

Psychosocial Stress and Low Resilience: a Risk Factor for Hypertension

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SUMMARY

Background

Chronic psychosocial stress (CPS) was proposed as a cardiovascular risk factor (CRF); however, the complexity and the lack of objective measures to evaluate it, together with the fact that not all individuals react in the same way, determined the lack of conclusive studies.

Objective

To determine if low resilience (LR) against CPS is associated with hypertension and target organ damage in outpatients free of treatment that undergo a periodic health examination and to check if this association is related to the pattern of neurohormonal activation.

Material and Methods

A preliminary, observational and cross-sectional study, in which 53 individuals, 32 men and 21 women were consecutively enlisted, was carried out. Patients answered two questionnaires: one to measure CPS and the other, the Connor-Davidson Resilience Scale. Patients were divided into four groups: 1, with no CPS and with normal resilience (NR); 2, with no CPS and low resilience (LR); 3, with CPS and NR; 4 with CPS and LR.

Results

The percentage of hypertensive patients was greater in group 4 ($p < 0.001$), as in individuals with increased waist circumference (IWC) ($p = 0.05$). Although norepinephrine, cortisol and vanillylmandelic acid levels were slightly superior in group 4, the differences did not reach statistical significance. To determine if CPS combined with LR is a risk factor for the development of hypertension, a model of logistic regression, controlled by confounders was used; the *odds* ratio was 10.9 with confidence intervals of 95%, lower than 1.8 and higher than 65.2.

Conclusions

Preliminary data suggest that individuals with CPS combined with LR have a high risk for the development of hypertension.

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Key words

> Hypertension - Chronic psychosocial stress - Resilience - Catecholamines - Cortisol

Abbreviations

>	BMI Body mass index	CPS Chronic psychosocial stress
	CVD Cardiovascular disease	DBP Diastolic blood pressure
	ECG Electrocardiogram	HTN Hypertension
	HDL cholesterol High density lipoprotein cholesterol	IWC Increased waist circumference
	LDL cholesterol Low density lipoprotein cholesterol	LR Low resilience
	NR Normal resilience	SBP Systolic blood pressure
	VMA Vanillylmandelic acid	

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BACKGROUND

“When a disease occurs in a massive way, it reflects cultural problems”. This reflection was carried out by the German anatomopathologist Virchow (1821-1902). Hypertension (HTN) and other risk factors are the cause of the development of cardiovascular diseases (CVD), they happen in a massive way and may be considered as an epidemic of our time; so much so that they make up the main cause of death in developed and developing countries. For this reason, we could imagine that there are cultural problems that influence their development.

But, which were the cultural changes that took place in our society that determined the presence of this epidemic? Some of them, as the excessive consumption of salt, (1-4) inappropriate diet and lack of appropriate physical activity which lead to obesity (5-7) or cigarette consumption, (8-9) have been analyzed and evaluated in several observational and experimental studies. Stress is bound or promotes the aforementioned risk factors or it acts independently.

During many years, the word stress was used with reference to factors that modify the normal physiological and psychological functioning. Hans Selye introduced a new concept of stress, as a state in which the demands of life produce a stereotypical syndrome with a wide range of biological effects, included the disease.

The stress system performs an essential role when generating adaptive mechanisms in view of psychosocial stress to which all individuals that live in an industrialized society are exposed. This system consists of a central nervous system, included the neurons that produce corticotropin-releasing hormones, paraventricular nucleus of the hypothalamus and most of the brainstem nucleus and their peripheral branches, hypothalamic-pituitary-adrenal axis and peripheral autonomic system. (10)

The repeated activation of the stress system could produce, as a result, a long exposition to glucocorticoids or catecholamines and interleukin-6 production (IL-6). This promotes obesity and visceral fat accumulation, which with genetic factor dependance and properties acquired by the organs, produce hyperinsulinemia, insulin resistance, hypertension, hyperlipidemia.

We may consider life as an order in dynamic balance where forces that change the homeostasis act, as for example aggressive elements and adaptive mechanisms generated by the organism that counteracts or eases them.

Multiple researches related the CPS with HTN. Individuals who carried out stressful jobs, (11) unemployed, (12, 13) or individuals with low means of support and educational deficit (14, 15) or people with psychosocial stress at work (16) were studied. The association between acute myocardial infarction and psychosocial stress was also studied. (17)

However, not all individuals react in the same way against stress; resilient people may face stress or adversity with success and even they get strength after painful or adverse experiences. Different behaviors are probably defined by the genetic ability to maintain an appropriate basal activity in response to certain stimuli. (18)

Resilience was defined by several authors as the ability to arise from adversity, adapt and recover itself and gain access to a significant and productive life, (19) the effective confrontation considering the

stressful and cumulative circumstances of life, or as a virtue to face adversity. (20-22)

Although many studies, which relate CPS with HTN, risk factors and target organ damage were carried out, there is no research work that studies CPS and LR.

Considering that CPS triggers abnormally the stress system and particularly, individuals with low resilience would be more vulnerable to its harmful effects, we consider the importance of relating LR against CPS with HTN. The objective of the present work was to determine if LR against CPS is a risk factor for the development of HTN and target organ damage in outpatients free of treatment who underwent a periodic health examination or due to the presence of HTN, with the secondary objective of checking if this association has a relationship with the pattern of neurohormonal activation.

MATERIAL AND METHODS

Population and sample

A preliminary study from April 2008 was performed. 53 individuals, which went to the consultation in the external doctor's office of clinical medicine or cardiology in order to do a periodic health control or due to HTN, were consecutively admitted. All of them were free of treatment and gave their permission in writing for the filling of a self-administered questionnaire. 32 men with a mean age of 41 ± 12.2 years and 21 women with a mean age of 43 ± 9.1 years were studied. The range of age was between 25 and 65 years old.

Patients with serious diseases of any etiology, established CVD, secondary hypertension, patients under psychiatric treatment or those that received treatment with corticosteroids or that consumed drugs which interfere with the neurohormonal axis and pregnant women were excluded from the study.

After reading the instructions, patients completed the questionnaire and answered the questioning.

Variables

Once patients were included in the study, a medical history was performed. The following variables were considered in it: sex (gender), age, personal history of risk factors, diabetes, hypertension, dyslipidemia, smoking habit, physical activity, medication, use of toxic substances, presence of menopause and family history of CVD, in women before 65 years of age and in men before 55 years of age.

Weight, size, body mass index (BMI) and waist circumference were established in the physical examination. The average between systolic and diastolic blood pressure, measured in three occasions with a calibrated mercury manometer, was determined.

Routine laboratory analyses: total cholesterol, HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), glycemia, insulinemia, triglycerides, uric acid, blood creatinine, microalbuminuria, potassium and calcium in plasma and urine, hematocrit, complete urine and adrenaline, norepinephrine, vanillylmandelic acid and a 24-hour urine cortisol, were carried out. Catecholamines were determined by HPLC-DE.

An electrocardiogram (ECG) and an echocardiogram were performed; the left ventricular mass was calculated. An Aloka 2000 ultrasound was used.

Two questionnaires were given to the patients in order to be filled in: the first one used in the INTERHEART study to measure the psychosocial stress (23) and the second one, an adaptation into Spanish of the Connor-Davidson Resilience Scale (CD-RISC). (22)

Resilience was significantly less in hypertensive

individuals against normotensive controls. To determine the low resilience, the 25th percentile of the normal was used as a cutting point. In order to establish if individuals were exposed to stress, the same criteria of the INTERHEART study were used. (17)

Design

This is a study of prospective, transverse and observational design. Patients filled in a stress and resilience test. Based on that, four groups were classified:

- Group 1: with no psychosocial stress and with normal resilience.
- Group 2: with no psychosocial stress and with low resilience.
- Group 3: with psychosocial stress and normal resilience.
- Group 4: with psychosocial stress and low resilience.

Statistical analysis

The statistical analysis was carried out with statistical programs: S Plus and Statistic. The continuous variables are expressed as mean and standard deviation for descriptive variables and standard error when comparisons were performed, or as median and percentile, according to the type of distribution. The nominal or ordinal variables are expressed as percentages.

Normality was controlled with Normal Probability Plot and Shapiro-Wilk test. The appropriate comparisons were done with Student's t-test if variables had normal distribution or failing that with Mann-Whitney test. The proportions were compared with Chi-square test or Fisher's exact test. For the analysis of multiple groups, Kruskal-Wallis test was used. A value of $p \leq 0.05$ was considered significant.

CPS plus LR, as a risk factor for the presence of HTN, was determined through a logistic regression model, according to sex (gender), age and other confusion factors.

RESULTS

Analysis according to stress and resilience groups

Differences among the four groups as regards age, sex (gender), family history of CVD, number of alcoholic drinks per week, tobacco smoking, education, and BMI were not observed; all of them had complete primary education and the ones that completed the secondary education are shown in table 1. The percentage of individuals with IWC was greater in groups 2 and 4 ($p = 0.05$) (See Table 1).

The percentage of hypertensive patients was greater in group 4 ($p < 0.001$, Fisher's exact test).

Significant differences as regards SBP and DBP among groups (Kruskal-Wallis test) were detected; when the range means were compared, there were differences between group 1 and groups 3 and 4 for SBP and DBP (See Table 1).

Significant statistical differences among groups according to HDL-C, LDL-C, total cholesterol, triglycerides and uric acid were not detected. Plasma creatinine was different among groups ($p = 0.03$, Kruskal-Wallis test). Although norepinephrine, cortisol and vanillylmandelic acid were slightly superior in group 4, the differences did not reach statistical significance (Table 2).

Hypertension and psychosocial stress combined with low resilience

With the aim of analyzing the impact on the target organ and the hormonal levels in a 24-hour urine, normotensive patients with no psychosocial stress

(group 1) and hypertensive patients with low resilience exposed to psychosocial stress (group 2) were analyzed.

Significant differences in age, sex (gender), family history of CVD, number of alcoholic drinks per week, tobacco smoking, education and BMI were not detected; the percentage of individuals with increased waist circumference was different among groups ($p = 0.02$, Chi-square test) (Table 3). As regards routine laboratory analyses, they showed significant differences in plasma creatinine ($p = 0.02$, Student's t-test).

Cortisol levels in a 24-hour urine were superior in hypertensive patients, with psychosocial stress and low resilience *against* normotensive patients, with no psychosocial stress ($p = 0.01$, Student's t-test). Although norepinephrine levels were slightly superior, they did not reach statistical significance ($p = 0.08$, Mann-Whitney test). Vanillylmandelic acid and adrenaline in a 24-hour urine did not show significant statistical differences. (Table 4).

A model of logistic regression was used to determine if patients with low resilience, who underwent stress, have high risk of suffering hypertension. Potential confounders, such as age, sex (gender) and levels of plasma creatinine were included. The coefficient for CPS combined with LR was 2.39 with a standard error 0.90 and $p < 0.01$. The corresponding *odds ratio* was 10.9 with confidence intervals of 95% less than 1.8 and higher than 65.2. Age, sex (gender) and levels of plasma creatinine did not show significant coefficients. (Figure 1).

DISCUSSION

In the last years, several works relate CPS with CVD. (23-26) Recently, a revision that showed the positive relationship between the constant chronic stress and HTN was performed. (26)

Most of the aforementioned works study patients with advance CVD and in medication treatment. The effect of different therapeutic diagrams may slant the results. In our study, we had into account these potential confusion factors.

As regards the activation of the neuroendocrine axis due to CPS, several laboratory works relate CPS and HTN in animals. (28-30) During stress, there is a uniform excitation of both, adrenal sympathetic system and hypothalamic-pituitary-adrenocortical system. (30, 31)

Goldstein carried out a meta-analysis of all the published studies in which plasma norepinephrine was measured and it was significantly high in patients with hypertension in comparison with normotensive controls, paired up according to age. (32)

In our preliminar study, between hypertensive patients with LR and CPS, we found a significant increase in cortisol and an increase in the limit of statistical significance in figures of norepinephrine in a 24-urine with regard to normotensive patients who were not exposed to stress.

As regards resilience, in our normal controls, the average and median were similar to the ones published

	With no stress and NR (G 1)	With no stress and LR (G 2)	With stress and NR (G 3)	With stress and LR (G 4)	p value
Age (years)	40,7 ± 1,9	38,2 ± 7,5	47 ± 2,5	42 ± 3,5	0,47
Male	61,5%	80%	30%	68%	0,15
Family history of CVD	36,4%	50%	60%	36,4%	0,62
Number of alcoholic drinks per week	6,6 ± 4,1	7,6 ± 4,8	6,1 ± 3,4	5,7 ± 1,7	0,98
Smokers	50%	60%	22%	52%	0,43
Complete secondary education	20%	60%	60%	32%	0,19
BMI	28,9 ± 1,2	26,9 ± 0,8	29,6 ± 1,3	30,4 ± 6,1	0,55
IWC	27%	65%	20%	70%	0,05
SBP (mm Hg)	120 ± 5	138 ± 6	151 ± 6	143 ± 3	< 0,001
DBP (mm Hg)	80 ± 3	96 ± 4	97 ± 4	97 ± 2	< 0,001
Percentage of hypertensive patients	23%	80%	80%	92%	< 0,001
n	13	5	10	25	

G: Group. NR: Normal resilience. LR: Low resilience. CVD: Cardiovascular disease. BMI: Body mass index. IWC: Increased waist circumference. SBP: Systolic blood pressure. DBP: Diastolic blood pressure. n: Number of patients.

Table 1. Characteristics of patients according to stress and resilience groups

	With no stress and NR (G 1)	With no stress and LR (G 2)	With stress and NR (G 3)	With stress and LR (G 4)	p value
Norepinephrine	47,8 ± 10,4 µg/24 h	40 ± 11,5 µg/24 h	41,5 ± 8,5 µg/24 h	52,8 ± 10,3 µg/24 h	0,88 0,57
Cortisol	57,3 ± 40 µg/24 h	82,4 ± 12,9 µg/24 h	64,4 ± 17,8 µg/24 h	104 ± 17,9 µg/24 h	0,45 0,25
Adrenaline	2,37 ± 0,5 µg/24 h	4,55 ± 1,7 µg/24 h	1,73 ± 0,6 µg/24 h	3,86 ± 1,16 µg/24 h	
VMA	4,97 ± 0,5 mg/24 h	3,70 ± 0,7 mg/24 h	3,78 ± 0,7 mg/24 h	5,38 ± 0,5 mg/24 h	
n	13	5	10	25	

G: Group. NR: Normal resilience. LR: Low resilience. VMA: Vanillylmandelic acid. n: Number of patients.

Table 2. Laboratory analysis results according to stress and resilience groups

by Connor and Davidson for their controls. (22)

In our study, we considered low resilience and chronic stress as a risk factor for hypertension and, moreover, we also determined if hypertensive patients with low resilience and psychosocial stress had the neurohormonal axis activated. Although cortisol levels in a 24-hour urine were superior, norepinephrine levels did not reach statistical significance and there were no differences in adrenaline or vanillylmandelic acid levels in a 24-hour urine. The inadequate sample size could be related to these findings.

In this first stage, measurements to determine the subclinical target organ damage, as intima-media thickness, endothelial test, pulse wave velocity and the presence of plaques in carotid and femoral arteries were not performed. We are planning to do those measurements in a second stage, due to we consider that stress combined with low resilience may be a risk factor for the early vascular involvement.

CONCLUSIONS

Preliminary data suggest that individuals with CPS

combined with LR have a high risk of developing hypertension. The proportion of hypertensive patients and of individuals with IWC was superior in the group with CPS and LR regarding the other groups.

Cortisol levels in a 24-hour urine were superior in hypertensive patients, with CPS and LR, regarding normotensive patients who did not undergo a CPS. Norepinephrine values were placed in the limit of the statistical significance and adrenaline and VMA values did not show differences.

RESUMEN

Estrés psicosocial y baja resiliencia, un factor de riesgo de hipertensión arterial

Introducción

El estrés psicosocial crónico (EPC) fue propuesto como un factor de riesgo cardiovascular (FRC); sin embargo, la complejidad y la falta de medidas objetivas para evaluarlo, unidas al hecho de que no todas las personas reaccionan ante él de igual manera, determinaron que en la actualidad no se cuente con estudios concluyentes al respecto.

Table 3. Characteristics of normotensive patients with no psychosocial stress (group 1) and hypertensive patients with low resilience exposed to psychosocial stress (group 2)

	Normotensive patients with no CPS	Hypertensive patients with CPS and LR	p value
Age (years)	41,7 ± 2,4	42,9 ± 2,5	0,76
Male	39%	69%	0,07
Family history of CVD	36%	38%	0,92
Number of alcoholic drinks per week	5,6 ± 3,8	6,3 ± 1,8	0,86
Tobacco smoking	45,5%	47,8%	0,89
Complete secondary education	22,2%	77,8%	0,39
BMI	28,7 ± 1,4	30,2 ± 1,3	0,49
IWC	25%	66,7%	0,02
SBP (mm Hg)	115 ± 3	145 ± 3	< 0,001
DBP (mm Hg)	75 ± 2	100 ± 1	< 0,001
Creatinine	0,80 ± 0,03 mg/dl	0,96 ± 0,05 mg/dl	0,02
n	13	23	

CPS: Chronic psychosocial stress. LR: Low resilience. CVD: Cardiovascular disease. BMI: Body mass index. IWC: Increased waist circumference. SBP: Systolic blood pressure. DBP: Diastolic blood pressure. n: Number of patients

Table 4. Laboratory analysis results in normotensive patients with no psychosocial stress (group 1) and in hypertensive patients with low resilience exposed to psychosocial stress (group 2)

	Normotensive patients with no CPS	Hypertensive patients with CPS and LR	p value
Noradrenaline	31,5 ± 3,6 µg/24 h		0,08
Cortisol	28,7 ± 14 µg/24 h		0,01
Adrenaline	1,8 ± 0,5 µg/24 h		0,16
VMA	4,3 ± 0,6 mg/24 h		0,19
n	13		

CPS: Chronic psychosocial stress. LR: Low resilience. VMA: Vanillylmandelic acid. n: Number of patients.

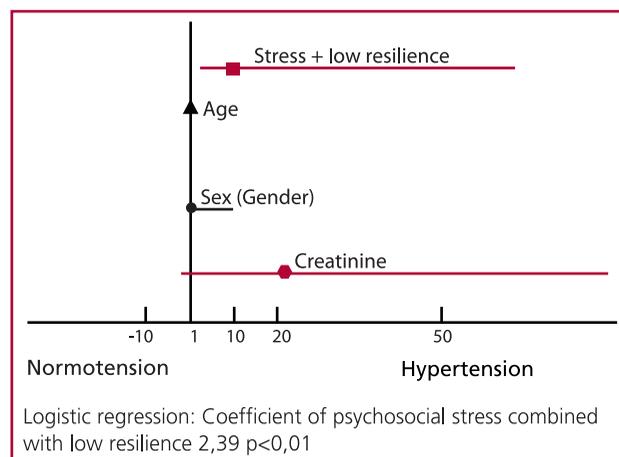


Fig. 1. Psychosocial stress combined with low resilience and hypertension

Objetivos

Determinar si la baja resiliencia (BR) frente al EPC se asocia con hipertensión arterial y daño de órgano blanco en pacientes ambulatorios libres de tratamiento que concurren a realizarse un examen periódico de salud y comprobar si esta asociación tiene relación con el patrón de activación neurohormonal.

Material y métodos

Se realizó un estudio preliminar, observacional

transversal, en el que se enrolaron en forma consecutiva 53 individuos, 32 varones y 21 mujeres. Los pacientes completaron dos cuestionarios: uno para medir EPC y el otro, la Escala de Resiliencia de Connor-Davidson. Quedaron divididos en cuatro grupos: 1, sin EPC y con resiliencia normal (RN); 2, sin EPC y con baja resiliencia (BR); 3, con EPC y RN; 4, con EPC y BR.

Resultados

El porcentaje de hipertensos fue superior en el grupo 4 ($p < 0,001$), como también el de individuos con incremento de la circunferencia de la cintura (ICC) ($p = 0,05$). Si bien los niveles de noradrenalina, cortisol y ácido vanililmandélico fueron ligeramente superiores en el grupo 4, las diferencias no alcanzaron significación estadística. Para determinar si el EPC unido a BR es un factor de riesgo para el desarrollo de hipertensión arterial se empleó un modelo de regresión logística, controlado por confundidores; el odds ratio fue de 10,9 con intervalos de confianza del 95%, inferior de 1,8 y superior de 65,2.

Conclusiones

Datos preliminares sugieren que individuos con EPC unido a BR tienen un riesgo alto para el desarrollo de hipertensión arterial.

Palabras clave > Hipertensión arterial - Estrés psicossocial crónico - Resiliencia - Catecolaminas - Cortisol

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