

ORIGINAL ARTICLE

Proportion of isolated clinical hypertension in primary care settings. Comparison of target organ damage in patients with isolated clinical hypertension and patients with sustained arterial hypertension

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Abstract

The aim of this study was to determine the proportion of isolated clinical hypertension (ICH) in newly diagnosed hypertensive patients, and to compare the incidence of target organ damage (TOD) in ICH and sustained hypertension patients. *Participants.* In a multi-centre study involving 14 primary care centres in Girona, Spain, 140 researchers recruited 214 newly diagnosed hypertensive patients 15–75 years of age, without history of cardiovascular events. *Period of study.* 2004–6. *Method.* Self-blood pressure monitoring (SBPM) and ambulatory blood pressure monitoring (ABPM). *Evaluation.* Anamnesis including blood pressure, physical examination and analysis (creatinine, albumin/creatinine index), electrocardiogram (left ventricular hypertrophy) and retinography (fundus damage). *Results.* In 129 (60.3%) subjects with sustained hypertension and 85 (39.7%) with ICH, no significant differences were found relative to gender, age, body mass index or blood pressure (155/90 vs 154/90 mmHg, respectively). Cholesterol levels were significant differences between both groups (5.97 mmol/l in sustained hypertension vs 5.64 mmol/l in ICH, $p=0.029$). The proportion of ICH was approximately 40%. TOD incidence in sustained hypertensives was similar to that of ICH patients.

Key Words: Ambulatory blood pressure monitoring, isolated clinical hypertension, self-blood pressure monitoring, target organ damage

Introduction

Isolated clinical hypertension (ICH) is defined as a persistently elevated average office blood pressure values ($>140/90$ mmHg) and normal readings for ambulatory pressure outside the centre ($<135/85$ mmHg) (1). The proportion of ICH is 10% in the general population (2).

The impact of ICH is still debated in the literature. In some studies, cardiovascular risk for ICH patients seems to be lower than for those with sustained hypertension (3); more recent studies suggest a higher

cardiovascular risk than for normotensives (4). In particular, the incidence of ictus tends to increase over time in the group with ICH (5).

Few studies have evaluated the incidence of ICH and target organ damage (TOD), one of the cardiovascular risk markers in hypertensive patients, in Spain (6).

This research aims to determine the proportion of ICH as documented by self-blood pressure monitoring (SBPM) in primary care settings and to compare the incidence of TOD in ICH and sustained hypertension patients.

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Materials and methods

This work is part of a validation study on SBPM in isolated clinical hypertension (VAMPAHICA study). The details of the study have been published previously (7).

Study population

VAMPAHICA is a prospective registry of patients with sustained hypertension, those with ICH and normotensives. This multi-centre study involved 14 primary care centres of the Girona Health Region (Catalonia). A total of 140 researchers (doctors and nurses) participated in data collection between September 2004 and March 2006.

Inclusion and exclusion criteria

Patients between the ages of 15 and 75 with clinical hypertension (at least two blood pressure readings taken at 2-min intervals on 3 consecutive days, with average $\geq 140/90$ mmHg) were included in the study. All subjects were newly diagnosed and had not received any antihypertensive treatment.

Exclusion criteria were: (i) patent inability to perform SBPM, in the opinion of the health professional; (ii) diabetes mellitus; (iii) secondary hypertension; (iv) prior cardiovascular disease; (v) renal or hepatic insufficiency; (vi) alcoholism or serious psychological illness; (vii) serious endocrine or haematological illness or other illnesses or limitations that the doctor considered a motive for exclusion; and (viii) lack of patient consent.

Monitoring

Multiple monitoring techniques were implemented for all participants. Nurses conducted an initial blood pressure measurement using Omron 705 CP or Omron 705 IT monitors with a cuff bladder adapted to the circumference of each patient's arm. International standard protocols were followed and all devices were calibrated annually. Following 5 min of rest in a sitting position, two readings were taken at intervals of 2 min. If the difference between readings on the same day was >5 mmHg, an additional measurement was required. The recorded blood pressure value was the mean of all the measurements taken for each subject.

SBPM was then performed by all participants over 3 consecutive working days. Each patient was instructed by a nurse and given an instructional leaflet on correct procedure. Using a bladder cuff adapted to the circumference of the arm, the

following measurements were taken each day: two in the morning before breakfast and two at night before dinner. The patient was instructed to rest for 5 min prior to the first measurement and 2 min prior to the second, noting the measurements on a form provided for this purpose. The first day's readings were not included in calculating the mean. All SBPM measurements were made with Omron 705 CP and Omron 705 IT monitors.

Ambulatory blood pressure monitoring (ABPM) using a Spacelab 90217 monitor was carried out on all patients included in the study. Each participant was instructed on the use of the device by an experienced nurse, who also adjusted the bladder cuff to the patient's arm circumference. Standard methodology was used; automatic measurements were taken every 20 min during the daytime (08.00–23.00 h) and every 30 min during the night (23.00–08.00 h).

Evaluation of subjects

All patients included in the study were given an initial evaluation involving hypertension history, physical examination, blood analysis, electrocardiogram and retinal imaging. The retinal camera used was a non-mydratic colour digital camera (Canon CR6-45NM, EOS D30 camera). Retinal images were interpreted by an experienced doctor who did not know the patient's personal details. To detect renal lesions, the albumin/creatinine ratio was determined in the first urine sample in the morning and, where positive, the presence of leucocytes, erythrocytes or nitrites was ruled out using a reactive strip. Once the reactive strip anomaly had been studied and treated, it was tested again 2 weeks later. If at least two of three tests were positive, a renal lesion was diagnosed. The presence of ischaemia, arrhythmia and left ventricular hypertrophy was determined from the electrocardiogram.

Definitions and measurement methods of the main variables

ICH was defined by blood pressure values $\geq 140/90$ mmHg in the centre and a normal SBPM ($< 135/85$).

Clinical variables included age, gender, weight, height, body mass index, clinic blood pressure, SBPM, ABPM, family and personal history, and hypertension history.

TOD variables were serum creatinine (women > 107 $\mu\text{mol/l}$, men > 115 $\mu\text{mol/l}$), left ventricular hypertrophy (electrocardiography criteria per Cornell, modified by Dalfó (8), and/or Sokolow–Lyon criteria), microalbuminuria

(women ≥ 3.5 mg/mmol in women, men ≥ 2.5 mg/mmol per 2003 guidelines of the European Society of Hypertension/European Society of Cardiology) (2), and retinal lesions following Dodson's classification (9). Renal function alteration was also calculated, using the Cockcroft and Levey formulae, and expressed as a glomerular filtrate < 60 ml/min.

All patients or their legal representatives were asked to give informed consent. The study was approved by the Ethics Committee of the Girona Institute of Healthcare (Spain).

Statistical analysis

A thorough descriptive analysis of all the hypertensive patients included in the study was carried out (Table I). These patients were stratified as hypertensives with sustained hypertension and ICH (Table II). In the latter case, several cut-off points

were also considered in the definition of ICH (Table III).

Measurements of continuous variables in patient groups with sustained hypertension and ICH (at different cut-off points) were compared using Student's *t*-test for mean difference in independent samples. In accordance with the results obtained by applying Levene's test equality of variances and Snedecor's *F* distribution, we assumed either equal or different variances in each group.

The proportion of subjects with sustained hypertension and ICH (also at different cut-off points) was compared using a non-parametric test for proportion differences, distributed as a chi-square test.

Results

Overall, 214 patients with definite hypertension were included: 129 (60.3%) with sustained hypertension

Table I. Hypertensive patients included in the study. Patients with sustained arterial hypertension and isolated clinical hypertension (cut-off point 135/85 mmHg).

	Sustained hypertension	Isolated clinical hypertension	<i>p</i> -value
<i>n</i>	129	85	
Men	53.5%	61.2%	0.26
Age, years	58.6 (9.9)	56.4 (14.2)	0.19
Weight, kg	77.2 (17.0)	77.7 (15.4)	0.81
Height, cm	162 (22)	163 (20)	0.78
Body mass index	28.4 (5.51)	28.5 (5.05)	0.85
Tobacco	13.2%	18.8%	0.26
Alcohol	17.1%	25.9%	0.11
Physical activity	23.3%	27.1%	0.52
Total cholesterol, mmol/l	5.97 (1.02)	5.64 (1.00)	0.029
HDL, mmol/l	1.68 (0.68)	1.82 (1.52)	0.36
LDL, mmol/l	3.77 (0.87)	3.47 (0.79)	0.021
Creatinine, μ mol/l	83.98 (17.68)	78.67 (15.02)	0.039
Clinic blood pressure systolic, mmHg	155 (9)	154 (10)	0.70
Clinic blood pressure diastolic, mmHg	90 (8)	90 (9)	0.91
SBPM systolic, mmHg	148 (11)	131 (12)	<0.001
SBPM diastolic, mmHg	89 (9)	78 (10)	<0.001
SBPM heart rate	74 (9)	69 (11)	0.001
ABPM day systolic, mmHg	141 (12)	132 (11)	0.009
ABPM day diastolic, mmHg	90 (10)	85 (8)	0.06
ABPM 24h systolic, mmHg	136 (12)	129 (11)	0.035
ABPM 24h diastolic, mmHg	85 (8)	80 (8)	0.026
Left ventricular hypertrophy	26%	25.9%	0.93
Microalbuminuria, mg/mmol	0.58 (1.09)	0.57 (1)	0.95
Abnormal microalbuminuria ^a	3.1%	2.4%	0.74
GF Cockcroft–Gault, ml/min	112.9	102.1	0.48
GF Levey, ml/min	106.4	91.1	0.36
Eye fundus I/II	62.8%	44.7%	0.009
Eye fundus III/IV/V	14%	8.2%	0.20
Eye fundus, some lesion	67.4%	48.2%	0.005

Mean and (standard deviation) unless stated otherwise. In bold, statistically significant at 95%. ^aNormal values: < 2.5 mg/mmol in men and < 3.5 mg/mmol in women. HDL, high-density lipoproteins; LDL, low-density lipoproteins; SBPM, self-blood pressure monitoring; ABPM, ambulatory blood pressure monitoring; GF, glomerular filtrate.

Table II. Distribution of cardiovascular risk in hypertensives with sustained arterial hypertension and those with isolated clinic hypertension

		Points	Sustained arterial hypertension	Isolated clinical hypertension	p-value
Tables of cardiovascular risk	SCORE ^a	2	0%	49.3%	0.532
		3	100%	50.7%	
	Framingham-REGICOR ^b	4	36.6%	100%	0.089
		6	63.4%	0%	

^aSCORE, 10-year risk of fatal cardiovascular disease populations at low cardiovascular risk by gender, age, systolic blood pressure, total cholesterol and smoking status (10) 2%: ■ 3–4%: ■ ^bCalibrated Framingham function for Catalan population (Girona Heart Register, Registre Gironí del Cor: REGICOR), 10-year risk of coronary heart disease by gender, age, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol and smoking status (11): <5%: ■ 5–9%: ■

and 85 (39.7%) with ICH. The baseline characteristics of all subjects (sustained hypertension and ICH) are shown according to hypertension type in Table I.

No significant differences between the two groups can be observed with regards to gender, age and body mass index.

Systolic and diastolic clinic blood pressure in the group with sustained hypertension was similar to that of the group with ICH. The incidence of left ventricular hypertrophy and microalbuminuria was similar in both groups.

SBPM values were significantly higher in the group with sustained hypertension. Eye fundus lesions at all stages were more frequent in patients with sustained hypertension, although only stage I/II and the presence of some lesion were of statistical significance (Table I). Renal function determined by creatinine showed a discrete but significant increase in patients with sustained hypertension. However, the values obtained for glomerular filtrate using the Cockcroft–Gault and Levey formulae did not show any significant differences. The 10-year cardiovascular risk in patients with sustained hypertension and patients with ICH was estimated using SCORE (10) and Framingham–REGICOR tables (11). Although patients with ICH show less risk potential than those with sustained hypertension, the differences are not statistically significant (Table II).

Table III shows the results of the different variables (gender, age, body mass index, left ventricular hypertrophy, microalbuminuria and eye fundus lesions) for different cut-off points in the definition of ICH. It can be observed that TOD decreased in frequency at the lowest threshold values; however, the change is not statistically significant. In all cases, the least risk is observed with values below the currently established norm (135/85).

Discussion

Our results show that the proportion of ICH in the study population is approximately 40%. Incidence of TOD is similar in patients with sustained hypertension and those with ICH.

The proportion of ICH reported by other researchers varies by methodology used. International data from 24 studies performed with ABPM – in which most patients had stage I hypertension (140–159/90–99 mmHg) – showed results from 10% to 50% (12). Verdecchia et al. found 33% in those with stage I hypertension, 11% at stage II and 3% at stage III (13). A recent study found a proportion of 19.4% through SBPM (14). Non-population studies in Spain using ABPM yield a variable proportion of ICH, between 33% and 46%. Torres Jiménez et al. obtained a finding of 20.1% ICH using SBPM (15). Finally, a study published this year and performed with SBPM found ICH in 3.6% of the sample and 12.8% of individual subjects with hypertension in the general population (6).

The two groups in our study did not present significant differences with regard to gender, age, body mass index, smoking habits, alcohol consumption and physical exercise. Other studies point out that patients with ICH are predominantly older women who do not smoke and have lower clinic blood pressure (16,17). Our study found a significant difference in cholesterol levels (5.97 mmol/l in sustained hypertension vs 5.64 mmol/l in ICH, $p=0.029$). This finding concurs with a study that reported higher cholesterol and body mass index in sustained hypertensive patients, compared with “white-coat hypertensives” (18), although our work and others failed to find differences in body mass index (19).

SBPM is a technique that offers a higher correlation with TOD (left ventricular hypertrophy by echocardiogram and electrocardiography, microalbuminuria, intima-media thickness and alterations

Table III. Target organ damage and other characteristics at various cut-off points for isolated clinical hypertension (ICH) and sustained arterial hypertension.

	130/85 mmHg			130/80 mmHg			125/80 mmHg		
	Sustained hypertension	ICH	<i>p</i> -value	Sustained hypertension	ICH	<i>p</i> -value	Sustained hypertension	ICH	<i>p</i> -value
N	142	72		153	61		167	47	
Men	56.3%	56.9%	0.933	56.2%	57.4%	0.876	56.9%	26(55.3)	0.848
Age, years (SD ^a)	58.4 (9.9)	56.30(14.9)	0.293	58.4 (10.1)	56 (15.4)	0.201	58.1 (10.1)	56.1(16.7)	0.454
Body mass index (SD)	28.5 (5.3)	28.5(5.4)	0.761	28.4 (5.3)	28.5 (5.5)	0.928	28.5 (5.1)	28.4 (6.1)	0.931
Left ventricular hypertrophy	25.4%	27.8%	0.703	25.5%	17.0(27.9)	0.721	26.3%	25.5%	0.911
Abnormal microalbuminuria ^b	2.8%	2.8%	0.977	2.6%	3.3%	0.790	3.0%	2.1%	0.751
Eye fundus I/II	61.3%	44.4%	0.019	60.1%	44.3%	0.035	59.9%	40.4%	0.018
Eye fundus III/IV	12.7%	9.7%	0.525	13.7%	6.6%	0.141	13.2%	6.4%	0.200
Eye fundus, some lesion	65.5%	49.6%	0.017	64.7%	47.5%	0.021	64.1%	44.7%	0.017

In bold, statistically significant at 95%. ^aSD, standard deviation. ^bNormal values: <2.5 mg/mmol in men and <3.5 mg/mmol in women.

in the eye fundus) than clinic BP (20–22). However, there are no studies associating ICH diagnosis by SBPM with TOD, since all studies use ABPM. In our study, there is no relationship between ICH and microalbuminuria; neither in left ventricular hypertrophy nor in advanced retinal lesions, although in both there is a non-statistically significant tendency to a higher frequency in the sustained hypertension group. These results are similar to those of a Spanish group, which, using ABPM values as a definition of ICH, did not find significant differences in the presence of left ventricular hypertrophy and damage in the eye fundus (23). Where differences were observed was in stage I/II eye fundus lesions: patients with sustained hypertension showed more lesions of this type (62.8% vs 44.7%; $p=0.009$), and also in the presence of some eye fundus lesion (67.4% and 48.2% respectively; $p=0.005$). Although only advanced retinopathy lesions are considered associated clinical conditions when stratifying cardiovascular risk (2), it is known that alterations in the artery–vein ratio indicates a high cardiovascular risk (24) and the artery–vein crossings have a high predictive value for evaluating the risk of ictus (25).

Incidence of TOD varies by study. For example, our study shows incidence of left ventricular hypertrophy (by electrocardiogram) at 26% and of retinopathy I/II at 54.4%. Others have found the incidence of the incidence of hypertrophy (by echocardiography) at 14% and moderate retinopathy (stages I/II) to be within the range of 42.4–55% (26,27). It is interesting to highlight the high occurrence of advanced lesions (exudations and haemorrhages) in the eye fundus (10.8%) among our subjects, which coincides with a recent review of

the literature (24). The presence of these lesions represents a large increase in cardiovascular risk (25), and provides decisive information needed to start pharmacological treatment and hypertensive control, independent of ICH. It is essential to carry out an initial assessment of all hypertensives, with or without ICH, since the presence of TOD is high in either case (35.3% in ICH hypertensives vs 40.3% hypertensives with sustained hypertension, $p=0.460$). In particular, we must insist on examining the eye fundus to identify patients with high cardiovascular risk, as the presence of advanced retinopathy is high in both groups (8.2% in ICH hypertensives and 14% in those with sustained hypertension).

The similarity in the incidence of TOD between patients with sustained hypertension and those with ICH can be attributed to the fact that ICH may not be as benign as it has been considered until now. Indeed, the current definition of ICH may not adequately determine a patient's hypertensive status.

Blood pressure cut-off points to define ICH by means of SBPM have been discussed (28,29). However, even with lower cut-offs (Table III), TOD still exists; it is possible that this may be the same incidence of these lesions that would be found in the non-hypertensive general population.

On the basis of the available evidence, some authors propose adopting a therapeutic strategy in patients with ICH, based on changes in lifestyle in those stratified as low risk, with correctly defined ICH, absence of co-morbid conditions and TOD, and the potential for satisfactory monitoring (30). There is still not enough evidence for the use of hypotensive medication in patients with ICH in the absence of co-morbid conditions and/or TOD (31,32).

In all hypertensive patients (especially those with ICH), the presence of TOD must be ascertained through the most accessible and efficient means. It must be pointed out that the mere presence of TOD makes it absolutely necessary to start antihypertensive treatment, independent of criteria for ICH or sustained hypertension (33). In this respect, it can be affirmed that the SBPM and ABPM are useful in monitoring the hypertensive with ICH and other forms of hypertension (34). Determination of TOD and ICH status are essential to clinical decisions regarding this type of patient. Patients with persistently high ambulatory blood pressure levels – independent of subsequent confirmation of ICH – must be assessed as thoroughly as possible to detect the presence of TOD. It is crucial to examine and monitor patients with ICH, since this appears to be a transition to established hypertension (35,36).

In our study, recruitment was strictly consecutive and included newly diagnosed ICH patients with no personal history of cardiovascular disease. Most studies use ABPM as defining values for ICH; our study was based on SBPM criteria, which are still not sufficiently validated for the diagnosis of ICH. Some authors have even advised against using SBPM (37–40). This methodology could partially account for the discrepancies found. Our study was conducted in primary care centres and is not a population study. However, it must be borne in mind that the populations studied belong mainly to semi-urban areas where the majority of the population receives healthcare in these public centres. Finally, we must mention that the exclusion of diabetes patients to avoid interferences in interpreting retinal lesions undoubtedly influenced the results.

We conclude that almost half the cases of newly diagnosed hypertension patients were identified in primary health care as ICH, based on self-monitoring of blood pressure. TOD was found to be similar to that of patients with sustained hypertension, although the results might have been different if more sensitive techniques had been used for detecting TOD.

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