CORRESPONDENCE

Response to Hermida

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We have recently published the largest cross-sectional study to date that provides a direct comparison of ambulatory blood pressure (ABP) with home blood pressure (BP) measurements in terms of their ability to detect white coat and masked hypertension phenomena among 613 untreated or treated subjects attending a hypertension clinic.¹

Hermida *et al.*² criticized our paper for ignoring night time ABP measurements, and using only day time (awake) ABP for defining white coat and the masked hypertension phenomena.¹ This criticism is valid given the accumulating evidence on the prognostic ability of night time ABP, which in some studies has exceeded that of day time measurements.³ In addition, it appears reasonable that, as far as possible, all of the information provided by 24-h-ABP monitoring should be used in diagnosing hypertension phenotypes.

Definitions of white coat and masked hypertension phenomena

We looked at the definitions applied for white coat and masked hypertension phenomena in published papers. White coat and the masked hypertension phenomena have been extensively investigated in cross-sectional diagnostic trials. In line with our study,¹ the cross-sectional studies that evaluated white coat and masked hypertension phenomena have been based almost exclusively on day time or awake ABP measurements.^{4,5} This was also the case in long-term outcome trials that assessed the prognostic significance of these phenomena, which also used day time or awake ABP measurements,^{6–10} with a few exceptions that used average 24-h-ABP values.^{11,12}

Several guideline documents and statements by hypertension societies have provided recommendations on the evaluation of white coat and the masked hypertension phenomena in clinical practice. The 2007 European Society of Hypertension guidelines defined

white coat hypertension on the basis of day time or 24-h-ABP.¹³ On the other hand, the American Heart Association recommended the use of awake ABP for the diagnosis of white coat hypertension.^{14,15} More recently, the UK National Institute for Health and Clinical Excellence, in its recommendations for the management of hypertension, defined white coat and masked hypertension on the basis of day time ABP.¹⁶

The above mentioned data on the definitions used for white coat and masked hypertension in short-term and long-term trials, and in hypertension guidelines suggest that nocturnal ABP levels are largely ignored. By defining white coat hypertension on the basis of day time ABP measurements, there might be cases with low day time ABP but elevated night time ABP that remain undetected. On the other hand, by defining masked hypertension on the basis of day time measurements, there might be cases with low day time ABP but elevated night time ABP that also remain undetected.

Isolated nocturnal hypertension: additional data analysis

We investigated this issue raised by Hermida *et al.*² by performing additional analysis of our data, with the aim of evaluating (i) the proportion of subjects who had elevated nocturnal ABP, but have been labeled as white coat hypertensive on the basis of low day time ABP and, (ii) the proportion of subjects with masked hypertension due to isolated nocturnal ABP elevation, who have been missed (classified as normotensives) because of low day time ABP.

According to our initial analysis, the white coat hypertension phenomenon was present in 88 of the 613 study subjects (14.4%) when night time (awake) ABP was ignored.¹ When night time (asleep) ABP was also evaluated, one quarter of these subjects ($n = 23$, 3.8%) were not classified as white coat hypertensives

because of elevated night time ABP (Table 1). As expected, these subjects tended to have higher 24-h-ABP levels than those with low day time and night time ABP or normotensives (low clinic, day time and night time ABP, Table 2). It is important to note, however, that only 5 out of these 23 subjects had an elevated 24-h-ABP (systolic and/or diastolic $> 130/80$ mm Hg). Moreover, when a 5 mm Hg gray zone of diagnostic uncertainty was applied to define isolated nocturnal hypertension (> 5 mm Hg above the diagnostic threshold for night time ABP), only 10 subjects (1.6%) changed classification as a result of nocturnal hypertension (Table 1).

We also looked at the classification of the masked hypertension phenomenon, which was observed in 94 study subjects (15.3%) in our initial analysis that ignored night time ABP.¹ When night time ABP was taken into account, there were 27 more cases of masked hypertension due to isolated nocturnal hypertension (Table 3). Subjects with isolated nocturnal hypertension tended to have lower 24-h-ABP levels than those with masked hypertension due to day time ABP elevation only, or day and night time ABP elevation (Table 4). It is important to note that average 24-h ABP was normal in 24 of the 27 subjects with isolated nocturnal masked hypertension. Moreover, when a 5 mm Hg gray zone of diagnostic uncertainty was applied to define isolated nocturnal hypertension (> 5 mm Hg above the diagnostic threshold for night time ABP), only seven subjects (1.1%) changed classification because of isolated nocturnal hypertension (Table 3).

The above analyses suggest that in our study sample, by taking into account night time ABP in the detection of white coat and masked hypertension phenomena, there are few cases which the diagnosis changes as a result of isolated nocturnal hypertension. More importantly, in most of

Table 1 Prevalence of the white coat hypertension phenomenon defined on the basis of clinic blood pressure and several different aspects of the ambulatory blood pressure profile among 613 subjects attending a hypertension clinic

	Different definitions of white coat hypertension			White coat hypertensives n (%)
	Clinic BP	Awake ABP	Asleep ABP	
Day time WCH	High	Low	Ignored	88 (14.4)
Day and night time WCH	High	Low	Low	65 (10.6)
WCH with elevated night time ABP only	High	Low	High	23 (3.8)
Day time WCH with high Night time ABP that is clinically relevant	High	Low	High (> 5 mm Hg above night time ABP threshold)	10 (1.6)

Abbreviations: ABP, ambulatory blood pressure; BP, blood pressure; WCH, white coat hypertension.

Table 2 Characteristics of subjects with white coat hypertension phenomenon defined on the basis of clinic blood pressure and several different aspects of the ambulatory blood pressure profile among 613 subjects attending a hypertension clinic

	Different definitions of White Coat Hypertension			
	Day time WCH	Day and night time WCH	Day time WCH with high night time ABP	Normotension
Clinic BP	High	High	High	Low
Day time ABP	Low	Low	Low	Low
Night time ABP	Ignored	Low	High	Low
N	88	65	23	98
Men (%)	35	39	26	56
Age (years)	55	54	58	55
BMI (kg m ⁻²)	28.5	29	27	28
Treated (%)	48	42	65	74
Smokers (%)	11	11	9	18
Clinic BP	144/89	144/91	145/86	125/79
24 h ABP	119/72	117/71	124/74	117/71
Awake ABP	124/77	124/77	126/78	123/76
Asleep ABP	111/64	107/62	122/70	106/62

Abbreviations: ABP, ambulatory blood pressure systolic/diastolic in mmHg; BMI, body mass index; BP, blood pressure systolic/diastolic in mmHg; WCH, white coat hypertension.

Table 3 Prevalence of the masked hypertension phenomenon defined on the basis of clinic blood pressure and several different aspects of the ambulatory blood pressure profile among 613 subjects attending a hypertension clinic

	Different definitions of masked hypertension			Masked hypertensives n (%)
	Clinic BP	Awake ABP	Asleep ABP	
Daytime MH	Low	High	Ignored	94 (15.3)
Daytime MH only	Low	High	Low	29 (4.7)
Day and night time MH	Low	High	High	65 (10.1)
Day and/or night time MH	Low	High, or low if high night time ABP	High, or low if high day time ABP	121 (19.7)
Night time MH only	Low	Low	High	27 (4.4)
Night time MH only (clinically relevant)	Low	Low	High (> 5 mm Hg above night time ABP threshold)	7 (1.1)

Abbreviations: ABP, ambulatory blood pressure; BP, blood pressure; MH, masked hypertension.

these cases, individuals have a normal average 24-h-ABP, which makes the diagnosis of ABP hypertension and the need for treatment questionable.

Remaining research questions

In our cross-sectional study, the vast majority of the participants attending a hypertension clinic had uncomplicated hypertension and low to moderate cardiovascular risk.¹ There are three important issues that cannot be investigated in our data set. The first is the prevalence of isolated nocturnal hypertension in other populations, such as patients with established cardiovascular disease, nephropathy, diabetes or sleep apnea, in whom the prevalence of non-dipping is higher than in those with uncomplicated hypertension. Second, we could not investigate whether individuals with isolated nocturnal hypertension have a higher cardiovascular risk than normotensives. Third, we also could not investigate whether in these cases the selective reduction of night time BP with drug dosing before bedtime is more effective in preventing cardiovascular events than the usual morning dosing.

The International Database on Ambulatory Blood Pressure In Relation to Cardiovascular Outcomes Investigators included 8711 individuals from 10 populations, and identified 577 untreated individuals (6.4%) with isolated nocturnal hypertension (low office and day time ABP). After a follow-up of 10.7 years, this condition was found to be associated with a higher overall mortality (hazard ratio 1.29, $P=0.045$) and cardiovascular event risk (1.38, $P=0.037$).¹⁷ Several studies in diabetic^{18,19} and non-diabetic subjects^{20,21} have suggested that elevated nocturnal ABP should be taken into account in decision making, even when day time ABP levels are low.

The usefulness of bedtime dosing of antihypertensive drug treatment aimed at improving nocturnal BP control, and thereby providing more effective protection against cardiovascular events has been inadequately investigated.²² A recent study in hypertensive patients with nephropathy who were followed for 5.4 years showed that taking at least one antihypertensive drug at bedtime improved the control of nocturnal and 24-h-ABP and reduced the risk of cardiovascular events compared to taking all drugs in the morning.²³ On the other hand, another report by the African American Study of Kidney Disease showed that bedtime dosing of once-daily antihypertensive treatment or the addition

Table 4 Characteristics of subjects with masked hypertension phenomenon defined on the basis of clinic blood pressure and several different aspects of the ambulatory blood pressure profile among 613 subjects attending a hypertension clinic

	Different definitions of Masked Hypertension				
	Day time MH	Day time MH only	Day and night time MH	Night time MH only	Normotension
Clinic BP	Low	Low	Low	Low	Low
Day time ABP	High	High	High	Low	Low
Night time ABP	Ignored	Low	High	High	Low
N	94	29	65	27	98
Men (%)	61	55	63	59	56
Age (years)	54	49	56	56	55
BMI (kg m ⁻²)	28	28	28	28	28
Treated (%)	54	55	54	56	74
Smokers (%)	23	20	25	16	18
Clinic BP	128/82	128/84	128/82	125/81	125/79
24 h ABP	132/81	126/79	134/83	123/76	117/71
Awake ABP	138/87	136/87	139/87	126/79	123/76
Asleep ABP	119/72	109/65	124/74	119/71	106/62

Abbreviations: ABP, ambulatory blood pressure systolic/diastolic in mm Hg; BMI, body mass index; BP, blood pressure systolic/diastolic in mm Hg; MH, masked hypertension.

of drugs taken at bedtime did not significantly reduce nocturnal BP compared to morning dosing.²⁴

Despite the considerable number of studies that have demonstrated the prognostic relevance of nocturnal hypertension, there is still no conclusive evidence on whether a treatment strategy specifically targeting nocturnal BP can eliminate the associated cardiovascular risk.^{7,22} Although it seems reasonable that all aspects of the 24-h-BP profile should be normalized, randomized trials are still needed to demonstrate whether more complex and individualized treatment regimens can achieve more efficient cardiovascular protection than morning dosing with long-acting drugs.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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