Warfarin Use Has no Effect on Blood Pressure of Patients With Diabetes and Hypertension

Uso da Warfarina Não Tem Efeitos Sobre a Pressão Arterial em Pacientes com Diabetes e Hipertensão Arterial Sistêmica

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ABSTRACT

Introduction: Warfarin causes arterial calcification, arterial stiffness and systolic hypertension in animals. Early evidence in humans indicates that a similar effect may occur in patients with diabetes mellitus (DM) and/or hypertension. **Objective:** To evaluate whether warfarin use causes elevated blood pressure and pulse pressure in patients with both DM and hypertension. **Methods:** Cross-sectional study of 159 subjects with both DM and hypertension who received warfarin for at least 2 years and 159 age-matched control subjects with DM and hypertension never exposed to warfarin. The primary focus of analysis was the difference in systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse pressure (PP) between the two groups. **Results:** Average age was 73±10 years in both groups. Patients in the warfarin group had received it for an average of 5.5±3.1 years. Subjects in the warfarin group had higher rates of coronary disease and heart failure. SBP and PP were lower in the warfarin group (SBP 130±14 mmHg vs. 134±12 mmHg, P=0.003; PP 58±12 mmHg vs. 62±11 mmHg, P=0.004), while DBP was not different (72±8 vs. 72±7 mmHg, P=0.64). Warfarin patients received more antihypertensive drugs and were seen more often than controls. Multiple regression analyses adjusting for relevant variables did not disclose an association between warfarin use and higher BP; on the contrary, exposure to warfarin was associated with lower SBP and PP on the multivariable models. **Conclusion:** Use of warfarin in conventional doses for an average of 5.5 years was not associated with increased BP in this cross-sectional study of patients with DM and hypertension. **(J Bras Nefrol 2006; 28(3):128-133)**

Keywords: Warfarin. Anticoagulants. Blood pressure. Pulse pressure. Hypertension. Systolic hypertension. Arteriosclerosis

RESUMO

Introdução: Em animais, a warfarina provoca calcificação arterial, rigidez arterial e hipertensão arterial (HA) sistólica. Dados preliminares em humanos sugerem que o mesmo efeito pode acontecer em pacientes com diabetes mellitus (DM) e/ou HA. **Objetivo:** Determinar se o uso da warfarina em pacientes com DM e HA resulta em elevação da pressão arterial ou pressão de pulso. **Métodos:** Estudo transversal de 159 pacientes com DM e HA que haviam sido tratados com warfarina por pelo menos 2 anos, e 159 controles pareados por idade, com DM e HA, mas que nunca haviam usado warfarina. O enfoque principal na análise foi a diferença na pressão arterial sistólica (PAS), diastólica (PAD) e pressão de pulso (PP) entre os dois grupos. **Resultados:** A média de idade foi 73±10 anos em ambos os grupos. Os pacientes no grupo da warfarina haviam usado a droga por 5.5±3.1 anos. Pacientes no grupo da warfarina tinham uma prevalência maior de doença coronariana e insuficiência cardíaca. A PAS e PP foram mais baixas no grupo warfarina (PAS 130±14 mmHg vs. 134±12 mmHg, P=0.003; PP 58±12 mmHg vs. 62±11 mmHg, P=0.004), mas a PAD não diferiu entre os grupos (72±8 vs. 72±7 mmHg, P=0.64). Pacientes do grupo warfarina usaram mais drogas antihipertensivas e foram avaliados clinicamente com maior freqüência do que os controles. Regressão múltipla ajustada para fatores de relevância clínica não demonstrou nenhuma associação entre o uso da warfarina e elevação da pressão arterial. Pelo contrário, nos modelos de regressão múltipla, a exposição à warfarina associou-se a valores mais baixos de PAS e PP. **Conclusão:** O uso da warfarina em doses convencionais, por 5.5 anos, não associou-se a um aumento da pressão arterial neste estudo tranversal de pacientes com DM e hipertensão. **(J Bras Nefrol 2006; 28(3):128-133)**

Descritores: Warfarina. Anticoagulantes. Pressão arterial. Pressão de pulso. Hipertensão arterial. Hipertensão arterial sistólica. Arteriosclerose.

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INTRODUCTION

Systolic hypertension is an important cardiovascular risk factor in elderly patients, wherein elevated systolic blood pressure (BP) is more reliable than diastolic BP as a determinant of cardiovascular risk[1]. Increased arterial stiffness is a major pathophysiological component of systolic hypertension in the elderly[2]. Aging, diabetes mellitus, and kidney disease are the most prominent factors that lead to increase collagen accumulation and calcification of the vascular wall, the two key processes that lead to increased arterial stiffness[3,4]. These wall changes lead to faster pulse wave conduction, amplified pulse wave reflection and abnormal diastolic decay of the BP curve, resulting in higher systolic BP, lower diastolic BP, and consequently higher pulse pressure[2]. Elevated pulse pressure (PP) is an independent predictor of cardiovascular events[1].

Recent evidence has linked warfarin therapy to arterial calcification, arterial stiffening and systolic hypertension[5,6]. Warfarin causes inhibition of gamma carboxylation of matrix GLA protein, a step necessary for the activation of this vitamin K-dependent protein with important anti-calcifying activity[7]. There is preliminary evidence from cross-sectional studies in humans indicating that chronic exposure to warfarin is associated with increased calcification of the coronary arteries and cardiac valves[8,9]. In order to define the blood pressure effects of warfarin in humans, we performed a post-hoc analysis of "Stroke Prevention in Non-rheumatic Atrial Fibrillation" (SPINAF) study[10]. This study did not reveal any change in BP in patients receiving warfarin for atrial fibrillation. However, subgroup analyses of that study suggested that subjects with diabetes mellitus (DM) or hypertension were at increased risk of developing significant elevations in systolic BP and PP during follow-up. The aim of the present investigation is to expand on the findings of our previous study by analyzing the effects of warfarin on BP parameters in a large cohort of individuals with both DM and hypertension.

METHODS

Design and Subjects

This is a cross sectional study of 159 male veterans aged 50 years or older with DM and hypertension who had received chronic warfarin therapy for at least 2 years, and 159 age-matched control subjects with DM and hypertension who never received warfarin. Due to the strong predominance of males in the Department of Veterans Affairs system, only male patients were enrolled in the study. The Human Investigation Committee of the VA Connecticut Health Care System gave approval for this protocol. Because all data were collected from the VA Connecticut electronic medical records, the committee granted a waiver of informed consent.

We identified patients exposed to warfarin using the log of all enrollees in the outpatient Coumadin clinics at VA Connecticut between January 2000 and December 2002 who had been on continued warfarin treatment and were still alive in July 2005, thus representing at least 2 years of exposure to warfarin. We screened 2202 records, of which 159 subjects fulfilled inclusion criteria.

Control subjects were identified from a VA Connecticut database of patients used for quality improvement initiatives. This database included 2901 patients with DM and hypertension seen in Primary Care clinics between April and June 2005. We sorted the database according to age and matched patients to the warfarin-treated individuals using a 1:1 ratio. For each warfarin subject we selected the first patient with the same age until all warfarin subjects had a matched control. When the selected control was ineligible (see below), the next subject with the same age was chosen.

In order to be included in the study, subjects had to have at least one recorded BP value in the VA Computerized Patient Record System (CPRS) between August 2004 and June July 2005. Subjects were excluded if they were female; had a history of hospitalization during the time of data collection (as the intercurrent illness could have an independent effect on blood pressure); had end-stage renal disease on dialysis or a history of cardiac valve replacement (as these conditions are associated with vascular calcification).

Measurements

The average BP values were obtained over a period of 12 months (August 2004-July 2005). We collected values registered in the CPRS vital signs package and also reviewed the progress note to the visit associated with the BP measurement. If another BP reading was available for the visit, they were averaged. For subjects with four or more available BP readings during the 12-month period, only the last four readings of the period were averaged. These BP readings were obtained during routine clinical care, and given the retrospective nature of this study, were not obtained as part of a research protocol.

We collected relevant information including demographics and biometric data. We reviewed progress notes and laboratory records in the medical record to abstract data focused on existing cardiovascular disease (coronary artery disease, congesting heart failure, cerebrovascular disease, peripheral vascular disease), cardiovascular risk factors (smoking, lipid profile), duration and control of DM (glycohemoglobin), duration of hypertension, and the total number of visits with a recorded BP value during the 12-month period.

The use of antihypertensive medications was recorded according to the Defined Daily Doses (DDD) method based on the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHO-CCDSM: *http://www.whocc.no/atcddd*). In this system, the most common daily dose of an agent is given the value of 1. For the sake of illustration, a DDD value of 1 for some of the most commonly used drugs in our study are: hydrochlorothiazide 25 mg/day, lisinopril 10 mg/day, felodipine 5 mg/

day, and atenolol 75 mg/day. Fractions and multiples are calculated according to this value. The WHO-CCDSM website has up-to-date definitions for all anti-hypertensive drugs in clinical use.

We also collected data on the indication for warfarin use, duration of exposure (in years), and target international normalized ratio (INR), all of which were in the 2.0-3.5 range. Renal function was estimated based on serum creatinine, age and body weight using the Cockcroft-Gault formula[11].

Statistical analysis

Based on our preliminary data, the sample of 318 subjects had a power of 80% (two-tailed alpha 0.05) to detect a 4.4mmHg difference in systolic BP, a 2.5mmHg difference in diastolic BP, and a 3.8mmHg difference in pulse pressure between the two groups.

We used standard statistical methods to compare the two groups. Parametric continuous variables were compared using Student T tests. Non-parametric continuous variables were compared with Mann-Whitney U tests. Dichotomous variables were compared with Chi-square tests with Yates correction for continuity. We evaluated the bivariate relationships between clinical variables and BP parameters using Pearson correlation coefficients for parametric variables and Spearman Rho coefficients for non-parametric variables. Finally, we constructed multiple linear regression models using systolic BP, diastolic BP and PP as dependent variables. We included all variables that tested positive in the bivariate analyses and forced warfarin therapy status (yes or no) in the models. We considered P values <0.05 as statistically significant. We performed all calculations using the SPSS statistical package (SPSS version 11.0.3 for Macintosh, SPSS Inc., Chicago, IL, USA).

RESULTS

Warfarin-treated patients received, per enrollment protocol, at least two years of continuous warfarin treatment (mean 5.5±3.1 years). Indications for warfarin therapy included atrial fibrillation (121 patients, 76 %), recurrent thromboembolic events (16 patients, 9%), stroke (18 patients, 13%), cardiomyopathy or intracardiac thrombus (4 patients, 2 %). The general characteristics of the population are listed in **table 1**. As is readily apparent, this is a population characterized by older age, obesity and a high burden of comorbidity. The warfarin-treated group had a substantially higher prevalence of coronary disease and congestive heart failure.

BP levels, antihypertensive drug use and numbers of visits during the observation period are displayed in **table 2**. The warfarin group had lower systolic BP and PP, possibly explained by the larger number of antihypertensive drugs (both by DDD and absolute numbers) and more frequent visits to their primary care clinicians. A pictorial representation of the BP data is displayed in **figure 1**.

Table 1. General characteristics of the study population

	Warfarin (mean±SD) n=159	**Placebo** (mean±SD) n=159	P value
Age (years)	73.0±10	73.0±10	1
Weight (kg)	99.5±18.1	93.6±18.3	0.004
Body mass index (kg/m^2)	33.0 ±5.8	31.9 ±6.0	0.11
Coronary artery disease	65%	42%	<0.01
Heart failure	27%	6%	<0.01
Cerebrovascular disease	16%	11%	0.25
Peripheral vascular disease	28%	19%	0.12
Current smoking	11%	14%	0.49
Hemoglobin (g/dl)	13.8±1.6	13.6±1.5	0.212
Glycohemoglobin (g/dl)	7.0 ±1.1	7.0 ±1.3	0.63
Cholesterol (mg/dl)	156 ± 32.8	162.1 ± 32.5	0.11
HDL (mg/dl)	41 ±12	43 ± 11	0.03
LDL (mg/dl)	80 ± 24	84 ± 27	0.19
Triglyceride (mg/dl)	177.8 ± 98.5	193.9 ± 272	0.50
Creatinine clearance	78 ± 32	77 ± 35	0.79

Table 2. Blood pressure parameters, antihypertensive drug use, and blood pressure-related visits.

	Warfarin (mean±SD) n=159	**Placebo** (mean±SD) n=159	P value
Systolic BP (mm Hg)	130±14	134 ±12	0.003
Diastolic BP (mm Hg)	71.6 ± 7.8	72.0 ± 7.0	0.64
Mean arterial pressure (mm Hg)	91 ±8.4	93 ± 7.1	0.058
Pulse pressure (mm Hg)	58 ± 12	62 ± 11	0.004
Number of visits per year	5.2 ± 4	3.5±3	<0.0001
Drug DDD	4.1 ± 2.8	3.2 ± 3.6	0.0002
Number of antihypertensive medications	2.8 ±1.1	2.33 ± 1.2	0.001

BP = blood pressure.

Blood pressure-related visits refer to visits where BP was measured in the 12 months of inquiry.

DDD = defined daily doses based on the World Health Organization Collaborating Centre for Drug Statistics Methodology (see text for details).

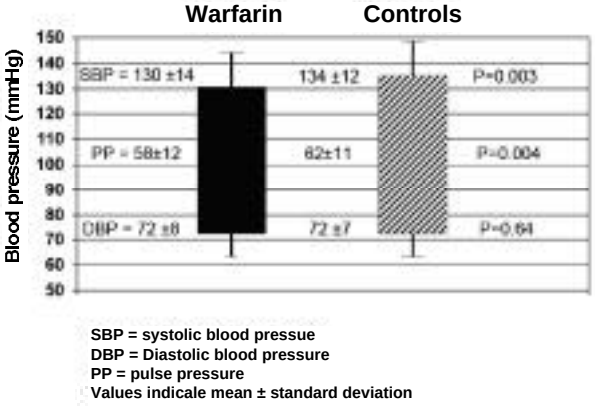

Figure 1. Blood pressure differences between warfarin-treated patients and controls.

A history of heart failure (r=-0.15, P<0.01) and the number of clinic visits (r=-0.16, P<0.01) were significant correlates of systolic BP. Diastolic BP was correlated with age (r=-0.25, P<0.01), body mass index (r=0.12, P<0.05), history of coronary artery disease (r=-0.13, P<0.05) or peripheral vascular disease (r=-0.22, P<0.01), creatinine clearance (r=0.24, P<0.01), hemoglobin concentration (r=0.3, P<0.01), total cholesterol (r=0.15, P<0.01) and LDL-cholesterol (r=0.16, P<0.01). Pulse pressure correlated with age (r=0.29, P<0.01), history of heart failure (r=-0.12, P<0.05), hemoglobin concentration (r=-0.18, P<0.01), and number of clinic visits (r=-0.14, P<0.05). The multivariate analysis models are summarized in **table 3**. They demonstrated that systolic BP was negatively associated with a history of heart failure or being in the warfarin group. Diastolic BP was positively associated with hemoglobin concentration, and negatively associated with age or a history of peripheral vascular disease. Finally, PP was positively associated with age, and negatively associated with exposure to warfarin. As indicated by the low R^2 values for each model, the impact of measured variables on BP was modest at best, implicating other unmeasured variables as important determinants of BP parameters.

We had a specific interest in exploring the interaction between a diagnosis of heart failure and BP parameters. This was important because heart failure is known to decrease systolic BP and PP, and its overrepresentation in the warfarin group could be responsible for part of our observations. Fifty-one subjects in the warfarin group had a history of heart failure and were excluded. Their matched controls were excluded as well, leaving 108 subjects in each group for analysis. The profile of the differences in BP parameters was essentially the same as in the entire group (systolic BP: 131±13 mmHg warfarin vs. 135±12 mmHg control, P=0.04; diastolic BP: 72±8 mmHg warfarin vs. 72±7 mmHg control, P=0.71; and pulse pressure: 59±11 mmHg warfarin vs. 63±12 mmHg control, P=0.01).

DISCUSSION

Our results show that long-term (average 5.5 years) warfarin therapy in older men with diabetes mellitus and hypertension did not result in higher BP or PP. In fact, warfarin therapy was associated with lower systolic BP and PP. These observations were independent of many other relevant covariates, including the presence of heart failure. However, the intensity of antihypertensive drug therapy and number of outpatient visits was higher in warfarin-treated patients than controls, perhaps accounting for part of the results.

Our initial hypothesis of a hypertensive effect of warfarin was based on both laboratory and preliminary clinical evidence, as warfarin is a cause of vascular calcification and arterial stiffness. Mechanisms underlying the effects of warfarin on the arterial wall are related to extracellular matrix (ECM) calcification, a process that is regulated by a number of factors. One such factor is matrix Gla protein (MGP) which, when absent in the MGP knock-out mouse, results in severe arterial calcification and death due to aortic rupture[7]. MGP is a 10kDa protein secreted by vascular smooth muscle cells, macrophages and chondrocytes. Activation of MGP

Table 3. Summary table for multiple regression analysis

Dependent variable	Independent variables	β	P
Systolic blood pressure			
R^2 = 0.04	Heart failure No = 0 Yes = 1	-0.13	0.031
	Group Warfarin = 0 Control = 1	0.12	0.035
Diastolic blood pressure	Age (years)	-0.25	<0.0001
R^2 = 0.21	Hemoglobin (g/dl)	0.28	<0.0001
	Peripheral vascular disease No = 0 Yes = 1	-0.22	<0.0001
Pulse pressure	Age (years)	0.28	<0.0001
R^2 = 0.10	Group Warfarin = 0 Control = 1	0.14	0.027

β = standardized regression coefficients

involves gamma carboxylation of five glutamate residues to form calcium-binding Gla residues, a process that is vitamin K-dependent. In presence of warfarin, MGP remains inactive favoring calcification of ECM, especially vascular smooth muscle in larger vessels[6]. These pro-calcifying effects have been corroborated by several laboratories[5,12,13], and were further translated into hypertensive effects by Essalihi et al, who established that treatment of Wistar rats with warfarin resulted in a phenotype of increased aortic calcification, aortic collagen-to-elastin ratio, aortic stiffness (measured by pulse wave velocity), and isolated systolic hypertension[5].

In humans, early data have pointed in the same direction as animal studies. Schurgers et al found more than a two-fold increase in calcium content in aortic valves removed from patients who had previously received warfarin compared with patients who had never received warfarin[9]. Likewise, Koos et al recently reported increased coronary calcification (by multislice spiral computer tomography) in patients treated with warfarin for at least six months compared with controls[8]. These studies did not report on BP or arterial function. In that sense, our analysis of SPINAF was the first report on the impact of warfarin on BP[10]. In that randomized, placebo-controlled clinical trial involving 525 patients with atrial fibrillation, warfarin did not result in increased BP in the overall group analysis. However, subgroup analyses indicated that subjects with DM, hypertension, or uncontrolled BP were at increased risk of developing significant elevations in systolic BP and PP during follow-up. We hypothesized that a scenario of increased vascular risk factors leads to an amplification of the potential effects of warfarin on vascular calcification and arterial compliance.

The present study sought to further the observations suggested by the SPINAF sub-analysis in a larger group of patients. However, our findings are in contrast to SPINAF. Several possibilities may explain the different results. First, it is possible that the older age of our patients may have obscured the effects of warfarin on BP. Price et al demonstrated that older rats (42 days old) were found to have less calcification than younger animals (20 days old), and 10-month old rats did not have any evidence of warfarin-induced calcification in the carotid artery or aortic heart valves[14]. However, the average age of subjects in the Schurgers' and Koos' studies was 73 and 71 years, respectively[8,9]. Therefore, it is not clear that age is a relevant factor in humans, at least for calcification. Since we did not have an objective measure of arterial calcification or stiffness, we cannot conclude that warfarin does not cause vascular calcification leading to arterial stiffening in humans, but apparently, this does not readily translate into worse systolic BP or PP.

Another possibility is that MGP might not be important in calcification of human arterial system as compared to rats. Patients with Keutel syndrome who lack MGP have extensive cartilaginous calcification but their vascular tree is not severely affected and these patients do not develop hypertension[15]. However, long-term follow-up of a patient with Keutel syndrome did reveal extensive calcification of coronary, hepatic, renal and cerebral arteries, but unfortunately there was no mention of the aorta or its major branches[16]. The precise role of MGP in humans remains to be further defined.

Dose may also have affected the results. Rat studies use a larger dose as compared to humans. Also, our study included predominantly elderly white males, thus we cannot generalize our results to other populations. Mineral metabolism is regulated by multiple factors that include the levels of calcium, phosphorous and vitamin D. We could not look at these factors, as data were not available for the entire population. In addition, we did not exclude anyone based on the medical history significant for musculoskeletal illness e.g. Paget's disease and secondary hyperparathyroidism that have been known to affect soft tissue calcification.

The large sample size is the strongest asset of this study. Its most important limitation is its cross-sectional nature. Our study subjects were not followed longitudinally for trends in BP and PP, therefore, it is possible that they may reached lower BP levels by virtue of receiving more intensive antihypertensive therapy, as suggested by our observations of a larger number of antihypertensive drugs prescribed to patients in the warfarin group. However, the present observations dampen the impetus generated by the SPINAF analysis.

CONCLUSION

Although there is strong evidence to support the role of warfarin in ECM calcification especially in vascular smooth muscle leading to increase in BP in rat models, we were not able to show the same effect in humans with diabetes mellitus and hypertension.

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