Impact of Allostatic Load on Cognitive Level, Memory and Left Ventricular Mass

SARA C. COSTA DE ROBERT

ABSTRACT

Background: Allostatic load (AL) has been proposed as a general framework for understanding the cumulative effects of life stress on individuals. Despite growing interest in AL, no research has been conducted in Argentina related to its impact on the heart and brain.

Objective: The aim of this study was to evaluate the association of AL, functionally defined by a range of measurements from the sympathetic and parasympathetic systems, hypothalamic-pituitary-adrenal axis, and inflammatory, cardiovascular and metabolic systems, with the cognitive level (CL), memory and left ventricular mass in middle-aged adults.

Results: A total of 86 patients were evaluated with mean age of 53.5 years (95% CI: 51.3 - 55.7). Allostatic load had a significant inverse association with the CL (coefficient -1.1; standard error: 0.5; p=0.04) that was independent of age, sex and educational attainment (adjusted square R: 0.40; p <0.001). Of the seven systems evaluated, only the cardiovascular and inflammatory systems had significant inverse associations with AL. An inverse relationship was also observed between AL and memory. In the heart, a positive correlation was found between AL and left ventricular (LV) mass (coefficient: 10.86; p <0.001; adjusted square R: 0.23; p <0.001).

Conclusions: Allostatic load is an objective tool to measure chronic stress. The results obtained indicate that high AL damages the brain (early cognitive and memory deficits) and the heart (increased LV mass).

Key words: Chronic stress – Allostatic load – Cognitive deficit – Memory– Left ventricular mass

RESUMEN

Introducción: La carga alostática (CA) se ha propuesto como un marco general para comprender los efectos acumulativos del estrés a lo largo de la vida de las personas. A pesar de su creciente interés no se han realizado, en la Argentina, investigaciones que relacionen su impacto en el corazón y en el cerebro.

Objetivos: Evaluar la asociación de CA, definida en forma operativa por un rango de mediciones de los sistemas simpático, parasimpático, el eje hipotálamo hipofisario adrenales, y de los sistemas inflamatorio cardiovascular y metabólico), con el nivel cognitivo (NC), la memoria y la masa del ventrículo izquierdo en adultos de mediana edad.

Resultados: Fueron estudiados 86 pacientes con un promedio de edad de 53,5 años IC (intervalo de confianza) 95% de 51,3 a 55,7. La CA se asoció en forma inversa y significativa con el NC: coeficiente -1,1 Error estándar (EE) 0,5 p = 0,04 independientemente de la edad, el sexo y el nivel educacional R cuadrado ajustado 0,40 p < 0,001. De los 7 sistemas estudiados solo el cardiovascular y el inflamatorio mantuvieron una asociación inversa y significativa. También la CA se asoció en forma inversa con la memoria. En cuanto a su impacto en el corazón, la CA se asoció en forma positiva con la masa del ventrículo izquierdo (VI), coeficiente 10,86 p < 0,001. R cuadrado ajustado 0,23 p < 0,001.

Conclusiones: La CA nos permite contar con una herramienta objetiva para medir el estrés crónico. Los resultados obtenidos indican que el incremento de la CA produce un daño en el cerebro (déficit cognitivo y en la memoria tempranos) y en el corazón (incremento de la masa del VI).

Palabras clave: Estrés crónico - Carga alostática - Déficit cognitivo - Memoria - Masa del ventrículo izquierdo

Abbreviations

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<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
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<tbody>
<tr>
<td>A</td>
<td>Adrenaline</td>
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<tr>
<td>ACE</td>
<td>Addenbrooke’s Cognitive Examination</td>
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<td>AL</td>
<td>Allostatic load</td>
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<td>BMI</td>
<td>Body mass index</td>
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<td>CI</td>
<td>Confidence interval</td>
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<td>CL</td>
<td>Cognitive level</td>
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<td>CRP</td>
<td>C-reactive protein</td>
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<td>CVD</td>
<td>Cardiovascular disease</td>
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<td>DBP</td>
<td>Diastolic blood pressure</td>
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<td>EA</td>
<td>Educational attainment</td>
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<td>HPA</td>
<td>Hypothalamic-pituitary-adrenal axis</td>
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<td>HTN</td>
<td>Hypertension</td>
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<td>LV</td>
<td>Left ventricular</td>
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<td>LVH</td>
<td>Left ventricular hypertrophy</td>
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<td>MIDUS</td>
<td>Midlife in the United States</td>
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<td>NA</td>
<td>Noradrenaline</td>
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<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
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<td>PSS</td>
<td>Psychosocial stress</td>
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<td>PSNS</td>
<td>Parasympathetic nervous system</td>
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<td>PWV</td>
<td>Pulse wave velocity</td>
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<td>SBP</td>
<td>Systolic arterial pressure</td>
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<td>SE</td>
<td>Standard error</td>
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<tr>
<td>SNS</td>
<td>Sympathetic nervous system</td>
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<td>WHR</td>
<td>Waist-hip ratio</td>
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INTRODUCTION

The concept of “allostasis” has played a significant role in recent research of stress in animals and humans. People are exposed to numerous stressful factors, both psychosocial and environmental, which induce a stress response. (1) Allostasis is a process of fluctuating activity of the organism’s physiological systems as a response to these factors. The primary mediators of allostatic load and the stress response include the neuroendocrine axis, the sympathetic nervous system (SNS) and the immune, metabolic, cardiovascular and hypothalamic-pituitary-adrenal (HPA) systems.

When both physical and psychosocial stressors reach an elevated level, or are chronic, repeated over time, the brain as well as the rest of the organism pay a price for the adaptation, known as allostatic load (AL). (2)

Allostatic load implies injury in the regulatory mechanisms of multiple systems, as those acting in the primary response to stress and the traditional risk factors, which also depend on constitutional and genetic factors.

Up to the end of the last century, psychosocial stress (PSS) was subjectively measured by situational or perceived stress. Nowadays, a battery of biomarkers can measure objectively AL. The focus is targeted on how the individual perceives AL and whether he/she has or not the capacity to adapt his/her life experiences to that load.

At the beginning, Seeman et al. described 10 biomarkers of AL, (3, 4) which were well supported by physiological researches and were able to predict cognitive decline in elderly subjects. (5, 6)

The Midlife in the United States (MIDUS) study (8) performed in 2014, identified AL markers by systems: cardiovascular, glucose metabolism, lipid metabolism, inflammation, HPA axis, SNS, and parasympathetic nervous system (PSNS).

Some authors consider the impact of AC either on mortality; (7, 9, 10) or morbidity. (11-13) However, the impact of accumulated stress not only affects the body but also the brain, producing, among others, cognitive, memory, attention and visual-spatial impairment. (14-19)

Concerning the impact of AL on cognition and health, it is important to highlight the study by Seeman et al, who measured AL in 1,189 men and women aged between 70 and 79 years and evaluated four health categories. A high AL score was significantly associated with increased risk of mortality, cardiovascular events, cognitive decline and lower physical function, resulting in a better predictor than the metabolic syndrome. (20)

In 2012, Kobrosly et al. (21) studied 4,511 middle-age adults participating in the NHANES III study, and investigated the relationship between AL and cognitive function. Results suggested that AL is associated with work memory.

In 2014, Booth et al. (22) published a study associating AL with brain volume and cognitive ability measured in a large cohort of elderly adults. They found that AL was inversely correlated with total brain and white matter volume, and positively with hippocampal volume. Moreover, it was negatively associated with general cognitive ability.

Between 2001 and 2010, the NHANES study (23) assessed AL in disabled and non-disabled persons with mean age of 29.4±23.6 years. Disabled persons has significantly higher body mass index (BMI), C-reactive protein, percentage of neutrophils and lower HDL cholesterol, i.e. higher AL than non-disabled persons.

The MIDUS study (8) examined the association between AL and cognitive performance, in a large population of young, middle-age and elderly individuals and found a strong age-independent inverse correlation between AL and episodic memory and executive function. Among the 7 systems considered to assess AL, only the cardiovascular system was associated with both episodic memory and executive function, while inflammation was related with episodic memory and glucose metabolism with executive function.

In the last years, there has been special interest in the study of PSS associated with cardiovascular disease (CVD), both myocardial infarction and stroke. (24, 25) However, few studies assessing intermediate CVD markers are available, such as increased LV mass, presence of plaques, and increased pulse wave velocity (PWW).

Animal studies show that chronic stress exacerbates hypertension (HTN), as well as LV hypertrophy, LV diastolic dysfunction, fibrosis and oxidative stress, and also increases cardiac and visceral adipose tissue inflammation. (26) Similarly, acculturation was associated with LV mass. (27)

Pickering studied the relationship between psychological stress and development of HTN and coronary heart disease and concluded that men in high strain jobs had more probability of being hypertensive and presenting LV hypertrophy (LVH) than men in less stressful jobs. (28)

Siegrist et al. pose the relationship between HTN, LVH and psychosocial risk and conclude that the greatest incidence of CVD among the lowest socioeconomic groups is explained by a co-manifestation of established risk factors, including LVH and psychosocial factors measuring chronic stress at work. (29)

The association between AL and LVH might be attributed to the cardiovascular component of this multi-system index of AL. However, other factors derived from neurohormonal activity could participate, such as SNS activation, PSNS dysfunction and HPA axis or inflammatory component activation. It could be enquired whether increased AL could predict the increase in LV mass.

Based on these considerations, the aim of the present study was to determine the impact of AL on the brain and heart of middle-age adults.
METHODS
The target population consisted of middle-age patients with cardiovascular risk factors, no history of known CVD or other invalidating chronic diseases.

The sample comprised patients consecutively attending an ambulatory cardiology clinic, agreeing to participate in the study and fulfilling the inclusion and exclusion criteria of the target population. Ninety-eight patients were included and 86 completed all the studies. Educational attainment (EA) was measured according with the following scale: (0) no education, (1) incomplete primary school, (2) complete primary school, (3) incomplete secondary school, (4) complete secondary school, (5) incomplete tertiary or university education, and (6) complete tertiary or university education.

A color Doppler ultrasound of the heart, neck and femoral arteries was performed and the indexed LV mass per square meter of body surface area, presence of plaques, carotid intima-media thickness and PWV were obtained.

Continuous variables were described as mean, standard error and 95% confidence interval (CI) and dichotomous variables as percentage and 95% confidence interval.

Statistix software package was used to perform the analysis. Continuous variables were analyzed by multiple linear regression analysis. The impact of the different AL subsystems on CL was also analyzed. Among the 7 subsystems, only the cardiovascular and inflammatory subsystems showed a strong inverse relationship with global CL evaluated by ACE and adjusted by age, sex and EA (Table 3).

Relationship of allostatic load and its constitutive subsystems with cognitive level
A multilinear regression model with CL through the ACE score as dependent variable and AL adjusted by age, sex and EA. The results show a strong inverse association between AL and global CL, indicating that the greater the AL the lower the CL.

The impact of the different AL subsystems on CL was also analyzed. Among the 7 subsystems, only the cardiovascular and inflammatory subsystems showed a strong inverse relationship with global CL evaluated by ACE and adjusted by age, sex and EA (Table 3).

Impact of global allostatic load and its cardiovascular, lipid metabolism and inflammatory subsystems on left ventricular mass
Mean LV mass was 127.9 ± 7 g/m2 of body surface area (95% CI 118.5 to 137.2). In men, it was 131.1 ± 7.7 g/m2 (95% CI 115.3 to 146.8) and in women 125.4 ± 5.8 g/m2 (95% CI 113.6 to 137.2). (Table 2)

Global AL adjusted by age and sex had a positive impact on LV mass. Cardiovascular, lipid metabolism and inflammation abnormalities adjusted by age and sex were also positively associated with LV mass (Table 5)
Allostatic load and cardiovascular abnormalities were inversely associated with visual-spatial activities, but without attaining statistical significance (p=0.09).

The SNS was positively associated with LV mass (p=0.08).

Although there was a positive trend between AL, presence of plaques and PWV, this did reach statistical significance.

**DISCUSSION**

The study indicates that the multi-system score used to assess AL has a strong inverse association with global CL, particularly memory, in a sample of ambulatory patients.

Also, the cardiovascular and inflammatory components of AL were inversely related with global CL and memory.

It is worth mentioning that the relationship of inflammation and HTN with changes in the hippocampus (34) provide a biological framework to the results of the study.

The MIDUS II study, (8) involving 1,076 individuals (much larger than the 86 patients included in our study) and with an average age of 57 years, higher than that in our study of 53.5 years, found an inverse association to both, episodic memory and executive function. In the same study, the cardiovascular system was inversely related both with episodic memory and inflammation only with episodic memory.

The way of administering the cognitive test was another important difference; in our case it was performed through personal interviews, while in the MIDUS study this was done by telephone interviews. We consider that the personal interviews provide preci-
Age did not influence the association between AL and CL and memory in both studies, suggesting that the association was not restricted to elderly adults.

Another limitation of the MIDUS and our study was that they were both cross-sectional studies and, although the multiple linear regression analysis used in the present study was adjusted by age, sex and EA, it could not be controlled by all the environmental and genetic factors. It is important to point out that a causal relationship cannot be established through a cross-sectional study, since the CL could also increase the AL.

An additional limitation is that lab tests were not performed in a single central laboratory, although all measurements were expressed in the same units for all the patients.

Regarding the association between PSS and LV mass, animal studies conclude that chronic stress exacerbates HTN as well as LVH, LV diastolic dysfunction, fibrosis and oxidative stress. In addition, it enhances cardiac and visceral adipose tissue inflammation. (26) These observations provide biological support to our observations about a positive association between AL and LV mass.

Although some studies relate PSS with LVH (28, 29) and that several authors (35, 36) consider the increase in LV mass as a secondary marker of AL, no studies were found in the literature associating AL with LV mass.

CONCLUSIONS
Both global AL as its inflammatory and cardiovascu-
lar components reduced CL and memory, corrected by EA, age and sex. The greater the AL or its cardiovascular or inflammatory components, the lower the global CL and memory. Global AL and inflammatory, lipid metabolism and cardiovascular components, adjusted by age and sex, increased LV mass. The greater the AL, the greater the LV mass. Dysregulation of systems that respond to chronic stress produces brain injury (early cognitive deficit and memory) and heart damage (increased LV mass). Chronic PSS is not subjectively defined, but objectively identified by means of clinical assessments and measurement of the different biomarkers constituting AL.

Conflicts of interest
(See authors conflicts of interest forms on the website/Supplementary material).

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