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Is Chronic Inflammation a Determinant of Blood Pressure in the Elderly?

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Background: Previous studies have shown that a rise in blood pressure (BP) causes chronic inflammation of the endothelium which, in turn, may be responsible for further damage of endothelium and worsening of BP control. On the other hand, several metabolic abnormalities such as dyslipidemia, hyperinsulinemia/insulin-resistance, diabetes, and obesity causes inflammation followed by a later rise in arterial BP. We investigated the role of chronic inflammation in the modulation of BP independently of other traditional cardiovascular risk factors and atherosclerotic lesions.

Methods: A total of 537 aged subjects, selected from the whole population of the INCHIANTI cohort, were enrolled. All subjects underwent plasma insulin, glucose, interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-1β (IL-1β), interleukin-1 receptor antagonist (IL-1ra), C-reactive protein, and tumor necrosis factor-α (TNF-α) levels determination. The IL-6-174 C/G promoter polymorphism was also evaluated.

Results: After adjusting for age, sex, insulin resistance syndrome score, and severity of carotid atherosclerosis, serum IL-1β ($P < .001$), IL-1ra ($P < .005$) concentration and the insulin resistance syndrome score ($P < .001$) were the only predictors of diastolic BP. Indeed, age ($P < .001$), insulin resistance syndrome score ($P = .05$), IL-1β ($P < .05$), and severity of carotid atherosclerosis ($P < .05$) were the only significant predictor of systolic BP.

Conclusion: These results suggest that chronic inflammation may play a role in the modulation of arterial BP. Am J Hypertens 2003;16:537–543 © 2003 American Journal of Hypertension, Ltd.

Key Words: Blood pressure, IL-6, IL-1β, IL-1ra, IL-6 genotype, atherosclerosis.

It is widely accepted that long term impact of proatherosclerotic factors on endothelium results in chronic inflammation with a consequent rise in vascular and plasma concentration of several soluble mediators of the immune response such as interleukin-6 (IL-6).[1] It has been recently suggested that this mechanism may explain why high plasma IL-6 levels predict a poor clinical course of cardiovascular diseases[2] and identify a subgroup of older patients with cardiovascular diseases who have high risk of death over a 3-year period.[2] Persons with hypertension who are free of any other important medical conditions have high circulating levels of intercellular circulating adhesion molecules (sICAM), IL-6, tumor necrosis factor-α (TNF-α), and fibrinogen, supporting a possible role of hypertension as a proinflammatory stimulus.[3] It has been hypothesized that a rise in blood pressure (BP) activates a vicious cycle, causing chronic inflammation of the endothelium, which in turn might be responsible for a further damage of endothelium and worsening of BP control. That notwithstanding, several metabolic abnormalities such as dyslipidemia, hyperinsulinemia/insulin-resistance, diabetes, and obesity cause endothelium inflammation, and through this mechanism may cause a rise in arterial BP.[4] Furthermore, it has been suggested that aging is associated with a primary dysregulation of the inflammatory response, and therefore that aging in itself should be considered a proinflammatory factor.[5] Thus, the joined effect of proatherosclerotic risk factors and aging on the deranged arterial BP regulation could be mediated at least in part by the immune system. Such a hypothesis is strengthened by the existing evidence that plasma IL-6, interleukin-1β (IL-1β), and interleukin-1 receptor antago-

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nist (IL-1ra) affect arterial BP control.[6,7] Overall, these findings suggest that chronic inflammation is a common link between cardiovascular risk factors and hypertension and act as an independent determinant of arterial BP. Although this hypothesis has been suggested, it has never been formally tested. Furthermore, because plasma IL-6 levels are also regulated by soluble plasma IL-6 receptor (sIL-6R)[8] and IL-6 genotype,[9] which have also been shown to be implicated in BP control,[10] studies looking at the relationship between IL-6 and high BP should take these factors into account.

In light of these premises, using data from a large population based sample of the older population, we investigated the role of chronic inflammation on the levels of arterial BP independently of other more traditional cardiovascular risk factors and atherosclerotic lesions.

Materials and Methods

Study Population

The analyses presented in this manuscript use data from the INCHIANTI study, a prospective population-based survey of older persons, designed by the Laboratory of Clinical Epidemiology of the Italian National Research Council of Aging (Florence, Italy) and carried out in the Chianti geographic area of Tuscany, Italy. As previously reported, this database includes data from 1453 participants (age range, 20 to 102 years) randomly selected from the residents in the two municipalities of Greve in Chianti and Bagno a Ripoli using a multistage stratified sampling method.[11] The data collection started in September and was completed in March 2000, 1998

The study population for this analysis consists of 537 subjects (mean age 74.0 ± 7.6 years), selected from the whole population of the INCHIANTI cohort, with the exclusion of those who were affected by diabetes mellitus and prevalent clinical cardiovascular diseases based on a previous physician diagnosis, examination of medical charts, or current sign and symptoms. Diabetes mellitus was diagnosed according to American Diabetes Association criteria.[12]

Subjects were asked to provide the commercial names of all drugs that they had taken in the last 5 years. Subjects who were currently taking drugs known to affect BP, glucose metabolism, and interleukin activity were also excluded from the study population.

Baseline BP was recorded by standard mercury sphygmomanometer. The disappearance of sound (phase V) was used for diastolic reading. All determinations were performed three times, 2 min apart while the subject was in supine position. The average of the last two recorded measurements was considered in the analysis.

All subjects gave informed consent to participate in the study, which was approved by the Ethical Committee of the Italian National Research Centers on Aging.

Echo-Color Doppler Determination

Duplex scanning assessment of carotid arteries was performed by using an AU3 Partner apparatus (ESAOTE, Florence, Italy) equipped with a 7.5-MHz linear array transducer with color-coded Doppler.

External carotid artery was explored in its first segment, and internal carotid artery was explored to the inferior angle of the jaw. The presence of internal carotid artery stenosis was assessed on the basis of the residual lumen in the transverse section, by using the color-coded Doppler. A significant stenosis was considered when the residual lumen was 40% or less of the original one. The presence of the intimae media thickness of the common carotid artery was qualitatively evaluated (yes/no) during the examination by the finding of a clear-cut resolution of the two echogenic zones within both the near and far vascular walls at standard magnification. Participants were categorized according to the results of the carotid color Doppler scan examination into three groups: 1) those without any type of abnormalities, 2) those with intimae media thickness, and 3) those with atherosclerotic lesions.

Assays

Blood samples were collected in the morning after the participants had been fasting for at least 8 h. Serum glucose, serum lipid, and serum lipoprotein levels were quantified immediately. Serum glucose was determined by an enzymatic colorimetric assay using a modified glucose oxidase-peroxidase method and a Roche-Hitachi 917 analyzer (Roche Diagnostics, GmbH, Mannheim, Germany). Commercial enzymatic tests (Roche Diagnostics) were used to determine serum total and HDL cholesterol and triglycerides levels. Serum LDL cholesterol levels were calculated by the Friedewald formula.[13] The interassay coefficient of variation was <3.8% for total cholesterol, <5.0% for HDL cholesterol, and <2.5% for triglycerides.

Several 0.5-mL aliquots of serum were immediately obtained and stored at −80°C, and were subsequently used for assessment of hormones and cytokines. Plasma insulin (Sorin Biomedica, Milan Italy; intra-assay coefficient of variation 3.1% ± 0.3%) concentration was determined by radioimmunoassay. The degree of insulin resistance (IR) was calculated according to the homeostasis model assessment (HOMA),[14] which is widely considered a valid index for assessment of insulin resistance over a wide range of severity,[15] and is highly correlated with insulin-mediated glucose uptake calculated by the euglycemic hyperinsulinemic glucose clamp.[14,15] The IL-6, IL-1β, TNF-α, were quantified with immunoassay kits (BioSource Cytoscreen, Camarillo, CA human IL-6, human IL-1β and human TNF-α ELISA UltraSensitive kits). The minimum detectable concentrations were 0.10 pg/mL for IL-6, 0.09 pg/mL for TNF-α, 0.01 pg/ml for IL-1β, and the interassay coefficient of variation was 7.0% for all kits. Serum concentrations of IL-1ra and sIL-6R were measured using commercially available ELISA kits (BioSource Cyto-

Table 1. Clinical characteristics of study groups

Characteristic	All (n = 537)	No Atherosclerosis (n = 42)	Intimae Media Thickness (n = 194)	Plaques/Stenosis (n = 234)	P†
Age (y)	74 ± 7	70 ± 5	71 ± 6	76 ± 7	<.001
Sex (male/female)	255/282*	18/24	78/116*	128/106	
Body mass index (kg/m^2)	26.97 ± 4.09	28.0 ± 4.8	27.1 ± 3.5	27.1 ± 4.01	.348
Waist/hip ratio	0.91 ± 0.07	0.91 ± 0.06	0.91 ± 0.07	0.92 ± 0.06	.579
IL-6 (pg/mL)	2.04 ± 3.91	1.5 ± 1.8	1.6 ± 1.6	2.06 ± 2.18	<.05
IL-6 receptor (ng/mL)	105.9 ± 58.9	88.7 ± 43.2	104.5 ± 65.3	106.5 ± 57.3	.205
IL-1β (pg/mL)	0.32 ± 1.51	0.16 ± 0.11	0.26 ± 0.91	0.28 ± 1.17	.770
IL-1ra (pg/mL)	150.7 ± 124.3	153 ± 69	152 ± 160	147 ± 95	.900
TNF-α (pg/mL)	6.2 ± 6.6	7.49 ± 5.11	5.76 ± 5.76	5.85 ± 7.19	.281
CRP (mg/dL)	0.75 ± 0.6	0.75 ± 0.6	0.71 ± 0.6	0.74 ± 0.5	.846
SBP (mm Hg)	146.2 ± 19.1	141.8 ± 18.2	143.9 ± 17.5	149.2 ± 19.2	<.001
DBP (mm Hg)	82.9 ± 8.2	81.2 ± 9.7	83.4 ± 7.3	84.3 ± 8.6	<.001

IL-6 = interleukin-6; IL-1β = interleukein-1β; IL-1ra = interleukin-1 receptor antagonist; TNF-α = tumor necrosis factor-α; CRP = C-reactive protein; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Data are mean ± SD.

* χ^2 Test; men v women, $P < .05$.

† Statistical difference among the three atherosclerotic degree groups.

screen human IL-1ra and human sIL-6R kit) The minimum detectable doses were 8 pg/mL for sIL-6R and 4 pg/mL for IL-1ra.The inter-assay coefficients of variation were 7.0% for sIL-6R and 4.5% for IL-1ra. The plasma Reactive Protein C levels were determined by routine laboratory tests (Roche Diagnostics).

Genomic DNA was obtained from blood lymphocytes using a standard salting-out DNA extraction technique. To evaluate the IL-6-174 C/G promoter polymorphism, amplification of the −174 C/G site was performed according to the method of Olomolaiye et al.[16] The PCR amplification was followed by an overnight restriction digest of 15 μL PCR product with Nla III enzyme. The presence of a cytosine (C allele) at nucleotide −174 was revealed by the detection of an Nla III cutting site by electrophoresis in 2.0% agarose gel.

Statistical Analysis

To approximate normal distributions, log-transformed values for plasma IL-6, triglycerides, insulin, and degree of insulin resistance were used in the analyses. The degree of atherosclerosis was calculated as follows: 0 = absence of atherosclerosis; 1 = presence of intimae media thickness; and 2 = presence of carotid artery plaques or stenosis.

A cluster analysis was used to elucidate the role played by the insulin resistance syndrome (IRS) on the relationship between chronic inflammation and BP. For this purpose, we created a compound score (IRS score) as the sum of Z scores of the main variable of the insulin resistance syndrome (IR degree, body mass index, waist/hip ratio, triglycerides, and LDL and HDL cholesterol). A Z score indicates the position of an individual value within the total distribution of the variable in the population, and is calculated as follows: (individual value − mean value)/SD. Pearson product–moment correlations were calculated to test associations among variables.

To investigate the relationship among chronic inflammation, BP, metabolic parameters, and atherosclerotic lesions, data were stratified according to the degree of atherosclerosis. Analysis of variance was used to evaluate differences among the three groups. In addition, multivariate linear regression analyses were used to test the independent association of anthropometric parameters, markers of chronic inflammation, IL-6-174 C/G polymorphism, IRS score, and degree of carotid atherosclerosis with systolic and diastolic BP. Statistical analyses were performed using the SPSS statistical package (SPSS, Chicago, IL).

Results

The study population included an equal number of men and women. The subjects were slightly overweight, tended to have a central adipose tissue distribution, had a moderate degree of insulin-resistance (Table 1) without diabetes mellitus (plasma glucose 87.8 ± 9.5 mg/dL; plasma insulin 10.5 ± 5.3 mU/mL) and dyslipidemia (HDL cholesterol 57 ± 15 mg/dL; LDL cholesterol 140 ± 36 mg/dL; total cholesterol 217 ± 41 mg/dL).

In simple correlation analyses (Table 2), systolic BP (SBP) was associated with age and plasma IL-6 concentrations. Diastolic BP (DBP) was positively correlated with plasma IL-6 and IL-1ra and was negatively associated with plasma IL-1β. Serum TNF-α, C-reactive protein, and sIL-6R were not significantly associated with either SBP or DBP.

Subjects with atherosclerotic lesions of the carotid arteries were older and had more elevated plasma IL-6 levels and arterial BP than did those with no lesions or with

Table 2. Simple correlations between systolic and diastolic blood pressure and several soluble markers of inflammation

Variable	*n*	SBP	*P*	DBP	*P*
Age	537	0.18	<.001	0.26	NS
IL-6*	537	0.14	<.001	0.09	<.05
sIL-6R	537	−0.07	NS	−0.04	NS
IL-1β	511	−0.06	NS	−0.12	<.05
IL-1ra	537	0.08	NS	0.13	<.005
TNF-α	534	0.04	NS	−0.01	NS
CRP	518	0.01	NS	0.02	NS

NS = not significant; sIL-6R = soluble plasma IL-6 receptor; other abbreviations as in Table 1.
* Back log transformed.

isolated intimal thickness. The serum concentrations of other cytokines and the main anthropometric parameters were not significantly different across the various levels of carotid atherosclerosis (Table 1).

The IL-6 genotype was associated with a more elevated BP in non–C carrier subjects (Fig. 1), an effect that was evident in women but not in men. In fact, non–C carrier women had SBP (149 ± 19 *v* 144 ± 19 mm Hg, $P < .05$) and DBP (83 ± 9 *v* 81 ± 8 mm Hg, $P < .05$) that was higher than in sex-matched C carriers. In contrast, men had SBP (145 ± 18 *v* 147 ± 18 mm Hg, P = NS) and DBP (83 ± 8 *v* 83 ± 7 mm Hg; P = NS) values that were independent of the IL-6-174 C/G polymorphism.

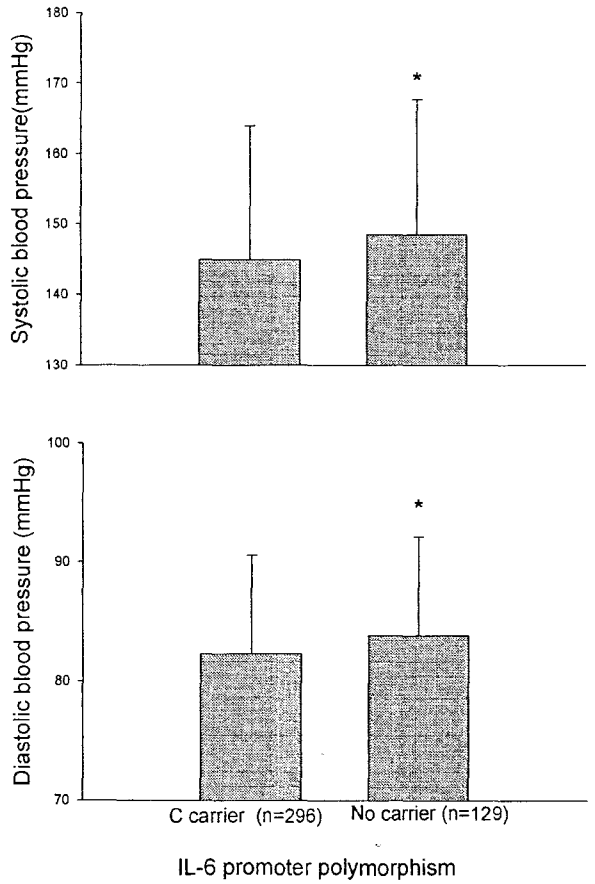

FIG. 1. Systolic and diastolic blood pressure in carriers and non-carriers the allele C of the −174 IL-6 promoter polymorphism. *$P <$ .05 *v* "C carriers." IL-6 = interleukin-6.

The predictive role of chronic inflammation on SBP and DBP after adjusting for age and sex was tested in multivariate analyses (Table 3). In particular, we tested the independent association of serum IL-6, sIL-6R, IL-1β, IL-1ra, TNF-α concentrations, IL-6 genotype, and IRS score (model 1) with SBP and DBP after adjusting for age and sex. In such analyses, only age and serum IL-6 and IL-1β levels were independently associated with SBP. Nevertheless, after further addition of the degree of atherosclerosis to the model of (model 2), age, IRS score, and severity of carotid atherosclerosis were the only significant predictors of SBP. It is noteworthy that, in both analyses, serum IL-1β levels showed a significant negative association with SBP. With regard to DBP, the serum IL-1β and IL-1ra levels, IL-6 genotype, and IRS score were independent predictors of DBP. However, after adjusting for severity of carotid atherosclerosis, serum IL-1β, IL-1ra concentrations, and IRS score were the only predictors of DBP. Again, serum IL-1β levels showed a negative significant association with DBP.

Discussion

Our study demonstrates that chronic inflammation is independently associated with BP in elderly persons. In particular, the effect of interleukins was almost trivial on SBP, whereas it was particularly evident on DBP. Finally, in our study population, the IL-6-174 C/G polymorphism did not show any major independent role as a modulator of both SBP and DBP.

The reciprocal relationship between arterial BP and chronic inflammation is more complex than previously understood. In fact, both elevated BP and inflammatory response reflect underlying alterations present in vascular, reticuloendothelial, and other tissues.

Several previous studies have pointed out that BP may have a proinflammatory role on the arterial wall because of two different possible mechanisms. First, increased BP may promote atherogenesis by modulating the biomechanical stimuli of the pulsatile blood flow (increased hydrostatic pressure or cyclic strain), which in turn affects endothelial cell gene expression and function.[17] Second, hypertension may result in enhanced endothelial responsiveness to factors promoting monocyte adhesion and subsequent atherosclerosis. This last hypothesis is suggested by in vitro[18] and in vivo[19] studies that demonstrated an increased sICAM expression and greater monocyte adhesion in spontaneously hypertensive rats compared with normotensive rats.

The hypothesis that BP is the main cause of arterial

Table 3. Linear multiple regression analyses with systolic and diastolic blood pressure as dependent variables (n = 537)

	Systolic Blood Pressure			Diastolic Blood Pressure		
	β	t	P	β	t	P
Model 1						
Age	0.19	3.89	<.001	0.02	0.42	.670
Sex	0.03	0.64	.517	−0.03	−0.62	.532
IL-6*	0.11	1.97	<.05	0.07	1.40	.160
IL-6 receptor	−0.08	−1.74	.082	−0.03	−0.70	.479
TNF-α	0.06	1.31	.190	0.01	0.19	.845
IL-1β	−0.09	−1.93	.05	−0.08	−2.01	<.05
IL-1ra	0.05	1.09	.276	0.13	2.57	<.05
−174 C/G polymorphism†	0.07	1.61	.107	0.09	2.03	<.05
IRS score	0.07	1.58	.113	0.11	2.36	<.05
Model 2						
Age	0.17	3.24	<.001	0.01	0.14	.885
Sex	0.04	0.90	.367	−0.03	−0.75	.453
IL-6*	0.07	1.44	.149	0.05	0.99	.322
IL-6 receptor	−0.09	−2.03	0.85	−0.04	−0.90	.366
TNF-α	0.07	1.54	.123	−0.01	−0.01	.986
IL-1β	−0.10	−2.20	<.05	−0.11	−2.27	<.05
IL-1ra	0.06	1.31	.190	0.15	2.78	<.005
−174 C/G polymorphism†	0.07	1.51	.130	0.08	1.64	.102
IRS score	0.08	1.75	.050	0.12	2.47	<.05
Atherosclerosis‡	0.11	2.16	<.05	0.02	0.37	.706

IRS = insulin resistance syndrome; other abbreviations as in Tables 1 and 2.
For systolic blood pressure: R^2 = 0.08 (model 1); R^2 = 0.08 (model 2). For diastolic blood pressure: R^2 = 0.06 (model 1); R^2 = 0.07 (model 2).
* Back log transformed.
† Calculated as C carrier *v* non carrier.
‡ Calculated as: 0 = absence of atherosclerosis; 1 = presence of intimae media thickness; 2 = presence of carotid artery plaques and/or stenosis.

wall inflammation is somewhat limiting, as pathophysiologic conditions other than atherosclerosis (such as dyslipidemia, obesity, hyperinsulinemia/insulin resistance, and diabetes mellitus) may cause inflammation involving the arterial wall, and through this mechanism, may influence BP regulation.[4] In addition, aging, a condition frequently associated with a rise in BP, might itself exert a further proinflammatory role.[5,20] In fact, it has been suggested that a direct relation between age and macrophage activation accounts for the subclinical chronic activation of the inflammatory response in the elderly.[21] Indeed, plasma IL-6 levels are low or undetectable in most young persons and start to increase even in healthy persons at about 50 to 60 years of age. Thus, one could hypothesize that chronic inflammation is a common pathway through which different proatherosclerotic factors may operate for increasing BP, especially diastolic BP. On the contrary, our data suggest that chronic inflammation does not significantly contribute to the age-related derangement in systolic arterial BP, given that age, IRS score, and degree of atherosclerosis were the only independent determinants of a rise in SBP. In this context, serum IL-1β levels seems to contribute to lowering SBP. On the other hand, chronic inflammation seems to exert a main modulator effect on DBP, given that serum IL-1ra levels was a significant determinant of the rise in DBP, an effect counteracted by serum IL-1β levels. Interestingly, the IRS score was also a significant determinant of DBP, independent of chronic inflammation.

The lack of a significant effect of serum IL-6 on arterial BP was unexpected. In fact, IL-6 has also been shown to promote vascular smooth muscle cell proliferation, a hallmark of the early stage of hypertension and atherosclerosis.[22] Indeed, such a hypothesis is supported by several observations. First, simple correlation analysis demonstrated that plasma IL-6 levels correlated with both SBP and DBP. Second, categorizing the subjects for degree of atherosclerosis, subjects with evidence of carotid artery plaques also had more elevated levels of arterial BP and serum IL-6 levels. Third, the IL-6-174 promoter polymorphism, which has been demonstrated to affect serum IL-6 levels in women[23] and to be associated with SBP in men,[10] was also a determinant of BP, especially in women. Fourth, in a multivariate analysis, we demonstrated that IL-6 was a predictor of systolic BP independently of age, sex, IRS score, and the IL-6-174C/G polymorphism. Nevertheless, in a model including the degree of atherosclerosis, the analysis failed to highlight the independent role of the IL-6-174 promoter polymorphism, serum IL-6 levels, and sIL-6R concentrations as modulators of arterial BP. A possible explanation for such apparent discrepancy might be that IL-6 pathways could be more useful as a marker of endothelium damage but as a less powerful determinant of change in BP.

Our findings suggest that the serum IL-1ra/IL-1β ratio is a specific marker of the modulating effect of inflammation on BP. In fact, serum IL-1ra concentration significantly correlated with DBP in the simple correlation analysis and was the strongest determinant of DBP in the multivariate analysis. Such data are in agreement with previous findings that acute mental stress raises plasma IL-1ra and arterial BP, suggesting a link between plasma cytokine concentration and sympathetic reactivity.[24] Because plasma IL-1ra competitively inhibits IL1-binding to cell-surface receptors, it is most likely an impaired balance between IL-1ra overproduction and IL-1β impaired production may exert a regulator role on arterial BP. Although the cross-sectional design of our study does not allow us to draw conclusions about a cause-and-effect mechanism, the lowering effect of plasma IL-1β on BP that is suggested by our data may also be supported by the following observations: 1) IL-1β downregulates SNS activity, and such modulation is mediated by increased local expression of neuronal NOS mRNA[25]; and 2) angiotensin II–mediated increase in arterial BP is caused by inhibition of the expression of IL-1β and neuronal NOS at the brain level.[26]

According to several previous reports, an expected finding of our study was that age and degree of atherosclerosis were significant determinant of SBP,[27] whereas clustering variables of the insulin resistance syndrome was a significant determinant of both SBP and DBP.[4]

A potential limitation of our study was the lack of data regarding oxidative stress, as previous studies have shown that inflammation is a pro-oxidant factor and also that oxidative stress is a determinant of BP.[28] Further studies should address such a relationship.

In conclusion, our study results suggest a potential role of serum IL-1ra and IL-1β in the regulation of arterial BP. This activity is not mediated by the aging process, and it is, at least in part, independent of chronic inflammation. These findings support the hypothesis that chronic inflammation is the common link between different pathophysiologic conditions (aging or metabolic abnormalities) and the development of hypertension. Furthermore, the evidence that the relationship between serum IL-1ra or IL-1β and BP was independent of the degree of atherosclerosis and clustering variables of the IRS emphasize a different mechanism or site of action (brain versus vessel) for such cytokines. Further studies will be needed to confirm our findings in a longitudinal prospective and to gain insight into the pathophysiologic mechanism by which chronic inflammation affects systolic and diastolic BP over the course of aging process.

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