Dynamics of Extravascular Pulmonary Water and Intracranial Pressure in Patients With Ischemic Stroke

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Abstract

The objective of the present study was to examine the relationship among extravascular pulmonary water, intracranial and cerebral perfusion pressure, hemodynamic parameters (e.g., cardiac index, systemic vascular resistance index), and brain stem function during acute ischemic stroke. The subjects were 17 comatose patients with ischemic stroke who were admitted to an intensive care unit. The results revealed an elevation in extravascular lung water in the absence of cardiac dysfunction. The absence of correlation between indices of brain vascular resistance and mean arterial pressure confirmed that a disturbance of cerebrum blood flow was present. There was a correlation between auditory-evoked potential parameters and extravascular lung water during the study period. The correlation between auditory-evoked potentials and extravascular lung water may imply that ischemic brainstem injury plays a significant role in the development of increased pulmonary capillary permeability and the elevation of extravascular lung water. Brain stem injury is a cause of noncardiogenic lung edema in comatose patients following acute ischemic stroke.

Keywords
coma, acute ischemic stroke, brain stem, extravascular lung water, noncardiogenic pulmonary edema

Introduction

Comas caused by acute ischemic stroke (AIS) are characterized by systemic hemodynamic and pulmonary complications regardless of the etiological agent. The changes in hemodynamics are characterized by a combination of disorders of myocardial mechanics and systemic vascular resistance. In addition to the effects of the central nervous system on myocardial mechanics, coronary arteries, preload, and afterload, cardiac depression may be exacerbated by iatrogenic factors.1,2

Pulmonary morbidity is one of the main extracerebral sequelae of AIS. Disturbances of the respiratory center of the brainstem initially result in alveolar hyperventilation and hyperventilation and progress to more serious pulmonary complications after AIS. Mucous hypersecretion with airway obstruction, a reduction in the cough reflex, and aspiration may result from damage to the caudal group of cranial nerves nuclei. These factors lead to inflammatory diseases of the lungs and possibly also to the development of the acute respiratory distress syndrome (ARDS).

The pathogenesis of ARDS in patients after AIS and its relationship to AIS is unclear. Possible mechanisms for ARDS development include increased pulmonary vascular permeability and extravascular pulmonary fluid deposits; however, its relation to intracranial pressure (ICP), cerebral perfusion pressure (CPP), and brainstem function have not been well defined.2,6

Early diagnosis of pulmonary damage allows for early intervention, perhaps decreasing the likelihood of progression to severe forms of ARDS and pneumonia, with the aim of improving the outcome of patients with AIS. Transpulmonary thermodilution allows for the estimation of extravascular fluid in the lungs and vascular permeability in real time, thus facilitating more precise control of hemodynamics. This method has been used successfully for differentiation
of cardiac versus noncardiac etiologies of increased extracranial pulmonary fluid.4,7-9

The goal of the present study was to examine the progression and relationship of extracranial pulmonary fluid, ICP, CPP, hemodynamics, and the functional condition of brainstem structures in patients with coma caused by AIS.

Materials and Methods

This project was approved by the institutional human ethics committee. This prospective study involved 17 comatose patients after AIS who were followed for a 7-day period. The inclusion criteria were the following:

1. Patients in the initial hours following diagnosis of AIS that was confirmed by spiral computed tomography
2. Absence of pulmonary aspiration
3. Patients who were eventually discharged from the hospital
4. Initial Glasgow Coma Scale of 4 to 7 points

A Codman subdural/intraparenchymatous ICP sensor (Johnson & Johnson, London, UK) was inserted on the day following AIS to monitor ICP. CPP was estimated using the standard formula: CPP = mean arterial pressure – ICP. Daily patient evaluations included clinical assessment of neurological status, measurements of neurophysiological dynamics, and radiographic and clinical laboratory testing.

Transpulmonary thermodilution was used to determine central hemodynamic parameters (“PICCO plus”; PULSION Medical Systems, Munich, Germany). The following measured and calculated parameters were derived from the PICCO pulse system: mean arterial blood pressure (MBP, mm Hg), cardiac index (CI, L/min/m²), systemic vascular resistance index (SVRI, dyne s cm⁻⁵ m⁻²), global end-diastolic volume index (GEDI, mL/m²), intrathoracic blood volume (ITBV, mL/m²), extravascular lung water index (ELWI, mL/kg), pulmonary vascular permeability index (PVPI, point), global ejection fraction (GEF, %), cardiac function index (CFI, 1/min), and maximum rate of rise of the systolic segment of the pulse wave—an index of contractility of the left ventricle (dP_max, mm Hg/s).

Brainstem function was measured using brainstem acoustic evoked potentials (BAEP) (NeuroMVP; Neurosoft, Ivanovo, Russia). The following parameters were measured and expressed as the latency periods of peaks (ms): P1, distal part of auditory nerve; P3, complex bilateral superior olivaries; and P5, colliculi inferioris. The following intervals were calculated from these latencies (ms): P1–P3, the time of conduct of impulses in the caudal portions of the brainstem; P3–P5, conduction in the diencephal portions; and P1–P5, the time of central conduction.10 Middle cerebral artery velocity was determined using transcranial Doppler (Angiodin ECHO/U, BLOOD, Moscow, Russia). The following parameters were recorded: systolic blood flow velocity (S) (cm/s), diastolic blood flow velocity (D) (cm/s), mean blood flow velocity (m) (cm/s), Gosling pulsatility index (PI), resistance index (RI), and the spectral broadening index.11-13

Indices of central hemodynamics, transcranial Doppler, ICP, and BAEP measurements were acquired on days 1 through 3 and 5 through 7 of the study. All critical care management was at the discretion of the attending intensivist and included mechanical ventilation, prevention and treatment of infectious complications, nutritional support, normalization and optimization of cerebral blood flow, antiplatelet and anticoagulation therapy, as well as prevention and treatment of brain edema.

All analyses were performed with GraphPad and InStat 3 (GraphPad Software, La Jolla, CA) as well as Statistica 7 (StatSoft, Tulsa, OK). All results are expressed as means ± standard deviations. Statistical differences among time points were determined using 1-way ANOVA, with post hoc comparisons using Tukey’s test. The significance of linear regression models were determined by Spearman’s rank correlation. A 2-tailed P < .05 was considered significant.

Results

Patients had APACHE II scores of 19.4 ± 2.3. The mean age was 61.0 ± 3.2 years. All patients had arterial hypertension and ischemic heart disease.

Neurological, radiological, and neurophysiological tests were used to assess the hemispheric cortical level of brain injury of each patient. ICP was slightly elevated during all periods of examination but significantly increased on days 3 and 5 and diminishing by day 7. CPP was maintained above 80 mm Hg. BAEP detected dysfunction of brainstem function that was confirmed by clinical neurological examination (Table 1).

There were no clinically significant changes in central hemodynamic values among patients during the study period. Specifically, there were no changes in CI, SVRI, dP_max, CFI, GEDI, or ITBV (Table 1).

The extravascular lung water index (mL/kg) was in the high normal range on day 1 and significantly increased from the fifth to seventh day to reach 9.5 ± 0.6 mL/kg (Table 1).

There were statistically significant correlations between ELWI and the values of BAEP peaks and latencies: P1 (r = .78), P3 (r = .74), P5 (r = .81) (all with P < .05), and the latency for P1–P5 (r = 6; P < .05). We also detected a correlation between GEF and indices of cerebral vascular resistance: PI (r = .53) and RI (r = .69) (both with P < .05) (Figures 1–6). We found weak associations of mean arterial pressure with indices of cerebral vascular resistance for all
time points of the study: MAP versus PI \((r = -0.51)\) and MAP versus RI \((r = -0.55)\) (both with \(P < .05\)).

**Discussion**

We found associations between damage to brainstem structures and ELWI deposits, with related development of non-cardiac pulmonary edema. The correlations between GEF and indices of cerebral vascular resistance may be indicative of impaired autoregulation of brain blood flow. This was further supported by the weak associations of hemodynamics with cerebral autoregulation calculations.

It is known that brain hypoxia and ischemia lead to activation of pressure receptors that are localized in the hypothalamus, brain stem, and spinal cord. Increased \(\alpha\)-adrenergic stimulation is mediated via the medulla oblongata, vagus nerves, and boundary sympathetic chains. Spastic stricture of postcapillary sphincters raises systemic arterial blood pressure and is associated with hypertension in the pulmonary circulation, presumably to maintain/restore disturbed cerebral blood flow. With hypothalamic dysfunction, this is theorized to exceed the compensatory limits of the pulmonary vascular system, leading to extravasation of fluid into pulmonary alveoli and hemorrhage within the perivascular spaces\(^{8,13,14}\).
During AIS, the development of disseminated intravascular coagulation, pulmonary aspiration, and infection also promote the accumulation of extravascular lung water, contributing to the occurrence of ARDS. The etiologies of pulmonary complications are multifactorial, and the interactions of Starling forces in these conditions are difficult to determine. There are dynamic changes in oncotic balance, hydrostatic pressure, the state of lymphatic drainage, and the morphology of interstitial spaces. Therefore, it is very difficult to define the primary etiology of extravascular lung water accumulation: Is it heart failure or increased permeability of lung vessels?8,9,15

In our cohort of intensive care patients, we did not observe cardiac dysfunction. The contractility of the left ventricle was within the normal range during the entire period of study, demonstrating that cardiac failure was not present. Normal GEDI and ITBI during the period of study demonstrated adequate preload and afterload.

The increase in ELWI and PVPI in the absence of concurrent changes in CFI, GEF, and \( d_P \text{ max} \) support the noncardiogenic etiology of increasing ELWI in our patient cohort. The correlation between ELWI and values of BAEP supports the hypothesis that the increasing volume of extravascular water in the lungs was related to stroke-related brainstem dysfunction, as a consequence of ischemia-impaired cerebral blood flow autoregulation. The correlation between MAP and cerebral vascular resistance indices (PI and RI) by transtemporal Doppler examination indirectly confirmed this observation.
Conclusion

Damage to brainstem structures (especially damage of the pons and medulla oblongata after supratentorial herniation) is one of the causes of noncardiogenic pulmonary edema among patients with coma after AIS. The vascular permeability of the lungs has a major role in this process.

Declaration of Conflicting Interests

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