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Brain atrophy and cognitive impairment in survivors of acute respiratory distress syndrome

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Abstract

Primary objectives: Acute Respiratory Distress Syndrome (ARDS) is characterized by severe acute lung injury, hypoxemia and is associated with neurological and cognitive impairments. This study assessed quantitative brain and ventricular volumes in survivors of ARDS with brain computed tomography (CT) scans compared to normal controls. It also compared the medical and cognitive outcome data of patients with ARDS with and without CT scans.

Research design: Observational cohort study.

Methods: Sixty-six consecutive acute respiratory distress patients, of which 15 patients with ARDS underwent brain CT and 51 patients had no brain imaging. Brain CT scans from 15 survivors of ARDS were compared to age- and sex-matched normal controls. Clinical radiological findings and ventricular volumes, brain volume and generalized brain atrophy.

Results: The patients with ARDS and brain imaging had cognitive impairments, significant brain atrophy, ventricular enlargement and 53% had atrophy or lesions by radiological report.

Conclusions: Clinicians need to be aware that ARDS can cause significant long-term brain-related morbidity manifest by brain atrophy, lesions and neurocognitive impairments.

Keywords: *Quantitative neuroimaging, acute respiratory distress syndrome, computed tomography, brain atrophy, cognitive impairments*

Introduction

The acute respiratory distress syndrome (ARDS) is a common cause of mortality and morbidity and affects 150 000 people per year [1] or more [2] in the US. Survival has improved to ~70% [3–5] resulting in ~100 000 survivors with ARDS per year. Acute respiratory distress syndrome is characterized by acute lung injury, hypoxemia, reduced total thoracic compliance and diffuse bilateral infiltrates [6, 7]. Although the pathophysiology of ARDS is unclear, it occurs in response to a variety of insults including sepsis, shock, trauma, pneumonia, massive transfusion and other medical/surgical conditions. Treatment of ARDS requires aggressive supportive care including positive pressure ventilation [5] and increased oxygen concentration with risks of barotrauma, oxygen toxicity and nosocomial infection.

Information is limited regarding neurological dysfunction in critically ill patients. Neurologic complications of acute critical illnesses, including ARDS, involve the central and peripheral nervous systems and contribute to mortality and morbidity. Encephalopathy and polyneuropathy are associated with critical illness [8], sepsis [9] and prolonged mechanical ventilation [10]. Only two studies have assessed clinical brain computed tomography (CT) findings in critically ill patients with sepsis. In one study 12 patients with encephalopathy due to sepsis

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found that all patients had normal brain CT scans [9, 11]. A second study of 69 critically ill patients, only four patients underwent brain CT imaging all of which were normal [11]. There is currently no information regarding brain-imaging outcomes in ARDS patients.

Acute respiratory distress syndrome patients may experience prolonged periods of hypoxemia [12, 13], hypotension and metabolic abnormalities that predispose them to peripheral and central nervous system injury, neurologic and cognitive sequelae. Current research indicates that survivors of ARDS have cognitive impairments that persist to 1 year post-hospital discharge [13, 14]. The prevalence of cognitive impairments varies from 46% at 1 year [15] to 25% at 6-year (median) follow-up [16] suggesting that ARDS may cause brain-related morbidity.

Little is know regarding the mechanisms of ARDS-induced brain injury, but hypoxemia is undoubtedly implicated [12, 13]. Supportive evidence includes CA1 neuronal death in the hippocampus and increased S-100B protein serum levels in pigs with acute lung injury, a mild form of ARDS [17] and cognitive impairments in chronic obstructive pulmonary disease (COPD) [18, 19], cardiac and/or respiratory arrest [20–22], obstructive sleep apnea syndrome (OSAS) [23] and post-operative hypoxia following cardiac surgery [24].

Hypoxia can cause cerebral atrophy [13, 23] and ventricular enlargement, a sensitive indicator of structural damage [23, 25]. Non-specific neuronal cell loss results in brain volume reduction manifest by reduced gyral volume, increased sulcal space, passive increase in ventricular volume (i.e. hydrocephalus *ex vacuo*) and an increase in whole brain cerebral spinal fluid (CSF) [26]. These changes can be quantified using computerized tomography (CT) or magnetic resonance (MR) image analyses [27]. Hypoxic induced hippocampal atrophy [21, 28, 29] occurs in patients with asthma [30], carbon monoxide poisoning [31, 32], obstructive sleep apnea [23] and anoxia post-cardiac or respiratory arrest [25].

Since patients with ARDS may experience long periods of hypoxia, it was hypothesized that they might develop brain lesions and atrophy similar to that observed in other disorders with concomitant hypoxia. To investigate the effects of ARDS on brain morphology, brain CT morphometric measures of 15 survivors of ARDS were compared with 15 age- and sex-matched normal control subjects. A second purpose of this study was to assess the relationship between CT morphometric measures and neurocognitive function in survivors of ARDS. In addition, medical and neurocognitive outcome data for the patients with ARDS who underwent brain CT imaging for clinical reasons were compared to patients without brain CT imaging.

Methods

Patient selection

Archival data was obtained for 66 patients with ARDS who were enrolled in a prospective 1-year neurocognitive outcome study. This prospective cohort outcome study was approved by the LDS Hospital Institutional Review Board and conformed to institutional and federal guidelines for the protection of human subjects. Written informed consent was obtained from the patients with ARDS prior to hospital discharge, but after treatment in the intensive care unit. Patient demographic, medical data, Acute Physiologic and Chronic Health Evaluation II (APACHE II) score [33], LDS Hospital multiple organ failure score (MOF) [34], laboratory values, ventilator and outcome data were collected prospectively.

Eligible patients with ARDS included in the brain imaging study were from a 1-year neuropsychological outcome study [15]. Inclusion criteria were: tracheal intubation, arterial oxygen tension/fraction of inspired oxygen ratio PaO_2/FiO_2 ratio ≤ 150 mm Hg, pulmonary capillary balloon occlusion pressure ≤ 18 mm Hg (when available), no clinical evidence of congestive heart failure, diffuse alveolar infiltrates in three out of four quadrants on chest radiographs, age ≥ 16 years and presence of an ARDS risk factor (e.g. aspiration, multiple trauma, pancreatitis, pneumonia or sepsis). Patients were excluded if they had disease states that were not reversible (e.g. liver failure, malignancy, acquired immune deficiency syndrome), traumatic brain injury, prior neurologic disease, prior cognitive disability or if they were enrolled in another ARDS study. Of the 66 patients with ARDS, 15 patients underwent brain CT as part of their clinical care. Brain CT findings were compared to healthy age- and sex-matched control subjects. The medical data and neurocognitive function of the 15 patients with ARDS who underwent cranial CT were compared to 51 patients with ARDS who did not undergo neuroimaging studies.

Brain CT control subjects

Archival age- and sex-matched medical control subjects were selected for brain image analysis only. The controls were selected from LDS Hospital's computerized archive of patients who underwent brain CT as part of headache evaluations and whose brain CT scans were normal per radiological report. Once the controls were identified as having normal

brain CT scans they were age- and sex-matched to the 15 patients with ARDS who underwent brain imaging. Controls with a history and/or diagnosis of neurologic disorder, TBI or psychiatric disorder were excluded.

Assessment of hypoxemia

Continuous oxygen saturation data to assess hypoxemia was automatically collected using the Ohmeda (Louisville, Kentucky) Biox 3700 and 3740 devices and data recorded by a computer. Continuous pulse oximetry measurements (SpO_2) were assessed during ventilatory support [13]. The saturation readings were sampled every 2 minutes and the median value for each 15-minute period was recorded [35] and categorized if <90%, <85% and <80% saturation. The duration of desaturation events was calculated by adding consecutive measurements (each measurement represents a 15-minute interval) that were below the saturation threshold.

Neurocognitive function

Neurocognitive tests assessed intelligence, attention/concentration, memory, mental processing speed, executive function and visual-spatial abilities were assessed at hospital discharge and 1-year. The neurocognitive tests included Weschler Adult Intelligence Test-Revised (WAIS-R) [36], Weschler Memory Scale-Revised (WMS-R) [37], Rey Auditory-Verbal Learning Test (RAVLT), Rey-Osterrieth Complex Figure Test (copy, immediate recall and 30 minute delay recall) [38], Trail Making Test Parts A and B [39] and Verbal Fluency test [40].

Brain CT clinical and volumetric analysis

The clinical radiological brain CT reports were reviewed for abnormalities. Quantitative (volumetric) analysis of cerebral structures obtained from axial CT scans was performed using the NIH software package IMAGE (National Institutes of Health, Bethesda, MD) as per the methods described previously [41–43]. Quantitative CT analyses of brain structures were performed on all patients as per methods described previously [44, 45]. Quantitative CT image analysis was performed with the rater (SDG) blind to patient identity and group; however, significant atrophy is often unmistakable and, therefore, the identity of ARDS scans could not be fully masked. Volumetric measures included the lateral ventricles, III ventricle, IV ventricle, temporal horns, total brain volume, cerebral spinal fluid (CSF) and ventricle-to-brain ratio (VBR). The VBR is the total ventricular volume (lateral, III and IV ventricle total volume) divided by total brain parenchymal volume multiplied by 100. The VBR is a measure of diffuse atrophic change and a general index of white matter integrity [23, 27]. Intra-rater and inter-rater reliability exceeded 0.98.

Statistical analysis

Descriptive statistics were carried out for demographic, medical, brain imaging and neurocognitive data. Independent *t*-tests were used to compare medical and neurocognitive scores between ARDS patients with brain CT scans and those with no brain CT scans. A one-way ANOVA was used to compare brain volume, ventricular volumes and VBR for the ARDS group compared to the normal control group. Pearson correlation coefficients were carried between brain volumes, VBR and medical data; between ventricular volumes, VBR and hypoxemia; and ventricular volumes, VBR and neurocognitive function for the ARDS patients with CT scans.

Results

There were six females and nine males in the patients with ARDS brain CT and normal control groups. The ARDS patients' mean age was 39.2 ± 18.1 years (range 15–72 years) and the controls mean age was 40.1 ± 20.2 years (range 15–75 years). There was no difference for age between the ARDS brain CT and control groups. The patients with ARDS CT scans were obtained an average of 16.4 ± 11.9 days (range 7–40 days) from ARDS onset. The reasons for the brain CT scans include: not awakening or mental status change $n = 12$, rule out intracranial pathology $n = 2$ and fever $n = 1$. The brain CT radiological findings in the patients with ARDS are shown in Table I.

Medical data and demographic data for the patients with ARDS with and without CT scans are shown in Table II. The patients with ARDS and brain CT scans had a longer hospital length of stay [$t(1, 72) = 2.01$, $p = 0.05$], ICU length of stay [$t(1, 72) = 3.32$, $p = 0.001$], duration of mechanical ventilation [$t(1, 72) = 3.65$, $p < 0.001$] and a lower FiO_2 [$t(1, 72) = 2.56$, $p = 0.013$] compared to ARDS patients without brain imaging.

Brain CT volumetric analysis

Brain CT scans for two patients with ARDS and their matched normal controls are shown in Figure 1. The patients with ARDS had significantly larger ventricular volumes for the lateral ventricles [$F(1, 28) = 6.12$, $p = 0.02$], III ventricle

Table I. Brain CT radiological findings from the radiological reports for the 15 patients with ARDS who underwent brain imaging.

ARDS patient	Radiological findings
1	Normal
2	Normal
3	Normal
4	Normal
5	Normal
6	Normal
7	Normal
8	Small petechial haemorrhage 5 mm at vertex of right cerebral convexity, increased temporal horns of the lateral ventricles especially on the left
9	Lesion in central pons with the transverse fibers most affected, slight ventricular enlargement
10	Mild diffuse atrophy, prominent cortical sulci
11	Hypodensity in medial left parietal lobe, white matter hyperintensity in subcortical right frontal lobe
12	Borderline prominent cerebral sulci and ventricles
13	Diffuse cerebral atrophy, ventricular enlargement, hippocampal atrophy
14	Diffuse mild atrophy, diffuse mild-to-moderate ventricular enlargement
15	Diffuse cerebral atrophy

ARDS = Acute Respiratory Distress Syndrome; CT = computed tomography.

Table II. Medical data for the patients with ARDS. The comparison of medical data between ARDS patients with and without CT data.

	With CT scans ($n = 15$)	Without CT scans ($n = 51$)	p
Age (years)	36 ± 16.9	47.8 ± 15.7	0.02
Education (years)	12.7 ± 1.9	13.1 ± 2.5	ns
Hospital length of stay (days)	49.9 ± 25.6	36.4 ± 20.2	0.05
ICU length of stay (days)	47.1 ± 26.8	30.9 ± 14.7	0.01
Intubation duration (days)	44.7 ± 28.2	24.6 ± 14.7	<0.001
Study enrolment			
PaO_2 mm Hg	69.0 ± 17.1	68.5 ± 12.6	ns
MOF score	8.3 ± 3.1	7.0 ± 3.6	ns
FiO_2 mm Hg	78.2 ± 16.6	65.7 ± 14.5	0.01
APACHE II	17.3 ± 4.1	18.3 ± 7.0	ns
PaO_2/FiO_2 ratio	92.7 ± 34.3	109.2 ± 30.7	ns
Total ICU stay			
Mean PaO_2/FiO_2	70.2 ± 6.9	68.8 ± 5.8	ns
Mean FiO_2 mm Hg	55.5 ± 11.2	51.0 ± 9.1	ns
Hours oximetry $SaO_2 < 90\%$	146.1 ± 179.7	99.1 ± 115.0	ns
Hours oximetry $SaO_2 < 85\%$	14.3 ± 22.5	10.0 ± 24.7	ns
Hours oximetry $SaO_2 < 80\%$	1.1 ± 2.2	0.7 ± 2.5	ns

ARDS = Acute Respiratory Distress Syndrome; CT = computed tomography; ICU = Intensive Care Unit; APACHE II = Acute Physiology and Chronic Health Evaluation [33]; MBP = mean blood pressure; MOF = multiple organ failure [34]; ns = not significant; PaO_2/FiO_2 = Ratio of arterial oxygen tension to fraction of inspired oxygen; FiO_2 = fractional inspired concentration of oxygen; PaO_2 = arterial oxygen tension; SpO_2 = oximetric arterial oxygen saturation; ARDS Risk Factors are aspiration, multiple trauma, pancreatitis, pneumonia, or sepsis.

[$F(1, 28) = 6.56$, $p = 0.02$], left temporal horn [$F(1, 28) = 8.57$; $p = 0.006$], right temporal horn [$F(1, 28) = 3.8$, $p = 0.05$], total ventricular volume [$F(1, 28) = 6.58$, $p = 0.02$] and VBR [$F(1, 28) = 7.86$, $p = 0.008$], compared to the normal control subjects (Figures 2 and 3). There were no significant differences in total brain volume or the IV ventricle between the two groups.

Neurocognitive function

Neurocognitive scores at hospital discharge and 1-year for patients with ARDS ($n = 15$) and brain CT scans were compared to those without CT scans ($n = 51$). There were no differences in neuropsychological scores between the patients with ARDS and brain CT scans compared to those without

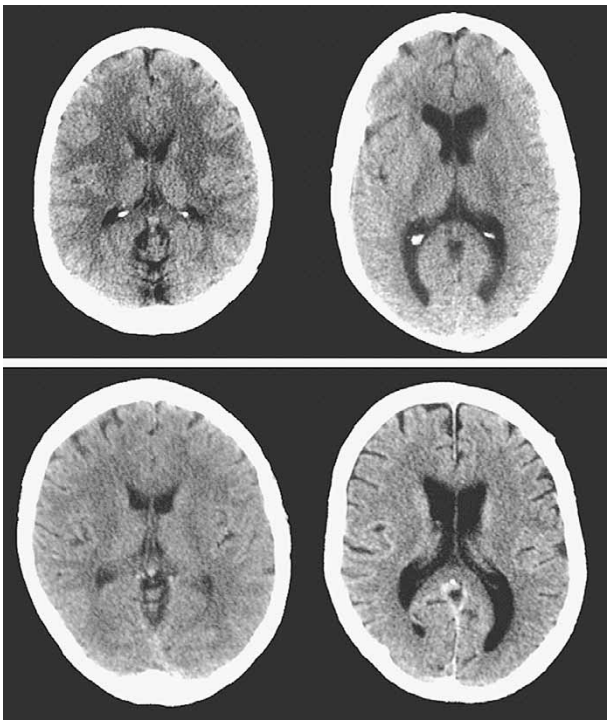

Figure 1. Brain CT scans in normal controls and patients with ARDS. The figure shows brain CT images in the axial plane through the mid body of the lateral ventricles in patients with ARDS and normal controls. The top row shows two 34-year-old women. On the left is the control subject and on the right is a patient with ARDS. The bottom row shows two 54-year-old men. The control subject is on the left and the patient with ARDS is on the right.

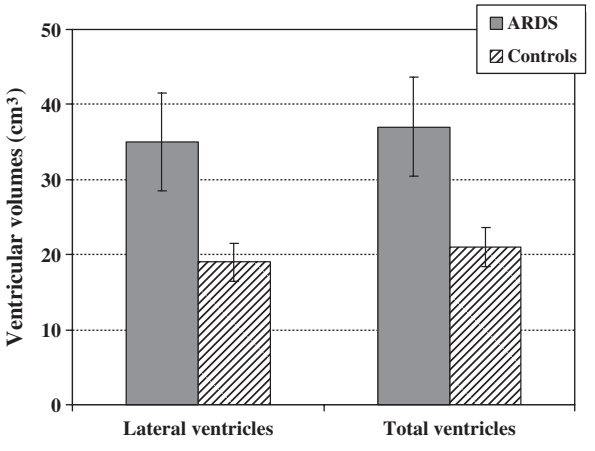

Figure 2. Lateral and total ventricular volumes in patients with ARDS and normal controls. The figure shows the mean lateral ventricle and the total ventricle volumes ± standard error for patients with ARDS and age- and sex-matched normal controls. The ARDS patients have significantly larger volumes for the lateral ventricles and total ventricles compared to controls.

CT scans, except for verbal memory at hospital discharge (Table III). At the time of hospital discharge all patients with ARDS had cognitive deficits, including impaired memory, attention/

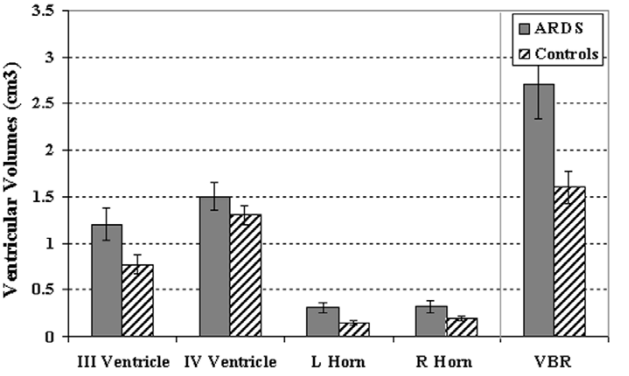

Figure 3. Volumes for the IV ventricle, temporal horns and ventricle-to-brain ratio. The figure shows III ventricle, IV ventricle, right horn and left horn of the lateral ventricles volumes ± standard error in cm^3 and ventricle-to-brain ratio (right side) for patients with ARDS and age- and sex-matched normal controls. The patients with ARDS have significantly larger volumes for the III ventricle, IV ventricle and temporal horns of the lateral ventricles and ventricle-to-brain ratio compared to controls. Abbreviations are: III = III ventricle, IV = IV ventricle, L horn = left horn of the lateral ventricles, R horn = right horn of the lateral ventricles and VBR = ventricle-to-brain ratio.

concentration and/or impaired processing speed. At 1-year follow-up the patients with ARDS and CT scans scores improved on the Performance Intelligence Quotient, Visual Memory Index, Attention/Concentration Index and Trail Making Test Parts A & B (e.g. mental processing speed and executive function). However, all patients with ARDS and brain CT scans continued to have significant memory impairments.

Correlations

There were no significant correlations between ventricular volumes (i.e. VBR, lateral ventricles, third ventricle, fourth ventricle and right and left temporal horns) with medical data or duration and severity of hypoxemia in the patients with ARDS and brain CT scans. There were no significant correlations between brain atrophy or ventricular enlargement and neurocognitive scores in the patients with ARDS and brain CT scans.

Discussion

The survivors of ARDS who underwent brain CT imaging had significant brain atrophy manifested by ventricular enlargement and enlarged VBRs compared to age- and sex-matched normal control subjects. The patients' radiological reports identified seven patients with atrophy, which supports the finding of ventricular enlargement and brain atrophy on volumetric analyses. Six of the patients

Table III. Comparison of neuropsychological test scores in patients with ARDS with and without brain CT imaging.

	Hospital discharge			1 Year		
Neuropsychological test	CT scans	No CT scans	*p*	CT scans	No CT scans	*p*
WAIS-R						
VIQ	95.4 ± 13.2	91.9 ± 12.0	ns	100.1 ± 14.7	98.1 ± 10.9	ns
PIQ	86.2 ± 15.2	86.7 ± 9.4	ns	96.4 ± 19.0	98.8 ± 10.4	ns
FSIQ	91.1 ± 14.2	89.7 ± 10.4	ns	98.0 ± 17.2	97.9 ± 10.4	ns
Information	8.7 ± 2.9	9.0 ± 2.7	ns	9.5 ± 3.5	9.2 ± 2.8	ns
Digit span	8.8 ± 2.5	8.1 ± 2.3	ns	9.4 ± 3.0	9.1 ± 2.2	ns
Vocabulary	9.5 ± 2.4	9.0 ± 2.1	ns	9.6 ± 2.4	9.3 ± 2.2	ns
Arithmetic	7.6 ± 2.7	7.7 ± 2.5	ns	8.9 ± 3.1	8.9 ± 3.0	ns
Comprehension	7.9 ± 2.5	8.5 ± 2.5	ns	8.7 ± 2.2	8.6 ± 2.2	ns
Similarities	8.8 ± 2.1	8.7 ± 2.4	ns	10.4 ± 3.0	9.9 ± 2.4	ns
Picture completion	7.2 ± 2.2	7.6 ± 2.4	ns	8.6 ± 2.2	8.5 ± 2.3	ns
Picture arrangement	6.9 ± 2.5	6.7 ± 1.8	ns	7.9 ± 1.5	8.3 ± 2.4	ns
Block design	7.4 ± 2.5	6.6 ± 2.3	ns	8.5 ± 2.5	8.4 ± 2.4	ns
Object assembly	6.5 ± 2.4	6.3 ± 2.2	ns	8.8 ± 3.9	8.2 ± 2.2	ns
Digit symbol	6.1 ± 2.1	5.2 ± 2.4	ns	8.4 ± 3.4	7.5 ± 2.5	ns
Verbal fluency						
Total score	28.2 ± 13.6	28.1 ± 8.8	ns	37.5 ± 14.2	38.6 ± 10.8	ns
Mean score	9.4 ± 4.5	9.4 ± 3.3	ns	12.5 ± 4.7	12.9 ± 3.6	ns
Complex figure						
Copy	24.2 ± 8.5	26.2 ± 8.6	ns	31.5 ± 6.1	31.4 ± 7.3	ns
Immediate recall	10.2 ± 4.3	11.2 ± 7.4	ns	14.1 ± 6.5	16.4 ± 7.1	ns
30' delay recall	10.6 ± 5.7	12.0 ± 10.9	ns	13.5 ± 6.5	15.6 ± 7.4	ns
RAVL						
Trial 1	4.1 ± 1.6	4.9 ± 1.7	ns	6.1 ± 1.8	5.7 ± 1.9	ns
Trail 5	10.6 ± 2.6	8.4 ± 2.8	0.009	10.1 ± 2.3	10.5 ± 2.3	ns
30' delay free recall	7.8 ± 3.6	5.7 ± 3.1	0.04	7.9 ± 2.5	8.5 ± 2.5	ns
WMS-R						
Verbal memory index	91.2 ± 12.4	90.3 ± 12.2	ns	91.0 ± 15.6	94.8 ± 11.1	ns
Visual memory index	91.8 ± 14.8	95.5 ± 13.5	ns	99.5 ± 16.8	99.9 ± 12.6	ns
General memory index	90.1 ± 15.7	92.5 ± 14.0	ns	96.7 ± 11.8	95.8 ± 10.4	ns
Atten/concen index	87.3 ± 16.9	85.4 ± 15.5	ns	91.7 ± 21.8	91.8 ± 12.8	ns
Delay recall index	76.0 ± 21.5	81.0 ± 11.4	ns	86.8 ± 14.3	87.4 ± 11.8	ns
Trail making test						
Part A (time in seconds)	59.8 ± 32.4	54.7 ± 27.6	ns	39.5 ± 20.6	35.8 ± 14.9	ns
Part B (time in seconds)	136.1 ± 74.0	150.8 ± 77.8	ns	88.4 ± 42.1	83.5 ± 33.3	ns

Neurocognitive test scores for the ARDS patients with and without brain computed tomography (CT) scans. Data are presented as mean ± SD. WAIS-R = Wechsler Adult Intelligence Scale-Revised, scores are presented as intelligence quotients ($M = 100$, SD = 15) and sub-tests are presented as scaled scores ($M = 10$, SD = 3). WMS-R = Wechsler Memory Scale-Revised, scores are presented as Index scores ($M = 100$, SD = 15). All other tests are presented as raw scores. VIQ = Verbal Intelligence Quotient, PIQ = Performance Intelligence Quotient, FSIQ = Full Scale Intelligence Quotient and ns = not significant. Atten/Concen = attention concentration.

with ARDS had mild-to-moderate cerebral atrophy or ventricular enlargement, one of which had hippocampal atrophy and one patient had increased temporal horns of the lateral ventricles. The observed brain atrophy may be due to hypoxia that occurred during the critical illness and ICU treatment [12, 13]. Non-specific brain injury manifested by reduced gyral volume, increased sulcal space, passive increase in ventricular volume and increased cerebrospinal fluid CSF is common following hypoxic brain injury [26]. Hypoxia can cause diffuse neuronal loss, generalized brain atrophy [46–48] and is a common finding on brain imaging [47] in disorders associated with hypoxia or anoxia. The generalized atrophy and ventricular enlargement in the patients with ARDS is similar to that reported following carbon monoxide poisoning [23, 31], cardiac or respiratory arrest [25, 46] and in patients with severe asthma [30].

Significant enlargement was found in the left ($p = 0.006$) and right ($p = 0.05$) temporal horns in the patients with ARDS compared to controls, which may reflect temporal lobe or hippocampal atrophy. Radiological reports indicate one patient with ARDS had hippocampal atrophy and one had temporal horn enlargement. White matter pathways, with the exception of the boundary between the hippocampus and amygdala, surround the temporal horns. Temporal horn volumes are a common reference used to evaluate clinical hippocampal and

white matter integrity. Correlations between hippocampal atrophy and temporal horn enlargement are found in patients with TBI [44, 49]. Alternatively, temporal horn enlargement is associated with loss of temporal lobe white matter [50]. The temporal horn enlargement observed in the patients with ARDS and brain CT scans is likely an indirect index of the integrity of temporal lobe white matter, hippocampus or both [44, 51].

The ventricle volumes and VBR did not correlate with any measure of illness severity (e.g. ICU and hospital length of stay, duration of mechanical ventilation, APACHE II score, MOF score, etc.) in the patients with ARDS and brain CT scans. The duration and severity of hypoxemia did not correlate with brain atrophy, ventricular enlargement or VBR. The reasons for the lack of a relationship between hypoxemia and brain atrophy in this study are unclear but may be related to the small sample size, the large variance of the ventricular volumes or limitations of the SpO_2 measurement. Other possible mechanisms for the observed atrophy include inflammation or hypotension. Alternatively, other neural structures including the hippocampus [15, 22, 29], basal ganglia and cerebellum have known selective vulnerability to hypoxic injury; therefore, hypoxia may more likely be associated with lesions or atrophy in these structures. Brain CT scans were used for this study, but MRI may be more sensitive to brain-related pathology in ARDS and other critically ill patients. High-resolution MRI studies may detect additional lesions or atrophic changes in ARDS patients. Magnetic resonance imaging has superior anatomic resolution and freedom from bone artifact [52], MR is more sensitive than CT in detection of white matter lesions especially on T2 sequences [53], detection of tumour metastases [54] and detection of structural changes (e.g. hippocampal atrophy, etc.) in patients with mild cognitive impairment and dementia [55].

Both the patients with ARDS with and without CT scans had significant cognitive impairments including impaired memory, attention, mental processing speed and executive function at hospital discharge and 1 year post-hospital discharge. At 1 year, ~50% of ARDS survivors' cognitive scores were below the 8th percentile of the normal distribution of cognitive function. The cognitive impairments at 1-year in the group of ARDS patients are similar to those observed in other survivors of ARDS [16, 56, 57], medical ICU survivors [14], following carbon monoxide poisoning [58] and elective coronary-artery bypass surgery [59]. The lack of difference in cognitive impairments between the ARDS groups suggest two possibilities; (1), the morphometric changes found in the group of ARDS patients with brain CT scans are unrelated to neurocognitive outcome or (2) the patients with ARDS without CT scans may have similar morphometric changes. Given that the prevalence of neurocognitive impairment of 20–46% 1-year after ARDS [14, 16, 56] perhaps brain CT could be used as a predictor of cognitive impairments in survivors of ARDS.

As stated above, current data suggest that approximately one third or more of patients with ARDS will develop ongoing and persistent cognitive impairment [13, 14]. Although early detection of cognitive impairment in patients with ARDS is an important and achievable goal, even overt cognitive impairment remains unrecognized in most cases. Gordon et al. [60] suggest that all critically ill patients, including those with ARDS, should be screened for cognitive impairments. An alternative approach would be to screen only those individuals with an increased likelihood of developing cognitive impairment; however, only a few investigations have assessed mechanisms or risk factors of cognitive impairment following critical illness [60]. Thus, patients with ARDS with known risk factors such as hypoxemia [13], hypotension [48] or hyperglycemia [61] or are thought to have cognitive impairments should be referred to a clinical neuropsychologist for a comprehensive neuropsychological evaluation. If cognitive impairments are identified, then brain imaging may be warranted.

There are several limitations of the study including small sample size and the group of patients with ARDS was a convenience cohort, scanned for clinical reasons at variable times (7–40 days) during their ICU treatment. While these limitations are fully acknowledged, however to the authors' knowledge this is the first study to assess brain CT outcome in critically ill patients with ARDS. Both the radiological reports and quantitative brain imaging findings provide support for the observed atrophic changes in patients with ARDS. Future studies should prospectively assess brain imaging in patients with ARDS at consistent time intervals.

Another limitation is the patients with ARDS and brain CT imaging had longer ICU and hospital length of stays and longer duration of mechanical ventilation compared to patients with ARDS patients without brain CT. Therefore, brain atrophy may be due to factors other than ARDS such as systemic hypotension or duration of mechanical ventilation. However, patients with ARDS with and without brain CT imaging did not differ in terms of cognitive function at hospital discharge or 1 year. Therefore, the patients with ARDS and CT scans may be representative of the larger group of ARDS patients. A final limitation is that the findings may not generalize to all survivors with

ARDS as the patients had moderate-to-severe ARDS (PaO_2/FiO_2 ratio $\leq$150) and the brain CT scans were acquired for clinical reasons (e.g. not awakening, fever and rule out intra-cranial pathology) and, therefore, may not reflect the brain integrity in all such patients.

The patients with ARDS who underwent clinical brain CT scanning as part of their intensive care treatment had significant brain atrophy by both radiological report and on quantitative brain imaging, indicating permanent brain injury. Clinicians should be aware that patients with ARDS are at risk to develop brain atrophy and cognitive impairments. This study used brain CT scans but MRI may be more sensitive to brain-related pathology in ARDS and other critically ill patients.

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