CARDIORESPIRATORY RESPONSES OF HEALTHY MIDDLE-AGED MEN TO STEADY-STATE POSITIVE AND NEGATIVE WORK PERFORMED ON A CYCLE ERGOMETER

By

FRANK CHUNG

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We accept this thesis as conforming to the required standard

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ABSTRACT

The physiological responses of negative work involving predominantly eccentric muscle contraction were compared to positive work involving predominantly concentric muscle contraction in twelve older healthy subjects between 39 and 65 years of age. A motorized cycle ergometer was used for steady state exercise testing. To study the physiological response to positive and negative work, pedalling frequencies of 35, 55, and 75 rpm and a constant power output of 60 Watts were chosen. Steady state values of oxygen consumption (VO$_2$), heart rate (HR), minute ventilation (VE), tidal volume (VT) and breathing frequency (fb) were obtained during six test conditions, namely, positive and negative work at each of the three pedalling frequencies. All physiological measures were greater during positive work than negative work (p<0.001) except for fb (p>0.05). The greater VO$_2$ (1.14±0.13 and 0.62±0.18 l/min (mean±standard deviation) during positive and negative work respectively), HR (95.8±10.7 and 81.8±13.6 bpm) and VE (26.7±5.5 and 16.5±5.2 l/min) during positive work were consistent with the greater energy efficiency of negative work. The greater VE during positive work reflected a greater VT (1.46±.32 l/br) than negative work (0.99±.31 l/br) while fb was the same (18.7±4.0 and 17.5±5.6 br/min) for both positive and negative work. During positive work, all physiological variables were greatest at 75 compared to 35 and 55 rpm (p<0.05) except for fb which showed no significant difference.
across the three pedalling frequencies (p>0.05). During
negative work, VO2 and HR were greatest at 75 and 35 rpm
compared to 55 rpm (p<0.05), and VE and VT were greater at 75
than at 55 rpm (p<0.05), whereas fb was not different among
pedalling frequencies (p>0.05). The slopes and intercepts of
the regression lines relating HR and VO2, VE and VO2, VT and
VE, and fb and VE were identical between positive and negative
work except for a higher intercept for the VE and VO2
relationship during negative work. Thus, it was concluded that
at a power output of 60 Watts, physiological responses such as
VO2, HR and VE during positive and negative work were
qualitatively similar. When changes in VT and fb were compared
from baseline to steady-state for positive work, however, VT
and fb both increased. In contrast, for negative work, VT
increased minimally while relatively greater increases in fb
were observed for pedalling frequencies of 35 and 55 rpm.
The relatively greater effect of negative work on fb compared
with positive work is not predicted from the known ventilatory
responses to low intensity exercise. Further study is needed
to elucidate the precise mechanism for this predominant
increase in fb during negative work.
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INTRODUCTION

I GENERAL PURPOSE

The unique physiologic properties of negative work have been of considerable interest since 1952 when Abbott and his colleagues connected two bicycles back-to-back supported on a frame and demonstrated that negative work (eccentric muscle contraction) required less total energy than positive work (concentric muscle contraction). In that study, the normal forward pedalling by one cyclist (positive work) was resisted by the second cyclist who attempted to pedal forwards although the legs were forced backwards (negative work). A dramatic example of the efficiency of negative work was reported by Hill in 1954. He had a small woman resist the forward pedalling of a large athletic man. The woman performing negative work resisted the athletic man with ease supporting the finding that torque production during eccentric muscle contraction requires significantly less total energy than positive work. This observation has been confirmed for other forms of negative work including going downstairs [Benedict and Parmenter, 1928], climbing down a laddermill [Kamon, 1970], and lowering a weight [Seliger et al, 1968].

The general purpose of this study was to extend our present understanding of the effects of negative work on the exercise responses of healthy persons, and in particular
middle-aged men. Specifically, we hoped to further our understanding of the ventilatory responses to negative work, performed with the legs, on a cycle ergometer. This work extended previous studies in our laboratory on the ventilatory responses during negative work in the form of downhill walking.

In addition to an interest in the energy-efficiency of negative work, we were interested in the optimization of energy cost as a function of pedalling frequency. The existence of an optimal walking and pedalling frequency for individuals is well known [Seabury et al, 1977]. However, the effect of pedalling frequency during negative work performed at a constant work rate has not been well studied. In the present study, pedalling frequencies of 35, 55, and 75 rpm were chosen to examine the effects of speed on oxygen consumption and heart rate at a constant work rate of 60 Watts during both positive and negative work. In addition, the effect of pedalling frequency during positive and negative work on the components of minute ventilation, namely tidal volume and breathing frequency were studied.

These preliminary studies were designed to ultimately evaluate the potential therapeutic role of negative work in the management of physically disabled individuals. We purposefully studied middle-aged men who would be more representative of our future patient population. Moreover, the response of middle-aged men to negative work has not been
In summary, we investigated the ventilatory responses and energy cost of middle-aged men during positive and negative work using a cycle ergometer. In addition, the effects of pedalling frequency (speed) at a constant work rate on ventilatory responses and energy cost were also examined. Elucidation of the effects of negative work on the exercise responses of healthy middle-aged men will provide the basis for future studies with physically disabled individuals as well as further our knowledge with respect to negative work in general.

II PHYSIOLOGICAL RESPONSES TO NEGATIVE WORK

Negative work is characterized by eccentric muscle contraction and positive work is characterized by concentric muscle contraction. Knuttgen et al [1971a] reported that when a muscle developed tension concentrically, a portion of the energy is conserved as potential energy. The conserved energy and work is equal to the product of the weight of the subject lifted and its vertical displacement. In contrast, in eccentric muscle contraction, the potential energy is passed on to the muscle during lengthening. In concentric contraction, total heat production equals metabolic heat minus work performed. During eccentric contraction, work is being performed on or absorbed by the muscle. Knuttgen et al [1971b] further stated that total heat production in negative work is
equal to the sum of mechanical work and metabolic heat. Hence, during eccentric muscle contraction, work is enhanced and metabolic energy requirement is reduced. During eccentric muscle contraction, part of the force generated comes from the stretching of the series elastic component utilizing the kinetic energy imparted from the stretch or gravitational force [Moritani et al, 1988]. Stretching prior to concentric muscle contraction, or stretch-shortening cycle, also increases the mechanical efficiency, peak force and power output of subsequent muscle work [Astrand and Rodahl, 1986; Bosco and Komi, 1979; Bosco et al, 1982; Bosco et al, 1987; Chapman, 1985; Thomson and Chapman, 1988].

Characteristics of Negative Work

Negative work has several physiologically distinct characteristics [Knuttgen, 1986]. First, when the same velocities of concentric and eccentric muscle contractions are compared, greater force can be produced in eccentric than other forms of muscle contraction [Asmussen, 1953; Eloranta and Komi, 1980; Komi and Buskirk, 1972]. In eccentric contraction where muscle is stretched, individual cross bridges develop greater resistance when stretched, consequently greater total force is generated than in concentric contraction [White, 1977]. The molecular mechanism of eccentric muscle contraction, however, is not fully understood. Goldspink [1977] proposed that when the cross bridges are stretched during eccentric muscle
contraction, the cross bridges are disengaged from their original active site before complete cycling. In this way the cross bridges can glide across a couple of sites without having to depend on ATP to provide energy. Energy may therefore be conserved through this mechanism. Goldspink [1977] also reported considerable compliance exists at the cross bridge level. Therefore parts of the cross bridge, in particular the S2 fragment, act like a spring. The spring-like cross bridge will then produce extra tension when stretched. In terms of muscle mechanics, the stretching of the series elastic component which is located at the cross bridges of the contractile protein [Astrand and Rodahl, 1986; Kirchberger and Schwartz, 1985; Huxley and Simmons, 1971] is responsible for the greater force generated. Fig. 1 shows the classic force and velocity relationship for both muscle shortening and lengthening contractions. Lengthening contractions produce greater force than shortening contractions at any muscle contraction velocity.

A second distinct characteristic is that integrated electromyographic (IEMG) activity is lower in eccentric than concentric muscle contractions [Asmussen, 1953; Asmussen, 1956; Bigland-Ritchie and Woods, 1976; Komi and Buskirk, 1972, Moritani et al, 1988]. In addition, IEMG activity has been observed to increase with increasing knee angular velocity or mechanical work in positive work. But in negative work, IEMG has been reported to remain at very low levels over a range of
power outputs [Komi et al 1987]. The slope of the regression line relating IEMG and force was less steep in negative compared with positive work [Bigland-Ritchie and Woods, 1976; Eloranta and Komi, 1980; Komi and Buskirk, 1972]. The EMG spike amplitude was also lower in motor units activated during eccentric muscle contraction [Moritani et al, 1988]. This evidence supported the notion that production of a given force required less motor unit activation in eccentric compared with concentric muscle contraction [Knuttgen, 1986; Komi et al, 1987; Moritani et al, 1988].

A third distinct characteristic of negative work is its lower energy requirement compared to positive work for the same power output (work/time) [Abbott and Bigland, 1953; Abbott et al, 1952; Asmussen, 1953; Klausen and Knuttgen, 1971; Knuttgen et al, 1971a; Knuttgen et al, 1971b]. Other investigators have shown various related physiologic responses are also relatively lower for negative work, for example, heart rate, cardiac output, pulmonary ventilation, respiratory exchange ratio, muscle blood flow and muscle temperature [Abbott et al, 1952; Asmussen, 1953; Davies and Barnes, 1972b; Knuttgen, 1986; Knuttgen et al, 1971a; Knuttgen et al 1971b; Nielsen et al, 1972].

At comparable oxygen consumption, the total heat production in negative work is higher and the skin blood flow needed for maintenance of thermal equilibrium is higher than
positive work [Nielsen et al, 1972]. To achieve comparable oxygen consumption, the work rate of negative work could be as high as five times that of positive work [Nielsen et al, 1972]. Heart rate has been reported to be higher in negative work compared to that in positive work [Nielsen et al, 1972; Thomson, 1971; Knuttgen et al, 1971b]. Heart rate increases linearly with oxygen consumption in negative work, however, the rate of increase is greater in negative work [Hesser et al, 1977]. Davies and Barnes [1972b] reported that at comparable oxygen consumption, the cardiac output and heart rate were higher and stroke volume was unchanged in negative work compared to positive work. With prolonged negative work, the investigators found that cardiac output was similar to positive work over the same time interval but heart rate was higher and stroke volume decreased by 18%. Others [Nielsen et al, 1972; Thomson, 1971] have reported that cardiac output was the same in positive and negative work at the same oxygen consumption level indicating stroke volume was lower in negative than in positive work. Similar observations of unaltered cardiac output, increased skin blood flow, increased heart rate and decreased stroke volume have been made in subjects working in a hot compared to a cool environment [William et al, 1962].

Minute ventilation is reported to be similar or elevated during negative work compared with positive work at comparable oxygen consumption when performed on a treadmill or cycle ergometer [Dean and Ross, 1989; Hesser et al, 1977; Knuttgen et
al, 1971a; Knuttgen et al, 1971b; Thomson, 1971]. The effects of negative work on the components of minute ventilation (VE) specifically tidal volume (VT) and breathing frequency (fb), however, have not been documented. One exception is the work of Dean and Ross [1989] who reported rapid shallow breathing in healthy subjects during downhill walking at 3.5 mph with a -7% grade on a treadmill. Of particular interest, two subjects in this study had tidal volumes as low as 0.25 l and breathing frequencies greater than 70 br/min at this work load. Dean and Ross [1989] speculated that it was unlikely this ventilatory response was an adaptive physiologic response per se but rather it reflected postural and abdominal wall adjustments to walking downhill even at low grades.

The net mechanical efficiency calculated for positive work has been reported to range between 19%-27% [Aura and Komi, 1986]. In negative work mechanical efficiency is directly related to mechanical work or movement velocity. Thus unlike positive work, efficiency can be in excess of 100% in negative work [Komi et al, 1987]. This improved efficiency as proposed by Aura and Komi [1986] has to do with greater muscle stiffness in eccentric muscle contraction at increasing work rates. The investigators proposed that eccentric muscle contraction required lower oxygen consumption due to the increased stiffness phenomenon.

A fourth distinct characteristic of negative work is
that when it is performed at high intensity and for a prolonged period, ultrastructural damage may result with severe delayed onset muscle soreness [Clarkson and Tremblay, 1988; Newham, 1988; Newham et al, 1988]. These two phenomena are probably directly related. However the exact mechanism for delayed-onset muscle soreness is still not understood [Armstrong, 1985; Newham, 1988]. Disturbances are observed in the cross-striated band pattern and as disorganized myofibrillar material. The lesions are mostly localized in the Z-band which undergoes streaming, broadening, and often, total disruption. Z-lines have been reported to disappear completely [Asmussen, 1956; Friden et al, 1981; Friden et al 1983] In addition, plasma creatine kinase, interleukin-1 and urinary 3-methylhistidinuria were observed to increase significantly after negative but not positive work. Negative work involving the legs also caused significant intramuscular pressure elevation in the anterior compartment of the lower leg, which was not seen following positive work. This may be one of the factors associated with the development of delayed muscle soreness [Friden et al, 1986]. Sargeant and Dolan [1987] observed that a bout of negative work performed by the knee extensor muscles resulted in a significant decrease in maximum voluntary isometric contraction, short term anaerobic power output, and knee extension force generated at a low frequency (20 Hz) relative to a higher frequency (50 Hz) percutaneous stimulation of the quadriceps muscle. Newham et al [1988] reported a greater drop in strength and increase in
pain during eccentric muscle contraction when the muscle contracts from a stretched position. However, individuals previously exposed to negative work may adapt such that the muscles become more resistant to damage [Clarkson and Tremblay, 1988; Evans et al, 1986; Sargeant et al, 1987].

The fifth interesting phenomenon associated with negative work is a progressive upward drift of oxygen consumption which occurs during prolonged moderate to high intensity steady-rate work. This drift of oxygen consumption has been reported to range from 25%-40% in various types of negative work [Klausen and Knuttgen, 1971; Davies and Barnes, 1972b; Burke et al, 1985]. Dick and Cavanagh [1987] reported a 10% increase in oxygen consumption and 23% increase in IEMG between minutes 10 and 40 during downhill running. They hypothesized that an upward drift in oxygen uptake and increasing IEMG during downhill running reflected increased motor unit recruitment within the eccentricly contracting muscles. These effects were attributed to a combination of muscle damage, connective tissue damage, and local muscle fatigue.

In summary, at a comparable power output negative work is associated with a lower IEMG activity, oxygen uptake, and related physiological responses compared with positive work. At comparable oxygen consumption, the ventilatory response is reported to be rapid and shallow during negative work. Other
physiological responses to negative work are similar to those observed during positive work performed in a warm environment. An upward drift in oxygen consumption has been associated with submaximal negative work whereas this drift is less pronounced during positive work. Also, high intensity submaximal negative work can be associated with muscle damage and delayed-onset muscle soreness, but these effects are less marked in trained subjects.

III EFFECT OF SPEED AND POWER OUTPUT ON ENERGY CONSUMPTION AND EFFICIENCY

With respect to power output, muscle physiologists have known since Hill's early studies [1938] that the force a muscle can generate and the velocity at which the muscle shortens are interdependent. Optimal power or the optimal rate of doing work can be defined by a discrete point on the force-velocity curve for any muscle. Metabolic studies have shown an interesting relationship between exercise speed, load and oxygen demand. Abbott and Aubert [1952], for example, have shown that during cycling on an ergometer, a subject's energy cost was not directly related to absolute work load. Rather, a very low pedalling rate was more demanding in terms of energy cost than an intermediate rate or even higher rate. Benedict and Parmenter [1928] showed that in healthy young women the optimal rate of walking was about 65 meters per minute and that sauntering (34 meters per minute) was uneconomical with respect
to energy cost. In fact, fast walking rates of 89 meters per minute were more economical with respect to energy cost than the slow sauntering rate. Similar findings were also reported by Banister and Jackson [1967].

In the more recent literature on efficiency of positive work, contradictory findings are noted [Aura and Komi, 1986; McCann and Gliner, 1982; Suzuki, 1979]. Suzuki [1979] reported when pedalling frequency was increased from 60-100 rpm, mechanical efficiency decreased from 24% to 20% in slow twitch muscle fibers. McCann and Gliner [1982] reported no significant difference between mechanical efficiency and pedalling speeds at a certain work rate. Gaesser and Brooks [1975] observed increased net efficiency with increase in power levels but considered these to be computational artifacts. All formulas of efficiency, for example, gross, net or mechanical, work or muscle, delta or apparent, regardless of whether one calculates efficiency using the theoretical-thermodynamic method or traditional method (see Appendix A), yield decreasing efficiency with increments in speed. Aura and Komi [1986] reported that in positive work mechanical efficiency was inversely related to the work intensity and angular velocity of the joint. The decrease in mechanical efficiency with increasing work intensity could be explained by the motor unit recruitment patterns at different work intensities. Specifically, the increased force and power output associated with increasing intensities of positive work could reflect the
greater recruitment of fast-twitch motor units. This is consistent with the so-called size principle of motor unit recruitment [Henneman et al, 1965]. The larger fast twitch muscle fibers reportedly have a lower mechanical efficiency and economy than the small slow twitch muscle fibers because of greater rate of actomyosin turnover [Awan and Goldspink, 1972; Crow and Kushmerick, 1982; Heglund and Cavagna, 1987; Wendt and Gibbs, 1973]. Increased recruitment of fast twitch fibers would then be expected to lower the overall efficiency of the working muscles. Komi et al [1987] concluded that the fairly constant net mechanical efficiency (ranged between 19% to 27% [Aura and Komi, 1986]) in positive work was likely due to the fact that EMG activity, energy expenditure, and mechanical work paralleled changes in exercise intensity. But when greater contraction velocities were used, the mechanical efficiency of positive work decreased [Aura and Komi, 1986]. Others [Hansen et al, 1988; Luhtanen et al, 1987] reported that isometric work, co-contraction of trunk muscles, elevated body temperature, increased catecholamines, increased O2 uptake in cardiac and respiratory muscles can be additional causes of decreased efficiency at high work rates.

Whipp and Wasserman [1969] observed that total muscle efficiency derived from a theoretical-thermodynamic perspective, assuming that carbohydrate was the sole metabolic substrate, was similar to work efficiency. Thus they promoted the use of the term work efficiency. In contrast, Gaesser and
Brooks [1975] reported that the traditional method of calculating efficiency (based upon oxygen uptake and respiratory exchange ratio) was judged to be superior to the theoretical-thermodynamic method because in real life other metabolic substrates are used during exercise evidenced by a respiratory exchange ratio (R) less than 1.0. Furthermore, Gaesser and Brooks [1975] attributed the inconsistencies in mechanical efficiency reported for a given type of work in the literature to differences in methodology including the selection of an appropriate baseline correction factor for calculating efficiency. They claimed that delta efficiency with a 'floating base-line' represented the most accurate estimate of muscular efficiency.

The mechanical efficiency of negative work has been reported to range between 61% -116% during cycle ergometry [Pahud et al, 1980; Pimenthal et al, 1982]. Komi et al [1987] showed that mechanical efficiency of negative work was directly related to work intensity. On the basis of White's work [1977], these investigators proposed that during eccentric muscle contraction, greater force is produced because of greater resistance at the cross bridge level when compared to concentric muscle contraction. This proposal can be demonstrated by the force-velocity characteristics of skeletal muscle [Fig. 1].

In summary, numerous inconsistencies exist in the
literature regarding the effect of rate of work (speed) and power (work/time) on the efficiency of positive work. These disagreements reflected the use of different definitions of efficiency. This resulted in different base line values being subtracted from the gross metabolic consumptions in various studies giving different efficiency values. The more recent literature generally agreed that efficiency is inversely related to rate of work and power in positive work. This observation supports the size principle of motor unit recruitment [Henneman et al, 1965], that is fast-twitch fibers which are metabolically more expensive are recruited at higher power output. In contrast, the results of the studies in the literature on the efficiency of negative work were more consistent. In negative work, net mechanical efficiency is directly related to work intensity. This phenomenon can be explained by the fact that with increasing velocity of stretch, the increases in force (and work) of the cross bridges are not associated with increases in motor unit activation and energy expenditure [Komi et al, 1987].

**Incorporation of Internal Work into Calculation of Efficiency**

Winter [1979] reported that it is important to account for internal work in calculating mechanical efficiency. Internal work is that required to raise and lower the limbs and to produce different movement velocities. When pedalling frequency increases and work rate is constant, the internal
work increases [Wells et al, 1986]. However, when pedalling frequency is kept constant, increasing work rate induces no change in the internal work [Luhtanen et al, 1987]. Wells et al [1986] have shown that by considering the total power including internal work the difference between the metabolic cost of positive and negative work performed on a cycle ergometer can be reduced. They pointed out that previous investigators probably overestimated the amount of negative work and underestimated the amount of positive work that was done by the musculature by not including internal work in their calculations.

In summary, both the numerator and denominator of the efficiency calculation have been questioned in the literature. More detailed discussion on efficiency appears in Appendix A and more detailed discussion of internal work appears in Appendix B. Investigators need to come to some agreement about the term efficiency in evaluating muscle work and develop a standardized and valid definition of efficiency. Also the issue of internal work has to be addressed in future studies. For the purpose of this present series of studies, we propose to assess efficiency primarily on the basis of economy of energy utilization, and thereby avert the dilemmas associated with a discussion of 'efficiency' discussed above.
IV EFFECT OF AGING ON ACUTE EXERCISE RESPONSES

Aging is a continuous process from birth. While its effect is offset by rapid growth during childhood and adolescence, by the third decade in life the effect of aging becomes noticeable. All bodily systems are affected to varying extents [McArdle et al, 1986; Shephard, 1987; Skinner, 1987]. Initially, functional reserves are decreased with little change in physical function. With time, functional impairment can appear especially under stress or during exercise.

We have been particularly interested in studying the potential role of negative work as a therapeutic intervention for chronically-disabled populations. However, the relatively few studies on negative work that appear in the literature have involved young healthy subjects [Aura and Komi, 1986; Clarkson and Tremblay, 1988; Davies and Barnes, 1972a,b; Dick and Cavanagh, 1987; Hesser et al, 1977; Komi et al, 1987; Pandolf et al, 1978; Pimental et al, 1982]. Thus, although effects of aging on the body are well known [McArdle et al, 1986; Shephard, 1987; Skinner, 1987; Silbermann et al, 1983; Vandervoort et al, 1986], the exercise responses of older subjects to negative work have not been described previously.

Effect of Aging on the Cardiorespiratory System

Various studies [Bates, 1989; Jones, 1988; McArdle et
al, 1986; Shephard, 1987; Skinner, 1987] have reported that pulmonary function and elastic recoil of the lung decrease with age. Consequently, pulmonary function measures such as forced vital capacity (FVC), forced expiratory volume in one second (FEV1), FEV1/FVC, tidal volume (VT), maximum voluntary ventilation (MVV) and expiratory flow rate are decreased compared to young healthy subjects. The residual volume and closing volume also increase with age. Alveolar ventilation decreases with age largely because of progressive destruction of alveolar and capillary surface. The reduction in diffusion capacity of the lung and increased proportion of lung units with low ventilation perfusion ratio (VA/Q) at rest can explain the decrease in arterial oxygen partial pressure (PaO2) and the increase in the alveolar-arterial oxygen partial pressure gradient at rest. The central responses to hypoxia and hypercapnia are blunted with age. Aging has also been associated with stiffening of the chest wall and costal vertebral joints [Shepard, 1987], and increasing bone loss in the vertebrae [Skinner, 1987; Smith et al, 1982] resulting in thoracic kyphosis. These factors can contribute to an increased cost of breathing. Older subjects reach peak VT (approximately 57% VC) at a lower VE than young subjects and therefore have to rely on increasing respiratory rate to further increase VE [DeVries and Adams, 1972]. The ventilatory equivalent for oxygen i.e. minute ventilation / oxygen uptake (VE/VO2) has also been shown to increase with age indicating a less efficient ventilatory system [Shephard, 1987; Skinner,
Maximum oxygen uptake (VO2max) decreases by about 0.4 to 0.9 ml/kg/min each year after the second decade of life [Dehn and Bruce, 1972; Larson and Bruce, 1986; Skinner, 1981]. The maximum heart rate, stroke volume and cardiac output similarly decrease with age [Astrand, 1967; Shephard, 1987; Skinner, 1970]. Older people tend to have a higher incidence of anemia which may further decrease the oxygen carrying capacity of the blood [Shepard, 1987]. The decrease in VO2max is thought to be related to decreased oxygen transport [McArdle et al, 1986, Skinner, 1970]. The recovery time of heart rate post exercise is longer for the older than the younger person. ECG abnormalities are more prevalent in the elderly [Astrand, 1963; Skinner, 1970] thus close monitoring during exercise testing is essential [McArdle et al, 1986; Skinner, 1987]. Pulmonary resistance increases somewhat with age [Bates, 1989] but peripheral vascular resistance and arterial wall stiffness tend to be higher at rest and during exercise leading to a higher systemic blood pressure [Shepard, 1987; Skinner, 1970]. The skin blood flow is higher in the elderly because of an impaired ability to lose heat therefore diverting blood flow away from the exercising muscles. Blood flow to the exercising muscle is also limited to a greater extent in the older person at a given muscular pressure than in a younger person. Hence, oxygen delivery to the exercising muscles is further lowered in older subjects [Shephard, 1987]. Consequently, for a given
work rate, blood lactate concentration is higher in the older subject [Skinner, 1970]. Thus, overall, older subjects tend to have a less efficient cardiorespiratory system than young healthy subjects, and are less able to adapt efficiently to increased cardiorespiratory demands.

Effect of Aging on Skeletal Muscle

Aging is associated with a decrease in lean body mass. This decrease in muscle mass is due to the loss of muscle protein and progressive replacement with connective tissue and fat cells [McArdle et al, 1986; Silbermann et al, 1983]. At the same time muscle strength decreases minimally between 30 to 55 years of age. After the fifth decade, muscle strength decreases sharply with age [McArdle et al, 1986; Shephard, 1987; Shock and Norris, 1970; Vandervoort et al, 1986]. Vandervoort et al [1986] reported that the mean maximum voluntary contraction for a muscle group is more than 20% lower in individuals over 70 years of age compared with younger people. Reduced neuromuscular coordination is another factor that contributes to the decrease in maximum power output observed in older subjects [Shock and Norris, 1970]. Isokinetic muscle torque measured at high velocity drops significantly with age [Larson et al, 1979; Shephard, 1987]. The number of fast-twitch fibers also has been shown to decrease with age in humans [Grimby and Saltin, 1983; Shephard et al, 1987; Vanderoort et al, 1986] while Silbermann et al
[1983] using an animal model reported a decrease in slow-twitch fibers. Machinery involved in excitation-contraction coupling such as the neuromuscular junction, T-tubules, sarcoplasmic reticulum, and other cell structures such as the sarcolemma, Z-line and mitochondria also exhibited age-related changes [Shephard, 1987; Vandervoort et al, 1986].

In summary, the body undergoes considerable changes with age especially after the fifth decade. Body systems tend to function less efficiently in the elderly. Shephard et al [1988] have attributed the reduction in physical work capacity in the elderly to peripheral as well as central mechanisms.

V. RATIONALE FOR STUDY

Although our knowledge of the physiological characteristics of negative work has grown since the work of Abbott and co-workers almost 40 years ago, the literature on negative work is scant compared to positive work. Studies that have been reported on negative work have focused on the relation of force to power generation, energy consumption and efficiency, electromyographic activity, cardiovascular responses, heat regulation, and muscle damage [Abbott and Bigland, 1953; Abbott et al, 1952; Armstrong, 1985; Asmussen et al, 1953; Asmussen et al, 1956; Aura et al, 1986; Bigland-Ritchie et al, 1976; Clarkson and Tremblay, 1988; Eloranta et al, 1980; Friden et al, 1981; Hesser et al, 1977; Klausen et

With respect to ventilation during negative work, previous studies have largely reported a commensurate drop in VE which parallels the decrease in VO2 when compared with positive work across the same work rates [Knuttgen et al, 1971a, Knuttgen et al, 1971b, Thomson, 1971].

Although some studies have examined gross ventilatory changes in VE during negative work, little is known about the specific effects on the components of VE, namely tidal volume (VT) and breathing frequency (fb) [Knuttgen et al, 1971a, Knuttgen et al, 1971b, Thomson, 1971]. Dean and Ross [1989] reported rapid shallow breathing in healthy subjects during downhill walking on a treadmill at 3.5 mph with a -7% grade. They further observed that the fb and VT during negative work in their study were not consistent with the notion that downhill walking is merely a low-intensity form of positive work. These investigators argued that postural distortion of the chest wall, restriction of abdominal wall motion or both during downhill walking may contribute to the rapid shallow breathing response observed. In order to minimize any effect of postural distortion, we used a cycle ergometer rather than treadmill in the present study. Thus, the present study which extends the previous work of Dean and Ross in our laboratory will hopefully shed further light on the effect of negative
work on the components of ventilation.

In addition to the reduced energy cost of negative compared with positive work, the energy cost of a given work rate may be affected by the pedalling frequency. The existence of optimal walking and pedalling frequencies for individuals has been reported [Abbott and Aubert, 1952; Banister and Jackson, 1967; Benedict and Parmenter, 1928; Knuttgen et al, 1971a; Seabury et al, 1977]. Banister and Jackson reported that a low work rate achieved with a high pedalling frequency and low resistance is metabolically equivalent to a much higher work rate which is achieved with a low pedalling frequency and high resistance. The existence of optimal pedalling frequencies for different work rates during positive work has been identified, however such values for negative work are less clear.

The literature to date on negative work in general, and that on positive work examining energy cost at different work rates, has primarily reported the responses of young healthy male subjects [Aura and Komi, 1986; Davies and Barnes, 1972a,b; Dick and Cavanagh, 1978; Hesser et al, 1977; Komi et al, 1987; Pandolf et al, 1978; Pimental et al, 1982]. Despite the well-known physiological consequences of aging [Shephard, 1987; Skinner, 1987; Vandervoort et al, 1986], and age-related changes in the responses to conventional exercise during positive work, the responses of older adults to negative work
are not known. Because of our long-term interest in investigating the therapeutic potential of negative work in the rehabilitation of older and disabled individuals, this study was designed to examine the exercise responses of middle-aged men. In addition, this study would also provide information about the ability of middle-aged men to utilize stored potential energy during negative work.

In summary, this thesis will help to elucidate the responses of positive vs negative work at different pedalling frequencies in middle-aged men. Specifically, this research will provide insight into whether negative work performed on a cycle ergometer is equivalent to low 'intensity' positive work when performed at the same work rate or whether negative work elicits physiologically-distinct responses compared with positive work.

VI THESIS QUESTIONS

The specific questions addressed in this study are:-

1. What are the effects of positive and negative work on oxygen consumption (VO2) and heart rate (HR) when performed by middle-aged men on a cycle ergometer?

2. Under these conditions, what are the effects of positive and negative work on minute ventilation (VE), tidal volume (VT),
and breathing frequency (fb)?

3. What are the effects of the three pedalling frequencies on VO2, HR, VE, VT and fb?

4. Are the relationships of VT and VE, and fb and VE different in positive and negative work?

5. Are the relationships of VE and VO2 and HR and VO2 different in positive and negative work?
Fig.1 Force velocity curve for muscle shortening contraction or positive work (solid line) and muscle lengthening contraction or negative work (solid line). As the load (V) decreases until V=0 when P=P_o, maximal isometric tension, is reached. As forces greater than P_o are applied, the muscle lengthens. Power (force x speed) is produced during shortening - broken line; absorbed during lengthening - broken line.
METHODS

I RESEARCH DESIGN

We used a 2 (positive and negative work) by 3 (35, 55, 75 rpm pedalling frequencies) factorial design with repeated measures on both factors. Each subject performed six tests, specifically one at each of the three pedalling frequencies for each of the two types of muscle work. Power was held constant, specifically, 60 Watt for all tests. Subjects were randomly selected to perform positive or negative work on the first of two test days which were scheduled one week apart. The order of the pedalling frequencies was also randomly selected by each subject at the beginning of each test by means of card selection. The exercise responses that were of particular interest included oxygen uptake (VO2), heart rate (HR), minute ventilation (VE), tidal volume (VT) and breathing frequency (fb).

II SUBJECTS

Twelve healthy middle-aged men with no history of cardiopulmonary disease participated in the study. No subject had participated in any formal exercise program or training over the past year. A detailed explanation of the research design and purpose of the study was given to each subject. Each subject was then asked to sign an informed...
consent form approved by the University of British Columbia Ethics Committee.

III EQUIPMENT AND MEASURES

Cycle Ergometer

The assembly of the bicycle ergometer is shown in Fig. 2. All parts were bolted onto two connected rigid wooden frames with wheels for easy transportation. Brakes were applied during testing to maintain stability of the assembly.

A sturdy chair with arm support was mounted onto the wooden frame on an adjustable linkage to allow optimal leg extension and comfort for each subject. The chair was fixed so that the subject could sit approximately level with the pedals so that the legs were extended forward, rather than downward. A chair with arm support was used to minimize the contribution of sitting and the movements associated with balancing and body fixation to the total energy cost of cycling [Knuttgen et al, 1971b; Hesser et al, 1977]. The center of rotation of the subject’s ankle joint was positioned close to the center of the pedal to standardize mechanical leverage and equalize thigh and lower leg muscle involvement [Bigland-Ritchie et al, 1976; Ericson, 1986]. Foot straps were applied to ensure the subject maintained the required foot position throughout the test.
A standard cycle ergometer (Monark) was modified by the U.B.C. Health Science Center Bio-medical Engineering Department to perform positive and negative work. The modification followed that described in the literature [Bigland-Ritchie et al, 1973]. The modified cycle ergometer has a 1:3.8 gear ratio between the pedals and flywheel. For either positive or negative work, the flywheel is driven through a bicycle-chain connected to a 1.5 horsepower d-c motor (Baldor). The d-c motor is connected to a solid-state reversible speed control. Imposed torque is determined by measuring the current drawn by the motor. A signal conditioning circuit converts measured current to torque (Newtons) which is displayed on a digital meter (Texmate Inc). The speed is held constant by a constant current feedback control, the output of which is also displayed by a digital output gauge (Minarik magnetic pickup). The pedal frequency control ranges from 0 to 120 rpm. Maximum allowable torque registrable at the pedals is 70 N for pedal speeds ranging from 40-120 rpm. At pedal speeds less than 40 rpm, the maximum allowable torque is decreased in proportion to the decrease in pedal speed. The original friction belt braking system of the ergometer is retained for forward pedalling or positive work and for calibration. In this motor-driven cycle ergometer, the pedalling speed is controlled by the motor and the load is controlled by the subject. A second set of speed and torque output gauges are placed in front of the subject to provide direct visual feedback.
The control panel is attached to the frame of the motorized ergometer. The control panel has an on-off control, speed control, forward or reverse control, stop or run control, clutch engage or disengage switch, torque calibration, torque zero, and speed calibration knobs. The circuitry and fuse are contained within the control panel.

Both speed and torque calibrations were done prior to testing and recalibrated whenever there was a change in speed or work setting. Speed calibration was done by matching the frequency of the turning pedals with the aid of a stop watch for a given speed to the speed output gauge. Subsequently, torque reading was zeroed at each test speed. Torque calibration was done using the original friction band on the ergometer as reference in the forward direction. The friction band on the ergometer was tightened to a known resistive force and the torque digital output gauge was calibrated to match the resistive force. Torque calibration for the reverse direction was tested by the U.B.C. Health Science Center Bio-medical Engineering Department by using the original friction band and a known resistive force and was identical to the forward direction. Therefore for a given speed, torque calibration performed in the forward direction also serves to calibrate the reverse direction [G. Sandford, Biomedical Technologist, personal communication]. These procedures constituted the calibration for each speed for both
positive and negative work i.e. pedalling in the forward and backward directions [Bigland-Ritchie et al, 1973; G. Sandford, Biomedical Technologist, personal communication].

**Metabolic Measurement Cart**

A Sensormedics Metabolic Measurement Cart (MMC) was used during exercise testing to perform breath-by-breath gas sampling. Subjects were connected to the MMC by a head-piece assembly and mouth piece. A nose clip was used to avoid air leakage through the nose. Expired gas was then analyzed over each 15 sec interval during testing. Measures included oxygen consumption, minute ventilation, tidal volume and breathing frequency. Before each test, the MMC was calibrated according to the operator-guided calibration procedures recommended by the manufacturer using specific calibration gases.

Heart rate and rhythm were continuously monitored using a three lead ECG monitor (Hewlett-Packard). Oxygen saturation was measured using an Ohmeda oximeter with an ear lobe sensor. Both monitors were calibrated before each test. Analog circuitry boards also allowed heart rate and arterial saturation to be averaged every 15 seconds and appear on the collective data print-out.
Other Measures

Blood pressure was measured manually using a brachial cuff and stethoscope at minute intervals throughout each test by the same experienced individual. In addition, subjective measures of breathing difficulty were recorded every minute. Borg's modified scale with ratio properties was used to measure breathing difficulty. The scale ranged from 0 or 'nothing at all' to 10 or 'very, very strong' (Borg, 1982). Appendix C describes the breathing difficulty scale in greater detail.

Tests were carried out in a temperature-controlled exercise laboratory (21 ± 2 C).

IV GENERAL PROCEDURES

Performance of Positive Work

The subject was seated for forward cycling or positive work in the same manner as for negative work. The clutch of the motor mechanism was engaged in the forward position. An extra 10 N load was added onto the pre-determined resistance for the subject to prevent damage to the motor by inadvertently driving it above its set speed. A lap seat belt was fastened to stabilize the subject. The standard distance of the chair from the pedals was determined by the length of the fully extended leg and the pedal which was in the horizontal position.
furthest away from the subject. Then the distance of the seat from the pedal was adjusted for subject comfort prior to the start of testing allowing no more than 10 degrees of knee flexion. Since the tension generated by a muscle is dependent on its resting length (Hill, 1938), care was taken to ensure that each test was performed at a comparable seat position for each subject. The feet were strapped into position on the pedals. The subject was encouraged to relax the upper body and trunk while allowing the lower extremities to cycle. After the test speed was set by the tester, the subject pedalled forward to assist the cycle ergometer with sufficient effort so that the torque output gauge fell to 10 N. The motor maintained the speed set by the tester while the subject assisted the movement of the pedals until the desired torque reading was registered. The subject then maintained the same effort for the duration of the test.

**Performance of Negative Work**

The friction band was left slack while the motor drove the pedals in the reverse (backward) direction. At the designated speed set by the tester, the subject was directed to resist the movement of the pedals until the desired torque reading was registered. A forced stretch was therefore imposed on the same muscles that were used to generate power during conventional cycling using concentric muscle contraction. The work produced by the motor was transferred to the active
muscles. The rate at which the muscles were 'worked upon' was the power being transferred to the subject [Knuttgen, 1986]. The subject was then told to maintain the level of resistance for the duration of the test.

**Performance of Free Pedalling**

For free pedalling prior to positive work, the seated subject placed his feet in the appropriate position on the pedals and then the feet were strapped into place. He was instructed to relax while the motor drove the feet around at the desired speed. The subject maintained foot contact with the pedals while passively allowing the pedals to carry the legs around forward. During the test session, the subject free pedalled at the test speed during the warm up and cool down period.

For free pedalling prior to negative work, the procedure was the same except that the subject allowed the pedals to carry the legs around in the backward direction.

**Practice Sessions**

All subjects attended two to three practice sessions of positive and negative work using the cycle ergometer. A subject was deemed to have learned the negative work cycling technique when he could maintain a given torque output for one
minute for a range of torques determined by the tester. Our initial pilot work suggested that negative work cycling was more difficult to learn than positive work cycling. However, no major difficulty was encountered with the practice and test sessions. Practice sessions were also used to familiarize the subjects with the testing environment, general procedures and monitoring equipment. Practice sessions lasted an average of 25 minutes and were purposefully designed to promote a learning effect while minimizing any training effect.

Test Protocol

Upon completion of the practice sessions, subjects were then eligible to participate in the two test conditions, specifically positive and negative work using the cycle ergometer. Tests were conducted at least one week apart.

Subjects were requested not to have a large meal at least three hours prior to testing and not to consume any substances that contain stimulants (such as coffee or soft drinks with caffeine). They were asked to have a restful 24 hr period prior to testing and to wear comfortable attire and shoes when they visited the laboratory.

When a subject arrived at the exercise laboratory on each test day, height and weight were taken and routine pulmonary function testing including three trials of forced
expiratory maneuvers, was performed. Subsequently, the subject relaxed while seated on the testing chair which was adjusted for leg length and comfort, for at least five minutes. Two active electrodes were placed bilaterally over the upper trapezius area and the ground electrode was placed over the lateral chest for ECG monitoring. The subject was then connected to the MMC by means of the head-piece assembly and mouth piece, and a nose clip was applied. The subject inspired room air via a low resistance, one-way, non-rebreathing valve. The subject was then again asked to relax in this comfortable position for another three minutes while resting metabolic measures were taken. Baseline physiological measures were usually taken in the second to third minute of the test when V02 and HR of the subject had stabilized. After warming up with free pedalling for two minutes, the subject pedalled at the assigned speed (the first of the three randomized speeds) and power output. A steady-state was defined as the state at which the heart rate and V02 had stabilized. After a steady-state was reached (usually within three minutes) data were collected for five to seven minutes before the test at the assigned speed was terminated. The subject free pedalled during the cool down period for several minutes. Vital signs were continuously monitored until they were within 10 to 15% of baseline. The subject then rested for 30 minutes prior to being tested at the next speed. This procedure was continued until all three speeds were completed. This protocol was repeated on the second test day for the other type of work.
The test protocol is summarized in Fig. 3.

V Data Analysis

Descriptive statistics for the five dependent variables for each of the six steady-state tests were calculated.

A 2 by 3 (two types of muscle work and three pedalling frequencies) factorial design with repeated measures on both factors was used to analyze the data. An ANOVA for repeated measures was used for each of the five dependent variables. MANOVAs for repeated measures were used to analyze the main effects for pedalling frequency and the interaction when the assumptions for ANOVA for repeated measures were violated resulting in inflated p-values [Wilkinson, 1988]. Newman-Keuls post hoc tests were used to test the effect of pedalling frequency when a significant omnibus F was found.

Linear regression was used to determine the relationship between VT and VE, fb and VE, HR and VO2, and VE and VO2 during both positive and negative work. The regression lines for each of the four relationships were then tested for homogeneity of the regression coefficients between positive and negative work. An alpha of less than 0.05 was used as the critical value.
Fig. 2 Motorized Cycle Ergometer

Motor & Clutch

Control Panel

Display (Speed & Torque)

Chair

Frame

Locking / Pivoting Wheels
Fig. 3 Flow diagram of the test protocol

Rest 5 min

Connected to MMC + Rest 5 min

Free Pedal 2 min

Steady State Exercise Test <7 min

Cool Down 2 min

Disconnected from MMC + Rest for 30 min then Re-tested
RESULTS

I SUBJECT CHARACTERISTICS

Subjects were healthy men with a mean age of 49.7 years ranging from 39 to 65 years. Their Body Mass Indexes (BMI) averaged 26.1 kg/m² and ranged from 21.8 to 31.5 kg/m². Pulmonary function test results were within normal range for each individual (Table I). We used Morris' norms [1976] for assessing pulmonary function.

All exercise tests were performed without any untoward episodes. The average SaO₂ was 97% and remained stable throughout exercise testing. Overall, the ECGs were considered to be within normal limits during rest, exercise and post exercise recovery for all subjects. The Borg's subjective rating of breathing difficulty was on the average 1.1 and 0.8 units for positive and negative work respectively during the steady-state portions of the exercise tests.

II OXYGEN CONSUMPTION

Descriptive statistics for VO₂ are shown in Fig. 4. The baseline values preceding positive and negative work represent a composite mean of the three baseline periods for each test day. During positive work, VO₂ (means ± standard deviations) was 1.04±.13, 1.12±.13 and 1.25±.13 l/min for
pedalling frequencies of 35, 55, and 75 rpm respectively. For negative work, these were 0.64±0.17, 0.55±0.14 and 0.67±0.24 l/min for pedalling frequencies of 35, 55, and 75 rpm respectively.

The results of the ANOVA are shown in Table II. Overall, the VO2 was lower during negative than positive work (p<0.001) and there was a significant effect of speed on VO2 (p=0.002). Post hoc tests revealed that the VO2 during positive work was significantly higher at 75 rpm than at 35 and 55 rpm (p<0.05). During negative work, the VO2 was significantly higher at 75 than 55 rpm. There was also a significant interaction (p<0.01) showing that VO2 increased linearly during positive work while the VO2 was the lowest at 55 rpm during negative work.

III HEART RATE

Descriptive statistics (means ± standard deviations) for HR are shown in Fig. 5. The baseline values preceding positive and negative work represent a composite mean of the three baseline periods for each test day. During positive work, the HR was 93.0±9.4, 95.4±10.5 and 99.2±12.1 bpm for pedalling frequencies of 35, 55, and 75 rpm respectively. For negative work, these were 82.5±11.5, 77.8±14.0 and 85.1±15.4 bpm for pedalling frequencies of 35, 55, and 75 rpm respectively.
The results of the ANOVA are shown in Table III. Overall, the HR was lower during negative than positive work (p<0.001) with a significant effect of speed on heart rate (p=0.003). Post hoc tests revealed that the HR during positive work was significantly higher at 75 rpm than at 55 and 35 rpm (p<0.05). During negative work, the HR was significantly higher at 75 than 55 rpm. There was also a significant interaction (p<0.05) showing that HR increased linearly during positive work while the HR was lowest at 55 rpm during negative work.

The results of the scatter plot for the HR and VO2 relationship are shown in Fig. 6. The significant HR and VO2 relationship during positive work can be described by the equation HR = 62.1 + (29.8)VO2 and the Pearson product-moment correlation coefficient (r) which was 0.42 (p<0.05). The significant HR and VO2 relationship during negative work can be described by the equation HR = 52.0 + (47.8)VO2 and r which was 0.66 (p<0.05). The slopes and intercepts of the regression lines during both positive and negative work for the relationship of HR and VO2 did not differ (p>0.05).

IV MINUTE VENTILATION

Descriptive statistics (means ± standard deviations) for VE are shown in Fig. 7. The baseline values preceding positive and negative work represent a composite mean of the
three baseline periods for each test day. During positive work, the VE was 24.6±4.9, 26.2±5.7 and 29.4±6.0 l/min for pedalling frequencies of 35, 55 and 75 rpm respectively. For negative work, the VE was 16.0±4.1, 14.8±4.2 and 18.6±7.2 l/min for pedalling frequencies of 35, 55 and 75 rpm respectively.

The results of the ANOVA are shown in Table IV. Overall, the VE was lower during negative than positive work (p<0.001) with a significant effect of speed on VE (p<0.01). Post hoc tests revealed that the VE during both positive and negative work was significantly higher at 75 rpm than 55 and 35 rpm for each type of work (p<0.05). There was no interaction (p>0.05).

The results of the scatter plot for the VE and VO2 relationship are shown in Fig. 8. The significant relationship of VE and VO2 during positive work can be described by the equation VE = -8.86 + (31.4)VO2 and r which was 0.81 (p<0.05). The significant VE and VO2 relationship during negative work can be described by the equation VE = 1.24 + (24.4)VO2 and r which was 0.85 (p<0.05). The slopes of the regression lines during both positive and negative work for the VE and VO2 relationship did not differ statistically (p>0.05) while the intercept was significantly smaller during positive work (p<0.05).
V TIDAL VOLUME

Descriptive statistics (means ± standard deviations) for VT are shown in Fig. 9. The baseline values preceding positive and negative work represent a composite mean of the three baseline periods for each test day. During positive work, VT was 1.40±.31, 1.41±.30 and 1.57±.35 l/breath for pedalling frequencies of 35, 55, and 75 rpm respectively. For negative work, the VT was 0.93±.24, 0.93±.29 and 1.12±.41 l/breath for pedalling frequencies of 35, 55, and 75 rpm respectively.

The results of the ANOVA are shown in Table V. Overall, the VT was lower during negative than positive work (p<0.001) with a significant effect of speed on VT (p=0.03). Post hoc tests revealed that the VT during both positive and negative work at 75 rpm was significantly higher than at 55 and 35 rpm (p<0.05). The interaction was non-significant (p>0.05).

The results of the scatter plot for the VT and VE relationship are shown in Fig. 10. The significant relationship of VT and VE during positive work can be described by the equation VT = 0.89 + (0.022)VE and r which was 0.39 (p<0.05). The significant VT and VE relationship during negative work can be described by the equation VT = 0.51 + (0.030)VE and r which was 0.49 (p<0.05). The slopes and intercepts of the regression lines during both positive and
negative work for the VT and VE relationship did not differ (p<0.05).

VI  BREATHING FREQUENCY

Descriptive statistics (means ± standard deviations) for fb are shown in Fig. 11. The baseline values preceding positive and negative work represent a composite mean of the three baseline periods for each test day. During positive work, fb was 18.1±4.1, 18.8±3.6 and 19.3±4.2 br/min for pedalling frequencies of 35, 55, and 75 rpm respectively. For negative work, the fb was 18.2±6.3, 16.8±4.7 and 17.5±5.8 br/min for pedalling frequencies of 35, 55, and 75 rpm respectively.

The results of the ANOVA are shown in Table VI. There were no differences in fb between positive and negative work nor among pedalling frequencies (p>0.05).

The results of the scatter plot for the fb and VE relationship are shown in Fig. 12. The relationship of fb and VE during positive work can be described by the equation fb = 9.62 + (0.34)VE and r which was 0.51 (p<0.05). The relationship of fb and VE during negative work can be described by the equation fb = 11.08 + (0.393)VE and r which was 0.39 (p<0.05). The slopes and intercepts of the regression lines during both positive and negative work for the fb and VE
relationship did not differ ($p > 0.05$).
TABLE I
SUMMARY OF PULMONARY FUNCTION TESTS AND ANTHROPOMETRIC DATA FOR TWELVE HEALTHY MEN

<table>
<thead>
<tr>
<th>AGE (yr)</th>
<th>WEIGHT (kg)</th>
<th>HEIGHT (cm)</th>
<th>BMI (kg/m.m)</th>
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<tr>
<td>Mean</td>
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<td>177.9</td>
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<tr>
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<td>9.5</td>
<td>5.2</td>
</tr>
<tr>
<td>Minimum</td>
<td>39</td>
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<tr>
<td>Maximum</td>
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<td>101.1</td>
<td>188.0</td>
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<table>
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<tr>
<th>FEV1 (l)</th>
<th>FEV1% (%)</th>
<th>FVC (l)</th>
<th>FVC% (%)</th>
<th>RATIO (%)</th>
<th>RATIO% (%)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>4.93</td>
<td>102</td>
<td>79.5</td>
</tr>
<tr>
<td>S.D.</td>
<td>0.51</td>
<td>10.1</td>
<td>0.52</td>
<td>7.3</td>
<td>4.9</td>
</tr>
<tr>
<td>Minimum</td>
<td>2.92</td>
<td>92</td>
<td>4.18</td>
<td>90</td>
<td>70</td>
</tr>
<tr>
<td>Maximum</td>
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<td>124</td>
<td>5.95</td>
<td>113</td>
<td>87</td>
</tr>
</tbody>
</table>

ABBREVIATIONS:

Ratio is FEV1/FVC.
FEV1% is the percentage of subject's FEV1 divided by the predicted FEV1 from a nomogram.
FVC% is the percentage of subject's FVC divided by the predicted FVC from a nomogram.
Ratio is the percentage of subject's ratio divided by the predicted ratio from a nomogram.
S.D. is standard deviation.
Fig. 4 Descriptive statistics for oxygen consumption for three pedalling frequencies during positive and negative work. Vertical bars represent standard deviations. Legend: +ve is positive work.
-ve is negative work.
* different from 55 rpm (p<0.05).
** different from 35 rpm (p<0.05).
OXYGEN CONSUMPTION
Positive vs Negative Work

VO2 (l/min)

Pedalling Frequency (rpm)

- Positive Work
- Negative Work
**TABLE II**

OXYGEN CONSUMPTION DURING POSITIVE AND NEGATIVE WORK AT THREE PEDALLING FREQUENCIES. UNIVARIATE AND MULTIVARIATE REPEATED MEASURES ANALYSIS.

**TEST FOR EFFECT CALLED: TYPE OF WORK (A)**

<table>
<thead>
<tr>
<th>SOURCE OF VARIATION</th>
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<th>DF</th>
<th>MS</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>4.713</td>
<td>1</td>
<td>4.713</td>
<td>219.634</td>
<td>0.000</td>
</tr>
<tr>
<td>ERROR</td>
<td>0.236</td>
<td>11</td>
<td>0.021</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TEST FOR EFFECT CALLED: PEDALLING FREQUENCY (B)**

<table>
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<tr>
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<th>MS</th>
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<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>0.239</td>
<td>2</td>
<td>0.119</td>
<td>15.465</td>
<td>0.000</td>
</tr>
<tr>
<td>ERROR</td>
<td>0.170</td>
<td>22</td>
<td>0.008</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MULTIVARIATE TEST STATISTICS**

WILKS' LAMBDA = 0.299
F-STATISTIC = 11.711 DF = 2,10 PROB = 0.002

**TEST FOR EFFECT CALLED: INTERACTION (A X B)**

<table>
<thead>
<tr>
<th>SOURCE OF VARIATION</th>
<th>SS</th>
<th>DF</th>
<th>MS</th>
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<th>P</th>
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<tbody>
<tr>
<td>A X B</td>
<td>0.113</td>
<td>2</td>
<td>0.057</td>
<td>7.050</td>
<td>0.004</td>
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<tr>
<td>ERROR</td>
<td>0.176</td>
<td>22</td>
<td>0.008</td>
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<td></td>
</tr>
</tbody>
</table>
Fig. 5  Descriptive statistics for heart rate for three pedalling frequencies during positive and negative work. Vertical bars represent standard deviations.
Legend: +ve is positive work.
-ve is negative work.
* different from 55 rpm (p<0.05).
** different from 35 rpm (p<0.05).
HEART RATE
Positive vs Negative Work

Pedalling Frequency (rpm)

<table>
<thead>
<tr>
<th>Pedalling Frequency</th>
<th>Positive Work</th>
<th>Negative Work</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75</td>
<td></td>
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</tr>
</tbody>
</table>
### TABLE III
HEART RATE DURING POSITIVE AND NEGATIVE WORK AT THREE PEDALLING FREQUENCIES. UNIVARIATE AND MULTIVARIATE REPEATED MEASURES ANALYSIS.

**TEST FOR EFFECT CALLED: TYPE OF WORK (A)**

<table>
<thead>
<tr>
<th>SOURCE OF VARIATION</th>
<th>SS</th>
<th>DF</th>
<th>MS</th>
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<th>P</th>
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<tbody>
<tr>
<td>A</td>
<td>3560.273</td>
<td>1</td>
<td>3560.273</td>
<td>49.661</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>ERROR</td>
<td>788.612</td>
<td>11</td>
<td>71.692</td>
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**TEST FOR EFFECT CALLED: PEDALLING FREQUENCY (B)**

<table>
<thead>
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<th>DF</th>
<th>MS</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>414.309</td>
<td>2</td>
<td>207.154</td>
<td>8.411</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>ERROR</td>
<td>541.858</td>
<td>22</td>
<td>24.630</td>
<td></td>
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</tr>
</tbody>
</table>

**MULTIVARIATE TEST STATISTICS**

WILKS' LAMBDA = 0.317  
F-STATISTIC = 10.766 DF = 2, 10 PROB = 0.003

**TEST FOR EFFECT CALLED: INTERACTION (A X B)**

<table>
<thead>
<tr>
<th>SOURCE OF VARIATION</th>
<th>SS</th>
<th>DF</th>
<th>MS</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>A X B</td>
<td>151.585</td>
<td>2</td>
<td>75.793</td>
<td>3.413</td>
<td>&lt;0.051</td>
</tr>
<tr>
<td>ERROR</td>
<td>488.595</td>
<td>22</td>
<td>22.209</td>
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</tr>
</tbody>
</table>
Fig. 6 Scatter plot of heart rate and oxygen consumption relationship.
Legend: HR and VO2 values for positive work are represented by 'p'.
HR and VO2 values for negative work are represented by 'n'.
The regression lines between positive and negative did not differ (p>0.05) and can be described by a common equation HR = 61.2 + 31.5(VO2) with r=0.69 and standard error of estimate (SEE) = 10.3.
Fig. 7 Descriptive statistics for minute ventilation for three pedalling frequencies during positive and negative work. Vertical bars represent standard deviations. Legend: +ve is positive work.
   -ve is negative work.
   * different from 55 rpm (p<0.05).
   ** different from 35 rpm (p<0.05).
MINUTE VENTILATION
Positive vs Negative Work

VE (l/min)

Pedalling Frequency (rpm)

- Positive Work
- Negative Work

Baseline

35

55

75

Values represent the mean ± standard deviation. Statistically significant differences are indicated by asterisks (*) above bars.
TABLE IV
MINUTE VENTILATION DURING POSITIVE AND NEGATIVE WORK AT THREE PEDALLING FREQUENCIES. UNIVARIATE AND MULTIVARIATE REPEATED MEASURES ANALYSIS.

TEST FOR EFFECT CALLED: TYPE OF WORK (A)

<table>
<thead>
<tr>
<th>SOURCE</th>
<th>SS</th>
<th>DF</th>
<th>MS</th>
<th>F</th>
<th>P</th>
</tr>
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<tr>
<td>A</td>
<td>1901.594</td>
<td>1</td>
<td>1901.594</td>
<td>93.240</td>
<td>0.000</td>
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<tr>
<td>ERROR</td>
<td>224.341</td>
<td>11</td>
<td>20.395</td>
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TEST FOR EFFECT CALLED: PEDALLING FREQUENCY (B)

<table>
<thead>
<tr>
<th>SOURCE</th>
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<th>P</th>
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<tbody>
<tr>
<td>B</td>
<td>210.611</td>
<td>2</td>
<td>105.306</td>
<td>11.806</td>
<td>0.000</td>
</tr>
<tr>
<td>ERROR</td>
<td>196.228</td>
<td>22</td>
<td>8.919</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

WILKS’ LAMBDA = 0.394
F-STATISTIC = 7.684 DF = 2, 10 PROB = 0.010

TEST FOR EFFECT CALLED: INTERACTION (A X B)

<table>
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<tr>
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<th>MS</th>
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<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>A X B</td>
<td>26.604</td>
<td>2</td>
<td>13.302</td>
<td>3.370</td>
<td>0.053</td>
</tr>
<tr>
<td>ERROR</td>
<td>86.844</td>
<td>22</td>
<td>3.947</td>
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</tr>
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</table>
Fig. 8 Scatter plot of minute ventilation and oxygen consumption relationship.
Legend: VE and VO2 values for positive work are represented by 'p'.
VE and VO2 values for negative work are represented by 'n'.
The slopes of the regression lines between positive and negative did not differ (p>0.05). However, the intercepts differed between positive and negative work (p<0.05). The common slope of the regression line was 22.2(VO2). For positive work, the intercept was -8.9 with r=0.81 and SEE=3.45. For negative work, the intercept was 1.2 with r=0.85 and SEE=3.0.
Minute Ventilation (l/min) vs. Oxygen Consumption (l/min)
Fig. 9 Descriptive statistics for tidal volume for three pedalling frequencies during positive and negative work. Vertical bars represent standard deviations. Legend: +ve is positive work.
-ve is negative work.
* different from 55 rpm (p<0.05).
** different from 35 rpm (p<0.05).
TIDAL VOLUME
Positive vs Negative Work

Pedalling Frequency (rpm)

VT (l/br)

Positive Work
Negative Work

Baseline 35 55 75
TABLE V
TIDAL VOLUME DURING POSITIVE AND NEGATIVE WORK AT THREE PEDALLING FREQUENCIES. UNIVARIATE AND MULTIVARIATE REPEATED MEASURES ANALYSIS.

TEST FOR EFFECT CALLED: TYPE OF WORK (A)

<table>
<thead>
<tr>
<th>Source</th>
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<th>MS</th>
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<th>P</th>
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</thead>
<tbody>
<tr>
<td>A</td>
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<td>3.926</td>
<td>56.818</td>
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<tr>
<td>ERROR</td>
<td>0.760</td>
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TEST FOR EFFECT CALLED: PEDALLING FREQUENCY (B)

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<tr>
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<tr>
<td>B</td>
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<td>2</td>
<td>0.248</td>
<td>7.619</td>
<td>0.003</td>
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<tr>
<td>ERROR</td>
<td>0.717</td>
<td>22</td>
<td>0.033</td>
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</table>

MULTIVARIATE TEST STATISTICS
WILKS' LAMBDA = 0.523
F-STATISTIC = 4.559 DF = 2, 10 PROB = 0.039

TEST FOR EFFECT CALLED: INTERACTION (A X B)

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<th>P</th>
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<tr>
<td>C</td>
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<td>0.003</td>
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<td>0.248</td>
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<td>0.011</td>
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</table>
Fig. 10 Scatter plot of tidal volume and minute ventilation relationship.
Legend: VT and VE values for positive work are represented by 'p'.
VT and VE values for negative work are represented by 'n'.
The regression lines between positive and negative did not differ (p > 0.05) and can be described by a common equation VT = 0.48 + 0.035(VE) with r = 0.66 and SEE = 0.30.
Fig. 11 Descriptive statistics for breathing frequency for three pedalling frequencies during positive and negative work. Vertical bars represent standard deviations. Legend: +ve is positive work. -ve is negative work.
BREATHING FREQUENCY
Positive vs Negative Work

Pedalling Frequency (rpm)

fb (br/min)

Baseline
35
55
75

Positive Work
Negative Work
TABLE VI
BREATHING FREQUENCY DURING POSITIVE AND NEGATIVE WORK AT THREE PEDALLING FREQUENCIES. UNIVARIATE AND MULTIVARIATE REPEATED MEASURES ANALYSIS.

<table>
<thead>
<tr>
<th>TEST FOR EFFECT CALLED: TYPE OF WORK (A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNIVARIATE REPEATED MEASURES F-TEST</td>
</tr>
<tr>
<td>SOURCE</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>ERROR</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>TEST FOR EFFECT CALLED: PEDALLING FREQUENCY (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNIVARIATE REPEATED MEASURES F-TEST</td>
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<tr>
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<tr>
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</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>ERROR</td>
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</table>

<table>
<thead>
<tr>
<th>TEST FOR EFFECT CALLED: INTERACTION (A X B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNIVARIATE REPEATED MEASURES F-TEST</td>
</tr>
<tr>
<td>SOURCE</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>A X B</td>
</tr>
<tr>
<td>ERROR</td>
</tr>
</tbody>
</table>

MULTIVARIATE TEST STATISTICS
WILKS' LAMBDA = 0.564
F-STATISTIC = 3.863  DF = 2, 10  PROB = 0.057
Fig. 12 Scatter plot of breathing frequency and minute ventilation relationship.
Legend: $fb$ and $VE$ values for positive work are represented by 'p'.
$fb$ and $VE$ values for negative work are represented by 'n'.
The regression lines between positive and negative did not differ ($p>0.05$) and can be described by a common equation $fb = 12.7 + 0.25(VE)$ with $r=0.40$ and $SEE = 4.4$. 
Breathing Frequency (bpm)

Minute Ventilation (l/min)
DISCUSSION

The 12 subjects who participated in this study represented a cross-section of healthy middle-aged men based upon pulmonary function tests, body mass index (although this tended to be on the higher side), ECGs, and the absence of resting and exercise-induced arterial desaturation. As predicted for these healthy subjects, the constant work rate of only 60 Watts for both positive and negative work was generally associated with reports of minimal exertion.

I EFFECTS OF STEADY-STATE CYCLING ON OXYGEN CONSUMPTION

Oxygen consumption during negative work was about 55% that for positive work at the same work output of 60 Watts. There was more variation in VO2 between subjects during negative than positive work. The lower oxygen consumption associated with negative work is well established in the literature [Abbott et al, 1952; Abbott and Bigland, 1953; Asmussen, 1953; Aura and Komi, 1986; Bigland-Ritchie and Wood, 1976; Hesser et al, 1977; Knuttgen et al, 1971a,b; Komi et al, 1987]. At correspondingly low work rates of 60 Watts, these studies reported that the energy cost measured by oxygen uptake during negative work ranged from 45 to 65% of positive work [Abbott et al, 1952; Bigland-Ritchie and Wood, 1976, Hesser et al, 1977; Knuttgen et al, 1971a,b]. The coefficients of variation or CV (standard variation divided by the mean)
reported in the literature for negative work range from 1.4 to 4.4 times those reported for positive work [Bigland-Ritchie and Woods, 1976; Dick and Cavanagh, 1987; Hesser et al, 1977; Knuttgen, 1986]. In this study, the average CV for negative work was about two and a half times that for positive work. The lower oxygen consumption can be explained by the higher "efficiency" of negative work [Abbott et al, 1952; Abbott and Bigland, 1953; Asmussen, 1953; Aura and Komi, 1986; Bigland-Ritchie and Wood, 1976; Hesser et al, 1977; Knuttgen et al, 1971a,b; Komi et al, 1987]. However, the higher coefficient of variation associated with negative work has not been explained in the literature.

In this study, three factors could have potentially influenced the greater variation observed during negative work. The first factor involves the novelty of negative work using cycle ergometry, even though all subjects had had three practice sessions and were deemed to have attained the necessary skill for the test sessions. However the work output appeared to fluctuate more during negative than positive work. More practice sessions may attenuate these fluctuations. The second factor is that negative work may demand more concentration from the subjects. Constancy of work output during negative work was prone to being disrupted during blood pressure measurements and when the subject responded to the breathlessness scale. Even though these interruptions were simulated closely during the practice session, more habituation
to negative work may decrease the concentration required during negative work. Further, by recording power output during exercise would directly establish any significant difference in variablility in work output between positive and negative work. The third factor could be related to differences in the degree of muscle co-contraction in non exercising muscles during positive and negative work. Anecdotally, negative work was often reported to require more attention to perform than positive work. Some subjects appeared to tense their arms and trunk muscles more than required despite use of a seat belt for stabilization. Although more practice sessions could also help address this difficulty, inclusion of these could increase the drop out and non-participation rate in the study. With the current procedure, subjects were required to come to the laboratory on five separate occasions over three weeks. Any increase in the frequency of attendance and the length of involvement could decrease the number of participants. In summary, oxygen consumption observed in this study was within the range reported for positive and negative cycle ergometry in the literature. The higher coefficient of variation during negative work could be due to the novelty involved in this activity compared with more conventional forward pedalling during positive work.

Banister and Jackson [1967] observed large variations in oxygen consumption when pedalling frequency varied during positive work on a cycle ergometer at a constant power output.
A subsequent study by Gaesser and Brook [1975] further illustrated this point. As observed in the present study, oxygen consumption increased with pedalling speed during positive work with oxygen consumption being greatest at the highest pedalling speed of 75 rpm. Less is known about the effect of pedalling speed on oxygen consumption during negative work performed at a constant work rate. Previous studies [Knuttgen et al, 1971a; Komi et al, 1987] have reported a gentle rise in VO2 with increasing work rate during negative work. The increase we observed in VO2 at 75 rpm could be explained by the recruitment of fast twitch fibers [Aura and Komi, 1986; Hansen et al, 1988; Komi et al, 1987; Luhtanen et al, 1987]. Furthermore, Knuttgen et al [1971a,b] reported lowest VO2, HR and VE at 60 rpm during negative work when compared to 20 and 100 rpm at a low work rate similar to that used in our study. This interesting finding, however, was not explained. Our work needs to be extended to study in detail the VO2 during negative work at intermediate pedalling frequencies such as 55 rpm. Even though VO2 at 55 rpm was not statistically different from 35 rpm, further study is needed to determine if a pedalling frequency of 55 rpm is more efficient than lower and higher pedalling frequencies using our model.

When VE and HR were plotted against VO2 during both positive and negative work, significant linear relationships were found (p<0.05). These results also showed that at a work rate of 60 Watts, VE and HR during both positive and negative
work increased correspondingly with VO2. However, the intercepts of the VE and VO2 regression lines differed between positive and negative work (p<0.05). Thomson [1971] reported comparable VE when comparing positive and negative work using a cycle ergometer at the same VO2. However, others have reported that both VE and HR were higher during negative than positive work when compared at the same VO2 [Dean and Ross, 1989; Knuttgen et al, 1971a; Knuttgen et al, 1971b]. The VE and VO2 relationship reported in the present study are similar to those reported in the literature [Dean and Ross, 1989; Knuttgen et al, 1971a; Knuttgen et al, 1971b]. However, studying a wider range of exercise intensities would enable us to examine these relationships more thoroughly.

II EFFECTS OF STEADY-STATE CYCLING ON HEART RATE

In this study, the heart rate response followed the same trends as VO2 during positive and negative work. Since VO2 and HR are highly correlated [Astrand and Rodahl, 1986; McArdle et al, 1986], this similarity could be expected. In general, the HR during negative work was about 85% that during positive work. Similarly, the lower HR measured at 55 rpm during negative work could be explained by the lower VO2. In turn, the lower VO2 is possibly explained on the basis of less muscle co-contraction elicited at 55 rpm, which could reduce peripheral vascular resistance, hence lower the heart rate.
III EFFECTS OF STEADY-STATE CYCLING ON MINUTE VENTILATION AND ITS COMPONENTS

Minute ventilation during both positive and negative was not different at 35 and 55 rpm followed by a significant increase at 75 rpm. Moreover, there was no interaction in this study reflecting a negligible difference in trend between positive and negative work. The lower VE at 55 rpm was also reported by Knuttgen et al [1971a, 1971b]. This phenomenon was likely related to lower metabolic demand at 55 rpm.

Changes in VE reflect change in its components, VT and fb. In the steady-state component of this study, the fb was statistically the same for all three pedalling speeds in both positive and negative work. Variation in VT therefore largely explained the change in VE. However, when VT and fb were plotted against VE during positive and negative work, significant positive linear relationships between VT and VE, and fb and VE were found (p<0.05). Furthermore, the regression equation for each of these relationships did not differ for positive and negative work (p>0.05). The potential significance of these findings, however, needs further clarification given that the ranges for all three variables, i.e, VE, VT and fb, were relatively small. To illustrate, the mean difference for VE between positive and negative work was 15 l/min and the mean difference for fb was only 2 br/min. In
addition, the mean increase in VT during exercise ranged from 18% to 32% of mean FVC. Thus, the change in VT could explain the increase in VE in this ventilatory range. Further, the lowest mean VE, observed at 55 rpm during negative work, could be explained by the low fb (Fig. 11).

The ventilatory responses observed in this study during low intensity exercise resemble those reported in the literature [Cunningham et al, 1986; Hey et al, 1966; Whipp and Pardy, 1986]. In theory, for a given VE, there is an optimal combination of VT and fb employed which minimizes the work of the respiratory muscles [Bellemare and Grassino, 1982; Clark and von Euler, 1971; Cunningham et al, 1986; Hey et al, 1966; Whipp and Pardy, 1986]. Ventilatory responses have been described as having two stages, namely Range 1 and Range 2, which enable the respiratory system to adapt efficiently to increasing demands imposed by exertion. Range 1 is characterized by a small change in fb with a linear increase in VT to account for the increase in VE observed during low levels of exercise i.e. associated with a VT of less than 50% of VC [Cunningham et al, 1986; Hey et al, 1966; Whipp and Pardy, 1986]. In addition, Range 1 is characterized by shortening of the expiratory duration (Te) with no change in inspiratory duration (Ti) [Clark and von Euler, 1971]. Range 2 is characterized by a relatively constant VT above 50% of VC, while fb accounts for most of the increase in VE associated with moderate to high intensities of exercise [Cunningham et
al, 1986; Whipp and Pardy, 1986]. Both Ti and Te are shortened in Range 2 (Clark and von Euler, 1971).

In the present study, the mean VT was below 50% of the mean FVC during both steady-state positive and negative work. In addition, the changes in fb and VT followed closely those described above for Range 1. The strong positive linear relationship between VT and VE in this study regardless of the type of muscle work, is consistent with the characteristics of Range 1 described by Hey et al (1966). The results of our study therefore showed that at a low work rate of 60 Watts, the VT and VE relationship during positive work is qualitatively similar to that during negative work for the three pedalling frequencies. The result contrasts that of Dean and Ross (1989) who observed rapid shallow breathing during negative work in the form of downhill walking on a treadmill. This difference may reflect the fact their subjects were weightbearing whereas ours were not. Thus, greater musculoskeletal afferent stimulation may have been involved in their study in addition to greater activity of the postural muscles to maintain stability during walking. Although Dean and Ross (1989) also examined healthy subjects, their protocol involved measurements taken after two minutes at a given walking intensity whereas measurements in our study were taken after at least five minutes of steady-state cycling.

The negligible change in fb observed in our study over
the three pedalling frequencies for each type of work probably reflects the relatively low intensity of the exercise, hence represents the flat plateau stage of Range 1. It is also possible that the negligible change in fb reflects entrainment of fb to exercise rhythm [Bechbache and Duffin, 1971; Hey et al, 1977; Kay et al, 1975; Paterson et al, 1986]. Entrainment of fb to exercise rhythm is characterized by adopting a fb which is a multiple (subharmonic frequency) of the exercise rhythm [Paterson et al, 1986]. The breathing frequencies in our study were comparable over the three pedalling frequencies for each type of work resulting in an overall mean fb of 18 br/min. The mean fb of 18 br/min was approximately the second, third and fourth subharmonics of pedalling frequencies 35, 55 and 75 rpm chosen in our study. It can then be argued that the subjects entrained their fb onto the subharmonic of the exercise rhythm. However, on closer examination of the individual data, only two subjects entrained their fb to 18 br/min which is a multiple of their exercise rhythm. Furthermore, the VT and VE relationship has a significant positive intercept which does not support any contribution of entrainment of fb to exercise rhythm [Whipp and Pardy, 1986]. In summary, the relationship of both fb and VT to VE during both positive and negative work can be described by the Range 1 ventilatory response described in the literature. However, to verify this conclusion Ti and Te will need to be measured in future studies.
In negative work, the increase in VE from baseline to steady-state exercise was relatively small compared to positive work (Fig. 7). This reflects the characteristics of negative work, i.e. metabolically less demanding and greater 'efficiency' compared with positive work. This change in VE during negative work was associated with relatively small changes in VT 0.85 l/br at baseline to 0.93 l/br at 35 and 55 rpm, and 1.12 l/br at 75 rpm (Fig. 9). In contrast, for positive work, the increase in VT were more marked from 0.81 l/br at baseline to 1.4 l/br at 35 and 55 rpm, and 1.57 l/br. Fig. 11 shows that for negative and positive work, fb increased statistically to the same extent from baseline to steady-state exercise. Thus, despite the difference in VE between positive and negative work at steady-state exercise, the ventilatory response from baseline to steady-state exercise at a power output of 60 Watts showed a comparable quantitative increase in fb for positive and negative work. The difference in VE for positive and negative work from baseline to steady-state exercise can therefore be explained by a differential increase in VT. For negative work, the increase in VE from baseline to steady-state exercise was largely effected by an increase in fb with relatively small increase in VT. In contrast, for positive work, the increase in VE from baseline to steady-state
exercise was effected by increases in both VT and fb. Thus, although a comparable quantitative increase in fb was observed, for positive and negative work this increase appears to be disproportionally high in negative work given its relatively low intensity compared to positive work. In addition, this observation is not consistent with the typical Range 1 ventilatory response that was evident in positive work. The predominant increase in fb during negative work at the onset of exercise has been reported by Dean and Ross [1989]. However, the mechanism for this ventilatory response to negative work is not well understood. Dean and Ross [1989] who observed rapid shallow breathing during downhill walking acknowledged that this response may be related to factors other than negative work. The results of the present study, however, support that negative work may indeed contribute. The explanation for this finding warrants more detailed investigation.

V EXERCISE RESPONSES OF OLDER SUBJECTS TO STEADY-STATE CYCLING

Individual variation in response to negative work was noted especially at the highest pedalling speed of 75 rpm. Two of the oldest subjects for example, showed a relatively high VO2, 1.0 and 1.2 l/min, during negative work at 75 rpm. When a box plot [Wilkinson, 1988] was used to map the distribution of VO2 at 75 rpm during negative work, the subject with a VO2 of
1.2 l/min was an outlier. Tests were repeated for these two subjects and the results of these were comparable to each of these subjects’ initial tests. Two factors could explain this interesting variant. First, one subject appeared tense throughout the test sessions particularly during negative work at 75 rpm. The subject needed frequent reminding to relax his upper body. This factor could increase the V02 due to isometric muscle work. The greater V02 observed for the other subject, however, was not apparently associated with an increase in upper body stabilization. An alternate explanation is that negative work for this subject was especially novel involving relatively more concentration and co-ordination to perform than for the other subjects. Shock and Norris (1970) reported that neuromuscular coordination generally decreases with age. Others also have reported a corresponding decrease in muscle torque at high velocities of muscle contraction (Grimby and Saltin, 1983; Larson et al, 1979; Shephard, 1987) and in the number of motor units (Grimby and Saltin, 1983). Vandervoort et al (1986) has reported that older subjects did not perform activities requiring rapid muscle contraction well. In this case, it is possible that other muscle groups not normally involved in performing negative work were recruited. This additional muscle work could explain the increase in V02. Another hypothesis is that age-related changes of the series elastic component reduce the muscle’s ability to harness elastic energy during negative work. Aging has been reported to induce degenerative changes in the fibro-elastic tissue.
[Shephard, 1987] which may also affect the series elastic component of muscle. Thus, older persons may lose the normal integrity of the fibro-elastic connective tissue, hence series elastic component, making it less able to perform negative work efficiently. This hypothesis was not examined in this study. Two patients with interstitial lung disease who were studied in our laboratory and who were similar in age to these two subjects did not show this exaggerated increase in VO2 at 75 rpm during negative work (Appendix D).

VI LIMITATIONS OF THE STUDY

Little is known about the biomechanics of cycling a motorized cycle ergometer such as that used in the present study. The exact proportions of positive and negative work performed are unknown. Studies are needed to investigate the biomechanics of positive and negative work performed on a motorized ergometer.

Because a small sample size of 12 subjects was used for this study, low statistical power or a high probability of Type II error can be assumed [Glantz, 1987; Shavelson, 1988]. In the present study, five variables were examined using a 2 by 3 (two types of muscle work by three pedalling speeds) factorial design with repeated measures on both factors. Computation of statistical power for each single contrast is complex. However, we observed 10 statistically significant findings out
of the 15 possible sources of variation consisting of two main
effects and the interaction for each of the five variables.
Thus, the overall statistical power in this study appears
adequate with 12 subjects. Effect size is the difference
between the two test values for a given dependent variable
divided by the standard deviation of the pre-test value
(Shavelson, 1988; Olejnik, 1983; Cohen, 1977). Large effect
size and high correlation between test values enhances the
overall statistical power (Olejnik, 1983; Cohen, 1977). With
the variable fb, no statistically significant effects were
detected. This may be explained by a small effect size as
defined by Cohen (1977). Because of the small differences
observed in fb among all test conditions, a larger sample size
may detect a significant difference. However, the small range
of values for VE that were observed and the characteristics of
ventilatory response associated with Range 1 can explain the
non-significant findings associated with fb.

Conversely, since multiple univariate F tests were used
to analyze the data in this study with an alpha level of 0.05,
an overall Type I error rate of about 20% is expected
theoretically. This rate of overall Type I error rate in
experiments is not uncommon in the literature (Chung et al,
1989). Decreasing the alpha for F tests for each of the five
dependent variables will lower the overall probability of
experimental Type I error but this is at the expense of
increasing the probability of a Type II error. An alternative
is to use multivariate ANOVA for repeated measures such as doubly multivariate ANOVA and multiple mixed model MANOVA, to reduce the probability of making a Type I error. However, criteria for selecting multivariate tests and subsequent F tests are not commonly agreed upon (Schutz and Gessaroli, 1985). For these reasons conventional univariate F tests were selected to analyze the data.

Two of the oldest subjects had the highest VO₂ and other associated measures during negative work at 75 rpm. Further studies using subjects older than sixty and pedalling speeds greater than 75 rpm could provide more insight into this interesting finding. A larger sample size would also further improve the statistical power and decrease the influence of skewed data inherent in a small sample size.

The motorized cycle ergometer was observed to produce a slight upward drift in frictional resistance at high speeds. This could be due to the vibration of the platform where the motor was mounted affecting the spring that regulates the tension. It could also be due to an increase in friction generated by prolonged high speed work. This potential problem was identified prior to data collection, thus care was taken to maintain the frictional resistance constant throughout the tests.

Additional measures including EMG of the upper body
might be useful to compare possible unmeasured muscle activity occurring during positive and negative work and during cycling at different pedalling frequencies. Such information would help to account for the performance of work extraneous to the experimental manipulation of interest.
CONCLUSIONS

The conclusions from this study are:

1) VO2, HR, VE and VT were greater during positive than negative work at a constant power output of 60 Watts performed on a cycle ergometer.

2) The fb was comparable between positive and negative work at power output of 60 Watts.

3) At a power output of 60 Watts, a pedalling frequency of 75 rpm during positive work was more demanding physiologically in terms of VO2, HR, VE and VT than 35 and 55 rpm.

4) At a power output of 60 Watts, a pedalling frequency of 75 rpm during negative work was more demanding physiologically in terms of VO2, HR, VE and VT than 55 rpm.

5) At a power output of 60 Watts, the slopes and intercepts of the regression lines for the VE and VO2, VT and VE, and fb and VE relationships were comparable for positive and negative work.

6) At a power output of 60 Watts, the slopes of the regression lines for the VE and VO2 relationship for positive and negative work were comparable while the intercept was
higher for negative work.

7) High pedalling frequencies such as 75 rpm are physiologically more demanding than lower pedalling frequencies such as 35 and 55 rpm.

8) The lower VO2, HR and VE during negative work are consistent with higher efficiency when utilizing predominately eccentric muscle contraction.

9) The higher VE during positive work could be explained by the higher VT because the fb was comparable for the two types of work. The resulting ventilatory response can be considered consistent with a Range 1 response.

10) The change in VE from baseline to steady state for positive work was effected by increases in VT and fb which is consistent with a Range 1 response.

11) The change in VE from baseline to steady state for negative work was predominantly effected by an increase in fb at pedalling frequencies at 35 and 55 rpm. At 75 rpm, an increase in fb also contributed to the increase in VE. This response is not consistent with the Range 1 response.

In summary, our data confirm and extend previous
work examining the ventilatory responses to negative work compared to positive work. On considering the effect of pedalling frequency on ventilation, we concluded VE was determined primarily by a change in VT because fb is not significantly different among the three pedalling frequencies between the two types of work. However, on considering the effect of negative versus positive work per se, we observed that changes in VE from baseline in this study was effected primarily by a disproportionate increase in fb in relation to VT. This finding sheds new light on the ventilatory responses described by Range 1 and 2 for low and high intensity exercise. Thus, further investigation is warranted in relation to the unique effect of the type of work versus pedalling frequency on ventilation. In addition to characterizing these different responses in greater detail, further study would help to shed light on the mechanism underlying these responses.
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Definitions and Comparisons of the Calculation of Exercise Efficiency

The following definitions of the calculation of exercise efficiency are based on the work of Whipp et al, 1969; Gaesser and Brooks, 1975; Hesser et al, 1977; and Stainsby et al, 1980.

Gross efficiency = \( \frac{\text{work accomplished}}{\text{energy expended}} \times 100\% \)

Net efficiency = \( \frac{\text{work accomplished}}{\text{energy expended above at rest}} \times 100\% \)

Work efficiency = \( \frac{\text{work accomplished}}{\text{energy expended above that in cycling without a load}} \times 100\% \)

Delta efficiency = \( \frac{\text{delta work accomplished}}{\text{delta energy expended}} \times 100\% \)

where \( W \) = caloric equivalent of external work performed
\( E \) = gross caloric output, including resting metabolism
\( e \) = resting caloric output
\( E_i \) = caloric output, loaded cycling
\( E_u \) = caloric output, unloaded cycling
\( W \) = caloric equivalent of increment in work performed
above previous work rate

\[ E = \text{Increment in caloric output above that at previous work rate} \]

The above definitions of efficiency can be calculated using the traditional method (based on oxygen uptake and respiratory exchange ratio) and the theoretical-thermodynamic method. Three assumptions \((P/O = 3; \ G \text{ for ATP} = -11 \text{ Kcal/mole}; \ \text{phosphorylative-coupling efficiency} = 60\%)\) have to be made when using the theoretical-thermodynamic method [Whipp et al, 1969]. The key difference among the efficiency definitions is the selection of the baseline correction factor which changes the estimates of energy expenditure and as a result the efficiency calculation.

The theoretical-thermodynamic method, however, cannot be used to validate any one particular method of efficiency calculation because, irrespective of the method, the estimation of energy expended by the subject is still obtained from oxygen consumption. When comparing the two methods, Gaesser and Brooks [1975] found no difference in the calculated efficiencies in two-thirds of the cases studied. In those that differed, the range of difference in efficiencies was between 0.2% -1.2%. The investigators concluded that since the traditional method considers the substrate utilized during exercise in the estimation of energy expenditure, this method may yield a more accurate measure of efficiency.
Of the four definitions of efficiency, work efficiency is viewed to be theoretically sound but difficult to obtain depending on the ergometer used. Delta efficiency is considered to be the most practical estimate of muscle efficiency. However, as pointed out by Hesser et al [1977], in calculations of both work and delta efficiency, unmeasured work at rest is ignored. Stainsby et al [1980] stated that when baseline subtraction was used in calculating efficiency, the validity depended on whether the baseline remained constant even at different work rates. In most activities studied, the baseline energy consumption varied directly with work rate. Hence the investigators cautioned against the use of baseline subtraction and promoted quantification and description of the determinants of energy expenditure.
APPENDIX B

The Contribution of Internal Work to Total Work Performed

Winter [1979] defined internal work as "work involving all potential and kinetic energy components, all exchange of energy within and between segments, and both positive and negative work done by the muscle". Since the numerator of the efficiency formula ignored the internal work done by the body, common every day activities such as level walking will have a zero efficiency and thus this formula is inadequate in measuring efficiency of human activities. With the inclusion of internal work into the calculation of efficiency, more meaningful and consistent efficiency estimates can then be made.

Wells et al [1986] in their study on concentric and eccentric cycling defined internal work as the work component required to raise and lower the limbs and to change their velocity. They measured internal work by directly using an eccentric cycle ergometer and calculated internal work from segmental energy changes using cinematography. They found no significant difference between the two approaches. The mean internal work rates (power output) obtained at pedal frequencies of 30, 60, 90 per minute were 11.5, 20, 62 W respectively. When the internal work rate was added to a positive external work rate (i.e. concentric cycling), the
algebraic sum of total work rate was increased. When the same procedure was applied to a negative external work rate (ie. eccentric cycling), the algebraic sum of total work rate was decreased. Wells et al therefore concluded that previous investigators had over-estimated the amount of negative work and underestimated the amount of positive work that was done by the musculature. Hence, the huge difference in efficiency reported previously between positive work and negative work is reduced when internal work is added to the numerator.

In summary internal work tends to be ignored during efficiency calculation. This leads to inaccurate efficiency values especially at high pedalling frequencies and low work rates. This finding therefore challenges the various efficiency values reported previously in the literature.
APPENDIX C

Borg's Scales of Subjective Perceived Exertion and Breathlessness during Positive and Negative Work with Special Reference to Patients with Cardiorespiratory Disease.

Many perceived exertion scales have been used to quantify subjective perception of exertion and thereby correlate this sensation to physiological responses [Borg, 1970; Borg, 1982; Jones et al, 1985; Killian et al, 1985; Leblanc et al, 1986; Mihevic, 1981; Silverman et al, 1988; Stubbing et al, 1983]. However, Borg scales have been reported to be superior to others [Jones et al, 1985; Mihevic, 1981; Silverman et al, 1988]. Mihevic [1981] concluded that multiple sensory inputs of local and central origin were integrated by the brain and gave rise to the subjective perception of exertion. This notion was supported by subsequent studies on exercise and ventilation in normal subjects and patients with lung disease [Jones et al, 1985; Leblanc et al, 1986; Stubbing et al, 1983; Silverman et al, 1988].

Borg's [1970, 1982] rating of perceived exertion (RPE) is an ordinal scale consisting of 15 points ranging from 6 to 20. Descriptive terms such as "very light", "hard", "very hard", are listed beside the odd numbers. Borg [1982] advocated the use of this scale to measure perceived exertion during exercise testing in patient as well as healthy populations. He
concluded that RPE is correlated with heart rate and blood lactate during exercise. These scales are potentially useful in monitoring the exertion of ILD patients because they have the same ability to detect added resistive or elastic loads as normal subjects [Burki et al, 1985]. Silverman et al [1988] reported that RPE was highly reliable and correlated well with physiological variables such as VE, HR, and VO2 during exercise of obstructive lung disease patients. These investigators found that RPE was more reproducible in repeated testing than physiological variables.

More recently, Borg [1982] proposed a modified scale with ratio properties. This scale ranged from 0-10 with descriptive terms such as "very weak", "strong", "very strong". Borg [1982] advocated this scale for assessing breathing difficulty and general discomfort during exercise. Jones et al [1985] reported perceived respiratory effort using this new scale was highly related to mouth pressure, inspiratory time and breathing frequency. Leblanc et al [1986] used this new scale to measure breathlessness in patients with cardiopulmonary disease. These investigators reported that breathlessness was related to respiratory muscle effort such as the sum of duty cycle, breathing frequency and inspiratory flow rate. Harver et al [1988] used this scale to evaluate breathlessness in ILD patients and normal subjects during progressive exercise tests. They found that Borg scores (0-10) were related linearly to minute ventilation in both groups of subjects, however, the
slope of the regression line was steeper in the ILD patients than normal subjects. Killian [1987] reported that breathlessness was inversely related to ventilatory capacity and inspiratory muscle strength. But, subjects with impaired ventilatory capacity and healthy subjects terminated exercise at similar levels of breathlessness as assessed by Borg’s scale (Killian, 1987).

In summary, both scales proposed by Borg [1970, 1982] have sound physiological bases and good measurement reliability. These scales correlated well with changes in physiological parameters during exercise in patients with cardiorespiratory disease and also showed good measurement reproducibility.
APPENDIX D

The Exercise Responses of Two Patients with Interstitial Lung Disease to Positive and Negative Work Performed on a Cycle Ergometer. A Case Report.

INTRODUCTION

I General Purpose

In the rehabilitation of disabled and/or older subjects, endurance training and efficient use of energy are treatment priorities. Although traditional approaches to improve endurance, strength and power may have demonstrable therapeutic value [Lertzman and Cherniak, 1976; Cockcroft et al, 1981; Komi, 1986], little information, if any, is available on optimizing energy utilization in patients with chronic disease.

We propose that the effectiveness of traditional endurance programs could be enhanced by incorporating parameters of exercise whereby the patient can conserve energy yet effectively perform a greater amount of work. Negative work (eccentric exercise) and rate at which work is performed are two examples of exercise parameters that could enhance the functional work capacity of patients with reduced physiologic reserves.
Interstitial lung disease (ILD) is a serious lung affliction which like chronic obstructive airway disease (COAD), can lead to severe functional impairment, morbidity and mortality. Limitations of the existing literature have hindered the characterization of the cardiorespiratory responses of ILD patients at rest and during exercise [Chung and Dean, 1989]. Given that symptoms of cardiorespiratory disease become more problematic for patients during physical stress than at rest, exercise testing can be considered an essential component of the clinical evaluation. However, the acute and especially long term exercise responses of ILD patients have not been well studied. The paucity of such information has hampered advances in the long term management of ILD and rehabilitation of patients with these diseases.

The focus of this preliminary investigation, therefore, was to examine negative work and pedalling frequency (speed) as parameters that could be used to optimize efficiency during exercise using cycle ergometer. Furthermore, the use of negative work and "efficient" pedalling speed might enable ILD patient to take part in active exercise programs with less strain on the cardiorespiratory system and at lower energy cost. However, this hypothesis needs to be further tested.
II Etiology and Prevalence of ILD

Various etiological factors are responsible for interstitial lung disease (ILD). ILD is comprised of over 130 diseases such as pneumoconiosis, extrinsic allergic alveolitis, sarcoidosis and chronic fibrosis [Demeter, 1986; Lenfant, 1980]. The disease can be localized, eg, lung abscess or suppurative pneumonitis, or diffuse, eg, inhalation of organic dusts or toxic fumes [Cherniack and Cherniack, 1983]. Various liver disorders, cigarette smoking and a genetic predisposition can also lead to fibrotic lung disease [Hammar, 1987]. No apparent cause, however, can be identified in the majority of patients with ILD [Hammar, 1987; Lenfant, 1980].

Sharma and Balchum [1983] reported various causes of ILD and their relative incidence. To summarize, fibrosis of the lung can result from bacterial, viral and fungal infections. In addition, lung fibrosis may be associated with rheumatoid and collagen diseases such as rheumatoid arthritis and systemic lupus erythmatosis. One to 9% of farming populations and 6-15% of pigeon breeders are afflicted with ILD. Several years ago, a National Institute of Health task force attempted to characterize the epidemiologic features of ILD [Lenfant, 1980]. Explanations for the epidemiological characteristics of ILD, however, have yet to be identified. Based on prevalence statistics for ILD, this task force projected hospital admissions for patients with nine of the most common
Interstitial lung diseases (eg. pulmonary sarcoidosis and asbestosis) in 1977 in the United States to be 142,500 [Lenfant, 1980]. For the same period, the projected number of hospital admissions for asthma patients was 32,000 [Lenfant, 1980].

III Pathophysiology and Clinical features of ILD

Approximately forty years ago, Austrian et al [1951] coined the term "alveolar-capillary block" to describe arterial hypoxemia in patients with fibrotic lung disease. Later, however, Finley et al [1962] suggested that the alveolar-capillary membrane in interstitial pulmonary disease was affected in a non-uniform manner leading to ventilation and perfusion (VA/Q) mismatch, and consequently, arterial hypoxemia. More recently, VA/Q mismatch has been reported to be the source of hypoxemia at rest in both mild and advanced fibrotic lung disease [Jernudd-Wilhelmsson, 1986; Spiro et al, 1981].

Interstitial lung disease is characterized by inflammation of the lung parenchyma which may resolve completely or progress to fibrosis [Snider, 1986]. Interstitial pulmonary fibrosis (IPF) refers to the latter, ie, fibrosis resulting from inflammation of the lung parenchyma which leads to the deposition of excess connective tissue. Because some ILD patients recover completely while others progress to chronic
fibrosis [Jernudd-Wilhelmsson, 1986], Snider [1986] considered IPF a subset of ILD. IPF can be subdivided into granulomatous or nongranulomatous types. Some common diagnoses associated with IPF are shown in the Figure.

Although patients with ILD form a heterogeneous group with respect to disease etiology, they share some similar clinical, radiological, physiological, and pathological features. Finucane and Prichard [1984] reported ILD patients have abnormalities in alveolar function consistent with morphological changes of interstitial infiltration and fibrosis, intra-alveolar exudate and alveolar replacement. Functionally, these abnormalities can lead to reduced lung volume, increased expiratory flow at mid lung volume and decreased lung distensibility, ie, a reduced lung volume change for a given pressure change [Finucane et al, 1984; Renzi et al, 1986; Risk et al, 1984; Spiro et al, 1981]. The characteristic shift of the pressure-volume curve (down and to the right) [Bates et al, 1989] reflects increased lung elasticity in ILD which resists lung expansion [Weitzenblum et al, 1983; Whipp and Pardy, 1986; Winterbauer and Hutchison, 1980]. Patients with ILD, however, typically have negligible air flow obstruction [Athos et al, 1986; Perez-Padilla et al, 1985]. The diffusion capacity for carbon monoxide (DLCO) is decreased and arterial blood gas analysis may reveal hypoxemia in the absence of hypercapnia [Huang et al, 1979; Snider, 1986]. These patients commonly complain of shortness of breath on exertion
[Burdon et al, 1983] and, in severe cases, at rest. This limitation can terminate a patient's gainful employment and severely compromise the quality of the patient's life.

Physiologic predictors of exercise limitation in patients with ILD are summarized in Table I. A decrease in DLCO [Anderson and Bye, 1984; Athos et al, 1986; Cotes et al, 1988; Finucane and Prichard, 1984; Risk et al, 1982b; Shaw and Kataria, 1982; Winterbauer and Hutchison, 1980] and reduced pulmonary function measures [Athos et al, 1986; Bye et al, 1982; Cotes et al, 1988; Finucane et al, 1984; Markos et al, 1988; Shaw and Kataria, 1982] have received the most support for predictors of abnormal exercise response, eg, arterial oxygen desaturation. However, Cotes et al [1988] reported when minute ventilation at oxygen uptake of 1 l/min during exercise was considered along with resting pulmonary function measures, the prediction of exercise limitation in ILD patients significantly improved.

The causes of morbidity and mortality of patients with ILD vary according to the specific underlying pathophysiology. In general, functional impairment has been reported to be least in patients with sarcoidosis and extrinsic allergic alveolitis; and most severe in idiopathic pulmonary fibrosis [Markos et al, 1988; McNicholas et al, 1986 Spiro et al, 1981; Weitzenblum et al, 1983].
IV Physiologic Responses of ILD Patients at Rest

The effect of sleep on arterial desaturation in patients with ILD is controversial. Oxygen desaturation during sleep has been reported in some ILD patients especially during periods of snoring and REM sleep [Bye et al, 1984; McNicholas et al, 1986; Midgren et al, 1987; Perez-Padilla et al, 1985]. However, others [McNicholas et al, 1986; Midgren et al, 1987] reported little change in oxygen saturation between wakefulness and sleep in these patients. The discrepancies among studies could be explained by the presence of sleep disturbances in those subjects. Thus nocturnal oxygen therapy does not appear to be necessary in those patients who have acceptable PaO2 levels when awake [McNicholas et al, 1986].

Table II summarizes the cardiorespiratory function of ILD patients during an awake restful state. In general, ILD patients have varying degrees of pulmonary and cardiovascular abnormalities at rest. Minute ventilation at rest tends to be normal or elevated [Dimarco et al, 1983; Leblanc et al, 1986; Lupi-Herrera et al, 1985; Renzi et al, 1986; Spiro et al, 1981] while the breathing pattern is rapid and shallow [Jernudd-Wilhelmsson et al, 1986; Renzi et al, 1986; Spiro et al, 1981]. The ventilatory dead space per breath and the oxygen consumption at rest are also elevated [Jernudd-Wilhelmsson et al, 1986]. Some ILD patients have decreased PaO2 at rest while PaCO2 tend to be decreased [Huang et al, 1979]. Resting heart
rate tends to be elevated [Spiro et al, 1981; Wasserman et al, 1979]. Pulmonary vascular resistance and pressure are also increased at rest while pulmonary capillary wedge pressure and mean systemic blood pressure are comparable to the healthy population [Havrylkiewicz et al, 1982; Jernudd-Wilhelmsson et al, 1986; Lupi-Herrera et al, 1985; Sturani et al, 1986; Wasserman et al, 1979; Weitzenblum et al, 1983].

V Physiologic Responses of ILD Patients at Submaximal Exercise

Table III summarizes the cardiorespiratory responses of ILD patients to submaximal exercise. Several investigators [Arita et al, 1981; Anderson et al, 1984; Burdon et al, 1983; Jernudd-Wilhelmsson et al, 1986; Lupi-Herrera et al, 1985; Merrhaeghe et al, 1981] have reported that minute ventilation is markedly increased in relation to VO2 in patients with ILD, even at very low work rates. This increase was effected by an increase in the breathing frequency and a decrease in tidal volume compared with normal subjects [Anderson and Bye, 1984; Bradley and Crawford, 1976; Bye et al, 1982; Dimarco et al, 1983; Jones and Rebuck, 1979; Merrhaeghe et al, 1981; Spiro et al, 1981].

Merrhaeghe et al [1981] suggested this breathing pattern reflected the use of a lower peak and total inspiratory muscle force which may effectively delay the onset of respiratory
muscle fatigue. Renzi et al [1986] observed increased VD/VT in exercising ILD patients and attributed it to the reduced tidal volume, increased breathing frequency and increased lung elasticity. Furthermore, an increased physiological dead space and VA/Q mismatch necessitated an increased ventilation to remove carbon dioxide.

Occlusion pressure [Hesser and Lind, 1983; Milic-Emili et al, 1975], an index of the neural output of the respiratory center, was reported to be increased in ILD patients [Meerhaeghe et al, 1981; Renzi et al, 1986]. The increase in respiratory drive may reflect increased afferent reflex activity from the lung or chest wall [Meerhaeghe et al, 1981; Renzi et al, 1986]. Some investigators [Aldrich et al, 1982; Dimarco et al, 1983] have concluded that neural mechanisms such as vagal stimulation and mechanoreceptor stimulation in the chest wall increase respiratory drive and thereby alter breathing pattern. The relative significance of these determinants of breathing pattern, however, is unclear [Shannon, 1986].

Patients with a low DLCO at rest tend to desaturate during exercise [Anderson and Bye, 1984; Risk et al, 1982a]. Spiro et al [1981] studied patients with fibrosing alveolitis and sarcoidosis, and reported that at submaximal work rates heart rate was significantly increased, stroke volume was reduced and cardiac output was normal. The disproportionate increase in
submaximal exercise heart rate similar to the resting tachycardia [Spiro et al, 1981; Wasserman et al, 1979] observed in ILD patients may reflect reduced saturation or increased pulmonary artery pressure. However these explanations do not rule out the effect of cardiorespiratory deconditioning in patients with ILD.

Cardiac hemodynamics can be compromised during exercise in ILD patients [Hawrylkiewicz et al, 1982; Lupi-Herrera, 1985; Sturani et al, 1986; Weitzenblum et al, 1983]. Risk et al [1982b] reported oxygen desaturation and decreased right ventricular ejection fraction in severe ILD patients. The right ventricular dysfunction, directly related to the severity of exercise-induced hypoxemia, was observed only during exercise and was reversed when patients breathed 100% oxygen [Hawrylkiewicz et al, 1982; Risk et al, 1982b]. Increased right ventricular work in ILD patients has also been reported [Sturani et al, 1986].

In summary, rapid shallow breathing is prevalent in ILD patients during submaximal exercise. The degree of oxygen desaturation observed depends on the severity of the disease. The ventilatory drive is apparently increased with an increase in VD/VT and no change in Ti/Ttot. Pulmonary vascular resistance may increase resulting in increased right ventricular work.
VI Rationale for Pilot Study

Young athletic subjects have been typically used in the literature to study physiologic responses using negative work and to study the effects of pedalling frequency. We are interested in the potential therapeutic benefit of energy-efficient negative work in the management of individuals with cardiorespiratory limitation, such as individuals with interstitial lung disease. We were particularly interested in determining the effect of negative work on individuals with ILD given that our work has shown negative work elicits a rapid shallow breathing response which is the typical response of these individuals to exercise. In addition, it is not known whether the individual with ILD who tends to be older could harness the potential energy stored in the series elastic component during negative work as effectively as younger athletic subjects.

This pilot study was therefore designed to look at the oxygen consumption, heart rate and the ventilatory responses of two ILD subjects during positive and negative work at 35, 55 and 75 rpm at a work rate of 60 Watts. The results of this preliminary work will provide the basis for future large scale studies.
VII Study Questions

1) To compare VO2, HR, VE, VT and fb of ILD subjects between positive and negative work.

2) To examine the effect of pedalling frequency on VO2, HR and VE in ILD subjects.

3) To compare in a general way the exercise responses of ILD subjects to those of healthy middle-aged men.
Figure Schematic classification of interstitial pulmonary fibrosis with common diagnosis in each category.

Interstitial Pulmonary Fibrosis

Granulomatosis
- Known Etiology
  - Hypersensitivity pneumonia
- Unknown Etiology
  - Sarcoidosis

Nongranulomatosis
- Known Etiology
  - Asbestosis, Silicosis
- Unknown Etiology
  - Idiopathic IPF, Fibrosis Alveolitis
**TABLE I**  
PREDICTORS OF EXERCISE LIMITATION IN PATIENTS WITH ILD.  
ADAPTED FROM CHUNG AND DEAN [1989].

<table>
<thead>
<tr>
<th>PREDICTOR</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Increased resting $P(A-a)O_2$</td>
<td>3, 23</td>
</tr>
<tr>
<td>2) Decreased DLCO</td>
<td>3, 6, 8, 11, 23, 25, 30</td>
</tr>
<tr>
<td>3) Reduced pulmonary function</td>
<td>3, 6, 8, 11, 25</td>
</tr>
<tr>
<td>(eg. TLC, FVC, FEV1)</td>
<td></td>
</tr>
<tr>
<td>4) Severity of chest X-ray findings</td>
<td>3</td>
</tr>
<tr>
<td>5) VE at VO2 of 1.0 l/min</td>
<td>8</td>
</tr>
</tbody>
</table>

$P(A-a)O_2$ - difference in oxygen partial pressure between alveolar space and arterial blood  
DLCO - index of diffusing capacity of the lung using carbon monoxide  
TLC - total lung capacity  
FVC - forced vital capacity  
FEV1 - forced expiratory volume in one second  
VE - minute ventilation  
VO2 - oxygen consumption
### TABLE II
RESTING CARDIORESPIRATORY PARAMETERS OF ILD PATIENTS COMPARED TO NORMAL SUBJECTS. ADAPTED FROM CHUNG AND DEAN [1989].

<table>
<thead>
<tr>
<th>RESPIRATORY PARAMETER</th>
<th>RESPONSE</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>VE</td>
<td>no change, increased</td>
<td>6, 10, 15, 17, 18, 22</td>
</tr>
<tr>
<td>RR</td>
<td>increased</td>
<td>5, 15, 22</td>
</tr>
<tr>
<td>Tidal volume</td>
<td>decreased</td>
<td>5, 22</td>
</tr>
<tr>
<td>V02, VD/VT</td>
<td>increased</td>
<td>15</td>
</tr>
<tr>
<td>PaO2</td>
<td>no change, decreased</td>
<td>6, 10-14, 29</td>
</tr>
<tr>
<td>PaCO2</td>
<td>decreased</td>
<td>10, 12, 13</td>
</tr>
<tr>
<td>Occlusion pressure</td>
<td>increased</td>
<td>10, 18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CARDIOVASCULAR PARAMETER</th>
<th>RESPONSE</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>increased</td>
<td>26, 28</td>
</tr>
<tr>
<td>PCWP</td>
<td>no change</td>
<td>13, 27, 29</td>
</tr>
<tr>
<td>PVR</td>
<td>increased</td>
<td>13, 15, 18, 27, 28</td>
</tr>
<tr>
<td>PAP</td>
<td>increased</td>
<td>13, 15, 18, 27-29</td>
</tr>
<tr>
<td>Mean systemic BP</td>
<td>no change</td>
<td>15</td>
</tr>
<tr>
<td>Cardiac Output</td>
<td>normal, decreased</td>
<td>15, 21</td>
</tr>
</tbody>
</table>

VE - minute ventilation
RR - respiratory rate
VD/VT - the ventilatory dead space per breath
PaO2 - arterial oxygen partial pressure
PaCO2 - partial pressure of arterial carbon dioxide
Occlusion pressure - an index of central respiratory drive
PCWP - pulmonary capillary wedge pressure is an index of left heart function
PVR - pulmonary vascular resistance
PAP - pulmonary arterial pressure
BP - blood pressure
### TABLE III
CARDIORESPIRATORY RESPONSES OF ILD PATIENTS COMPARED TO NORMAL SUBJECTS DURING SUBMAXIMAL EXERCISE. ADAPTED FROM CHUNG AND DEAN [1989].

<table>
<thead>
<tr>
<th>RESPIRATORY PARAMETER</th>
<th>RESPONSE</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>VE/VO2</td>
<td>increased</td>
<td>1, 2, 5, 6, 15, 18, 20</td>
</tr>
<tr>
<td>RR</td>
<td>increased</td>
<td>1, 4, 4, 10, 15, 16, 19, 20, 26</td>
</tr>
<tr>
<td>Tidal volume</td>
<td>decreased</td>
<td>1, 4, 5, 10, 16, 26</td>
</tr>
<tr>
<td>Duty cycle (Ti/Ttot)</td>
<td>no change or decrease</td>
<td>4, 5, 10</td>
</tr>
<tr>
<td>Ti, Ttot</td>
<td>decreased</td>
<td>2, 3, 9, 11, 22</td>
</tr>
<tr>
<td>VD/VT</td>
<td>increased</td>
<td>11, 15, 22</td>
</tr>
<tr>
<td>V/Q mismatch</td>
<td>increased</td>
<td>1, 3, 15, 23, 24, 29</td>
</tr>
<tr>
<td>Occlusion pressure</td>
<td>increased</td>
<td>26, 29</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CARDIOVASCULAR PARAMETER</th>
<th>RESPONSE</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>increased, no change</td>
<td>5, 26</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>decreased, no change</td>
<td>18, 26</td>
</tr>
<tr>
<td>Right ventricular ejection fraction</td>
<td>decreased</td>
<td>24</td>
</tr>
<tr>
<td>PAP</td>
<td>increased</td>
<td>13, 27</td>
</tr>
<tr>
<td>PVR</td>
<td>increased</td>
<td>27, 29</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>decreased, no change</td>
<td>11, 18, 26</td>
</tr>
<tr>
<td>RVSWI</td>
<td>increased</td>
<td>27</td>
</tr>
</tbody>
</table>

VE/VO2 - ventilatory equivalent for oxygen  
Duty cycle - inspiratory duration (Ti) divided by the sum of inspiratory duration and expiratory duration  
Ttot - sum of inspiratory duration and expiratory duration  
V/Q - ventilation-perfusion ratio  
RVSWI - right ventricular stroke work index
TABLE IV
REFERENCES FOR TABLES I-III


METHODS

The research design, equipment and measures, and general procedures are described on pages 30 to 39. The inclusion criteria for the ILD subjects into this pilot study were: (1) a clinical course consistent with interstitial lung disease; (2) chest radiographs characteristic of interstitial lung disease; (3) forced vital capacity between 45 to 75% of the predicted value (4) absence of clinical or spirometric evidence of airflow obstruction (FEV1/FVC>75% of predicted), ischaemic heart disease, or other conditions affecting exercise capacity.

Individual data are presented for the two ILD subjects studied. Some general comparisons of the responses of these subjects to those of the healthy middle-aged male subjects studied in the thesis are presented.
RESULTS

SUBJECT CHARACTERISTICS

The two ILD subjects, J.H., a 71 yr old man and M.H., a 64 yr old woman, were older than the mean age of the healthy subjects studied in the thesis. The BMIs for both ILD subjects were also higher than the healthy subjects.

The results of the pulmonary function tests are summarized in Table V. J.H. had a more severe restrictive pattern of lung disease with a FVC that was 50% of predicted. M.H. showed mild to moderate restrictive pattern with a FVC that was 61% of predicted. Their FEV1/FVC ratios showed no sign of airway obstruction and were higher than predicted which is consistent with a restrictive pattern of lung disease.

J.H. had moderately severe lung dysfunction and had to terminate the positive work tests between 2.5 to 3 minute of steady rate exercise due to shortness of breath. During the negative work tests, J.H. completed 4 minutes of steady rate exercise. The data presented for J.H. were therefore the test results at the last minute of steady rate exercise. M.H. was able to complete five minutes of steady-rate cycling during both positive and negative work as required.

J.H. had a Sa02 of 94.5% at rest and showed
desaturation during positive work to about 90% at 35 and 75 rpm and 93% at 55 rpm. During negative work, the SaO2 remained at 94% for the four minutes of steady-rate cycling. In contrast, M.H. had a SaO2 of 96% at rest and remained stable during cycling in both types of work.

J.H. reported a breathlessness score of 4.0 and 1.75 using Borg’s scale during positive and negative work respectively. M.H. reported a breathlessness score of 0.75 and 0.0 using Borg’s scale during positive and negative work respectively.

The raw data for VO2, HR, VE, VT and fb for the two ILD subjects during steady rate positive and negative work are shown in Table V.

OXYGEN CONSUMPTION

The VO2 for the two subjects during both positive and negative work generally followed the same trend as healthy middle aged men. J.H. who had relatively severe restrictive lung function had a VO2 close to one standard deviation above that for healthy subjects during positive work. M.H. who had mild to moderate restrictive lung function had a VO2 close to the mean value for healthy subjects. In negative work, both subjects had a VO2 close to the mean value for healthy subjects.
HEART RATE

J.H. had a heart rate response similar to the healthy subjects while M.H. has a higher heart rate response than healthy subjects. The trend was generally comparable to healthy subjects.

MINUTE VENTILATION

Minute ventilation tended to be higher for both subjects during positive work. For example, J.H. had a VE greater than one standard deviation above the mean for healthy subjects at 75 rpm during positive work. In contrast, during negative work the VE tended to be closer to the mean VE of healthy subjects for both ILD subjects. The VE was comparable to the healthy subjects during positive and negative work.

TIDAL VOLUME

The tidal volume tended to be smaller for M.H. while VT for J.H. was close to the mean value for the healthy subjects. The VT response tended to follow the same trend as the healthy subjects during positive and negative work.
BREATHING FREQUENCY

The breathing frequency tended to be higher in both subjects and was greater than one standard deviation above the mean for the healthy subjects, during the more demanding positive work. During negative work, the breathing frequency for both ILD subjects was closer to the mean value for healthy subjects.
### TABLE V
RESULTS OF PULMONARY FUNCTION TESTS AND ANTHROPEMETRIC DATA OF ILD SUBJECTS

<table>
<thead>
<tr>
<th>SUBJECT</th>
<th>SEX</th>
<th>AGE (years)</th>
<th>WEIGHT (kg)</th>
<th>HEIGHT (cm)</th>
<th>BMI (kg/m.m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.H.</td>
<td>Male</td>
<td>71</td>
<td>111.1</td>
<td>189.0</td>
<td>31.1</td>
</tr>
<tr>
<td>M.H.</td>
<td>Female</td>
<td>64</td>
<td>86.2</td>
<td>173.0</td>
<td>28.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>FEV1 (l)</th>
<th>FEV1% (%)</th>
<th>FVC (l)</th>
<th>FVC% (%)</th>
<th>RATIO (%)</th>
<th>RATIO%</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.H.</td>
<td>1.98</td>
<td>60</td>
<td>2.48</td>
<td>50</td>
<td>80.0</td>
<td>119</td>
</tr>
<tr>
<td>M.H.</td>
<td>1.80</td>
<td>72</td>
<td>2.08</td>
<td>61</td>
<td>86.5</td>
<td>119</td>
</tr>
</tbody>
</table>

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### TABLE VI
SUMMARY OF EXERCISE TEST RESULTS OF TWO ILD SUBJECTS

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>SUBJECT</th>
<th>POSITIVE WORK (rpm)</th>
<th>NEGATIVE WORK (rpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>35</td>
<td>55</td>
</tr>
<tr>
<td>V02 (l/min)</td>
<td>M.H.</td>
<td>.94</td>
<td>.96</td>
</tr>
<tr>
<td></td>
<td>J.H.</td>
<td>1.28</td>
<td>1.29</td>
</tr>
<tr>
<td>V02 (ml/kg/min)</td>
<td>M.H.</td>
<td>10.9</td>
<td>11.1</td>
</tr>
<tr>
<td></td>
<td>J.H.</td>
<td>11.5</td>
<td>11.6</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>M.H.</td>
<td>122.8</td>
<td>123.2</td>
</tr>
<tr>
<td></td>
<td>J.H.</td>
<td>100.1</td>
<td>99.4</td>
</tr>
<tr>
<td>VE (l/min)</td>
<td>M.H.</td>
<td>30.5</td>
<td>27.5</td>
</tr>
<tr>
<td></td>
<td>J.H.</td>
<td>36.2</td>
<td>41.8</td>
</tr>
<tr>
<td>VT (l/br)</td>
<td>M.H.</td>
<td>1.13</td>
<td>1.11</td>
</tr>
<tr>
<td></td>
<td>J.H.</td>
<td>1.35</td>
<td>1.52</td>
</tr>
<tr>
<td>fb (br/min)</td>
<td>M.H.</td>
<td>27.0</td>
<td>24.8</td>
</tr>
<tr>
<td></td>
<td>J.H.</td>
<td>26.8</td>
<td>27.5</td>
</tr>
</tbody>
</table>
DISCUSSION

I  Effects of Cycle Ergometry on Oxygen Consumption

In general, the exercise responses of two ILD subjects followed the same general trend as the middle-aged healthy subjects studied in the thesis. J.H. who had relatively severe lung disease had a greater VO2 and VE during positive work. The increase in VE could be due to inefficient gas exchange while the increase in VO2 could be partially due to increased oxygen cost to operate the ventilatory pump. During negative work, VO2 and VE for both subjects were similar to the mean VO2 and VE for the healthy subjects.

II  Effects of Cycle Ergometry on Heart Rate

The ILD subjects reported a lower general activity level and greater physical exertion in performing activities of daily living than our healthy subjects. Thus we predicted these two individuals to have a higher HR compared to the healthy subjects during rest and exercise [McArdle et al, 1986; Astrand and Rodahl, 1988]. Indeed M.H. had an elevated HR response relative to the healthy subjects. However, J.H. had a lower heart rate response than expected and was comparable to the mean value for the healthy subjects. Investigation into the heart rate response of J.H. had been initiated by the referring physician. No apparent cause for this heart rate
response had yet been forwarded.

III Effects of Cycle Ergometry on Minute Ventilation and its Components

The minute ventilation of the two ILD subjects especially J.H. was greater than healthy subjects. This likely reflected a decrease in the efficiency of the ventilatory pump [Whipp and Pardy, 1986]. Tidal volume during positive work was similar to that of the healthy subjects. However the VT/FVCX was about 60% for J.H. and 54% for M.H. The breathing frequency was also higher than for the healthy subjects during positive work. This could be explained by the lower VC in the ILD subjects and hence early encroachment into Range 2 during the more demanding positive work when compared to the healthy subjects. In contrast, the VE during negative work was only slightly greater than the healthy subjects. The absolute VT was similar or slightly higher than the healthy subjects implying a higher but below critical VT/VC ratio, for the Range 2 ventilatory response. Hence the fb was only slightly higher due to the greater ventilatory demand on the two ILD subjects.

In summary for the two ILD subjects during positive work, their physiological responses during exercise were elevated compared to healthy middle-aged subjects. Even at the
low work rate of 60 Watts, one ILD subject had difficulty completing the positive work protocol. In contrast, during negative work at the same work rate, both subjects were able to cycle longer and with lower physical exertion.

V Limitations

The number of ILD subjects was small in this preliminary report on exercise responses during positive and negative work. The BMI of the two ILD subjects were also higher than the mean value for the healthy subjects. Further, one subject was male and the other female, both of whom were older than the mean age for the healthy male subjects. Thus, we could only glean general trends between the two ILD subjects and the 12 healthy men.

This preliminary work verified the suitability of our research design for the inclusion of subjects with ILD, and that steady-rate work may be maintained by individuals with significant disease. Future trials are planned to extend this work.

VI Clinical Implications

Since negative work elicited lower physiological responses and ILD subjects may be able to exercise longer performing this type of work, the role of negative work in
exercise testing and training of ILD subjects warrants more
detail study.