RISK OF CARDIOVASCULAR DISEASE ACCORDING TO BLOOD PRESSURE CATEGORIES IN AN ARGENTINIAN COHORT

RIESGO DE ENFERMEDADES CARDIOVASCULARES SEGÚN CATEGORIAS DE PRESIÓN ARTERIAL EN UNA COHORTE ARGENTINA

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Summary

Background: Hypertension is a recognized strong risk factor for cardiovascular disease. However, no data was available in our country to quantify the relationship between blood pressure and cardiovascular event.

Objective: to quantify the risk of cardiovascular events according to blood pressure categories.

Methods: A prospective epidemiological study was conducted in 1526 inhabitants from Rauch City, (Buenos Aires, Argentina) between 1997 and 2012. Subjects were classified into one of these blood-pressure categories: 1-optimal, 2-normal, 3-high-normal, 4-grade 1 hypertension, 5-grade 2 hypertension and 6-grade 3 hypertension. The first CVD event, including unstable angina pectoris, fatal and non-fatal myocardial infarction, myocardial revascularization, and fatal or non-fatal stroke, was defined as the primary endpoint. Multivariable Cox proportional-hazards regression models were used to estimate the relative risk (HR) of CVD according to base-line blood-pressure categories.

Results: In 2012, 1124 individuals (73.7% of the baseline sample), 719 women and 405 men (in 1997, aged 45±16 and 46±16 respectively) or their relatives in case of death, could be surveyed again in order to obtain information concerning incident CVD events. Cardiovascular event rates and HR values increased in a stepwise manner across the blood pressure categories (p for trend across categories <0.001 in both sex); however, in subjects aged ≥55 years a j-curve phenomenon was observed, showing the lowest incidence in the high-normal category. In all categories CVD events rates were higher for men.

Conclusion: This study quantified relationships between BP and CVD starting from high-normal blood pressure in Argentina.

Key Words: cardiovascular diseases, epidemiology, general population, high blood pressure

Resumen

Antecedentes: La hipertensión arterial es un reconocido factor de riesgo de enfermedad cardiovascular (ECV). Sin embargo, no hay información en Argentina que cuantifique la relación entre la presión arterial (PA) y ECV.

Objetivo: Cuantificar el riesgo de ECV de acuerdo a categorías de PA.

Método: Se realizó un estudio epidemiológico prospectivo en 1526 habitantes de la ciudad de Rauch (Buenos Aires, Argentina) entre octubre de 1997 y febrero de 2012. Los individuos fueron clasificados en las categorías de PA: 1-óptima, 2-normal, 3-normal-alta, 4-hipertensión grado 1, 5-hipertensión grado 2 y 6-hipertensión grado 3. Fue definido como punto final el primer evento de ECV (angina de pecho inestable, infarto fatal y no fatal, revascularización, y accidente cerebrovascular fatal y no fatal). El riesgo relativo (HR) de tener un evento fue estimado usando

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modelos de regresión multivariable de Cox.
Resultados: En 2012, fueron re-encuestados 1124 individuos (73,7% de la muestra basal), 719 mujeres y 405 hombres, o sus parientes en caso de muerte (edad en 1997 45±16 y 46±16 años, respectivamente). Las tasas de ECV y los HR se incrementaron para cada categoría de PA por encima de la óptima (p < 0.001 en ambos sexos); sin embargo, en sujetos mayores de 55 años se observó un fenómeno de curva en J, con la incidencia más baja en la categoría normal-alto. En todas las categorías la tasa de eventos fue mayor en hombres.
Conclusión: Este estudio demostró y cuantificó la relación entre de PA y ECV a partir de PA normal alta en una población de Argentina.

Palabras clave: enfermedad cardiovascular, epidemiología, población general, presión sanguínea elevada.

Introduction

Many cohort studies have demonstrated that hypertension is a strong risk factor for total mortality and cardiovascular disease (CVD) in both developing and developed countries[1-3.] Blood pressure (BP) and cardiovascular risk are related in a continuous, direct and linear way. This relation is consistent in both women and men, even within normal levels of BP[4]. Furthermore, BP above the optimal values (> 120/80 mmHg) seems to be by far the most powerful cardiovascular risk factor, accounting for about 54% of stroke and 47% of acute myocardial infarction [5].

Although the prevalence of high BP in Argentina has been studied and seem to be similar compared to other western countries (~30%), to the best of our knowledge, no data was collected in our country that quantifies the relationship between BP and cardiovascular event. As a matter of fact, a recently published study about the burden of cardiovascular disease in Argentina had used data from foreign studies to estimate the relationship between BP and CVD[6]. For clinical purposes, BP categories have been developed in order to classify the risk for cardiovascular event; among the most widely used, those published by the European Society of Cardiology and the European Society of Hypertension were selected (ESH-ESC)[7].

Therefore, the aim of this study was to evaluate the relationship between ESC-ESH BP categories and the consequent cardiovascular outcome in an Argentinian population.

Material and methods

A prospective epidemiological study, focused on hypertension and other cardio-metabolic risk factors, was conducted in Rauch City, Buenos Aires province, Argentina (36° 45’ 00’’ south latitude and 59° 04’ 00’’ west longitude) between October 1997 and February 2012. According to the last national census available in 1997 (1991 census), there were 13 909 inhabitants in Rauch, 8246 between 15 and 75 years of age (4166 men and 4080 women). Rauch is a small rural town located in the Pampean region of Argentina, near Buenos Aires city. The region received a major influx of immigrants throughout the late nineteenth and early twentieth centuries, being in vast majorities from Spain and Italy. Individuals of African and Asian ethnicity represent a small minority in this area, but there is undoubtedly some genetic admixture between subjects of European ancestry and Amerindian. There are no quantitative data concerning the genetic admixture in Rauch, but it does seem reasonable to assume it would be comparable to the results of a study performed in Buenos Aires in 2006 which demonstrated a genetic admixture of approximately 80% European, 16% Amerindian, and 4% African.[8]

In 1997 a survey was conducted among subjects all aged between 15-75 who lived in random chosen blocks (969 women 45±17 years old and 557 men 46±17 years old, p between gender = 0.526). The methodology used to obtain measurements of clinical and biochemical variables has already been published[9]. Relevant health authorities approved the program and all participants gave a written informed consent. In brief, BP was measured sitting, after a minimum resting-period of five minutes, using a mercury sphygmomanometer. Phase I and V Korotkoff sounds were used to identify systolic BP (SBP) and diastolic BP (DBP), respectively; SBP and DBP values were an average of three different measurements separated from one another by two minutes. Weight was determined with individuals wearing light clothes and no shoes. Concentrations of plasma glucose and total cholesterol were determined after an overnight (12 hours) fast; diabetes mellitus was defined as fasting plasma glucose ≥ 126 mg/dL or use of glucose-lowering drugs; hypercholesterolemia was defined as total cholesterol ≥ 200 mg/dL.

At baseline examination, the subjects were classified into one of these BP categories on the basis of 2013 ESH-ECS criteria[7]: 1- optimal (SBP <120 mmHg and DBP <80 mmHg), 2- normal (SBP 120-129 mmHg or DBP 80-84 mmHg), 3- high-normal (SBP 130-139 mmHg or DBP 85-89 mmHg), 4- grade 1 hypertension

(SBP 140-159 mmHg or DBP 90-99 mmHg), 5- grade 2 hypertension (SBP 160-179 mmHg or DBP 100-109 mmHg) and 6- grade 3 hypertension (SBP ≥ 180 mmHg or DBP ≥ 110 mmHg). When SBP and DBP readings belonged to different categories, the higher reading was used to assign the category.

In 2012, 1124 individuals (73.7% of the baseline sample), 719 women and 405 men (age in 1997 45±16 and 46±16 years old, respectively; p = 0.192 between gender), or their relatives in case of death, could be surveyed again in order to obtain information concerning incident CVD events; the remaining inhabitants could not be found mainly because they had stopped living in Rauch city by the moment of the second survey. As table 1 shows, there were no significant differences in baseline characteristics between subjects with and without follow-up period.

	Follow-up period				
	Yes		No		
	N 1124		N 402		
	Mean	(SD)	Mean	(SD)	p[a]
Age	45	16	45	20	0.722
Women (%)	64.0		62.2		0.525
Systolic BP	138	20	139	22	0.570
Diastolic BP	89	14	88	14	0.225
BMI	25.8	(4.5)	25.7	(6.6)	0.828
Glucose	80	19	81	18	0.437
Total cholesterol	188	28	187	32	0.686

[a] Independent-samples t test for continuous variables and chi square for proportions,
Continuous variables as mean and standard deviation (SD) and proportions as percentage (%)
SD: standard deviation, BP: blood pressure, BMI: body mass index.

The first CVD event, including severe or unstable angina pectoris, fatal or non-fatal myocardial infarction, myocardial revascularization, and fatal or non-fatal stroke was defined as the primary endpoint. A structured interview was conducted with each participant by trained nurses and social workers. The collected data was then evaluated by a highly qualified internist (blinded with respect to the subjects' baseline CVD risk factors) to assign a specific outcome for every event. When necessary, available medical records were also reviewed. Sex-specific cardiovascular-event rates for each BP category were calculated by dividing the number of subjects who had such events by the number of person-years of observation contributed by subjects within a BP category. Kaplan-Meier procedure was used to estimate the mean survival and hazard risk for women and men and for subjects above and below the age of 55, separately; loq-rank, Breslow and Tarone-Ware tests were used to estimate linear trend for factor according to their baseline BP category. Also, multivariable Cox proportional-hazards regression models were used to estimate the relative risk of first CVD event according to the base-line BP category, after adjustment by sex, smoking status, diabetes mellitus and hypercholesterolemia. The risk was expressed as hazard ratio (HR) and its 95% confidence interval (CI95%). Two additional analyses were performed:
1-excluding individuals who had referred myocardial infarction or stroke in the initial (1997) survey and
2- only using individuals without antihypertensive drugs.

Continuous variables were expressed as mean and standard deviation (SD) and compared using independent-samples t test or ANOVA, and proportions were expressed as percentages and compared by x^2; statistical analyses were performed using SPSS software (SPSS Inc., Chicago, IL, USA); two-tailed and p values < 0.05 were considered statistically significant.

TABLE 2. Base-line characteristics of the study subjects according to blood pressure category at base

	Optimal	Normal	High-normal	Grade 1 hypertension	Grade 2 hypertension	Grade 3 hypertension	p[a]
	N 162	N 204	N 264	N 213	N 178	N 103	
Age, years	33 (12)	37 (15)	43 (15)	51 (15)	55 (13)	57 (12)	< 0.001
% women	82	67	70	54	57	49	< 0.001
Systolic BP, mmHg	112 (7)	124 (5)	132 (5)	143 (8)	157 (11)	176 (18)	< 0.001
Diastolic BP, mmHg	73 (6)	79 (5)	84 (5)	92 (5)	102 (6)	117 (9)	< 0.001
BMI, Kg/m^2	23.2 (3.4)	23.7 (3.7)	25.1 (3.8)	27.5 (4.5)	27.9 (4.4)	28.8 (5.0)	< 0.001
Glucose mg/dL	75 (11)	76 (16)	81 (26)	80 (17)	83 (15)	84 (21)	< 0.001
Diabetes prevalence, %	1.2	1.0	3.4	3.8	5.1	4.9	0.126
Total cholesterol, mg/dL	177 (18)	179 (19)	188 (27)	194 (34)	195 (31)	196 (30)	< 0.001
Hypercholesterolemia, %	6.8	8.8	17.4	26.3	31.5	29.1	< 0.001
Current smokers, %	28.4	25.5	26.9	20.2	26.4	17.5	0.189
Antihypertensive drugs, %	1.9	2.9	3.0	13.1	29.1	38.3	< 0.001

[a] ANOVA for continuous variables and chi square for proportions, continuous variables as mean and standard deviation (SD)and proportions as percent
BP: blood pressure, BMI: Body mass index

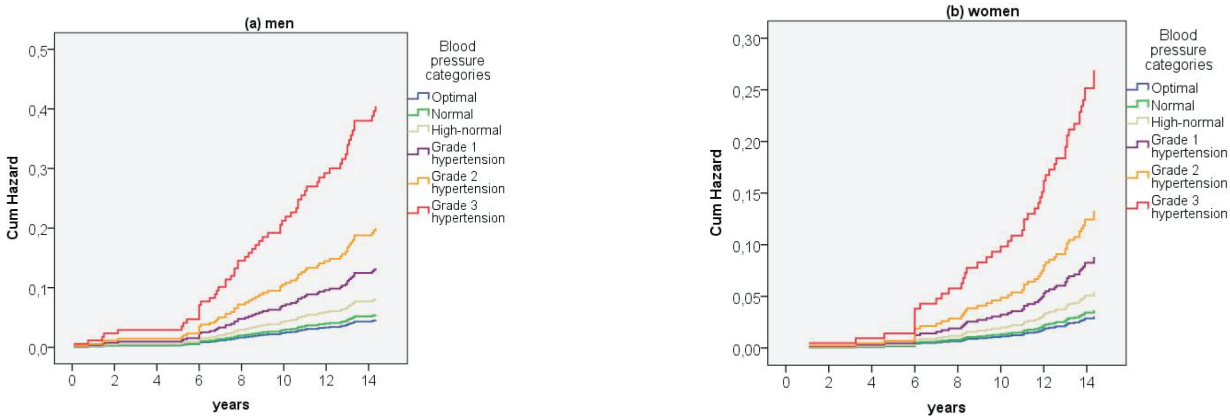

Figure 1. Adjusted cumulative hazard of combined cardiovascular events (angina pectoris, fatal or non-fatal myocardial infarction, myocardial revascularization, and fatal or non-fatal stroke) according to blood pressure categories at baseline in men (a) and in women (b).

Results

Characteristics of the study subjects

At baseline, 14.4% of the subjects had optimal BP, 18.1% had normal BP, 23.5% had high-normal BP and 43.9% hypertension. Table 2 shows baseline characteristics of the sample according to BP categories at baseline. In our sample, a higher proportion of women had optimal BP, compared to men. Age, body mass index (BMI), glucose, total cholesterol and percentage of subjects with antihypertensive treatment increased throughout BP categories.

Blood pressure categories and cardiovascular risk

During the follow-up period (mean 14±0.06 years; 15 377 person-years), 111 subjects (51 women and 60 men) had their first cardiovascular event: 10 fatal stroke, 19 non-fatal stroke, 20 fatal coronary heart disease, 62 non-fatal coronary heart disease. There were also 58 non-cardiovascular deaths. Of these events, 4.5%, 7.2%, 14.4%, 20.7%, 25.2% and 27.9% occurred in individuals with optimal BP, normal BP, high-normal BP, grade 1 hypertension, grade 2 hypertension and grade 3 hypertension, respectively. Thus, a quarter of the events occurred in individuals with BP < 140/90 mmHg and almost half of them in individuals with BP < 160/100 mmHg.

CVD-event rates increased in a stepwise manner across the BP categories (p for trend across categories < 0.001 in both sexes, figure 1)

In all categories the CVD-event rates were higher in men than in women. In subjects with age < 55 the cru-

TABLE 3. Mean survival and crude cumulative incidence of a first cardiovascular event according to blood pressure category.

Blood pressure categories	women			men			age < 55 years			age ≥ 55 years		
	mean survival	SD	rate	mean survival	SD	rate	mean survival	SD	rate	mean survival	SD	rate
Optimal	14.2	0.07	1.6	14.3	0.05	4.9	14.3	0.00	0.5	12.4	1.05	41.6
Normal	14.2	0.07	1.6	14.0	0.17	5.2	14.3	0.05	1.2	13.3	0.48	16.7
High-normal	14.1	0.09	4.3	14.0	0.20	4.6	14.2	0.07	2.1	13.6	0.29	12.7
Grade 1 hypertension	14.2	0.06	5.0	13.4	0.25	11.4	14.0	0.13	4.2	13.6	0.23	13.0
Grade 2 hypertension	13.9	0.16	8.7	13.0	0.37	16.4	13.8	0.23	6.6	13.3	0.26	16.2
Grade 3 hypertension	12.8	0.44	22.4	13.2	0.42	25.9	13.9	0.43	15.1	12.4	0.39	30.7
P for trends												
log rank		< 0.001			< 0.001			< 0.001			0.008	
Breslow		< 0.001			< 0.001			< 0.001			0.010	
Tarone-Ware		< 0.001			< 0.001			< 0.001			0.009	

de incidence of first CVD event increased through all BP categories; however, in subjects with age ≥ 55 a J-curve phenomenon was observed, showing the lowest incidence values in the high-normal BP category (Table 3). Table 4 shows the relative risk on CVD-events estimated by several cox regression models, unadjusted (Model 1), adjusted by sex (Model 2), and adjusted by sex, diabetes, hypercholesterolemia and smoking status (Model 3). In all models the HR increased significantly through BP categories.

Twelve percent of the subjects were under antihypertensive treatment. As table 2 shows, this proportion increased through BP categories. Adjusted multiple variable Cox-model (Model 3) performed excluding subjects under antihypertensive treatment showed very close HRs to those found using the complete sample (data not shown). However, when the analysis was performed excluding individuals with a previous myocardial infarction or stroke the relationship between BP and CVD became more noticeable (Table 5).

TABLE 4. Cox proportional-hazards regression models examining the relation of blood-pressure category to the risk of a first major cardiovascular event

Blood pressure categories	Model 1	Model 2	Model 3
	HR (95%CI)	HR (95%CI)	HR (95%CI)
Optimal	1	1	1
Normal	1.3 (0.4-4.0)	1.2 (0.4-3.6)	1.2 (0.4-3.7)
High-normal	2.0 (0.7-5.5)	1.9 (0.7-5.2)	1.8 (0.6-4.9)
Grade 1 hypertension	3.8 (1.4-9.9)	3.2 (1.2-8.5)	2.9 (1.1-7.7)
Grade 2 hypertension	5.7 (2.2-14.8)	5.0 (1.9-13.1)	4.3 (1.7-11.4)
Grade 3 hypertension	11.8 (4.6-30.4)	9.8 (3.8-25.5)	8.83 (3.3-23.0)
P for trends	< 0.001	< 0.001	< 0.001

HR (95%CI): hazard ratio (95% confidence interval)
Model 1 Unadjusted
Model 2 Adjusted by sex
Model 3 Adjusted by sex, diabetes, hypercholesterolemia, smoking status and previous (before 1997) cardiovascular disease

Discussion

Although numerous investigators have reported that cardiovascular risks is associated with elevated BP, there is no information about the absolute and relative risks of CVD according to BP categories in Argentina. Our data confirms that BP above optimal (> 120/80 mmHg) implies a continuous, graded, strong and independent relationship with cardiovascular outcome.

A comparison of our results with the previously published studies would be hampered by differences in the sample, ages, end points, antihypertensive treatment, associated risk factors and BP classification. Moreover, several population-based studies have opted to evaluate the relationship between CVD and systolic and diastolic BP separately instead of using clinical BP categories (those including individuals who meet SBP, DBP or both criteria). A study performed using six populations from different parts of the world showed that among populations, the increase in relative risk of death from coronary heart disease for a given increase in BP was similar, but that the absolute risk at a given BP value varied substantially[10].

TABLE 5. Hazard ratios (HR) of cardiovascular events occurring according baseline blood pressure categories excluding individuals with a previous myocardial infarction or stroke

Blood pressure categories	Model 1	Model 2	Model 3
	HR (95%CI)	HR (95%CI)	HR (95%CI)
Optimal	1	1	1
Normal	2.09 (0.55-7.89)	1.91 (0.51-7.22)	1.91 (0.51-7.26)
High-normal	3.28 (0.95-11.25)	3.05 (0.89-10.48)	2.89 (0.83-9.87)
Grade 1 hypertension	5.44 (1.62-18.32)	4.70 (1.39-15.92)	4.27 (1.26-14.54)
Grade 2 hypertension	8.80 (2.66-29.01)	7.74 (2.33-25.69)	6.85 (2.05-22.87)
Grade 3 hypertension	18.74 (5.71-61.54)	15.69 (4.74-51.97)	14.41 (4.32-48.00)
P for trends	< 0.001	< 0.001	< 0.001

HR (95%CI): hazard ratio (95% confidence interval)
Model 1 Unadjusted
Model 2 Adjusted by sex
Model 3 Adjusted by sex, diabetes, hypercholesterolemia and smoking status

In individuals with high-normal BP Vasan et al. found a 10-year cumulative incidence of CVD of 4% among women and 8% among men. In our sample the 10-year cumulative incidence of CVD in subjects with high-normal BP was 4.3% in women and 4.6% in men[11]. The adjusted relative risk of individuals with high-normal BP found in Rauch population (HR = 1.9) was similar to those reported in previous publications. In the multiracial Atherosclerosis Risk in Communities (ARIC) study, compared to optimal BP the relative risk of CVD for high-normal BP was 2.33[12]. In a recently published study performed in a general urban population cohort in Japan the adjusted relative risks for CVD in high--normal BP were 2.46 and 1.54 in men and women respectively, and only slightly lower when antihypertensive drug users were categorized as hypertensive subjects[13]. Thus, we can state that compared to optimal BP, high-normal BP means about twice as CVD risk in several different populations and ethnic groups, including Rauch´s.

When concerning hypertensive individuals the comparison turns even more difficult due to the different levels of knowledge, treatment and control of the disease among populations; for instance, the relative risk as well as the absolute risk may be affected by their control level. The relative risk for grade 1 hypertension found in Rauch was higher to the one found in the Framingham cohort[14]. In Japanese people[12] the HR was 2.7 in men but only 1.35 in women. Therefore, ~3 folds increase in cardiovascular risk found in grade 1 hypertension seems similar to previously communicated values in both occidental samples and Japanese men. The relative risks for grade 2 and 3 hypertension found in Rauch were similar to the values described for subjects without treatment in the Framingham cohort[14]. However, the relative risk for BP > 180/110 mmHg was higher than the one found in the Framingham cohort.

Interestingly, when individuals who had referred myocardial infarction or stroke in the initial (1997) survey were excluded of the Cox analysis, the relative risk of incident CV events increased markedly trough BP categories. This fact may be related to the exclusion of subjects with both, very high CVD and BP in the lower range (probably due to cardiac failure and/or antihypertensive drugs), that developed an event early in the follow-up period.

As mentioned before, in subjects under the age of 55 the risk increased through all BP categories, whereas when we analyze the subset of subjects above the age of 55 a J-curve phenomenon can be observed. The phenomenon of J-curve has been described in the Progress[15], LIFE[16] and HOT[17] studies in patients under antihypertensive treatment. Furthermore, in the INDANA[18], PREVENT[19] and TNT[20] studies, this phenomenon seemed to exist independently of the use of antihypertensive drugs. Although the J-curve phenomenon has already been described, its mechanisms are still a matter for discussion. A plausible explanation for this may consist in the advanced degree of structural heart disease (due to, for instance, previous acute myocardial infarct, dilated cardiomyopathy) and/or the antihypertensive effect of drugs for its treatment (atenolol, angiotensin converting enzyme inhibitors).

Remarkably, ~1/4 of the CVD events were observed in individuals without hypertension at baseline. Therefore, controlling the burden of disease related to high BP requires the use of two policies: 1- “high risk” strategies designed for those individuals that show the highest levels of BP and 2-“mass population” intervention designed to change the whole BP curve downwards[21]. In our country, we have demonstrated that population-based strategies have been able to modify the entire distribution of BP[22].

Our study has several limitations. The main one is a dilution bias: this study was based on a single-day measurement of BP, which may lead to a misclassification of BP categories; nevertheless, previous epidemiological evidence has suggested that BP measurements taken on a single day are accurate for risk estimations[23]. Second, approximately 1/4 of subjects who underwent the baseline survey could not be found for the follow up period, mainly because they no longer resided in Rauch city. Although this loss was slightly bigger than expected, it does seem reasonable for a population sample after a 14 year follow-up. Furthermore, there were no clinical differences at baseline between subjects with and without follow-up period, suggesting that the loss was not source of bias. Third, a cardiovascular prevention program that took place in Rauch city between 1997 and 2003 could have modified the results. In addition to this, due to the relatively scarce number of events, we had to include angina as end-point. However, all the end-points were codified by a highly qualified internist using all the data available. In consequence, we believe that our data represents “true” CVD. Finally, the results may not be applicable to other population and ethnical groups. Notwithstanding this, the present study is, to the best of our knowledge, the first intent to quantify the relationships between BP and cardiovascular outcome in Argentina.

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