COMPARISON OF CARDIAC OUTPUT DETERMINANTS IN RESPONSE TO PROGRESSIVE UPRIGHT AND SUPINE EXERCISE IN CYSTIC FIBROSIS PATIENTS

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PART II: EXPERIMENTAL STUDY

In memory of Steve Rossen

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ABSTRACT

The reduced maximal oxygen uptake (VO_2max) generally observed in cystic fibrosis (CF) patients is related to disease severity and can be attributed to limitations of pulmonary and cardiac origin, although the nature of the latter remains to be determined. This study was designed to characterize the cardiac output (Q_c) response to progressive submaximal upright (U) exercise in CF patients. Secondly, the Q_c adjustments were compared to those of similar supine (S) exercise, in an attempt to assess myocardial accomodation to the enhanced ventricular preload in the S posture. Thirty-one CF patients classified as mild (gr.II), moderate (gr.III) or severe (gr.IV) on the basis of FEV_1, as well as 11 age-matched controls (gr.I) had Q_c determined (CO_2 Rebreathing) at rest, and submaximal exercise corresponding to 30,50 and 75% VO_2max in U and S positions. VO_2max was similar in groups I,II and III, but lower in gr.IV ($p \leq .01$). Q_c generally increased with exercise intensity in both U and S positions, although gr.IV plateaued at 50% VO_2max (S). Maximal stroke volume index (SI) was achieved at 50% VO_2max (U) in all groups, except gr.IV and at 30% VO_2max (S) in all groups. The change from U to S posture resulted in a significant ($p \leq .05$) increase in SI at rest and for every submaximal exercise in gr.I, but not in CF patients, independent of disease severity eg(Rest:gr.I:27±7(U) vs 39±8(S); gr.II:24±5vs28±10;

gr.III:18±4 vs 22±5; gr.IV:17±4 vs 20±6 ml/bt/m^2). These observations suggest a limitation in ventricular volume accomodation in CF patients which becomes apparent under the S exercise conditions.

RESUME

La réduction de la consommation maximale d'oxygène (VO_2max) observée généralement dans les patients atteints de fibrose kystique (FK) est reliée à la sévérité de la maladie et peut etre attribuée à des limitations pulmonaires aussi bien que cardiaques, quoi que la nature de ce dernier reste à determiner. Le but de ce projet était de caractériser la réponse du débit cardiaque (Q_c) à un exercise d'intensité progressive et scus-maximale en position debout (D) chez les patients atteints de FK. Aussi, ces réponses de Q_c ont été comparées aux reponses obtenues pendant des exercices similaires en position couchee (C) dans le but de juger de l'accomodation myocardiale par rapport à l'augmentation du retour veineux dans cette position. Trente et un patients atteints de FK, classifiés sur une base de FEV_1 comme étant léger (gr.II), moyen (gr.III) ou sévère (gr.IV) et 11 contrôles (gr.I) du même âge ont complété une détermination de Q_c (CO_2 Rebreathing) au repos et avec exercice sous-maximal correspondant à 30,50 et 75% du VO_2max dans des positions D et C. Le VO_2max était similaire pour les groupes I,II et III, mais était réduit pour le gr.IV. Une augmentation de l'intensité de l'exercice était généralement accompagnee par une augmentation de Q_c dans les deux positions quoi que le Q_c du gr.IV à cessé d'augmenter à 50% VO_2max (C). L'index du volume d'éjection systolique (SI) maximale a été atteint à 50% VO_2max (D) dans tous les

groupes excepté le gr.IV, et à 30% VO_2max (C) dans tous les groupes. Comme prévu, le passage de la position D à la position C à produit une élévation significative du SI au repos et pour tous les niveaux d'exercices sous-maximaux dans le gr.I, mais pas pour les patients atteints de FK, indépendamment de la sévérité de la maladie (ex. Repos: gr.I:27±7(D)vs39±8(C); gr.II:24±5vs28±10; gr.III:182414vs 22±5; gr.IV:17±4vs20±6 ml/bt/m^2). Ces observations suggèrent une limitation de l'accomodation du volume ventriculaire chez les patients atteints de FK, cela devenu apparent sous conditions d'exercice dynamique debout.

Part I: REVIEW OF RELATED LITERATURE

1.0 GENERAL PERSPECTIVE OF CYSTIC FIBROSIS

Cystic fibrosis is the most common lethal genetic disease in caucasian children (Merritt et al. 1962; Matthews et al. 1980). Despite its prevalence, only recently has the location of the genetic defect been specified. Localization of the cystic fibrosis gene to the long arm of chromosome 7 has been suggested and confirmed through DNA probe studies (Tsui et al. 1985; Wainwright et al. 1985). The result of this discovery will be improved diagnosis, and genetic counselling of persons carrying the cystic fibrosis gene and more effective treatment of the disease manifestations (Fisher & Wood-Klinger, 1985).

1.1 Definition

Cystic fibrosis is an inherited disorder of the exocrine secretory glands (diSant'Agnese, 1956; Lipow & McQuitty, 1987). The exocrine gland dysfunction involves both the mucous and non-mucous producing glands found in many organs throughout the body (diSant'Agnese et al. 1953).

Dysfunction of the non-mucous producing exocrine glands results in secretion of an excessive amount of sodium and chloride by the gland (diSant'Agnese & Powell, 1962; Wood et al. 1976; Blythe & Farrell, 1984). These abnormal

electrolyte concentrations may be found in the secretions from the sweat glands, lacrimal glands, salivary glands (both parotid and submaxillary), pancreas, and bronchial epithelium (diSant'Agnese, 1956; Lipow & McQuitty, 1987). Alterations of the electrolyte concentrations of the tears and salivary secretions are minimal (Gugler et al. 1967; Goodchild & Dodge, 1985). Most prominent is the elevated sodium and chloride electrolyte concentrations found in the secretion from the sweat glands (diSant'Agnese, 1956). Because of the consistent presence of high sodium chloride levels in the sweat of cystic fibrosis patients, this phenomena has become a cardinal indicator in the diagnosis of cystic fibrosis.

More significantly, dysfunction of the mucous producing glands leads to secretion of an abnormally thick and sticky mucous. Due to the altered physicochemical characteristic of the mucous, it tends to precipitate in the glandular duct, obstructing the secretory flow. Obstruction can be seen in the ducts of the pancreas, lung bronchi, small intestine, and occassionally in the liver (diSant'Agnese, 1956; Shwachman, 1975), ultimately disturbing the function of the organ involved.

1.2 Historical Perspective

Cystic fibrosis was first recognized as a disease entity by Fanconi in 1936 (diSant'Agnese, 1956; Matthews et al. 1980) and described in detail by Dorothy Anderson two years later (Anderson, 1938). Anderson provided the original nomenclature, "cystic fibrosis of the pancreas" in reference to the syndrome that included pancreatic dysfunction and was often associated with lung disease (Anderson, 1938). At that time, "cystic fibrosis of the pancreas" seemed to affect mostly young infants and was inevitably fatal. Subsequent studies by Farber identified a variety of clinical and pathological features concurrent with those symptoms of "cystic fibrosis of the pancreas". It became apparent that cystic fibrosis had a more systemic nature than originally believed. Farber suggested the name "mucoviscidosis" which included dysfunction of all mucous secreting glands (Farber, 1944). However, in the early 1950's, it was discovered that patients who had this general mucous gland dysfunction also had an altered electrolyte composition of the secretion from the sweat and salivary glands (diSant'Agnese, 1953; diSant'Agnese, 1956). As a result of this new finding, there was a re-assessment of the symptoms associated with the disorder and another change in nomenclature. Since then, the name "cystic fibrosis" has

been most widely accepted in describing the disorder that disturbs most, if not all exocrine glands.

Although research of cystic fibrosis disease is omnipresent, the basic lesion(s) that could account for the complex of symptoms manifest in any cystic fibrosis individual remain(s) undocumented. Until the basic pathology is fully understood the traditional "cystic fibrosis" heading will be retained (Phelan, 1982; Matthews & Drotar, 1984).

Research investigating the nature of cystic fibrosis has allowed for a better understanding of the complete pathophysiology of the disorder. The evolution of the most appropriate description of the disorder is a reflection of a more complete understanding of the disorder. The effect of this is evident clinically, where earlier diagnosis, more effective management, a better prognosis and consequently an increase in the life expectancy of a person with cystic fibrosis are generally seen (Huang et al. 1970; Crozier, 1974; Orenstein et al. 1977; Huang et al. 1987).

In the 1930's and 1940's, it was estimated that more than 80 % of children afflicted with cystic fibrosis died before 5 years of age (George & Norman, 1971; Goodchild & Dodge, 1985). Data from the 1980's now indicate a 50 % survival to 22 years (Thompson, 1980; Huang et al. 1987). While effective treatment and preventive approaches to

cystic fibrosis disease have evolved, the genuine etiology of the disease remains uncertain.

1.3 Etiology

There now appears to be general agreement that cystic fibrosis is a genetic disease.

Epidemiological data indicates a genetic etiology consistent with an autosomal recessive mode of inheritance (Roberts, 1960; Brunecky, 1972; Thompson, 1980). Incidence of cystic fibrosis among siblings of cystic fibrosis patients respects the theoretical 25 percent expected by an autosomal recessive pattern (Brunecky, 1972; Thompson, 1980; Romeo et al. 1985). Reports of cystic fibrosis incidence in other relatives, such as mothers and cousins, show reasonable agreement with theoretical figures. In fact, an incidence of 1 : 46 in children of known cystic fibrosis mothers was reported in studies from England and Czechoslovakia (Roberts, 1960; Brunecky, 1972), which is not significantly different from the theoretical 1 : 40 ratio ascertained from genetic transmission patterns.

Inheritance of cystic fibrosis is generally consistent with it being a recessive defect caused by mutation at a single autosomal loci (Conneally et al. 1973; Schaap & Cohen, 1976). Recently, the cystic fibrosis gene has been localized to the long arm of chromosome 7 (Colten, 1986).

This localization is based on studies that reported linkage between the cystic fibrosis gene and the enzyme paraoxonase (PON) (Tsui et al. 1985; Eiberg et al. 1985) and with anonymous DNA probes which have been assigned to chromosome 7 (Wainwright et al. 1985; Knowlton et al. 1985; White et al. 1985). Other studies, however, have documented linkage of the cystic fibrosis gene to chromosome 21 (Fisher & Wood-Klinger, 1985). The apparent discrepancy may be explained by the possibility that several loci are involved in cystic fibrosis disease (Fisher & Wood-Klinger, 1985). Furthermore, genetic incongruencies raised by some familial and population studies limit the credibility of the single gene defect hypothesis. Firstly, several studies have found an excess (>25 %) of affected siblings (Roberts, 1960; Brunecky, 1972). Secondly, calculations indicate a higher carrier frequency than can be explained by the single gene defect theory (Romeo et al. 1985). Although the high carrier frequency may reflect a heterozygote survival advantage (Romeo et al. 1985; Sturgess et al. 1985), both arguments taken together can be explained by the existence of an interactive multiple allele model of inheritance (Conneally et al. 1973; Schaap & Cohen, 1976; Lloyd-Still, 1983).

While localization of the genetic defect in cystic fibrosis has important implications with respect to

diagnosis and genetic counselling, the gene product and basic defect remain to be identified.

Results from investigations conducted on humans and animal models have lead to the suggestion that the basic defect in cystic fibrosis disease involves problems in regulating intracellular calcium, sodium transport, and/or ciliary motility (Spock et al. 1967; Mangos et al. 1967; Sutcliffe et al. 1968; Gibson et al. 1971).

Electrophoretic analysis of salivary mucous, taken from cystic fibrosis and normal human subjects, has identified the presence of calcium as the distinguishing feature between the salivary mucous of the diseased and healthy subjects (Gugler et al. 1967; Gibson et al. 1971). In fact, addition of a calcium chloride solution to normal salivary mucous produces an electrophoretic pattern identical to the pattern of the cystic fibrosis mucous. Conversely, removal of calcium from the cystic fibrosis saliva, using a calcium chelator, produces an electrophoretic pattern like that of normal saliva.

Results from human studies completed by Sutcliffe et al. in 1968, and confirmed by Gibson et al. in 1971 revealed that following iontophoresis of calcium into the skin of normal healthy subjects, and immediate analysis of collected sweat, there was an increased sodium concentration, similar to that found in the sweat of cystic fibrosis patients.

In general, the permeability of mucous is increased by the presence of calcium (Gibson et al. 1971). Moreover, the presence of calcium in cystic fibrosis mucous distinguishes it from mucous from healthy controls. Thus it is probable that the mucous lining the cystic fibrosis sweat duct is hyperpermeable, and this could possibly explain the elevated levels of sodium and chloride in the cystic fibrosis sweat (Gibson & Cooke, 1959; Anderson & Freeman, 1960).

The existence of a "sodium transport inhibitory factor", in saliva and sweat of cystic fibrosis patients, has been documented (Mangos et al. 1967), and is believed to be responsible for the electrolyte abnormalities found in these secretions.

Following retrograde perfusion of cystic fibrosis saliva into the parotid gland of rats, there was an increase in the sodium concentration of the saliva secreted from the rat (Mangos et al. 1967). This abnormality was not seen, however, when normal human saliva was perfused, in which case, the composition of the rat saliva was the same as the saliva samples collected from intact rat parotid glands.

Detailed investigation of the mechanism responsible for the inhibition of sodium reabsorption is lacking. While a defect in the ductal reabsorption of sodium could account for the elevated sodium concentration in the sweat, it would not explain other electrolyte abnormalities, such as the high chloride concentration found in the exocrine secretions

(Anderson & Freeman, 1960; Sutcliffe et al. 1968). A disturbance in the regulation of a single electrolyte, however, could initiate imbalances in other electrolytes due to the cooperative and interdependent nature of the membrane exchange proteins. Recent work examining chloride channels in cystic fibrosis patients provides strong evidence that the regulatory mechanism for transmembrane chloride transport could be the major defect in cystic fibrosis disease (Quinton, 1983). These findings, undoubtedly will dictate the direction for future investigations into the pathogenesis of cystic fibrosis.

A second factor has also been proposed to explain the pathogenesis of cystic fibrosis. The factor, referred to as "ciliary dyskinesia factor", was discovered by Spock in 1967 in an experiment that involved exposing rabbit tracheal mucosa to human cystic fibrosis serum (Spock et al. 1967). In this study, serum from a cystic fibrosis patient was applied to a specimen of rabbit tracheal epithelium. Within five to ten minutes a disturbed ciliary beat was apparent. In oppositon to this finding, the ciliary beat remained unaffected when exposed to normal human serum.

Ciliary dyskinesia has also been observed following exposure of oyster gill cilia to cystic fibrosis serum (Lockhart et al. 1968), as well as, a cell-free medium of cultured skin fibroblasts taken from either cystic fibrosis

homozygotes or heterozygotes (Danes & Bearn, 1972; Beratis et al. 1973).

At present, a mechanism for the production of the disturbed ciliary motion, observed in various ciliary systems upon exposure to cystic fibrosis serum, remains to be identified. In light of the general observation of disturbed electrolyte levels, it may be proposed that the ciliary dyskinesia factor prevents the normal exchange of ions necessary for generation of the ciliary beat. Consequently, mucous clearance of the glands and ducts is impaired.

1.4 Incidence

The most commonly quoted incidence of cystic fibrosis is 1 in 2000 live births (Conneally et al. 1973; Warwick, 1978). This value has been generally reported in studies from North America and pertains to caucasian populations. A similar rate has been reported in most European countries (Roberts, 1960; Brunecky, 1972; Warwick, 1978; Romeo et al. 1985), however, a lower incidence of cystic fibrosis has been reported in European countries such as Sweden, Finland, and Germany (Brunecky, 1972; Warwick, 1978; Thompson, 1980). Cystic fibrosis is even more rare in non-caucasian populations e.g. orientals and negroes, where incidence of 1 in 90,000 and 1 in 17,000 respectively, have been reported

(Oppenheimer & Esterly, 1968; Conneally, 1973; Thompson, 1980). Although a significant race-specificity is apparent, the discrepancy in disease frequency may result from variable environmental influences on the expression of the disease (Gordis, 1973).

Males and females appear to be affected equally (Phelan, 1982; Sturgess, 1985). This lack of gender specificity indicates that the cystic fibrosis gene defect is not sex-linked.

On the basis of the autosomal nature of cystic fibrosis and an incidence of 1 in 2000, the frequency of heterozygotes is estimated to be 1 in 20, or 5 % of the population (Crozier, 1974; Matthews & Drotar, 1984).

2.0 PATHOLOGY OF CYSTIC FIBROSIS DISEASE

Multiple organ systems are involved in the pathogenesis of cystic fibrosis disease. Dysfunction in the lungs, pancreas, intestinal tract, liver, salivary glands, male reproductive system and sweat glands have all been linked to cystic fibrosis disease (diSant'Agnese, 1967; Phelan, 1982). Incomplete development and obstruction of the vas deferens and/or the epididymis in the male reproductive tract results in sterility in over 95% of the male cystic fibrosis patients (Crozier, 1974; Matthews & Drotar, 1984). Female cystic fibrosis patients are also less fertile than normal which most likely results from the presence of abnormal mucous in the cervix (Matthews & Drotar, 1984). Secretions from the salivary gland may have an altered composition and the salivary ducts may be obstructed. The consequences of the pathologies observed in the salivary glands and reproductive tract are minimal. In comparison, the dysfunction observed in the lungs, pancreas, heart and intestinal tract, contribute significantly to the morbidity and mortality of cystic fibrosis patients.

2.1 The Gastrointestinal System

Function of the gastrointestinal system is compromised in approximately 85 percent of those patients with cystic

fibrosis disease (Shwachman, 1975; Park & Grand, 1981; Dodge, 1986). Pathological changes in the histology of the exocrine glands and cells of the intestinal tract, the pancreas, and in the liver and biliary system are apparent at autopsy. Obstruction of small ducts and glands by a viscid secretion appears to be common to all the gastrointestinal organs (diSant'Agnese, 1956). As a result of this obstruction, their function may be limited which in turn may lead to malabsorption and malnutrition (Chase et al. 1979; Dodge, 1986).

2.1.1 The Intestinal Tract

Intestinal involvement in cystic fibrosis is consecutive to the presence of mucous secreting glands in the intestinal lining and their imminent secretion of a viscid mucous. The excessive secretion and accumulation of this thick mucous results in obstruction of the mucous glands, and on a more gross scale, the intestinal lumen (diSant'Agnese, 1956; Crozier, 1974).

Early studies using light and electron microscopy to examine tissue sections of the small intestine report normal columnar and goblet cell structures, and a typical microvilli border in the cystic fibrosis population (Thomaidis & Arey, 1963; Freye et al. 1964). Despite the ordinary structural appearance of the intestinal lining, a

thick luminal coating of inspissated mucous may be present (Freye et al. 1964; Anderson et al. 1987). Similar studies completed on the large intestine generally reveal a normal number of goblet cells in the cystic fibrosis patients when compared to sibling controls, although the epithelial lining may be flattened and disorganized and the crypt lumen dilated (Park & Grand, 1981). Typically, abdominal radiographs of cystic fibrosis patients with gastrointestinal pathology will show evidence of thickened intestinal folds and dilatation of intestinal loops which may even be visible or palpable through the abdominal wall (Taussig et al. 1973, Park & Grand, 1981).

The earliest clinical complication of the intestinal disorder in cystic fibrosis disease is "meconium ileus" (Thomaidis & Arey, 1963; Crozier, 1974; Matthews & Drotar, 1984). Meconium is an accumulation of desquamated cells, mucous and bile in the intestinal tract during fetal life. In health, the meconium is discharged shortly after birth. Failure to pass the meconium shortly after birth indicates obstruction of the intestine, most often in the terminal ileum (Crozier, 1974; Shwachman, 1975).

Retrospective studies conducted to assess the predominance of intestinal involvement in cystic fibrosis disease indicate that meconium ileus is present in 7 to 25 percent of infants born with cystic fibrosis (McPartlin et al. 1973; Crozier, 1974; Wood et al. 1976). The presence of

meconium ileus in a neonate indicates the need for further diagnostic tests to confirm the presence of cystic fibrosis disease.

The mechanism responsible for the intestinal obstruction remains uncertain. The most reasonable explanation for the inspissated matter is a combined effect of insufficient pancreatic secretion of digestive enzymes and bicarbonate for proper digestion, as well as an excessive quantity of intestinal mucous (Park & Grand, 1981).

The possibility that an abnormal quality and quantity of pancreatic secretion in the cystic fibrosis population could be partly responsible for the development of meconium ileus is suggested by the discovery that addition of pancreatic enzymes to the thick and sticky meconium, liquefies the mass (Anderson, 1938; Shwachman, 1975). Similarly, there is evidence to support the suggestion that the intestinal mucous may play a role in the development of meconium ileus. Autopsied cases of infants with cystic fibrosis dying from meconium ileus have revealed normal histological appearance of pancreatic specimen with normal pancreatic secretion of enzymes and bicarbonate (Thomaidis & Arey, 1963; Oppenheimer & Esterly, 1973). This suggests that the atypical mucous secretion, rather than pancreatic dysfunction may be involved in the development of meconium ileus.

Complications of intestinal obstruction include progressive abdominal distension, due to the accumulation of fluid and gas proximal to the obstruction, and bile-stained emesis (Park & Grand, 1981; Matthews & Drotar, 1984). More serious complications of the intestinal disorder that may be present in the cystic fibrosis patients include bowel perforation, peritonitis, intussusception and intestinal atresia (Crozier, 1974; Park & Grand, 1981; Matthews & Drotar, 1984).

"Meconium ileus equivalent", also known as "distal intestinal obstruction syndrome", is a similar obstructive lesion of the intestinal tract found in older children and adults with cystic fibrosis (Jensen, 1961; Wood et al. 1976). Meconium ileus equivalent is a partial obstruction of the terminal ileum and caecum which most likely results from the impaction of inspissated mucous and partially digested foods (Phelan, 1982). Much the same as for meconium ileus, the development of abdominal pain and constipation signal the presence of meconium ileus equivalent (Holsclaw et al. 1974; Wood et al. 1976; Park & Grand, 1981). As well, meconium ileus equivalent has complications similar to those found accompanying meconium ileus, including abdominal distension, intussusception, and peritonitis (Holsclaw et al. 1974).

Although the precise etiology of meconium ileus equivalent remains uncertain, it is probably due to a

combined effect of malabsorption and maldigestion. The presence of pancreatic achylia and insufficient secretion of pancreatic digestive enzymes, as well as the observed layer of mucous lining the intestinal tract may lead to maldigestion and malabsorption, and as such, are probable contributors to the development of intestinal obstruction in the later years of the cystic fibrosis patient. Additional factors that would encourage obstruction include inappropriate enzyme therapy for a particular diet or non-adherence to pancreatic enzyme therapy (Park & Grand, 1981). Moreover, a change in diet without a concommitant adjustment in enzyme replacement could result in undigested food matter in the intestinal tract which could then become impacted and would encourage further obstruction (Park & Grand, 1981).

Treatment of the intestinal obstruction in cystic fibrosis patients varies, depending on the degree of obstruction. Nonoperative relief of mild obstruction may be achieved with stool softeners and/or enemas (McPartlin et al. 1973; Weller, 1986). In the more severe cases of obstruction, surgical intervention is warranted to relieve the obstruction and deter and/or correct for any of the secondary consequences of intestinal obstruction that may develop and which could include bowel perforation, peritonitis, or intestinal atresia (Crozier et al. 1974; Park & Grand, 1981).

2.1.2 The Liver

Manifestations of cystic fibrosis disease are commonly seen in the liver. Pathological changes in the liver and biliary system were described as early as 1938 (Anderson, 1938). Liver involvement in cystic fibrosis disease is often undetected during the lifespan of the patient. The exception to this statement would be those cases in which liver disease reaches an advanced stage, at which point in time, symptoms and clinical assessment may indicate a disturbance in hepatic function, or when hepatomegaly is observed on x-ray or physical examination.

The liver of cystic fibrosis patients examined visually at autopsy is most commonly described as having a normal external appearance, although some livers may appear shrunken and nodular with areas of fibrous scar tissue (Craig et al. 1957; Shier & Horn, 1963). Microscopic examination of liver sections, however, reveals significant histopathologies of the liver in most patients. Basic changes in liver histology seen in the cystic fibrosis liver, include cell atrophy, cell necrosis, bile ducts plugged by an inspissated mixture of mucous and bile, bile duct proliferation and dilatation, and fatty infiltration (Anderson, 1938; Craig et al. 1957; Stern et al. 1976). Less prevalent yet still common, microscopic observation of liver tissue sections reveals areas of fibrosis, prominent

periportal tracts, and periportal fibrosis (Shier & Horn, 1963; Anderson et al. 1987). These hepatic changes are characteristic of focal biliary cirrhosis (Anderson et al. 1938; Park & Grand, 1981), and may present in the cystic fibrosis population at any age (Park & Grand, 1981). Post-mortem studies, conducted on cystic fibrosis patients, estimate that focal biliary cirrhosis may be present in 9 to 25 percent of the cystic fibrosis population (diSant'Agnese, 1956; Shier & Horn, 1963; Wood et al. 1976).

Certain cystic fibrosis patients may show more advanced liver involvement at autopsy. In this event, the liver appears as a small, firm, lobulated mass with obvious fibrous scar tissue (diSant'Agnese, 1956; Craig et al. 1957; Anderson, 1987). Fatty liver remains one of the most common hepatic pathologies in cystic fibrosis patients and is easily detected on gross examination of the liver in cases of moderate to severe liver involvement. Microscopically, the liver demonstrates extensive bile duct dilatation, fatty deposition and unrestricted fibrosis, and in this state would be typically classified as multilobular biliary cirrhosis (Craig et al. 1957; Shier & Horn, 1963; Anderson et al. 1987). Multilobular cirrhosis is relatively rare, however, and presents in less than 5 percent of autopsied cases of cystic fibrosis (diSant'Agnese, 1956; Craig et al. 1957; Lipow & McQuitty, 1987).

Normal hepatic function is maintained in the majority of cystic fibrosis patients with liver involvement, as sufficient viable liver tissue remains, despite the focal biliary cirrhosis (Craig et al. 1957; Wood et al. 1976; Lipow & McQuitty, 1987). In cases of advanced liver cirrhosis, liver function may be disturbed and secondary complications of liver disease may be seen. Clinically detected jaundice has been noted in some cystic fibrosis infants and children (Craig et al. 1957; Taylor & Qaqundah, 1972). Jaundice is believed to result from the widespread obstruction of the liver ductules by inspissated bile and cell debris which may obstruct the orthograde flow of bile leading to the retrograde flow of bile into the circulation (Craig et al. 1957; Park & Grand, 1981). Hypoalbuminemia, edema, and poor blood clotting have been reported in some cystic fibrosis patients. These complications may be explained by a decrease in the synthesis of important protein products of the liver, for example albumin and blood clotting factors, which have been documented in those cystic fibrosis patients demonstrating these disturbances (Shwachman, 1975). Once the liver disease advances to the degree of severe cirrhosis, portal hypertension may develop due to obstruction of the portal circulation by the extensive amount of fibrotic scar tissue that replaces the liver tissue. Splenomegaly and bleeding esophageal varices

are often seen in association with the portal hypertension (Shier & Horn, 1963; Stern et al. 1976).

Autopsy reports generally indicate that the gallbladder and cystic duct are abnormal in approximately one third of patients with cystic fibrosis disease (Bass et al. 1983). X-ray examination of the gall bladder during life may reveal an unusually small structure (Shier & Horn, 1963; Bass et al. 1983). Biopsy studies of gall bladders of cystic fibrosis patients often produce evidence that the gall bladder contains mucous and a slight amount of viscid bile (Shier & Horn, 1963; Shwachman, 1975). Post-mortem studies indicate the occassional presence of gallstones in the cystic fibrosis gallbladder, although this is usually found only in the older cystic fibrosis patients (Shwachman, 1975).

While the symptoms of liver involvement in the cystic fibrosis population are often subtle and rare (Park & Grand, 1981), liver disease can present serious complications, which must be palliated. Management of cystic fibrosis patients who develop portal hypertension and show secondary complications of this portal hypertension, such as splenomegaly and esophageal varices, usually involves surgery (Craig et al. 1957; Stern et al. 1976). The liver operation, preferred at the present time, is a portacaval shunt, whereby the blood in the portal circulation bypasses the liver and flows directly into the inferior vena cava.

Although the portacaval shunt procedure can relieve the portal hypertension effectively, it is a major operation, and often times the cystic fibrosis patient may be too ill to undergo such a traumatic surgery (Shwachman, 1975).

2.1.3 The Pancreas

As the early nomenclature suggests, cystic fibrosis disease includes pathological involvement of the pancreas (Anderson, 1938). Visual inspection of the cystic fibrosis pancreas at autopsy may show a pancreas with a normal gross appearance in some patients, however, it is more likely that the pancreas will have obvious areas of fibrosis and scarring. In the most extreme cases, the pancreas will be small, firm, and nodular due to extensive fibrosis and scar tissue.

Microscopic examination of the pancreas at autopsy shows a similar range of pancreatic histopathologies. The most characteristic changes recognized in the cystic fibrosis pancreas include achylia, small duct and acinar obstruction by an inspissated secretion and cell debris, flattened epithelial cells and an increase in fibrous connective tissue (Anderson, 1938; Sturgess, 1984; Dodge, 1986). These pancreatic lesions may be minimal or progress to an end stage where the normal architecture of the pancreas is disrupted and replaced by fibrotic connective

tissue, cysts, and fatty infiltrates (Park & Grand, 1981; Anderson, 1987). Occasionally, widespread pancreatic calcification is apparent from x-ray examination (Ring et al. 1973). Identification of such lesions in cystic fibrosis patients dying within the first few months after birth, would suggest that the structural changes seen in the pancreas evolved in utero, during the development of the pancreas.

In most cases of pancreatic fibrosis, the islets of Langerhans are spared from fibrosis and the integrity of the endocrine tissue of the pancreas is unaltered (Park & Grand, 1981). In some situations, however, the pancreatic lesions and fibrosis may eventually impinge on the pancreatic endocrine tissue disorganizing the islets of Langerhans histology (Larsson, 1958; Rodman et al. 1986). The etiology of the pancreatic lesions is basic to the general nature of cystic fibrosis disease, in that the fibrosis is caused by the presence of a chronic obstruction of the small pancreatic ducts by viscid pancreatic secretions and cellular debris (Anderson, 1938). The obstruction leads to hyperplasia and eventual necrosis of pancreatic acinar and ductule cells and progressive fibrosis (Anderson, 1938; Park & Grand, 1981).

The primary manifestation of the pancreatic fibrosis is a small volume of viscous pancreatic secretion, that contains low concentrations of water, bicarbonate,

electrolytes and pancreatic digestive enzymes (Hadorn et al. 1968; Dodge, 1986). In the more severe cases of pancreatic fibrosis low serum levels of insulin may exist (Rodman et al. 1986) which would suggest that the lesions have impinged on the pancreatic endocrine tissue. Complications extending from these functional abnormalities include fat and protein maldigestion and glucose intolerance, respectively (Shwachman, 1975; Dodge, 1986). Maldigestion of fat and protein, consecutive to insufficient pancreatic function is evidenced by frequent and foul-smelling stools with marked steatorrhea and azotorrhea (Park & Grand, 1981), and may render the cystic fibrosis patient susceptible to malnutrition. Hypoinsulinemia in the cystic fibrosis patients is believed to evolve from a combination of a decrease in the number of insulin-producing beta cells, and an impaired blood supply to the islets (Rodman et al. 1986), both of which would occur in the presence of extensive fibrosis. Abnormal glucose tolerance in the cystic fibrosis patient, consecutive to hypoinisulemia, is seen in approximately 20 to 30 percent of the cystic fibrosis population (Park & Grand, 1981). Clinically significant diabetes mellitus has been found in 1 to 3 percent of patients with cystic fibrosis, a frequency that is twenty-fold higher than in the normal population (Park & Grand, 1981; Rodman et al. 1986).

Treatment for those cystic fibrosis patients with pancreatic dysfunction may include pancreatic enzyme therapy to supplement or replace insufficient exocrine pancreatic function, and when necessary, insulin therapy is prescribed to control hyperglycemia.

Pancreatic enzyme therapy is the standard practice to attend to pancreatic insufficiency in cystic fibrosis patients. Enzyme therapy replaces those pancreatic enzymes, namely lipase and trypsin, that are insufficient, yet necessary for proper digestion of fat and protein in the diet. Enzyme dosage depends on the degree of pancreatic insufficiency, as well as the type and quantity of food in the diet (Phelan, 1982). Consequently, pancreatic enzyme therapy is individualized for each cystic fibrosis patient (Green & Doershuk, 1984). Appropriate enzyme replacement may be indicated by a normal quality and frequency of bowel movements (Weller, 1986). Numerous effective pancreatic enzyme preparations are available. In the past, there were problems in maintaining enzyme activity. While orally ingested pancreatic enzymes require an alkaline environment for activity, exposure to an acidic milieu, most likely a result of low pancreatic bicarbonate secretion and an increased gastric secretion, led to inactivation of the enzyme supplements (Park & Grand, 1981; Green & Doershuk, 1984). This is no longer a problem, however, as enzyme preparations are now protected by an acid-resistant coating.

The only drawback of pancreatic enzyme therapy is the potential side effect of perioral and perianal irritations, especially in infant patients, and secondly, problems of hypersensitivity to the powdered enzyme preparations have been reported in those people administering the enzyme to the patient (Park & Grand, 1981; Green & Doershuk, 1984).

Insulin treatment may be implemented in those patients that are hyperglycemic and hypoinsulinemic, and such treatment is generally effective in maintaining normal blood glucose levels (Matthews et al. 1980; Rodman et al. 1986).

2.1.4 Overall Consequences

Cystic fibrosis patients with abnormal gastrointestinal function are often unable to compensate for these disturbances in spite of attempts to manage and control the problems. The results of all of the above dysfunctions, taken together, are poor growth and malnutrition.

Poor growth of the cystic fibrosis patients is indicated by the general finding of weight and height values that fall in the lower percentile range i.e. below the 50th percentile, as compared to healthy age-matched controls (Sproul & Huang, 1964). Poor physical growth has been observed in all age periods, although the problem is most pronounced in the adolescent age group (Crozier, 1974; Gurwitz et al. 1979). Whereas the height growth in the

cystic fibrosis population conforms to a near normal distribution, the weight growth demonstrates a deviation from the normal weight distribution, with a significant skew towards the lower percentile area. Subnormal weight gain is a more prominent feature of the female cystic fibrosis population, although a formal explanation for this gender effect has not been provided (Crozier, 1974).

This poor growth is believed to be related to both pancreatic dysfunction and pulmonary disease (Taussig et al. 1973; Shwachman, 1975; Gurwitz et al. 1979). Growth failure appears to be more prevalent in those cystic fibrosis patients that have insufficient pancreatic function (Shwachman, 1975). Poor growth is most likely the result of an inadequate energy intake. Studies have demonstrated that cystic fibrosis patients often do not meet the recommended dietary allowance of energy. In turn, this energy intake deficiency is a probable consequence of several factors including; inappropriate low fat diets, a depressed appetite often associated with illness (Chase et al. 1979; Park & Grand, 1981), excessive fat excretion due to poor digestion and extreme energy expenditure for respiration in this population (Taussig et al. 1973; Chase et al. 1979; Gurwitz et al. 1979). A relationship between the respiratory disease and poor growth is suggested by the observation that the inferior growth status becomes more apparent as the patient gets older, and as the disease progresses with the

pulmonary dysfunction becoming a more significant feature in the patient (Park & Grand, 1981).

Malnutrition is a direct consequence of the maldigestion and malabsorption in the cystic fibrosis patient. Specific deficiencies may be found in essential fatty acids, fat-soluble vitamins A, D, E, and K, and also in certain elements and minerals (Chase et al. 1979). It has been suggested that patients with cystic fibrosis may be more susceptible to infection due to deficiencies in certain essential fatty acids e.g. linoleic acid (Chase et al. 1979). Similarly, vitamins A, D, E, and K, are required by the body for optimal growth and night vision, bone and muscle metabolism as well as regulation of calcium and phosphorus in the body, reproduction, and hemostasis, respectively (Chase et al. 1979).

2.2 The Pulmonary System

Pulmonary dysfunction represents the most significant component of cystic fibrosis disease, accounting for over 90 % of the mortality in this patient population (Ryland & Reid, 1975). The age of onset of the pulmonary disease may vary from a few days after birth to several years of age, even into adolescence (diSant'Agnese, 1956). The initial pulmonary pathology typically appears between six months to two years of age (diSant'Agnese, 1956). The extent and course of the pulmonary dysfunction is usually gradual, with time periods where the patient's condition remains static (Phelan, 1982). In other patients, the pulmonary disease can be extremely progressive and debilitating. It is certain, however, that the pulmonary dysfunction progresses with age. An explanation for the cause of the variable course of deterioration in lung function in cystic fibrosis disease has not been provided.

The usual pattern of respiratory disease in cystic fibrosis begins with an excessive amount of mucous in the respiratory tract. This mucous obstructs the airways, and ultimately disturbs alveolar ventilation and effective gas exchange (Beier et al. 1966). The mucous that accumulates in the respiratory tract most probably results from a combined effect of a dysfunction of the mucous glands in the epithelial lining of the airways which results in the

secretion of excessive mucous, acute respiratory infection, and perhaps an impaired pulmonary clearance (Wood et al. 1976). Consequently, the respiratory system of the cystic fibrosis patients constitutes an optimal environment for bacterial colonisation. Staphylococcus aureus is the initial respiratory pathogen (Phelan, 1982). Subsequent infection is more commonly evoked by pseudomonas aeruginosa (Matthews & Drotar, 1984).

Post-mortem studies of cystic fibrosis infants dying with meconium ileus, generally suggest that the lungs have a near normal macroscopic appearance at birth and a normal histological integrity (Reid & De Haller, 1967). However, lesions of the lung tissue develop soon after birth (Beier et al. 1966). The earliest and most striking pulmonary lesion seen under microscopic examination is a hyperplasia and distension of the mucous-producing goblet cells and bronchial gland hypertrophy in the epithelium and submucosa of the respiratory tract (Wood et al. 1976; Lipow & McQuitty, 1987). These pathohistologies are often present in the absence of pulmonary infection and are first seen at the bronchiolar level, with the disorder proceeding to the larger upper airways in the more advanced stages of the disease. The considerable accumulation and inspissation of mucous, and the resulting obstruction, contribute to the eventual destruction of the airway walls (Ryland & Reid, 1975). In advanced cystic fibrosis disease the respiratory

system may be characterized by bronchiectatic areas and the presence of abcesses along the airways (Gurwitz et al. 1979). The morphological changes in the pulmonary system are usually found in all regions of the respiratory system. Some reports, however, suggest that the lesions are more commonly found in the apices of the lungs (Wood et al. 1976).

2.2.1 Symptomatology

The consequences and complications of the pulmonary pathology in cystic fibrosis disease are multiple. Physical examination and clinical evaluation provide a useful description of the pulmonary manifestations of cystic fibrosis. The simplest consequence and perhaps the most traditional symptom of cystic fibrosis disease is the presence of a chronic cough. The cystic fibrosis patient coughs in an effort to clear the mucous from the respiratory tract. In the beginning stages of the disease, the cough may be dry and hacking, yet eventually becomes lose and productive. Other early physical signs of pulmonary involvement in cystic fibrosis include chest hyperinflation which is suggested by an increased anterior-posterior chest diameter, increased frequency of breathing, shortness of breath, exercise intolerance, respiratory rales on auscultation, and digital clubbing (Green & Doershuk, 1984).

Radiological examination may indicate a flattening of the diaphragm and areas of the lungs with bronchiectasis and atelectasis (Gurwitz et al. 1979; Green & Doershuk, 1984).

Changes in lung volumes identified in cystic fibrosis patients through standard pulmonary function tests include an increase in residual volume (RV), in functional residual capacity (FRC), and in tidal volume (V_T), as compared to normal healthy age-matched controls (Featherby et al. 1970; Wood et al. 1976; Matthews & Drotar, 1984). A decrease in vital capacity (VC) and forced vital capacity (FVC), relative to control values, are also seen in cystic fibrosis patients (Featherby et al. 1970; Russell et al. 1982). Total lung capacity (TLC) has been found to be increased, or unchanged from expected values (Featherby et al. 1970). As the respiratory disease advances these changes in the lung subdivisions become more marked. The reason for these changes is ascribed to the obstruction of small airways by mucous as well as a decrease in the elastic recoil of the lungs (Mansell et al. 1974). The loss of recoil properties of the lung tissue is probably due to the chronic overinflation and destruction of the lung parenchyma (Mansell et al. 1974; Ingram & McFadden, 1980).

2.2.2 Functional Status

Functional consequences of the pulmonary obstruction in cystic fibrosis disease are manifest as inadequate alveolar ventilation, insufficient flow rates, and ineffective gas exchange (Wood et al. 1976). As in other pulmonary disorders with an obstructive component, cystic fibrosis disease is characterized by a reduction in airflow rates. This dysfunction is evidenced clinically by decreases in the forced expiratory volume in one second (FEV_1), the peak expiratory flow rate (PEFR), the forced expiratory volume in one second relative to the forced vital capacity (FEV_1/FVC), and in the maximal voluntary ventilation (MVV) (Levison & Godfrey, 1976). Progression of the disease to the larger airways is indicated by increased obstruction to airflow (Lipow & McQuitty, 1987), as seen by a decrease in the mid-expiratory flow rate ($FEV_{25-75\%}$), as well as further decrements in the above mentioned indices (Levison & Godfrey, 1976).

The lung diffusion capacity (DL_{CO}) of cystic fibrosis patients has been reported to be increased (Keens et al. 1979), decreased (Goldring et al. 1964; Featherby et al. 1970) or unchanged (Beier et al. 1966) when compared to normal predicted values. Most commonly, however, DL_{CO} is reported to be reduced in cystic fibrosis patients with the most marked reduction developing in the more severely

affected patients (Godfrey et al. 1971; Russell et al. 1982; Cotton et al. 1985).

Inasmuch as the above pulmonary manifestations of cystic fibrosis disease are relevant and indicative of the status of the disease, the most significant and consequential dysfunction of the respiratory system is the altered gas exchange resulting from inadequate ventilation/perfusion characteristics. Inefficient intrapulmonary gas distribution in cystic fibrosis patients is indicated by a decrease in alveolar ventilation (V_A), a disturbed alveolar ventilation-perfusion ratio (V_A/Q), and an increase in the ratio of dead space volume to tidal volume (V_D/V_T) (Featherby et al. 1970). These disturbances result from the airway obstruction and are likely reflecting the non-homogeneity of the obstructive process (Couriel et al. 1985). In addition these respiratory pathophysiologies may explain the potentially decreased lung diffusion capacity in the cystic fibrosis population. Other indications of the ineffective gas exchange include an increase in the alveolar to arterial oxygen difference ($P_{A-a}O_2$ difference) and a decrease in the arterial partial pressure of oxygen (PaO_2) (Featherby et al. 1970; Matthews & Drotar, 1984). The decrease in PaO_2 is one of the earliest signs of the disturbed gas exchange (Beier et al. 1966) and may be accompanied by a decrease in the arterial oxygen saturation (SaO_2). Significant decrements in SaO_2 from

normal healthy values to as low as 80 % may be seen in patients with a range of pulmonary function, although this consequence is predominantly observed in the severe cystic fibrosis patients (Versteegh et al. 1986). In the early stages of the disease, cystic fibrosis patients may have a lower than normal arterial content of carbon dioxide ($CaCO_2$) (Lloyd-Still, 1983) which could probably be explained by the tendency of these patients to hyperventilate, in an effort to maintain adequate alveolar ventilation. An increase in the $PaCO_2$, indicating CO_2 retention in the blood, is prominent in the later stages of the disease (Featherby et al. 1970, Russell et al. 1982).

2.2.3 Management of Pulmonary Dysfunction

Treatment of the respiratory disorder in cystic fibrosis disease is aimed at preventing and/or controlling the pulmonary infection and removing the mucopurulent secretion causing the obstruction.

Pulmonary infection in cystic fibrosis patients is attended to with comprehensive antibiotic therapy individualized for each patient (Phelan, 1982). Acute respiratory infection is treated by administration of antibiotics. Specific antibiotics are prescribed according to the infectious agents in each patient as determined by sputum culture analysis. Antibiotic dosages are often two

to three times higher than the recommended dose, in order to achieve effective drug levels (Blythe & Farrell, 1984). Persistent and severe pulmonary infection demands hospitalization of the cystic fibrosis patient for intensive intravenous antibiotic therapy. In fact, regular hospital admission every 3 months for a two week duration with intravenous antibiotic therapy is recommended in patients with advanced pulmonary involvement (Phelan, 1982). Due to the fact that some pathogenic organisms can develop resistance to certain antibiotics, continuous low dosage antibiotic therapy is not advised (Green & Doershuk, 1984).

The effectiveness of antibiotic therapy is dependent on the appropriateness of the antibiotic for the particular type of respiratory infection, as well as, the degree of pulmonary dysfunction. In the early stages of the disease, the pulmonary infection can be relieved and even totally eradicated (Weller, 1986). The infection, however, will reoccur within a short period of time. Pseudomonas infection in the respiratory system is difficult to treat and impossible to eradicate (Weller, 1986). At this stage of pulmonary involvement, the emphasis of the treatment is to reduce the symptoms, minimize permanent lung damage, and maintain or improve the existing lung function (Phelan, 1982; Green & Doershuk, 1984).

Regular chest physiotherapy consisting of postural drainage, clapping and percussion, as well as vigorous

coughing, is essential in the management of the pulmonary obstruction and important in preventing chronic lung infection (Goodchild & Dodge, 1985; Weller, 1986). Postural drainage is conducted in multiple positions which facilitates drainage of the obstructive material from specific lung segments. Chest physiotherapy is proven to be a very effective means of draining the bronchial secretion, and thus is recommended on a daily basis (Green & Doershuk, 1984). The advent of mechanical percussion instruments and the ability of parents and other family members to learn correct percussion procedures offers the cystic fibrosis patient a small amount of independance in the treatment of their condition.

Physical activity followed by forced expiration and coughing appears to facilitate significant expectoration of bronchial secretion and thus is encouraged (Zach et al. 1982; Phelan, 1982; Green & Doershuk, 1984). In the past, aerosol inhalation therapy was used to deliver antibiotics, mucolytic agents, and bronchodilators to the bronchial mucosa (Green & Doershuk, 1984). The efficacy of this management strategy remains controversial, however, as the deposition of the medication is largely limited to areas that are unobstructed (Phelan, 1982). Bronchodilators are sometimes administered to those patients who demonstrate a reversible component of airway obstruction (Green & Doershuk, 1984). Endoscopy and bronchial lavage can relieve

serious mucoid obstruction and atelectasis, although this procedure is rarely employed (Wood et al. 1976; Green & Doershuk, 1984).

2.3 The Cardiovascular System

The function of the cardiovascular system may be compromised in cystic fibrosis patients. The problem remains to understand whether the pathologies seen in the cardiovascular system are primary manifestations of the disease or are the consequences of associated pathologies from other organ systems (Oppenheimer & Esterly, 1973; Lloyd-Still, 1983). Although seemingly secondary in nature, complications of the cardiovascular system, in particular the heart, are one of the major and immediate causes of death in the cystic fibrosis population (Piepsz et al. 1987). Autopsy reports suggest that cardiac dysfunction is present in up to 70% of cystic fibrosis deaths, although not necessarily responsible for the demise (Royce, 1951; Rosenthal et al. 1976; Moss, 1982).

2.3.1 Anatomical and Functional Evidence of Cardiovascular Pathology

2.3.1.1 Myocardial Fibrosis

Cardiac lesions of necrosis and fibrosis have been observed in autopsied cases of cystic fibrosis (Barnes et al. 1970; Oppenheimer & Esterly, 1973; Nezelof & LeSec, 1979). The fibrotic lesions are found in both boys and girls and are definitely present in those cystic fibrosis

patients dying within the first few years of life (Chipps et al. 1979; Nezelof & LeSec, 1979). These anatomical lesions are well characterized and easily identified on gross examination of the heart (Nezelof & LeSec, 1979).

Microscopically, the lesions consist of simple fibrous connective tissue (Nezelof & LeSec, 1979) that may be found in continuous or isolated regions of both atria and ventricles. The connective tissue develops in the area where the necrotic myocardial cells are located such that almost no myocardial fibres are found inside the lesion (Barnes et al. 1970; Nezelof & LeSec, 1979). The myocardial fibrosis is generally found throughout the entire myocardium, more frequently in the ventricles than in the atria (Nezelof & LeSec, 1979), and with no consistent location between right and left sides of the heart (Barnes et al. 1970; Oppenheimer & Esterly, 1973; Nezelof & LeSec, 1979).

A number of explanations for the myocardial fibrosis have been postulated and include nutritional cardiomyopathy, infection in the myocardium, secondary to pulmonary infection, which results in myocarditis and fibrosis, and cytopathological changes in the myocardium resulting from exposure of the myocardium to some undetermined factor.

It has been suggested that fibrosis could be a consequence of the malnourished state of the cystic fibrosis patient that arises consecutive to the malabsorption in the

gastrointestinal tract (Nezelof & LeSec, 1979; Moss, 1982). Nutritional deficiencies, in general, disrupt the normal growth and development of all tissue and more specifically, effect the integrity of the myocardium and could lead to necrosis and fibrosis of the tissue. A deficiency in vitamins A, E, and B_{12}, each proven to be essential to the development and maintenance of healthy myocardial tissue, could explain at least in part the cardiomyopathy observed in the cystic fibrosis patients (Nezelof & LeSec, 1979; Moss, 1982).

A second possible etiology to explain the presence of myocardial fibrosis in the cystic fibrosis population is that of myocardial infection (Oppenheimer & Esterly, 1973). The myocardium can become infected, secondary to the pulmonary infection, as the infectious agent may be transported in the bloodstream from the lungs to the cardiac tissue. Moreover, cystic fibrosis disease is characterized by chronic pulmonary infection and documented cases of myocarditis in cystic fibrosis patients have been reported in the literature (Oppenheimer & Esterly, 1973).

Alternatively, the fibrotic lesions could be the consequence of the presence in the blood of some factor, unidentified to date, released from the diseased pancreas, such as a proteolytic enzyme, which could disturb the protein metabolism of the tissue and consequently alter the physical and functional qualities of the myocardium (Nezelof

& LeSec, 1979). Such a proposal could explain the diffuse fibrosis, although cardiac lesions are frequently found in patients with normal pancreatic function and this evidence is in direct contradiction to the suggestion that a diseased pancreas is the source of the insulting agent.

In addition to all of the above hypotheses, the deleterious effects of hypoxemia on the integrity of individual cells and tissue should be mentioned. Cystic fibrosis patients may be subject to a relenting state of hypoxemia, and in this situation, the hypoxia could cause fibrosis and necrosis of the myocardium (Barnes et al. 1970; Oppenheimer & Esterly, 1973; Jacobstein et al. 1981).

Experimental evidence alludes to the possibility that each hypothesis is not necessarily exclusive of the other, and the actual etiology of the myocardial fibrosis maybe confounded or disguised by secondary etiologies. It has become apparent, however, from investigations of the etiology of myocardial fibrosis in cystic fibrosis, that there is a connection between the development of myocardial disease and other progressive complications of cystic fibrosis (Oppenheimer & Esterly, 1973).

2.3.1.2 Ventricular Hypertrophy

The heart of the cystic fibrosis patient is often enlarged, characterized by the presence of ventricular

hypertrophy and may present a significant ventricular dilatation (Rosenthal et al. 1976).

Results from echocardiographic measurements of right ventricular dimensions in the cystic fibrosis population indicate right ventricular anterior wall hypertrophy, septal wall thickening and an increase in right ventricular end-diastolic dimension (Rosenthal et al. 1976; Allen et al. 1979). These changes are most noticeable in those patients with severe cystic fibrosis. In fact, cor pulmonale may be expected in approximately 70 % of all infants and children who die from cystic fibrosis disease (Moss et al. 1965; Rosenthal et al. 1976; Moss, 1982), as well as those patients living with severe disease.

By definition, cor pulmonale refers to "right ventricular hypertrophy which results from disease affecting the function and/or structure of the lung" (Moss, 1982). The presence of cor pulmonale in the cystic fibrosis population may be seen as an adaptive response of the heart to the presence of a chronic right ventricular afterload consecutive to pulmonary hypertension. The pulmonary hypertension, in turn, results from a series of reactions that begin with airflow obstruction causing alveolar hypoventilation, as well as ventilation-perfusion inequality and resulting in hypoxia-induced vasoconstriction of the pulmonary vasculature (Crozier, 1974; Lloyd-Still, 1983). Although the vasoconstriction is probably a reflex response

to the relative hypoxia seen in these patients, this vasoconstriction may be further aggravated in the presence of hypercapnia and acidemia that usually accompany hypoxemia (Rosenthal et al. 1976). Clinically, the presence of cor pulmonale is indicated by a PaO_2 less than 50 mmHg, especially if the $PaCO_2$ is greater than 45 mmHg (Siassi et al. 1971; Wood et al. 1976). Furthermore, hypoxia has been seen to cause a medial thickening of the pulmonary vasculature which may contribute to the increased pulmonary resistance (Moss et al. 1965; Rosenthal et al. 1976; Moss, 1982; Geggel et al. 1985).

Echocardiographic evaluation of cystic fibrosis patients reveals a reduced left ventricular internal diameter associated with left ventricular wall hypertrophy (Allen et al. 1979). This reduced left ventricular internal diameter is seen during both systole and diastole and may be detected independent of disease severity (Allen et al. 1979).

2.3.1.3 Functional Disturbances

As expected from the morphological changes in the cardiac structure, functional disturbances of both left and right ventricles have been reported in patients with mild to severe cystic fibrosis using echocardiography (Rosenthal et al. 1976; Allen et al. 1979; Chipps et al. 1979; Hirschfeld et al. 1979) and radionuclide angiography (Matthay et al.

1980; Jacobstein et al. 1981; Canny et al. 1984; Piepsz et al. 1987).

Results from angiographic studies measuring right ventricular ejection fractions indicate the presence of resting right ventricular dysfunction in some cystic fibrosis patients. An abnormally low (<45 %) right ventricular ejection fraction was found in 41 % to 72 % of the cystic fibrosis patients examined (Matthay et al. 1980; Canny et al. 1984; Piepsz et al. 1987). Echocardiographic evidence of right ventricular dysfunction includes an elevated pre-ejection period/right ventricular ejection time ratio (>.40) in 87 % of the cystic fibrosis patients examined (Hirschfeld et al. 1979).

A priori comparisons between right ventricular ejection fraction and pulmonary function scores, arterial hypoxemia or Shwachman clinical score (a 100 point rating of patient health on the basis of individual scores out of 25 in the four areas of general activity, physical examination, chest x-ray and nutritional assessment) suggest that a relationship exists between ventricular function and other complications of cystic fibrosis disease (Gewitz et al. 1977; Hirschfeld et al. 1979; Matthay et al. 1980; Piepsz et al. 1987). Excellent correlations between pre-ejection period/right ventricular ejection time and percent predicted vital capacity, residual volume and Shwachman scores in cystic fibrosis patients were in fact reported using

echocardiography (Hirschfeld, 1979). Similar findings in support of this association between severity of cystic fibrosis disease and ventricular function include the co-presence of severe cystic fibrosis and right ventricular dysfunction (Matthay et al. 1980). Moreover, normal right ventricular function is indicated by the consistent finding of a mean right ventricular ejection fraction equal to 46 % in "normal" cystic fibrosis patients (that is people diagnosed as having cystic fibrosis with normal lung function) (Piepsz et al. 1987). Matthay et al (1980) also suggest that when a patient has any sign or symptom of cor pulmonale, an abnormally low right ventricular ejection fraction may be expected. Specifically, low right ventricular ejection fractions ranging from 27 % to 44 % have indeed been reported in those patients with low PaO_2 (Piepsz et al. 1987).

The discrepancies and variations in the results from studies completed to assess right ventricular function in the cystic fibrosis population may be attributable to heterogeneous cystic fibrosis samples. Cystic fibrosis subjects exhibit a wide range of pulmonary function, hypoxemia levels, arterial CO_2 retention and Shwachman clinical scores. Moreover, there are difficulties and limitations in interpreting echocardiographs from the cystic fibrosis population due to the hyperinflated chests of this patient group (Wood et al. 1976; Moss, 1982).

Right ventricular involvement in the pathogenesis of cystic fibrosis disease begins with little right ventricular hypertrophy and can advance to the extent where there may be serious right ventricular hypertrophy, right ventricular pressure overload and eventually right heart failure (Moss, 1982).

Substantiation of the presence of cardiac failure in the cystic fibrosis population comes from the observed right ventricular dilatation in echocardiographic profiles of terminally ill patients (Allen et al. 1979). This dilatation most probably results from the pressure-volume overload experienced by the failing right ventricle and may be seen as a compensatory adaptation attempting to make use of the Starling mechanism to increase ventricular ejection, in light of the already maximally sollicited inotropic state of the myocardium (Allen et al. 1979).

Results of echocardiographic and angiographic studies conducted in cystic fibrosis patients of varying disease severity indicate the presence of a left ventricular dysfunction in approximately 20 % of the patients (Chipps et al. 1979; Canny et al. 1984).

The inquiry into left ventricular function in cystic fibrosis patients, completed by Chipps et al in 1979, found a mean left ventricular ejection fraction within the normal range, although, a lower than average ejection fraction was determined in 41 % of all the patients examined. Left

ventricular dysfunction was also suggested in 23 % of cystic fibrosis subjects by the discovery of an increased (>.45) pre-ejection period/left ventricular ejection time ratio (Hirschfeld et al. 1979). Studies using radionuclide angiography to determine left ventricular ejection fraction present data that indicate a normal left ventricular ejection fraction in 72 % to 100 % of the cystic fibrosis patients examined (Chipps et al. 1979; Matthay et al. 1980).

While the right ventricular dysfunction seen in the cystic fibrosis population may be explained by the chronic pulmonary hypertension and possible disturbances in ventricular shape and myocardial morphology, the mechanism responsible for the left ventricular dysfunction is controversial.

Left ventricular dysfunction may be partly attributed to the presence of myocardial fibrosis which could limit both diastolic filling and contractile properties of the myocardium (Jacobstein et al. 1981). As well, the generation of large intrathoracic pressures, commonly observed in the cystic fibrosis population can lead to an increase in the left ventricular afterload (Jacobstein et al. 1981; Canny et al. 1984) which can force the myocardium to its inotropic limit.

It has also been suggested that the normal geometric and compliance properties of the left ventricle may be disturbed as a consequence of the right ventricular

enlargement (Allen et al. 1979; Jacobstein et al. 1981; Moss, 1982) which may cause bulging of the interventricular septum into the left ventricle.

2.3.1.4 Other Pathologies

Minor alterations in other areas of the cardiovascular system have been reported. An increase in the thickness of the media of pulmonary arteries and arterioles has been described in autopsied cases of cystic fibrosis (Ryland & Reid, 1975; Lloyd-Still, 1983). While the precise stimulus for this observed medial thickening remains to be identified, it may be associated with the reduced pulmonary blood flow (Symchych, 1971). The increased medial layer of the pulmonary arteries and arterioles could lead to a reduced vascular compliance which in turn could contribute to the presence of pulmonary hypertension in the cystic fibrosis population (Ryland & Reid, 1975). Further evidence to support this idea is the finding of a positive relationship between arterial wall thickness and right ventricular hypertrophy (Ryland & Reid, 1975), wherein a patient with a more substantial right ventricular hypertrophy would be expected to have a significant arterial wall thickening, while normal control subjects would have the least thickness of arterial wall.

Compression and collapse of small pulmonary vessels have also been observed (Moss et al. 1965, Moss, 1982).

Moreover, close examination of x-rays often reveal dilated bronchial arteries (Moss et al. 1965; Symchych, 1971). Both of the aforementioned pathologies are likely the consequence of the inflammation, fibrosis and edema present in the pulmonary tissue (Moss et al. 1965, Symchych, 1971; Moss, 1982). The accumulation of fluid in the interstitium could increase the hydrostatic pressure within the tissue and cause a collapse of the vessel. Bronchial arterial dilatation could reflect a basic inflammatory response initiated by the presence of infection in the pulmonary tissue.

2.3.2 Treatment of Cardiac Dysfunction

Treatment of heart failure in the cystic fibrosis patient should begin with its prevention. By ensuring adequate ventilation and maintaining a normal blood oxygen content, the probability of a reflex pulmonary vasoconstriction causing right ventricular afterload, may be reduced. In turn this may limit the right ventricular dysfunction.

Patients who exhibit abnormal blood oxygen content are generally submitted to oxygen therapy (Moss, 1982), the goal of which is to decrease the workload of the right ventricle by decreasing the pulmonary arterial pressure (Fishman, 1980). Once chronic cor pulmonale has developed, treatment

is generally aimed at retarding the onset of heart failure. This may be accomplished by administration of inotropic agents and pulmonary vasodilators, that serve to enhance myocardial contractility and relieve the pulmonary hypertension, respectively (Moss, 1982). The efficacy of these pharmacological agents remains uncertain. The majority of vasodilators seem ineffective in reducing pulmonary artery pressure, and consequently right ventricular afterload. Moreover, the enhanced contractile state, created by inotrope therapy, increases pulmonary vascular blood flow which may be associated with an erroneous increase in pulmonary artery pressure (Stern et al. 1980; Moss, 1982). Thus, in an effort to enhance heart function, excessive demands are placed on the heart (Fishman, 1980). In effect, for the cystic fibrosis patient inotrope therapy seems to be futile.

The cardiovascular pathologies present in cystic fibrosis disease are multiple and pose a serious threat to the patient. Prevention, early detection and treatment of such pathologies are essential to the patients' well-being. Despite attempts to relieve and manage the cardiac dysfunction seen in the cystic fibrosis population, the presence of cardiac pathologic involvement in the cystic fibrosis patient usually indicates that the disease is systemic and irreversible, and death of the cystic fibrosis patient imminent.

2.4 The Sweat Abnormality

In the early years of discovery and clinical description, cystic fibrosis disease was believed to be a disorder of the mucous-producing glands, involving primarily the lungs, gastrointestinal tract, and pancreas. By 1953, however, abnormalities of the sweat and serous salivary glands were included in the pathology of cystic fibrosis (diSant'Agnese et al. 1953). The disorder of the non-mucous producing glands e.g. sweat glands, salivary glands, and lacrimal glands, was noted for the increased electrolyte concentration of the glands' secretion. While increased levels of chloride and sodium in mixed saliva and tears have been found in cystic fibrosis patients, in contrast to normal controls (diSant'Agnese et al. 1958; Wood et al. 1976), the profound elevation of chloride and sodium concentrations in the eccrine sweat of this population is the most significant and consistent disturbance of the non-mucous exocrine glands (Anderson & Freeman, 1960; diSant'Agnese & Powell, 1962).

The individual concentrations of both sodium and chloride ions in the cystic fibrosis sweat usually exceed 60 mEq/L, and commonly reach values of 100 mEq/L (Anderson & Freeman. 1960; Sutcliffe et al. 1968) which remains distinct from the sodium and chloride electrolyte concentrations of 10 to 60 mEq/L in normal children (diSant'Agnese & Powell,

1962; Sutcliffe et al. 1968; Paunier et al. 1973). Other electrolytes may be altered in the cystic fibrosis sweat. Potassium levels are usually about 50 to 100% higher in cystic fibrosis, as compared to normal sweat, reaching values of 15 mEq/L versus 9 mEq/L in controls (diSant'Agnese & Powell, 1962; Paunier et al. 1973), however, there is a considerable overlap between normals and cystic fibrosis patients. Concentrations of magnesium and calcium in the sweat appear to be no different between cystic fibrosis patients and normals (Paunier et al. 1973). The consistency of this sweat abnormality is substantiated by its' presence at birth, throughout life and in the presence or absence of pancreatic function and/or pulmonary involvement (diSant'Agnese & Powell, 1962). In contrast to the highly discrepant sweat electrolyte composition, studies of cystic fibrosis patients submitted to thermal sweating or iontophoreses have shown that the rate of sweating (total volume per unit time) was not significantly different between patients and controls (diSant'Agnese and Powell, 1962).

A second feature of the sweat gland abnormality found in some cystic fibrosis patients is an abnormal physiological adaptation to heat stress or to a low salt diet. In normal subjects heat acclimatization or a low salt diet is usually associated with a decrease in sweat electrolyte concentration (diSant'Agnese & Powell, 1962;

Simopoulos et al. 1971). In comparison, while some cystic fibrosis patients may demonstrate a normal response to exercise, heat stress, low salt diet or exogenous aldosterone with a decrease in sweat electrolyte levels, most patients continue to secrete excessive amounts of sodium and chloride in the sweat regardless of the stress or period of exposure to the stress (diSant'Agnese, 1962; Oliver & Watson, 1964). It has been postulated that sweat glands in cystic fibrosis patients do have some response to heat stress, exercise, low salt diet or exogenous aldosterone, however, the sweat sodium and chloride levels remain abnormally high even after the decrease (Simopoulos, 1971).

An explanation for this disturbance in sweat gland function remains to be found. Metabolic studies have shown that the increase in sweat electrolyte concentration in cystic fibrosis is not a consequence of impaired kidney or adrenal function (diSant'Agnese & Powell, 1962). Hormonal regulation of fluid and electrolyte balance, and indirectly sweat composition in the body may be influenced by aldosterone. In general, aldosterone secretory rates, plasma and urinary concentrations of aldosterone and metabolic clearance rates are normal (Montalvo et al. 1968; Rapaport et al. 1981), or only slightly elevated (Rapaport et al. 1981; Stanghelle et al. 1988d) in cystic fibrosis patients suggesting that aldosterone function is intact.

Although the condition of hyperaldosteronism has been reported in some cystic fibrosis patients (Simopoulos et al. 1971; Rapaport et al. 1981), it is believed to be secondary in response to sodium depletion following longterm low sodium dietary intake (Rapaport et al. 1981).

Evidence from both light and electron microscopy reveals that the histology of the sweat glands is intact (Lipow & McQuitty, 1987). Analyses of sweat samples extracted by micropuncture from various regions of the sweat gland indicate that the composition and volume of the sweat precursor solution, located in the secretory coil, is normal (Johansen et al. 1968; Schulz, 1969). This may be taken to suggest that the defect in the sweat gland, that is causing the altered sweat composition is localized to the reabsorptive duct.

Theories to explain the sweat gland abnormality are conflicting and none is completely accepted. It is reasonable, however, to suggest that the phenomena results from a decreased transport of sodium or chloride from the duct lumen into the interstitial space. Dysfunction of the sodium-potassium ATPase ion exchange pump has been suggested as a partial explanation for the poor ductal reabsorption of sodium. This explanation, however, is limited as studies using radioactive ouabain report that the function and location of the Na^+-K^+ ATPase pumps in the cystic fibrosis sweat glands, do not appear to be different from normal

(Taussig et al. 1973). More recently, evidence has been presented that implicates low chloride permeability in the ductal portion of the gland as the cause of the failed sodium reabsorption (Quinton, 1983).

Usually, the sweat gland pathology does not present a problem to the cystic fibrosis patients. Occassionally, however, complications related to the elevated electrolyte concentrations in the sweat and consequently, the large salt loss, occur. Acute complications of the sweat defect are often caused by high environmental temperatures or fever. Such heat related difficulties may include heat stroke, heat exhaustion and shock, and muscle cramping (Lipow & McQuitty, 1987). Chronic salt loss may lead to hyponatremia, hypochloremia, and metabolic alkalosis (diSant'Agnese, 1953). The loss of large amounts of sodium and chloride through sweating in the cystic fibrosis patients may be compensated for by ensuring adequate dietary salt intake. Salt supplements are occassionally prescribed during hot and humid environmental conditions. In the rare event that salt loss becomes so extensive as to significantly reduce the extracellular fluid volume and perhaps lead to cardiovascular collapse, hyperthermia, and coma, intravenous isotonic saline can be administered (diSant'Agnese & Powell, 1962).

3.0 DIAGNOSTIC PROCEDURES FOR CYSTIC FIBROSIS

The diagnosis of cystic fibrosis is classically based on a combination of a positive sweat test with clinical findings of chronic obstructive pulmonary disease, exocrine pancreatic insufficiency, or a positive family history of cystic fibrosis (Blythe & Farrell, 1984). Each test used in the diagnosis of cystic fibrosis involves one of the three main organs affected in the early stages of cystic fibrosis, namely the sweat glands, the respiratory system and the pancreas.

3.1 The Sweat Test

The sweat test is a clinical procedure that allows analysis of the specific composition of a sweat sample. The idea to analyze the sweat of patients suspected of having cystic fibrosis developed from the confirmed observation that sweat sodium and chloride levels in children with cystic fibrosis are three to four times higher than those found in normal children (Gibson & Cooke, 1959; Anderson & Freeman, 1960). Different methods of sweat collection, have been employed (Gibson & Cooke, 1959; Phelan, 1982), however, the most reliable and accepted method of sweat testing for the diagnosis of cystic fibrosis is the quantitative pilocarpine iontophoresis test developed by Gibson and Cooke

(1959). The three basic steps of this method are i) sweat gland stimulation by the iontophoresis of pilocarpine, a cholinergic stimulant of sweat glands, into the forearm or some other localized area of the body, ii) collection of a sufficient quantity of sweat (>100 mg), and iii) analysis of the electrolyte concentrations of the sweat. Traditionally, both sodium and chloride concentrations of the sweat are measured. In practice, however, often only a chloride analysis is performed because it is more reliable than sodium values and discriminates better between normal and cystic fibrosis populations (Blythe & Farrell, 1984).

The most generally accepted upper limit of sweat sodium and chloride in normal healthy children is 60 mEq/L (diSant'Agnese, 1956; Anderson & Freeman, 1960; Kollberg, 1982). A positive diagnosis of cystic fibrosis would be suggested by sodium and chloride concentrations in the sweat in excess of 60 mEq/L. Values between 50 and 60 mEq/L of sodium, and especially chloride, are suspiciously elevated and under these circumstances, the sweat test should be repeated. Sweat sodium and chloride levels tend to rise with age, to the point that sweat sodium and chloride levels, measured in normal older teenagers and adults, have been measured in the range of 60 to 80 mEq/L (Anderson & Freeman, 1960; Lipow & McQuitty, 1987). Keeping this phenomena in mind, it has been suggested that sweat sodium and chloride levels over 90 mEq/L should be required for the

diagnosis of cystic fibrosis, especially in adults. Carriers of the cystic fibrosis defect do not seem to have elevated levels of electrolytes in their sweat (Gibson & Cooke, 1959; Anderson & Freeman, 1960). Studies conducted to determine sweat electrolyte levels in unaffected siblings and parents of cystic fibrosis patients indicate that the sweat electrolyte values are within the normal range (<60 mEq/L) (Gibson & Cooke, 1959; Anderson & Freeman, 1960). This suggests that cystic fibrosis heterozygotes do not have the sweat gland pathology typical of the cystic fibrosis homozygote. Thus, the sweat test would appear to be ineffective in detecting a person that is heterozygous for cystic fibrosis.

Sweat tests are indicated and performed in those patients afflicted by chronic respiratory problems, and in those patients with gastrointestinal symptoms, such as meconium ileus (Wood et al. 1976; Blythe & Farrell, 1984). Other indications for sweat testing include a positive family history, failure to thrive, and salty sweat (Wood et al. 1976; Blythe & Farrell, 1984).

When properly conducted by an experienced technician, the sweat test is highly accurate and will detect 98 percent of those patients with cystic fibrosis disease (Matthews & Drotar, 1984). The remaining 2 percent will usually have borderline electrolyte levels in the sweat, and would probably be detected by a second sweat test (Matthews &

Drotar, 1984). Although the sweat test is painless, simple to perform, and provides reliable results, it is not without limitations. Firstly, it is often difficult to execute a valid sweat test in newborns as it is often impossible to attain a sufficient quantity of sweat (Hardy et al. 1973). Sweat test results may be confounded by other factors such as edema, dehydration, and electrolyte imbalances (Wood et al. 1976) which might limit the collection of a sufficient quantity of sweat or could possibly disturb the electrolyte concentration of the sweat. Moreover, elevated sweat chloride levels have been associated with other conditions such as adrenal insufficiency, hypothyroidism, glucose-6-phosphatase deficiency and malnutrition (Wood et al. 1976).

3.2 Pancreatic Function Tests

Cystic fibrosis disease is often characterized by exocrine pancreatic insufficiency and this finding is used in the diagnosis of cystic fibrosis. Partial or complete loss of pancreatic exocrine function in the cystic fibrosis patient could be suggested on the basis of a patient history of excessive appetite, abdominal pain, and frequent fatty bowel movements (Wood et al. 1976; Matthews et al. 1980; Kollberg, 1982). Confirmation of exocrine pancreatic

insufficiency is obtained from results of specific pancreatic function tests.

Qualitative examination of stool fat is often used as a preliminary check for the possibility of pancreatic dysfunction. The presence of excessive fat in the stool is suggestive of an exocrine pancreatic insufficiency (Green & Doershuk, 1984). A more exact evaluation of steatorrhea consecutive to pancreatic insufficiency is obtained from a quantitative evaluation of stool fat. This procedure involves a three to five day stool collection, and subsequent measurement of fat excreted. The quantity of fat excreted is expressed as a percentage of the dietary fat intake. If the stool fat exceeds 10 percent of the fat intake, fat maldigestion most likely attributable to insufficient exocrine pancreatic secretion, is suggested (Anderson et al. 1987).

The most common laboratory procedure to assess pancreatic function is the direct measurement of trypsin or chymotrypsin activity in the stool (Durie et al. 1979). A finding of trypsin/chymotrypsin stool activity below normal expected levels indicates that the patient has insufficient pancreatic function. Due to the potential inactivation of trypsin by colon bacteria, measurement of chymotrypsin activity is considered to be more reliable than trypsin activity (Barbero et al. 1966; Dyck, 1967).

Alternatively, the actual stool content of trypsin or chymotrypsin can be measured. In this case, pancreatic insufficiency is indicated and cystic fibrosis suggested when trypsin and chymotrypsin levels fall below 20 and 30 units per gram of stool, respectively (Barbero et al. 1966; Dyck, 1967).

In general, tests that measure the activity or content of trypsin or chymotrypsin in the stool are easy to complete. The stool chymotrypsin test appears to provide a reliable indication of pancreatic insufficiency, although the test is insensitive until severe pancreatic insufficiency develops (Barbero et al. 1966).

Analysis of the serum from patients being tested for cystic fibrosis for substances such as vitamin A, vitamin E, pancreatic isoamylase, trypsin, lipase, and PABA (p-amino benzoic acid) can provide evidence of exocrine pancreatic insufficiency (Kollberg, 1982; Anderson et al. 1987).

Serum levels of vitamins A or E are measured following oral administration of these vitamins. Vitamins A and E are fat-soluble and consequently their intestinal absorption occurs only in the presence of properly digested fat. Low serum levels of vitamins A or E, after oral administration, is suggestive of fat maldigestion and insufficient exocrine pancreatic secretion (Kollberg, 1982). The assessment of serum vitamin concentrations, however, is an indirect

measurement of pancreatic function and should not be taken as conclusive evidence of pancreatic insufficiency (Durie et al. 1984).

A rise in serum levels of trypsin, amylase, and lipase may suggest that the pancreas is inflammed or there is obstruction of pancreatic flow into the duodenum. If serum levels of such pancreatic enzymes are lower than normally expected, the presence of severe pancreatic dysfunction is implied (Anderson et al. 1987). The decrease in pancreatic enzyme levels indicates that synthesis of the enzymes is reduced possibly due to the presence of fibrotic lesions in the pancreatic tissue and a loss of functional pancreatic tissue.

More recently, the presence of PABA (p-amino benzoic acid) in the serum has been used to evaluate pancreatic function. The "PABA test" requires the subject to ingest BT-PABA (N-benzoyl-L-tyrosyl p-amino benzoic acid), and following this a serum sample is taken and analysed for the presence of PABA. BT-PABA is a compound that is hydrolyzed to PABA in the presence of chymotrypsin. Moreover, BT-PABA is normally hydrolyzed to PABA in the small intestine due to the pancreatic secretion of chymotrypsin (Durie et al. 1984). The PABA is then absorbed across the intestinal mucosa into the bloodstream, and can be detected in a serum analysis. Significantly reduced serum PABA levels, following oral ingestion of BT-PABA, are indicative of insufficient

exocrine pancreatic secretion (Durie et al. 1984). Another test, similar to the serum PABA test, involves analysis of a urine sample for PABA, following oral ingestion of BT-PABA. By the same principle as in the serum analysis, low PABA concentration in the urine, usually expressed as a percentage of the oral dose of BT-PABA, may be taken to reflect a reduced chymotrypsin activity (Durie et al. 1984). In a normal healthy individual, within six to eight hours of urine collection, more than 65 % of the ingested dose of BT-PABA will be recovered as PABA (Anderson et al. 1987). Recovery of less than 15 % of the ingested BT-PABA indicates exocrine pancreatic dysfunction (Anderson et al. 1987).

Examination of duodenal fluid for pancreatic enzyme concentrations, water and bicarbonate levels, can determine the presence and extent of exocrine pancreatic dysfunction. The duodenal fluid is obtained by duodenal intubation following pancreatic stimulation by exogenous hormones, such as secretin or pancreozymin. Pancreatic insufficiency would be suggested by a decreased volume of duodenal fluid, below normal bicarbonate concentrations and reduced levels of pancreatic enzymes, for example, amylase (Durie et al. 1984). This procedure, aside from being technically difficult to perform and uncomfortable for the patient, is subject to error as the fluid aspired from the duodenal region may actually be a mixture of pancreatic juice, duodenal secretions and bile (Matthews et al. 1980; Green &

Doershuk, 1984). Thus, the results from the analysis of duodenal fluid are probably an approximate estimate of pancreatic function, and may be unspecific for pancreatic insufficiency.

Recently, efforts have been made to develop a neonatal screening test for cystic fibrosis. The most promising screening procedure involves a radioimmunoassay that measures the serum or plasma trypsin concentration. The "immunoreactive-trypsin assay" developed from the discovery in 1979 by Crossley et al. that infants with cystic fibrosis had increased levels of immunoreactive trypsin (IRT) in their blood (Crossley et al. 1979; Wilcken et al. 1983). Elevated levels of IRT in cystic fibrosis patients, as much as four times normal values, were determined from newborn screening and retrospective assays of neonatal serum samples taken from children who were diagnosed as having cystic fibrosis late in life (Crossley et al. 1979; King et al. 1979; Kirby et al. 1981). The general hypothesis to explain the increased concentrations of IRT in the serum of newborn cystic fibrosis infants states that elevated serum IRT results from the secretory obstructive defect in the pancreas (Durie et al. 1984). In the early stages of the disease, the pancreas retains sufficient exocrine tissue and can produce IRT, however, the obstructive lesions force the IRT into the circulation (Elias et al. 1977; Crossley et al. 1979; Davidson et al. 1984). The procedure involves

assaying serum samples in the form of dried blood samples for the presence of IRT. The immunoreactive trypsin assay is a promising neonatal screening procedure for the detection of cystic fibrosis. The diagnostic importance of the IRT assay is potentiated by factors such as the tests' accuracy (Crossley et al. 1979; Davidson et al. 1984), reliability, and the practicality of executing the assay due to the fact that the IRT assay can be incorporated into the routine newborn screening programs for certain metabolic disorders, such as phenylketonuria and hypothyroidism, that are already performed in newborns and thus require collection of a blood sample from the infant. Widespread use of the IRT assay is hindered by dissimilarities in radio-immuno assay systems, which are based on the same theory but produce significantly different results (Kirby et al. 1981; Davidson et al. 1984). The assay of IRT is limited to the newborn population, as screening older cystic fibrosis patients has lead to the discovery that most cystic fibrosis children, over one year of age, have normal or decreased circulating IRT levels (Kirby et al. 1981; Davidson et al. 1984). Low IRT levels found in older cystic fibrosis patients can be explained by the diminution of viable pancreatic tissue in this group (Davidson et al. 1984).

3.3 Respiratory Function Tests

Diagnosis of cystic fibrosis can often times be made from a thorough evaluation of respiratory function including a detailed patient history and physical examination, respiratory sputum culture, chest X-rays, and pulmonary function tests.

Consideration of the patient history and physical examination of the patient may provide evidence of chronic pulmonary obstruction, typical of cystic fibrosis disease. The presence of a chronic cough, increased respiratory rate, and a decreased exercise tolerance, all compared to expected norms, as well as, barrel chest, and/or clubbing of the fingers, indicates pulmonary obstruction and may suggest cystic fibrosis disease (Matthews & Drotar, 1984), especially when other cystic fibrosis diagnostic tests, such as the sweat test or tests of pancreatic function, are affirmative for cystic fibrosis disease.

Sputum cultures may provide information useful in the diagnosis of cystic fibrosis. Analysis of sputum involves taking a mucous sample from deep within the throat, and culturing the mucous sample to determine the dominant infectious agents. An excessive amount of staphylococcus aureus bacteria in the sputum might suggest cystic fibrosis disease, as staphylococcus aureus is commonly found in patients with cystic fibrosis (Kollberg, 1982). The

presence of staphylococcus aureus is usually limited to the early stages of cystic fibrosis disease, when respiratory dysfunction is mild (Matthews & Drotar, 1984). The presence of pseudomonas aueruginosa in the sputum supports a positive diagnosis of cystic fibrosis disease, although it predominates in the more advanced stages of cystic fibrosis, at which time a positive diagnosis would most likely have been established. Although sputum cultures are limited with respect to the actual diagnosis of cystic fibrosis, sputum analysis provides specific information about the type of pulmonary infection and this in turn facilitates proper antibiotic therapy for the management of the pulmonary infection.

Diagnosis of cystic fibrosis can be suggested and/or confirmed from the findings of chest X-rays. The chest X-ray of a cystic fibrosis patient will show evidence typical of pulmonary obstruction. In the early stages of cystic fibrosis disease, X-rays usually show generalized or irregular hyperinflation of the chest, areas of atelectasis, and a depressed diaphragm (Phelan, 1982; Green & Doershuk, 1984). Chest X-rays that show evidence of peribronchial thickening, chest hyperinflation, and an increased anterior-posterior chest diameter are diagnostic for cystic fibrosis in a more advanced stage of respiratory involvement (Kollberg, 1982). An apparent cardiac enlargement, as seen on a chest X-ray (Hirschfeld et al. 1979; Moss, 1982),

indicates severe cystic fibrosis, however, by this stage of the disease a positive diagnosis would most likely have been established.

The final diagnostic consideration referring to the respiratory system are the tests of pulmonary function. In general, studies of both static and dynamic pulmonary function will reveal the presence and extent of obstruction in the lungs. Cystic fibrosis disease would be suggested by a decreased vital capacity, decreased flow rates and an increased residual volume compared to normal values (Gurwitz et al. 1979; Matthews & Drotar, 1984). The main criticism of the pulmonary function studies is that valid test results are not obtained until 4 to 6 years of age (Green & Doershuk, 1984), at which age an affirmative diagnosis of cystic fibrosis would most likely have been established. Pulmonary tests are intended more for clinical monitoring of the progression of the disease and for evaluation of the efficacy of certain respiratory management strategies.

Although these diagnostic tests and criteria are quite specific, the diagnosis of cystic fibrosis remains difficult due to the spectrum of clinical symptoms and complications associated with cystic fibrosis that can occur at any age. As a consequence of this varied presentation of cystic fibrosis, diagnosis may occur soon after birth or be delayed until adulthood. Efforts are being made to develop accurate pre-natal diagnostic techniques and presently involve assays

of amniotic fluid and amniotic fluid cells for activity of enzymes such as alkaline phosphatase and trypsin, and mucociliary inhibitory factors (Lloyd-Still, 1983). The accuracy and reliability of these approaches is controversial at the present time. As well, DNA probes are being utilized prenatally for the detection of the cystic fibrosis gene defect (Weller, 1986), again through analysis of amniotic fluid.

Development of new and effective diagnostic techniques, will allow for earlier and highly accurate diagnosis of cystic fibrosis, the importance of which cannot be overemphasized in light of the better management and improved prognosis that result from early diagnosis (Orenstein et al. 1977).

4.0 RESPONSE TO EXERCISE

In the past decade, a large number of studies have examined the exercise response of patients with cystic fibrosis.

Maximal exercise tolerance in the cystic fibrosis population has mostly been evaluated by exercise protocols completed on cycle ergometer (Table 1). Generally, the cycling protocol is a progressive, incremental, continuous exercise to maximal exertion with voluntary exhaustion. Maximal work capacity is reported in terms of power output corrected for body weight (Cropp et al. 1982; Marcotte et al. 1986a), or as a percent predicted from control values (Godfrey & Mearns, 1971; Coates et al. 1982), although direct measurements of peak oxygen consumption are also reported (Henke & Orenstein, 1983; Orenstein et al. 1983). Less frequently, treadmill protocols have been used and evaluated exercise tolerance through direct measurement of oxygen consumption (Inbar et al. 1989), or considered the total treadmill running time to exhaustion (Edlund et al. 1986).

4.1 Maximal Exercise Tolerance

Results from maximal work capacity, or peak oxygen consumption, generally demonstrate a reduced exercise

tolerance compared to normal expected values (Table 1). More specific examination of those studies presented in table 1 reveals a wide range of maximal work capacity in this patient population, extending from 49 % up to 100 % of the normal predicted exercise performance. The maximal exercise performance has also been reported as peak oxygen uptake, usually in units of $mlO_2 \cdot min^{-1} \cdot kg^{-1}$. Such studies indicate peak oxygen consumption values that vary from 27.2 to 53.5 $mlO_2 \cdot min^{-1} \cdot kg^{-1}$ (Stanghelle et al. 1988d; Nixon & Orenstein, 1989), in cystic fibrosis patients ranging in age from 6 to 38 years. Comparison of these values to the maximal oxygen uptake achieved by the control counterparts, or to the standard normal values, reveals an impairment in the exercise performance which ranges from 5 % to 47 % (Edlund et al. 1986; Marcotte et al. 1986a; Stanghelle et al. 1988d).

Although most studies agree that the exercise tolerance of cystic fibrosis patients is below predicted values, the extent of intolerance is highly discrepant.

The reduced maximal exercise tolerance, relative to controls, observed in the cystic fibrosis patients may probably be explained in part, by different activity levels between these two groups. It is possible that patients with cystic fibrosis are not as active as their normal healthy co-horts, in part, due to time restrictions and limitations that result from the daily physiotherapy and periodic

Table 1

This table shows the response to maximal upright or supine, cycling or treadmill exercise in cystic fibrosis patients relative to controls.

Table 1. Response to Maximal Exercise in Cystic Fibrosis Subjects

AUTHOR	N m/f	AGE range	MODE/ POSITION	EXERCISE CAPACITY CF vs CONTROL	HR bts/min	HR% predicted
Godfrey et al. 1971	41 24/17	6-22	B/U	< (83)	NA	NA
Coates et al. 1980	20 14/6	8-16	B/U	< (76)	175+10	90
Coates et al. 1981	18	5-16	B/U	< (62)	NA	NA
Orenstein et al. 1981	31	10-30	B/U	< (84)	176+19	88
Coates et al. 1982	10	12-19	B/U	< (89)	178+11	89
Cropp et al. 1982	20	13.9	B/U	<	176	92
Orenstein et al. 1983	7	12-31	B/U	=	NA	96
Benson et al. 1984	31	10-35	B/S	=	155+3	79
Cerny et al. 1984	17	7-23	B/U	<	170+2	87

Table 1. Response to Maximal Exercise in Cystic Fibrosis Subjects cont'd

AUTHOR	N m/f	AGE range	MODE/ POSITION	EXERCISE CAPACITY CF vs CONTROL	HR bts/min	HR% predicted
Henke et al. 1984	91	7-35	B/U	=	175+16	90
Holzer et al. 1984	41	8-14	B/U	=	157+20	76
Edlund et al. 1986	23	10.1	T/U	=	NA	NA
Marcotte et al. 1986a	22 15/7	16-38	B/U	< (58)	172+13	92
Marcotte et al. 1986b	50 40/10	11-38	B/U	< (74)	175+13	93
Versteegh et al. 1986	24 12/12	10-22	B/U	<	NA	NA
Andreasson et al. 1987	7 4/3	6-20	B/U	< (86)	180+13	90
Lebecque et al. 1987	21 8/13	14-29	B/U	<	163+8	83
Coates et al. 1988	16 11/5	15-35	B/U	< (55)	174	89

Table 1. Response to Maximal Exercise in Cystic Fibrosis Subjects cont'd

AUTHOR	N m/f	AGE range	MODE/ POSITION	EXERCISE CAPACITY CF vs CONTROL	HR bts/min	HR% predicted
Hortop et al. 1988	11 4/7	12-25	B/U	< (77)	174+9	89
Stanghelle et al. 1988	8	15.9	B/U	< (73)	174	85
Stanghelle et al. 1988	8	9-21	B/U	<	180	92
Stanghelle et al. 1988	8	10-13.5	B/U	<	195+11	100
Stanghelle et al. 1988	3	18	B/U	=	185	92
Inbar et al. 1989	13	NA	T/U	< (70)	NA	NA
Loutzenhiser et al. 1989	34	6-18	T/U	<	NA	NA
Nixon et al. 1989	36	8-29	B/U	<	174+15	89

B, cycle ergometer. T, treadmill.
U, upright. S, supine.
HR, heart rate at maximal exercise. HR%, heart rate expressed as a percentage of normal predicted maximal heart rate according to Godfrey et al. 1971.
<, or = indicates exercise capacity relative to control. Values in parentheses expresses exercise capacity of cystic fibrosis subjects as a percentage of control values.

hospitalization. Furthermore, it is not unreasonable to suggest that some patients adopt a sedentary lifestyle due to the likely quick onset of dyspnea.

Moreover, the level of activity in the cystic fibrosis patient may be minimized due to psychosocial factors (Tropauer et al. 1970). Psychological studies of parents of children with disease have revealed that the parents may restrict the participation of their child in physical activity due to their concern for the child's health (Tropauer et al. 1970). An overprotective attitude, as such, could result in a child, adolescent or adult, that is unfamiliar with the feelings that accompany exertion i.e. increasing heart rate, and muscular soreness, and consequently, apprehensive about exercise. As a result, the actual exercise test may be pre-empted prior to maximal effort.

Nonetheless, a very probable and important reason for the reported lower exercise tolerance in the cystic fibrosis patients, as compared to normal healthy controls, is the reality of the diseased state of these patients. The respiratory disease, cardiovascular dysfunction and malnutrition that characterize cystic fibrosis disease contribute to the impaired maximal exercise tolerance of the patients, as compared to healthy control subjects.

A relationship between disease severity and exercise tolerance in the cystic fibrosis population was first

demonstrated by Godfrey et al. in 1971. In this study, patients were classified into grades according to clinical and radiological findings, and general health. The grade I group i.e. the group with the best health status, had a normal maximal work capacity (Wmax), as compared to healthy age-matched controls. Grade II and III groups, respectively, completed 82 % and 69 % of expected maximal work. The association between lung function and exercise tolerance is supported by the findings of Cerny et al. in 1984, which showed significant and concurrent improvements in FEV_1 and pulmonary function score and a significant increase in peak work capacity as a result of acute in-hospital therapy.

Differences in nutritional status between cystic fibrosis subjects and controls may also account, at least in part, for the discrepant exercise tolerance observed between these two groups. In 1980, Coates et al. demonstrated that nutritional status is influential in determining the exercise capacity of patients with cystic fibrosis. This general relationship between poor nutritional status and exercise tolerance was confirmed by the study of Marcotte et al. (1986a), which reported that "well-nourished" cystic fibrosis patients were able to complete 69 % of the expected maximal work, while the "malnourished" patients could only complete 49 % of the predicted work. These discrepant results between cystic fibrosis patients with varying

nutritional conditions may be accounted for by the effects of malnutrition on muscle mass. Lean muscle wasting has been associated with malnutrition. This could be manifest as a loss of leg muscle mass (Russell et al. 1984), insufficient function of the respiratory muscles (Coates et al. 1980), and/or possibly alterations of the integrity of the cardiac muscle (Oppenheimer & Esterly, 1973; Marcotte 1986a), all of which could contribute to limit exercise capacity in the cystic fibrosis patients.

Furthermore, the lack of classification of the subjects into specific groups of disease severity in many of the studies may add to the confusion when comparing results from different studies. To demonstrate this point, consider the study by Marcotte et al. (1986b) in which the cystic fibrosis subjects have a mean FEV_1 of 60 % predicted, indicative of moderate airflow obstruction, but a range from 22% to 120% predicted of normal, indicative of normal to severe lung obstruction. Given the previous findings that demonstrate a relation between disease severity and maximal exercise performance, it is difficult to compare these findings to other studies that perhaps have a more specific patient description.

4.2 The Oxygen Transport System

While the limitation in exercise tolerance may be accounted for by multiple factors associated with the very nature of cystic fibrosis disease, further explanation is required. The reduced exercise tolerance and the lower than predicted maximal oxygen uptake, observed in the cystic fibrosis population, may be explained by considering the individual determinants of oxygen consumption. As described by the Fick equation (equation 1), oxygen consumption is the product of cardiac output and the peripheral oxygen extraction, calculated from the arterio-venous difference in oxygen content:

$$VO_2 = Qc \times a\text{-}vO_2diff \quad \text{(equation 1)}$$

Considering that cardiac output is determined by heart rate and stroke volume, this equation can be rewritten as:

$$VO_2 = (HR \cdot SV) \cdot (CaO_2 - CvO_2) \quad \text{(equation 2)}$$

Limitations in either oxygen transport, or uptake by peripheral tissues, or a combination of these factors, could thus contribute to the exercise intolerance reported in cystic fibrosis patients.

4.2.1 Cardiac Output

Cardiac output determined through either the thermal dilution technique (Michael et al. 1984; Geggel et al. 1985), direct Fick method (Goldring et al. 1964; Dantzker et al. 1982), or by the indirect Fick procedure (CO_2 rebreathing) (Godfrey et al. 1971; Marcotte et al. 1986a,b; Coates et al. 1988; Hortop et al. 1988) has been evaluated in cystic fibrosis patients, both at rest and in response to upright or supine submaxial exercise (Table 2).

Results from table 2 generally indicate that the cardiac output measured at rest or during submaximal exercise, expressed either in absolute values ($L \cdot min^{-1}$) or relative to body surface area ($L \cdot min^{-1} \cdot m^{2-1}$) are within normal limits. In particular, cardiac output values measured for exercise intensities between 33 and 66 percent of the maximal work capacity, range from 6.2 to 13.7 $L \cdot min^{-1}$, and are comparable to those expected from healthy controls for equivalent work outputs (Godfrey et al. 1971; Dantzker et al. 1982; Marcotte et al. 1986a; Coates et al. 1988; Hortop et al. 1988). Similar findings have been reported in studies measuring cardiac output at rest and submaximal exercise in adult patients with chronic obstructive pulmonary disease (Mahler et al. 1985).

None of the cystic fibrosis studies, however, provided age and/or height matched controls. Consequently,

comparison between the cystic fibrosis subjects and the control subjects is based on Godfrey's predicted values from normal standards for pediatrics (Godfrey, 1974), despite the fact that the cystic fibrosis study populations are predominantly young adults. Furthermore, the ability of the patients to maintain a normal cardiac output response to exercise intensities greater than 66% maximal work capacity, up to maximal exertion is undocumented.

4.2.2 Heart Rate

The resting heart rate of patients with cystic fibrosis disease has been found to be within normal limits or elevated, as compared to normal control values (Goldring et al. 1964; Cropp et al. 1982; Geggel et al. 1985). Maximal heart rates, however, generally appear to be reduced in the cystic fibrosis patients, relative to normal healthy control subjects (Table 1). From table 1, it can be seen that the maximal heart rate achieved by the cystic fibrosis patients is in the range of 155 to 185 beats per minute ($bts \cdot min^{-1}$). The maximal heart rate attained by the cystic fibrosis subjects is found to lie between 76 and 100 percent of that predicted from healthy controls or from Godfrey's standards for normal children (Godfrey, 1974).

The reason for the reduced maximal heart rate seen in the cystic fibrosis patients is unexplained, yet again there

appears to be a link with disease severity. This phenomena was first demonstrated by Cropp et al. in 1982. In this study, cystic fibrosis patients were placed in groups according to their "pulmonary function score", derived from results of six pulmonary function tests. It was reported that a mean maximal heart rate of 191 bts$\cdot$min^{-1} was achieved by the "normal CF" group, which was equal to the mean maximal heart rate achieved by the control group. The mean maximal heart rate was lower, however, in the groups designated as mild, moderate, and severe cystic fibrosis reaching values of 184 bts$\cdot$min^{-1}, 182 bts$\cdot$min^{-1}, and 162 bts$\cdot$min^{-1}, respectively. In this same study, the ratio of peak heart rate to peak work capacity (PHR/PWC) was reported to increase with increased disease severity.

The heart rate response to a given bout of submaximal dynamic exercise appears to be elevated, compared to Godfrey standards (Michael et al. 1984; Geggel et al. 1985; Marcotte et al. 1986a,b; Hortop et al. 1988). Inferences about the heart rate response to submaximal exercise are limited. Only a single study actually expressed the submaximal steady state heart rate obtained by their subjects relative to normal healthy co-horts (Marcotte et al. 1986a). At best, comparison of the heart rate response to submaximal exercise is restricted to using Godfrey standards (Godfrey, 1974).

The observation that cystic fibrosis patients, generally, do not reach the predicted maximal heart rate has

been interpreted in several ways. It may be proposed that there is a general chronotropic limitation to exercise in the cystic fibrosis population, perhaps associated with the pathogenesis of the disease and affecting the control of heart rate. However, the ability of some patients to reach an expected maximal heart rate does not support this theory. It has also been suggested that a pulmonary or metabolic component is responsible for the limited exercise tolerance seen in the cystic fibrosis patients. It is possible that exercise performance of the cystic fibrosis patients is pre-empted by such pulmonary or metabolic factors before the expected maximal heart rate is reached (Godfrey & Mearns, 1971; Cropp et al. 1982; Orenstein et al. 1983). None the less, to date, a satisfactory explanation for the atypically elevated heart rate at rest and submaximal exercise intensity has not been provided.

Differences in methodologies employed by each of the studies make it difficult to accurately compare results between the exercise studies. Investigations are diverse with respect to exercise protocols, nondescript and heterogenous patient groups in terms of age or health, and the reporting of exercise tolerance in dissimilar units. Furthermore, and most significant, between study comparison is difficult, because many studies do not use control subjects or fail to report results from age and/or sized matched controls. As can be seen in table 1, there is a

Table 2

This table presents the mean values for cardiac output, stroke volume and heart rate at rest and submaximal exercise intensities during upright, supine, and semi-recumbent exercise positions on cycle ergometer in cystic fibrosis subjects. Where indicated, values are expressed relative to normal predicted values.

Table 2. Comparative Exercise Hemodynamics in Cystic Fibrosis Patients

AUTHOR	AGE range	POSITION	INTENSITY	CO L/min	SV ml/bt	HR bt/min	METHOD
Goldring et al. 1964 (n=12)	6-22	R	Rest	5.1 (=)	43.6 (<)	119 (>)	Direct Fick
			Submax	6.2 (=)	47.0 (<)	133 (>)	
Godfrey et al. 1971 (n=41)	6-22	U	33% Wmax	†	NA	NA	CO2 Rebreathing
			66% Wmax	†	NA	NA	
Dantzker et al. 1982 (n=6)	17-30	R	Rest	6.2 (=)	NA	NA	Direct Fick
			Submax	11.0 (>)	NA	NA	
Michael et al. 1984 (n=2)	20-21	S	Rest	4.6*	44.7*	102 (>)	Thermo-dilution
			Submax	7.4*	56.4*	132 (>)	
Geggel et al. 1985 (n=6)	24-31	S	Rest	4.2*	37.8*	111 (>)	Thermo-dilution
			Submax	6.9*	49.3*	140 (>)	
Marcotte et al. 1986b (n=21)	11-38	U	50% Wmax	13.7 (>)	87.0 (<)	158 (>)	CO2 Rebreathing
Marcotte et al. 1986a (n=22)	16-38	U	50% Wmax	10.0 (=)	67.0 (<)	154 (>)	CO2 Rebreathing
Coates et al. 1988 (n=16)	15-35	U	50% Wmax	NA (=)	NA (<)	NA (>)	CO2 Rebreathing
Hortop et al. 1988 (n=11)	12-25	U	66% Wmax	8.4 (=)	51.7 (<)	162 (>)	CO2 Rebreathing

U, upright. S, supine. R, semi-recumbent.
CO, cardiac output. SV, stroke volume. HR, heart rate. Wmax, maximal work capacity. Submax, unspecified submaximal exercise intensity.
NA, not available. †, reported to be "within normal limits".
(<),(>), or (=) indicates result relataive to controls or normal values (Godfrey, 1974).
*, result is expressed relative to body surface area.

broad age range of cystic fibrosis subjects within and between studies. Without any control subjects or control values it is difficult to make interpretation of the exercise results. Considering that the age of subjects often spans from childhood to adulthood it is difficult to evaluate the maximal heart rate relative to normal expected values because of the documented decrease in maximal heart rate observed with increasing age (Astrand, 1970). As well, attention should be given to the large age span of the subjects, as cystic fibrosis is a disease that advances with age, and thus a more reduced maximal exercise tolerance, relative to normal, may be expected in the older patients.

4.2.3 Stroke Volume

Stroke volume, calculated from cardiac output determination, has been found to be lower in cystic fibrosis patients, as compared to normal expected values, both at rest and during submaximal exercise evaluation.

Table 2 presents mean stroke volumes for cystic fibrosis patients at rest and submaximal exercise. Resting stroke volume for the cystic fibrosis subjects examined range between 37.8 to 44.7 $ml \cdot min^{-1}$. These values appear to be decreased relative to clinically normal controls, as resting stroke volume values between 50 to 75 $ml \cdot min^{-1}$ are generally considered to be normal (Godfrey, 1974). Given a

similar myocardial inotropic state, the apparently reduced stroke volume observed in the cystic fibrosis patients may be partly explained by the higher resting heart rate observed in this study population, which would reduce the ventricular filling time. On the other hand, this may also reflect an impairment in the inotropic potential of the myocardium. Furthermore, it is difficult to compare the stroke volume values observed in the cystic fibrosis patients with standard normal values (Astrand, 1970; Godfrey et al. 1972; Godfrey, 1974) because of discrepancies in the age span and stature of the cystic fibrosis patients.

Stroke volume values assessed during submaximal exercise intensities up to 66 % maximal work capacity, measured in cystic fibrosis patients, are reported to range from 49.3 to 87 $ml \cdot min^{-1}$ (Table 2). In those studies that express the submaximal exercise stroke volume of the cystic fibrosis patients, as a percent predicted, relative to normal standards, the stroke volume response appears subnormal and may be reduced to 74 % of the expected value (Marcotte et al. 1986a,b; Hortop et al. 1988). Other studies, however, do not include a comparative expression of the stroke volume response to submaximal exercise. Thus, it is difficult to suggest or confirm a possible disturbance in the stroke volume response in the cystic fibrosis population because of the lack of control subjects within studies, and/or because

of dissimilar patient profiles and varying exercise intensities across investigations.

4.2.4 Arterial Oxygen Content

The exercise intolerance and lower than predicted maximal oxygen consumption reported in cystic fibrosis patients may be partly attributed to a limitation in gas exchange and/or gas transport.

Cystic fibrosis patients often exhibit subnormal arterial oxygen saturation. Resting arterial oxygen saturation (SaO_2) below 95 % are not uncommon in the cystic fibrosis population. Significant arterial oxygen desaturation, by as much as a 10 % decrement (Germann & Orenstein, 1981; Marcotte et al. 1986a; Nixon & Orenstein, 1989) or to values as low as 78 % (Lebecque et al. 1987), are often reported in cystic fibrosis patients at maximal exercise (Table 3). In general, there apears to be a direct relationship between the presence of exercise-induced arterial oxygen desaturation and increasing disease severity (Cropp et al. 1982; Cotton et al. 1985). In contrast, however, not all cystic fibrosis patients desaturate with exercise. In fact, in some patients that have a resting SaO_2 less than 95%, an increase in arterial oxygen saturation above their resting levels has been observed with exercise (Henke & Orenstein, 1984; Marcotte et al. 1986b).

In this situation, an improved arterial oxygen saturation may be explained by more effective matching of ventilation to perfusion and/or the increase in pulmonary capillary blood volume that accompany exercise.

The exercise-induced arterial desaturation may probably be accounted for by a decrease in alveolar ventilation, an increase in dead space to tidal volume ratio, as well as the disturbed alveolar ventilation to perfusion ratio that results from the pulmonary obstruction (Cropp et al. 1982; Henke & Orenstein, 1984; Versteegh et al. 1986; Lebecque et al. 1987).

Indeed, as mentioned previously, the diffusion capacity for carbon monoxide (DL_{CO}) in cystic fibrosis patients at rest is reported to be either decreased (Goldring et al. 1964; Featherby et al. 1970; Cotton et al. 1985), increased (Keens et al. 1979) or unchanged (Beier et al. 1966) as compared to normal expected values. Only a single study has evaluated the response of the lung diffusion capacity to exercise (Zelkowitz & Giammona, 1969). Results from this study indicate that cystic fibrosis patients do not exhibit the usual increase in DL_{CO} with increasing exercise intensity (Zelkowitz & Giammona, 1969).

Alveolar hypoventilation and ventilation-perfusion inequalities are present in most cystic fibrosis patients at rest (Featherby et al. 1970), as a consequence of the pulmonary obstruction. Although the response of alveolar

ventilation and ventilation-perfusion ratio to progressive exercise in cystic fibrosis patients has not been documented per se, the ventilatory reponse to maximal exercise has been reported.

Results from cystic fibrosis exercise studies that measured ventilation and parameters related to respiratory function, are presented in table 3. Data generally indicates that there is an impaired and ineffective ventilatory response to maximal exercise in the cystic fibrosis population.

Ventilation ($L \cdot min^{-1}$) at maximal exertion in the cystic fibrosis patients appears to be equal to or increased above normal control values for the amount of work completed (Godfrey & Mearns, 1971; Cropp et al. 1982; Marcotte et al, 1986a,b). The relative hyperventilation is most probably a compensatory response in order to maintain effective alveolar ventilation during exertion, in the face of an increased physiological deadspace (Coates et al. 1980,1981,1988; Henke & Orenstein, 1984). As previously discussed, however, the efficacy of this response is doubtful, since a decrease in arterial oxygen content and/or even an increase in arterial carbon dioxide have been reported in some patients, especially in those patients with advanced disease, during exercise (Orenstein et al. 1981; Cropp et al. 1982; Marcotte et al. 1986a; Inbar et al. 1989). Lower than predicted levels of ventilation at

Table 3

This table presents the pulmonary response to maximal upright cycling exercise in cystic fibrosis subjects. Values are expressed relative to normal predicted values.

Table 3. Comparative Pulmonary Parameters at Maximal Exercise

AUTHOR	AGE range†	V_E	V_E/MVV (%)	V_E/VO_2	SaO_2*
Godfrey et al. 1971 (n=41)	6-22	>	>		
Orenstein et al. 1981 (n=31)	10-30		> (76)		
Germann et al. 1981 (n=171)	9-35			>	<<
Cropp et al. 1982 (n=20)	13.9	>		>	<
Cerny et al. 1984 (n=17)	7-23				<
Henke et al. 1984 (n=91)	7-35				<,>
Holzer et al. 1984 (n=41)	8-14	=		=	
Marcotte et al. 1986b (n=50)	11-38	<	> (93)		<,>
Marcotte et al. 1986a (n=22)	16-38	<	> (94)		<
Lebecque et al. 1987 (n=21)	14-29		>		<<
Stanghelle et al. 1988 (n=8)	15.9	<	> (83)		<
Stanghelle et al. 1988 (n=3)	18	<		>	
Coates et al. 1988 (n=16)	15-35		> (100)		<,=
Nixon et al. 1989 (n=36)	8-29	<		>	<,=

V_E, ventilation. V_E/MVV, ventilation relative to maximal voluntary ventilation. Values in parentheses are ventilation expressed as a percentage of maximal voluntary ventilation. V_E/VO_2, ventilatory equivalent for oxygen consumption. SaO_2, arterial oxygen saturation. <,> or = expresses value measured at maximal exercise in cystic fibrosis patients relative to controls, or predicted values (Godfrey, 1974).
*, saturation espressed relative to resting value.
†, age expressed as mean age when range not available.

maximal exercise have also been reported in cystic fibrosis patients with severe pulmonary dysfunction, which may be explained by the limited ability of the cystic fibrosis patient to increase their tidal volume with exercise. It has been suggested that the presence of lung hyperinflation found in some cystic fibrosis patients may limit the inspiratory reserve. As a consequence, it may be impossible to increase the tidal volume during exertion above resting levels (Godfrey & Mearns, 1971; Cerny, 1981).

Evaluation of the ventilatory equivalent for oxygen consumption (V_E/VO_2) in exercising cystic fibrosis subjects indicates that the amount of ventilation is excessive for the amount of work performed or the amount of oxygen consumed compared to normal values (Germann & Orenstein, 1981; Katsardis et al. 1986; Inbar et al. 1989). The elevation in ventilatory equivalent for oxygen consumption appears to be related to increased disease severity (Canny et al. 1982).

Moreover, at maximal exercise, cystic fibrosis patients are commonly utilizing a more substantial portion of their ventilatory reserve than is predicted from normal healthy controls. While ventilation at maximal exercise in healthy individuals is usually equivalent to 60 % to 70 % of their maximal voluntary ventilation ($V_E/MVV=.6$ to .7) (Godfrey, 1974b), cystic fibrosis subjects are usually using greater than 70 % of their MVV (Table 3). At times their

ventilation at maximal exercise may even exceed their MVV (V_E/MVV > 1.0) (Godrey & Mearns, 1971; Coates et al. 1988). A greater energy cost of breathing may contribute to limit the exercise performance of the cystic fibrosis subjects.

5.0 RESPONSE TO EXERCISE TRAINING

Participation of cystic fibrosis patients in physical activities has been recommended and encouraged for many years. This recommendation, however, was primarily based on the results of exercise studies completed on patients with chronic obstructive pulmonary disease (COPD). Findings from these studies indicated that those COPD patients that were physically active on a regular basis were in better health than those COPD patients that were sedentary (Barach et al. 1952; Chester et al. 1977).

The effects of chronic exercise in cystic fibrosis patients has only recently been examined. Investigations of the consequences of chronic exercise in patients with cystic fibrosis disease have examined the effects of a variety of training programmes. Swimming (Edlund et al. 1986), running (Orenstein et al. 1981; Holzer et al. 1984), circuit training (Andreasson et al. 1987), recreational games (Orenstein et al. 1981; Andreasson et al. 1987), as well as other forms of physical activity suited to personal interest and capacity (Blomquist et al. 1986) were used in these studies. Training periods were generally prescribed for a minimum frequency of three sessions per week (usually more), at an intensity that kept the heart rate between 60-85 % of the peak heart rate for 30 minutes or more. The training programs lasted anywhere between 12 weeks (Orenstein et al.

1981, Holzer et al. 1984; Edlund et al. 1986) to 30 months (Andreasson et al. 1987).

The response of cystic fibrosis patients to exercise training may be regarded in three schemes: cardiorespiratory fitness, pulmonary function and psychological effects.

Survey of cystic fibrosis patients that participated in regular physical activity, either self-initiated or as subjects in a research project, generally indicates that there is a positive attitude towards physical activity. Physical activity appears to have psychological benefits for the patients with respect to improved self-image and confidence, and an overall sense of well-being (Edlund et al. 1986; Canny & Levison, 1987). The effects of regular physical activity in the cystic fibrosis population, however, is not limited to emotional advantages.

Exercise conditioning in patients with cystic fibrosis has been shown to result in an increase in exercise capacity (Orenstein et al. 1981; Andreasson et al. 1987; Stanghelle et al. 1988c). In some cystic fibrosis subjects, working capacity was reported to be unchanged pre-training to post-training (Blomquist et al. 1986). It was, however, noted that these patients were often those in very poor clinical condition and consequently were most likely too ill to exercise (Blomquist et al. 1986). An increase in exercise tolerance as evaluated by time on the treadmill (Edlund et al. 1986) or maximal workload attained on a cycle ergometer

(Andreasson et al. 1987) has been demonstrated following adherent participation in a physical exercise program for a minimum of three months. Improved physical fitness in cystic fibrosis patients is suggested by an increase in maximal oxygen consumption following exercise training (Orenstein et al. 1981; Holzer et al. 1984). Furthermore, a reduction in heart rate at any given submaximal workload post-training was observed in some participants (Orenstein et al. 1981) which is a well-established effect of training in normal healthy populations (Clausen, 1977). This training bradycardia was not observed in non-exercising control groups of cystic fibrosis patients (Orenstein et al. 1981).

Effects of chronic exercise specific to the pulmonary system in cystic fibrosis patients have been observed and are usually beneficial. Generally, studies that have evaluated the effect of long-term physical activity on lung function report no change in resting pulmonary function (Orenstein et al. 1981; Holzer et al. 1984; Edlund et al. 1986; Blomquist et al. 1986). Most commonly, there does not appear to be any significant changes in pulmonary volumes e.g. vital capacity, residual volume, or flow rates e.g. FEV_1, following chronic physical conditioning. In exception to this, Blomquist et al. (1986) submit that there is a tendency to improve FVC and FEV_1 in most patients that followed the prescribed exercise program. It has been noted

that physical activity promotes coughing and mucous clearance (Edlund et al. 1986; Andreasson et al. 1987). Consequently, physical activity has been suggested as an alternative and/or adjunct to routine chest physiotherapy due to the coughing and mucous clearance that results following exercise. Thus if exercise is practiced on a regular basis, the enhanced mucous expectoration and airway clearance may potentially benefit the pulmonary system. Another effect of chronic exercise, occassionally observed in the cystic fibrosis population is the apparent improvement in arterial oxygen content at rest and maximal work capacity following exercise training (Blomquist et al. 1986; Andreasson et al. 1987). This phenomena is usually observed in those cystic fibrosis patients that have a low resting arterial oxygen content prior to training. The improved PaO_2 in some of the cystic fibrosis patients, most probably reflects more effective ventilatory function and gas exchange derived from effective mucous clearance and the forced respiration during exercise.

An increase in respiratory muscle strength and endurance, as measured by duration of sustained hyperpnea, has been reported following regular participation in physical activity (Keens et al. 1977; Orenstein et al. 1981). This training effect is most pronounced when the conditioning exercises involved the upper body musculature (Keens et al. 1977; Orenstein et al. 1981). Enhanced

respiratory muscle endurance (Keens et al. 1977) and strength (Asher et al. 1982) may also result from specific respiratory muscle training. These ventilatory muscle training programs, however, did not have a significant effect on the exercise endurance of these patients (Asher et al. 1982). In contrast, studies conducted on adult patients with chronic obstructive pulmonary disease have shown that ventilatory muscle training can improve both respiratory muscle endurance and exercise tolerance (Belman & Mittman, 1980).

Overall, the effect of chronic exercise training on both the physical and mental well-being of cystic fibrosis patients is encouraging. While most studies report no change in pulmonary function or clinical condition following participation in a training program, it has been suggested that regular physical activity is actually helping to maintain existing health status and may retard further pulmonary deterioration (Andreasson et al. 1987).

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Part II: EXPERIMENTAL STUDY

ABSTRACT

The reduced maximal oxygen uptake (VO_2max) generally observed in patients with cystic fibrosis (CF) is related to the severity of disease and could be attributed to limitations of both pulmonary and cardiac origin, although the nature of the latter remains to be determined. The present study was designed to characterize the cardiac output (Q_c) response to progressive submaximal upright (U) exercise in CF patients. Secondly, the Q_c adjustments were compared to those of similar supine (S) exercise, in an attempt to assess myocardial accomodation to the enhanced ventricular preload in the S posture. Thirty-one CF patients classified as mild (gr.II), moderate (gr.III) or severe (gr.IV) on the basis of FEV_1, as well as 11 age-matched controls (gr.I) completed Q_c determination (CO_2 Rebreathing) at rest, and submaximal exercise corresponding to 30,50 and 75% VO_2max in U and S positions. VO_2max was similar in groups I,II and III, but lower in gr.IV. Q_c generally increased with exercise intensity in both U and S positions, although in gr.IV values plateaued at 50% VO_2max (S). Maximal stroke index (SI) was achieved at 50% VO_2max (U) in all groups, except gr.IV and at 30% VO_2max (S) in all groups. As expected, the change from U to S posture resulted in a significant increase in SI at rest and for every submaximal exercise in gr.I, but not in CF patients, independent of disease severity e.g. (Rest:gr.I:

27±7(U)vs39±8(S); gr.II:24±5vs28±10; gr.III:18±4vs22±5; gr.IV:17±4vs20±6 ml/bt/m^2). These observations suggest a limitation in ventricular volume accomodation in CF patients which becomes apparent under conditions of S dynamic exercise.

INTRODUCTION

Patients with cystic fibrosis generally demonstrate a decrease in maximal exercise capacity (1-3), the extent of the impairment being directly related to the severity of disease (4-6). While a pulmonary limitation has been proposed, on account of the fact that exercise was stopped before the predicted maximal heart rate was reached (6), abnormal right and/or left ejection fractions found in some cystic fibrosis patients (7-9) under resting and exercise conditions suggest that limiting factors of both pulmonary and cardiovascular origin could be involved. Characterization of the cardiac output and/or stroke volume adjustments to graded submaximal exercise in cystic fibrosis patients remains very fragmented. While cardiac output values measured through direct Fick, indirect Fick, and thermal dilution methods at rest and at one given submaximal exercise load have been reported (6,10-17), the kinetics of these adjustments from rest through a series of submaximal loads remains to be documented. The present study was intended to characterize the kinetics of the cardiac output determinants in response to progressive incremental submaximal exercise loads. Secondly, the study was designed to examine the stroke volume response to a ventricular volume overload created by the recumbent position and further exaggerated by dynamic exercise, in an attempt to

evaluate the myocardial ability to cope with an exaggerated ventricular preload.

METHODS

Subject population

The study population consisted of 31 patients (15 males, 16 females) with cystic fibrosis disease, who were followed on a regular basis at the cystic fibrosis clinic of Ste-Justine Hospital, and 11 asymptomatic age-matched control subjects (gr.I). Cystic fibrosis patients were categorized, on the basis of their forced expiratory volume in one second expressed as a percent of the predicted normal value, into groups of mild (gr.II:FEV_1>75%predicted;n=10), moderate (gr.III:FEV_1=50-75% pred.;n=12) and severe (gr.IV:FEV_1<50%pred.;n=9) cystic fibrosis. Informed consent was obtained from all participants and the project had received approval from the ethics committee of the hospital research centre.

Evaluations

Anthropometric measurements, including height and weight for determination of body surface area, were obtained on all participants. Biceps brachii, triceps brachii, subscapular and suprailiac skinfold thicknesses (Harpenden calipers) were obtained for determination of sum of four skinfolds and percent body fat (18).

All participants completed standard static and dynamic pulmonary function tests at rest using a computerized pulmonary function testing device (Gould 2450). Forced expiratory volume in one second was used to confirm the patients' classification into mild (FEV_1= 89.5±11.3 %predicted (X±SD), moderate(FEV_1= 60.9±7.6 %pred.) or severe (FEV_1= 39.4±4.6 %pred.) patient groups. Pulmonary diffusion capacity (DL_{CO}) was assessed according to the modified Krogh method (19).

All subjects were submitted to a progressive continuous maximal exercise protocol on an electrically braked cycle ergometer (20) in both the upright and the supine position for determination of their maximal oxygen uptake, using open circuit spirometry (Sensor Medics-MMC Horizon). The subjects completed the upright and supine tests on two separate visits. The order of exercising position was random. Electrocardiographs, as well as oxygen saturation measured through finger oxymetry (Ohmeda BIOX 3700) were monitored throughout the test. All subjects were verbally encouraged to pursue as long as possible. Tests were terminated when the subjects were unable to continue or maintain the given pedalling cadence (60 rpm).

Following a 45-minute rest period the CO_2-rebreathing maneuvre (21) was performed to evaluate cardiac output (Q_c) at rest, and at exercise intensities corresponding to 30,50 and 75% of the previously determined maximal oxygen uptake.

Upon achievement of steady-state, usually after 5-6 minutes of cycling, a sample of arterialized blood was obtained from the subject's finger which had been prepared with a vasodilating agent (Finalgon) and kept warm by a heating pad. Following this, the rebreathing maneuvre was initiated. Arterialized pCO_2 was used as a reflection of arterial CO_2 content (20) for subsequent calculation of cardiac output. Mixed venous pCO_2 was obtained from the equilibrated plateau pCO_2 resulting from the rebreathing maneuvre. The Denison extrapolation method was used to estimate mixed venous pCO_2 when a satisfactory plateau could not be obtained (22). The "downstream" correction factor was applied for calculation of the exercise cardiac outputs (23). Heart rate (HR) was obtained from the electrocardiographic tracing and was used in the calculation of stroke volume (Q_s). In order to standardize measurements for possible differences in subjects' stature, both Q_c and Q_s measurements were corrected for body surface area and expressed as cardiac index (CI) and stroke index (SI), respectively.

Statistical analyses

Results of maximal and submaximal exercise tests are expressed as mean ± standard deviation. Analyses were carried out using the SPSSX statistical software package (24). Comparison between control subjects and patient groups, as well as between exercise level or body position

was achieved through multiple analyses of variance (MANOVA) followed by simple main effects analyses of variance (ANOVA) when a significant interaction between group, level or position was found. Post-hoc analyses (Scheffe test) were carried out to isolate specific differences due to position, within groups or exercise intensity. Statistical significance was set at $p \leq .05$.

RESULTS

Resting evaluations

Anthropometric characteristics of patients and control subjects appear in table IV. No significant difference in height or body surface area was observed between groups. The mean weight of gr.IV, however, was significantly lower than controls. Comparison of the sum of skinfolds did not reveal significant differences between control subjects and patients nor between patient groups although lower values were calculated in gr.IV.

As expected, results of pulmonary function tests indicate significant pulmonary impairment in moderate and severe patient groups as reflected by the lower VC, FEV_1/FVC, MVV and DL_{CO}, and an increased RV/TLC when compared to the control or mild CF group (Table V).

Legend to table IV

This table presents anthropometric characteristics of each study group. Values are expressed as mean ± SD (range). Statistical significance between controls and CF groups II,III, or IV is indicated by † for $p \leq .05$.

Table IV ANTHROPOMETRIC CHARACTERISTICS

	I	II	III	IV
AGE (years)	14.1 ± 3.3 (8-18)	12.8 ± 2.7 (10-19)	13.0 ± 2.8 (10-18)	15.8 ± 3.2 (10-19)
HEIGHT (cm)	161.6 ± 20.4 (130-182)	146.7 ± 9.3 (134-166)	151.8 ± 14.1 (134-176)	156.2 ± 12.4 (133-176)
WEIGHT (kg)	53.9 ± 18.4 (27.5-78.0)	35.7 ± 7.4 † (26.8-53.0)	38.9 ± 10.7 (23.9-60.0)	41.7 ± 9.3 (28.0-57.0)
B.S.A. (m^2)	1.55 ± .38 (.94-2.00)	1.23 ± .16 (1.01-1.58)	1.29 ± .24 (.97-1.74)	1.36 ± .20 (1.03-1.70)
sum of 4 skinfolds (mm)	36.7 ± 8.9 (24.5-55.1)	27.0 ± 10.0 (18.0-49.8)	30.1 ± 10.1 (20.6-38.4)	27.6 ± 9.0 (18.8-43.8)
body fat (%)	20.4 ± 3.5 (15.3-25.6)	16.4 ± 4.5 (11.5-24.1)	19.3 ± 5.8 (13.2-27.7)	18.7 ± 5.3 (12.1-26.5)

B.S.A., body surface area.

Legend to table V

Table V presents results of resting static and dynamic pulmonary function tests. Values are expressed as mean ± SD (range).

A significant difference between controls and CF groups II,III, or IV is indicated by * for $p \leq .01$, and by † for $p \leq .05$.

Table V PULMONARY FUNCTION TEST RESULTS

	I	II	III	IV
VC (L)	3.74 ± 1.28 (2.15-5.47)	?.58 ± .97 (1.61-5.01)	2.39 ± .89 (1.29-4.38)	1.85 ± .69* (1.14-2.88)
RV/TLC (%)	24.0 ± 4.8 (18-36)	26.7 ± 8.1 (16-38)	33.4 ± 4.9* (23-42)	44.1 ± 5.8* (37-55)
FEV_1/FVC (%)	87.7 ± 4.1 (79-93)	80.2 ± 10.1 (57-94)	69.6 ± 14.7* (48-94)	60.9 ± 10.8* (40-77)
MVV (L/min)	107.4 ± 41.6 (51-191)	73.6 ± 20.2† (42-121)	61.7 ± 16.8* (41-97)	42.3 ± 17.1* (25-80)
PinspMAX (cmH2O)	87.3 ± 9.9 (65-96)	71.9 ± 20.9 (40-101)	71.7 ± 22.7 (25-96)	63.4 ± 25.2 (30-92)
DL_{CO} (mlCO/ min/mm Hg)	30.1 ± 9.1 (19.6-45.8)	19.9 ± 7.8 (12.8-37.9)	20.8 ± 6.3 (14.6-34.9)	14.0 ± 4.3* (10.1-21.9)

VC, vital capacity; RV/TLC, residual volume/total lung capacity; FEV_1/FVC, forced expiratory volume in 1 second/forced vital capacity; MVV, maximal voluntary ventilation; PinspMAX, maximal inspiratory pressure; DL_{CO}, diffusion capacity for carbon monoxide

Exercise evaluations

Maximal exercise tolerance, as reflected by maximal work or maximal oxygen uptake, was comparable in groups I, II and III, in either the upright or the supine position. These values were, however, significantly lower in patients with severe cystic fibrosis (gr.IV) compared to all other groups (Table VI). Similarly, a significant reduction in maximal ventilation ($V_E$max) and oxygen saturation (SaO_2max) was observed in gr.IV, in either position. Between-group comparison of maximal heart rates does not indicate statistical significance for differences between controls and patient groups in either position, although values recorded in gr.IV are systematically lower than those of other groups.

Comparison of maximal oxygen consumption (VO_2max), maximal work and maximal ventilation between positions reveals values that are generally lower in the supine position for all subject groups, reaching significance in some instances. Oxygen saturation was not significantly different between the two positions, although gr.IV showed a substantial desaturation during the supine protocol. The maximal heart rate recorded in response to supine exercise was, however, significantly lower than that for upright exercise in all groups, except gr.IV, where similar values were observed.

Legend to table VI

Table VI presents results of maximal exercise tests completed in both the upright (U) and supine (S) positions . Values are expressed as mean ± SD.

A significant difference between controls and CF groups II,III or IV is indicated by * for $p \leq .01$, and by † for $p \leq .05$.

Within a group, statistical significance between U and S positions indicated by ‡ for $p \leq .01$ and by § for $p \leq .05$.

Table VI MAXIMAL EXERCISE RESULTS

		I	II	III	IV
WORKmax (kpm/min)	U	‡1137 ± 572	‡683 ± 236	‡653 ± 216	567 ± 148*
	S	‡ 891 ± 424	‡583 ± 251	‡552 ± 184	417 ± 151†
VO2max (ml02/min/ kg)	U	‡45.1 ± 9.9	41.9 ± 8.6	§37.6 ± 4.7	26.0 ± 5.5*
	S	‡39.8 ± 11.6	38.0 ± 8.4	§33.8 ± 4.4	26.4 ± 5.6*
HRmax (bpm)	U	§187 ± 13	‡188 ± 14	‡192 ± 8	176 ± 10
	S	§172 ± 22	‡178 ± 11	‡180 ± 10	169 ± 16
VEmax (L/min)	U	79.2 ± 40.1	§52.4 ± 16.4	‡59.9 ± 18.9	39.7 ± 9.9†
	S	68.4 ± 37.8	§43.8 ± 16.5	‡50.3 ± 14.9	36.8 ± 9.0
VEmax/MVV (%)	U	§71.6 ± 18.1	73.1 ± 19.9	‡98.9 ±25.4†	100.4 ±23.0††
	S	§63.2 ± 23.8	62.7 ± 15.9	‡83.9 ±22.4	94.5 ±23.0†
(VE/VO2)max (%)	U	31.3 ± 3.6	35.9 ± 8.6	41.8 ± 7.4*	37.8 ± 3.4
	S	30.7 ± 4.0	32.5 ± 3.8	39.1 ± 7.5	35.7 ± 4.5
SaO2max (%)	U	95.8 ± .7	94.8 ± 1.5	93.2 ± 2.3†	91.7 ± 2.6*
	S	96.5 ± .9	94.7 ± 2.4	94.0 ± 2.3	85.7 ±11.7*

VO_2max, oxygen consumption at maximal work; HRmax, maximal heart rate; $V_E$max, maximal ventilation during exercise; $V_E$max/MVV, maximal ventilation/maximal voluntary ventilation; (V_E/VO_2)max, ventilatory oxygen equivalent at maximal exercise; SaO_2, arterial oxygen saturation at maximal exercise.
U, upright; S, supine.

Cardiac index measured at rest and at each submaximal load in both the upright and supine positions are shown in figure 1. Results indicate a significant increase in CI from rest through intensities of 30,50 and 75% VO_2max in both upright and supine exercise protocols, in all groups except gr.IV. Results obtained in the latter group indicate that in the supine posture CI values are maximal at an exercise intensity of 50% VO_2max and do not significantly increase thereafter, despite increasing exercise intensity. All groups had similar CI values in both positions, at rest and at each exercise level, with the exception of gr.IV where a lower CI value was recorded, for the highest exercise intensity in the supine position. Between-group comparison of results reveals no significant difference in resting or exercise cardiac index in either the upright or the supine position in all groups, except gr.IV where a lower cardiac index was observed while exercising in the supine position at intensities of 50 and 75% VO_2max.

Heart rate variations in response to both supine and upright exercise protocols are illustrated in figure 2. As expected, an increase in HR is observed in all groups in response to increasing exercise intensities, in each position.

Resting, as well as exercising heart rates were generally lower in the supine versus the upright position

for all groups, except gr.IV, in which similar maximal heart rates were found in both positions. Between-group comparison of heart rates while in the upright position reveals a higher resting HR in all patient groups, compared to controls, although statistical significance was not reached. Heart rates recorded for upright submaximal intensities are not significantly different in any of the groups. In the supine posture, resting heart rates were found to be significantly higher in all cystic fibrosis groups compared to controls, whereas, the HR response to submaximal exercise was similar in all groups.

Stroke index measured at rest and in response to submaximal exercise in both the upright and the supine positions are shown in figure 3. Results generally indicate a curvilinear relationship between SI and progressive exercise intensity for either position. In the upright position, SI values plateau at an intensity of 50% VO_2max, despite a further increase in exercise intensity for groups I,II and III. In contrast, SI plateaued at a lower exercise intensity (30% VO_2max) in gr.IV. Stroke index variations recorded in the supine position indicate plateauing of values for exercise intensity superior to 30% VO_2max, in all groups.

Examination of SI data with respect to position difference in control subjects reveals the expected higher

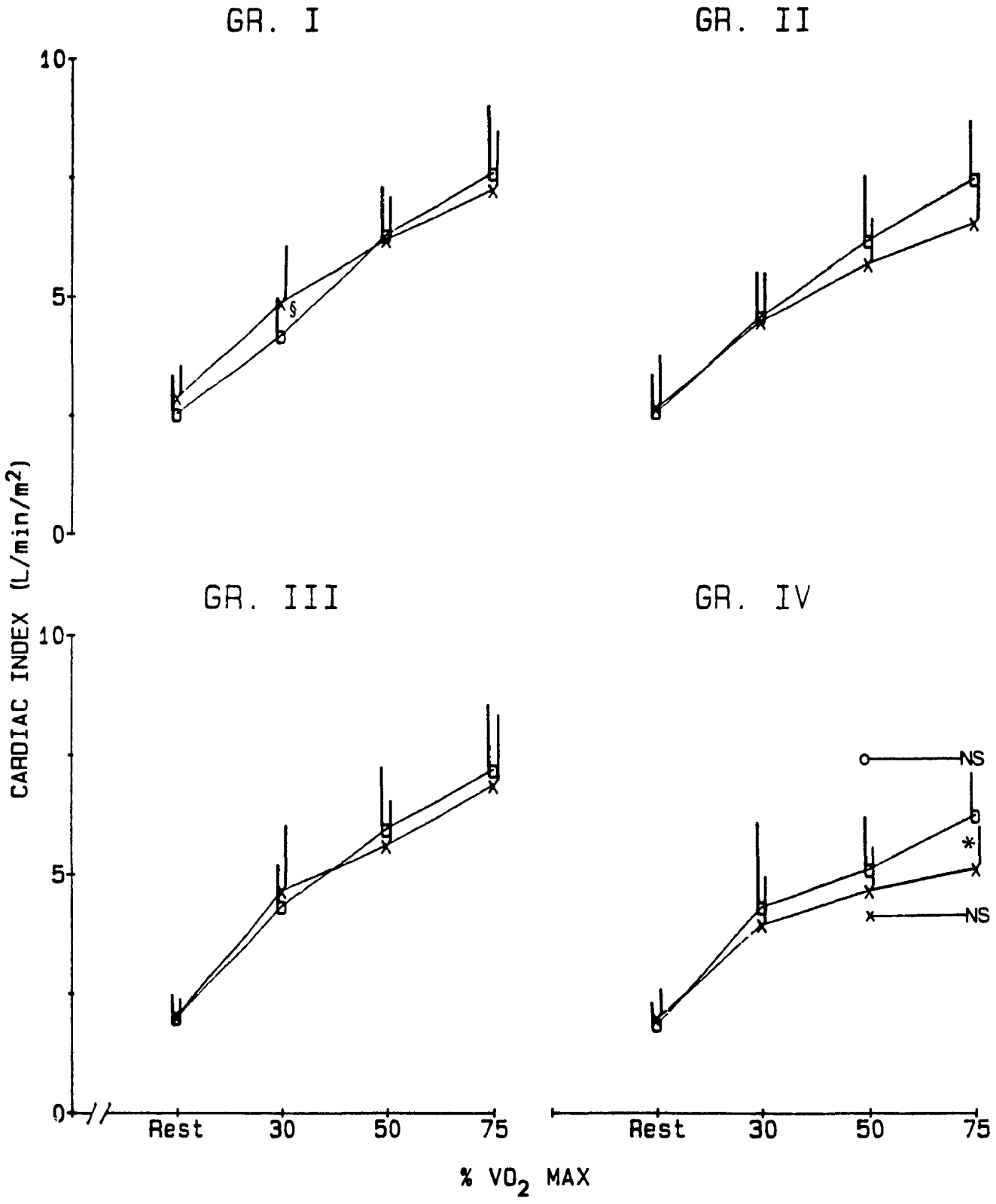
SI in the supine versus the upright position under resting, as well as exercising conditions. A significant adjustment of the SI to the recumbent position was not observed in any of the CF groups, where similar SI, in both positions, were generally found at rest and at any submaximal exercise load. In gr.IV, at 75% VO_2max, SI was lower in the supine than in the upright condition ($p=.15$). Between-group comparison of SI values recorded in the upright position indicates significant differences between patient groups III and IV, as compared to controls, at rest, however no differences were observed between any of the groups during exercise. Results obtained in the supine position indicate a significantly lower resting SI in all patient groups when compared to control. Similarly, exercising values appear to be lower in all patient groups, relative to controls, although statistical significance was only achieved for gr.IV.

Legend to figure 1

This figure presents mean cardiac index ($L/min/m^2$) at rest and at exercise intensities of 30, 50, and 75% of maximal oxygen consumption ($\%VO_2max$), in both upright (O) and supine (X) positions, for all groups.

A significant difference between positions is indicated by * for $p \leq .01$, and by § for $p \leq .05$.

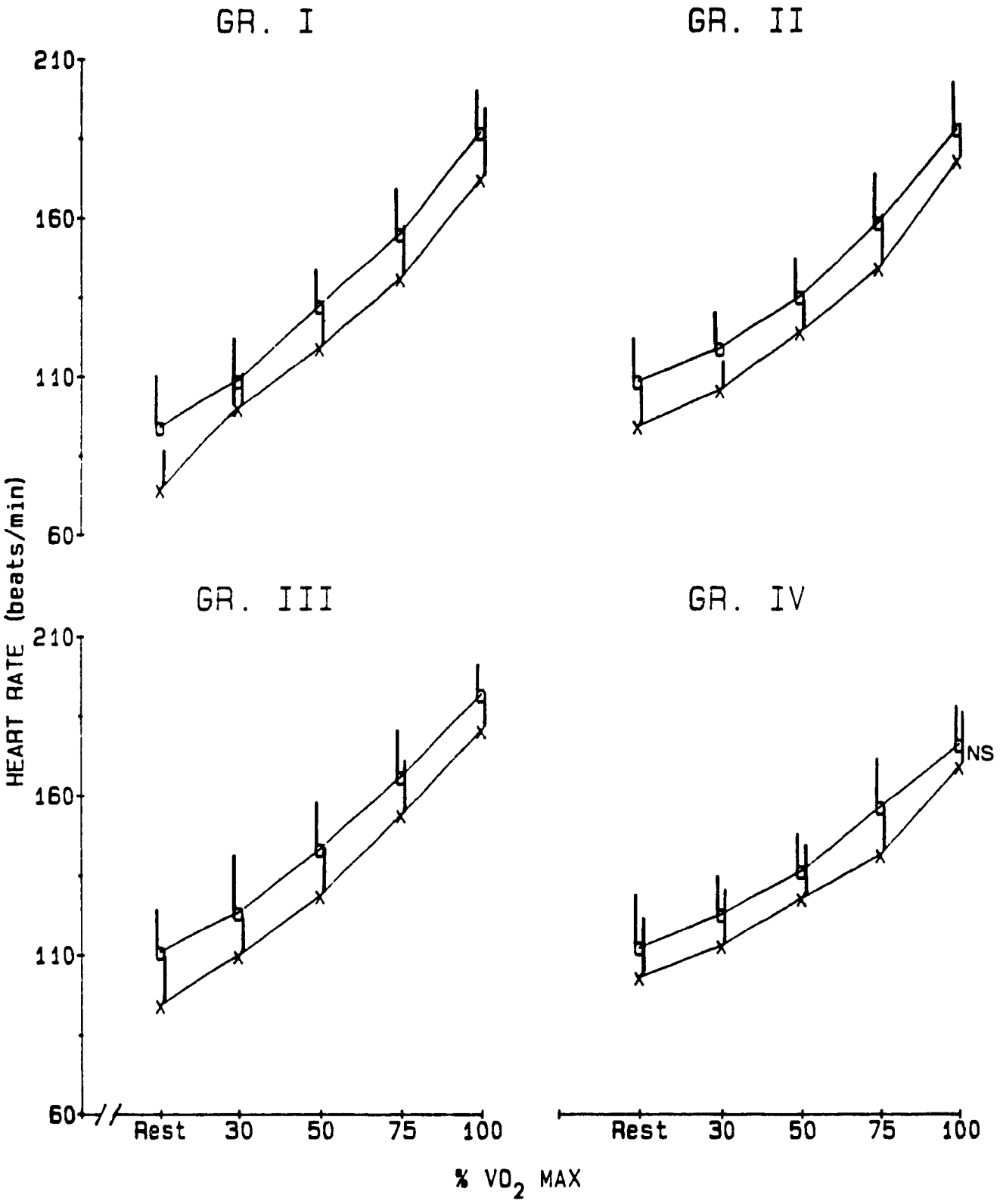
o——NS, or x——NS indicates non-significant increase in CI ($p > .05$) for upright (O) or supine (X) position, respectively, with subsequent increase in exercise intensity.


GR. I
GR. II
GR. III
GR. IV
10
5
0
§
NS
*
NS
Rest
30
50
75
CARDIAC INDEX (L/min/m²)
% VO₂ MAX

Legend to figure 2

This figure presents mean heart rate (bts/min) at rest, at submaximal exercise intensities of 30, 50, and 75% VO_2max, and at maximal exercise, in both upright (O) and supine (X) positions, for all groups.

A significant increase in HR is observed between rest and successive exercise intensities in both positions ($p \leq .05$). NS indicates non-significant difference in HR between positions for the given intensity.

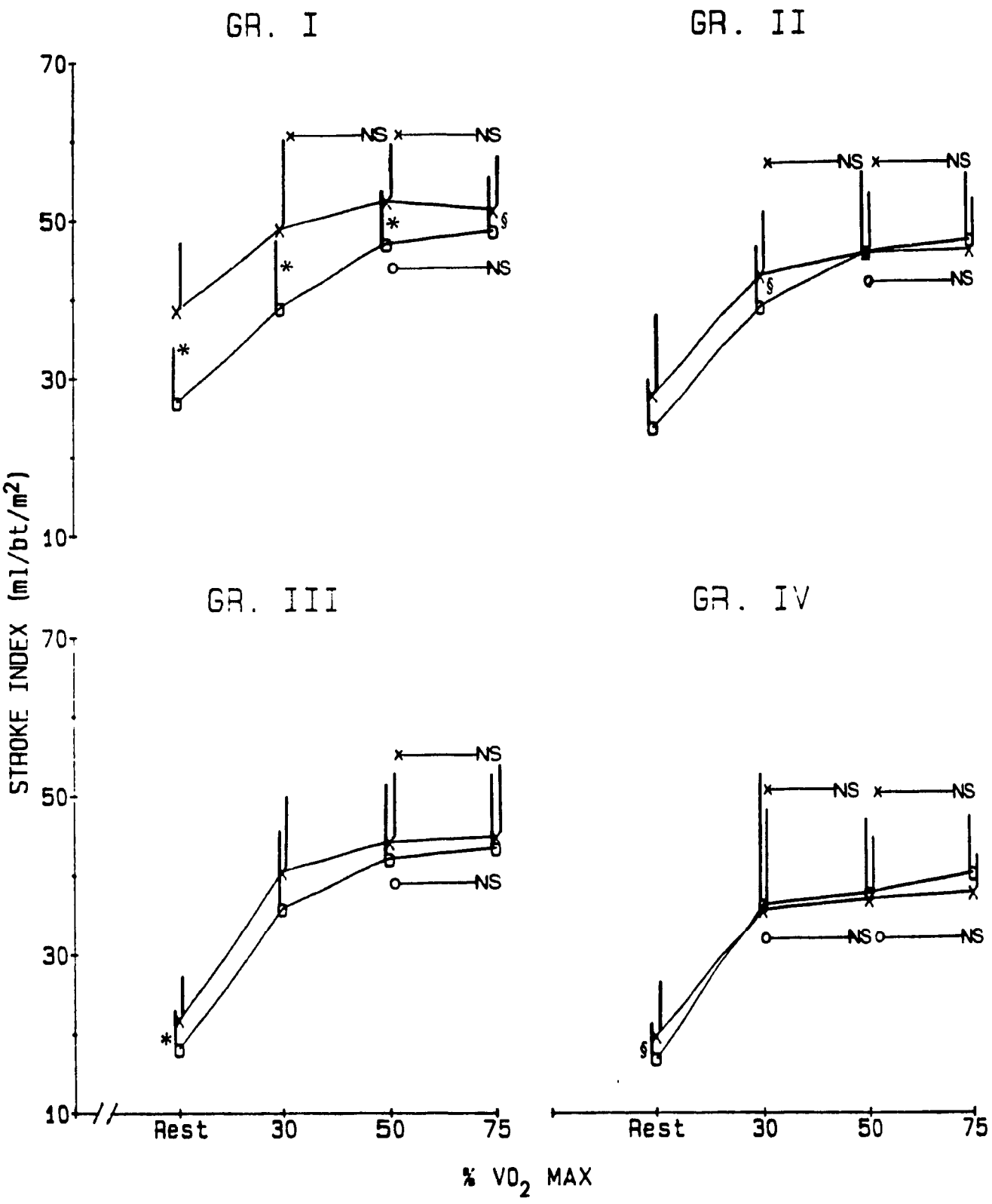

GR. I
GR. II
GR. III
GR. IV
210
160
110
60
HEART RATE (beats/min)
Rest
30
50
75
100
% VO2 MAX
NS

Legend to figure 3

This figure presents mean stroke index (ml/bt/m^2) at rest and at exercise intensities of 30, 50, and 75% of maximal oxygen consumption (%VO_2max), in both upright (O) and supine (X) positions, for all groups.

A significant difference between positions is indicated by * for p≤.01 and by § for p≤.05.

o——NS, or x—NS indicates non-significant change in SI for upright (O) or supine (X) position, respectively, with subsequent increase in exercise intensity.


GR. I
GR. II
GR. III
GR. IV
STROKE INDEX (ml/bt/m²)
70
50
30
10
NS
*
§
Rest
30
50
75
% VO₂ MAX

DISCUSSION

Results from the present study indicate normal maximal exercise tolerance in patients with mild or moderate cystic fibrosis disease when compared to asymptomatic aged-matched controls, whereas a significant reduction in exercise tolerance is observed in the severe CF group. Such observations are in accordance with the general findings of an inverse relationship between severity of disease and exercise tolerance, as well as the prevailing agreement that a significant exercise intolerance will be systematically observed only in patients with a moderate to severe degree of pulmonary dysfunction (5,14,25,26).

In the present study, arterial desaturation below resting values was generally observed at maximal exercise in all cystic fibrosis patients, reaching statistical signiicance in the severe qroup (Table VI). A relationship between exercise-induced desaturation and lung diffusion capacity has been shown in patients with cystic fibrosis (26a), and in patients with chronic obstructive pulmonary disease (26b). Considering that the lung diffusion capacity may be taken to reflect the degree of pulmonary vascular disease involvement, a relationship between pulmonary lung diffusion and exercise hemodynamics could be suggested. In fact, a weak, although significant ($p<.05$) correlation ($r=.485$) was found between resting lung diffusion capacity and stroke volume index at 75% maximal oxygen consumption

while upright. This further supports the well-established relationship between pulmonary disease severity and exercise tolerance.

The most striking finding of the present study concerns the stroke volume index adjustment to exercise and to the change in posture. The failure of CI to increase despite an increase in oxygen consumption from 50% to 75% VO_2max in gr. IV (figure 1), may be taken to reflect a cardiac dysfunction. The dysfunction could probably be attributed to a stroke volume limitation, since a compensatory higher heart rate than controls is observed in these patients (Figure 2). This proposed limitation is further evidenced by the stroke index response to upright exercise where the SI was observed to plateau at a lower exercise intensity in gr.IV (Figure 3). Although in the present study none of the patients presented clinical evidence of "cor pulmonale", the suggestion of ventricular dysfunction in response to exercise is not uncommon in patients with severe cystic fibrosis. The disturbed cardiac perormance observed in patients with obstructive airway disease may be partly attributed to the damaging effects of poor gas exchange and hypoxia on the pulmonary vasculature (10,17). As well, Hortop et al. (1988) have suggested that the altered respiratory mechanics associated with expiratory airflow limitation may limit cardiac function in patients with cystic fibrosis disease. The increased transpulmonary

pressure during expiration and lung hyperinflation often observed in COPD patients may disturb normal hemodynamics in this population (26c). Hortop et al. (1988) suggest that a similar mechanical element of cardiopulmonary interdependence may be present in cystic fibrosis patients (17).

Previous data from echocardiographic (27-29) or radionuclide angiographic (9,30,31) examination of patients with severe cystic fibrosis has provided evidence of abnormal right and left ventricular ejection fractions under resting conditions (7,9,30). Failure of the right and/or left ventricular ejection fraction to increase in similar proportions as controls in response to dynamic exercise was also taken to confirm the presence of myocardial dysfunction in patients with severe disease (7,8,31).

Moreover, the present observation of an abnormal adjustment of stroke volume to the change in body position, from upright to supine, in all patient groups when compared to controls at rest and during exercise, suggests a certain degree of ventricular dysfunction in all patients independent of disease severity. Results obtained in the control group are in accordance with the normally described increase in resting stroke volume that occurs upon transition from an upright to a supine position (32,33). This response results from the enhanced venous return and subsequent increased contribution of the Frank-Starling

mechanism to ventricular ejection for any submaximal or maximal exercise load, as venous return continues to be favored by the supine position (32,34). Investigations of the relative contributions of the Frank-Starling mechanism and myocardial inotropism, in ensuring stroke volume adjustments to a change in body position or dynamic exercise in asymptomatic individuals, have clearly established the dual involvement of both diastolic and systolic ventricular functions (32,33). In the present study, failure of the stroke volume to increase in response to the enhanced venous return associated with the supine position in cystic fibrosis patients may thus imply a certain degree of ventricular dysfunction. Although the nature of this dysfunction remains unidentified, a number of hypotheses may be proposed.

First, it may be suggested that placing the cystic fibrosis patient in the supine position creates a further ventricular volume overload of an already failing heart, allowing the systolic impairment to become evident. In terms of the classic ventricular function curves (35), this may be translated into a rightward shift of the end-diastolic volume, which in light of an already maximally solicited contractile state of the myocardium, places myocardial performance closer to the downward portion of the curve. An impairment in right ventricular contractility has indeed been reported in patients with cystic fibrosis on account of

the increased right ventricular afterload resulting from the presence of pulmonary hypertension (10,13). The hypothesis of a right ventricular systolic dysfunction remains doubtful in the present study, however, as patients showing any clinical evidence of right heart enlargement or dysfunction were excluded from the study and considering that a similar response was observed in gr.II where significant pulmonary hypertension is not expected.

A second hypothesis considers the possiblity of a decrease in right and/or left ventricular compliance leading to a diastolic ventricular dysfunction. A right ventricular diastolic dysfunction would limit the contribution of the Frank-Starling mechanism to right ventricular ejection and lead to a reduction in venous return to the left side of the heart, while a left diastolic dysfunction could possibly limit the systemic ejection of blood. The presence of myocardial fibrosis of both left and right myocardium has been reported following post-mortem analysis of cardiac specimens from patients dying of cystic fibrosis (36-38), and could account, at least in part, for a reduction in ventricular compliance. Moreover, recent observations obtained through doppler echocardiography in CF patients indicate less passive left ventricular filling suggestive of an impairment in ventricular compliance (39). The question would remain, however, to distinguish whether extreme conditions of ventricular systolic dysfunction and even

failure lead to myocardial fibrosis or whether an ongoing fibrotic process results in the ventricular diastolic dysfunction.

Finally, it is possible to suggest that histological differences in cardiac tissue may exist in cystic fibrosis patients, on account of impaired metabolic conditions resulting from the malabsorption syndrome often associated with the disease (15,38,40) or on account of alterations in the histological maturation of myocardial tissue as a consequence of the disease (29,37). This in turn could lead to impairments in myocardial properties such as compliance and/or contractile state, which would equally affect both right and left ventricular functions. A satisfactory explanation for the atypical stroke volume response to the change in position, from upright to supine, at rest and during exercise in the cystic fibrosis groups still remains to be provided.

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