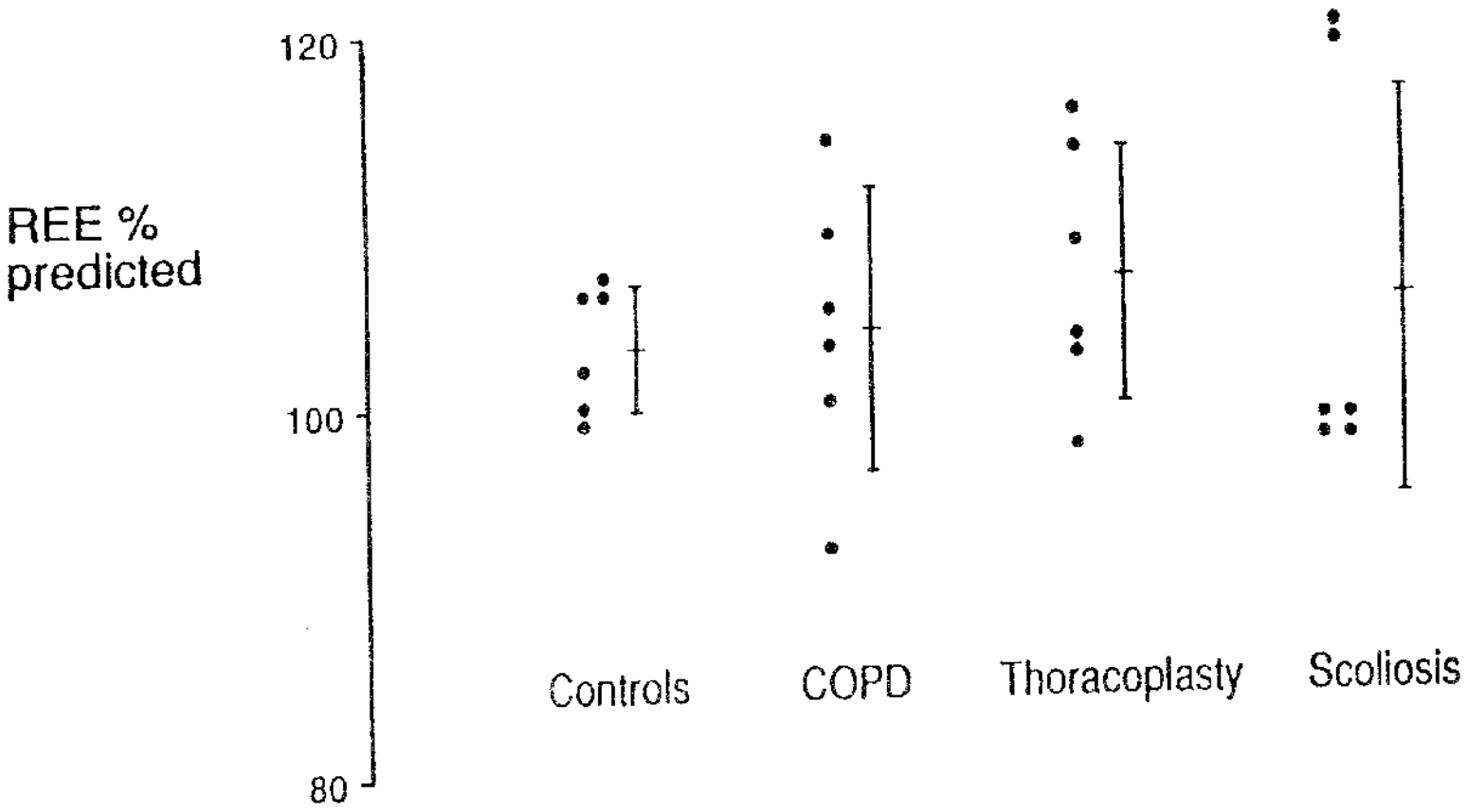


Figure 4.1: REE (as % predicted by Harris- Benedict equation) in controls, patients with COPD, scoliosis and thoracoplasty.

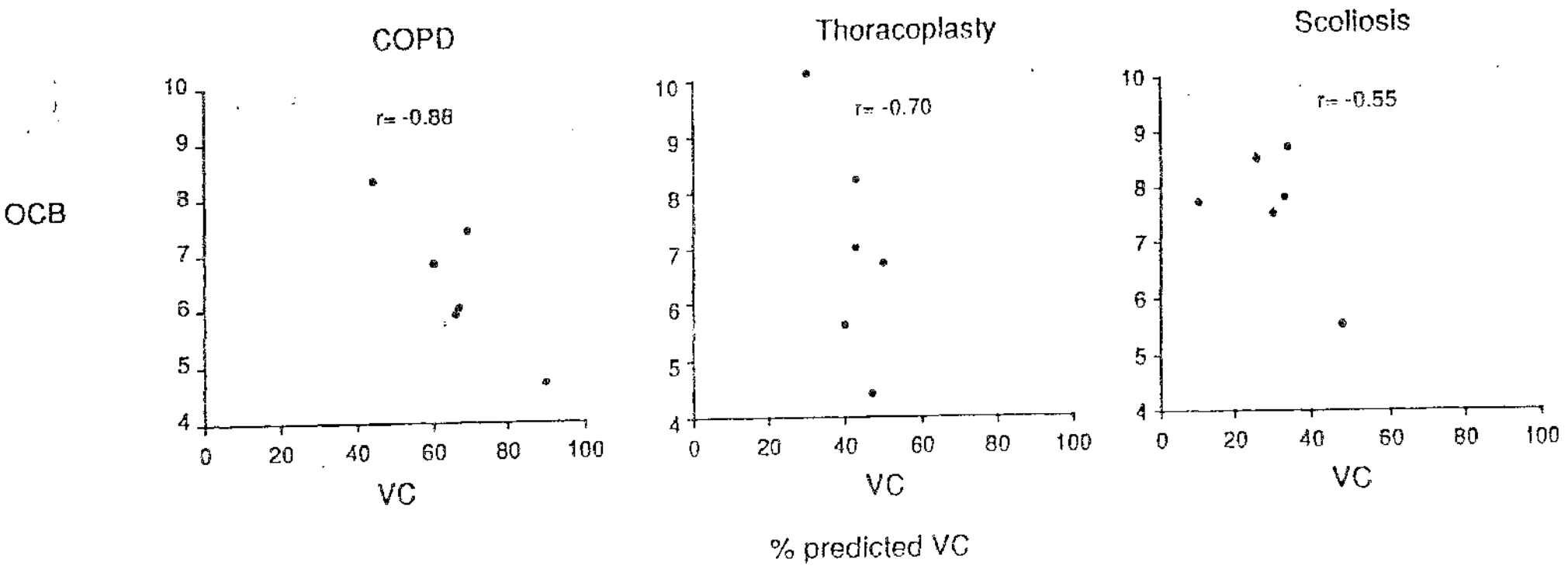


Figure 4.2: Relation between oxygen cost of breathing and Vital capacity in the three patient groups.

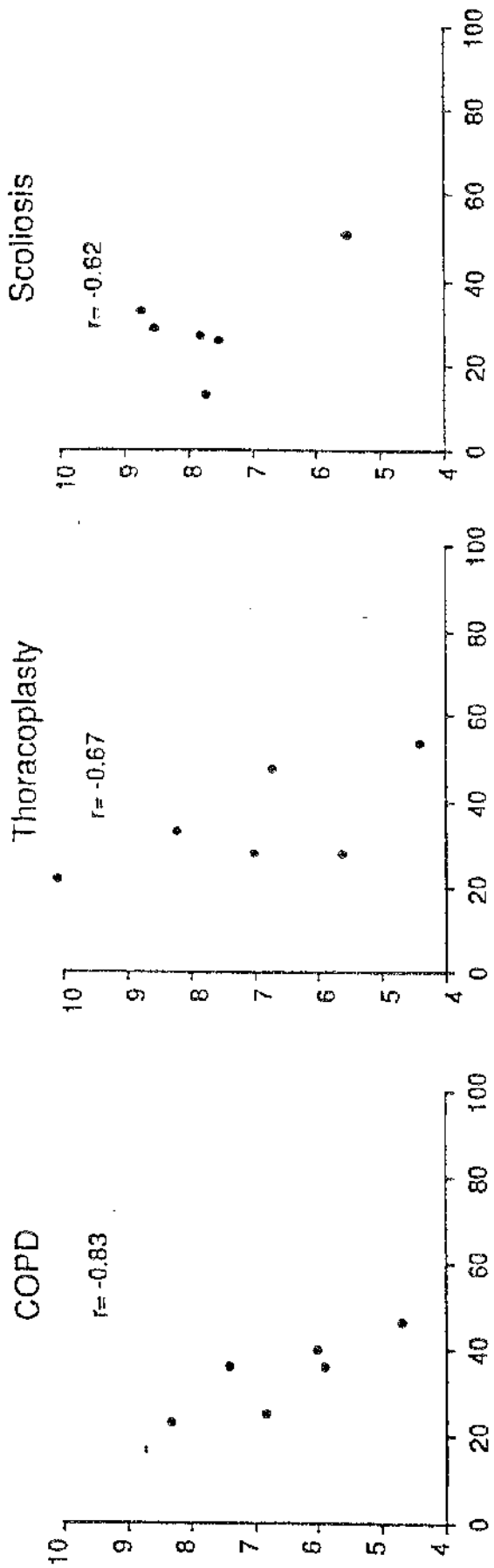


Figure 4.3: Relation between oxygen cost of breathing and FEV1 in the three patient groups.

CHAPTER 5: Pharmacological influences on energy balance in patients with COPD: thermogenic response to salbutamol

5.1 Introduction

Adrenergic drugs increase energy expenditure in a dose related manner (Fellows et al, 1985). It has recently been shown in healthy adults that even therapeutic doses of inhaled β agonists result in a considerable increase (in the order of 10-20%) in oxygen consumption and carbon dioxide production (Amoroso et al, 1993). Whilst the exact mechanisms by which this thermogenic effect is mediated are still unclear, it is possible that this effect may have a bearing on the energy balance of COPD patients with chronic use leading to a state of hyper metabolism, which, in the face of normal or reduced intake, may contribute to negative energy balance. Studies in healthy volunteers have shown that this thermogenic effect, like other systemic, non-bronchodilator effects of β agonists, is abolished by regular use of the drug (Wilson et al, 1993). However it is not known whether this applies in a clinical situation in patients with COPD who have been long term users of the drug. It is also possible that while beta agonists could increase thermogenesis in patients with COPD, they might also decrease energy expenditure by their salutary effect on the energy cost of breathing by relieving airflow obstruction. In order to clarify the net

effect of therapeutic doses of inhaled beta agonists on the energy balance of patients with COPD, a study of the thermogenic response to inhaled salbutamol was undertaken in these patients.

5.2 Methods

5.2.1 Patient characteristics

Twelve patients with COPD and twelve non-smoking controls were studied (Table 5.1). The COPD patients were all in a clinically stable state, free from signs of decompensated cor pulmonale and respiratory tract infection. All patients were ex-smokers. Three patients were on regular diuretic therapy and two on anti-anginal drugs, one on nitrates and another on Diltiazem. None of the patients was on oral steroids or theophyllines at the time of study. All patients had been on inhaled beta agonists for at least the three years preceding the study, taking at least 800µgms a day of salbutamol. Patients on oral salbutamol were not included in the study.

5.2.2 Study protocol

Subjects were studied in the morning in the fasting state. Patients were requested to abstain from using their usual beta agonist inhaler on morning of the study. Height and body weight were measured and after a rest of 30 minutes resting energy expenditure (REE) was measured by indirect calorimetry for 20 minutes. Following this all subjects were asked to inhale 800 µg of salbutamol via a spacer device

(Volumatic, Allen and Hanburys Ltd, United Kingdom) and calorimetry was continued for a further 30 minutes. During calorimetry pulse rate and oxygen saturations were monitored by a pulse oximeter (OXImeter, Radiometer Ltd., Copenhagen). After the 30 minute period subjects were asked to report any symptoms following the administration of salbutamol.

5.2.3 Indirect calorimetry

Energy expenditure (EE) was estimated by indirect calorimetry using a ventilated canopy system (Deltatrac ™ Metabolic monitor, Helsinki, Finland) as described in detail previously, measuring $\dot{V}O_2$, $\dot{V}CO_2$ and respiratory exchange ratio (RER) ($\dot{V}CO_2/\dot{V}O_2$) every minute. Energy expenditure (EE) was calculated by the Weir equation (Weir, 1949). The data obtained in the first five minutes spent inside the hood were discarded and artefacts produced by coughing were eliminated in the final calculations. Arterial oxygen saturation was monitored during the study to ensure that subjects, particularly patients, did not desaturate whilst inside the hood. Gas calibration was performed as described previously. The system was checked by a methanol burning test every week during the study period and the average RER values for the last 15 minutes of a 30 minute methanol burning run were confirmed to be between 0.64 and 0.69. Flow calibration was performed once during the study period by calculating the total amount of CO_2 produced during the methanol burning test and the flow constant adjusted if appropriate. REE

was expressed both in absolute terms and as percentage of values predicted by the Harris- Benedict equation from age, sex, height and weight (Harris and Benedict, 1919).

5.2.4 Statistical analysis

On the basis of previous studies showing a 10-25% increase in $\dot{V}O_2$ following inhalation of salbutamol and previously available data on the variance of EE measures, it was estimated that a number of twelve subjects would have a power of greater than 90% in detecting a 5% change in EE following salbutamol administration. Therefore twelve patients and an equal number of controls were studied.

Following salbutamol administration the mean of EE, $\dot{V}O_2$, $\dot{V}CO_2$, RER and HR measured in the three minutes around the 5, 10, 15 and 30 minute marks (i.e., at minute 4,5 and 6; 9,10 and 11 etc.,) were taken as the values at 5,10, 15 and 30 minutes; based on these values the area under the curve (AUC) for the 30 minute period for each measure was calculated (Matthews et al, 1990). Changes from baseline for each measure were also calculated in patients and controls and expressed as mean change with 95% confidence intervals. Baseline measures and post salbutamol EE and HR (AUC) measures were compared in patients and controls by Mann-Whitney U test.). Changes in HR, $\dot{V}O_2$, $\dot{V}CO_2$ and RER were also compared similarly. Significance was assessed at the 5% level. All statistical calculations were performed using a standard

computer software programme (MINITAB Release 9.2, Clecom Ltd, Birmingham

All subjects, including controls, had taken part in previous studies, were familiar with the calorimetry equipment and gave their informed consent.

5.3 Results

Mean (SE) REE was 102.1 (1.5)% predicted in patients and 101.7 (1.5)% predicted in controls.

The trend of EE, HR, $\dot{V}O_2$, $\dot{V}CO_2$, and RER following inhalation of salbutamol in controls and patients are shown in Figures 5.1 -5.4. In both patients and controls peak values for $\dot{V}O_2$, $\dot{V}CO_2$, RER and HR occurred at about 5 minutes after inhalation of salbutamol, in keeping with the known pharmacokinetic profile of the inhaled drug. The increases in $\dot{V}O_2$, $\dot{V}CO_2$, EE and HR were far greater in controls than in patients (Tables 5.2 and 5.3). Two controls and none of the patients complained of feeling anxious following salbutamol inhalation. Tremor was not observed in any of the subjects.

5.4 Discussion

Two conclusions of this study merit detailed discussion. Firstly, the study suggests that chronic β agonist therapy does not have an adverse impact on the energy balance of patients with COPD. Not

only did the patients with COPD who were regular users of inhaled salbutamol show no elevation of REE, in line with a recent report on the REE of patients on chronic beta agonist therapy (Congleton et al, 1994), they also showed a blunting of the acute thermogenic response to the drug. Secondly, the study also adds to the large body of evidence on the phenomenon of tolerance to the systemic, non-bronchodilator effects of beta-agonist drugs (Tattersfield, 1985). From these results it seems unlikely that regular inhaled beta agonist therapy leads to a state of chronic hyper metabolism and negative energy balance in patients with COPD.

Whilst it is well established that beta adrenergic drugs increase energy expenditure, how they do so is still unclear. Various mechanisms, not mutually exclusive, may be in operation (Tattersfield and Wilding, 1994): (1) By their positive chronotropic and inotropic effect β agonists increase cardiac output and hence EE by a direct effect on the heart, although increase in metabolic rate by any mechanism will lead to secondary elevations of heart rate and cardiac output; (2) by increasing the ventilatory drive (Leitch et al, 1976) and (3) by augmenting muscular activity in the form of a tremor. In animals studies it has been shown that the thermogenic effect of beta agonists may be mediated by a specific category of beta receptors (β_3 receptors) which are believed to activate lipolysis in brown adipose tissue. The evidence for the existence of such a system in humans is incomplete and its precise role in thermogenesis is still unclear (Rosenbaum et al, 1993). The time

course of the increase in EE following salbutamol inhalation mirrors the rise in heart rate closely and it has been suggested that the differential increase in $\dot{V}CO_2$ (and consequently of RER) seen after salbutamol inhalation is a manifestation of increased cardiac output, CO_2 flux into the lungs and resultant increase in ventilation, a phenomenon termed cardiodynamic hyperpnoea (Wasserman et al, 1974).

In a previous study, the acute thermogenic response to salbutamol was abolished by regular use of the drug but this tolerance to the thermogenic effect was not accompanied by a diminished heart rate response (Wilson et al, 1994). In this study COPD patients on long term beta agonist therapy have shown not only a diminished thermogenic response but also a diminished chronotropic response to the drug, perhaps suggesting that the thermogenic response to beta agonists is mainly the result of increased cardiac function.

It is of course possible that in patients, the blunting of the thermogenic response is due, at least in part, to the decreased energy expenditure resulting from the decreased work of breathing following bronchodilation by salbutamol. In this study the oxygen cost of breathing before and after salbutamol was not measured and thus data on the beneficial effect of salbutamol on the energy cost of breathing and on overall energy expenditure are not available. However under normal circumstances the work of breathing constitutes less than 5% of the total energy expenditure (Millic-Emili and Petit, 1960). Given that the patients were studied in a relatively stable state and that they also showed a

blunting of the heart rate response to the drug it seems reasonable to conclude that the decrease in thermogenic effect is a manifestation mainly of tolerance to the systemic effects of the drug rather than the result of a decrease in the energy cost of breathing, although this study has not measured the energy gain resulting from bronchodilation.

There are a few problems with this study that merit mention. Firstly, the control group is younger than the patient group and this limitation must be borne in mind in the assessment of this study. Other investigators have provided some evidence that there is an age related blunting of the thermogenic effect of beta agonists, and this may have accentuated the difference between patient and control groups (Cruetzberg et al, 1994). Patients and subjects were studied only on one occasion the coefficient of variation for post salbutamol calorimetry measurements performed in three patients, although higher than that for resting measurements was still within acceptable limits (less than 10%). Ideally, it still would have been preferable to study the subjects on two different occasions and to have confirmed that the calorimetry measurements following salbutamol inhalation were repeatable in every subject. Also, it might have been valuable to have measured the thermogenic response to a placebo inhaler in patients and controls.

5.5 Conclusions

In conclusion, this study has shown that the thermogenic response to inhaled beta agonist drugs is diminished in patients with COPD who have been long term users of the drug. Blunting of the thermogenic response is associated with a blunting of the heart rate response, probably suggesting a systemic tolerance phenomenon. In view of the impaired thermogenic response to beta agonist drugs seen in these patients, it appears unlikely that drug induced hyper metabolism contributes significantly to the weight loss seen in COPD patients.

Table 5.1

Characteristics of study population. Values as Mean (SE).

	COPD patients	**Controls**
Number	12	12
Sex	7 males; 5 females	5 males; 7 females
Age (in years)	64. 8 (1.8)	53.6 (2.3)
FEV 1(as % predicted)	44.5 (4.5)	97.8 (1.3)
Height (cm)	165 (3.1)	163.1 (3.7)
Weight (kg)	55.3 (4.0)	63.5 (3.5)

Table 5.2

$\dot{V}O_2$, $\dot{V}CO_2$, EE and HR before and after inhalation of Salbutamol in controls and patients. Post inhalation values are values of area under curve for 30 minutes post inhalation.

	Controls		**Patients**	
	Before salbutamol	After salbutamol	Before salbutamol	After salbutamol
Energy expenditure (kcal/24h)	1346 (61)	1548 (64) *	1226 (61)	1259 (62)
Heart rate (beats / min)	64.3 (1.6)	76.5 (1.7)**	76.3 (1.5)	78.2 (1.5)
$\dot{V}O_2$ (ml / min)	195.1 (9.1)	218.7 (9.9)	177.3 (8.8)	182.0 (9.1)
$\dot{V}CO_2$ (ml/ min)	155.2 (6.9)	181.7 (7.3) *	139.8(6.8)	144.0 (7.1)

* $P < 0.05$

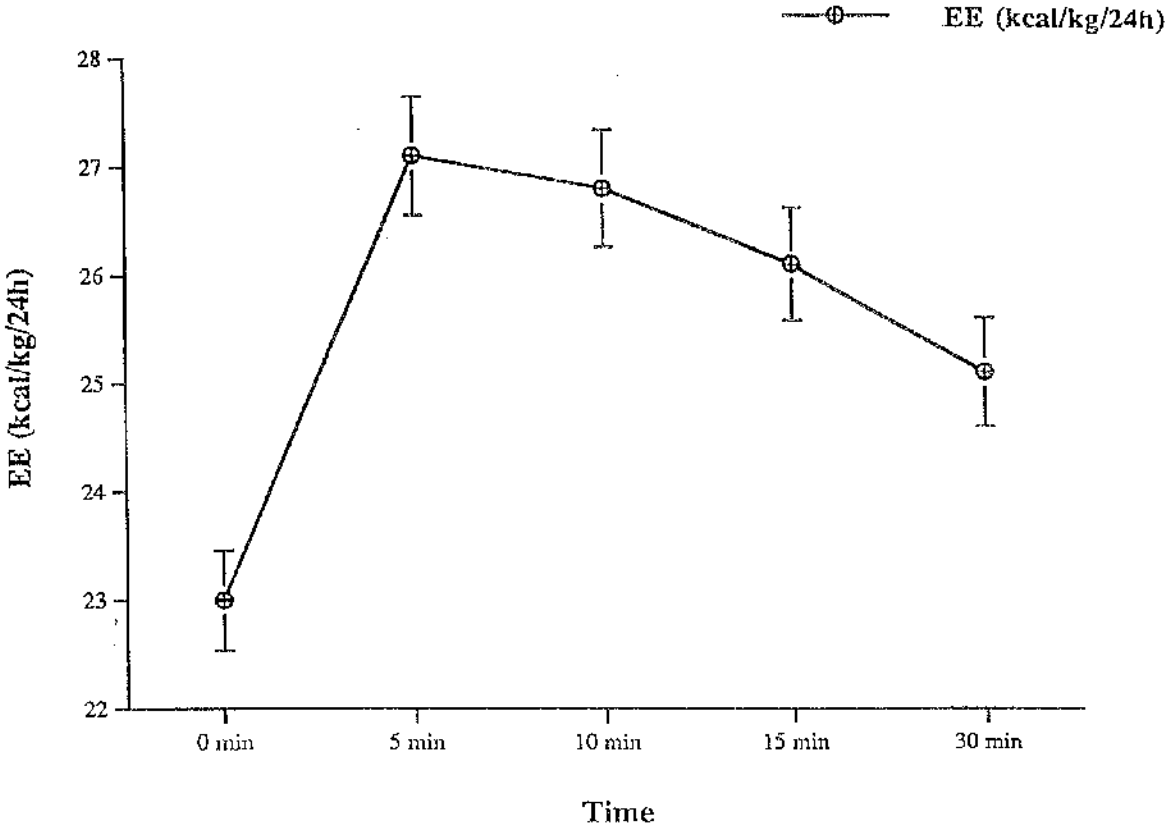
** $P < 0.01$

Table 5.3

Increases in EE, $\dot{V}O_2$, $\dot{V}CO_2$ and heart rate following salbutamol inhalation in controls and patients. Values as mean increase(95% confidence intervals).

	Controls	**Patients**
Energy expenditure (kcal/ 24 h/ kg)	2.89 (2.3, 3.4)	0.62 (0.46, 0.78)
$\dot{V}O_2$ (ml/ kg/ min)	0.39 (0.32, 0.46)	0.09 (0.06, 0.10)
$\dot{V}CO_2$ (ml/ kg / min)	0.36 (0.30, 0.42)	0.07 (0.03, 0.12)
Heart rate (beats/ min)	12.2 (11.1, 13.4)	1.2 (1.4, 2.3)

Figure 5.1: Changes in energy expenditure and heart rate in controls following salbutamol inhalation.



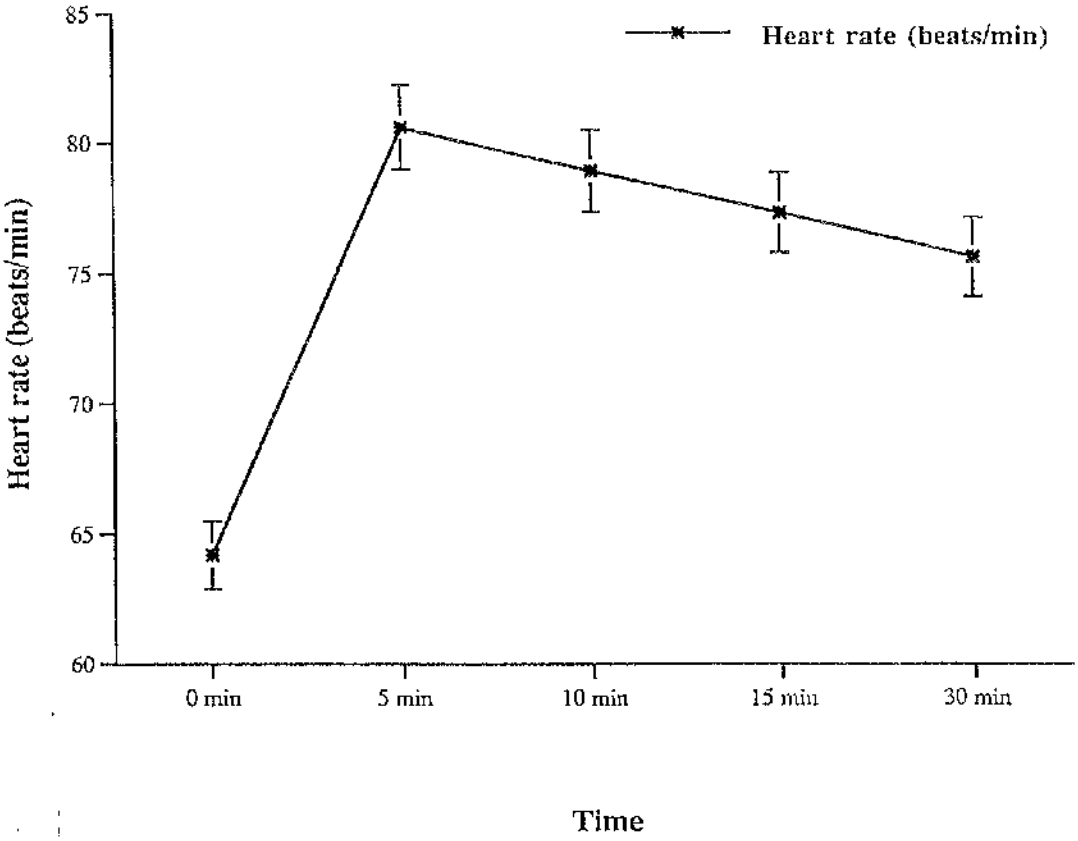


Figure 5.2: Changes in energy expenditure and heart rate in patients after salbutamol.

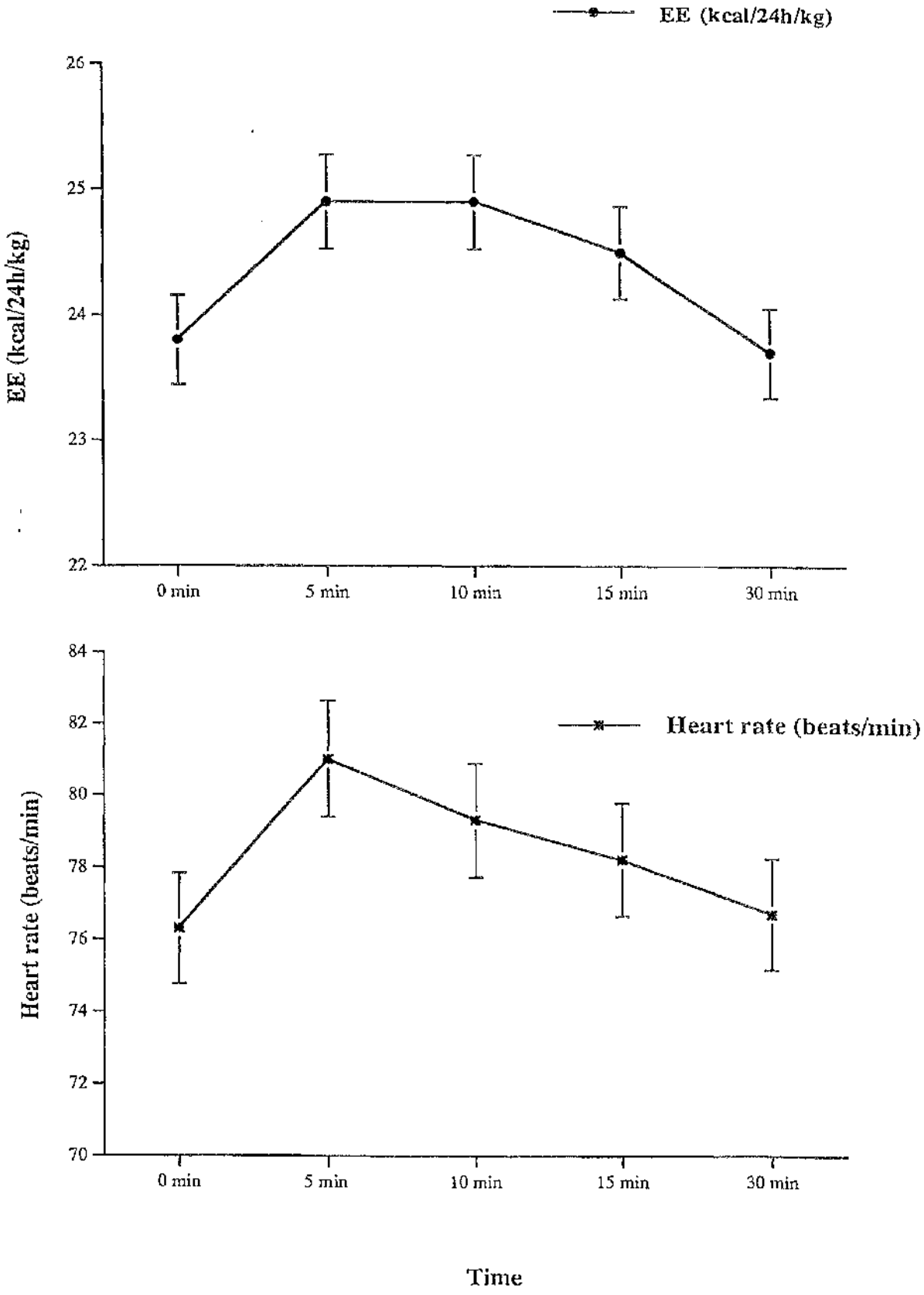
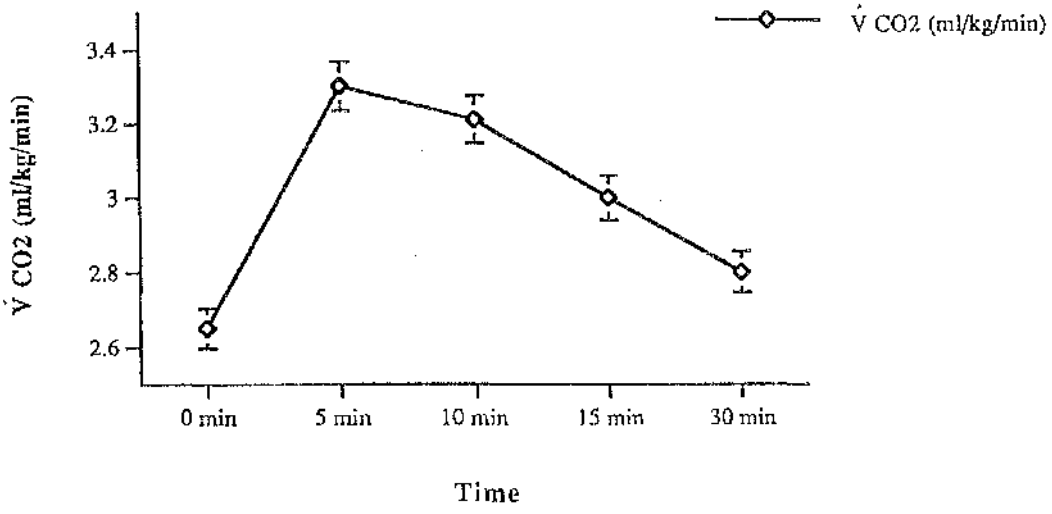
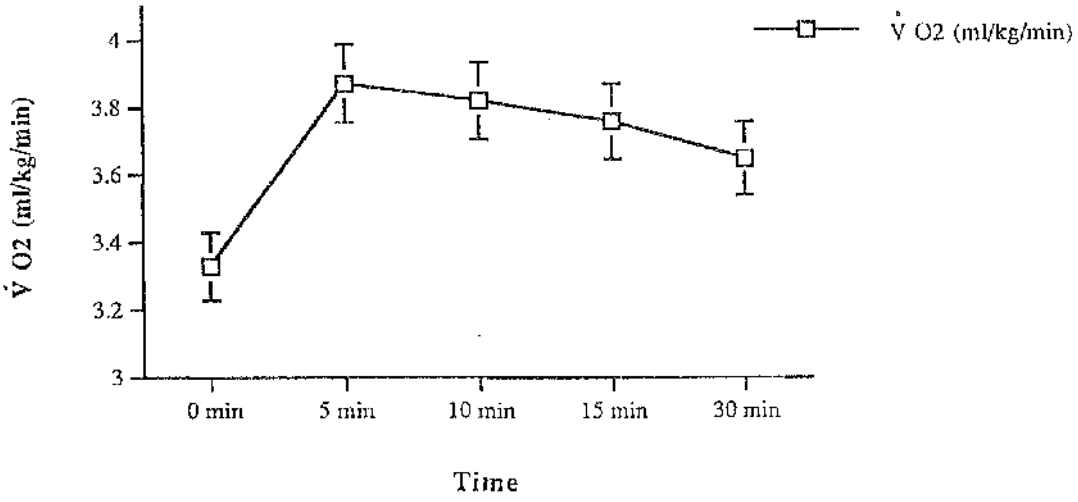


Figure 5.3: Changes in $\dot{V}O_2$, $\dot{V}CO_2$ and RER in controls after salbutamol inhalation.





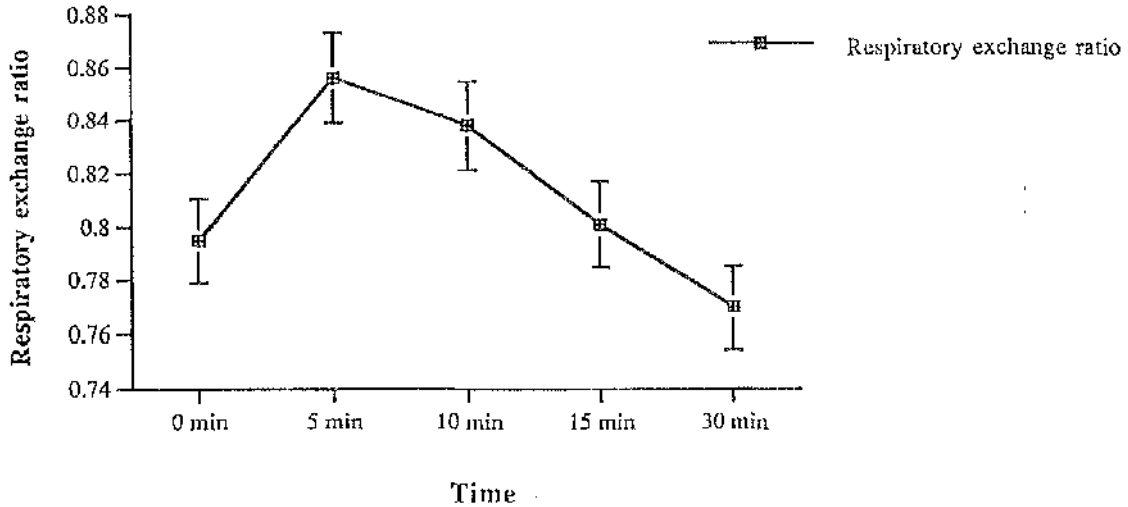
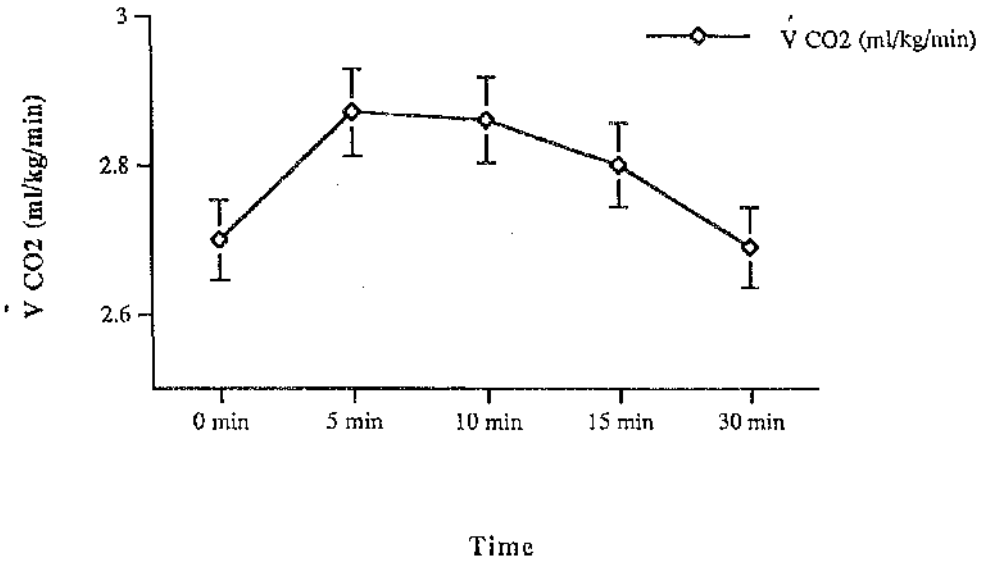
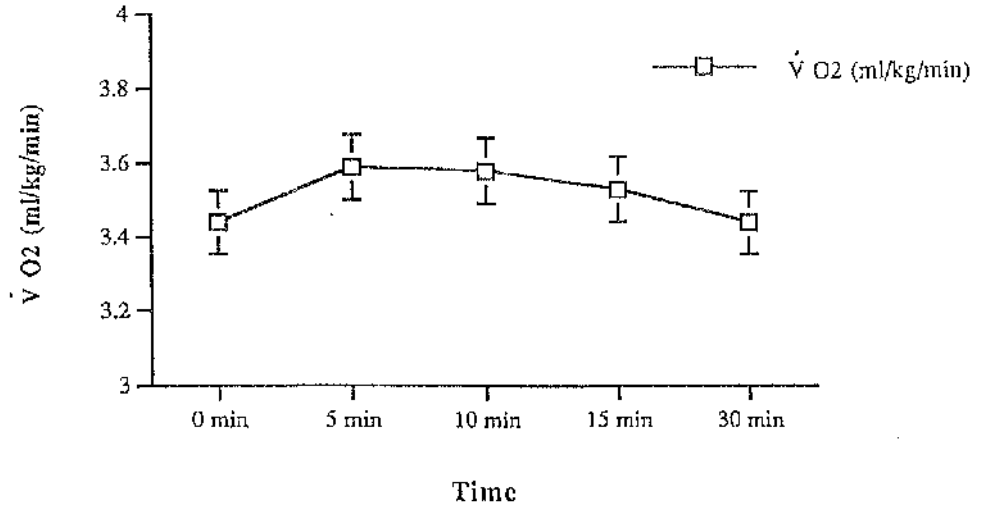
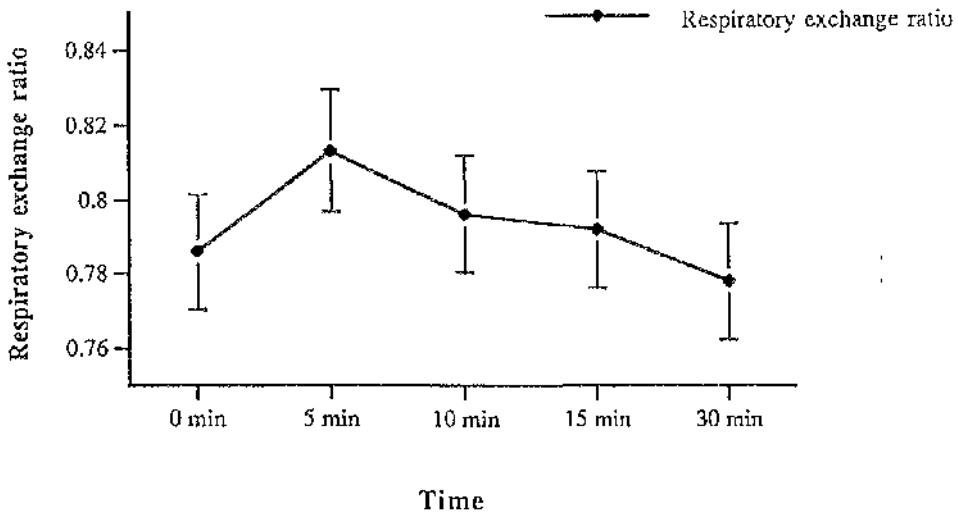


Figure 5.4: Changes in $\dot{V}O_2$, $\dot{V}CO_2$ and RER in patients after salbutamol inhalation.







CHAPTER 6: Energy balance of patients hospitalised with an acute exacerbation of COPD

6.1 Introduction

It is well recognised that metabolic stress related to injury and infection is associated with an elevation of the metabolic rate (Cuthbertson, 1954; Halmagyi et al, 1974). Infection is usually accompanied by fever and it has been estimated that for each degree centigrade increase in body temperature, basal metabolic rate increases by 12% (Du Bois, 1921). Other investigators have provided evidence to suggest that hypermetabolism in sepsis is greater than that would be expected from the mere thermic effect of a fever; and that hypermetabolism can accompany a state of normothermia in infection (Roe and Kinney, 1965; Halmagyi et al, 1974). In any event the view that infection elevates energy expenditure is beyond dispute. Even in patients with an impaired immune response such as patients with Acquired Immune Deficiency Syndrome (AIDS), there is an unequivocal thermogenic response to infection, such that it has been suggested that measurement of REE in such patients might be a useful indicator of secondary infections where other conventional clinical signs fail (Melchior et al, 1993).

Patients with chronic airflow obstruction suffer from more episodes of respiratory tract infections than controls (Monto et al, 1975). The clinical picture of a patient with COPD gradually becoming progressively malnourished with each intercurrent illness, including respiratory tract infections, is well described (Bates,1973; Fig 1.5). Whilst this impression of infections adversely affecting the energy balance of patients with COPD and resulting in weight loss is in keeping with clinical experience, surprisingly little data exist on the exact effect of a respiratory tract infection on the energy balance of patients with COPD.

In a study of the resting energy expenditure of eighteen elderly patients (mean age 84.9 yr.) hospitalised with a respiratory tract infection, investigators found that REE was elevated by 32.5 percent above that of healthy age matched controls (Hodkinson et al, 1990). Likewise a study of young patients with an acute infective exacerbation of cystic fibrosis revealed a significantly elevated REE which gradually decreased with antibiotic therapy (Naon et al, 1993). There are however no studies of REE in patients with COPD. Given that infection is associated with an increased energy demand and that patients with COPD suffer from more infections than average, the energy cost of respiratory tract infections could play a significant role in causing a state of negative energy

balance and weight loss in these patients. This study was designed to quantify the state of energy balance in patients with COPD hospitalised with an acute infective exacerbation.

6.2 Patients and methods

Twenty patients admitted to the Glasgow Royal Infirmary with an acute infective exacerbation of COPD were studied. An acute exacerbation was considered to be infective if the patient suffered from an increase in cough, sputum production and/ or breathlessness which was unresponsive to an increase in the use of bronchodilators, and/or fever, with or without haematological, bacteriological or radiological evidence of acute infection.

6.2.1 Study Protocol

Twenty patients (10 male; 10 female) admitted acutely unwell to Wards 10 and 11 of the Glasgow Royal Infirmary were studied (Table 6.1). Patients were studied within 36 hours of admission to the hospital. The investigations, including indirect calorimetry were performed in a separate room in the medical wards.

REE was estimated after an overnight fast on the morning after hospitalisation, and again on the day before discharge. In view of the results of the previous study beta agonists were not withheld on the morning of the study, but

calorimetry was performed at least two hours after the last dose of beta agonists. Oxygen therapy was discontinued fifteen minutes before calorimetry. All patients were on antibiotics at the time of both the initial and subsequent calorimetry. REE was expressed both in absolute values and as percentage of values predicted by the Harris-Benedict equation (Harris and Benedict, 1919).

The respiratory rate and oxygen saturation breathing room air and body temperature (oral) were measured whilst the patient was resting in the semi-recumbent posture. Oxygen saturation was measured by a pulse oximeter (Radiometer Ltd., Copenhagen). Prior to calorimetry, body weight, height and skin fold thickness were measured. The sum of the skin fold thickness at four standard sites was calculated and percentage body fat estimated from standard equations (Durnin and Womersley, 1974). Fat free mass was derived from this value and expressed in kilograms.

No specific bacteriological, haematological or biochemical tests were performed as part of the study. In those patients in whom C- reactive protein levels were estimated at the time of admission (n=13) as part of indicated clinical care, theses values were obtained. C- reactive protein levels were estimated by a standard immunoassay technique (Olympus AU 5230).

Patients who were grossly oedematous and patients who exhibited signs of decompensated cor pulmonale (raised jugular venous pressure) were not included in the study.

On the day before discharge the total dietary intake was recorded by a member of the nursing staff, with particular attention being paid to the portion sizes consumed. From this the calorific intake was measured by a previously validated computer based technique (Food Meter™, Medi-Matica s.r.l., San Benedetto Tr, Italy; McCance and Widdowson, 1991). Energy balance was estimated by relating energy intake to total twenty- four hour energy expenditure, which was taken as 1.4 times measured REE (Department of Health, 1991).

All patients gave their informed consent and the study was approved by the Glasgow Royal Infirmary Ethics Committee.

6.2.2 Statistics

Changes in REE, weight, respiratory rate and oxygen saturation between admission and discharge were expressed as mean change with 95% confidence intervals. Correlation between variables was estimated by the Spearman rank correlation coefficient. Stepwise multiple regression was performed with REE as a dependent variable, fat free mass, C-reactive protein, respiratory rate and oxygen saturation as

explanatory variables. Significance was assessed at the 5% level. All statistical calculations were performed with the aid of a computer using a standard software package (MINITAB Inc., Clecom Ltd, Birmingham).

6.3 Results

The median duration of stay in the hospital was 5 days (range 4 - 12).

6.3.1 Anthropometric and clinical measures

The baseline anthropometric and clinical characteristics are shown in Table 6.2. Seven patients had a body mass index of less than 18 kg/m ^{2}. There was no significant change in weight during the stay in hospital. There was however a significant fall in respiratory rate (mean fall 8.8 breaths / minute; 95% CI 7.4, 10.2); there was also an increase in resting oxygen saturation during stay in hospital (mean increase: 2.9%; 95% CI: 2.1, 3.6).

6.3.2 Evolution of REE during the stay in hospital (Table 6.3; Figure 6.1)

REE was elevated above predicted values in all patients at the time of admission (Mean (SD) 115.4 (7)%). It fell by 9.3 (95% CI: 7.2, 11.5) of predicted values during the stay in hospital to 106.1 (4.5)%.

On retrospective analysis of data, there was some suggestion that patients on maintenance steroid therapy (n = 8), as a group, exhibited a lesser elevation in REE (112.8 (5.9)% predicted) than those not on steroids (n = 12) (117.1 (7.40)% predicted), although this difference did not reach significance (p = 0.18) (Figure 6.2). In patients on steroid therapy there was no relation between dose of steroids and percentage predicted REE.

6.3.3 Dietary intake and energy balance at discharge

Dietary intake was very poor even on the day before discharge. Mean (SD) energy intake was only 895 (518) kcal/ day, making for a net negative energy balance (calorific deficit) of 889 (296) kcal/day below predicted 24 hr energy expenditure (Figure 6.3).

6.3.4 Relation between REE and other variables

There was a strong relation between REE and C-reactive protein levels on admission in the thirteen patients in whom C-reactive protein measurements were available (r = 0.60; p <0.01) (Fig 6.4).

There was no relation between body temperature and REE or between respiratory rate, oxygen saturation and REE.

The fall in REE during hospitalisation was strongly related to the initial elevation of REE above predicted levels i.e., higher the initial REE above the predicted value, greater the fall with treatment (r = 0 78).

On multiple regression analysis, fat free mass alone accounted for 65.9% of the variation (R^2) in REE on admission, C-reactive protein and FFM increased explained variance to 79.7%. The addition of respiratory rate or oxygen saturation did not improve this, although FFM and respiratory rate on admission gave an R^2 value of 75.6%.

6.4 Discussion

This study confirms the clinical impression that COPD patients suffer a state of considerable negative energy balance during an acute infective exacerbation. The study has not only quantified the degree of imbalance but has also shown that both the increased resting energy expenditure stemming from sepsis and a profound depression of food intake during the acute illness contribute to this state of energy imbalance. Whilst the main finding as regards negative energy balance during the acute illness is unsurprising, there are certain aspects of the study that merit discussion.

Although the patients were in a state of negative energy balance during their stay in hospital, they did not

exhibit any major weight loss. This could be due to two reasons. One, the short duration over which the measurements were made (median stay was 5 days; the interval between weight measurements was four days in most cases) meant that major sustained changes in body cell mass were less likely to have occurred. A negative energy balance of 1000 kcal / 24 hr for five days would result in a loss of under 1 kg, assuming that 75% of the loss is fat. This is still within the range of day-to-day fluctuation in weight. The other possibility is that, although patients were not overtly oedematous, there may have been a degree of right heart failure and fluid retention during the acute exacerbation which might have confounded the use of weight as an indicator of body cell mass. In this regard the fact that all patients with an acute infective exacerbation of COPD were either already on or were placed on steroid therapy immediately after hospitalisation is of relevance, as steroids are a well recognised cause of fluid retention and could conceivably have resulted in maintaining weight, masking the loss of body cell mass (Hayes, 1990).

The effect of steroid therapy on the results of the study are also worthy of some discussion. The patients who were on maintenance steroid therapy (doses of 5-20 milligrams of Prednisolone) showed a slightly lesser elevation of REE than those patients who were not on maintenance

steroids. Although corticosteroids are catabolic as regards intermediate protein metabolism, and have been shown to worsen nitrogen balance in arthritic patients even when producing signs of clinical improvement (Roubenoff et al, 1990), their marked anti-inflammatory effect (Hayes, 1990) may well have resulted in a suppressive effect on REE. The numbers in each group are too small for any conclusions to be drawn in this regard. But with the increasing use of steroids in COPD their effect on energy balance, body composition and natural history of the disease, in particular, their well recognised ability to mask the depletion of fat free mass merit further study.

In contrast to the study of patients with cystic fibrosis (Naon et al, 1993), the patients in this study did not show any increase in weight during their stay in hospital whilst recovering from the acute illness. This is due to the fact that, whereas the dietary intake of the young cystic fibrosis patients gradually increased during their stay in hospital, the calorific intake of this group of COPD patients remained very poor even up to the time of discharge. One of the factors that could account for this very low dietary intake , in addition to the anorexia associated with infection (Tracey et al, 1989) and its treatment (anorectic effect of antibiotic), is the breathlessness and oxygen desaturaion caused by the effort of

eating in these patients with severely compromised lung function (Brown et al, 1983; Schols, 1992). It was also noticed that the most common method of oxygen delivery used in the wards was a face mask, which cannot be used whilst eating. It would be a matter of interest whether the use of nasal cannulae , which allow eating, in place of oxygen masks, improves food intake.

The lack of relation between FFM and the increase in REE associated with an infective exacerbation may be interpreted as suggesting that patients who are nutritionally depleted do not show a relatively greater increase in REE during an exacerbation. This lack of difference between undernourished and well nourished COPD patients as regards the energy cost of an infection could be taken as evidence that variations in the thermogenic response to an infection (and by implication any other stress) is not the reason behind some patients with COPD exhibiting negative energy balance and weight loss whilst others do not. However such a conclusion cannot be made with certainty from this study due to the confounding effect of steroid therapy; slightly more of the underweight (BMI less than 18) patients (4 out of 7) were on maintenance steroids than the normal or overweight patients (4 out of 13).

6.5 Conclusion

The study comprising this chapter has shown that (a) patients with COPD suffer a state of considerable negative energy balance during an acute infective exacerbation; this could contribute to the weight loss seen in some of the patients (b) there was no evidence to suggest that the more nutritionally depleted patients exhibit an 'inappropriate' increase in REE compared with the well nourished (c) steroid therapy, which is being increasingly used in COPD, is likely to be a major confounding factor in future studies of energy balance and body composition of patients with COPD.

Sex	10 male; 10 female
Age (yr.)	66.0 (4.8)
Smoking history	18 ex-smokers; 2 current smokers
Drug therapy	
Inhaled therapy:	
Beta agonist	20 (100%)
Steroids	12 (60%)
Oral therapy:	
Steroids	8 (40%)
Aminophyllines	1 (5%)
Diuretics	7 (35%)
Nitrates	3 (15%)
Diltiazem	2 (10%)

Table 6.1: Characteristics of study population. Age as mean (SD)

Body weight (kg)	55.4 (16.0)	
Height (cm)	159 (8.0)	
Body mass index	22.1 (6.1)	
Fat free mass (kg)	38.3 (3.2)	
Clinical data	Admission	Discharge
Respiratory rate (breath/min)	26.7 (2.9)	17.1 (2.5)
Oxygen saturation (as%)	85.8 (5.1)	88.7 (3.9)
C- Reactive protein (n=13)	56.3 (25.3)	NA

Table 6.2: Anthropometric and clinical characteristics of patients admitted with an acute infective exacerbation of chronic obstructive lung disease. Values as mean (SD).
NA - not available

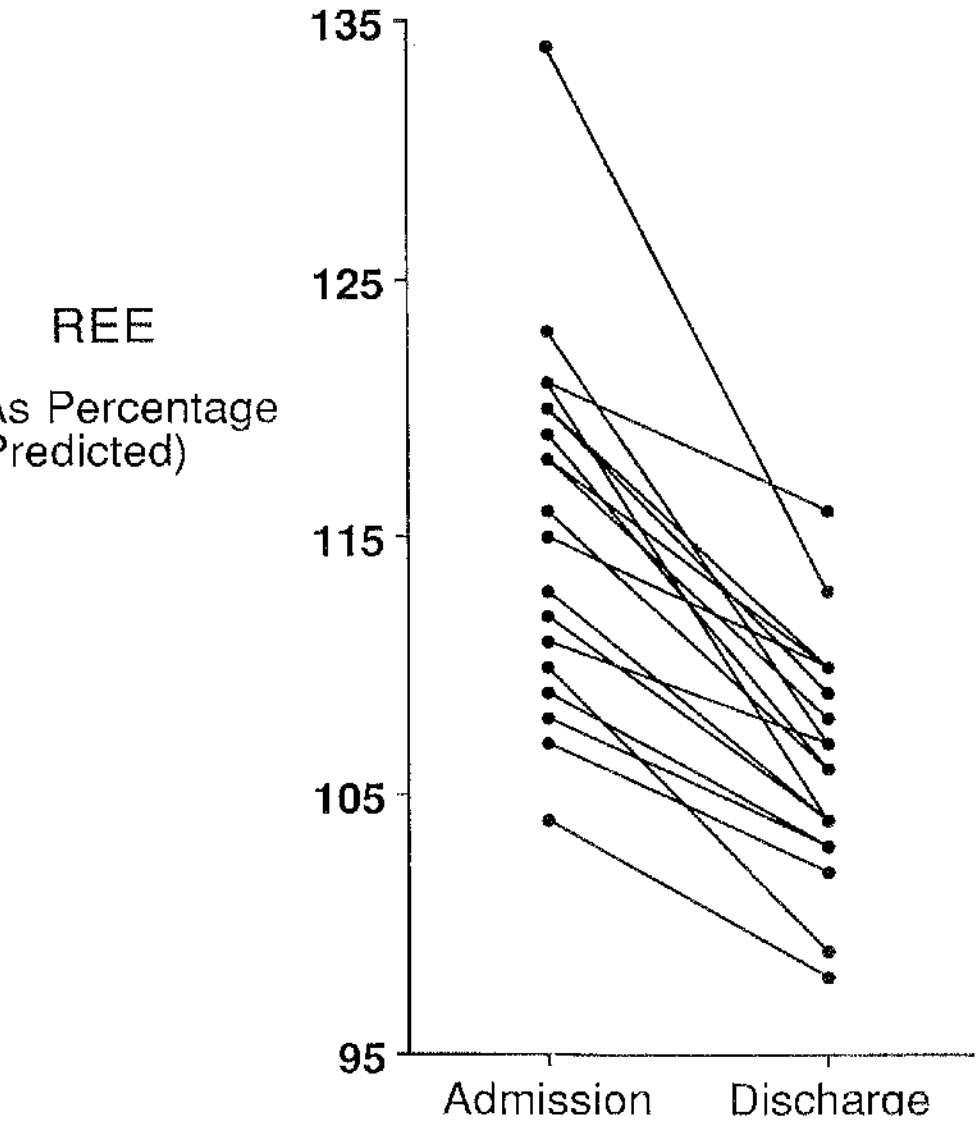


Figure 6.1: Changes in REE (as percentage predicted) during stay in hospital in twenty patients admitted with an acute exacerbation of COPD.

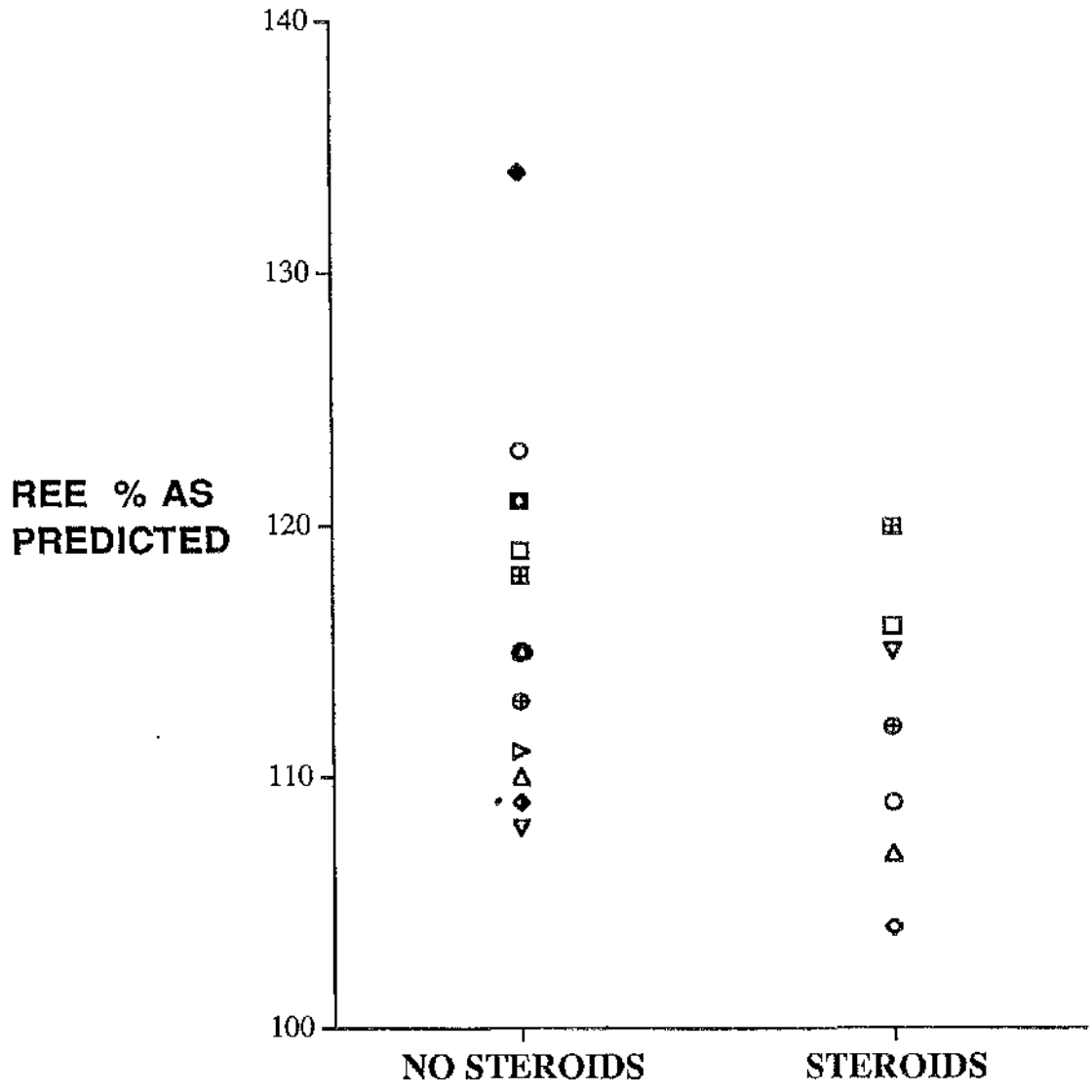


Figure 6.2: REE on admission (as percentage predicted) in patients on maintenance steroid therapy at the time of admission and those not on maintenance steroid therapy.

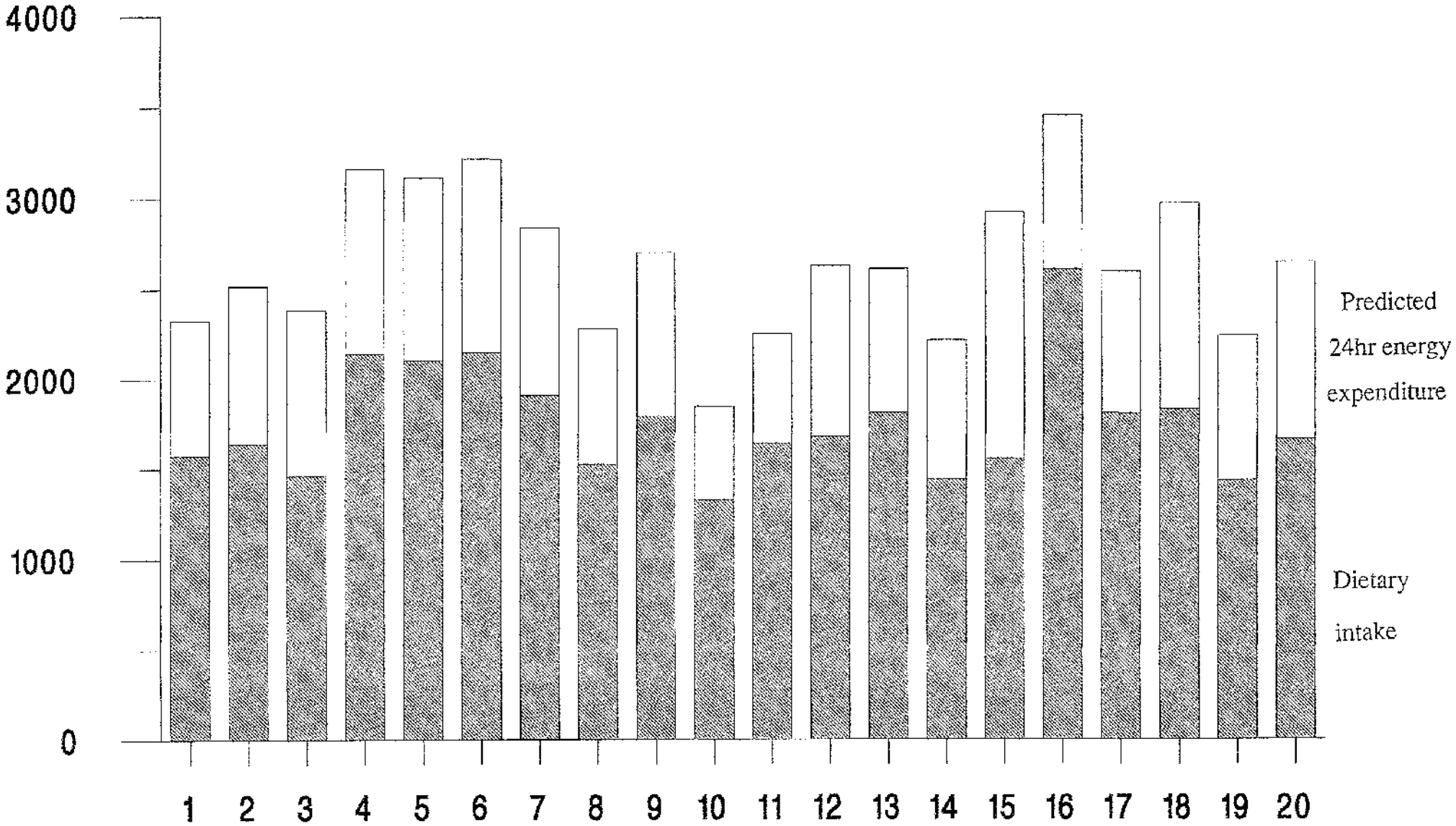


Figure 6.3: Energy deficit at the time of discharge in the twenty patients (all values in kcal).

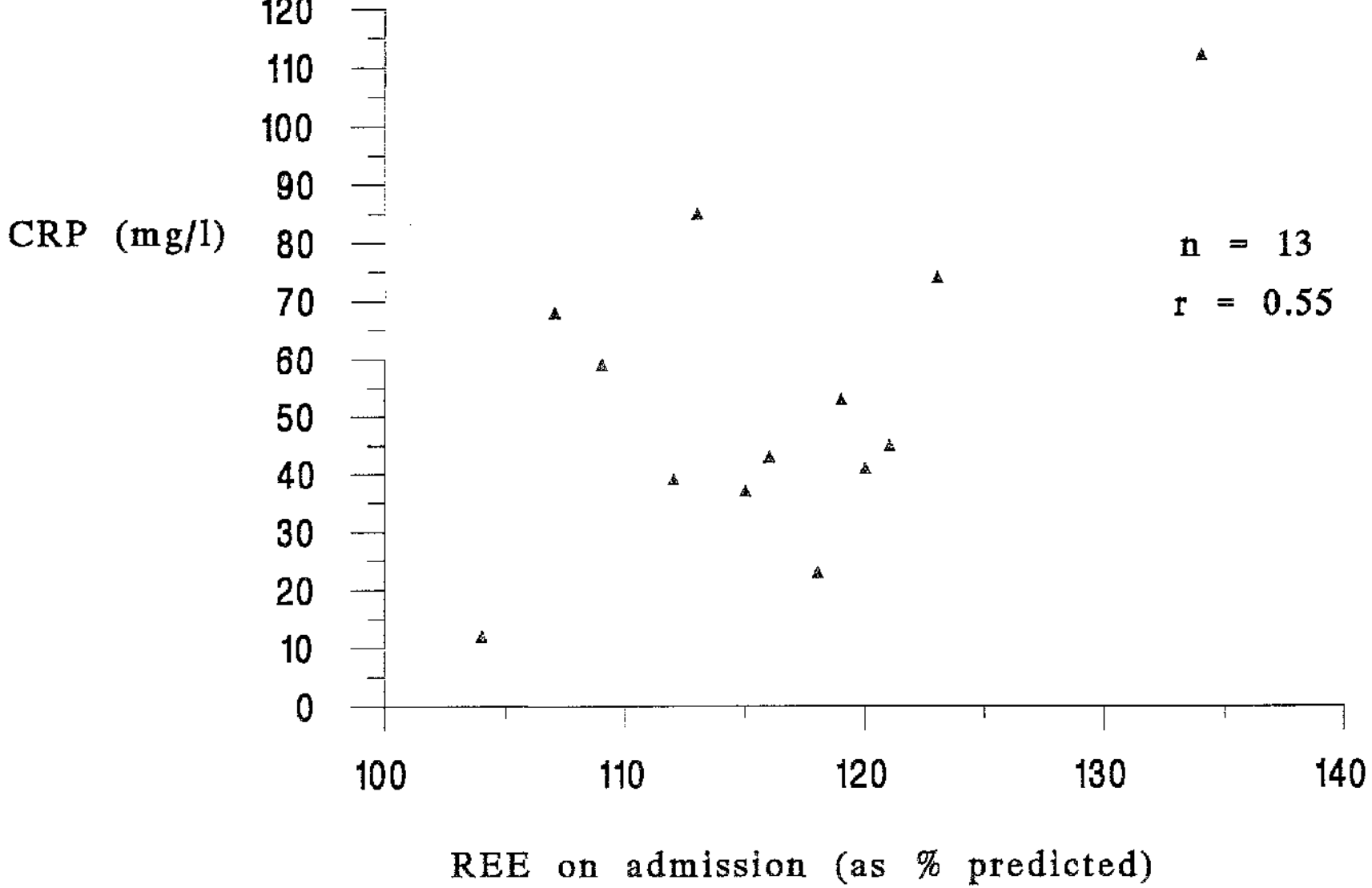


Figure 6.4: Relation between REE on admission (as percentage predicted) and C-reactive protein levels.

CHAPTER 7: Routine and novel outpatient nutritional programmes in COPD

7.1 Introduction

The logical extension of the observation that malnutrition was an adverse prognostic factor in patients with COPD was the attempt to restore the nutritional status of these patients with a view to improving the morbidity and mortality. The question of nutritional support in these patients and in particular its effect on their lung function, respiratory muscle strength (RMS) and exercise capacity has been well reviewed (Fitting and Spiro, 1991). Studies which showed an improvement in RMS and exercise capacity following nutritional supplementation involved intensive short-term refeeding techniques (Wilson et al, 1986)) or closely supervised outpatient programmes (Efthimiou et al, 1988; Rogers et al, 1992) with significant cost implications. However, if nutritional therapy is to have a practical role in rehabilitation programmes for COPD, simple outpatient programmes are required. Although studies have investigated outpatient provision of nutritional supplements in COPD, supplementation in these investigations has usually been

carried out under research conditions involving intensive use of dietary advice and follow-up. In this context it was felt that a study of a simple, sustainable outpatient nutritional support programme, delivered in a clinical setting without the benefit of research programme based resources, would help clarify the clinical role of nutritional support in COPD patients.

7.2 Patients and methods

7.2.1 Patient characteristics

Twelve patients (9 male, 3 female; mean age 65.9 yr.) (Table 7.1) were studied as outpatients. All patients had emphysema as manifested by a an FEV1/FVC of less than 60% predicted and a carbon monoxide single breath diffusing capacity of less than 60% predicted (Gelb et al, 1983). All patients were less than 90% ideal body weight (IBW) as determined from the midpoint of the weight range for sex, height and frame in the Metropolitan Life Insurance Company tables (Metropolitan Life, 1983) or had lost more than 5 kilograms in the previous year. All patients were ex-smokers. None of them suffered from cancer, diabetes, malabsorption or any other illness that could cause weight loss. Patients who suffered from overt cor pulmonale (ankle oedema, raised jugular venous pressure) or other cardiac disease were excluded from the study. Patients entered into the study were considered clinically stable and free of intercurrent respiratory

tract infection. All patients used inhaled and/or oral bronchodilator therapy. None was receiving oral steroid therapy but four patients were on long term inhaled steroids (more than 2 yr.) at a dose of less than 800 micrograms of beclomethasone dipropionate a day.

7.2.2 Anthropometry

Body height was measured to the nearest 0.5 cm with the patient standing barefoot; body weight was measured to the nearest 0.1 kg by a beam scale with the patient in light clothing and without shoes (Weylux Model 424, England). Body frame was estimated from wrist circumference measurements. Triceps skinfold thickness (TSF) was measured to the nearest 0.2 mm by Holtain skinfold calipers using standard techniques (Durnin and Rahaman, 1967). Mid-arm circumference (MAC) was measured and mid-arm muscle circumference (MAMC) derived.

7.2.3 Blood biochemistry

Serum albumin was measured. C-reactive protein levels were estimated as an indicator of the presence of an acute phase response.

7.2.4 Calorimetry

Indirect calorimetry was performed on an outpatient basis in all patients using a ventilated hood system (Deltatrac metabolic monitor, Datex instrumentarium Corporation, Helsinki) as previously described (Chapter 2). Patients were

tested in a separate laboratory after an overnight fast of at least 10 hours. After a resting period of 20 minutes oxygen consumption and carbon dioxide production were estimated for a period of 20 minutes with the patient in the semi-recumbent position. The data obtained in the last 15 minutes was used to estimate resting energy expenditure (REE) if there was less than 5% minute to minute variation in the oxygen consumption measurement. REE was calculated using Weir's formula (Weir, 1949).

7.2.5 Lung function tests and exercise capacity :

Forced expiratory volume in the first second (FEV 1) and forced vital capacity (FVC) were measured using a whole body plethysmograph (P.K.Morgan Ltd, England) (Grimby and Soderholm, 1963). Diffusing capacity was measured by the single breath technique (Burrows et al, 1961). Maximal inspiratory and expiratory mouth pressures (PI max and PE max) were measured using apparatus based on Black and Hyatt (Black and Hyatt, 1969). P I max was measured from functional residual capacity (FRC) and P E max from total lung capacity (TLC). The highest of three technically satisfactory measurements was taken as the value used for analysis in each case.

Symptom limited exercise tests were carried out using an electrically braked bicycle ergometer (Siemens Ltd) with the patient breathing through a low dead space low resistance

valvebox. The valve box incorporated a turbine ventilometer on the inspired limb for the measurement of ventilation. Expired gas was analysed for oxygen (O_2) and carbon dioxide (CO_2) by an infra-red spectrometer and para magnetic analyser respectively (P.K.Morgan Ltd, England). After a 2 minute rest period while seated on the bicycle the patients were instructed to cycle with no additional load for 2 minutes. Thereafter the load was increased by 25 watts every 2 minutes until symptoms limited exercise. Two trial tests were performed on separate occasions before the first exercise test to familiarise the patients with the equipment and avoid confounding of the results by a training effect.

The measures of respiratory function, exercise capacity and nutritional status were made before and after a four month period of nutritional support.

7.2.6 Dietary assessment and nutrition

The patients were assessed by a senior dietician on enrolment into the study. Mean daily carbohydrate, protein, fat and energy intake was estimated from a 7 day recall on two separate occasions. The patients were then advised on increasing their total caloric intake to at least 50% above predicted daily energy expenditure, which was calculated as 1.4 times REE (sedentary lifestyle); recommended protein intake to at least 1.5 g/kg . Nutritional supplementation was by the use of proprietary supplements. The patients were

allowed to choose the nature (liquid, pudding) and flavour of the supplements from a wide range of proprietary preparations (Buildup, Fortisip, Maxijul R). A fortnight's supply of the supplement was provided initially and the patients were asked to seek replenishments as required. Where applicable the patient's spouse was also instructed on the aims and nature of the dietary intervention. After the first interview the patients attended a monthly dietetic review when adherence to the recommended diet was confirmed verbally. Nutritional supplementation was continued for a period of four months. The dietary advise was provided during routine clinic hours.

7.2.7 Statistical analysis

The anthropometric measures, serum albumin, tests of lung function, exercise capacity and RMS before and after nutritional supplementation were compared using paired Student's 't' test. The mean values of the various measurements were considered significantly different when the probability of the differences of that magnitude, assuming the null hypothesis to be correct, fell below 5% (i.e. $p < 0.05$).

The study was approved by the hospital ethics committee and the patients gave their informed consent.

7.3 Results

Three patients withdrew from the study. Two patients withdrew due to intolerance of the supplements, one after the first fortnight and another after a month. Unacceptable taste and abdominal bloating after taking the supplements were given as reasons for intolerance to the supplements by the two patients. One patient withdrew due to a protracted episode of intercurrent lower respiratory tract infection.

Mean resting energy expenditure for the group was 109.3% predicted (Range 96 - 126). Nine of the twelve patients were in a state of net negative energy balance (Table 7.2). Of the nine patients a weight gain of more than 1 kilogram was achieved in only three and these patients were from a higher socio-economic class (Class I and II) than the patients in whom nutritional supplementation was unsuccessful (Class IV) (Office of Population censuses and Surveys, 1980).

There was no significant change in the nutritional status, FEV_1, RMS or $\dot{V}O_2$ max after the four month period of supplementation in the nine patients who completed the study (Tables 7.3 and 7.4; Figures 7.1 and 7.2).

7.4 Discussion

Well designed, randomised, controlled studies have shown that successful nutritional therapy is accompanied by an improvement in various measures of respiratory function and symptoms (Wilson et al, 1986; Efthimiou et al, 1988).The aim of this uncontrolled study was to see whether the beneficial effect of supplementary nutritional therapy as demonstrated under well controlled experimental conditions could be extended to the wider area of clinical practice. The study suggests that although weight gain and improvement in functional status may be achieved by some individuals under these circumstances, this approach is ineffective for the majority and a number of practical issues need to be addressed before nutritional therapy is accepted as routine clinical practice.

All studies of outpatient nutritional support in malnourished COPD patients, the present study included, point to the fact that these patients are unable to maintain an increased caloric intake over a long period. In one of the more recent studies (Rogers et al, 1992) the rate of weight gain achieved during stay in a clinical research unit could not be sustained in the outpatient setting despite the provision of full and intensive nutritional support. Thus, providing adequate and appropriate nutritional support alone does not in itself

guarantee an improvement in the nutritional status of these patients.

A number of factors could account for this finding. It has been pointed out that patients tend to decrease their own food intake whilst receiving enteral formulas and do not in fact improve their caloric intake while on nutritional supplements (Lewis et al, 1987). Breathlessness produced by the effort of eating may also limit food intake. Perception of nutritional therapy as making only a minor contribution to their well being might be another factor that may influence compliance with dietary advise and response to therapy. No attempt was made in this study to objectively confirm adherence to the dietary instructions provided as it was felt that under clinical conditions, which the study aimed to mimic, such measures would be clearly impractical.

Perhaps worthy of some note is the finding that the three patients who gained weight in this study were from a higher socio-economic class, Classes I and II. Unemployment, smoking habits, poor working and housing conditions are amongst the various factors that may influence the outcome of all medical treatment including nutritional therapy (Whitehead and Dahlgren, 1991).

7.5 Conclusion

Conventional nutritional supplementation provided for four months via a routine dietary clinic does not improve nutritional status, lung function or exercise capacity in malnourished COPD patients. In line with a recent study in the same field which concluded that although nutritional therapy is capable of producing significant clinical improvement in patients with COPD, it is 'costly, time-intensive and of limited therapeutic magnitude' (Rogers et al, 1992), this study leads to the conclusion that nutritional supplementation *per se* is of little value in the management of patients with COPD. Clearly, further studies in the outpatient setting should now assess the effect of nutritional therapy in conjunction with attempts at promoting anabolism either by pharmacological means (anabolic steroids) (Schols et al, 1992) or physical training (exercise prescription and respiratory muscle training).

One of these, the use of novel anabolic agents, is explored in the following section of this chapter.

7.6 Clenbuterol : Introduction

Clenbuterol is a sympathomimetic agent which has bronchodilator properties and has been used in the treatment of airways obstruction (Brusaco et al, 1980). In addition the drug has been shown to increase skeletal muscle protein as well as muscle fibre size and strength. These effects have been documented in normal muscle tissue (Maltin, Delday and Reeds, 1986; Zeman et al, 1988), denervated muscle (Maltin et al, 1986) and immobilised muscle (Delday, Williams and Maltin, 1990). Following animal studies suggesting an anabolic effect, the drug was studied as a muscle specific anabolic agent in improving muscle strength in a group of patients recovering from orthopaedic (knee) surgery (Maltin et al, 1993). Clenbuterol treatment was associated with a more rapid rehabilitation and an increase in knee extensor strength in the unoperated side, lending support to the view that the drug might have a role to play in the management of disease states associated with muscle wasting. Given that some patients with COPD exhibit depletion of muscle mass and that clenbuterol, in addition to its well documented bronchodilator effect also has an anabolic effect on muscle tissue, it was considered appropriate to conduct a randomised, double blind, placebo controlled pilot study of this drug in malnourished patients with COPD.

7.7 Clenbuterol study: Patients and methods

Six patients were studied (four female, two male; mean age: 64.5 yrs; range: 47-76). All the patients suffered from emphysema (Gelb et al, 1983) and had a body mass index < 18. All the patients had taken part in routine nutritional supplementation programme described above and had failed to improve. Patients with significant primary (i.e. not cor pulmonale) heart disease, hypertension and significant skin disease were excluded from the study in view of the known side effect profile of clenbuterol. There was no restriction on inhaled bronchodilator use but patients on oral β-agonist therapy were excluded.

After a 2 week run-in period patients were randomised to receive placebo or clenbuterol 20 μg twice daily for 4 weeks. After a 2 week washout period patients crossed over to the other treatment. Following 4 weeks of the second treatment patients underwent final investigations (Figure 7.1; Table 7.4). The dietary intervention during the two phases of the study was exactly the same as in the previous study, consisting of dietary advice with the provision of ad libitum supplements chosen by the patients (Section 7.2.6).

The various investigations performed are summarised in Table 7.4. In view of the reservations expressed by some of the patients in undergoing a formal exercise test, involving the measurement of V O_2 max, a

simple six minute walking test was used to assess exercise capacity (Section 2.6.4). Body composition was measured by whole body K 40 measurements (Chapter 2; Section 2.5.5). In addition to respiratory muscle strength, peripheral muscle strength was measured by handgrip dynamometry (Section 2.7).

Statistical analysis was performed using Wilcoxon signed rank test for changes in values from baseline after placebo and clenbuterol therapy.

7.8 Clenbuterol study: Results

Of the six patients one patient withdrew from the study owing to unacceptable side effects from clenbuterol (severe pounding headache and anxiety; code unblinded). The results of the various investigations of nutritional status, respiratory function and exercise capacity are given in Tables 7.5 and 7.6.

As shown there was no improvement in any of the parameters in the group as whole, although one patient showed a striking increase in exercise capacity following the active drug (Patient no:5).

7.9 Clenbuterol: Discussion

The result of this pilot study of clenbuterol in six malnourished COPD patients is disappointing. The addition of this agent with proven anabolic and 'repartitioning' effect to routine nutritional supplementation did not improve the poor results obtained from simple supplementation alone.

It is possible that 4 weeks was too short a period for a tangible effect on muscle structure and function to be discernible. But other studies in humans have used the same time frame and demonstrated an improvement (Maltin et al, 1994), and indeed it was the latter study and the advice of its principal investigator that was basis for the decision to study the drug for a 4 week period. A study of the drug given for a longer duration will clearly settle this issue and such a study is being planned.

It is also possible, indeed probable, that clenbuterol is relatively ineffective in severe pathological states and that its beneficial effect, particularly on muscle strength indices, is best seen in muscle tissue which is characterised by a normal metabolic state. Evidence for this assertion comes from the previous study in humans, where the improvement in muscle strength in patients undergoing knee surgery was seen, not in the thigh muscles operated upon, but on the unoperated side. Also a more recent study (Milliken et al, 1995) in a mice muscular dystrophy model has shown that diaphragm

dysfunction induced by threshold loading was not influenced by clenbuterol therapy, whilst in control mice clenbuterol improved the contractile properties of the diaphragm. It is thus likely that the benefits of clenbuterol demonstrated in isolated muscle preparations may not, for reasons that are as yet unclear, extend to disease states.

7.10 Conclusion

The addition of clenbuterol at a dose of 20 μ gms twice daily for a month to a conventional nutritional supplementation programme did not improve nutritional status, respiratory function or exercise capacity in a group of six malnourished emphysematous patients. It is possible that use of the drug for a duration longer than one month may better outcome but evidence is beginning to emerge that the muscle performance enhancing effect of clenbuterol may be limited to 'normal' muscle rather than disease states.

No:	Age (yr.)	Sex	% IBW	REE kcal / day (% predicted)	Daily caloric intake (%pred. daily EE)
1	79	M	89	1225 (108)	1899 (119)
2	64	F	70	1024 (111)	1387 (104)
3	72	M	82	1087 (96)	1554 (110)
4	65	F	71	1187 (112)	1635 (106)
5	67	M	92	1484 (126)	1982 (103)
6	67	M	76	1358 (1100	1617 (91)
7	64	M	84	1630 (108)	2159 (101)
8	60	M	66	1039 (114)	1337 (98)
9	67	M	92	1285 9109)	1798 (107)
10	60	M	85	1515 (117)	1890 (97)
11	64	F	82	1057 (99)	1516 (110)
12	62	M	77	1051 (102)	1270 (93)

Table 7.1 : Characteristics of patients studied in an investigation of outpatient nutritional support in COPD.

No::	Body weight in kg		TSF in mm		MAMC in cm		Albumin in g/dl	
	AS	BS	BS	AS	BS	AS	BS	AS
1	55.0	58.3	5.2	5.6	22.4	22.2	46	43
2	31.O	32.0	2.8	2.8	17.0	17.2	42	40
3	51.1	49.8	3.8	3.8	20.3	20.3	42	40
4	41.5	42.8	3.6	3.8	16.9	16.8	44	49
5	54.5	53.4	6.8	6.4	21.8	22.0	47	44
6	53.2	53.0	7.0	7.0	19.8	19.8	43	45
7	68.4	73.0	8.0	8.8	21.4	22.0	49	50
8	35.4	35.0	3.0	3.2	17.0	17.0	39	42
9	54.6	52.3	3.8	3.4	24.8	24.9	43	48
Mean (SE)	49.4 (3.8)	50.0 (4.3)	4.9 (0.64)	5.0 (0.70)	20.2 (0.92)	20.2 (0.94)	43.8 (1.0)	45.0 (1.2)

Table 7.2: Nutritional status before and after nutritional supplementation.

No::	FEV 1 in litres		V̇ O2 max. in litres / min		PE max in cms water		PI max in cms water	
	AS	BS	BS	AS	BS	AS	BS	AS
1	0.80	0.82	0.62	0.66	100.3	100.8	58.7	58.9
2	0.72	0.69	0.51	0.48	70.1	68.3	40.4	41.5
3	0.65	0.63	0.41	0.52	96.6	97.2	50.0	48.0
4	0.60	0.62	0.28	0.36	63.0	66.1	31.0	33.9
5	1.03	0.99	0.99	0.72	100.4	98.2	49.4	49.0
6	1.15	1.20	1.09	0.93	83.6	80.7	41.8	41.0
7	1.67	1.72	0.90	0.94	122.5	126.4	75.5	78.4
8	0.60	0.60	0.49	0.35	73.0	71.2	45.8	47.3
9	1.73	1.61	1.33	1.20	148.4	151.0	70.6	68.5
Mean (SE)	0.99 (0.15)	0.99 (0.14)	0.71 (0.11)	0.67 (0.08)	95.3 (9.1)	95.5 (9.5)	51.5 (4.8)	51.8 (4.8)

Table 7.3: Lung function, exercise capacity and respiratory muscle strength before and after supplementation.

Table 7.4 : Investigation schedule for study of clenbuterol.

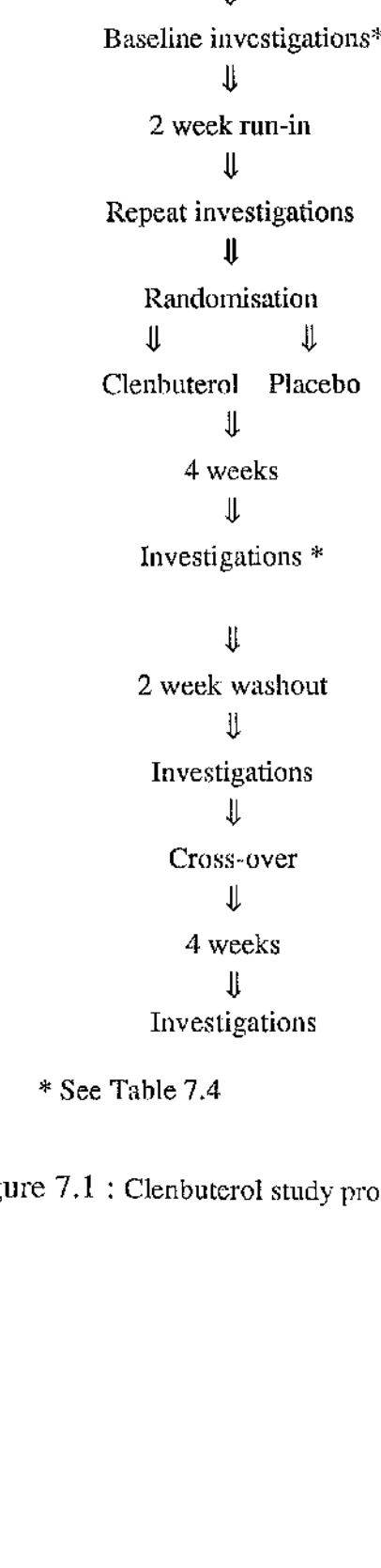
	Weeks			
	-2	0	4	10
Spirometry	X	X	X	X
Six minute walk	X	X	X	X
PI & PE max	X	X	X	X
Hand grip dynamometry	X	X	X	X
Anthropometry	X	X	X	X
Body composition		X	X	X

Table 7.5: Body composition and peripheral muscle strength after clenbuterol and placebo

No:	Body weight in kgs			FFM in kgs			Handgrip strength in kg-w		
	BL	AP	AC	BL	AP	AC	BL	AP	AC
1	42.7	43.3	41.8	33.8	33.6	32.7	12.0	12.5	12.8
2	59.4	57.7	58.5	44.5	43.6	44.5	10.0	10.2	10.2
3	41.4	41.8	41.9	31.7	30.3	29.4	8.0	8.6	8.4
4	41.9	41.9	41.6	33.0	31.8	33.2	5.8	5.5	5.3
5	54.1	52.4	52.9	45.1	45.4	46.6	31.8	31.0	33.5
Mean (SE)	47.9 (3.7)	47.4 (3.2)	47.3 (3.5)	37.6 (2.9)	36.9 (3.1)	37.3 (3.4)	13.5 (4.7)	13.5 (4.5)	14.0 (5.0)

Table 7.6 : Lung function, respiratory muscle strength and exercise capacity after clenbuterol and placebo.

No:	FEV 1 in litres			PI max (cms H_2O)			PE max (cms H_20)			Six minute walk (metres)		
	BL	AP	AC	BL	AP	AC	BL	AP	AC	BL	AP	AC
1	2.33	2.16	2.41	40.6	38.3	42.5	69.1	72.7	70.8	380	375	375
2	0.93	0.9	0.94	51.0	53.6	50.8	91.0	92.3	93.6	172	170	180
3	0.61	0.6	0.61	32.4	36.1	33.8	57.5	59.3	57.0	89	83	83
4	0.91	0.86	0.89	45.5	43.8	47.0	61.5	61.5	60.7	194	188	184
5	0.53	0.51	0.58	71.0	70.3	68.4	146.0	143.1	155.4	225	223	252
Mean (SE)	1.06 (0.32)	1.08 (0.3)	1.08 (0.33)	48.1 (6.5)	48.4 (6.3)	48.5 (5.7)	85.0 (16.3)	85.8 (15.5)	87.5 (18.1)	212.0 (47.7)	207.8 (47.7)	214.8 (48.3)



* See Table 7.4

Figure 7.1 : Clenbuterol study protocol

CHAPTER 8: Conclusions and future directions

This chapter summarises and brings together the results of the various investigations into aspects of energy balance of patients with chronic lung disease and reviews other new developments in the field. An attempt at providing a unified theory to explain the weight loss and energy imbalance seen in patients with chronic lung disease follows, taking into account the findings of the presented investigations and other new evidence gathered during the period of these investigations were in progress. The chapter concludes with a brief note on the directions that future research in this subject could profitably undertake.

8.1 Results of investigations comprising this thesis

The results of the various investigations that constitute this thesis are presented as answers to the specific questions posed in the first chapter.

8.1.1 Resting energy expenditure of patients with chest wall disease

Patients with chest wall disease are known to suffer from a mechanical inefficiency of the chest bellows mechanism and exhibit an increase in the work of breathing. The question posed was 'Does the increased work of breathing which is recognised to be a feature of patients with chest wall disease always elevate resting energy expenditure?'.

A study of REE in twenty patients with chest wall disease (eleven post-TB thoracoplasty and nine scoliosis) showed that patients with chest wall disease do not exhibit a consistent increase in REE despite an assumed increase in the work of breathing.

8.1.2 Relation between REE, oxygen cost of breathing and nutritional status in patients with emphysema and chest wall disease.

The previous study had shown that REE was not elevated in patients with chest wall disease despite an assumed increase in the work of breathing; however, no measurement, direct or indirect, was made of the energy cost of breathing. The next study of the thesis involved the measurement of the oxygen cost of augmenting ventilation and was designed to answer the question 'What is the relation between the oxygen cost of breathing, lung function, REE and nutritional status in

patients with different types of chronic respiratory impairment?

In a study of twelve patients with chest wall disease (six scoliosis and six thoracoplasty), six patients with emphysema it was found that whilst the oxygen cost of breathing was inversely related to lung function, there was no relation between oxygen cost, REE and the nutritional status of these patients. Increased oxygen cost of breathing and poor lung function did not predict a hypermetabolic state or poor nutritional status. These findings render untenable the theory that the increased energy cost of breathing is the sole or major cause of weight loss in patients with chronic lung disease.

8.1.3 Thermogenic effect of β agonist therapy

Adrenergic drugs are known to cause a dose dependent increase in energy expenditure. This thermogenic effect is apparent even when low doses of the drug are inhaled. The next study of the thesis addressed the questions 'What is the thermogenic effect of therapeutic doses of inhaled salbutamol in patients with COPD who are long term users of the drug ?' and 'Is it possible that the thermogenic effect of beta agonist therapy contributes to a state of negative energy balance in these patients?'.

In a study of twelve patients with COPD who had been using inhaled salbutamol for over three years it was

found that, compared with healthy volunteers, these patients showed a marked blunting of the thermogenic and heart rate response to therapeutic doses of inhaled salbutamol. It was concluded that the thermogenic effect of beta agonist therapy was not a factor contributing to weight loss in patients with lung disease.

8.1.4 Energy cost of acute exacerbation of disease

Although acute infective exacerbations have long been considered to contribute to a state of negative energy balance and weight loss in COPD patients, there are very few data on the subject. The next study of the thesis was conducted to answer the question ' What is the impact of an acute infective exacerbation on the energy balance of patients with COPD?'.

Indirect calorimetry performed within 36 hours of admission to hospital in 20 patients with an acute exacerbation of COPD showed that REE was not only significantly elevated at the time admission but that patients were in a state of significant negative energy balance even at the time of discharge from hospital. The conclusion was that the energy cost of an acute infective exacerbation could make a significant contribution to cachexia in COPD.

8.1.5 Renutrition in COPD

Investigators who have succeeded in demonstrating a benefit in terms of improvement of nutritional status and lung function in malnourished patients with COPD have done so employing cost and labour intensive supplementary feeding techniques under research conditions. If refeeding is to have a clinical role in the management of COPD patients it must be delivered by a simple and sustainable means, in a clinical setting. The concluding studies of the thesis were designed to answer the questions:

(a) Can successful renutrition and improvement in lung function be achieved by supplementation programmes delivered from a routine dietary clinic? and (b) Will the use of the agent Clenbuterol, a beta agonist with muscle performance enhancing properties, better the rather poor results obtained by routine nutritional supplementation studies?

The results of the refeeding studies, with and without Clenbuterol, much like many of the more clinically orientated studies carried out previously, were disappointing. A routine dietetic clinic based nutrition programme did not improve nutritional status, respiratory function or exercise capacity patients in a group of twelve malnourished COPD patients. The addition of Clenbuterol to nutritional supplementation did not improve matters; a randomised double blind, cross-over pilot trial of Clenbuterol plus

nutritional supplements for a month in six patients showing no improvement in respiratory function, exercise capacity or fat free mass compared with nutritional supplementation alone.

In summary the investigations of this thesis have provided evidence to suggest that the energy cost of breathing and thermogenic effect of beta adrenergic drugs are not important causes of energy imbalance and weight loss in patients with chronic lung disease; that an acute infective exacerbation of disease results in a significant state of energy imbalance which might contribute to weight loss in patients with COPD; and that routine dietary supplements given for four months and the drug Clenbuterol plus nutritional supplements given for a month do not improve nutritional status, respiratory function or exercise capacity in malnourished COPD patients.

8.2 Results of other investigations in the field

During the time that the investigations that constitute this thesis were being pursued other workers have made significant contributions to the body of knowledge on this subject of nutritional status of patients with COPD. In particular, studies utilising techniques of molecular biology have uncovered interesting new evidence that may enable a coherent hypothesis to be formulated to explain the weight

loss that is a feature of patients with emphysematous COPD. This section summarises the results of these and other recent investigations in the field.

8.2.1 Weight loss in COPD and cytokines

Cytokines are a group of hormone-like non antibody proteins released by one cell population which act as intercellular mediators in the generation of the inflammatory response (Billingham, 1989). Tumour Necrosis Factor (TNF) - α is a cytokine which is a primary mediator of injury and inflammation and provokes cachexia in a variety of clinical states including cancer (Tracey, Vlassara and Cerami, 1989). Recent studies have revealed that serum levels of TNF - α are high in weight losing but not weight stable COPD patients (Di Francia et al, 1994). Other investigators have shown that not only are circulating levels of cytokines higher in weight losing COPD patients but also that, compared with healthy elderly controls, monocytes from these patients produce a larger amount of cytokines both spontaneously and in response to stimulation (de Godoy et al, 1994). From these studies it appears that cytokines, in particular, TNF-α has a role to play in the pathogenesis of weight loss in COPD. Also of interest in this subject is the observation that priming of human monocytes by hypoxia *in vitro* results in an enhanced release of cytokines (Bain et al, 1994).

8.2.2 Nutritional depletion and gas exchange

Carrying on from their observation that use of depletion of muscle mass as an indicator of malnutrition uncovers more cases of malnutrition than the conventional measure of total body weight, the Dutch workers have now presented the results of a study on the relation between nutritional depletion and respiratory and peripheral skeletal muscle function (Engelen et al, 1994). In a study of seventy two patients with COPD they have shown that depletion of fat free mass was associated with diminished respiratory and peripheral muscle strength. More interestingly they observed that whilst the nutritionally depleted patients did not show a pronounced difference in spirometry or intrathoracic gas volumes compared with the well nourished patients, the transfer coefficient (K co) was significantly lower in the depleted group. In other words severity of airflow obstruction as measured by spirometry and body plethysmography did not discriminate between well and poorly nourished patients but measures of gas exchange i.e. the transfer coefficient (K co) did. This finding is entirely in keeping with the conclusion made in the first chapter of the thesis that it is not severe airflow obstruction per se that is associated with weight loss and malnutrition, but the gas exchange abnormalities that characterise emphysema.

8.3 Energy balance and weight loss in COPD - a unified theory

Why do COPD patients suffer from weight loss? And why is weight loss more a feature of emphysema and its attendant abnormalities of gas exchange rather than of chronic bronchitis and severe airflow obstruction alone? Why is weight loss a poor prognostic sign? Why are COPD patients relatively refractory to nutritional repletion?

Until recently the most widely accepted theory explaining weight loss in patients with lung disease was the mechanistic one - airflow obstruction causing an increase in the work of breathing, increased energy expenditure, negative energy balance and weight loss. However, the finding of the studies in this thesis that there is no relation between the oxygen cost of breathing, resting energy expenditure and nutritional status and the results of other studies on energy balance in patients with COPD (Ryan 1992, Green and Muers, 1993) render untenable the theory that the work of breathing is the main cause of weight loss in patients with lung disease.

Any theory which seeks to explain the tissue depletion must account for the now well confirmed observation that the best predictor of poor nutritional status

and low body weight in COPD is not the degree of airflow obstruction, as might be expected if it simply the work of overcoming airways resistance that leads to negative energy balance and weight loss, but the abnormality of gas exchange as measured by the transfer coefficient (K co). This implies either that the protease - anti protease imbalance that results in destruction of the alveolar walls, causing emphysema and gas exchange abnormalities, also causes protein destruction at a systemic level i.e., emphysema is a state of generalised tissue destruction of which the lung damage is only a part ; or that the generalised tissue depletion is the result of the abnormal gas exchange which is a characteristic, defining feature of emphysema (Gelb et al, 1973).

There is evidence to suggest that the latter is the case. Filley and co-workers in their meticulous study (1968) showed that the underweight pink puffers, compared with the blue bloaters, had a lower cardiac output at rest and also failed to increase their cardiac output significantly on exercise, in keeping with the pathology of emphysema which involves destruction of the alveoli and disruption of the pulmonary vascular bed , resulting in a relatively fixed cardiac output. Thus whilst resting arterial oxygen tensions were higher in the thin, emphysematous pink puffer, tissue oxygenation as estimated by the ratio of oxygen delivered (cardiac output x arterial oxygen content) to the oxygen consumed (arterial -

mixed venous oxygen content) was better in the plethoric blue bloater. Thus the emphysematous patients with their more pronounced gas exchange abnormalities are more starved of oxygen at the tissue level than the bronchitic, and it is possible that that the limited supply of this essential nutrient, oxygen, that leads to tissue loss and nutritional depletion.

How does tissue hypoxia lead to weight loss? Results of the recent investigations on the role of inflammatory mediators, cytokines, particularly TNF- α (cachexin) provide some clues. As noted, studies of TNF levels in COPD patients have revealed that not only are serum levels of TNF - α high in malnourished COPD patients but that monocytes from weight losing COPD patients produce a larger amount of cytokines both spontaneously and in response to stimulation (Di Francia et al, 1994; de Godoy et al, 1994). It has been demonstrated that priming of human monocytes by hypoxia *in vitro* results in an enhanced release of cytokines (Bain et al, 1994), and it is quite possible that such a phenomenon occurs *in vivo* in the 'tissue hypoxic' patients with emphysema , resulting in cachexia but not in the bronchitic patient with intact gas exchange. A similar explanation might well hold in patients suffering from cachexia due to severe heart failure (Pittman and Cohen, 1964), who also have high levels of circulating TNF- α (Levine et al, 19900.

The hypothesis that malnutrition in emphysema is simply a cytokine mediated marker of chronic progressive tissue hypoxia will account for many of the features of emphysema associated weight loss that have hitherto been difficult to explain. Firstly, the significance of weight loss as a poor prognostic sign even in patients with relatively less airflow obstruction (Wilson et al, 1989). Weight loss, being the result of a gas exchange abnormality is simply a reflection of worsening tissue oxygenation, not worsening airflow obstruction. The onset of weight loss is merely a sign of advancing tissue hypoxia, of a degree approaching a state which in due course will be incompatible with cellular function. Also in keeping with this would be the finding of this study that there is no relation between routine tests of airflow obstruction (FEV 1) and REE and nutritional status. Second, the stepped decline in weight and nutritional status that is witnessed in emphysematous patients during states of stress, including infections, on a background of a gradual decline in body weight (Bates, 1973). This is likely the result of a surge of inflammatory activity associated with infections and other stresses (Tracey et al, 1989), occurring in the context of a lesser but nevertheless significant hypoxia induced cytokine activity . The variable values of energy expenditure noted in emphysema patients with the comparable degree of

respiratory function abnormality (Donahoe et al, 1989; Green and Muers, 1992; Ryan et al, 1993), may be accounted for by variations in the level of cytokine activity at the time of study, TNF levels rather than lung dysfunction now being the primary determinant of energy expenditure (Elborn et al, 1993). Also, the absence of polycythemia in emphysema, is explicable as the consequence of increased cytokine activity, TNF-α causing a relative suppression of the bone marrow (Tracey et al, 1988), counteracting the polycythemic effect of tissue hypoxia. Lastly, the relative refractoriness of emphysema associated malnutrition to nutritional supplementation noted in previous studies(Otte et al, 1989; Rogers et al, 1994) and the studies that comprise this thesis is explained on the basis that however plentiful the supply of energy providing substrate is, the lack of availability of tissue oxygen as an essential element in the energy generating process (Lehninger, 1982) will result in failure of optimal utilisation of the proferred nutrients.

Neither the theory that tissue hypoxia is a feature of emphysematous and not bronchial type of obstructive lung disease, nor the view that the cachectic states of emphysema and chronic heart failure might be the result of the same mechanism are new (Filley et al, 1968). However the new findings from cell biology techniques has enabled the

formulation of a theory that can offer a fuller explanation of the phenomenon of unexplained weight loss in these patients.

In summary (Figure 8.1), taking into account the results of the studies of this investigation and other more recent studies in the field, it appears that weight loss in patients with chronic lung disease results mainly from severe tissue hypoxia which causes an increased susceptibility to and enhanced release of cytokines; the negative energy balance that accompanies every acute infective exacerbation makes a sizeable contribution to the nutritional depletion, but the increased work of breathing in itself is not a major reason for weight loss seen in these patients.

8.4 Directions for future research

Quite clearly the mechanistic theories which were the focus of much attention in the seventies and eighties have been superseded by theories which seek to explain phenomena at a molecular/ metabolic level. In this regard it is worth pointing out that whilst the cytokine profile of emphysematous, weight losing patients is being studied actively, there is a relative neglect of patients who do not lose weight and do not suffer from nutritional depletion ('Blue bloaters'). It is crucial that these patients are studied as intensively as the weight losing patients as any mechanism which is postulated to account for weight loss in

emphysematous patients must be clearly demonstrated to be absent in those with COPD that do not.

Also worthy of note is that all studies of energy balance, including those that comprise this thesis have been cross-sectional. They have studied energy balance at particular points in time, at particular levels of lung dysfunction. However, if one were to seek an insight into the pathogenesis of energy imbalance and weight loss in patients with COPD, the most useful studies are likely to be longitudinal ones which follow patterns of energy balance, lung function and nutritional status in a cohort of COPD patients over long periods of time. Whilst such studies may prove to be labour and cost intensive, they may settle once for all the issue of what the best predictors are of nutritional depletion. For example, the demonstration that progressive deterioration in diffusing capacity presages weight loss would imply that patients with worsening gas exchange are at risk of nutritional depletion, and thus worthy of specific attention as regards nutritional intervention. It would likewise be a matter of great interest to study the cytokine profiles of patients with COPD over a period of time, during periods of relative clinical stability and during episodes of stress (infections and other intercurrent illnesses) and correlate these with changes in nutritional status.

One of the issues that is likely to dominate this area of research is the confounding of various measures of nutritional status, body composition and energy balance by oral steroid therapy, which is being used increasingly in patients with non-asthmatic chronic obstructive airways disease (Mitchell et al, 1984). It is very likely that a number of patients with COPD, who in the past may have lost weight and thus become visibly malnourished, will now maintain their weight due to lipogenesis associated with maintenance steroid therapy, but have a body composition that is akin to a state of profound malnutrition (severe reduction of fat free mass). It is imperative therefore that the potentially misleading use of body weight as an indicator of nutritional status be highlighted and accessible methods of measuring body composition be developed and used in patients with COPD.

As for attempts at improving prognosis by influencing the nutritional status of malnourished COPD patients, it is clear that conventional nutritional supplementation programmes are not the answer. The identification of cytokines as mediators of tissue depletion raises the possibility of using anti- TNF agents to treat weight loss, but clearly any intervention hoping to make significant impact on long term prognosis must deal with the underlying problem of tissue hypoxia, which is most likely the reason for these patients remaining relatively refractory to refeeding

regimes. In this regard the impact of lung transplantation on the nutritional status and energy metabolism of malnourished patients undergoing the procedure for emphysema would be an area worthy of investigation.

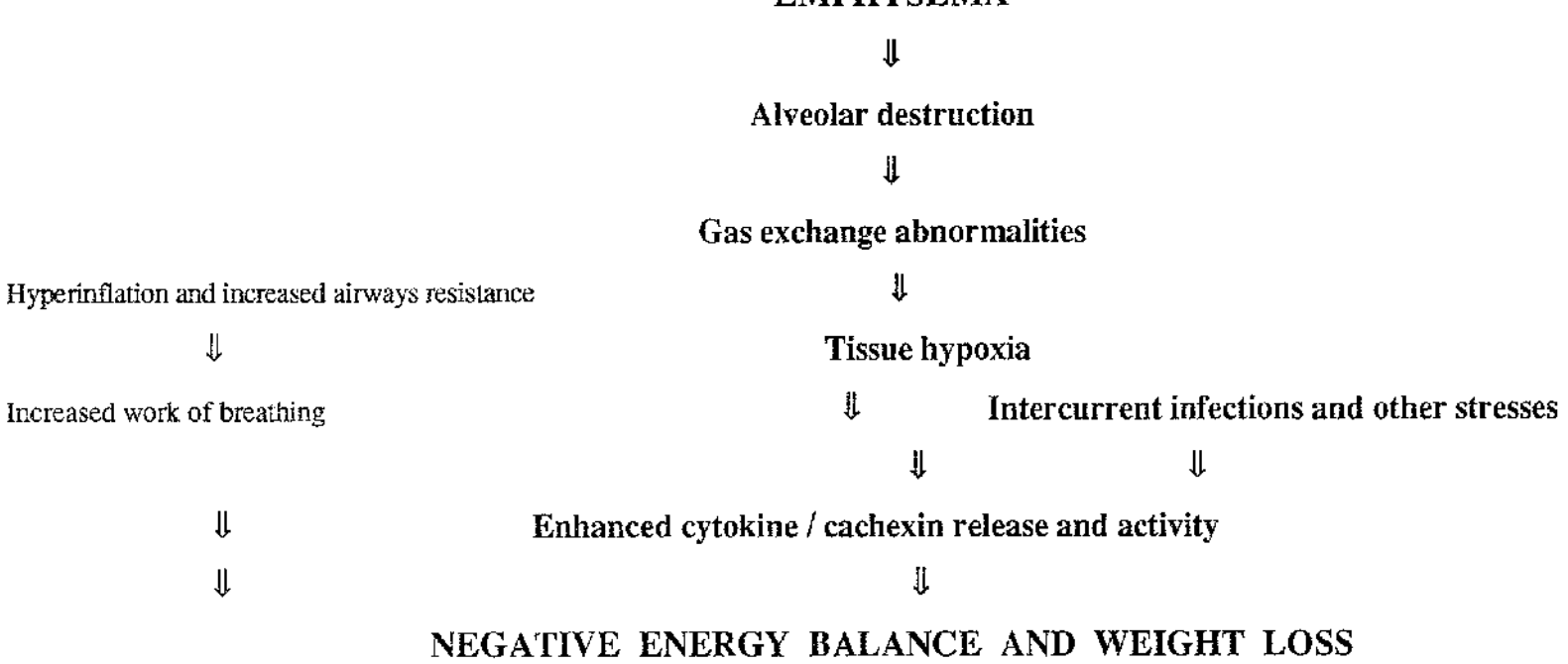


Figure 8.1: Theory proposed to explain weight loss in patients with emphysematous chronic obstructive pulmonary disease.

APPENDIX 1

A technical note on the indirect calorimetry system used in this study

The indirect calorimetry system used in this study was the Deltatrac Metabolic Monitor ™. The following is a brief account of its features, its merits and demerits.

A 1.1 : General description

The Deltatrac Metabolic Monitor is an example of a flow through, open system of indirect calorimetry. The general configuration is as shown in Fig 2.2. The system measures oxygen consumption ($\dot{V}O_2$) and carbon dioxide ($\dot{V}CO_2$) production, and calculates the energy expenditure according to the modified Weir equation (Weir, 1941). The main components of the system are:

(a) The gas analysers: Oxygen is measured by a differential oxygen sensor which uses the paramagnetic principle in a pneumatic bridge configuration. The carbon dioxide concentration is measured by an infrared sensor. It is worthy of note that the infrared sensor for CO_2 is always sensitive to O_2 concentration due to physical effects.

(b) A ventilated canopy: This is a half ellipsoid made of transparent plastic 1 mm thick, which encloses the subject's

head. The volume of the canopy is about 25 litres. The canopy is provided with an inlet port which draws in room air and an outlet port which conducts room air diluted by expired gas to the gas analysers. The edge of the canopy extends to a plastic cloth which is used to make the canopy relatively air tight (Figure 2.3).

(c) Constant flow generator: This is constructed from a centrifugal fan which generates flows of around 40-50 litres per minute.

(d) Mixing chamber: The expired air is drawn through (mixed with the air stream sucked in) a four litre mixing chamber from which a sample is drawn for analysis.

A 1.2 : Measurement principle

$\dot{V}\,CO_2$ and $\dot{V}\,O_2$ are calculated from the difference in gas concentrations measured up and downstream from the point where the subjects expired gas enters the airstream. If Q is the flow,

$$\dot{V}\,CO_2 = Q \,.\, \Delta F\,CO_2$$

$$\dot{V}\,O_2 = (Q/\,(1\text{-}F\,IO_2))\;(\Delta\,FO_2\text{-}FIO_2 \,.\, \Delta F\,CO_2)$$

where,

$$\Delta F\,CO_2 = FE\,CO_2 - FI\,CO_2$$

$$\Delta F\,O_2 = FI\,O_2 - FE\,O_2\,,$$

FI O_2 and FE O_2 being the concentration of oxygen in the inspired and expired gas, FI CO_2 and FE CO_2 the concentrations of carbon dioxide in the inspired and expired gases respectively.

The oxygen difference FI O_2 - FE O_2 is measured continuously with the differential oxygen sensor; the inspiratory carbon dioxide level is checked once every two minutes.

A 1.3 Advantages and disadvantages of the Deltatrac Metabolic Monitor

Clearly, the most important advantage of the Deltatrac was its non-invasive nature. As demonstrated in Chapter 2, the system, due to its non-invasive nature, permitted patients with lung disease to maintain a near normal pattern of breathing whilst measurements of oxygen consumption and carbon dioxide production were being made. Also, cough, which is a relatively common symptom in this patient population, was not inhibited by any apparatus.

Whilst indirect calorimetry with a ventilated hood system is clearly a convenient technique with superior patient acceptability, the system is not without its faults. Firstly there is an error inherent in the system with regards to the measurement of oxygen and carbon dioxide tensions in the

expired gas. Although calibration both of the gas analysers and the flow constant ensures minimal errors, the Haldane transformation which is used to calculate $\dot{V}O_2$ and RQ from expiratory volume only, amplifies errors progressively when the inspired fraction of oxygen is increased. The manufacturer's estimate of the baseline error and gain errors are given in Table 1. From this data, the final relative error depending on the level of $\dot{V}CO_2$, $\dot{V}O_2$, $FECO_2$, FIO_2 is computed as shown in Table 2. Inherent in the system is therefore a possible error of $\pm 3\%$ in the measurement of $\dot{V}O_2$ and $\dot{V}CO_2$ values. Whilst this does not in any way negate the findings of the studies of the thesis (all studies had controls), this limitation needs to be borne in mind when the data are used in absolute terms (for example to calculate energy needs during an infection).

In addition to the error inherent in the measurement, the other error that was not corrected for in the studies of REE that were conducted was correction for the incomplete oxidation of proteins in the body. In order to achieve a greater degree of accuracy measurements of urinary nitrogen excretion are made and an appropriate correction made of the REE values. But the errors induced if urinary nitrogen is not measured are small, and given that in all studies there were a group of controls, it seems reasonable to assume that this error did not in any way affect the results of the studies.

Also the fact that measurements made over a short period of time are being extrapolated to give 24 hour energy expenditure merits emphasis. In this regard, it might have been ideal and relatively simpler to study patients with COPD and matched controls by direct calorimetry in a calorimeter chamber over 24 hours, pursuing their own 'normal' daily activities, to settle the issue of whether 24 hour energy expenditure is indeed elevated in stable COPD patients. Such a system was unavailable in the institution where the investigations comprising this thesis were conducted.

Errors	Carbon-dioxide	Oxygen
Baseline	± 0.005	± 0.01
Gain	± 0.5	± 0.5

Table A 1.1: Baseline and Gain errors assumed whilst computing systematic errors in Deltatrac measurements (Manufacturer's data from Deltatrac prototypes, Datex Instrumentarium Corp., 1993)

	$\dot{V}$ CO_2 (ml/ min)		
	100	200	300
$\dot{V}$ CO_2	± 3.5 %	± 2.5 %	± 2.2 %
$\dot{V}$ O_2	± 5.5 %	± 3.5 %	± 3.0 %
RQ	± 7.5 %	± 4.5 %	± 3.5 %

Table A1.2: Maximum possible relative errors in measurement of $\dot{V}$ O_2, $\dot{V}CO_2$ and RQ at an RQ level of 0.85.

APPENDIX 2

This section presents data supporting the use of a time period of 20 minutes for making energy expenditure measurements and the data on the variability of $\dot{V}O_2$ and $\dot{V}CO_2$ measurements.

A 2.1 Duration of indirect calorimetry

In all the studies indirect calorimetry was performed for a period of twenty minutes. The data obtained in the first five minutes was discarded and the data obtained over the next fifteen minutes was used to calculate REE.

The data obtained in the first five minutes was discarded as the oxygen consumption and carbon dioxide production values were very variable as the subjects were settling into a regular breathing pattern, commencing from a state of relative hyperventilation (Figure A 2.1). On the basis of data collected in 5 patients with COPD who underwent calorimetry for one hour it was found that variability was consistently least i.e., $\dot{V}O_2$ and $\dot{V}CO_2$ values were more stable between ten and thirty minutes of measurement, particularly between ten and twenty minutes of measurement. There were wide individual variations in the stability of these measurements over time but most patients tended to show a greater variation in these measures after about 30 minutes in the hood (Table A2.1).

These variations were associated with visible signs of restlessness (crossing of legs, sighing breathing, movement of arms across chest) and it therefore seemed appropriate to restrict the duration of measurement to the shortest acceptable duration with least variations. The measurement period between five and twenty minutes was therefore chosen.

A 2.2 Coefficients of variation for $\dot{V}O_2$ and $\dot{V}CO_2$ measures with the Deltatrac Metabolic Monitor

$\dot{V}O_2$ and $\dot{V}CO_2$ were measured in 3 patients and 2 controls on 3 different occasions, each eight weeks apart. The measurements were made for a period of 20 minutes on each occasion, the data obtained in the first five minutes being discarded. The mean $\dot{V}O_2$ and $\dot{V}CO_2$ measured over the last 15 minutes on the three occasions in the five subjects (three patients, two controls) are shown in Table A2.2. The coefficient of variation for $\dot{V}O_2$and $\dot{V}CO_2$ ranged from 3-8%.

?
DELTATRAC Metabolic Monitor Prog. rev. 876849-1

PATIENT: male 169 cm 48 kg 72 yr 1.53 m2

CANOPY MODE ADULT 16-Jun-1992

CALIBRATIONS: AMB. CO2 CO2 MEAS./SET O2 MEAS./SET
16-Jun-1992 09:45 0.04 % 5.07 / 5.00 % 97.0 / 95.0 %

RESULTS IN STPD
NO AVERAGING

TIME	VCO2	VO2	RQ	EE	FiO2	FCO2*	FiO2-FO2*
h:min	ml/min	ml/min		kcal/d	%	%	%
09:49*	185	212	0.88	1460	20.9	0.48	0.53
09:50*	177	204	0.87	1410	20.9	0.46	0.51
09:51*	178	190	0.94	1330	20.9	0.46	0.48
09:52*	138	152	0.91	1050	20.9	0.36	0.38
09:53*	129	156	0.83	1060	20.9	0.33	0.39
09:54	163	184	0.89	1270	20.9	0.42	0.46
09:55	146	176	0.83	1200	20.9	0.38	0.44
09:56	149	176	0.85	1200	20.9	0.39	0.44
09:57	167	189	0.89	1300	20.9	0.43	0.47
09:58	158	184	0.86	1260	20.9	0.41	0.46
09:59	158	175	0.90	1220	20.9	0.41	0.44
10:00	148	172	0.86	1180	20.9	0.38	0.43
10:01	135	159	0.85	1080	20.9	0.35	0.40
10:02	137	164	0.83	1110	20.9	0.35	0.41
10:03	135	166	0.81	1130	20.9	0.35	0.41
10:04	153	188	0.82	1280	20.9	0.40	0.47
10:05	152	176	0.86	1210	20.9	0.39	0.44
10:06	142	170	0.84	1160	20.9	0.37	0.42
10:07	137	164	0.83	1120	20.9	0.36	0.41

Figure A2.1: REE measurements showing a progressive drop in oxygen consumption and carbon dioxide production values in the first five minutes.

Time interval	$\dot{V}\ O_2$ (ml / min)	$\dot{V}\ CO_2$ (ml/min)
0 - 5 min	318	241
6 - 10 min	272	213
11 - 15 min	283	222
16 - 20 min	277	222
21 - 25 min	284	210
26 - 30 min	289	228
31 - 35 min	294	232
36 - 40 min	278	219
41 - 45 min	270	208
46 - 50 min	285	216
51 - 55 min	279	222
56 - 60 min	291	235

Table A2.1: Indirect calorimetry data from a patient with lung disease showing oxygen consumption and carbon dioxide production measurements over an hour. Note greater variability in the measures in the period after thirty minutes compared with the periods between five and twenty minutes.

	VISIT 1		VISIT 2		VISIT 3	
Subject	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}O_2$	$\dot{V}CO_2$	$\dot{V}O_2$	$\dot{V}CO_2$
Patient 1	187	159	199	149	183	145
2	201	166	183	163	194	159
3	196	181	209	190	211	188
Control 1	285	183	269	180	274	191
2	202	150	190	163	195	162

Table A 2.2: Data on variability of $\dot{V}O_2$ and $\dot{V}CO_2$ measurements in a study of five subjects (three patients with chronic lung disease and two healthy controls). The measurements were made at 8 weekly intervals.

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Publications arising

Full papers

Sridhar MK, Galloway A, Lean MEJ, Banham SW. Study of an outpatient nutritional supplementation programme in malnourished patients with emphysematous COPD. Eur Resp J 1994; 7: 720-4.

Sridhar MK, Carter R, Lean MEJ and Banham SW. Resting energy expenditure, and nutritional status of patient groups with increased oxygen cost of breathing due to emphysema, scoliosis and thoracoplasty. Thorax 1994; 49: 781-5.

Sridhar MK, Banham SW, Lean MEJ. Prediction of Resting energy expenditure in patients with musculoskeletal deformities.Clin Nutr 1994; 13: 286-90.

Editorial

Sridhar MK. Why do patients with emphysema lose weight. Leading Commentary. The Lancet 1995; 354: 1190-91.

Submitted for publication

Sridhar MK, Lean MEJ, Banham SW. Resting energy expenditure in patients with chest wall disease.

Sridhar MK, Lean MEJ and Banham SW. Diminished heart rate and thermogenic response to salbutamol in patients with chronic obstructive pulmonary disease.

In preparation

Sridhar MK, Banham SW and Lean MEJ. Energy balance of patients hospitalised with an acute infective exacerbation of COPD.

Abstracts

Resting energy expenditure with the ventilated hood and mouthpiece systems in patients with chronic lung disease.
MK Sridhar, SW Banham, JJ Riley and MEJ Lean.
Proc Nut Soc 1993; 52: 6.

Basal metabolic rate in patients with chest bellows disease.
MK Sridhar, MEJ Lean and SW Banham.
Thorax 1993; 48 (10): 1074.

Insulin like Growth factor- 1 as an indicator of malnutrition in patients with emphysematous COPD.
MK Sridhar, G Beastall, MEJ Lean and SW Banham.
Eur Resp J 1993; 6 (17): 427.

Resting energy expenditure, oxygen cost of breathing and nutritional status of patients with chronic lung disease.
MK Sridhar, R Carter, MEJ Lean and SW Banham.
Am Rev Respir Dis 1994; 149 (2): 142.

Acute thermogenic response to inhaled salbutamol in patients with chronic obstructive pulmonary disease.
MK Sridhar, MEJ Lean, SW Banham.
Am J Res Crit Care Med 1995; 151 (4) : A 466.

Negative energy balance in patients hospitalised with exacerbation of chronic obstructive lung disease.
MK Sridhar, MEJ Lean and SW Banham.
Proc Nut Soc (in press).

REFERENCES

Amoroso, P., Wilson, S.R., Moxham, J. & Ponte, J. (1993) Acute effects of inhaled salbutamol on the metabolic rate of normal subjects. *Thorax*, **48**, 882-5.

Angelillo, V.A., Bedi, S., Durfee, D., Dahl, J., Patterson, A.J. & O' Donohoe, W.J. (1985). Effects of a low and high carbohydrate feedings in ambulatory patients with chronic obstructive pulmonary disease and chronic hypercapnia. *Annals of Internal Medicine*, **103**, 883-85.

Arora, N.S. & Rochester, D.F. (1982) Respiratory muscle strength and maximal voluntary ventilation in undernourished patients. *American Review of Respiratory Disease*, **126**, 5-8.

Arora, N.S. & Rochester, D.F. (1982) Effect of body weight and muscularity on human diaphragm muscle mass, thickness and area. *Journal of Applied Physiology*, **52**, 64-70.

Askanazi, J., Silverberg, P.A., Foster, R.J., Hyman, A.I., Millic-Emili, J. & Kinney, J.M. (1980) Effects of respiratory

apparatus on breathing pattern. *Journal of Applied Physiology* , **48**, 577-80.

Askanazi, J., Elwyn, D.H., Silverberg, P.A., Rosenbaum, S.H. & Kinney, J.M. (1980, ii) Respiratory distress secondary to a high carbohydrate load : a case report. *Surgery* , **87**, 596-8.

Askanazi, J., Nordenstrom, J., Rosenbaum, S.H., Elwyn, D.H., Hyman, A.I., Carpentier, Y.A. & Kinney, J.M. (1981) Nutrition for the patient with respiratory failure: Glucose vs Fat. *Anaesthesiology*, **54**, 373-77.

Astrup, A., Lundsgaard, C., Madsen, J. & Christensen, N.J.(1985) Enhanced thermogenic responsiveness during chronic ephedrine treatment in man. *American Journal of Clinical Nutrition*, **42**, 83-94.

Atwater, W.O. & Benedict, F.G. (1899) Experiments on the metabolism of matter and energy in the human body. *US Department of Agriculture Bulletin*, **No 69**.

Bain, M., Imrie, M., Matusiewicz, S. & Greening, A.P. (1994) Hypoxia primes monocytes for an enhanced stimulated release

of IL-6, IL-1 β and GM-CSF. *European Respiratory Journal*, **7**, 248.

Bartlett, D., Jr. (1979) Effect of hypercapnoea and hypoxia on laryngeal resistance to airflow. *Respiratory Physiology*, **37**, 293 - 9.

Bates, D. (1973) Amberson lecture : the fate of the chronic bronchitic. *American Review of Respiratory Disease*, **108**, 1043-65.

Benedict, F., Miles, W., Roth, P. & Smith, H. (1919) Human vitality and efficiency under prolonged restricted diet Carnegie Institute, 1919 (Publication no. 280): Washington, D.C.

Bergofsky, E.H. (1979) Respiratory failure in disorders of the thoracic cage. *American Review of Respiratory Disease*, **119**, 643-69.

Billingham, M.E.J. (1987) Cytokines as inflammatory mediators. *British Medical Bulletin*, **43** (2), 350-70.

Bjure, J., Grimby, G., Kasalicky, J., Lindh, M. & Nachemson, A. (1970) Respiratory impairment and airway closure in

patients with untreated idiopathic scoliosis. *Thorax*, **25**, 451-6.

Bingham, S.A., Gill, C., Welch, A., Day, K., Cassidy, A. and Khaw, K.T. (1994) Comparison of dietary assessment methods in nutritional epidemiology: weighed records v 24 h recalls, food frequency questionnaires and estimated diet records. *British Journal of Nutrition*, **72**, 619-43.

Bishop, C.W., Bowen, P.E. & Ritchey, S.J. (1981) Norms for nutritional assessment of American adults by upper arm anthropometry. *American Journal of Clinical Nutrition*, **34**, 2530-9.

Black, L.F. & Hyatt, R.E. (1969) Maximal respiratory pressures: normal values and relationship to age and sex. *American Review of Respiratory Disease*, **99**, 696-702.

Blackburn, G.L. & Bistrian, B.R. (1977) Nutritional support resources in hospital practice. In : Nutritional support of medical practice, pp 139-51. Harper and Row: Maryland.

Bland, J.M. & Altman, D.G. (1986) Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*, **i**, 307-10.

Bradley, M.E. & Leith, D.E . (1978) Ventilatory muscle training and the oxygen cost of sustained hyperpnoea. *Journal of Applied Physiology*, **45**, 885-92.1.

Branthwaite, M.A. (1986) Cardiorespiratory consequences of unfused idiopathic scoliosis. *British Journal of Diseases of the Chest*, **80**, 360-9.

Braun, S.R., Dixon, M.R., Kheim, N.L., Luby, M., Anderegg, A. & Shrago, E.S. (1984) Predictive clinical value of nutritional assessment factors in COPD. *Chest*, **85**, 353-7.

Braun, S., Keim, N.L., Dixon, R.M., Clagnaz, P., Anderegg, A. & Shrago, E.S. (1984) The prevalance and determinants of nutritional changes in chronic obstructive pulmonary disease. *Chest*, **86**, 558-63.

British Thoracic Society and the Association of Respiratory Technicians and Physiologists. Guidelines for the

measurement of respiratory function. (1994) *Respiratory Medicine*, **88**, 165-94.

Brown, S.E., Casciari, R.J. & Light, R.W. (1983) Arterial oxygen saturation during meals in patients with severe chronic obstructive pulmonary disease. *Southern Medical Journal*, **76**, 194-8.

Brown, S.E., Weiner, S., Brown, R.A., Marcarelli, P.A. & Light, R.W. (1985) Exercise performance following a carbohydrate load in chronic airflow obstruction. *Journal of Applied Physiology*, **58**, 1340-46.

Browning, R.J. & Olsen, A.M. (1961) The functional gastrointestinal disorders of pulmonary emphysema. *Proceedings of the Mayo Clinic*, **36**, 537.

Brusaco, V., Crimi, E., Mangini, S. & Vibelli, C. (1980) A clinical trial of oral Clenbuterol in chronic airways obstruction. *Current Medical Research and Opinion*, **6**, 449-56.

Burrows, B., Kasik, K., Niden, A.H. & Barclay, W.R. (1961). The usefulness of the single breath pulmonary diffusing

capacity test. *American Review of Respiratory Disease*, **84**, 789 - 806.

Buskirk, E.R., Thompson, R.H., Moore, R. & Whedon, G.D. (1960) Human energy expenditure studies in the National Institute of Arthritis and metabolic diseases metabolic chamber. i. Interaction of cold environments and specific dynamic effect. ii Sleep. *American Journal of Clinical Nutrition*, **8**, 602-13.

Burrows, B., Fletcher, C.M., Heard, B.E., Jones, N.L. & Wootliff, J.S. (1966) The emphysematous and bronchial types of chronic airways obstruction. A clinicopathological study of patients in London and Chicago. *Lancet*, **i**, 830-6.

Butland, R.J.A., Pang, J., Gross, E.R., Wodcock, A.A. & Geddes, D.M. (1982) Two-, Six- and Twelve minute walking tests in respiratory disease. *British Medical Journal*, **284**, 1007-8.

Campbell, E.J.M., Westlake, E.K. & Cherniack, R.M. (1959) The oxygen consumption and efficiency of respiratory muscles of young male subjects. *Clinical Science*, **18**, 55-64.

Campbell, R.H.A., Brand, H.L., Cox, J.R. & Howard, P. (1975) Body weight and body water in chronic cor pulmonale. *Clinical Science and Molecular Medicine*, **49**, 323-35.

Carroll, D. (1960) Pulmonary emphysema: Report of 26 cases followed to death. *Bulletin of the Hopkins Hospital*, **106**, 154-9.

Chandra, R.K. (1990) Nutrition and immunity. *American Journal of Clinical Nutrition*, **53**, 1087-1101.

Cherniack, R.M. (1959) The oxygen consumption and efficiency of the respiratory muscles in health and emphysema. *Journal of Clinical Investigation*, **38**, 494-9.

Collett, P.W., Perry, C. & Engel, L.A. (1985) Pressure-time product, flow, and oxygen cost of resistive breathing in humans. *Journal of Applied Physiology*, **58**, 1263-72.

Collett, P.W.& Engel, L.A. (1986) Influence of lung volumes on oxygen cost of resistive breathing in humans. *Journal of Applied Physiology*, **61**, 16-24.

Congleton, J., Green, J.H. & Muers, M.F. (1994) Resting energy expenditure and use of chronic nebulised β 2 agonists. *Thorax*, **49 (10)**, 1076.

Cruetzberg, E.C., Schols, A.M.W.J., Wesseling, G. & Wouters, E.F.M. (1994) Acute effects of inhaled salbutamol on lung function and energy metabolism in COPD patients and normal subjects. *European Respiratory Journal*, **7 (18)**, 2102s.

Cummings, J.H. (1993) Nutritional management of diseases of the stomach and bowel. In : James, W.P.T. & Garrow, J.S. (eds). Human Nutrition and dietetics, pp 480-503, Churchill Livingston: Edinburgh.

Cuthbertson, D.P. (1954) Interrelationship of metabolic changes consequent to injury. *British Medical Bulletin*, **10**, 33-37.

Dash, A., Agarwal, A., Venkat, N., Moxham, J. & Ponte, J. (1994) Effect of oral theophylline on resting energy expenditure in normal volunteers. *Thorax*, **49**, 1116-20.

de Godoy, I., Calhoun, W.J., Donahoe, M., Mancino, J. & Rogers, R.M. (1994) Cytokine production by peripheral blood monocytes of COPD patients. *American Journal of Respiratory and Critical Care Medicine*, **149**, 1017.

Delday, M.I., Williams, P.E. & Maltin, C.A. (1990) Effect of Clenbuterol on immobilised muscle. *Journal of Neurological Sciences*, **98**, 376.

Department of Health (1991) Dietary reference values for Food, Energy and Nutrients for the United Kingdom. HMSO: London.

Di Francia, M., Barbier, D., Mege, J. & Orehek J. (1994) Tumour necrosis factor - aloha and weight loss in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine*, **150**, 1453-55.

Dmochowski, J. & Moore, F. (1975) Chorolba glodowa. *New England Journal of Medicine*, **293**, 356-7.

Doll, R. & Peto, R. (1976) Mortality in relation to smoking : 20 years' observation on male British doctors. *British Medical Journal*, **2**, 1525 - 36.

Doll, R. & Peto, R. (1981) The causes of cancer : quantitative estimates of avoidable risks of cancer in the United States today. *Journal of the National Cancer Institute*, **66**, 1191-1308.

Donahoe, M., Rogers, R.M., Wilson, D.O. & Pennock, B.E. (1989) Oxygen consumption of the respiratory muscles in normal and in malnourished patients with chronic obstructive pulmonary disease. *American Review of Respiratory Disease*, **140**, 385-91.

Dornhurst, A. (1955) Respiratory insufficiency. *Lancet*, **268**, 1185-87.

Driver, A.G., Mc Alevy, M.T. & Smith, J.L. (1982) Nutrititonal assessment of patients with chronic obstructive pulmonary disease and acute respiratory failure. *Chest*, **82**, 568-71.

Du Bois, E.F. (1921) The basal metabolism in fever. *Journal of the American Medical Association*, **77**, 352-7.

Durnin, J.V.G.A. & Rahaman, M.M. (1967) The assessment of the amount of fat in the human from measurement of skinfold thickness. *British Journal of Nutrition*, **21**, 681-89.

Durnin, J.V.G.A. & Womersley, J. (1974) Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. *British Journal of Nutrition*, **32**, 77-97.

Efthimiou, J., Fleming, J., Gomes, C. & Spiro, S.G. (1988) The effect of supplementary oral nutrition in poorly nourished patients with chronic obstructive pulmonary disease. *American Review of Respiratory Disease*, **137**, 1075-1082.

Efthimiou, J., Mounsey, P.J., Benson, D.N., Madgwick, R., Coles, S.J. & Benson, M.K. (1992) Effect of carbohydrate versus fat rich loads on gas exchange and walking performance in patients with chronic obstructive lung disease. *Thorax*, **47**, 451-6.

Elborn, J.S., Cordon, S.M., Western, P.J., Macdonald, I.A. & Shale, D.J. (1993) Tumour necrosis factor-α, resting energy expenditure and cachexia in cystic fibrosis. *Clinical Science*, **85**, 563-8.

Engelen, M.P.K.J., Schols, A.M.W.J., Baken, W.C., Wesseling, G.J. & Wouters, E.F.M. 91994) Nutritional depletion in relation to respiratory and peripheral skeletal muscle function in out-patients with COPD. *European Respiratory Journal*, **7**, 1793-97.

FAO/WHO/UNU. (1985) Energy and protein requirements. Report of a joint FAO/WHO/UNU Expert consultation. (WHO technical report series 724). World Health Organisation: Geneva.

Fellows, I.W., Bennett, T. & MacDonald, I.A. (1985) The effect of adrenaline upon cardiovascular and metabolic functions in man. *Clinical Science*, **69**, 215-22.

Fiaccadori, E., Del Canale, S., Coffrini, E et al. (1988) Hypercapnoeic - hypoxemic chronic obstructive pulmonary disease (COPD) ; influence of severity of COPD on nutritional status. *American Journal of Clinical Nutrition*, **48**, 680-5.

Field, S., Kelly, S.M. & Macklem, P.T. (1982) The oxygen cost of breathing in patients with cardiorespiratory disease. *American Review of Respiratory Disease*, **126**, 9-13.

Filley, G., Beckwitt, H., Reeves, J. & Mitchell, R. (1968) Chronic obstructive pulmonary disease. Oxygen transport in two clinical types. *American Journal of Medicine*, **44**, 26-38.

Fitting, J.W., Frascarolo, P., Jequier, E. & Leuenberger, P. (1989) Energy expenditure and rib cage abdominal motion in chronic obstructive pulmonary disease. *European Respiratory Journal*, **2**, 840-45.

Fitting, J.W., Frascarlo, P., Jequier, E. & Leunberger, P. (1990) Resting energy expenditure in interstitial lung disease. *American Review of Respiratory Disease*, **142**, 631-5.

Fitting, J.W. & Spiro, S.G. (1991) Nutrition in chronic obstructive pulmonary disease. *European Respiratory Review*, **1:6**, 511-19.

Fitting , J.W. (1992) Nutritional support in chronic obstructive lung disease. *Thorax*, **47**, 141-3.

Forbes, G.B., Gallup, J. & Horst, J.B. (1961) Estimation of total body fat from potassium-40 content. *Science*, **133**, 101-2.

Fowler, J.K. & Goodlee, R. (1898) Emphysema of the lungs. In : Diseases of the lungs. Longmans, Green and co.: London.

Fredrix, E.W.H.M., Soeters, P.B., von Meyenfeldt, M.F. & Saris, W.H.M. (1990) Measurement of resting energy expenditure in a clinical setting. *Clinical Nutrition*, **9**, 229-304.

Fuenzalida, C.E., Petty, T.L., Jones, M.L., Jarrett, S., Harbeck, R.J., Terry, R.W. & Hambidge, K.M. (1990) The immune response to short-term nutritional intervention in advanced chronic obstructive pulmonary disease. *American Review of Respiratory Disease*, **142**, 49-56.

Gieseke, T., Gurushanthiah, G. & Galauser, F.L. (1977) Effects of carbohydrates on carbon dioxide excretion in patients with airways disease. *Chest*, **71**, 55-8.

Goldstein, S., Askanazi, J., Weissman, C., Thomashow, B. & Kinney, J.M. (1987) Energy expenditure in patients with chronic obstructive pulmonary disease. *Chest*, **91**, 222-4.

Goldstein, S.A., Thomashow, B.M., Ketan, et al. (1988) Nitrogen and energy relationships in malnourished patients with emphysema. *American Review of Respiratory Disease*, **138**, 636-44.

Green, J.H. & Muers, M.F. (1991) The thermic effect of food in underweight patients with emphysematous chronic obstructive pumonary disease. *European Respiratory Journal*, **4**, 813-9.

Green, J.H. & Muers, M.F. (1992) Comparisons between basal metabolic rate and diet induced thermogenesis in different types of chronic obstructive pulmonary disease. *Clinical Science*, **83**, 109-16.

Grimby, G. & Soderholm, B. (1963) Spirometric studies in normal subjects III. Static lung volumes and maximal voluntary ventilation in adults with a note on physical fitness. *Acta Medica Scandinavia*, **173**, 199-206

Guggenheim, K.Y. (1981) Nutrition and nutritional disease. The evolution of concepts. Heath: Lexington, Mass.

Guyatt, G.H., Pugsley, S.O., Sullivan, M., Thompson, P.J., Berman, L.B., Jones, N.L., Fallen, E.L. & Taylor, D.W. (1984) Effect of encouragement on walking test performance. *Thorax*, **39**, 818 - 22.

Halmagyi, D.F.L., Broell, J., Gump, F.E. & Kinney, J.M. (1974) Hypermetabolism in sepsis: Correlation with fever and tachycardia. *Surgery*, **75(5)**, 763-70.

Hansell, D.T., Richardson, R., Davies, J.W. & Burns, H.J.G. (1987) Estimation of resting energy expenditure by anthropometry. *Clinical Nutrition*, **6**, 51- 7.

Harper, N.G.G., Blake, L.F. & Fowler, W.S. (1965) Relationship of lung volume to height and armspan in normal subjects and patients with spinal deformity. *American Review of Respiratory Disease*, **91**, 356-64.

Harris, J.A. & Benedict, F.G. (1919) A biometric study of basal metabolism in man. Carnegie Institute: Washington, D.C.

Hayes, Jr R.C. (1990) Adrenocortical hormones: adrenocortical steroids and their synthetic analogues. In

Gilman, A.G., Nies, A.S. & Taylor P (eds): The pharmacological basis of therapeutics.1990 (8th Edition),pp 14336-44. Pergamon Press: New York.

Hodkinson, H.M., Cox, M., Lugon, M., Cox, M.L. & Tomkins A. (1990) Energy cost of chest infection in the elderly. *Journal of Clinical and Experimental Gerontology*, **12(4)**, 241-6.

Hofford, J.M., Milakofsky, L., Vogel, W.H., Sacher, R.S., Savage, G.J. & Pell, S. (1990) The nutritional status in advanced emphysema associated with chronic bronchitis. *American Review of Respiratory Disease*, **141**, 902-8.

Holgate, S.T., Stubbs, W.A., Wood, P.J., McCaughey, J., Alberti, K.G.M., Tattresfield, A.E. (1980) Airway and metabolic resistance to intravenous salbutamol: a study in normal man. *Clinical Science*, **59**, 155-61.

Hugli, O., Frascaarlo, P., Schutz, Y., Jecuier, E., Leuenberger, P. & Fitting, J. (1993) Diet induced thermogenesis in patients with chronic obstructive pulmonary disease. *American Review of Respiratory Disease*, **148**, 1479-83.

Hunter, A.M.B., Carey, M.A. & Larsh, H.W. (1981) The nutritional status of patients with chronic obstructive pulmonary disease.*American Review of Respiratory Disease*, **124**, 376-81.

Intermittent Positive Pressure Breathing Trial Group. (1983) Intermittent positive pressure breathing therapy of chronic obstructive pulmonary disease ; a clinical trial. *Annals of Internal Medicine*, **99**, 612-20.

Isbell, T.R., Klesges, R.C., Meyers, A.W. & Klesges, L.M. (1991) Measurement reliability and reactivity using repeated measurements of resting energy expenditure with a face mask, mouthpiece, and ventilated canopy. *Journal of Parenteral and Enteral Nutrition*, **15**, 165-8.

Jamal, K., Fleetham, J.A. & Thurlbeck, W.M. (1990) Cor pulmonale: Correlation with central airway lesions, peripheral airway lesions, emphysema and control of breathing. *American Review of Respiratory Disease*, **141**, 1172 - 1177.

James, W.P.T. & Garrow, J.S. (eds) (1993) Human Nutrition and Dietetics. Churchill Livingston : Edinburgh.

Jones, R.S., Kennedy, J.C., Hasham, F., Owen, R. & Taylor, J.F. (1981) Mechanical inefficiency of the thoracic cage in scoliosis. *Thorax*, **36**, 456 - 61.

Kafer, E.R. (1975) Idipoathic Scoliosis. Mechanical properties of the respiratory system and ventilatory response to carbon dioxide. *Journal of Clinical Investigation*, **55**, 1153-63.

Kastardis, C.V., Desmond, K.J. & Coates AL. (1986) Measuring the oxygen cost of breathing in normal adults and in patients with cystic fibrosis. *Respiratory Physiology*, **65**, 257-66.

Kemper, M.S. (1989) Indirect calorimetry. Equipment and practical care. *Problems in respiratory care*, **2**, 479-90.

Keys, A., Brozek, J., Henschel, A., Mickelson, O. & Taylor, H. (1950) The biology of human starvation. The University of Minnesota Press: Minneapolis.

Kinney, J.M. (1974) Energy requirements in injury and sepsis. *Acta Anaesthesia Scandinavia*, **Suppl 55**, 15-20.

Kinney, J.M. (1980) The application of indirect calorimetry to clinical studies. In: Kinney, J.M.(ed.) *Assessment of energy metabolism in health and disease.* Report on the first Ross conference on medical research, pp 42-8. Ross Laboratories: Columbus, OH.

Kinney, J.M. (1988) Energy metabolism: Heat, fuel and life. In : *Nutrition and metabolism in patient care.* Eds : Kinney, J.M., Jeejeebhoy, K., Hil,l G.L. & Owen OE., pp 1-34, WB Saunders: Philadelphia.

Knowles, J.B., Faibarn, M.S., Wiggs, B.J., Chan-Yan, C. & Pardy, R.L. (1988) Dietary supplementation and respiratory muscle performance in patients with COPD. *Chest*, **93(5)**, 977- 83.

Koretz, R. (1984) Breathing and feeding, can you have one without the other? *Chest*, **85**, 298-9.

Kraemer, R., Rudeberg, A., Hadorn, B. & Rossi, E. (1978) Relative underweight in cystic fibrosis and its prognostic value. *Acta Paediatrica Scandinavia*, **67**, 33-7.

Kuo, C., Shiao, G. & Lee, J. (1993) The effects of high-fat and high-carbohydrate diet loads on gas exchange and ventilation in COPD patients and normal subjects. *Chest*, **104**, 189-96.

Laaban, J., Kouchakji, B,, Dore, M,, Orvoen-Frija, E, David, P. & Rochemaure, J. (1993) Nutritional status of patients with chronic obstructive pulmonary disease and acute respiratory failure.*Chest*, **103**, 1362-68.

Lands, L., Desmond, K., Demizio, D., Pavilanis, A. & Coates, A.(1990) The effects of nutritional status and hyperinflation on respiratory muscle strength in children and young adults. *American Review of Respiratory Disease*, **141**, 1506-09.

Lanigan, C., Moxham, J. & Ponte, J. (1990) Effect of chronic airflow limitation on resting oxygen consumption. *Thorax*, **45**, 388-90.

Latts, E.M., Cummins, J.F. & Zeive, L. (1956) Peptic ulcer and pulmonary emphysema. *Archives of Internal Medicine*, **97**, 576-84.

Lean, M.E.J., Brenchley, S., Connor, H et al. (1991) Dietary recommendations for people with diabetes; an update for the 1990s. *Journal of Human Nutrition and Dietetics*, **4**, 393-412.

Lee, H.A. (1980) Nutritional support in renal and hepatic failure . In Karran, S.J. & Albe rti, K.G.M. (eds). *Practical nutritional support*, pp 275-82. Pitman medical: London.

Lehninger AL. (1982) Electron transport, oxidative phosphorylation and regulation of ATP production. In: *Principles of Biochemistry*, pp 467-505. Worth Publishers, Inc.: New York.

Levine, B., Kalman, J., Mayer, L., Fillit, H.M. & Packer, M. (1990) Elevated circulating levels of tumour necrosis factor in severe chronic heart failure. *New England Journal of Medicine*, **323**, 236-41.

Levison, H. & Cherniack R. (1968) Ventilatory cost of exercise in chronic obstructive pulmonary disease. *Journal of Applied Physiology*, **25(1)**, 21-7.

Levy, L.D., Durie, P.R., Pencharz, P.B. & Corey, M.L. (1985) Effect of long-term nutritional rehabilitation on body

composition and clinical status in malnourished children and adolescents with cystic fibrosis. *Journal of Paediatrics*, **107**, 225-30.

Lewis, M.I., Belman, M.J. & Dorr- Uyemura L. (1987) Nutritional supplementation in ambulatory patients with COPD. *American Review of Respiratory Disease*, **135**, 1062-68.

Liljestrand, G. (1918) Untersuchungen uber die utmungsarbiet. *Scandinavian Archives of Physiology*, **65**, 257-66.

Lisboa, C., Moreno, R., Fava, M., Ferretti, R. & Cruz, E. (1985) Inspiratory muscle function in patients with severe kyphoscoliosis. *American Review of Respiratory Disease*, **132**, 48-52.

Lohman, T.G., Roche, A.F., Martolrell, R. (eds). (1988) *Anthropometric Standardization Reference Manual*. Human Kinetics Books: Champagne, Illinois.

Lopes, J. (1962) Prognostic and therapeutic implications of deranged pulmonary function. *Proceedings of the Royal Society of Medicine*, **55**, 454-7.

Lukaski, H.C.(1987) Methods for the assessment of human body composition: traditional and new. *American Journal of Clincal Nutrition*, **46**, 537-56.

Maltin, C.A., Delday, M.I. & Reeds, P.J. (1986). The effect of growth promoting drug, clenbuterol, on fibre frequency and area in hind limb muscle of young male rats. *Bioscience Reports*, **6**, 293-9.

Maltin, C.A., Reeds, P.J., Delday, M.I., Hay, S.M., Smith, F.G. & Lobely, G.E. (1986). Inhibition and reversal of denervation indiced atrophy by the β agonist growth promoter, clenbuterol. *Bioscience Reports*, **6**, 811-19.

Maltin, C.A., Delday, M.I., Watson, J.S., Heys, S.D., Nevison, I.M., Ritchie, I.K. & Gibson, P.H. (1993). Clenbuterol, a β adrenoceptor agonist, increases relative muscle strength in orthopaedic patients. *Clinical Science*, **84**, 651-54.

Marmorston, J., Winer, J., Hopkins, C.E. & Stern, E. (1966) Abnormalities in urinary hormone patterns in lung cancer and emphysema. *Cancer*, **19**, 985-95.

McAnena, O., Harvey, L.P., Katzeff, H.L. & Daly, J.M. (1986) Indirect Calorimetry: Comparison of hood and mask systems for measuring resting energy expenditure in healthy volunteers. *Journal of Parenteral and Enteral Nutrition*, **10**, 555- 7.

McCance, R & Widdowson, E. (1991). *The Composition of foods (5 th edition)*. The Royal Society of Chemistry and Ministry of Agriculture, Fisheries and Food.

Melchior, J., Raguin, G., Boulier, A., Bouvet, E., Rigaud, D., Matheron S et al. (1993) Resting energy expenditure in human immunodefeciency virus-infected patients: comparison between patients with and without secondary infections. *American Journal Clinical Nutrition*, **57**, 614-9.

Metropolitan Life Insurance Company (1983) *New weight standards for men and women*. Metropolitan Life: New York.

Millic-Emili, G. & Petit, J.M. (1960) Mechanical efficiency of breathing. *Journal of Applied Physiology*, **15**, 359.

Milliken, C., Wilcox, P. & Bressler, B. (1995) Loading augments diaphragmatic dysfunction in animal muscular dystrophy model: absence of protective effect of clenbuterol. *American Journal of Respiratory and Critical Care Medicine*, **151 (4)**, A586.

Mitchell, D.M., Gildeh, P., Rehahn, M., Dimond, A.H. & Collins, J.V. (1984) Effects of prednisolone in chronic airflow limitation. *Lancet*, **2**, 193-6.

Monto, A.S., Higgins, M.W. & Ross, H.W. (1975) The Tecumseh study of respiratory illnesses. VII. Acute infection in chronic respiratory diseases and comparison groups. *American Review of Respiratory Disease*, **iii**, 27-34.

Moore, J.A. & Angelillo, V.A. (1988) Equations for prediction of resting energy expenditure in chronic obstructive lung disease. *Chest*, **94**, 1260-3.

Murgatroyd, P.R., Shetty, P.S. & Prentice, A.M. (1993) Techniques for the measurement of human energy

expenditure: a practical guide. *International Journal of Obesity*, **17**, 549-68.

Naon, H., Hack, S., Shelton, M.T., Gotthoffer, R.C. & Gozal, D. (1993) Resting energy expenditure. Evolution during antibiotic treatment for pulmonary exacerbation of cystic fibrosis. *Chest*, **103**, 1819-25.

Nocturnal Oxygen Therapy Trial Group. (1980) Continuous or nocturnal therapy in hypoxemic chronic obstructive lung disease ; a clinical trial. *Annals of Internal Medicine*, **93**, 391-98.

Office of Population Censuses and Surveys (1980) Classification of Occupations. HMSO: London.

Openbrier, D.R., Mc Alevy, M.T. & Smith, J.L. (1983) Nutritional assessment of patients and lung function in patients with emphysema and chronic bronchitis. *Chest*, **83**, 17-22.

Otis, A.B. (1951) The work of breathing. *Physiological Reviews*, **34**, 449-58.

Otte, K.E., Ahlburg, P., D' Amore, F.& Stellfield, M. (1989) Nutritional repletion in malnourished patients with emphysema. *Journal of Parenteral and Enteral Nutrition*, **13**, 152-6.

Pardy, R.L., Knowles, J.L., Fairbarn, M.S. & Chan-Yan, C. Supplemental nutrition does not alter respiratory muscle strength or endurance in ambulatory COPD patients *American Review of Respiratory Disease*, **133**, 204A.

Piers, L.S., Soares, M.J., Kulkarni, R.N. & Shetty, P.S. (1992) Thermic effect of a meal : Effect of dietary supplementation in chronically undernourished human subjects. *British Journal of Nutrition*, **67**, 187-94.

Pittman, J.G. & Cohen, P. (1964) The pathogenesis of cardiac cachexia. *New England Journal of Medicine*, **271**, 403-9.

Pugh, L.G.C.E. (1962) Physiological and medical aspects of the Himalayan scientific mountaineering expedition. *British Medical Journal*, **2**, 621-27.

Quebbeman, E.J. & Ausmann, R.K. (1982) Estimating energy requirements in patients receiving parenteral nutrition. *Archives of Surgery*, **117**, 1281-84.

Ravussin, E., Lillioja, S., Anderson, T.E., Christib, L. & Bogardus, C. (1986) Determinants of 24 hr expenditure in man: methods and results using a respiration chamber. *Journal of Clincal Investigation*, **78**, 1568-78.

Ravussin, E. & Bogardus, C. (1989) Relationship of genetics, age and physical fitness to daily energy expenditure and fuel utilization. *American Journal of Clinical Nutrition*, **49**, 968-75.

Renzetti, A.D., McClement, J.H. & Litt, B.D. (1966) The Veterans Administration cooperative study of pulmonary function. Mortality in relation to respiratory function in chronic obstructive pulmonary disease. *American Journal of Medicine*, **41**, 115-29.

Rochester, D.F. (1986) Body weight and respiratory muscle function in chronic obstructive pulmonary disease. *American Review of Respiratory Disease*, **134**, 646-8.

Roe, F.C. & Kinney, J.M. (1965) The caloric equivalent of fever. II. Influence of major trauma. *Annals of Surgery*, 140-8.

Rogers, R.M., Donahoe, M. & Constanino, J. (1992) Physiological effects of oral supplemental feeding in malnourished patients with chronic obstructive pulmonary disease. *American Review of Respiratory Disease*, **146**, 1511-1517.

Rosenbaum, M., Malbon, C.G., Hirsch, J. & Libel, R.L. (1993) Lack of β 3 adrenergic effect on lipolysis in human subcutaneous adipose tissue. *Journal of Clinical Endocrinology and Metabolism*, **77**, 352-55.

Roubenoff, R., Roubenoff, R.A., Ward, L.M. & Stevens, M.B. (1990) Catabolic effects of high dose steroids persist despite therapeutic benefit in rheumatoid arthritis. *American Journal of Clinical Nutrition*, **52**, 1113-117.

Roussos, C.S. & Macklem, P.T. (1977) Diaphragmatic fatigue in man. *Journal of Applied Physiology*, **43**, 885-72.

Ryan, C.F., Road, J.D., Buckley, P.A., Ross, C. & Whittaker, J.S. (1993) Energy balance in stable malnourished patients with chronic obstructive pulmonary disease. *Chest*, **103**, 1038-44.

Sahebjami, H. & Wirman, J. (1981) Emphysema like changes in the lungs of starved rats.*American Review of Respiratory Disease*, **124**, 619-624.

Sahebjami, H. (1986) Nutrition and pulmonary parenchyma.*Clinics in Chest Medicine*, **Vol7 (1)**, 111-26.

Saltzman, H.A. & Salzano, J.V. (1971) Effects of carbohydrate metabolism on respiratory gas exchange in normal man. *Journal of Applied Physiology*, **30**, 228-31.

Scheidegger, K., O'Connell, M., Robbins, D.C. & Danforth, E. (1984) Effects of chronic β- receptor stimulation on sympathetic nervous system activity, energy expenditure, and thyroid hormones. *Journal of Clinical Endocrinology and Metabolism*, **58**, 895-903.

Schofield, W.N. (1985) Predicting basal metabolic rate, new standards and review of previous work. *Human Nutrition: Clinical Nutrition*, **39c (Suppl 1)**, 5-41.

Schols, A.M.W.J., Mostert, R., Soeters, P.B., Greve, L.H. & Wouters, E.F.M. (1989) Inventory of nutritional status in patients with COPD. *Chest*, **96**, 24.

Schols, A.M.W.J., Mostert, R., Soeters, P.B., Greve, L.H. & Wouters, E.F.M.(1989) Nutritional state and exercise performance in patients with chronic lung disease. Thorax 1989; 44: 937-41.

Schols, A.M.W.J., Hoogeveen, C.E.M. & Wouters, E.F.M. (1990) Assessment of dietary intake in COPD. *European Respiratory Journal*, **3**, 148s.

Schols, A.M.W.J., Soeters, P.B., Mostert, R., Saris, W.H.M. & Wouters, E.F.M. (1991) Energy balance in chronic obstructive pulmonary disease. *American Review of Respiratory Disease*, **143**, 1248-52.

Schols, A.M.W.J., Fredrix, E.W.H.M., Soeters, P.B., Westerterp, K.P. & Wouters, E.F.M. (1991) Resting energy

expenditure in patients with chronic obstructive pulmonary disease. *American Journal of Clinical Nutirtion*, **54**, 983-7.

Schols, A.M.W.J., Cobben, N., Mostert, R., Soeters, P.B. & Wouters, E.F.M. (in press) Transcutaneous oxygen saturation and carbon dioxide tension during meals. *Chest.*

Schols, A.M.W.J., Fredrix, E.W.H.M., Soeters, P.B., Westerterp, K.P. & Wouters, E.F.M. (1993) Prevalence and characteristics of nutritional depletion in patients with COPD eligible for pulmonary rehabilitation. *American Review of Respiratory Disease*, **147**, 1151-56.

Segal, K.R. (1987) Comparison of indirect calorimetric measurements of resting energy expenditure with a ventilated hood, face mask and mouth piece. *American Journal of Clinical Nutrition*, **45**, 1420-3.

Semple, P.d'A, Watson, W.S., Beastall, G.H., Bethel, M.I.F., Grant, J.K. & Hume, R. (1979) Diet, absorption, and hormone studies in relation to body weight in obstructive airways disease. *Thorax*, **34**, 783-88.

Shepherd, R.W., Holt, T.L., Cleghorn, G., Ward, L.C., Isles, A. & Francis, P. (1988) Short-term nutritional supplementation during management of pulmonary exacerbations of cystic fibrosis ; a controlled study, including effects of protein turnover. *American Journal of Clinical Nutrition*, **48**, 235-39.

Shetty, P.S. (1993) Chronic undernutrition and metabolic adaptation. The Nestle lecture. *Proceedings of the Nutrition Society*, **52**, 267-84.

Simpson, T. (1958) Chronic bronchitis and emphysema. *Tubercle*, **39**, 307.

Smith, J., Wolkove, N., Colacone, A. & Kreisman, H. (1989) Coordination of eating, drinking and breathing in adults. *Chest*, **96**, 578-82.

Soares, M.J., Sheela, M.L., Krupad, A.V., Kulkarni, R.N. & Shetty PS.(1989) The influence of different methods on basal metabolic rate measurements in human subjects. *American Journal of Clinical Nutrition*, **50**, 731-6.

Stein, J. & Fenigstein, H. (1942) Anatomie pathologique de la maladie de famine. In *Maladie de famine. Recherches clinique sur la famines executees dan le Chatto de Varsovie.* pp 21-27. American Joint Distribution committee: Warsaw.

Steinkamp, G., Drommer, A. & van Hardt, H.(1993) Resting energy expenditure before and after treatment for Pseudomonas aeruginosa infection in patients with cystic fibrosis. *American Journal of Clinical Nutrition*, **57**, 685-9.

Sue, D., Chung, M., Grosvenor, M. & Wassermann, K. (1989) Effect of altering the proportion of dietary fat and carbohydrate on exercise gas exchange in normal subjects. *American Review of Respiratory Disease*, **139**, 1430-34.

Sukmalchantra, Y & Williams, M. Jr. (1965) Serial studies of pulmonary function in patients with COPD. *American Journal of Medicine*, **39**, 941-5.

Tattersfield, A.E. & Wilding, P. (1993) β agonists and ventilation. *Thorax*, **48**, 877-88.

Thurlbeck, W.M. (1975) Chronic airflow obstruction in lung disease. In *Major problems in Pathology*, Ed. Bennington, J.L. WB Saunders: London.

Tracey, K.J., Vlassara, H. & Cerami, A. (1989) Cachectin / Tumour necrosis factor. *Lancet* , i , 1122-26.

Tracey KJ, Wei H, Manogue KR et al. (1988) Cachectin / Tumour necrosis factor induces cachexia, anemia, and inflammation. J Exp Med 1988; 176: 1211-27.

Vaisman, N., Levy, L.D., Pencharz, P.B., Tan, Y.K., Soldin, S.J. & Canny, G.J. (1987) Effect of Salbutamol on resting energy expenditure in patients with cystic fibrosis. *Journal of Paediatrics*, **111**, 137-9.

Vandenberg, E., Van de Woestinge, K. & Gyselen, A. (1967) Weight changes in the terminal stages of chronic obstructive lung disease. *American Review of Respiratory Disease*, **96**, 556-65.

Wasserman, K., Whipp, B. & Casatgna, J. (1974) Cardiodynamic hyperpnoea: hyperpnoea secondary to cardiac

output increase. *Journal of Applied Physiology*, 1974, **86**, 457-64.

Weir, J.B. (1949) New methods for calculating the metabolic rate with special reference to protein metabolism. *Journal of Physiology*, **109**,1-6.

Weiner, J.S. & Lourie, J.A. (1969). Human Biology : A guide to field methods. International Biological Programme. IBP Handbook No: 9, Blackwell Scientific Publications, Oxford-Edinburgh.

Whitehead, M. & Dahlgren, G. (1991) What can be done about inequalities in health? *Lancet*, **338**, 1059-63.

Whittaker, J.S., Ryan C.F., Buckley, P. & Road J.D. (1990) The effects of refeeding on peripheral and respiratory muscle function in malnourished chronic obstructive pulmonary disease patients. *American Review of Respiratory Disease*,**142**, 283-288.

WHO Expert Committee. (1982) Prevention of coronary artery disease. Technical Report Series. World Health Organisation, Geneva.

Wilmore DW. (1977) The metabolic management of the critically ill. Plenum: New York.

Wilson, N., Wilson, R. & Farber, S. (1964) Nutrition in pulmonary emphysema. *Journal of the American Dietetic Association*, **45**, 530-6.

Wilson, D.O., Rogers, R.M. & Hoffman, R.M. (1985) Nutrition and chronic lung disease. *American Review of Respiratory Disease*, **132**, 1347-65.

Wilson, D.O., Rogers, R.M., Sanders, M.H., Pennock, B. & Reilly, J.J. (1986) Nutritional intervention in malnourished patients with emphysema. *American Review of Respiratory Disease*, **134**, 673-677.

Wilson, D.O., Rogers, R.M., Wright, E.C. & Anthonisen, N.R. (1989) Body weight in chronic obstructive pulmonary disease : The National Institue of Health Intermittent Positive pressure Breathing Trial. *American Review of Respiratory Disease*, **139**, 1435-38.

Wilson, D.O., Donahoe, M., Rogers, R.M. & Pennock, B.E. (1990) Metabolic rate and weight loss in chronic obstructive lung disease. *Journal of Parenteral and Enteral Nutrition*, **14**, 7-11.

Wilson, S.R., Amoroso, P., Moxham, J. & Ponte, J. (1993) Modification of thermogenic effect of acutely inhaled Salbutamol by chronic inhalation in normal subjects. *Thorax*, **48**, 886-9.

Winick, M. (1979) Hunger disease: Studies by Jewish physicians in the Warsaw ghetto. Wiley Inter-science publication: New York.

Wouters EFM, Schols AMWJ. Prevalence and pathophysiology of nutritional depletion in chronic obstructive pulmonary disease. *Respiratory Medicine*, **87 (Supplement B)**, 45-47.

Zasly, L., Baum, G.I. & Bumball, J.M. (1960) The incidence of peptic ulceration in chronic obstructive pulmonary emphysema. *Diseases of the Chest*, **37**, 400-5.

Zeman, R.J., Ludeman, R., Easton, T.G. & Etlinger, J.D. (1988) Slow to fast alterations in skeletal muscle fibres caused by clenbuterol, a β receptor agonist. *American Journal of Physiology*, **254**, E726-32.