Vascular Health and Risk Management

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ORIGINAL RESEARCH

Should we screen for masked hypertension in patient with vascular disease?

This article was published in the following Dove Press journal:
Vascular Health and Risk Management
7 May 2010
Number of times this article has been viewed

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Background: The influence of hypertension on cardiovascular risk is well known. Ambulatory blood pressure measurement (ABPM) is able to identify patients with masked hypertension (MH) underdetected by clinical BP measurement. The benefit of screening for MH in a high-risk population was investigated.

Aims: To detect MH in a population with no prior history of hypertension and medically treated for peripheral or coronary arterial disease.

Methods: Thirty-eight consecutive patients with peripheral or coronary artery disease documented with arteriography, without a history of hypertension, and with an admission BP $<$ 140/90 mmHg underwent ABPM after discharge. Ambulatory BP $\geq$ 125/80 mmHg were defined as MH.

Results: MH was found in 11 patients (28.9%). The MH group had a mean systolic and diastolic hospitalization BP significantly higher (127 versus 115 mmHg, respectively, $P = 0.002$ and 76 versus 66 mmHg, $P = 0.01$), and tended to have a higher admission systolic BP and pulse pressure (127 versus 121 mmHg, respectively, $P = 0.07$; and 54 versus 46 mmHg, $P = 0.06$). The first BP measurement on the 24-hour ABPM was significantly higher in the MH group 140 versus 121 mmHg, $P = 0.001$, for systolic BP and 84 versus 74 mmHg, $P = 0.03$, for diastolic BP.

Conclusions: MH was found in patients with documented and medically treated vascular disease. BP in the prehypertensive range is associated with MH. Systematic screening for MH in this high-risk population requires further investigation.

Keywords: blood pressure, monitoring, masked hypertension, vascular disease

Background

Arterial hypertension is a well documented risk factor in the cardiovascular disease continuum.[1] Its diagnosis has traditionally relied on clinical blood pressure (BP) measurement, but ambulatory BP monitoring (ABPM) offers a new method of identifying hypertensive disease and managing its consequences.

In addition to normotensive and "classically hypertensive" patients, it is now possible to distinguish between patients suffering from "white coat" hypertension and those with masked hypertension (MH). The definition of MH is BP values within normal limits on clinical examination which are increased during ABPM. Diagnosis of MH therefore relies on ABPM, which explains why a large portion of the population with MH is undiagnosed. MH has been recognized to have adverse consequences for patient prognosis in terms of cardiovascular morbidity, as well as target organ damage. Its prevalence varies widely depending on sources or method of BP measurement (ABPM or self-measurement) but the outcome of MH is important in that it concerns

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a large variety of patients, ranging from children to elderly patients, who are often already on treatment.[2,3]

Recent studies have shown that approximately 80% of patients suffering from vascular disease whether coronary, cerebral, or peripheral, have hypertension,[4] and lowering of arterial BP favorably influences the prognosis, especially in patients with coronary lesions and those with a history of stroke.[5,6]

Recommendations for management of vascular patients emphasize the importance of testing and treatment for hypertension.[7] However, the methods that should be used to test for it have not been well outlined, and ABPM has not yet been included in the recommendations.

The use of ACE inhibition in patients with vascular disease has been validated by many studies showing its long term benefits for patient prognosis regardless of BP values,[8,9] and prescription of ACE inhibitors has become routine in vascular patients, even in those not diagnosed with hypertension.

To date there are very little data available on MH, and it seems likely that mass screening will never be possible. However, it would be useful to determine risk factors which would raise suspicion of MH and thereby identify patients who would benefit from systematic testing. The purpose of this study was to confirm MH in patients with atherothrombotic vascular disease who are already on treatment, and to identify their risk factors.

Methods

Study population

We recruited patients from two wards of the Lille University Hospital Center from September 2007 to July 2008. These patients were scheduled for coronary angiography or lower limb angiography. Inclusion criteria were systolic BP (SBP) $<$ 140 mmHg, diastolic BP (DBP) $<$ 90 mmHg, and at least one proven vascular atherothrombotic site (defined as a stenosis $\geq$ 50%). Forty-one patients gave verbal consent for ABPM testing. Due to false positive results on noninvasive ischemic testing, three patients were found to be free of atherothrombotic lesions and were therefore excluded. The 38 remaining patients were included in the study.

Arterial blood pressure measurement

Arterial BP was measured after at least 10 minutes of rest using a cuff adapted to patient size and a manual manometer. Mean BP and heart rate (HR) over the period of hospitalization was calculated using seven measurements for each patient collected by nurses using the electronic Datascope Acutor Plus device.

The participants underwent ABPM during usual everyday activity a week later while still being treated, using a Spacelab Medical 90207 monitoring device, which recorded BP every 15 minutes over a 24-hour period divided into daytime (from 6 am to 10 pm) and nighttime (from 10 pm to 6 am).

Patients were then divided into two categories, ie, normotensive patients with SBP and DBP at admission $<$140 and $<$90 mmHg, respectively, as well as 24-hour ambulatory mean SBP $<$ 125 mmHg and DBP $<$ 80 mmHg, and MH patients with normal BP at admission but with 24-hour ambulatory mean SBP $>$ 125 and DBP $>$ 80 mmHg. This definition of MH is based on the European Society of Hypertension and European Society of Cardiology guidelines. This low BP level has already been used in a prospective, large-scale study using ABPM in patients who had never been previously treated with antihypertensive medication.[10]

The only antihypertensive drugs used in this patient population with stable vascular disease were renin-angiotensin inhibitors. Patients with a prior history of myocardial infarction or left ventricular ejection fraction $<$55% were excluded because they required beta-blockade therapy that could have influenced the study results.

Statistical analysis

SPSS software (SPSS, Chicago, IL) was used for statistical analysis. For the descriptive analysis, we extracted the median and frequency of each parameter for the two groups. The population of each group being under 30 patients, we chose a bivariate analysis with nonparametric testing. Quantitative testing relied on comparison of means using the Mann–Whitney U test. Qualitative comparison of means was done using the Chi-squared test or Fisher's exact test. Statistical significance was determined at $P < 0.05$.

Results

The prevalence of MH in our study population was 28.9% (Table 1). Of the 38 participants, 22 underwent lower limb angiography and the other 16 underwent coronary angiography. Four patients suffered from stable coronary disease diagnosed by coronary angiography during a previous hospitalization. No statistical differences between the masked hypertensive and normotensive groups were found for age, sex, or cardiovascular risk factors, nor were there any discernable differences in terms of treatment or biologic parameters.

Table 1 Population characteristics, and clinical and biologic data at hospital admission

Clinical and biologic data	Normotensive group (n = 27)	Masked hypertensive group (n = 11)	P
Age (years, n)	55 ± 1.9	49 ± 2.8	0.43
Male gender (n)	24	9	0.45
Cardiovascular family history (n)	10	3	0.43
Coronary disease (n)	17	3	0.05
Peripheral artery disease (n)	6	3	0.28
COPD (n)	5	0	0.16
Current smoker (n)	18	7	0.57
Dyslipidemia (n)	17	3	0.05
Diabetes mellitus (n)	3	2	0.45
BMI (kg/m²)	26.3 ± 1.5	25 ± 0.9	0.38
Treatment before admission			
ACE inhibitor (n)	15	5	0.42
Statin (n)	20	5	0.96
Antiplatelet therapy (n)	24	8	0.22
Biologic data			
Creatinine (mg/L)	9 ± 0.3	9 ± 0.5	0.78
GF Cockcroft (mL/min)	103.6 ± 6.9	94.1 ± 8.6	0.49
GF MDRD (mL/min)	95.9 ± 4.2	88.7 ± 11.7	0.63
HDL (g/L)	0.45 ± 0.02	0.46 ± 0.03	0.64
LDL (g/L)	0.99 ± 0.08	1.12 ± 0.07	0.58
Triglyceridemia (g/L)	1.18 ± 0.2	1.51 ± 0.4	0.29

Note: Values represent mean ± standard deviation.
Abbreviations: COPD, chronic obstructive pulmonary disease; BMI, body mass index; ACE, angiotensin converting enzyme; GF, glomerular filtrate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MDRD, modification of diet in renal disease.

BP at admission versus ABPM

We noticed a difference, albeit not statistically significant, in BP between the two groups on admission (Table 2) and on ABPM (Table 3). MH patients seemed to have a higher mean SBP ($P = 0.02$) as well as a higher mean DBP ($P = 0.01$).

The first measurement carried out by the ABPM device in the presence of a nurse is considered a clinical BP measurement and showed higher SBP ($P = 0.01$) and DBP ($P = 0.03$) in MH patients. We found the same significant difference while studying daytime SBP and DBP ($P < 0.01$ and $P = 0.009$, respectively) as well as nighttime SBP and DBP ($P = 0.001$ and $P = 0.03$).

The same classes of antihypertensive treatment were utilized in both groups of patients during ABPM periods. SBP and DBP were once again found to be significantly higher in MH patients both during daytime ($P < 0.001$ and $P = 0.009$, respectively) and nighttime measurements ($P = 0.001$ and $P = 0.03$).

Table 2 Inhospital data

Inhospital	Normotensive group (n = 27)	Masked hypertensive group (n = 11)	P
Admission			
SBP (mmHg)	121 ± 1.9	127.5 ± 2.7	0.07
DBP (mmHg)	73 ± 1.5	78 ± 2.6	0.26
HR (beats per minute)	68 ± 2.8	76.5 ± 4.1	0.19
PP (mmHg)	47 ± 1.1	51 ± 2.9	0.52
Inhospital stay			
Mean SBP (mmHg)	115.8 ± 1.6	127.2 ± 1.3	0.002
Mean DBP (mmHg)	66.6 ± 1.0	76.1 ± 2.6	0.01
Mean PP (mmHg)	46.7 ± 6.3	54.5 ± 5.9	0.06

Note: Values represents mean ± standard deviation.
Abbreviations: ACE, angiotensin converting enzyme inhibitors; BMI, body mass index; COPD, chronic obstructive pulmonary disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; PP, pulse pressure.

Discussion

MH is not a well recognized illness, even though its unfavorable prognostic consequences for patients in terms of subsequent cardiovascular events has been largely accepted.[11] Its influence on intermediary markers of cardiovascular risk is well known and is much the same as that of classical hypertension. Kotsis et al demonstrated that patients suffering from MH had more severe target organ damage, with a larger left ventricular mass and thicker intima media than that found in a normotensive population.[12] Ohasama observed a similarly unfavorable prognosis regarding cardiovascular morbidity and mortality in people with MH. The same study recorded a statistically higher risk of cardiovascular mortality and stroke in patients suffering from masked or regular hypertension than in normotensive patients or those with "white coat"

Table 3 Ambulatory 24-hour blood pressure monitoring data

	Normotensive group (n = 27)	Masked hypertensive group (n = 11)	*P*
ABPM			
SBP, first measurement (mmHg)	121 ± 3.3	140 ± 3.1	0.001
DBP, first measurement (mmHg)	74 ± 1.9	84 ± 4.1	0.03
24-hour ABPM			
SBP (mmHg)	112 ± 1.6	128.5 ± 1.3	<0.001
DBP (mmHg)	67 ± 1.0	78 ± 2.6	0.02
HR (beats/min)	64 ± 2.1	76 ± 4.5	0.12
PP (mmHg)	46 ± 5.9	51 ± 6.1	0.002
ABPM during day			
SBP (mmHg)	116 ± 1.7	133.5 ± 1.4	<0.001
DBP (mmHg)	72 ± 1.0	81.5 ± 2.8	0.009
HR (beats/min)	67 ± 2.1	75 ± 4.7	0.17
ABPM during night			
SBP (mmHg)	103 ± 22.4	120 ± 2.4	0.001
DBP (mmHg)	61 ± 1.4	68 ± 2.5	0.03
HR (beats/min)	67 ± 2.3	75 ± 4.6	0.17
Treatment at discharge			
ACE inhibitors (n)	19	7	0.80
Statin (n)	20	8	0.61

Values represent mean ± standard deviation.

Abbreviations: ABPM, ambulatory blood pressure monitoring; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; ACE, angiotensin-converting enzyme; PP, pulse pressure.

hypertension.[13] This is equally true in populations of patients with treated hypertension or untreated MH.[14,15]

When comparing MH patients with normotensive patients, we found a 15 mmHg gap between daytime and nighttime measurements for both SBP and DBP. This difference is important when considering the linear relationship between BP values and risk of cardiovascular events, and highlights the importance of considering the existence of MH when optimizing treatment in patients in need of secondary prevention.

Detection of MH during routine clinical examination is impossible and requires the use of ABPM, without which MH would probably be missed in patients requiring secondary prevention, thereby allowing undiagnosed and uncontrolled high blood pressure to increase their cardiovascular risk. Divergent data make it difficult to identify a specific kind of patient more likely to suffer from MH. However, Malion et al have suggested a profile of patients at high risk, ie, men who smoke and have higher triglyceride and lower HDL levels than the general normotensive population.[16] Our study could not confirm this hypothesis, mainly because of the low number of patients recruited and the predominance of male subjects.

Our work confirmed the existence of MH in a predetermined group of patients with no recorded history of hypertension but undergoing treatment with antihypertensive agents, prescribed principally for their antiatheromatous action. The existence of MH was indicated by higher BP, both during the hospitalization period and during measurement before a consultation. This phenomenon has already been described, and indicates that the cut-off values for the diagnosis of hypertension at SBP 140 mmHg and DBP 90 mmHg are inappropriate. This takes us in the same direction as the American guidelines for hypertension that define values for SBP of 130–139 mmHg and 80–89 mmHg for DBP as the prehypertensive range.[17] Unfortunately, this definition seems to encompass too large a population according to data collected by the National Health and Nutrition Examination Survey (NHANES) that showed that 31% of all adults over the age of 20 had BP in the prehypertensive range.[18]

Diagnosing MH requires the use of ABPM, but mass testing using this method is impractical and should only be used in selected populations. Our work confirms other recent findings that patients with MH often have BP values in the upper normal range.[19]

The prognostic value of classifying hypertensive patients for primary and secondary prevention purposes is well-known but the most effective diagnostic tools and the role of ABPM in this regard remain ill-defined. It seems reasonable to advocate that secondary prevention patients would benefit from ABPM because their BPs are at the upper limits of those considered to be normal according to recent European guidelines.[20]

The ideal solution would seem to be to determine other factors, whether clinical, anamnestic, or biologic, that could be used to calculate a score capable of predicting a high probability of MH in the same way that the prevalent score is used to determine which patients would benefit from systolic index pressure measurement. Self-measurement seems to be just as effective in detecting MH as ABPM but is more accessible, especially for general practitioners, and is more cost-effective. The optimal solution has yet to be defined and since ABPM has been the method of choice in a larger number of studies, it is more widely used.[21]

Our study shows a statistically significant difference between nighttime and daytime SBP and DBP. Self-measurement appears to be a more limiting tool than ABPM, one major difference being that ABPM simplifies measurement of nighttime BP values at regular intervals. Nighttime hypertension is a risk factor for cardiovascular events and can be responsible for target organ damage. Nocturnal hypertension can be a sign of sleep apnea syndrome. Detection of nocturnal hypertension should prompt the physician to prescribe an evening antihypertensive agent.

The main limitation of our study was its small sample size. Therefore it was not possible to assess frequency and outcomes of MH in a population of secondary prevention patients. However, patients with significant vascular disease, no prior history of hypertension, and free from any antihypertensive treatment (except for renin-angiotensin system inhibitors) are not so frequent in current practice. We chose to exclude patients on antihypertensive treatment at admission in order to facilitate the interpretation of results. Finally, the definition of MH is debated; we chose in the present study to use the lower range of BP in accordance with recent published guidelines for management of systemic hypertension. As a consequence, the results of this study should be interpreted within these limitations.

Conclusion

MH is a separate entity with very real prognostic consequences, as shown in studies comparing MH patients with normotensive patients. Its diagnosis in the setting of vascular disease appears to be necessary. Since mass testing is not practical, detection of MH should at the very least be undertaken in specifically targeted high-risk populations.

Disclosure

The authors report no conflicts of interest in this work.

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