

Review Article

Properly defining white coat hypertension

P. Verdecchia¹, J. A. Staessen², W. B. White³, Y. Imai⁴ and E. T. O'Brien⁵

¹Cardiologia e Fisiopatologia Cardiovascolare, Università di Perugia, Policlinico Monteluce, Perugia, Italy; ²Studiecoördinatiecentrum, Laboratorium Hypertensie, Campus Gasthuisberg, Katholieke Universiteit Leuven, Leuven, Belgium; ³Section of Hypertension and Clinical Pharmacology, The University of Connecticut Health Center, Farmington, Connecticut, U.S.A.; ⁴Department of Clinical Pharmacology and Therapeutics, Tohoku University Graduate School of Pharmaceutical Science and Medicine, Tohoku University Hospital Clinical Trial Center, Sendai, Japan; ⁵Blood Pressure Unit, Beaumont Hospital, Dublin, Ireland

Definition of white coat hypertension

White coat hypertension (also referred to as 'office hypertension'^[1], or 'isolated clinical hypertension'^[2]) is a term used to denote individuals who have blood pressures that are higher than normal in the medical environment, but whose blood pressures are normal when they are going about their daily activities. Like many other working definitions in clinical medicine, white coat hypertension is an arbitrary definition intended to assist clinicians by improving cardiovascular risk stratification—a key step in the management of patients with essential hypertension^[3,4]—by identifying a stratum of subjects at low risk of future cardiovascular disease because of a normal average daytime blood pressure outside the medical setting^[5,6]. Thus far, this definition is clear, but unfortunately it lacks the precision needed to make it clinically useful. It is when we define exactly what constitutes a normal average daytime blood pressure that confusion arises, and this confusion now threatens to obscure the clinical and epidemiological importance of identifying the condition.

White coat effect

The studies by Mancia and co-workers^[7] quantified precisely the transient blood pressure rise associated with the presence of a doctor (4 to 75 mmHg [mean, 27]

for systolic blood pressure, 1 to 36 mmHg [mean, 27] for diastolic blood pressure). This transient blood pressure rise ('white coat effect') could lead to a remarkable over-estimation of blood pressure in many subjects with a clinical diagnosis of essential hypertension. The superiority of ambulatory over clinic blood pressure is strongly supported by the evidence that target organ damage in hypertension is more closely associated with whole-day blood pressure than with clinic blood pressure^[1,8,9]. It is important to mention that white coat hypertension and white coat effect are different entities: the first is a binary (yes/no) definition imposed by stratification of blood pressure, the second is a quantitative measure of the blood pressure rise from before to during the visit, a phenomenon which may be expected to occur in the majority of patients^[7]. Although white coat hypertension is a consequence of the white coat effect, there is no automatic association between the two entities: patients with a high clinic blood pressure and a marked white coat effect may still have abnormally elevated ambulatory blood pressure levels; patients with mild hypertension and a small white coat effect may fall in the category of white coat hypertension if ambulatory blood pressure is normal^[10].

Is white coat hypertension clinically relevant?

Following on this observation, it has been postulated that patients with elevated blood pressure during the clinic visit and normal blood pressure during usual activities might be further characterized by the following three features:

- (a) absence of organ damage induced by hypertension;
- (b) absence of hypertension-related risk of future cardiovascular disease;
- (c) absence of blood pressure reduction from antihypertensive treatment.

Key Words: Hypertension, ambulatory blood pressure monitoring, left ventricular hypertrophy, prognosis, myocardial infarction, stroke, heart failure.

Revision submitted 12 February 2001, accepted 15 February 2001, and published online 4 October 2001.

Correspondence: Dr Paolo Verdecchia, Cardiologia e Fisiopatologia Cardiovascolare, Università di Perugia, Policlinico Monteluce, Via Brunamonti 51, 06100 - Perugia, Italy.

Methodological issues

Four steps are of paramount importance in dealing with white coat hypertensive patients:

First step

Identification of these patients on the basis of a valid definition of normal blood pressure outside the medical setting.

Second step

Assessment of target organ damage in these individuals in comparison with clinically normotensive subjects and in patients with higher values of ambulatory blood pressure.

Third step

Evaluation of risk of future cardiovascular morbidity and mortality in the white coat hypertensive patients, as compared with clinically normotensive subjects and patients with elevated ambulatory blood pressure.

Fourth step

Assessment of therapeutic intervention in patients with white coat hypertension compared with those with more elevated ambulatory blood pressure.

As yet, there is no universal agreement regarding a definition of normal and abnormal blood pressure outside the medical setting^[3,4,11–14]. In the only available general population study, carried out in Japan, the lowest overall mortality was observed in subjects with average 24-h blood pressure 120–133 mmHg systolic and 65–78 mmHg diastolic^[15] and the lowest cardiovascular mortality in subjects with average daytime blood pressure 117–123 mmHg systolic and 69–72 mmHg diastolic^[16]. The majority of published studies used different definitions of white coat hypertension, with the result that it has been difficult or impossible to compare one study with another^[17]. This is unfortunate because there is clear evidence that both the prevalence of white coat hypertension and echocardiographically determined left ventricular hypertrophy are markedly influenced if the restrictive (lower) rather than the more liberal (higher) limits of ambulatory blood pressure normality are used to define white coat hypertension^[18]. Furthermore, minor differences in the definition of white coat hypertension may also exert a significant impact on the risk of future cardiovascular disease in these subjects^[19].

Prognostic impact of white coat hypertension

Event-based studies have shown that the risk of future cardiovascular disease events is less in patients with white coat hypertension than in those with higher ambulatory blood pressure levels, even after controlling for concomitant risk factors^[20–22]. A follow-up extension of one of these studies has shown that the risk of future cardiovascular events did not differ between clinically

normotensive subjects and subjects with white coat hypertension defined by an average daytime ambulatory blood pressure <130 mmHg systolic and <80 mmHg diastolic^[19].

A recent important contribution to the white coat hypertension debate has come from the Syst-Eur study^[22], in which randomized antihypertensive treatment was effective in reducing the risk of cardiovascular disease events in subjects with average daytime ambulatory blood pressure >160 mmHg, but not in subjects with lower ambulatory blood pressure levels^[22]. It is apparent, therefore, that a reliable definition of normal blood pressure outside the medical setting is mandatory if misclassification and misunderstanding^[21] on the diagnosis of white coat hypertension are to be avoided.

An example of the persisting uncertainty and disagreement on this issue evolved from a recently published study^[23] in which 18 subjects with so-called white coat hypertension, 259 subjects with mild or persistent hypertension and 259 clinically normotensive subjects were followed for 21 years. Because there were four cardiovascular deaths (22.2%) in the white coat group, 10 deaths (3.9%) in the normotensive group, four deaths (2.7%) in the mild hypertension group and seven deaths (6.5%) in the persistent hypertension group, it was concluded that white coat hypertension was not a benign condition. However, in this study, white coat hypertension was not defined on the basis of a presumed normal blood pressure (self-measured or ambulatory) outside the medical setting, but, rather, by a medical clinic blood pressure that was <140 mmHg systolic or <90 mmHg diastolic when measured in the clinic by a nurse, and >160 mmHg systolic or >95 mmHg diastolic when measured by a doctor. Thus, this study has assessed outcome between different groups, one of which had a blood pressure by 20/5 mmHg lower in the clinic setting when measured by a nurse than by a doctor. These patients did not have white coat hypertension, they were exhibiting what has been shown previously using intra-arterial measurement, namely, that blood pressure measured by a doctor is higher than that measured by a nurse^[24]. It has never been demonstrated that blood pressure measured by a nurse is equivalent to ambulatory blood pressure. In one study^[25], blood pressure measured by a doctor was 152/100 mmHg ($\pm 18/12$), while that measured by a nurse was 148/97 mmHg ($\pm 18/12$) and awake ambulatory blood pressure was 141/96 mmHg ($\pm 13/10$). In the same study, regression coefficients of blood pressure with left ventricular mass were 0.24 ($P=ns$) for physician blood pressure, 0.44 for nurse blood pressure ($P<0.05$) and 0.63 ($P<0.01$) for awake ambulatory blood pressure^[25]. Thus, what the authors describe as white coat hypertension differs markedly from the condition described in all previous outcome studies and is, in fact, an entirely different concept from that used in the literature over the past two decades. The results of the study cannot therefore be compared with studies which measured blood pressure outside the medical environment using ambulatory blood pressure monitoring or self-measurement of blood

pressure. The conclusion from the study that white coat hypertension is not an innocent phenomenon^[23] is incorrect, which is not to deny that the patients with a doctor/nurse difference in blood pressure or an excessive blood pressure variability may not be at risk.

Uniform definition of white coat hypertension

At the last International Consensus Conference on Ambulatory blood pressure^[26,27], it was proposed that average daytime levels of blood pressure above 135/85 mmHg should be regarded as definitely hypertensive and levels below 130/80 mmHg as normotensive. It seems reasonable, therefore, to define white coat hypertension as being present if the conventional blood pressure is persistently equal to or greater than 140/90 mmHg, with average daytime ambulatory blood pressure below 135/85 mmHg. It would also seem reasonable to propose that all studies of white coat hypertension should perform analyses using this definition so as to permit comparison with other studies. Such a proposal does not preclude analyses using other definitions but will ensure comparability among the studies.

Conclusions

Available data strongly suggest that white coat hypertension, when defined by low levels of daytime blood pressure, either ambulatory or self-measured, identifies subjects at a lower risk from target organ involvement than subjects with sustained hypertension^[1,17-22]. These subjects require regular and accurate check-up visits. Under these conditions, ambulatory blood pressure monitoring may become a useful instrument in clinical practice^[28]. We need long-term intervention studies in order to definitely establish the most appropriate clinical management of these subjects^[29-31]. Large cohort studies are also needed to establish whether the long-term risk of cardiovascular disease is comparable between subjects with white coat hypertension and clinically normotensive individuals^[19], or whether an excessive blood pressure reactivity limited to the doctor's office may contribute to adversely affect prognosis. To be able to pursue this important issue, a major effort should be undertaken to maintain comparability with previous studies by using the stated definition of normal blood pressure outside the medical setting. Otherwise, misclassifications and misunderstandings will continue in the future, and misleading articles with non-standardized definitions of 'normal' blood pressure outside the medical setting will proliferate.

References

- [1] White WB, Schulman P, McCabe EJ, Dey HM. Average daily blood pressure, not office pressure, determines cardiac function in patients with hypertension. *JAMA* 1989; 261: 873-7.
- [2] Mancia G, Zanchetti A. White-coat hypertension: misnomers, misconceptions and misunderstandings. What should we do next? *J Hypertens* 1996; 14: 1049-52.
- [3] Guidelines Subcommittee. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. *J Hypertens* 1999; 17: 151-83.
- [4] The Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. The Sixth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. *Arch Intern Med* 1997; 157: 2413-46.
- [5] Pickering TG, James GD, Boddie C, Harshfield GA, Blank S, Laragh JH. How common is white-coat hypertension? *JAMA* 1988; 259: 225-8.
- [6] Staessen JA, Thijs L, Fagard R *et al* for the Systolic Hypertension in Europe Trial Investigators. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. *JAMA* 1999; 282: 539-46.
- [7] Mancia G, Bertineri G, Grassi G *et al* Effects of blood pressure measured by the doctor on patient's blood pressure and heart rate. *Lancet* 1983; 2: 695-8.
- [8] Sokolow M, Werdegar K, Kain HK *et al*. Relationship between level of blood pressure measured casually and by portable recorders and severity of complications in essential hypertension. *Circulation* 1966; 34: 279-88.
- [9] Mancia G, Zanchetti A, Agabiti Rosei E *et al* for the SAMPLE Study Group. Ambulatory blood pressure is superior to clinic blood pressure in predicting treatment-induced regression of left ventricular hypertrophy. *Circulation* 1997; 95: 1464-70.
- [10] Verdecchia P, Schillaci G, Borgioni C *et al*. White-coat hypertension and white-coat effect: similarities and differences. *Am J Hypertens* 1995; 8: 790-8.
- [11] Mallion J-M, Baguet J-P, Siché J-P, Tremel F, De Gaudemaris R. Clinical value of ambulatory blood pressure monitoring. *J Hypertens* 1999; 17: 585-95.
- [12] Pickering TG. White-coat hypertension in a changing era of medical care. *Blood Pressure Monitoring* 1996; 1 (Suppl 2): S27-S32.
- [13] Staessen JA, Bienaszewski L, O'Brien ET, Fagard R. What is a normal blood pressure on ambulatory monitoring. *Nephrol Dial Transplant* 1996; 11: 241-5.
- [14] O'Brien ET, Staessen JA. What is "hypertension". *Lancet* 1999; 353: 1541-43.
- [15] Ohkubo T, Imai Y, Tsuji I. Reference values for 24-hour ambulatory blood pressure monitoring based on a prognostic criterion. The Ohasama Study. *Hypertension* 1998; 32: 255-9.
- [16] Ohkubo T, Imai Y, Tsuji I *et al*. Prediction of mortality by ambulatory blood pressure monitoring versus screening blood pressure measurements: a pilot study in Ohasama. *J Hypertens* 1997; 15: 357-64.
- [17] Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Porcellati C. White-coat hypertension: not guilty when correctly defined. *Blood Pressure Monitoring* 1998; 3: 147-52.
- [18] Verdecchia P, Schillaci G, Boldrini F, Zampi I, Porcellati C. Variability between current definitions of 'normal' ambulatory blood pressure. Implications in the assessment of white-coat hypertension. *Hypertension* 1992; 20: 555-62.
- [19] Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Porcellati C. White-coat hypertension. *Lancet* 1996; 348: 1444-5.
- [20] Verdecchia P, Porcellati C, Schillaci G *et al*. Ambulatory blood pressure: an independent predictor of prognosis in essential hypertension. *Hypertension* 1994; 24: 793-801.
- [21] Khattar RS, Senior R, Lahiri A. Cardiovascular outcome in white-coat versus sustained mild hypertension: a 10 year follow-up study. *Circulation* 1998; 98: 1982-7.
- [22] Fagard RH, Staessen JA, Thijs L *et al*. Response to anti-hypertensive therapy in older patients with sustained and nonsustained systolic hypertension. *Circulation* 2000; 102: 1139-4.

- [23] Strandberg TE, Salomaa V. White coat effect, blood pressure and mortality in men: prospective cohort study. *Eur Heart J* 2000; 21: 1714–8.
- [24] Mancia G, Parati G, Pomidossi G, Grassi G, Casadei R, Zanchetti A. Alerting reaction and rise in blood pressure during measurement by physician and nurse. *Hypertension* 1987; 9: 209–15.
- [25] Veerman DP, de Blok K, Delemarre BJM, van Montfrans GA. Office, nurse, basal and ambulatory blood pressure as predictors of hypertensive target organ damage in male and female patients. *J Hum Hypertens* 1996; 10: 9–15.
- [26] Verdecchia P, Clement D, Fagard R, Palatini P, Parati G. Target organ damage, morbidity and mortality. *Blood Pressure Monitoring* 1999; 4: 303–17.
- [27] Pickering TG, Coats A, Mallion JM, Mancia G, Verdecchia P. Task force V: White-coat Hypertension. *Blood Pressure Monitoring* 1999; 4: 333–41.
- [28] Staessen JA, Byttebier G, Bintinx F, Celis H, O'Brien ET for the Ambulatory Blood Pressure Monitoring and Treatment of Hypertension Investigators. Antihypertensive treatment based on conventional or ambulatory blood pressure measurement. *JAMA* 1997; 78, No 13: 1065–72.
- [29] Verdecchia P. Prognostic value of ambulatory blood pressure. Current evidence and clinical implications. *Hypertension* 2000; 35: 844–51.
- [30] Spence DJ. Withholding treatment in white-coat hypertension: wishful thinking. *Can Med Ass J* 1999; 161: 275–6.
- [31] Verdecchia P, Schillaci G. Prognostic value of ambulatory blood pressure monitoring. In: White WB, ed. *Blood Pressure Monitoring in Cardiovascular Medicine and Therapeutics*, Totowa, NJ, Humana Press, Inc. 2000; 191–218.