Neuropsychological Sequelae and Impaired Health Status in Survivors of Severe Acute Respiratory Distress Syndrome

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Acute respiratory distress syndrome (ARDS) is a disease of acute respiratory failure manifested by severe hypoxemia with a high mortality rate. Previous outcome studies of ARDS have assessed survival and/or pulmonary function as the primary outcome variables. Cognitive or psychological outcomes following ARDS have not been described, despite the possibility that ARDS patients are at risk for brain injury through hypoxemia or other mechanisms. In the current study 55 consecutive ARDS survivors completed a battery of neuropsychological tests and questionnaires regarding health status, cognitive and psychological outcomes at the time of hospital discharge and 1 yr after onset of ARDS. At hospital discharge, 100% (55 of 55) of survivors exhibited cognitive and affective impairments, as well as problems with health status which affected their quality of life. At 1 yr after ARDS, 17 of 55 (30%) patients still exhibited generalized cognitive decline. Forty-three of 55 (78%) patients had all or at least one of the following: impaired memory, attention, concentration and/or decreased mental processing speed. One year after ARDS a substantial portion of ARDS survivors exhibit impaired health status and cognitive sequelae which may be due to hypoxemia, emboli, inflammation, drug toxicity, and/or other etiologies. Hopkins RO, Weaver LK, Pope D, Orme JF, Jr., Bigler ED, Larson-Lohr V. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome.

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Acute respiratory distress syndrome (ARDS) is characterized by severe acute lung injury and profound arterial hypoxemia which is often resistant to increases in inspired oxygen tension (1). ARDS may occur in response to various direct or indirect insults to the lungs including sepsis, trauma, massive transfusions, and other medical/surgical conditions (2–4). ARDS requires aggressive supportive care including positive pressure ventilation and high oxygen fractions with attendant risks of barotrauma, oxygen toxicity, and nosocomial infection. ARDS is often accompanied by multiple organ dysfunction, including central nervous system (CNS) dysfunction. The mortality associated with ARDS is high; however, recent reports suggest that survival has improved (5–9).

Outcome studies of ARDS survivors are limited. A number of studies have documented impaired pulmonary function abnormalities after recovery from ARDS (2, 10–13). Reduction in lung diffusion capacity for carbon monoxide (D_{LCO}) and restrictive and/or obstructive impairments of lung function are commonly found on pulmonary function tests (2, 10–12). One study has shown impaired general health and psychosocial problems in ARDS survivors (14). The investigators noted that the health complaints of the ARDS survivors were a result of nonpulmonary factors. They also found that a significant number of ARDS survivors had not resumed normal activities, including 44% who had not returned to work, 1 yr after recovery from ARDS (14).

No study has examined neuropsychological outcome, specifically cognitive and affective outcomes in ARDS survivors. CNS impairments following ARDS may be expected, given the severe hypoxemia that occurs as a result of this disease and other pathophysiological processes including inflammation (15). Psychological (emotional) changes may also be expected as a result of the psychological adaptation that follows any major illness. Because CNS impairments are well documented in other disorders characterized by acute hypoxic insults (e.g., chronic obstructive pulmonary disease [COPD] and obstructive sleep apnea syndrome [OSAS]), we designed a prospective, 1-yr outcome study to determine the effect of ARDS on quality of life, cognitive and psychological function.

METHODS

Patients

Consecutive ARDS patients were recruited from the Shock Trauma Intermountain Respiratory Intensive Care Unit (STIRICU) at LDS Hospital. LDS Hospital is a major referral and tertiary care center,

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participating in ongoing ARDS research (2, 8, 10, 11). Eligible ARDS patients met the following inclusion criteria: intubation; age ⩾ 16 yr; ratio of arterial oxygen tension to fraction of inspired oxygen ($Pa_{O_2}/F_{I_{O_2}}$) ⩽ 150 mm Hg (arterial to alveolar [a/A] ratio ⩽ 0.3); pulmonary arterial occlusion pressure ⩽ 18 mm Hg or no evidence of left atrial hypertension; diffuse infiltrates in three out of four quadrants on chest radiographs; and the presence of an appropriate ARDS risk factor (i.e., trauma, aspiration, pancreatitis, shock, sepsis syndrome, pneumonia, etc.). Ventilator management, including the use of sedatives, narcotics, and paralytic medications, was carried out using computerized decision support protocols (11, 16).

From February 1994 until July 1998, consecutive adult ARDS patients admitted to the STIRICU at LDS Hospital were assessed to determine eligibility for a ventilation management trial and for our prospective 1-yr quality of life and neuropsychological outcome study. There were 274 eligible ARDS patients, of which 106 patients were enrolled and 168 patients were excluded from the study. Sixty-nine of the 106 patients enrolled in the study have survived, 39 patients died, and two patients refused the study. The 67 survivors were enrolled in our 1-yr quality of life and neuropsychological outcome study. Five patients have not yet reached their 1-yr follow-up. This report describes the first 62 ARDS survivors, who have reached 1-yr follow-up. Of the first 62 patients, three patients died during the first year following hospital discharge and four patients were lost to follow-up. The follow-up rate at 1 yr for the first 62 patients was 89% (n = 62). Excluding those patients who died during the first year, the follow-up rate at 1 yr was 94%.

ARDS patients were excluded if they had disease states that were not reversible and in which 1-yr survival was unlikely or if they were enrolled in another ARDS study (n = 168) (i.e., liver failure [n = 32], enrolled in another ARDS study [n = 24], immunosuppression [n = 20], damage to the CNS resulting from injury or prior history of CNS disease [n = 19], patient or family refusal [n = 14], inability to obtain informed consent [n = 10], COPD [n = 10], severe ARDS for greater than 21 d [n = 8], malignancy [n = 8], primary care physicians refused consent [n = 6], died prior to enrollment [n = 6], chronic renal failure [n = 3], pregnancy [n = 2], cervical spinal cord injury [n = 2], pneumonectomy [n = 2], and chronic heart failure [n = 2]). Of the 168 patients who were excluded, 79 died prior to hospital discharge.

Methods and Instruments

The institutional review board at LDS Hospital approved this study. We recorded detailed medical, pulmonary, and laboratory data on all patients enrolled in the ARDS outcome study throughout their hospital course.

Continuous oxygen saturation data were automatically collected through the connection of bedside pulse oximetry using the Ohmeda (Louisville, KY) Biox 3700 and 3740 monitoring devices to a clinical data management computer, through the digital serial output port. The data are transmitted directly to a computerized data base, using a medical information bus (MIB). Continuous pulse oximetry measurements carried out during the period in which the patients were on ventilatory support were analyzed to assess hypoxemia in our ARDS survivors. The saturation readings were sampled every 2 min and the median value for each 15-min period was recorded in 55 of the surviving patients (17). Oximetry data were categorized as < 90%, < 85%, and < 80% saturation. We calculated the length of desaturation events by adding consecutive measurements (each measurement represents a 15-min interval) that were below saturation thresholds. Oximetry data were compared to the patients' arterial blood gas (ABG) oxygen saturation data, using the ABG values that were the closest in time to the stored oximetry measurement. That is, each Sa_{O_2} measurement was compared with the closest oximetry oxygen saturation measurement.

After discharge from the intensive care unit (ICU), the 1-yr quality of life and neuropsychological outcome study was presented to the patients and/or their significant other and informed consent obtained. Patients underwent a battery of standardized neuropsychological tests and questionnaires postextubation, just prior to hospital discharge and at 1 yr after entry into the ARDS study. All neuropsychological tests were administered by a Ph.D. neuropsychologist (R.O.H.). The first evaluation was carried out just prior to hospital discharge. In order to minimize fatigue, patients completed questionnaires and neuropsychological tests in four separate 1-h sessions on consecutive days. Testing was started 4 d before hospital discharge. The 1-yr follow-up evaluation was carried out in a single 3- to 4-h period. All patients were reimbursed for their time plus travel expenses for the 1-yr follow-up evaluation.

Patients underwent a standard battery of neuropsychological tests and questionnaires covering three major domains of quality of life. These domains included health status and functional outcome, cognitive outcome, and psychological or emotional outcome. Instruments used to assess health status and functional outcome included Activities of Daily Living (ADL) (18), the Medical Outcome Study Short Form (SF-36) (19), the Sickness Impact Profile (SIP) (20), and questions regarding quality of life which were developed for this study.

The instruments used to assess cognitive outcome measured several areas of cognitive abilities including intelligence or general cognitive function, attention/concentration, memory, speed of mental processing, and verbal production. For a description of the tests and test references refer to Naugle and coworkers (21). General cognitive function was assessed with the Wechsler Adult Intelligence Scale-Revised (WAIS-R). Tests of attention/concentration and memory included the Wechsler Memory Scale-Revised (WMS-R), Rey Auditory-Verbal Learning Test (RAVLT), and the Rey-Osterrieth Complex Figure Test (copy, immediate recall, and 30-min delay recall). Mental processing speed was assessed with the Trail Making Test Parts A and B, and Verbal Fluency which measured verbal production.

Psychological or emotional outcome questionnaires included the Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Symptom Checklist 90-R (SCL-90-R), and the Faschingbauer Short Form Minnesota Multiphasic Personality Inventory (MMPI). The short form MMPI was used because the short form takes less than half the time to complete and provides a good index of the long form. Psychological assessment was carried out only at the 1-yr follow-up visit.

Data Management and Statistical Analysis

The current research design is a prospective within-subjects' design. In addition to comparing baseline and 1-yr data, data were compared with normative population data using demographically corrected t-scores (mean = 50, SD = 10) (22, 23). Normative data allow the individual scores to be corrected for age, gender, and educational level, all of which are known to affect performance on cognitive tests (22, 23). The demographically corrected t-scores allow comparisons to be made across patients and across tests.

All statistical analyses were carried out using SPSS 8.0 for Windows. Descriptive statistics were carried out on demographic and medical data and are presented as mean ± SD. In order to determine if there was a significant difference in health status, cognitive function and/or psychological (affective) outcome at 1-yr survival from ARDS were compared with their initial hospital data, using analysis of variance or when appropriate paired *t* tests. Paired *t* tests were used to compare oximetry data and ABG oxygen saturation data. Bonferroni corrections were incorporated to correct for the number of variables analyzed. Pearson's correlations were carried out between neuropsychological data and age, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, arterial oxygen tension (Pa_{O_2}) at enrollment in the clinical study, fractional inspired concentration of oxygen ($F_{I_{O_2}}$) at enrollment, mean $F_{I_{O_2}}$, mean Pa_{O_2}, mean arterial carbon dioxide tension (Pa_{CO_2}), pH, ICU days, total hospital days, the number of days intubated, and oximetry data. Pearson's correlations were carried out comparing the neuropsychological data and the continuous oximetry oxygen saturation data.

RESULTS

Medical Data

Medical data results for ARDS survivors are presented in Table 1. The risk factors associated with ARDS, for the 55 survivors who underwent 1-yr follow-up evaluations included sepsis (n = 24), pneumonia (n = 13), trauma (n = 6), aspiration (n = 5), pancreatitis (n = 4), and near drowning (n = 3). There were 25 males and 30 females in the group, with a mean age of 45.5 ± 16.0 yr (range = 16 to 78 yr) and mean educa-

TABLE 1

MEDICAL DATA FOR THE ARDS SURVIVORS (n = 55)

	Mean	Standard Deviation	Minimum	Maximum
Hospital days	38.7	22.3	7	122
STIRICU days	29.2	18.8	4	96
Days intubated	28.6	19.5	3	94
APACHE II*	18.2	5.8	7	33
Mean MOF score	6.2	2.3	2.8	14.2
Pa_{O_2}/FI_{O_2} ratio*	96.2	26.0	42	150
Pa_{O_2},* mm Hg	66.7	11.4	56	109
Mean Pa_{O_2}, mm Hg	71.3	7.6	28	105
FI_{O_2},* %	73.0	18	40	100
Mean FI_{O_2}, %	54.9	8.3	39	75
Days from ARDS onset to enrollment in 1-yr outcome study	2.7	3.2	0	14

Definition of abbreviation: MOF = multiple organ failure.
* At time of enrollment in the study.

tional level of 12.8 ± 2.0 yr (range = 8 to 18 yr). Sixteen of the 55 patients developed pneumothoraces during their hospital course. None of the ARDS survivors had traumatic brain injuries, demyelinating diseases, encephalitis, strokes, or previous episodes of anoxia.

Pulse oximetry measurements on the 55 patients were monitored for 1,319 d or 126,649 15-min time intervals. We were able to collect 110,689 pulse oximetry measurements or 87% of all possible oximetry data points. The patients' oximetry was measured for a total of 31,665 h, with a mean of 609 ± 423 h. The patients' mean saturations < 90% = 122 ± 144 h, < 85% = 13 ± 28 h, and < 80% = 1 ± 3 h. On average the patients had 25 episodes of desaturation < 90% and 1 episode < 85% for a duration of more than 2 h. The mean oximetry Sa_{O_2} = 90.8 ± 4.3 and the mean ABG Sa_{O_2} = 88.7 ± 4.8 (t = 43.5, p ≤ 0.001). These results indicate that the arterial ABG Sa_{O_2} was significantly lower than the oximetry Sa_{O_2}. Thus, the oximetric Sa_{O_2} is a conservative measure of the patients' hypoxemia. There were significant correlations between the amount of time that the ARDS patients' saturation was < 90%, < 85%, and < 80% compared with attention, memory, intelligence, speed of processing (digit symbol and Trails B), visuospatial skills (block design) and executive function (Trails B) at 1-yr outcome (p ≤ 0.05 to p ≤ 0.01) (Table 2).

TABLE 2

PEARSON CORRELATIONS OF NEUROPSYCHOLOGICAL DATA WITH CONTINUOUS PULSE OXIMETRY DATA

Neuropsychological Test	< 90%	< 85%	< 80%
WMS-R Attention/Concentration	r^2 = 0.393* p = 0.004	r^2 = 0.332† p = 0.016	r^2 = 0.328† p = 0.018
Full-Scale Intelligence Quotient	r^2 = 0.462* p = 0.000	r^2 = 0.362* p = 0.008	r^2 = 0.340† p = 0.013
Verbal Intelligence Quotient	r^2 = 0.376* p = 0.005	r^2 = 0.320† p = 0.018	r^2 = 0.310† p = 0.022
Performance Intelligence Quotient	r^2 = 0.466* p = 0.000	r^2 = 0.348† p = 0.011	r^2 = 0.316† p = 0.021
Digit Span	r^2 = 0.324† p = 0.017	r^2 = 0.288† p = 0.034	r^2 = 0.305† p = 0.025
Block Design	r^2 = 0.360* p = 0.008	r^2 = 0.237 p = 0.087	r^2 = 0.185 p = 0.184
Digit Symbol	r^2 = 0.413* p = 0.002	r^2 = 0.341† p = 0.013	r^2 = 0.206 p = 0.151
Rey-Osterrieth Complex Figure Delay Recall	r^2 = 0.311* p = 0.023	r^2 = 0.224 p = 0.104	r^2 = 0.173 p = 0.216
Trails B T-score	r^2 = 0.439* p = 0.001	r^2 = 0.325† p = 0.018	r^2 = 0.344† p = 0.012

* Significant at ≤ 0.01.
† Significant at ≤ 0.05.

Health Status and Functional Outcome

All 55 ARDS survivors experienced difficulties with activities of daily living at the time of hospital discharge (Figure 1). All patients were able to perform all activities of daily living with no limitations 1 yr after onset of ARDS (Figure 1).

At the time of hospital discharge, ARDS survivors' self-reports on the SF-36 reveal impairments on all of the scales of health status (t = 20.03 to 3.96, p ≤ 0.01 to 0.0001). At 1 yr ARDS survivors' self-reports showed significant improvement for physical functioning (t = 5.23, p ≤ 0.01), social functioning (t = 6.15, p ≤ 0.01), role-physical (i.e., problems with work or other physical activities due to physical health) (t = 5.7, p ≤ 0.01), and vitality (t = 3.61, p ≤ 0.01). Alternatively, ARDS survivors had no improvement on the SF-36 for role-emotional, mental health, bodily pain, and general health, at 1 yr compared with their responses at the time of hospital discharge. In spite of significant improvement, survivors reported more bodily pain, physical problems, and impaired general health status than healthy individuals 1 yr after onset of ARDS (Figure 2) (20).

Results for the SIP show that 1 yr after onset of ARDS, patients reported mild to moderate impairments in physical, psychosocial, and general health (Figure 3).

Cognitive Outcome

At the time of hospital discharge 100% of the patients experienced cognitive impairments, including problems with memory, attention, concentration, and/or global loss of cognitive function (Table 3). At 1-yr follow-up most patients showed improvement in overall cognitive function as indicated by the improvement in the WAIS-R scores. Some cognitive skills such as memory did not show the same level of improvement. At 1 yr, 17 of 55 patients (30%) experienced deficits in cognitive function on the WAIS-R and 43 of 55 (78%) had impairment of at least one cognitive function including memory, at-

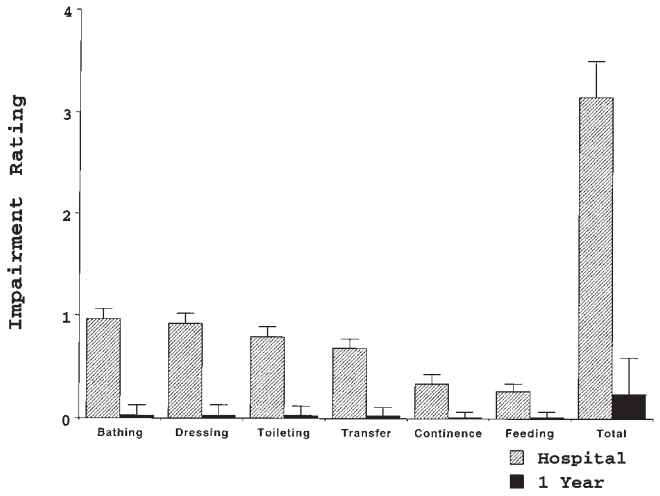

Figure 1. Mean scores ± standard errors impairment ratings for the ADL. 0 = normal, 1 = requires some assistance, 2 = requires complete assistance. Total score combines all categories.

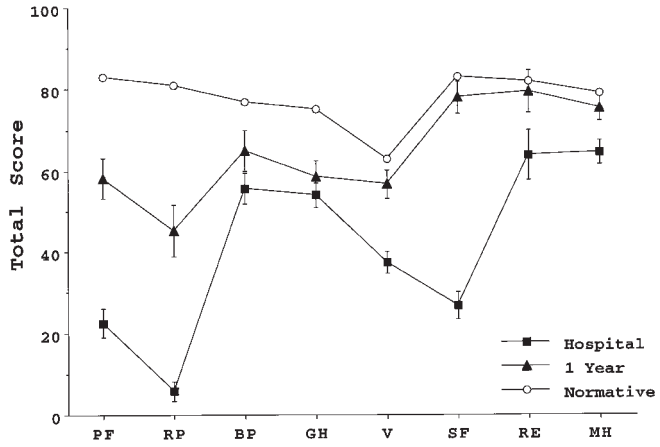

Figure 2. Mean scores ± standard errors on the SF-36 at the time of hospital discharge and 1-yr follow-up data compared with normative data. Normal score = 100. Health Status Scale abbreviations: PF = physical functioning; RP = role-physical; BP = bodily pain; GH = general health; V = vitality; SF = social functioning; RE = role-emotional; MH = mental health.

tention, and/or concentration as measured on the WMS-R, RAVLT, or Rey-Osterrieth complex figure test. Forty-eight percent of patients experienced decreased speed of mental processing as evidenced by their performance on the Trail Making Test Parts A and B and the Digit Symbol subtest.

There were no neuropsychological outcome differences between males and females and for patients who developed pneumothoraces versus no pneumothoraces. There were no significant cognitive outcome differences between patients who had APACHE II scores ⩽ 17 at the time of enrollment in the clinical study, when compared with patients whose APACHE II scores were ⩾ 18.

The Pa_{O_2} at enrollment was significantly related to all of the following: General Memory Index ($r^2 = 0.39$, $p = 0.04$), Attention/Concentration Index ($r^2 = 0.41$, $p = 0.03$), and Delayed Recall Index ($r^2 = 0.55$, $p = 0.002$) of the WMS-R, RAVLT Trial 1 ($r^2 = 0.52$, $p = 0.004$), RAVLT Trial 5 ($r^2 = 0.28$, $p = 0.14$), and RAVLT Delayed Recall ($r^2 = 0.38$, $p = 0.04$) and to the Trail Making Test Parts A ($r^2 = 0.63$, $p = 0.001$) and B ($r^2 = 0.61$, $p = 0.001$). There were no significant correlations between the cognitive outcome variables and age, APACHE II scores, mean Pa_{O_2}, FI_{O_2} at enrollment, mean FI_{O_2}, mean Pa_{CO_2}, pH, ICU days, total hospital days, or the number of days intubated.

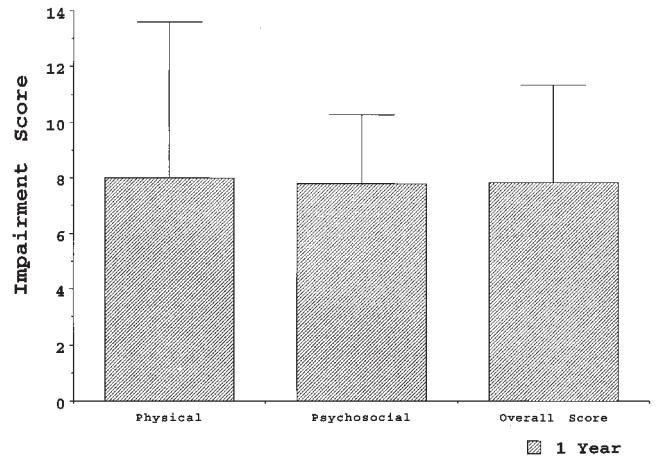

Figure 3. Mean scores ± standard errors on the SIPS at 1-yr follow-up. Normal score = 0.

Psychological Outcome

Results for the BDI and BAI at 1 yr were within normal limits, indicating that the patients did not report clinical levels of depression or anxiety. The patients' self-reports on the SCL-90-R at 1 yr were normal (Figure 4). The patient's self-reports at 1 yr on the Faschingbauer Short Form MMPI revealed no clinically significant levels on any of the scales (i.e., scores did not exceed 2 standard deviations) but four scales were all at or above 1 standard deviation, indicating that the patients reported some depressive symptoms, somatic focus, and disrupted cognitive functioning (Figure 5).

DISCUSSION

To our knowledge, this is the first study to assess the cognitive and psychological outcomes in ARDS survivors. At the time of hospital discharge all ARDS survivors had observable cognitive impairments, including impaired memory, attention, concentration, and decreased mental processing speed. The cognitive impairments at the time of hospital discharge are likely to impair the patients' ability to remember and follow medication and discharge instructions. One year after onset of ARDS, we found that 78% of ARDS survivors demonstrated

TABLE 3

NEUROPSYCHOLOGICAL TEST DATA AT THE TIME OF HOSPITAL DISCHARGE (INITIAL DATA) AND AT 1-yr FOLLOW-UP (1-yr DATA)

Neuropsychological Test	Initial Data (*mean* ± *SD*)	1-yr Data (*mean* ± *SD*)
WAIS-R		
Verbal IQ	92.1 ± 12.7	98.4† ± 12.1
Performance IQ	85.8 ± 10.5	98.1‡ ± 12.1
Full-Scale IQ	89.7 ± 11.0	97.8† ± 12.2
WMS-R		
Verbal Memory Index	90.8 ± 12.2	94.1 ± 13.7
Visual Memory Index	93.7 ± 13.7	100.0 ± 12.5
General Memory Index	90.7 ± 13.1	96.2† ± 11.6
Attention/Concentration Index	84.4 ± 16.1	93.6 ± 14.5
Delayed Recall Index	80.8 ± 15.1	87.8‡ ± 11.7
Verbal Fluency (CFL)		
Total number of words	29.89 ± 9.6	39.0‡ ± 12.6
Mean number of words	9.7 ± 3.5	13.0‡ ± 4.8
Rey-Osterrieth Complex Figure		
Copy	25.7 ± 8.9	30.9‡ ± 7.5
Immediate Recall	10.5 ± 7.0	15.2‡ ± 7.4
30-min Delayed Recall	11.2 ± 10.5	14.4† ± 7.3
Rey Auditory Verbal Learning Test		
Trial 1	4.5 ± 1.8	5.8‡ ± 1.9
Trial 5	8.7 ± 2.9	10.5 ± 2.3
Delay Trial	6.4 ± 3.4	8.5† ± 2.5
Recognition Trial	10.5 ± 3.2	13.2‡ ± 1.6
Trail Making Test		
Part A	54.1 ± 25.4	36.8‡ ± 17.6
Part B	145.2 ± 72.8	82.5‡ ± 34.0

* Tests and normal ranges are as follows: Wechsler Adult Intelligence Scale-Revised (WAIS-R) mean = 100, SD = 15; Wechsler Memory Scale Revised (WMS-R) mean = 100, SD = 15; Verbal Fluency Test normal = 31 to 44 total words generated; Rey-Osterrieth Complex Figure using Lezak scoring with 36 points possible; and the Rey Auditory Verbal Learning Test (RAVLT) mean range trial 1 = 6.3 to 7.8, mean range trial 5 = 12 to 14, mean range delay trial = 10 to 12 words.

† Significant at ⩽ 0.05.

‡ Significant at ⩽ 0.01.

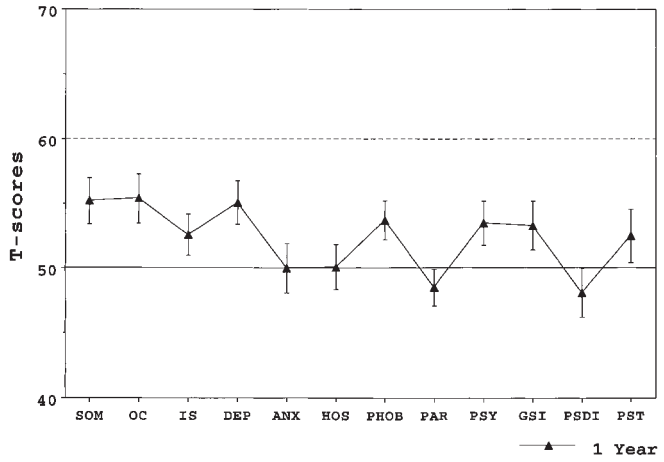

Figure 4. Mean scores ± standard errors on the SCL-90-R at 1-yr follow-up, normal mean = 50, SD = 10. Abbreviations for symptom indexes: SOM = symptoms of somatization; OC = obsessive-compulsive symptoms; IS = symptoms of interpersonal sensitivity; DEP = depression; ANX = anxiety; HOS = hostility; PHOB = phobic anxiety; PAR = paranoid ideation; PSY = psychoticism; GSI = global severity index; PSDI = positive symptom distress index; PST = total positive symptoms endorsed.

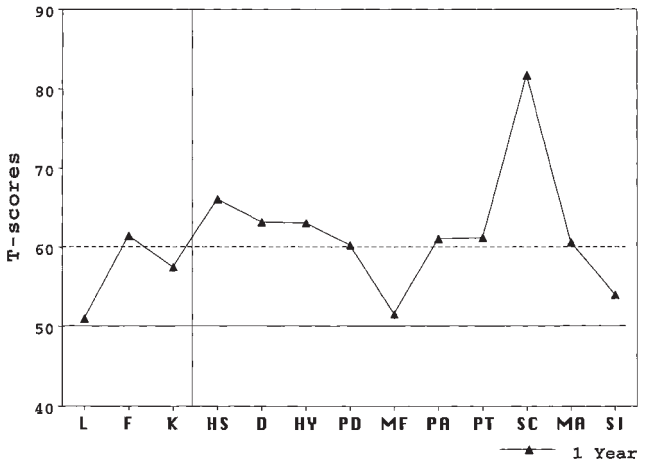

Figure 5. Mean scores ± standard errors on the Faschingbauer Short Form MMPI at 1-yr follow-up, normal mean = 50, SD = 10. Abbreviations for validity and clinical scales: L, K, and F = validity scales; HS = hypochondriasis; D = depression; HY = conversion hysteria; PD = psychopathic deviate; MF = masculinity–femininity; PA = paranoia; PT = psychasthenia; SC = schizophrenia; MA = hypomania; SI = social introversion.

impaired cognitive function including impaired memory, attention, and concentration; 48% had decreased mental processing speed; and 30% had global cognitive decline. For example, at this level of dysfunction ARDS patients reported that they had problems remembering appointments, what to buy at the grocery store, what people say to them, and if they took their medications. ARDS survivors reported difficulty remembering and following directions, especially if there were more than 2 or 3 items to be remembered. Several survivors reported that if distracted while cooking, they forgot that they had something on the stove, until the food was smoking and burning.

It should be noted that the initial neuropsychological data were collected in four separate sessions, whereas the 1-yr data were collected in one session. Initial data were collected in four sessions to reduce fatigue. At the 1-yr follow-up session, the patients' neuropsychological data were collected in one session with several rest periods. The patients were able to complete the 1-yr follow-up session with no evidence of fatigue. Therefore, it is unlikely that fatigue contributed to the ARDS patients' cognitive deficits.

The present study also confirms the previous observation that ARDS survivors manifest impaired health status as long as 1 yr after onset of ARDS (14). ARDS survivors reported impairments in physical health, body pain, and general health on both the SF-36 and the SIP questionnaire. In the previous study, the ARDS survivors' health complaints were associated with general health problems, as opposed to being related to respiratory complaints as measured by a lung SIP score (14). The investigators also noted that at 1 yr, 44% of the patients had not resumed normal activities or returned to work. The patients in our study indicated that they experienced both physical activity limitations owing to breathing difficulties and health complaints related to ARDS, which were not respiratory in nature. Examples of health impairments not related to breathing difficulties included vocal cord injury from tracheal intubation (n = 12) and movement limitations resulting from generalized weakness, traumatic limb fractures, and/or peripheral nerve injury (n = 9).

In the current study, ARDS survivors did not report significant affective symptoms on the BDI, BAI, or the SCL-90-R. However, on the Faschingbauer short form MMPI, ARDS survivors reported some symptoms of depression and somatic complaints that were more than one standard deviation above the normal values. These results indicate that when the patients are asked directly if they are experiencing emotional distress, they do not report any affective symptoms (i.e., BDI, BAI, and SCL-90-R). Conversely, when ARDS survivors are asked indirectly if they are experiencing emotional distress (i.e., MMPI), then they report some affective symptoms.

Our results indicate that ARDS survivors experience prolonged hypoxemia as measured by continuous pulse oximetry while on mechanical ventilation. The saturations $< 90\%$ occurred for a mean of 122 h, $< 85\%$ mean of 13 h, and $< 80\%$ mean of 1 h. In addition, the ABG arterial Pa_{O_2} was significantly lower than the pulse oximetry measurements. The desaturations measured by pulse oximetry significantly correlated with neurocognitive sequelae. Although cognitive impairment following ARDS with concomitant hypoxia has not been described previously, information is available for other disorders associated with hypoxia. Diseases that are characterized by hypoxia and result in cognitive impairments, including COPD (24–26) following cardiac and/or respiratory arrest (27–29) and OSAS (30, 31).

After acute anoxia or hypoxia individuals exhibit impaired attention and concentration, memory and visual–spatial deficits similar to what we observed in ARDS survivors. Recent studies have demonstrated that neuropathological changes (e.g., hippocampal atrophy) are associated with cognitive impairments (e.g., memory impairments) due to the hypoxia (27–29). The degree of cognitive impairment appears to parallel the degree of morphologic abnormality as demonstrated by quantitative magnetic resonance image analysis (15). Investigators have found that degree of hypoxemia, as measured by Pa_{O_2}, correlated significantly with cognitive impairments in patients with OSAS (30). Bedard and colleagues assessed OSAS patients and found that impaired executive function, memory, and psychomotor tasks were related to the severity

of hypoxemia, whereas impaired attention and vigilance were due to hypersomnolence (31). That is, the attention and vigilance improved on neuropsychological testing after treatment with nasal continuous positive airway pressure but impairments in executive function, memory, and psychomotor speed did not improve. Given that patients with ARDS often experience prolonged periods of hypoxia along with the known sensitivity of the temporal lobe limbic structures to hypoxia, it is possible that ARDS survivors may develop cognitive impairments similar to those observed in other patients who have experienced hypoxia.

One alternative explanation for the cognitive impairments exhibited in these ARDS survivors is that toxic or metabolic effects of associated disorders (e.g., sepsis) injure the brain. One study which assessed long-term outcome after sepsis and multiple organ failure found that three of five patients experienced long-lasting neuropsychological impairments (32). The toxic or metabolic effects on brain function following ARDS are largely unknown. It is also possible that the combination of hypoxemia and sepsis in ARDS survivors results in more severe impairments that either alone.

A second possibility is that the observed cognitive deficits may be caused by gas emboli to the CNS (33, 34) which result in decreased tissue oxygenation. Bricker and coworkers (33) observed venous gas emboli in selected mechanically ventilated ARDS patients with pneumothoraces. It may be possible that venous gas emboli caused the cognitive impairments in our ARDS survivors. However, only 16 of our 55 patients had pneumothoraces (29%), whereas 80% of patients had cognitive impairments. Given the observations of Bricker and coworkers, it is unlikely that gas emboli alone caused the cognitive impairments in our ARDS survivors. This does not completely eliminate the possible contribution of venous gas emboli to cognitive function, as venous gas emboli may occur as a consequence of mechanical ventilation in patients without evidence of barotrauma.

Finally, it is possible that the cognitive impairments are a result of the psychological state of the patients as indicated by their MMPI profile scores. However, it is unlikely that the patients' psychological status affected their cognitive performance as none of the patients were diagnosed with or reported symptoms consistent with severe depression. Other self-report measures of depression and anxiety were within the normal range. Our data suggest that cognitive impairments in ARDS survivors are associated with hypoxemia. Other possible contributors to the cognitive impairments include inflammation (systemic inflammatory response syndrome [SIRS]), emboli, or other insults associated with their critical illness.

There are several limitations of this study. The limitations include: (*1*) Only patients with severe ARDS were included in the study. Patients with a less severe form of lung injury and less severe gas exchange abnormalities (i.e., acute lung injury) were excluded from the study. Individuals whose illness is less severe may recover faster, have improved health status and cognitive outcome after acute lung injury compared with individuals with severe ARDS. (*2*) The neuropsychological battery administered to our ARDS patients did not assess all areas of cognitive function such as frontal lobe function, which includes problem-solving skills, cognitive flexibility, and perceptual motor skills. (*3*) The inclusion of appropriate control groups (i.e., other critically ill patients who did not have ARDS and/or matched normal control subjects) needs to be considered in future studies. Neuropsychological outcome studies are needed in other patients with sepsis or SIRS, in order to determine what effect, if any, sepsis or systemic inflammation in the absence of ARDS has on cognitive function. Future research should also include longitudinal follow-up (beyond 1 yr) to examine the natural history of impaired health status and cognitive impairment after ARDS.

ARDS is a life-threatening illness with a high mortality rate. ARDS survivors exhibit impaired health status and report some mild affective symptoms. Survivors of ARDS may experience prolonged periods of hypoxemia and are at risk for developing cognitive impairments. The cognitive impairments experienced by our ARDS survivors make it difficult, if not impossible, to return to work in jobs that require processing of complex cognitive information, rapid response times and make large demands on the memory system.

One question raised by this study is why haven't health care professionals recognized the cognitive sequelae in ARDS patients before? One reason may be that health care providers may not ask the appropriate questions to identify cognitive impairments in ARDS survivors. A related issue is that the cognitive impairments in our ARDS survivors were identified using sensitive neuropsychological tests. These cognitive impairments may be missed during routine physical and/or neurological examinations. Cognitive outcome information may not be recognized owing to the complexity of our health care system. For example, patients with ARDS may not return to see the critical care physicians after they leave the hospital, but return to their primary care physician in their community. That is, some members of the health care community may be aware that ARDS patients experience cognitive impairments, whereas other health care providers are not. Finally, it may be that more severely ill patients with ARDS are now surviving, and therefore the observed cognitive impairments are due to the severity of the disease and/or gas exchange abnormalities in these survivors. We believe that ARDS survivors should undergo neuropsychological assessments in order to determine potential neurobehavioral sequelae subsequent to ARDS. One way to assist ARDS survivors is by using a holistic evaluation that assesses their ability to return to work, identifying cognitive impairments, and educating the patients and their families regarding outcome and its life effects. Further research is warranted to establish the etiology of these deficits with an emphasis on developing methods of reducing the likelihood of brain injury in ARDS survivors.

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