Original article

Clin Ter 2012; 163 (4):299-305

Stress, abdominal obesity and intrarenal resistive index in essential hypertension

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Abstract

Aim. Although it is commonly believed that a strong causal link exists between psychological stress and hypertension, as well with other factors, such as obesity, just what kind of empirical evidence supports this assumption is still controversial. The aim of the study is to investigate if perceived stress have any interference with intrarenal resistance and hence with mechanisms related to Essential Hypertension (EH) and if Anxiety, Depression, Self efficacy and Illness Perception can account for perceived stress.

Patients and Methods. Obesity, insulin resistance (HOMA), Doppler Renal Resistive Index (RRI) and glomerular filtration rate (GFR) are studied along with Psychological Stress Measure (PSM), Illness Perception Questionnaire (IPQ-R), Generalized Self-Efficacy scale (GSE) and Hospital Anxiety and Depression Scale (HADS) in 119 hypertensive patients referred for stable lasting EH, and 150 normal controls. Lower salt/lower calories Mediterranean diet, physical activity increase and smoking withdrawal counseling were provided.

Results. By Odds Ratios, higher risk of EH is associated with greater perceived stress, older age, lower GFR, obesity, greater RRI and insulin resistance. By Multiple Linear Regression the most significant variable that accounts for higher RRI are abdominal obesity and arterial pulse pressure; the only significant independent psychological variable that accounts for abdominal obesity are PSM and identity IPQ subscale. Self-Efficacy anxiety and Illness perception subscales (IPQr), accounts significantly for 62.0% of the variance to PSM, with possible effects on RRI and on the pathophysiological hypertension cascade.

Conclusion. Worst identity and treatment control perceptions of EH, and a lower self-efficacy are the main psychological factors accounting for a greater stress. Interventions aimed to reduce perceived stress can be warranted in EH. ***Clin Ter 2012; 163(4):299-305***

Key words: *arterial hypertension, arterial stiffness, Cugini's syndrome, mediterranean diet, obesity, psychological stress, renal resistive index, self-efficacy*

Introduction

Although it is commonly believed that a strong causal link exists between psychological stress, hypertension and with other factors, such as obesity, just what kind of empirical evidence supports this assumption is still controversial and far from a comprehensive pathophysiologic framework. Mechanisms of increased sympathetic nervous system activity in hypertension are complex and involve alterations in baroreflex and chemoreflex pathways at both peripheral and central levels. Some studies show that hypertensive patients manifest greater vasoconstrictor responses to infused norepinephrine than normotensive controls (1). Moreover, hypertensive patients do not show the normal response to increased circulating norepinephrine levels which generally induces down-regulation of noradrenergic receptor, and it is believed that this abnormal response is genetically inherited (2). A greater incidence of hypertension in lower socioeconomic groups is explained considering that they must endure greater levels of stress associated with daily living. Persons with a family history of hypertension manifest augmented vasoconstrictor and sympathetic responses to laboratory stressors, such as cold pressor testing and mental stress, which may predispose them to hypertension: exaggerated stress responses may contribute to the increased incidence of hypertension (3). Mental stress is a powerful beta-adrenergic-related factor that selectively opposes endothelium-dependent vasodilation, while cold pressor and isometric handgrip tests induced a more general attenuation in vasodilatation (4, 5). Despite the recognized statistical associations between stress vs. cardiovascular and other prevalent diseases have not been fully explained (6), bidirectional relationship between stress, mood disorders and cardiovascular diseases are extensively documented; nonetheless, the effects of moods changes on cardiovascular risk are still

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controversial (7). At an epidemiological level, perceived mental stress was associated with increased mortality from stroke in women and with Coronary Artery Disease in men and women (8) and effect of psychological stress on total and cause-specific mortality was reported also in a large prospective study (9).

Data from epidemiological and clinical studies endorse the influence of psychological stress on the development of high blood pressure, and subjects with reactive hypertension have a strong cardiac response to mental stress and this could be a characteristic of this condition (10). Patients' illness perceptions have been shown to relate not only to adherence behaviors and functional status but also to emotional distress and can predict a number of health-related behaviors among patients with a chronic illness, notably Ischemic Heart Disease patients (11).

The Generalized Self-Efficacy (GSE) is a scale designed to assess optimistic self-beliefs to cope with a variety of difficult demands in life (12). Low self-efficacy is associated with poor health status, independent of IHD severity and depressive symptoms. There are relationships between self-efficacy and illness perceptions: stronger perception of illness identity and a stronger belief in the illness seriousness were associated with higher levels of self-management (12).

Patients with major depressive disorders are at increased risk of cardiovascular disease. Mechanisms involved include activation of the sympathetic nervous system, altered baroreflex sensitivity, and/or exaggerated platelet reactivity and endothelial dysfunction (13).

Arterial stiffness is a comprehensive hallmark of vascular ageing and of atherosclerotic effects which is assessed also by the Renal Resistive Index (RRI) (14, 15). A relationship between the Ultrasound RRI, blood pressure and renal function response is recognized and its relevance is confirmed also as a powerful predictor of death during follow-up of patients with atherosclerotic renovascular disease; RRI is associated with aorta stiffness and is useful for the evaluation of arterial stiffness in patients with essential hypertension (14, 15). Insulin resistance is a putative indicator of metabolic syndrome that encompasses obesity, notably expressed by waist-to-hip ratio, and arterial hypertension, and is involved in the development of arterial stiffness (16).

The aim of the study is to investigate if perceived stress have any interference with intrarenal resistance and hence with mechanisms related to Essential Hypertension (EH) and if Anxiety, Depression, Self efficacy and Illness Perception can account for perceived stress.

Patients and Methods

The study is designed as an observational study, enrolling all patients referred to a Day hospital clinic for clinical-nutritional counseling in January-June 2008 (Fig. 1). The study was done with 119 consecutive patients on maintenance therapy referred for stable lasting EH throughout January-June 2008 on a total of 269 patients. Lower salt/lower calories Mediterranean diet, physical activity increase and smoking

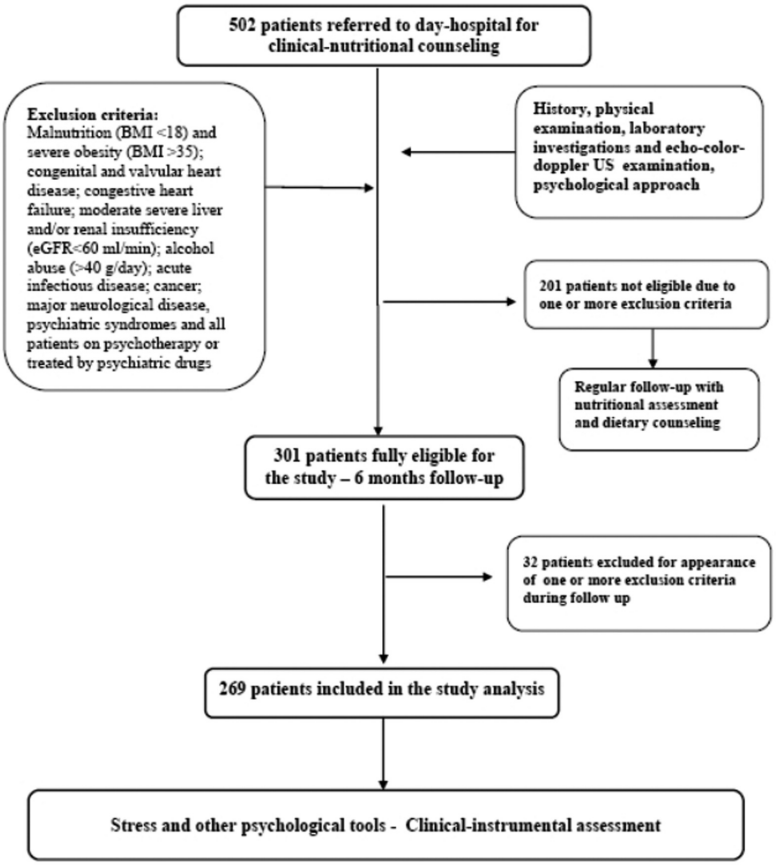

Fig. 1. Study design.

Table 1. Characteristic of study population

Age,y	49,43±16,00
Female, n	168 (62,5%)
Men, n	101 (37,5%)
Hypertension, n	119 (44,2%)
Obesity, n	90 (33,5%)
Systolic Blood Pressure, *mmHg*	125,26±11,83
Diastolic Blood Pressure, *mmHg*	78,44±8,67
BMI, Kg/m^2	27,65±5,32
WAIST/ HIP	0,90±0,05
Fat Mass, %	33,36±10,24
Blood glucose, mg/dl	92,44±20,08
Insulin, *μU/mL*	10,73±6,65
HOMA	2,55±1,96
Blood urea, mg/dl	35,75±11,88
Creatinine, *mg/dl*	0,78±0,18
GFR	85,83±20,69
Total Cholesterol, *mg/dl*	195,68±45,48
HDL Cholesterol, *mg/dl*	53,04±15,03
Triglycerides, *mg/dl*	112,61±67,29
LDL Cholesterol, *mg/dl*	119,67±41,50
RRI	0,63±0,05
General Self-Efficacy	18,44±5,00
Identity	9,51±3,16
Timeline	19,13±5,50
Consequence	16,48±4,27
Personal Control	21,01±3,82
Treatment Control	18,78±3,01
Illness Coherence	17,68±3,95
Timeline Cyclical	10,97±3,20
Emotional Representation	17,09±5,42
Anxiety	9,88±2,22
Depression	9,34±2,10
PSM	93,28±24,56

BMI: Body Mass Index; GFR: Glomerular Filtrate Rate; HDL: High-density lipoprotein;
LDL: low-density lipoprotein; RRI: Renal Resistive Index; PSM: Psychological Stress Measure

withdrawal counseling were provided. Traditional Mediterranean diet prescribed is characterized by a high intake of vegetables, legumes, fruits and nuts, and cereals, a high intake of olive oil and a low or no intake of saturated lipids, a moderately high intake of fish, a low-to-moderate intake of dairy products (and them mostly in the form of cheese or yogurt), a low intake of meat and poultry. Physical activity was encouraged in the form of walking using the "10 000 steps a day" suggestion. A portable electronic pedometer (*step counter*) was given also as motivation tool, because its use is associated with significant increases in physical activity and significant decreases in body mass index and BP.

Socio-demographic data age, gender distribution and BMI are presented in Table 1.

Eligible EH patients are on antihypertensive maintenance therapy with a satisfactory pharmacological response since at least 2 years: responders are conventionally defined as patients with arterial BP regularly below 140/90 mmHg (according to the European Society of Hypertension and to the European Society of Cardiology 2007 guidelines for the management of arterial hypertension).

No extensive pharmacological wash-out is arranged due to the inclusion criteria that encompass adequate therapeutic response. Medication is adjusted according to a stepwise treatment schedule after each visit, and included an angiotensin II-receptor blocker, losartan (50 mg, with possible and transient increase to 100 mg/day) in all patients. A calcium-channel blocker (felodipine, 5-10 mg) or, more occasionally, a beta-blocker (atenolol, 12.5-50 mg) are administered, as adjunctive or substitute therapy, when the angiotensin II-receptor antagonist is no longer effective. All patients have their drugs early in the morning; laboratory assays and ultrasound study are performed after 24 hours of complete drug withdrawal and before any drug assumption. All patients fast for more than 12 hours before blood collection (coffee and alcohol were totally excluded in this withdrawal period since 1.00 pm of the preceding day), without any special dietary or fluid restriction. Thereafter, in the morning (08:00:09.30 a.m.), ultrasound examination is performed after 30 minutes rest and the blood pressure (systolic and diastolic) and pulse rate are measured and recorded. Afterward, 10 mL of blood is collected from the median antecubital vein into a plain tube for biochemistry tests.

Glomerular Filtration Rate is estimated as eGFR by the MDRD formula (26) in ml/min per 1.73 m^2. Body Weight (BW) is measured in light clothing, without shoes, in kg and height (H) was measured in meters, using a scale-integrated stadiometer. Body mass index is calculated as BW/H^2. Obesity is defined as BMI ≥30.

Renal colour-Doppler echography is performed assessing intra-parenchymal renal artery mean velocity (mVRA) and intra-parenchymal renal artery RRI ((peak systolic velocity-end diastolic velocity)/peak systolic velocity). After recording pulse and BP, the first measurement is the size of the left and right kidney. For orientation purposes, perfusion in the whole of the left and right kidneys is then checked using colour duplex ultrasonography and the main trunk of the renal artery is displayed. Three measurements for each kidney are taken by pulsed Doppler within 5 min. in the vicinity of the interlobar artery. RRI is calculated as the average value of all measurements taken. RRI threshold is defined by the 75^{th} percentile derived by measurements of all eligible patients. Ultrasound examination is performed by the same echographist to reduce inter-observer variability. The physician is unaware of clinical details of any patients at the time of the procedure; a GE echo-colour-doppler device (GE Logiq 5 Expert US, manufactured by GE Medical Systems - Milwaukee - Wisconsin (USA)), high resolution, with real-time sectional scan transducers was used.

Insulin resistance is assessed by homoeostasis model-insulin resistance index (HOMA), according to the formula: 'fasting insulin value x fasting blood sugar level/405'. Two thresholds for insulin resistance are conventionally considered as HOMA >1.7 according to the Likelihood ratios for 11-year incident Cardio-Vascular Disease, and as

HOMA >3.0 according to the Likelihood ratios for 7-year incident Diabetes Mellitus type 2 (17).

Criteria of exclusion: malnutrition (BMI <18) and severe obesity (BMI >35); congenital and valvular heart disease; congestive heart failure; moderate severe liver and/or renal insufficiency (eGFR <60 ml/min); alcohol abuse (>40 g/day); acute infectious disease; cancer; major neurological disease, degenerative and vascular, including stroke and consequent disabilities; psychiatric syndromes and all patients on psychotherapy or treated by psychiatric drugs.

Measurements. Patients are asked while in hospital to complete the Psychological Stress Measure (PSM), the Illness Perception Questionnaire, revised version (IPQ-r), the Hospital Anxiety and Depression Scale (HADS) and the Generalized Self-Efficacy Questionnaire (GSE). All participants completed the questionnaires under direct supervision of a supporting psychologist. The four psychological tools were all validated also in Italy and in Italian language.

Sociodemographic data included age, sex, marital status, work status and level of education. Body Mass Index (BMI) was computed based on self-reported height and weight (kg/m^2), and checked by nurses in the ward. Clinical data including cardiac conditions (NYHA class), diabetes mellitus, drug use and smoking status (currently smoking, ex-smokers or never smoked) are included using clinical records.

The Psychological Stress Measure (PSM) was designed using 49 items drawn from descriptors generated by focus groups on stress (18, 19). It has been translated into English, Japanese, Spanish, Portuguese, and Italian (20), it was validated and it can be used for international comparisons.

The *Illness Perception Questionnaire* (IPQ-R) (21, 22) is administered to assess cognitive representations. All items were scored on a five-point Likert-type scale, which ranged from '*strongly disagree'* to '*strongly agree'*. The nine subscales of the revised IPQ are the following: (1) *identity*—the symptoms that the patient associates with the illness; (2) *timeline*—the perceived duration of the illness; (3) *consequences*—expected effects and outcome; (4) *personal control*—how one controls or recovers from the illness; (5) *treatment control*—the perceived efficacy of treatment; (6) *illness coherence*—the extent to which patients find their illness/symptoms puzzling; (7) *timeline cyclical*—how cyclical the patient perceives the illness; (8) *emotional representations*—emotional impact of the illness; and (9) *cause*—personal ideas about disease aetiology. The test-retest reliability and internal consistency of the questionnaire were confirmed. The psychometric properties of the Italian version of the IPQ-R were demonstrated to be robust. Hence, the Italian version of the IPQ-R, which resulted homogeneous with the original version, is useful in assessing the cognitive factors involved in patients' adjustment to various chronic illnesses (23).

The *Generalized Self-Efficacy* (GSE) is a 10-item psychometric scale designed also to assess optimistic self-beliefs to cope with a variety of difficult demands in life (12); the scale was internationally validated, also in Italy.

The *Hospital Anxiety and Depression Scale* (HADS) (24) was developed to measure anxiety and depression in patients with chronic physical disease. For both anxiety and depression scales, there are seven items each one scored on a scale of 0 to 3. The HADS has good validity and internal reliability and was validated also in Italy (25).

Each patient gave informed consent for this observational study aimed at the assessment of the relationship between illness perception, self-efficacy and stress with full adherence to current best-practice management guidelines, and to the principles confidentiality and privacy.

Statistics. After a preliminary definition of the quartile of the perceived stress and of those of the HAD (Anxiety and Depression) subscales and of GSE, different prevalences of PSM and Odds Ratio to higher risk of EH are calculated. Correlation analysis of all measurements vs. PSM is done. Regression models tested if self-efficacy, HAD and IPQr subscales (as psychological measurements) account for severity of perceived stress in EH. A subsequent model to RRI is challenged, testing if obesity (BMI and/or W/H ratio), PSM, anxiety and/or depression account for renal resistive index differences.

Results

All patients completed the questionnaires, and no specific difficulty and/or misunderstanding was reported to psychologist at the semi-structured final interviews. The approach was appreciated by patients and was found useful in order to describe their health and complaints in a comprehensive way.

In the comparison of EH patients vs. subjects with normal BP, significant differences observed are greater weight-obesity, higher cholesterol, increased RRI, older age and lower GFR, along with a greater prevalence of higher perceived stress (Table 2). By Odds Ratios, a higher risk of EH is associated with greater perceived stress, older age, lower GFR, greater renal resistive index (RRI) and greater insulin resistance (Fig. 2).

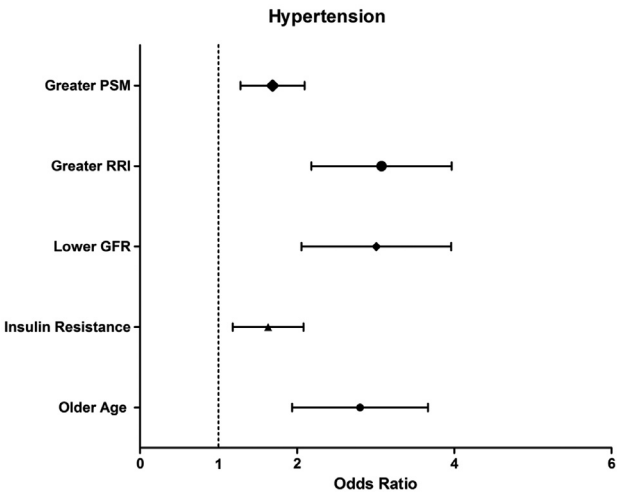

Fig. 2. Essential Hypertension. By Odds Ratios, a higher risk of EH is associated with greater perceived stress (PSM), older age, lower GFR, greater renal resistive index (RRI) and greater insulin resistance.

Table 2. Differences according to Hypertension

	Hypertensive patients (n 119)	**Normal Blood Pressure patients (n 150)**	**t**	**p**
Age,y	56,58±12,94	43,71±15,95	7,124	<0,0001
BMI, Kg/m^2	28,93±4,65	26,63±5,60	3,597	<0,0001
WAIST/ HIP	0,92±0,05	0,89±0,05	3,494	<0,001
Fat Mass, %	34,65±8,13	32,31±11,60	1,834	0,068
HOMA	2,96±2,14	2,22±1,73	3,131	0,002
GFR	82,57±21,02	88,42±20,10	-2,320	0,021
Total Cholesterol, mg/dl	205,18±42,54	188,15±46,46	3,086	0,002
HDL Cholesterol, mg/dl	51,93±15,31	53,92±14,79	-1,073	0,284
Triglycerides, mg/dl	122,58±65,96	104,71±67,50-	2,170	0,031
LDL Cholesterol, mg/dl	127,65±38,97	113,29±42,47	2,851	0,005
RRI	0,65±0,06	0,61±0,04	4,828	<0,0001
	Hypertensive patients (n 119)	**Normal Blood Pressure patients (n 150)**	χ^2	**p**
Men, n	50 (42%)	51 (34%)	1,493	0,222
Greater General Self-Efficacy, n	29 (24,4%)	39 (26%)	0,027	0,869
Greater HAD Anxiety, n	39 (32,78%)	54 (36%)	0,351	0,553
Greater HAD Depression, n	41(34,4%)	42 (28%)	1,215	0,270
Greater PSM, n	40 (33,6%)	32 (21,3%)	4,498	0,034

BMI: Body Mass Index; GFR: Glomerular Filtrate Rate; HDL: High-density lipoprotein; LDL: low-density lipoprotein; RRI: Renal Resistive Index ;PSM: Psychological Stress Measure (cut off: 75th percentiles); HAD: Hospital Anxiety Depression Questionnaire (cut off: 75th percentiles). Significant p in bold cases

Table 3. Linear Regression for PSM in Hypertension patients

	R	**R Square**	**F**	**sig**	**Beta**	**p**
	0,787	0,620	5,640	**<0,0001**		
Anxiety					0,524	**<0,0001**
Depression					-0,132	0,258
General Self-Efficacy					-0,244	**0,043**
Identity					-0,307	**0,013**
Timeline					-0,161	0,176
Consequence					0,146	0,320
Personal Control					0,280	0,155
Treatment Control					-0,495	**0,012**
Illness Coherence					0,328	0,072
Timeline Cyclical					0,212	0,095
Emotional Representation					0,085	0,622

PSM: Psychological Stress Measure; Weighted Least Squares Regression - Weighted by Gender

Table 4. Linear Regression for RRI in Hypertension patients.

	R	R Square	F	sig	Beta	p
	0,407	0,165	2,725	**0,009**		
Pulse Pressure, mmHg					0,310	**<0,001**
BMI, *Kg/m²*					0,035	0,749
WAIST/ HIP					0,209	**0,031**
HOMA					0,023	0,837
GFR					-0,177	0,060
Anxiety					0,025	0,815
Depression					0,159	0,101
PSM					0,003	0,974

RRI: Renal Resistive Index; BMI: Body Mass Index; GFR: Glomerular Filtrate Rate; PSM: Psychological Stress Measure Weighted Least Squares Regression - Weighted by Age

Table 5. Linear Regression for WAIST/ HIP ratio in Hypertension patients.

	R	R Square	F	sig	Beta	p
	0,511	0,261	3,095	**<0,001**		
General Self-Efficacy					-0,010	0,917
Anxiety					-0,045	0,672
Depression					-0,037	0,704
PSM					0,230	**0,048**
Identity					0,302	**0,002**
Timeline					-0,105	0,254
Consequence					-0,002	0,989
Personal Control					-0,176	0,146
Treatment Control					0,002	0,986
Illness Coherence					0,215	0,089
Timeline Cyclical					0,114	0,261
Emotional Representation					-0,024	0,826

PSM: Psychological Stress Measure - Weighted Least Squares Regression - Weighted by Age

By Linear Regression in Hypertension patients Self-Efficacy (GSE), anxiety, depression and illness perception subscales (IPQr) explain together 62.0% of the variance to perceived stress. In this subset the significant contributions are given by identity and treatment control IPQr subscales (Table 3). By multiple linear regression RRI is accounted by abdominal obesity (W/H ratio) and pulse pressure, but not by any psychological measurements (Table 4) in an age-adjusted model which accounts for 16.5% of the variance to RRI. The subsequent model designed in order to explain the independent variables that can account for obesity shows that PSM and Identity IPQr subscale account significantly for 26.1% of the variance to W/H ratio (Table 5).

Discussion

Greater perceived stress, assessed by PSM, is associated with a greater risk of EH. Direct psychological determinants of perceived stress are also different illness perceptions and anxiety, while lower self-efficacy shows an inverse relationship. Worst identity and treatment control perceptions of the specific disease, i.e., EH, and a lower self-efficacy are the main psychological factors accounting for a greater perceived stress. No particular relationship is observed with depression.

Using more composite models, self-efficacy, anxiety and depression explain together a great percentage of variance to PSM (Table 3). Moreover, apart the greater anxiety, illness perceptions, especially the identity and the perception of treatment control are the two individual subscales that strongly account for perceived stress.

RRI is accounted by abdominal obesity (W/H ratio) and pulse pressure, as already reported (26), but not by psychological measurements (Table 4), differently from peripheral artery disease whose association with greater insulin resistance is well demonstrated (27). This result confirms the great relevance of abdominal obesity as a factor associated with essential hypertension and with increased renal resistive index. Nonetheless, the only significant independent psychological variable that accounts for obesity is perceived stress (PSM) (Table 5), seemingly consequentially affecting RRI and also the subsequent pathophysiological hypertension cascade.

Despite that significant improvement in mood may have little impact on most traditional or atypical risk factors (7), it cannot be excluded that interventions aimed to reduce perceived stress by psychological approaches can be useful in EH and should be warranted.

Our study can be a contribution to the knowledge of mechanisms and effects on blood pressure, also related to circadian rhythms conceivably modulated also by psychological factors, which are potentially dangerous for the target organs, even though there is no evidence of manifest arterial hypertension. Such a hemodynamic condition causing hypertensive cardiovascular damage was defined "arterial pre-hypertension" alias "Cugini's syndrome" (28, 29).

In conclusion, our study results outline the relevance of illness perceptions in the context of perceived stress in essential hypertension. Greater perceived stress is associated with essential hypertension, along with greater anxiety and lower self-efficacy and is related to a greater RRI, i.e., Renal resistive Index, a measure related to vasoconstriction and/or arteriosclerosis. Therapeutic strategies and interventions aimed to reduce perceived stress can be warranted in EH along with other possible approaches.

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