What Happens to Survivors of the Adult Respiratory Distress Syndrome?*

Leonard D. Hudson, M.D., F.C.C.P.

The original description of the adult respiratory distress syndrome (ARDS) in 1967 reported a high mortality which was confirmed over the next decade or so by reports from many centers. Despite the high mortality, some consolation was taken from the impression that pulmonary function in most survivors returned to normal or near normal status. This impression was based upon a series of reports, most containing relatively small numbers of subjects with many survivors not accounted for. Since that time, a series of studies including three from the University of Utah, one from the ARDS Specialized Center of Research (SCOR) at the University of Texas, San Antonio, and a recent study from the ARDS SCOR at the University of Washington have provided new information on this subject. Although all of these studies have methodologic limitations, taken together they give us a more complete picture of the ultimate effect of ARDS on pulmonary function, overall functional ability, and the time course of recovery. This presentation will review the data to address the following three questions: (1) What happens to pulmonary function in survivors of ARDS and what is the time course of recovery? (2) If significant pulmonary dysfunction results, what are the determinants allowing its prediction? (3) What is the overall functional ability of survivors of ARDS, and what is the relationship of overall function to pulmonary functional status?

PULMONARY FUNCTION AND ITS DETERMINANTS IN SURVIVORS OF ARDS

Studies of function in ARDS survivors require a long period of follow-up and a high degree of patient cooperation. This makes these studies difficult to perform and is further complicated by the fact that many of the patients do not live in the city of the medical care facility in which they were hospitalized, but were transported there from somewhere in the region because of the specialized ability of these institutions to manage patients with ARDS. Other methodologic problems exist as well. These have resulted in limitations in all of the existing studies. The studies reviewed have one or all of the following limitations: (1) patient selection was not consecutive; (2) even with consecutive patient entry, a significant proportion of patients was missed or lost to follow-up; (3) sample size was relatively small; (4) pulmonary function was not performed at uniform times; and (5) no studies of overall functional ability were performed. These limitations should be kept in mind when interpreting studies; however, having several studies with differing study designs allows more accurate conclusions.

Elliott and coworkers from LDS Medical Center affiliated with the University of Utah in Salt Lake City reported on pulmonary function in ARDS survivors in 1981. They studied 13 subjects from a total of 19 patients who survived following ARDS in the years 1975 to 1978. The survivors were studied from 1 to 90 weeks following ARDS onset, and several were followed serially. The age range of the study subjects was 15 to 62 years with a mean of 30 years; 6 were men and 7 women, and 3 of the 13 were smokers. Progressive improvement in pulmonary function following recovery was seen for most of the pulmonary function measurements studied. Although the patients were not studied at uniform time points, and some patients were lost to study follow-up, their data suggest that peak pulmonary functional recovery occurs sometime between 6 and 12 months following ARDS onset, and that pulmonary function recovery is nearly complete. For example, all patients followed for at least 6 months had return of forced vital capacity (FVC) to 80 percent of predicted or greater. Although only 7 of their 13 subjects were followed to at least 6 months, an additional 4 subjects returned to within normal value limits prior to that time and were not followed subsequently. In addition to the usual pulmonary function measurements, they also serially measured deadspace (Vd/Vt) in seven survivors. The Vd/Vt values were elevated above normal on the initial measurement in six of the seven subjects and progressively decreased on subsequent testing in all seven subjects. There was a wider range of results from 6 months on in diffusing capacity measurements with several subjects having Dco measurements of between 60 and 80 percent of predicted.

A second report from this group appeared in 1987. Twenty-one individuals were studied from a total of 38 survivors during the years 1975 to 1983. Survivors were retrospectively identified from review of hospital records. Sixteen of these 21 study subjects were nonsmokers and did not have prior cardiopulmonary disease. Pulmonary function measurements were performed at greater than 1 year after ARDS onset with a range of 1 to 8 years and a mean of approximately 4 years. A similar pattern of pulmonary function values was found in this study of subjects at times relatively remote from their episode of ARDS. Although most patients’ lung volume measurements were normal, a few subjects had abnormal values. The diffusing capacity measurements tended to be lower than those of lung volumes. They performed analyses of relationships between pulmonary function and characteristics of the subjects during their episode of ARDS using...
simple linear regression analysis methods. They reported the following relationships: FVC was related to peak airway pressure and total static compliance (Cst); total lung capacity (TLC) was related to age. Cst, positive end-expiratory pressure (PEEP) and intrapulmonary shunt (Qs/Qt); and diffusing capacity was related to oxygen transport. Multiple logistic regression analysis was not performed. These investigators also reported a relationship between DCO measured at least 1 year following ARDS and duration of breathing an FIO2 greater than 0.6 during ARDS management. They reported data on 16 subjects. Of 7 subjects with an abnormal DCO at greater than 1 year, 5 of these had an FIO2 of greater than 0.6 for greater than 24 h during their acute management compared to 9 subjects with normal DCO of whom none had an FIO2 of greater than 0.6 for greater than 24 h.

A third study from Salt Lake City was reported by Ghio et al in 1989. They reported data from 41 ARDS survivors from the years 1976 to 1986. The total number of patients with ARDS during this time period was not stated. Because of the overlap in dates, I assume that some of the subjects included in the previous study were also included in this report. They reported being "particularly interested in those with impairment at 1 year or more after ARDS." The age range of their subjects was 7 to 61 years with a mean age of 28 years. There were 21 male and 20 female subjects. Clinical risks for ARDS included trauma (17), pneumonia (13), sepsis (7) and other causes (4). Twenty-three of their subjects were nonsmokers, 4 were exsmokers, and 12 were currently smoking at the time of study. They were able to make a determination of pulmonary functional impairment at greater than 1 year in 27 of the 41 survivors. As compared to the impression from the previous studies that most of the patients returned to normal, they reported that 18 or 67 percent of the subjects were impaired by American Thoracic Society standards. However, in most of these, the impairment was mild. One had severe impairment, 4 moderate, and 13 mild impairment. The basis for the impairment could be from either one or a combination of pulmonary function values obtained. The basis for impairment included FVC in 50 percent of those impaired, FEV, in 61 percent, FEV/FVC in 33 percent, and DCO in 82 percent. Thus, they reported a greater proportion of subjects with a mild restrictive impairment, at least on the basis of FVC, than had previously been reported. Their data supported previous isolated reports of possible development of airflow obstruction following ARDS, although in these subjects, it is unknown whether the airflow obstruction was present prior to ARDS onset.

They also reported correlations from single linear regression analyses between pulmonary function impairment and patient characteristics. Positive correlations were reported with patient age and several measures of ARDS severity. Although the only subjects with age greater than 60 were impaired, there was considerable overlap of the data with a wider spectrum of age, both young and old, in the impaired group. Correlations with pulmonary function impairment and ARDS severity included the following variables reflecting severity: maximal pulmonary artery pressure, maximal level of PEEP, Cst, and duration of mechanical ventilation. They also reported relationships between those with pulmonary function impairment and with symptoms as reported on a questionnaire. Twenty-five individuals completed the symptom questionnaire between 15 and 368 weeks. Twenty-one of the 25 reported symptoms which were nearly equally distributed between cough, phlegm production, dyspnea, and wheezing; however, only 10 of these subjects had impairment by pulmonary function testing. When data from the questionnaire regarding symptoms were limited to those who completed the questionnaire at greater than 1 year, the correlation between symptoms and impairment was much greater. Twenty subjects completed the questionnaire at greater than 1 year, 11 of these reported symptoms, and 9 of these 11 had pulmonary function impairment.

Peters and coworkers from the University of Texas at San Antonio also reported data on pulmonary function in survivors of ARDS in 1989. They studied 47 survivors of ARDS of whom 39 or 83 percent had at least one pulmonary function test following hospital discharge. Many patients had serial testing although the times of the studies were not uniform. Their subjects had the following clinical risks for ARDS: sepsis (13), trauma (7), aspiration of gastric contents (5), shock (5), pneumonia (4), and other (5). The age of their subjects ranged from 18 to 81 years with a mean of 45 years. There were 26 male and 13 female subjects. Twenty-four of the 47 subjects (62 percent) were smokers or exsmokers. This group reported a wider range of pulmonary function than previously reported. Similar to other reports, most of the patients showed progressive improvement, and although patients were not studied at uniform times, most of the improvement appeared to occur by 6 months. There was no evidence of substantial further improvement following 6 months in any of the patients studied at later times. However, they also reported a handful of patients who had very little pulmonary function improvement after surviving ARDS. The abnormalities in these patients included both severe restrictive impairment and severe abnormalities of diffusing capacity. Although the diffusing capacity measurements appeared to have a wider range with more abnormal values, they also reported a substantial number of patients who did not achieve 80 percent of the predicted value for the measurements of lung volume.

In evaluating possible determinants of pulmonary functional abnormalities, they performed linear regression analyses and found no correlation with age, duration of mechanical ventilation or Qs/Qt. They also found no significant correlations with clinical characteristics at days 1 through 3 of initial ARDS management. However, they were able to find positive correlations with some of the clinical characteristics from days 4 through 7 of the initial ARDS course. These correlations, again by linear regression analyses, included the following: FVC with pulmonary vascular resistance and maximal PEEP level; TLC with maximal PEEP level; and DCO with P(A-a)O2, peak airway pressure, and extent of chest x-ray film abnormality. This study added to our understanding of this subject by presenting data from a large number of
survivors and showing a wider range of pulmonary function on follow-up ranging from several months to years.

My colleagues at Harborview Medical Center and the University of Washington in Seattle designed a study in an attempt to address some of the limitations of previous studies.14 We entered consecutive survivors of ARDS and performed follow-up pulmonary function tests at uniform times following endotracheal extubation. In addition, we used a measurement tool to evaluate the patients' self-perceived physical and psychological condition, again at uniform times following extubation. Eighty-two survivors of ARDS were identified over a 2½-year period. Despite our intent to study all survivors, we were able to enroll only 52 (63 percent) of the eligible patients. Fourteen patients were missed in the hospital or were lost to follow-up. Six patients refused to consent to the study. An additional ten patients were unable to participate because of physical disabilities, primarily severe neurologic dysfunction or mental disabilities. The patients' ages ranged from 18 to 73 years with a mean age of 40 years. Thirty-six were men and 16 women and 88 percent were smokers. The clinical risks for ARDS included sepsis (17), trauma (23), aspiration of gastric contents or overdose requiring mechanical ventilation (8), and other causes (4). We intended to perform pulmonary function studies and administer a sickness impact profile (SIP) questionnaire within 2 weeks of the time of extubation and then at 3, 6, and 12 months. Again illustrating the difficulties of such a study, we found that we were only able to study 20 of the 52 patients at all of the intended time points. These so-called "core group" patients who completed all the studies were similar to those with incomplete data in terms of age and gender, they had a longer duration of mechanical ventilation (a median of 16 vs 10 days), but were similar in pulmonary function test results and results of the SIP questionnaire. Thus, although our data were incomplete, we felt that the core group of patients who completed all studies was similar to the group with incomplete data except for slightly greater severity of illness, and for purposes of analysis, the two groups could be combined. Pulmonary function progressively improved from time 0 through 6 months, but no additional improvement, either as a mean value or to any significant degree in any individual patient, occurred between 6 months and 1 year of follow-up. This suggests that future pulmonary function studies of survivors of ARDS can be performed at a single time point, that of 6 months, and patients can be expected to have maximal return of pulmonary function by that time. Mean pulmonary function values returned to normal or near normal values. The mean TLC was within the lower limit of normal, the FVC was slightly below the lower limit of normal, and the diffusing capacity returned to mildly to moderately abnormal values depending upon the normal values used (they were more severe at 60 percent of predicted when the Crapo and Morris20 normal values were used and less severely impaired when the normal values of Miller et al21 were used). Lung volume measurements returned to normal values in approximately half the patients, and half had mildly abnormal values. We found no patient with continuing severe abnormalities in this particular series such as were found in the San Antonio study, although we have seen individual patients in the past who remained severely impaired. A correlation between the number of days receiving mechanical ventilation and pulmonary function was found. Patients who were ventilated for greater than 2 weeks had significantly poorer pulmonary function than those who were ventilated for less than 2 weeks. We first used length of mechanical ventilation as a proxy for severity of injury. When we used a more complicated and sophisticated method of scoring severity of injury, this correlation was also present, but it appeared that length of time on the ventilator was a good proxy.

Overall Functional Ability and Quality of Life in Survivors of ARDS

The SIP measures the subject's self-perceived physical and psychological condition22,23 and has been used in several studies of chronic illnesses including COPD.24,25 The physical aspects of the score evaluate the patients' perception of their ambulation, mobility, and body care. The psychosocial aspects measure social interaction, communication, and emotional behavior. A normal score should be less than five with normal healthy individuals scoring a mean of 3.5. The more elevated the score the more abnormal the perception of the patient's functioning. As examples, in the Nocturnal Oxygen Therapy Trial of hypoxemic patients with COPD, the mean SIP score was 24.24 In the NIH-sponsored IPPB trial of patients with COPD but less severe hypoxemia, the mean SIP score was 18.25 We found that the SIP score was markedly abnormal immediately following extubation and substantially improved by 3 months with only slightly further improvement at 6 and 12 months. The mean value at 1 year was 10. We added an additional lung score by asking the patients how much of their perceived dysfunction in any area was thought to be due to their pulmonary status and found that patients perceived that only a small proportion of their overall dysfunction was related to their lungs. Thus, even though patients perceive some physical and psychological dysfunction following survival of ARDS, most of this appears to be related to other injuries or other illnesses and not to impairment of lung function.

Conclusion on Pulmonary Function and Quality of Life

What conclusions can we draw from these several recent studies and the previous literature? The picture is still generally optimistic in that most patients return to normal or near normal pulmonary function on recovery from an episode of ARDS. Nearly all patients have reached their maximal recovery by 6 months following endotracheal extubation with only a few subjects anecdotally reported in the literature who have further improvement after that time. Thus, 6 months following extubation could be used as a single time point for evaluation of pulmonary function recovery of patients following ARDS. Although most patients markedly improve their pulmonary function during recovery, approxi-
mately half of the patients continue to have some abnormality of pulmonary function; this is either mild restrictive impairment, or more often, a mild impairment in diffusing capacity. Those patients who have continuing pulmonary dysfunction are more apt to have had a more severe course of ARDS, identified either by failure to improve physiologic variables several days into the course of ARDS or by the duration of mechanical ventilation. There are occasional patients, thankfully rare, who continue to have severe pulmonary functional abnormalities. Finally, survivors of ARDS continue to have impairments in overall physical and psychosocial function, but these are mild and are not perceived by the patients to be related to their pulmonary condition. This knowledge about functional recovery allows the clinician to better inform the patient about expected improvement and final outcome following survival of a bout of ARDS.

REFERENCES
2 Downs JB, Olsen GN. Pulmonary function following adult respiratory distress syndrome. Chest 1974; 65:92-3
10 Lakshminarayan S, Hudson LD. Pulmonary function following the adult respiratory distress syndrome. Chest 1978; 74:489-90
13 Alberts WM, Priest GR, Moser KM. The outlook for survivors of ARDS. Chest 1983; 84:272-74

Elevated Lavage Levels of N-Terminal Peptide of Type III Procollagen Are Associated With Increased Fatality in Adult Respiratory Distress Syndrome*

Joan G. Clark, M.D.; John A. Milberg, M.P.H.; Kenneth P. Steinberg, M.D.; and Leonard D. Hudson, M.D., F.C.C.P.

Effective repair of injured lung in adult respiratory distress syndrome (ARDS) requires restoration of the extracellular matrix and presumably involves increased connective tissue synthesis. However, excessive matrix synthesis may result in pulmonary fibrosis and preclude recovery. To investigate the relationship between matrix synthesis and clinical course in ARDS, we performed serial bronchoalveolar lavage (BAL) in patients with ARDS and measured lavage levels of the N-terminal propeptide of type III procollagen (PCP-III) as a marker of collagen synthesis. We hypothesized that elevated PCP-III levels would be associated with increased fatality.

In 83 patients who had BAL 3 days after the onset of ARDS, 34 (41 percent) had PCP-III levels in unconcentrated lavage ≥ normal serum control value (1.75 U/ml), ie, more than tenfold the expected normal lavage level. In 74 patients who had BAL 7 days after onset of ARDS, 45 (61 percent) had PCP-III levels ≥1.75 U/ml. Using the Wilcoxon rank sum test for nonparametric data, we found that PCP-III levels obtained at 3 to 9 days were significantly higher (p = 0.002) in patients who died than those who survived. The fatality rate in patients with PCP-III

*From the University of Washington and Fred Hutchinson Cancer Research Center, Seattle.

126S
36th Annual Aspen Lung Conference